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A SURVEY OF BIOTECHNOLOGY REGULATIONS APPLIED TO CONTAINED USE

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Australia

The Australian Government has now issued "Guidelines for Small Scale Genetic Manipulation Work" December 1989 under the responsibility of the Genetic Manipulation Advisory Committee GPO Box 2183 Canberra ACT 2601.

The guide covers the Scope of and Exemptions from the guidelines which are:

1) Fusion of Mammalian Cells.
2) Protoplast fusion between non pathogenic micro-organisms.
3) Self exchanging organism work.
4) Work involving approved host/Vector systems where the donor DNA
   a) is not derived from micro-organisms able to cause disease in humans, animals or plants
   b) does not code for any protein which regulates the growth of mammalian cells
   c) does not comprise or represent more than 2/3rd of the genome of a virus and is not being used in an experiment where the missing genetic information is available in the cell in which the genetic material is introduced.

Under these guidelines, work exempt under small scale conditions will also be exempt from the RDMC/GMAC large scale guidelines.

Institutions which have an Institutional Biosafety Committee (IBC) should notify their committee of all work including experiments which fall in the exempt category. Institutions which do not have an IBC should notify GMAC.

The guidelines also detail categories of small scale work.

1) Category A - Experiments requiring GMAC advice and IBC approval. This is work which may carry a hazard.
2) Category B - Experiments for GMAC notification and IBC approval. This is work which carries a low level of hazard.
3) Category C - Experiments for Special Exemption - this is work which does not present a significant risk.

The guidelines define the role and responsibilities of GMAC which include advice and inspection of C2 or C3 laboratories. The guidelines also define the function of the IBC, the Biological Safety Officer and the Principal Investigator.

The guidelines detail requirements for Importation and Transportation and provide a list of GMAC Approved Host/Vectors, information on dealing with Toxins and Requirements for Physical Containment at levels C1, C2 and C3.

Belgium

Although the Belgian authorities have not officially adopted the OECD guidelines they have been carefully considered by the COMITÉ INTERMINISTÉRIAL DE LA POLITIQUE SCIENTIFIQUE.

The Belgian authorities also comply with the requirements and directives 90/219/EEC.

Recently the Services of the Prime Minister has produced a text for discussion entitled "Projet pour la mise en place en Belgique d'un Secretariat d'appui ADN-Recombinant". This paper summarises the Historical Background of the legislation particularly the influence of OECD and the Commission of the European Communities.

The paper then details proposals for a Consultative Committee for recombinant work with a suggested Mandate, Composition and Function. The paper also considers similar functions of Mandate, composition and function for the government Secretariat which would be available to the Consultative Committee which would consist of Experts, Scientific staff from the secretariat, Representatives of Public Authorities and others.

The text of the discussion document also includes a suggested method for dealing with an application to the Consultative Committee.

Byelorussia

No recent information is available for Byelorussia but the authorities of the late Soviet Socialist Republic of Byelorussia had produced guidelines for carrying out research activities in Biotechnology. These guidelines include:

(i) Classification of micro-organisms according to the level of their biological danger for persons working with them as well as for general public in accordance with the requirements established by the USSR Ministry of Health;

(ii) Determination of the level of pathogenecity of micro-organisms which produce biologically active substances;

(ii) Study of quality and medico-biological assessment of microbiosynthesis food and feed products;

(iv) Securing the infection safety in microbiological laboratories and industry;

(v) Securing of engineering and technical conditions for work safety in dealing with micro-organisms and biosynthesis products;

(vi) Protection of environment (disinfection of liquid and gas wastes and utilization of other production wastes);

(vii) Medical aspects of safety rules (specific preventive treatment of workers taking into account the epidemiological principle, clinic and laboratory diagnostics and dispensarization);

(viii) Determination of tolerable limits of micro-organisms and biosynthesis product concentration in working and effluent zones as well as control of concentration levels,

(ix) Utilization of micro-organisms, produced by methods of genetic engineering, under the conditions which prevent their uncontrolled multiplication.

Canada

Canada has developed regulatory guidelines under a wide range of product-oriented legislation which is administered by the department of Agriculture, Environment and Health and Welfare.

Most legislation applicable to biotechnology in Canada pertains to specific product categories, without regard to the process of production. These product categories include veterinary biologics, pest control products, foods, drugs, cosmetics, medical devices, feeds, plants and fertilizers. The new Canadian Environmental Protection Act has powers to assess potential health and environmental effects of new biotechnology products not similarly assessed under other legislation, e.g. products for pollution degradation, waste disposal, mineral leaching and speciality chemical manufacture.

Canadian guidelines for handling recombinant DNA, animal viruses and cells were developed in 1977 by the Medical Research Council (MRC). The guidelines were revised in 1979 and 1980 with progressive relaxation for rDNA research, justified by continued safe experience and consistent with international approaches. The most recent revision (1989), entitled "Laboratory Biosafety Guidelines", has been expanded to address laboratory procedures for handling infectious agents in general. Work with recombinant DNA is but one of the considerations. The MRC guidelines clearly apply to laboratory research and are not intended to address environmental releases or large-scale production.

The Food and Drugs Act, administered by the health Protection Branch of Health and Welfare Canada, requires pre-market notification, testing and/or approval of drugs, cosmetics and medical devices. Drugs manufactured by novel biotechnological processes, including recombinant DNA methods, cell fusion, or cell culture are designated as biologics and must comply with the Food and Drugs Act and Regulations for Schedule One Drugs. Drugs produced by these processes cannot be sold in Canada without a license. Evaluation criteria give considerable attention to product purification and removal of extraneous substances and infectious agents. There may be a need for new testing protocols, specifically designed for evaluation of new drugs produced through biotechnology.

Food additives are subject to pre-market evaluation at this time, and products developed through biotechnology would be subject to a similar process. Foods are not subject to pre-market requirements, but draft regulations to require pre-market notification and safety assessment of genetically modified organisms for sale as, in, or on foods, are under consideration. Included in this category would be foods manufactured by novel processes and novel foods. Evaluation criteria for food additives include end-product characterization and toxicity. Additional guidelines for testing and registration of genetically engineered organisms, or products thereof, are under development. There may be a need for new testing protocols specifically designed for the evaluation of whole foods.

It is proposed that the Department of National Health and Welfare Act should be amended to regulate the importation of human pathogens. Agriculture Canada,

pursuant to the Animal Disease and Protection Act, has authority for the importation into Canada of animal pathogens, but has been regulating the importation of all pathogens to date. The handling, packaging and labelling of all pathogens are adequately regulated under the Transport of Dangerous Goods Act and these aspects will be incorporated by reference into the proposed regulations.

The Animal Disease and Protection Act, administered by Agriculture Canada, prohibits importation, transportation or sale of veterinary biologics in Canada without special permit. Permit conditions for transportation consist of documentation and safety requirements specified in Transport Canada's Transportation of Dangerous Goods Act. License conditions for sale include purity, potency, efficacy and safety requirements.

The Pest Control Products Act, administered by Agriculture Canada, requires that all microbial pest control products be registered prior to manufacture, sale or use in Canada. Registration and field trial requirement guidelines for naturally occurring microbial pest control agents are available. General requirements include specifications, manufacturing methods, quality control methods, toxicology, residue data, environmental toxicology, environmental fate, efficacy and proper labelling. These guidelines are being used to regulate genetically engineered products on a case-by-case basis and will be the basis for requirements for genetically engineered and similar products. A workshop was held in March 1989 to discuss the above guidelines.

The Fertilizers Act, also administered by Agriculture Canada, regulates fertilizers and supplements offered for sale in terms of their safety, merit and value. Growth-promoting microbial products (genetically engineered and otherwise) are defined as supplements and must comply with the standards, guarantee, safety and labelling requirements outlined in the regulations. Additional guidelines for environmental release and research exemptions are presently under consideration.

The Plant Quarantine Act, administered by Agriculture Canada, prohibits importation of any pest organism capable of causing injury or damage to plants or plant products, or of any plant or other object that may carry a pest organism. The Act applies to pest organisms or plants produced by biotechnology, as well as to naturally occurring species. However, new expertise may be needed to evaluate capability of injury or damage by genetically engineered organisms.

The Feeds Act, administered by Agriculture Canada, regulates the manufacture, sale and importation of feeds and feed additives through pre-sale registration and post-sale inspection. The Act applies to feeds and supplements produced by biotechnology as well as conventional processes. Products must demonstrate compliance to health and safety standards by conforming to standards, guarantees, safety and labelling requirements outlined in the regulations. Experimental feeds are exempt from regulation. Additional guidelines for regulation of products and organisms of biotechnology regulated under the Feeds Act are currently under development.

The Seeds Act, administered by Agriculture Canada, ensures that imported, domestic and exported seed is safe, pure, viable, efficacious and accurately

represented to maintain identity and avoid fraud. The act applies to any plant part of any species belonging to the plant kingdom that is represented, sold or sowed to grow a plant. Thus, the Act applies to genetically altered plant material as well as plant material developed through traditional means. There are mechanisms in place for regulating imported transgenic plant material. Mechanisms for the control of domestically developed transgenic plant material and genetically altered horticultural plant material are under development. Genetically altered plant material is currently being tested in small-scale field trials. In order to be field tested, the plant material must be genetically characterised and stable. The material must show no evidence of weediness or toxicity. The trials must be reproductively isolated from plants of the same and related species. Control, over the disposition and disposal of resultant plant material are implemented as are the post-trial land use. Site inspections are conducted.

The Canadian Environmental Protection Act (CEPA), passed into law on 30 June 1988, addresses many areas of environmental concern. The Act includes provisions for pre-manufacture or importation assessment of Substances New to Canada for health and environmental effects. Products of biotechnology, including genetically modified organisms, have been identified as one class of substances for which pre-manufacture information requirements are being developed. Introduction of genetically modified organisms into the environment will be regulated under these provisions of CEPA. Products already assessed for health and environmental effects under other acts (e.g. microbial pesticides under the Pest Control Products Act) are not covered by CEPA. Regulations and guidelines specifying notification and assessment procedures and information requirements under CEPA are under development by Environment Canada and Health and Welfare Canada.

The Hazardous Products Act (HPA), administered by Consumer and Corporate Affairs Canada, provides for the scheduling and prohibition or regulation of hazardous products. Biotechnology products are not addressed as such but, unless exempt by virtue of being subject to the Food and Drugs Act or Pest Control Products Act, could be subject to control under the HPA. The Ministers of Consumer and Corporate Affairs and Health and Welfare Canada may request the submission, on a confidential basis, of formulation and other information for unregulated products subject to the Act to determine if they should b schedules. The HPA also establishes supplier requirements of the Workplace Hazardous Materials Information System (HHMIS). "Controlled Products" sold or imported for use in a Workplace in Canada, including toxic and infectious materials, must be labelled and accompanied by a material safety data sheet.

The Government Organisation Act requires all federal agencies to submit an environmental assessment for the Federal Environmental Assessment Review Office (FEARO) prior to any direct action or funding commitment which may be cause for environmental concern. FEARO is an independent office within Environment Canada. Public hearings are specified as part of the assessment process. The initiating department is responsible for defining categories of action which require assessment, following FEARO guidelines. While there is considerable room for departmental interpretation, it seems likely that any specific

biotechnology legislation, or approval or funding of major field trials involving genetically engineered organisms, would require such environmental assessment.

Animal Disease and Protection Act	Veterinary Biologics
Feed Act	Livestock feed
Fertilizers Act	Fertilizers
Pest Control Products Act	Pest control agents
Plant Quarantine Act	Plant pests
Seeds Act	New varieties of seeds
Environmental Protection Act	Pollution, Waste disposal, Chemical production
Environmental Contaminants Act	All chemicals imported in quantities greater than 500kg/year
Food & Drug Act	Foods, Drugs, Veterinary drugs and cosmetics
Drugs Directorate	Drugs, Veterinary drugs and cosmetics produced by biotechnology processes
Food Directorate	Food micro-organisms, food contaminants and residues produced through bio-technological processes.
Environmental Health Directorate	In vitro diagnostic kits
Hazardous Products Act	Consumer products which are considered hazardous and developed through bio-technological processes.

European Economic Community

The Council of the European Communities adopted legislation in the form of Directive 90/219/EEC on 23rd April 1990. Member states were intended to implement this directive by 23rd October 1991 but this has not happened in all cases. The legal basis of the directive is Article 130 of the Treaty establishing the EEC which states that action relating to the environment shall have the following objectives:

1) To preserve, protect and improve the quality of the environment
2) To contribute towards protecting human health
3) To ensure a prudent and rational utilization of natural resources.

For the purposes of the directive micro-organisms are divided into two groups. Group I are those which satisfy the criteria of Annex II which is the same set as proposed by OECD (GILSP). All other micro-organisms which do not satisfy these criteria are classed in Group II.

The directive also divides operations into two types A & B.

Type A operations include teaching, research, development, non industrial or non commercial and which is also of a small scale. The words (e.g. 10 litres culture volume or less) appear in the directive.

In the draft explanatory notes to the directive which were issued by DGXI in September 1991 the example of 10 litres is regarded as being indicative of small scale but was not regarded as being binding.

All other operations which do not come with the definition of Type A are regarded as Type B operations.

Having defined both, two classes of micro-organism I and II and two types of operation A and B, the directive then further defines the requirements of the EEC for the contained use of such organisms.

Article 5 states that the directive does not apply to the transport of genetically modified organisms by road, rail, inland waterway, sea or air.

Article 6 states that member states shall ensure that all appropriate measures are taken to avoid adverse effects on Human Health and the environment and to this end requires that the user shall carry out a prior assessment of the contained use as regards risks to Human Health and the Environment. Annex III of the directive lists parameters which should be taken into account when making the assessment, a record of which must be kept by the user and made available in summary form to the competent authority as part of the user's notification.

The directive requires that for GMMO's in Group I the principles of good Microbiological and good occupational safety and hygiene will apply.

a) Keep workplace exposure to lowest practicable level
b) Engineering control at source
c) Test and maintain control measures
d) Test for organisms outside physical containment
e) Provide training
f) Establish Biological Safety Committee
g) Local codes of practice for safety.

For use of Group II micro-organisms users are additionally required to apply containment shown in Annex IV which corresponds to Appendix G of the OECD recommendations.

When an installation is used for the first time the user is required to submit a notification to the competent authorities. The information required in the notification is set out in Annex V A of the directive. A separate notification is required for work with Group I and Group II micro-organisms.

Once having made the initial notification users in Group I Type A operations are required to keep records which must be made available to the competent authority upon request.

Users in Group I Type B (e.g. large scale) operations are required to make a notification which contains the information listed in Annex V B.

Users in Group II Type A are required to make a notification which contains the information listed in Annex V C and users in Group II Type B operations are required to make a notification which contains the information listed in Annex V D and which includes information upon:

a) The genetically engineered micro-organism
b) Personnel and training
c) The installation
d) Waste management
e) Accident prevention and emergency response plans
f) Assessment of risks to human health and the environment.

The member states are required by the directive to appoint a competent authority which will examine notifications to ensure that they conform with the requirements for example accuracy, completeness, correctness of classification, and as necessary adequacy of waste management, safety and emergency response.

The competent authorities are allowed to ask users for additional information where necessary and the user cannot proceed until the competent authority has given its approval on the basis of the further information or modified conditions of contained use.

For first time use operations may proceed after 90 days for Group I micro-organisms except where indicated by the competent authority. However for micro-organisms in Group II operations should not proceed without the consent of the competent authority - which would normally be given in 90 days or less.

For other than first time use, users may proceed 60 days after notification for Group I Type B and Group II Type A operations unless indicated, but for those users in Group II Type B operations, consent of the competent authority must be obtained before proceeding. This decision is normally given in 90 days or less.

The directive requires that significant new information should be notified to the competent authority who may also consult the public if appropriate. The competent authority also has the duty to ensure, where necessary, before an operation commences that the emergency plan is drawn up and that the emergency services are aware of the plan and that information on safety measures is supplied in an appropriate manner.

Member states are also required to ensure that in the event of an accident, users notify the competent authority, giving details of the circumstances, the identity and quantity of the micro-organism released, information to assess the effect of the accident and the emergency measures taken. The member state is also required to ensure that appropriate emergency measures are taken, that other member states which could be affected are also notified and to collect information where necessary to ensure that similar accidents do not appear in the future.

Member states are required to consult with other member states where they may be affected in the case of an accident in drawing up and implementing an emergency plan. The member states must also inform the Commission and the Commission shall in turn establish a procedure for the exchange of information.

Member states are also required to carry out a number of other duties.

a) Organise inspections to ensure compliance
b) Send to the Commission each year a Summary of Contained Uses
c) Send to the Commission every 3 years a summary report of their experiences.

In turn the Commission will every three years publish a summary based on reports it receives and produce general statistical information on the implementation of the directive.

The Commission is required to respect the confidentiality of information it receives under this directive and must not divulge any confidential information and it must protect intellectual property rights.

A notifier may indicate matters which he regards as confidential on a notification but verifiable justification must be given. It should be noted that the competent authority shall decide after consultation with the notifier what information shall be confidential but that in no case can the following information be regarded as confidential:

a) Description of the G.M.M.O.
b) Name and address of notifier
c) Purpose of contained use

d) Location of use
e) Method and plans for monitoring
f) Emergency response
g) Evaluation of foreseeable effects.

In the event of a notifier deciding to withdraw an application the competent authority must respect the confidentiality of the information supplied.

The Commission is also required under the directive to set up what has become known as an Article 21 Committee. This group under the chairmanship of a representative of the Commission shall consist of representatives of the member states. This committee shall consider amendments which are necessary to adapt Annexes II to V to technical progress.

Cyprus

In Cyprus the control of risks which are associated with biotechnological processes had so far been effected by enforcing the existing legislation on occupational health which provided generally for the protection of workers against materials and processes harmful to health. Special safety guidelines related solely to biotechnological processes have not been issued so far, since large scale biotechnology applications in Cyprus are mostly limited to industrial fermentations such as wine and beer making, milk fermentations and waste-water treatment. Risks associated with these processes are not different from those faced by workers in other processing industries. Other, newer, processes such as the recovery of valuable components from organic waste for introduction into feedstocks as well as the use of entomopathogens as pesticides at the present time find very limited application and only in pilot plant production or in research laboratories. When new processes with novel risks are introduced and applied on a large scale, the Government of Cyprus will review the existing legislation with a view to introducing new controls.

Denmark

Denmark is the first country to have introduced a new law specifically for biotechnology. In June 1986, the Parliament passed the Environment and Gene Technology Act concerning the environmental aspects of the application of genetic engineering and other gene technology. The Act covers the use of gene technology in research, production and some resulting products of such activities. Deliberate release is also covered. Gene technology is defined as recombinant DNA and recombinant RNA techniques and cell hybridization techniques. The Environment and Gene Technology Act is administered by the National Agency of Environmental Protection in the Ministry of the Environment. Only issues concerning food stay with the National Food Agency. The National Agency for Environmental Protection is responsible for the actual evaluation of the applications. Where appropriate, external experts and committees are consulted before the Ministry of Environment grants a permit.

The Environment and Gene Technology Act 1986 (Law 288) has been modified and extended by subsequent Danish legislation. The act was amended by Law 338 of 24th May 1989 to bring the rules on large scale genetic engineering experiments in line with the rules governing research in laboratories and to put a stop to the delaying effects of complaints.

Annex I to the Danish Order No. 578 was issued by the Ministry of Labour on 27th September 1990 and covers the classification of laboratories into Classes I, II, III IV, giving the detailed requirements for each type of laboratory.

In addition the Minister of the Environment tabled on 1st February 1991 a Bill on the environment and genetic engineering which was adopted on 6th June 1991 with some minor amendments.

One of the purposes of this Bill was to bring Danish legislation into line with the European Directive on Biotechnology.

The purpose of the Environment and Gene Technology Act is as follows.

The Act is to protect the environment, nature and health, including nutritional aspects, in connection with the application of genetically engineered organisms and cells. To achieve this purpose, the Act makes provision that production and products involving gene technology shall be subject to a permission to be sought in advance, in order to prevent genetically engineered organisms being released into the environment before the possible risks connected with them have been evaluated. An order exempting certain uses of genetically engineered cells was issued in May 1989. The exemption applies to the use in research and production of cells or cultures not regenerated into new organisms.

Research is only allowed in laboratories classified for this purpose. Biologically active materials should be inactivated before being brought out of these areas. An order on "Gene Technology and Working Environment" was issue in September 1987 by the Minister of Labour.

Production in which genetically engineered organisms or cells are used must be approved with respect to the discharge of genetically engineered material into the environment. The purpose of this provision is to ensure that production is not commenced before an evaluation has been made as to whether genetically engineered organisms being discharged in waste water, air or waste may affect the environment. In November 1986, the National Agency of Environmental Protection published guidelines on application approval, etc. in industrial production. The points to consider given in this publication are based mainly on the annexes of the OECD report.

Deliberate release of genetically engineered organisms or cells is prohibited. However, in special cases the Minister of the Environment may approve such release. Before an approval of deliberate release can be granted, an evaluation must be made, on a case-by-case basis, to establish whether the organism is likely to damage, disturb or other wide affect the ecological system in which it is to be released, or into which it might spread by accident. No detailed guidelines have been developed at present, but the OECD Guidelines are used when a notification is being reviewed or an applicant asks for advice prior to notification.

In January 1988 the Minister of the Environment gave the Parliament a report on experience with the Act and at the same time proposed an amendment. The main purpose of the proposal was to introduce a more flexible system for large-scale experiments. The proposed amendment to the Environment and Gene Technology Act was passed into law in May 1989.

The amendment includes only two parts. Part One is an administrative change to let large-scale research and development be regulated in a way similar to the regulation of small-scale research (less than 10 litres). The amendment also introduces a regulation whereby large-scale research and development with Class 1 organisms can begin if a notification has been sent to the competent authority. The amendment does not change the containment criteria, and it is stated that all genetically modified organisms must be inactivated by validated means before discharge from the contained area.

Part Two of the amendment changes the regulation so that complaints will not hold up the use of a permit if the modified organisms belong to a low-risk category. There will be no change in the Danish definition of "gene technology".

Finland

In Finland there are no specific national safety laws and guidelines for biotechnology or the introduction of organisms into the environment. However, some laws and statutes can be interpreted to concern biotechnological applications. Among these laws are:

(i) The law on infectious diseases. Its observance is controlled by the National Board of Health and other health authorities. The law authorizes the National Board of Health, inter alia, to give binding instructions on how to deal with microbes or components containing recombinant-DNA if a potential health risk to human beings exists.

(ii) The law on pesticides. Its observance is controlled by the National Board of Agriculture and district offices of agriculture. This law regulates plants, animals, viruses and organisms which can be used as pesticides. The National Board on Agriculture gives permission for the use of pesticides. There is a special pesticide committee - its existence is ordered by the law - which treats the applications. The committee consists of experts from the Ministry of Agriculture and Forestry, the Ministry of the Environment, the National Board of Agriculture, the National Board of Trade and Consumer Interests, the National Board of Labour Protection and the National Board of Health.

(iii) The law on water. It is administered by the Ministry of the Environment. It contains the restraint on water pollution and the regulations for licences. The pollution of groundwater is totally prohibited.

(iv) The law on air protection. It is administered by the Ministry of the Environment. It concerns precautions for air pollution and the duty to notify.

(v) The law on waste management. It is administered by the Ministry of the Environment. It can be interpreted to concern "biotechnological" waste materials.

The last three above-mentioned laws have not yet been used in the case of genetically modified organisms but it is possible that they will be used.

The National Board on Health has appointed a Recombinant-DNA Advisory Group. This group reviews laboratory experiments and industrial and agricultural applications using organisms which contain recombinant DNA. The guidelines of the United States National Institute of Health (HIH) and the recommendations of OECD (GILSP) are used as guidelines in Finland. All research projects and applications involving organisms containing recombinant DNA are to be registered, classified in respect of safety according to these guidelines, and the appropriate safety procedures approved or improved by the Recombinant-DNA

Advisory Group. The recommendations of the Group have been well followed by the research and industrial sectors of Finland on a voluntary basis.

The Ministry of the Environment appointed a committee on biotechnology on 12 April 1989, consisting of experts from administration, research laboratories and industry. Its aim is to prepare safety guidelines for biotechnology and for the introduction of modified organisms into the environment, and to consider the possible needs of a new legislation.

Finland participates in the Nordic committee on ethics in biotechnology, appointed by the Nordic Council of Ministers. This committee will probably accept in the near future ethic guidelines for biotechnology. It is quite obvious that Finland, among other Nordic countries, will follow these recommendations.

France

The French government has adopted an oversight system for the control of Biotechnology which has not required specific regulations but which has involved a number of existing more general regulations which are considered to be sufficient to ensure safety.

The French administrative system involves a network of several ministries, each of which has responsibility for various commercial stages from research to the marketing of commercial products.

The early legislation in France was LOI No. 76-663 of 19th June 1976 which dealt with installations which were classified in order to protect the environment. In a later décret 85-821 of 30th July 1985 a list of industries was published and on 19th September 1986 the list was modified in Circular 86-32 to include biotechnology installations which involved the use of either pathogenic or genetically manipulated organisms.

In May 1989 the Ministry of Research and Technology under Décret No. 89-306 set up a Commission on Genetic Engineering. On 12th March 1990 the names of the committee were formally promulgated. This commission is responsible for classifying the products of genetic engineering. This body has in France sole competence to draw up a scientific classification of existing or new organisms in all biotechnological applications, on the basis of the real or potential hazards they present.

The French government like other member states in the EEC has had to modify its legislation to correspond with the European Directives on Biotechnology and on 2nd October 1992 a Projet de Loi was presented which modified in detail Loi No. 76-663 of 19th July 1976.

Germany

The German House of Representatives, passed, on 29th March 1990 a new law regulating Genetic Engineering Issues in the Federal Republic of Germany (Document 11/5622).

The law consists of seven parts, which are:

1) General Rules
2) Genetic Works in Installations
3) Release and Distribution
4) Common Regulations
5) Rules regarding Liability
6) Rules regarding Fines and Imprisonment
7) Transition and final rules

Part one contains the purpose of the law. - To protect the life and health of men, animals and plants as well as to protect the rest of the environment and property against possible dangers which may arise from genetic engineering and genetic products by requiring precautions against such dangers.

The law contains definitions and also the setting up of a commission. The Commission for Biological Safety, which is an expert commission to be established within the Federal Health Office. The commission consists of 10 experts with broad experience in the field of microbiology, cell biology, virology, genetics, hygiene, ecology and safety techniques.

In addition to the 10 experts there must also be an expert from each of the following disciplines, trade unions, occupational safety, economy, ecology, and research supporting organisations. For each member an alternate must also be provided.

Members are appointed for a period of 3 years.

Part I of the law requires an operator to carry out a risk assessment and to keep records of all work carried out.

Part II of the law is concerned with Genetic works in Genetic Installations which it divides into 4 containment levels.

Level 1 does not involve any risk to human health and the environment

Level 2 only involves minor risk to human health and the environment

Level 3 activities which involve a moderate risk to human health and the environment

Level 4 activities which involve a high risk or the substantiated suspicion that such a risk to human health or the environment exists.

The Federal Government is authorised after a hearing of the Commission to regulate the classification of a certain works as to containment levels which will be determined by the characteristics of the recipient and donor organisms as well as the vector.

In carrying out work involving GMO's certain safety measures must be adhered to. These may be specified by the Federal Government.

Work involving the use of genetically engineered organisms can only be carried out in installations which are approved and which includes physical, biological and chemical barriers or a combination to limit contact of the organisms with man and the environment.

A genetic installation using Level 1 organisms for research work only must be registered at least 3 months in advance.

The conduct of further genetic work for research purposes at Containment Levels 2, 3 or 4 must be reported to the authority at least 2 months in advance.

Genetic work for commercial purposes must also be notified in advance.

Level I at least 2 months
Levels 2, 3, 4 requires separate approval

The following table summarises the requirements. The approval system requires a written application.

Notification and Review of Contained Use of GMOs	
Construction and operation of installations for Safety Level 1 research	- notification to State CA - use after 3 months if not prohibited
Continuation of Safety Level 1 use for commercial purposes	- notification to State CA - use after 2 months if not prohibited
Construction and operation of installations for research at Safety Levels 2 - 4	- notification to State CA - permit required - decision within 3 months - permit specifies authorized operations
Continuation at same Safety Level of further research	- notification to State CA - use after 2 months if not prohibited
Continuation of research at higher Safety Level or commercial use at same Safety Level	- notification to State CA - separate permit required - decision within 3 months

The application for approval of a genetic installation must include all the records and data necessary for the analysis of the presuppositions included therein. The following data are particularly important:

1. Location of the installation; name and address of the operator
2. Name of the project director and certificate of qualification
3. Name(s) of the person(s) in charge of biological safety and certificate(s) of qualification
4. Description of the existing or planned genetic installation and its operation; particularly of the equipment essential to the safety assessment of the hazardous potential
5. Description of the intended genetic works including the characteristics of the applied donor and recipient organisms; of the vectors and the GMO regarding the necessary containment levels and the safety related impact
6. Description of the techniques available to realize, identify and control the GMO
7. In addition to 1. - 6. for works for commercial purposes it is necessary to give data with regard to the number and qualifications of staff, management of waste, emergency plans and data with regard to measures for the prevention of accidents.

Should a hearing be required prior to a decision regarding construction and operation of a genetic installation, confidential information must be marked and presented separately. The contents of these documents must be presented in as much detail as possible without infringing the confidentiality of the information.

The Authority must acknowledge receipt of an application immediately and has the power to ask for additional information if that which is provided is incomplete.

The authority must give its decision within 3 months of its submission. The authority may extend this deadline one time for a period of up to 3 months because of the involvement of other authorities.

During this process the authority must call for an opinion of the Commission on the safety related classification of the intended work and the safety measures required by the Federal Health Office.

The expiry of a deadline is considered an agreement on the part of the authorities.

Approval must be given for the construction and operation of a genetic installation if -

1. There are no facts which could justify concern regarding the operating institution or against the persons responsible for construction, management and control of the operation of the installation. It is ensured that the project director and the person/s responsible for biological safety have the expertise necessary for their tasks and are capable of fulfilling their obligations.

3. It is ensured that the applying institution or person will carry out the obligations regarding the intended genetic works

4. It is ensured that, according to the required containment level all necessary precautions are met and therefore that there will be no hazardous impact

5. There are no facts which are in violation of the prohibitions of Article 2 of the law of concerning the prohibition of development, production and storage of bacteriological and toxicological weapons dated April 10, 1972 and about the destruction of such weapons in the wording of February 21, 1983, and

6. There are no other rules under public law which are in opposition to construction and operation of the genetic installation.

Only those parts of the law which relate to contained use will be considered in this paper and therefore Section 3 will for present purposes be ignored.

Under Section 4 of the law the authority must conduct a hearing procedure before making a decision for the construction and operation of a genetic installation according to containment levels 2, 3 or 4, for commercial purposes.

A hearing procedure will also be required for Level 1 commercial installations if an approval procedure according to Paragraph 10 of the Federal Emission Control Law is necessary.

The authority has the power to issue additional regulations and to enforce certain conditions particularly regarding certain operations or precautions or the use of certain equipment.

The operator must notify any change in project director or Biological Safety Officer to the authority together with certificates of the new persons expertise.

The operator is required to notify any changes in safety related equipment and he must also notify an incident.

The authority may enforce changes for work carried out under this legislation.

It is the obligation of the State authorities to implement the law and for this they may call on the assistance of the Federal offices of Health, Environment and Industrial Safety as experts.

The operator must provide all information required by the authority for control purposes.

The persons entrusted with control have the following rights -

1. to enter and inspect property, business premises and plants during business hours;

2. to execute all analysis necessary for the fulfilment of their obligations, including taking of samples,

3. to inspect all documents necessary for the fulfilment of their obligations, including copying them or making transcripts. In order to prevent extreme hazards to public safety and to insure that all measures according to sentence 1 can be carried out, these authorisations also apply to documents in private homes and at all times of day and night. The operator has the obligation to consent to measures taken pursuant to sentence 1, and sentence 2, and to support the persons concerned with control as far as it is important to the fulfilment of their task. The operator must also submit all relevant business documents. The basic right of inviolability of the home (Article 13, basic law), insofar as is necessary to comport with the dictates of this section, is restricted.

4. Persons with the obligation to provide information can refuse to answer such questions, if the answer would put them or one of their relatives mentioned in Par. 383, para. 1, # 1-3, Code of Civil Procedure, in danger of prosecution because of a crime or summary offence.

5. Personal information obtained pursuant to the obligation to provide information or give consent according to this law or on grounds of legal regulations promulgated pursuant to this law may be used only if necessary for the execution of this law, for the prosecution of a crime or for protection of the public from a hazard.

In the case of failure to comply the authority can prohibit the operation entirely or partially. It can call for the shut down of an installation or its removal if the interests cannot be protected sufficiently in any other way.

The Federal Government has the right to order after a hearing by the commission considerable information in connection with an installation. This may be summarised as follows -

1. how the workplace, the operating equipment and the technical working tools must be designed, installed and operated within the prescribed safety levels in order to meet the secured safety, technical, industrial, medical, hygienic and other ergonomic findings, which have to be observed in order to protect the employees and which are necessary to shape the work in a way that is suitable for humans;

2. the necessary operational measures, particularly:
   a) how the manufacturing process must be shaped in order not to endanger employees by genetic works or release,

b) how the operating area must be controlled in order to detect contamination by GMOs,
c) how GMOs must be stored in the installation and which hazards must be mentioned so as not to endanger employees by inappropriate storage and in order to inform them about hazards connected with the GMOs,
d) which precautions must be put into effect in order to prevent GMOs from being handled by unauthorised persons or being lost,
e) which personal safety equipment must be provided and be used by the employees pursuant to the rules,
f) that the number of employees who are dealing with GMOs can be limited and that the period of such a work assignment can also be limited,
g) how employees must act in order not to endanger themselves and others, and which measures must be taken,
h) under which circumstances access limitations must be implemented in order to protect the employees;

3. that the operator must appoint commissioners for biological safety and how many he must appoint. These commissioners must examine the fulfilment of the tasks of the project director and must advise the operator and the responsible persons concerning all questions of biological safety. In addition, the commissioners are required to give specific advice on how these tasks have to be performed, which expertise in the field of biological safety must be demonstrated and in what way the person(s) responsible for biological safety will receive their job assignments with the participation of a work council or personnel council;

4. which knowledge and qualifications are necessary for persons who deal with genetic works or release, and which certification is necessary;

5. how and at what intervals the employees must be instructed concerning hazards and measures for their prevention and how the employees are to be taught concerning the contents of the rules (to be applied within the installation) in work-related operating instructions with consideration given to advice concerning safety;

6. which precautions are necessary in order to prevent industrial accidents and operating difficulties as well as to limit their impact on employees; and which measures are necessary for the organisation of first aid;

7. that and which responsible supervisory staff must be assigned in order to control genetic works and release as well as all other works within the danger area and what degree of authority they should be given to fulfil the required level of industrial safety;

8. the operator must make an analysis of the hazards and develop a plan for protection against hazards with regard to the protection of employees; which documents must be created for this purpose and that such documents must be available for the purpose of checking the analysis of the hazards and of the plan for protection against hazards by the appropriate authority;

9. that the employees must be subject to health control and that therefore records must be kept for this purpose as well, specifically:
   a) the operator can be obligated to have those employees who are occupied with genetic works or releases examined by medical doctors
   b) the doctor who was engaged in the preventive medical check-up must meet certain obligations in connection with the examination findings, particularly with regard to the contents of an attestation he must complete, and the information and consultation concerning the findings of the examination,
   c) the appropriate authority decides in which case the findings of the physician are considered unfounded,
   d) the data to be kept in the records must be transmitted to the accident insurers or another institution authorised by them for the purpose of inquiries into health hazards or occupational diseases due to the work;

10. that the employer must provide all facts to the works council and personnel council which those councils require in order to fulfil their obligations;

11. that the appropriate state authorities are empowered to order the implementation of legal regulations; in individual cases even against control personnel and other employees, particularly if there is imminent danger;

12. that in case of completion of a genetic work or a release, certain precautions must be taken;

13. that the transportation of GMOs is dependent on taking certain precautions;

14. that in order to keep the regulations regarding the traffic and handling of products which contain or consist of GMOs, those products must be labelled and packed; in particular, information must be provided concerning the genetic alteration and the justifiable hazardous implications insofar as is necessary for the protection of those who apply the products;

15. the form the documents for application and registration must take and what they must contain; particularly which are the criteria for the assessment as well as details about the application and approval procedure;

16. that the appropriate authority must set up plans in case of emergency; must inform those persons who could be suffering from the effects of an accident; must inform the public concerning the safety measures implemented; must inform the Federal Office of Health regarding measures taken in the event of an accident.

In addition to the law the Berufsgenossenschaft Der Chemischen Industry (BG-Chemie) requires operators by law to comply with regulations concerning safety and exposure of employed to possible biological hazards. They apply to biotechnology and biomedical laboratories and plants, including those which work with genetically engineered organisms.

A biotechnology commission of the BG-Chemie drafted the Biotechnology Safety Regulations 1988 (UVV-Biotechnologie) which describe the broad scope of preventative safety measures and became effective in Spring 1988.

The Regulations impose safety requirements on about 90% of all commercial establishments in chemical industry, food industry, biomedical laboratories and health institutions.

Basically, employers are obliged to carry out a competent assessment to recognise possible health risks by exposure to organisms and viruses. This needs to be prevented by a suitable design of laboratory and plant facilities, containment equipment and guidelines for standard and special practices to be followed by personnel.

The Biotechnology Safety Regulations deal with all natural as well as experimental or genetically modified organisms and viruses, even if specific biohazards are not reasonably foreseeable or known.

If organisms which are known to carry a biohazard potential need to be handled, for example, in vaccine production, measures like the following are necessary:

- Health surveillance of personnel.
  The number of employees involved in such work must be kept as low as possible.

- Employees need to be identified on lists which describe position held and activities performed.

- Only persons who have been advised of a potential biohazard, who meet specific entry requirements, and who comply with safety procedures may enter or work in biotechnology facilities under the supervision of qualified personnel.

- If available, vaccination for immunoprophylasis must be offered.

- A biological safety officer must be appointed.

- The work facilities must be registered at the required legal or state institutions.

Since the Biotechnology Safety Regulations 1988 do not contain details on facility design, safety equipment etc., the BG-Chemie offers three separate Guidance Notes as additional resources for

(1) the risk assessment process to determine the risk group to which organisms are assigned (classification) and the biosafety level required (M 055),

(2) the laboratory equipment to be installed and the laboratory practices to be followed according to the selected biosafety level (M 056), and

(3) particular and possibly extended measures to guarantee safety in production facilities (M 057).

The Guidance Notes M 056 and M 057 have been published in March 1989. They give typical examples on the prevention or control of exposure to hazardous biological agents.

Guidance Note M 056 discusses laboratories in which biological agents are handled for research purposes, process development and production. Such laboratories may be micro biological laboratories, biochemical laboratories, genetic engineering laboratories, screening laboratories, analytical laboratories, seed culture or strain collection laboratories, virology laboratories, and cell culture laboratories. Included are peripheral laboratory facilities for activities like incubation, centrifugation, cooling and deep-freezing.

Guidance Note M 057 treats production facilities which handle biological agents. They are defined as manufacturing installations in which substances and preparations are produced or purified through the use of biological agents. Of course, it includes premises in which work is performed with biohazardous material of different risk groups as well as such organisms and viruses which have been modified to carry heterologous recombinant nucleic acids.

Technical details are presented concerning not only equipment but also, for example, the operation procedures for fermenters in pilot plants or larger units.

The Guidance Notes thus illustrate examples and list recommendations, but they do not represent unconditional , mandatory prerequisites. The safety measures explained in different sections on the biosafety levels L1 through L4 and P1 through P4 are meant to be standard procedure, equipment and practices for containment. Since biohazard potentials vary within a risk group, special equipment and special practices may be indicated due to the unique position of an organism within a risk group.

Therefore, it is usually a combination of standard and special procedures or precautions which yield safe working conditions. Most important, personnel must

observe all rules of safe practice and hygiene during work with biological agents. Otherwise objectives of safety regulations will not be reached.

Presently, a special committee of experts in bacteriology, virology, mycology and parasitology update previous lists in which individual oganisms and viruses are categorised on the basis of hazard according to the framework provided by the four risk groups of the World Health Organisation. In addition, rational and recognised procedures are also being developed to treat genetically engineered organisms likewise in order to help employers in research and industry to determine and control potential biohazard and known risks by suitable and sufficient safety measures.

Guidance Note M 055 includes a classification of organisms and viruses on the basis of hazard as well as the basic criteria in the risk assessment.

Greece

16. The authorities of Greece have participated in the OECD Group of National Experts for Safety in Biotechnology and in the various activities of EEC on the same subject. However, they have not yet adopted specified safety guidelines and rules on the mater, because they are not at present urgently confronted with safety problems. This does not in any way mitigate their interest in the development of biotechnology.

India

The Department of Biotechnology in the Ministry of Science and Technology of the Government of India have produced guidelines entitled Recombinant DNA Safety Guidelines in January 1990.

The guidelines comprise of 5 major chapters -

Chapter I	-	Introduction & Scope
Chapter II	-	Guidelines
Chapter III	-	Mechanism of Implementation
Chapter IV	-	Containment Facilities and Biosafety Practices
Chapter V	-	Recombinant DNA Safety Consideration

The 1st Chapter defines the scope of the guidelines as covering research, large scale and environmental risks

The 2nd Chapter firstly defines recombinant DNA and then a classification of Pathogenic organisms into 4 risk groups.

The chapter next deals with containment in terms of Biological and Physical containments.

Biosafety levels are defined in incremental order depending on the nature of the work as follows:

Biosafety Level I:
These practices, safety equipment and facilities are appropriate for undergraduate and secondary educational training and teaching laboratories and for other facilities in which work is done with defined and characterised strains of viable micro-organisms not known to cause disease in healthy adult humans. No special accommodation or equipment is required but the laboratory personnel are required to have specific training and to be supervised by a scientist with general training in microbiology or a related science.

Biosafety Level 2:
These practices, safety equipment and facilities are applicable in clinical, diagnostic, teaching and other facilities in which work is done with the broad spectrum of indigenous moderate-risk agents present in the community and associated with human disease of varying severity. Laboratory workers are required to have specific training in handling pathogenic agents and to be supervised by competent scientists. Accommodation and facilities including safety cabinets are prescribed, especially for handling large volume are high concentrations of agents when aerosols are likely to be created. Access to the laboratory is controlled.

Biosafety Level 3:
These practices, safety equipment and facilities are applicable to clinical, diagnostic, teaching research or production facilities in which work is done with indigenous or exotic agents where the potential for infection by aerosols is real and the disease may have serious or lethal consequences. Personnel are required to have specific training in work with these agents and to be supervised by scientists experienced in this kind of microbiology. Specially designed laboratories and precautions including the use of safety cabinets are prescribed and the access is strictly controlled.

Biosafety Level 4:
These practices, safety equipment and facilities are applicable to work with dangerous and exotic agents which pose a high individual risk of life-threatening disease. Strict training and supervision are required and the work is done in specially designed laboratories under stringent safety conditions, including the use of safety cabinets and positive pressure personnel suits. Access is strictly limited.

A specially designed suit area may be provided in the facility. Personnel who enter this area wear a one-piece positive pressure suit that is ventilated by a life support system. The life support system is provided with alarms and emergency break-up breathing air tanks. Entry to this area is through an airlock fitted with airtight doors. A chemical shower is provided to decontaminate the surface of the suit before the worker leaves the area. The exhaust air from the suit area is filtered by two sets of HEPA filters installed in the series. A duplicate filtration unit, exhaust fan and an automatically starting emergency power source are provided. The air pressure within the suit area is lower than that of any adjacent area. Emergency lighting and communication systems are provided. All penetrations into the internal shell of the suit area are sealed. A double doored autoclave is provided for decontamination of disposable waste materials from the suit area.

The guidelines then define 3 categories of rDNA research activities.

Category I
Which are exempt for the purpose of intimation and approval of competent authority.

(i) The experiments involving self cloning, using strains and also inter-species cloning belonging to organism in the same exchanger group.

(ii) Organelle DNA including those from chloroplasts and mitochondria.

(iii) Host-vector systems consisting of cells in culture and vectors, either non-viral or viral containing defective viral genomes (except from cells known to harbour class III, IV and special category etiologic agents).

Category II
Those requiring prior intimation of competent authority.

(i) Experiments falling under containment levels II, III and IV.

(ii) Experiments wherein DNA or RNA molecules derived from any source except for eukaryotic viral genome may be transferred to any non-human vertebrate or any invertebrate organism and propagated under conditions of physical containment PC1 and appropriate to organism under study.

(iii) Experiments involving non pathogen DNA vector systems and regeneration from single cells.

(iv) Large scale use of recombinants made by self cloning in systems belonging to exempt category (e.g. E. coli, Saccharomyces, and B. subtilis)

Category III
This section covers a wide range of work none of which is of direct impact on large scale activities.

The chapter then discusses the requirements for large scale experiments. These may be stated as follows.

Large scale production of bio-molecules from genetically engineered micro-organisms have not just been taken up in the country. However, the use of recombinant organisms in large scale operations is expected in the near future.

In the guidelines, experiments beyond 20 litres capacity for research as well as industrial purposes are included in the category of large scale experimentation/operations.

For such activities it is recommended that one should seek approval of the competent authority as described in Chapter III. In order to seek approval it will be necessary to furnish the relevant details in a prescribed format on the lines suggested by GEAC.

For good large scale practice (GLSP) as well as all levels of containment, the following principles of occupational safety and hygiene will be applied.

(i) to keep work place and environment exposure to any physical, chemical or biological agent to the lowest practicable level;

(ii) to exercise engineering control measures at source and to supplement these with appropriate personal protective clothing and equipment when necessary;

(iii) to test adequately and maintain control measures and equipment.

(iv) to test when necessary for the presence of viable process organisms outside the primary physical containment;

(v) to provide training of personnel

(vi) to formulate and implement local code of practice for the safety of personnel.

The following safety criteria are to be complied with for good large scale practice:

(i) The host organism should not be a pathogen, should not contain adventitious agents, and should have an extended history of safe use, or have built-in environmental limitations that permit optimum growth in the bioreactor but limited survival with no adverse consequences in the environment.

(ii) The vector/insert should be well characterised and free from known harmful sequences; the DNA should be limited in size as much as possible to perform the intended function; should not increase the stability of the recombinant in the environment unless that is a requirement of the intended function; should be poorly mobilisable; and should not transfer any resistance markers to micro-organisms not known to acquire them naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.

(iii) The genetically manipulated organism should not be a pathogen and should be assessed as being as safe in the bio-reactor as the host organism, and without adverse consequences in the environment.

The chapter also includes sections on Release to the environment, Imported Shipment and Quality control of Biologicals produced by rDNA technology.

Chapter III of the guideline deals with the mechanism of implementation which is through a series of four committees.

1) The Recombinant DNA Advisory Committee
2) Institutional Biosafety Committee
3) Review Committee on Genetic Manipulation
4) Genetic Engineering Approval Committee

The Recombinant DNA Advisory Committee is intended to take note of international and national developments in Safety Regulations and to meet every 6 months for this purpose.

Its terms of reference include:

a) Long term policy for research and development in Recombinant DNA work

b) To formulate Safety Guidelines

c) To recommend a training programme in Safety matters.

The other committees appointed by the government have the following terms of reference.

Institutional Biosafety Committee (IBSC)

Institutional Biosafety Committee (IBSC) are to be constituted in all centres engaged in genetic engineering research and production activities. The Committee will constitute the following:

(i) Head of the Institution or nominee

(i) 3 or more scientists engaged in rDNA work or molecular biology with an outside expert in the relevant discipline.

(iii) A member with medical qualifications - Biosafety Officer (in case of work with pathogenic agents/large scale use).

(iv) One member nominated by DBT.

The Institutional Biosafety Committees shall be the nodal point for interaction within institution for implementation of the guidelines. Any research project which is likely to have biohazard potential (as envisaged by the guidelines) during the execution stage or which involve the production of either micro-organisms or biologically active molecules that might cause bio-hazard should be notified to IBSC. IBSC will allow genetic engineering activity on classified organisms only at places where such work should be performed as per guidelines. Provision of suitable safe storage facility of donor, vectors, recipients and other materials involved in experimental work should be made and may be subjected to inspection on accountability.

The biosafety functions and activity include the following:

i) Registration of Bio-safety Committee membership composition with RCGM and submission of reports.

IBSC will provide half yearly reports on the ongoing projects to RCGM regarding the observance of the safety guidelines on accidents, risks and on deviations if any. A computerised Central Registry for collation of periodic reports on approved projects will be set up with RCGM to monitor compliance on safeguards as stipulated in the guidelines.

ii) Review and clearance of project proposals falling under restricted category that meets the requirements under the guidelines.

IBSC would make efforts to issue clearance certificates quickly on receiving the research proposals from investigators.

iii) Tailoring biosafety programme to the level of risk assessment.

iv) Training of personnel on biosafety.

v) Instituting health monitoring programme for laboratory personnel.

Complete medical check-up of personnel working in projects involving work with potentially dangerous micro-organisms should be done prior to starting such projects. Follow up medical check-ups including pathological tests should be done periodically, at least annually for scientific workers involved in such projects. Their medical records should be accessible to the RCGM. It will provide half yearly reports on the ongoing projects to RCGM regarding the observance of the safety guidelines on accidents, risks and on deviations if any.

vi) Adopting emergency plans.

So far, Biosafety Committees have been already set up in 24 institutions. The other institutes will be asked to take similar action.

REVIEW COMMITTEE ON GENETIC MANIPULATION (RCGM)

The RCGM will have the following composition:

i) Department of Biotechnology
ii) Indian Council of Medical Research
iii) Indian Council of Agricultural Research
iv) Council of Scientific & Industrial Research
v) Three Experts in Individual capacity
vi) Department of Science & Technology

The RCGM will have the functions:

i) To establish procedural guidance manual - procedure for regulatory process with respect to activity involving genetically engineered organisms in research, production and applications related to environmental safety.

ii) To review the reports in all approved ongoing research projects involving high risk category and controlled field experiments, to ensure that safeguards are maintained as per guidelines.

iii) To recommend the type of containment facility and the special containment conditions to be followed for experimental trials and for certain experiments.

iv) To advise customs authorities on import of biologically active material, genetically engineered substances or products and on excisable items to Central Revenue and Excise.

v) To assist Department of Industrial Development, Banks towards clearance of applications in setting up industries based on genetically engineered organisms.

vi) To assist the Bureau of Indian Standards to evolve standards for biologics produced by rDNA technology.

vii) To advise on intellectual property rights with respect to rDNA technology on patents.

The RCGM would have a Research Monitoring function by a group consisting of a smaller number of individuals (3 or 4). The monitoring group would be empowered to visit experimental facilities in any laboratory in India where experiments with biohazard potential are being pursued in order to determine the Good Laboratory practice and conditions of safety are observed.

In addition, if the RCGM has reasons to believe that there is either actual or potential danger involved in the work carried out by any laboratory (which might or might not have obtained prior clearance for the project), the monitoring group would be empowered to inspect the facility and assess the cause of any real or potential hazard to make appropriate recommendation to the RCGM. RCGM would be empowered to recommend alteration of the course of experiments based on hazard considerations or take steps to cancel the project grant, in case of deliberate negligence and to recommend appropriate actions under the provisions of Environmental Protection Act (EPA) where necessary.

GENETIC ENGINEERING APPROVAL COMMITTEE

Genetic Engineering Approval Committee (GEAC) will function under the Department of Environment (DOEn) as statutory body for review and approval of activities involving large scale use of genetically engineered organisms and their products in research and development, industrial production, environmental release and field applications.

The functions include giving approval from environmental angle on:

i) Import, export, transport, manufacture, process, selling of any micro-organisms or genetically engineered substances or cells including food stuffs and additives that contain products derived by Gene Therapy.

ii) Discharge of Genetically engineered/classified organisms/cells from Laboratory, hospitals and related areas into environment.

iii) Large scale use of genetically engineered organisms/classified micro-organisms in industrial production and applications. (Production shall not be commenced without approval).

iv) Deliberate release of genetically engineered organisms. The approval will be for a period of 4 years.

The composition of the Committee would be as follows;

i) Chairman - Additional Secretary, Department of Environment
Co-Chairman - Expert Nominee of Secretary, DBT

ii) Representatives of concerned Agencies and Departments:
- Ministry of Industrial Development
- Department of Science & Technology
- Department of Ocean Development
- Department of Biotechnology

iii) Expert Members;

- Director-General, Indian Council of Agricultural Research
- Director-General, Indian Council of Medical Research
- Director-General, Council of Scientific & Industrial Research
- Director-General, Health Services (Ministry of Health & Family Welfare)
- Plant Protection Adviser (Ministry of Agriculture)
- Chairman, Central Pollution Control Board
- 3 Outside experts in individual capacity.

iv) Member Secretary - Official of DOEn

GEAC will have the Biotechnology Co-ordination Committees under it which will function as legal and statutory body with judicial powers to inspect, investigate and take punitive action in case of violations of statutory provisions under EPA.

I) Review and control of safety measures adopted while handling large scale use of genetically engineered organisms/classified organisms in research, developmental and industrial production activities.

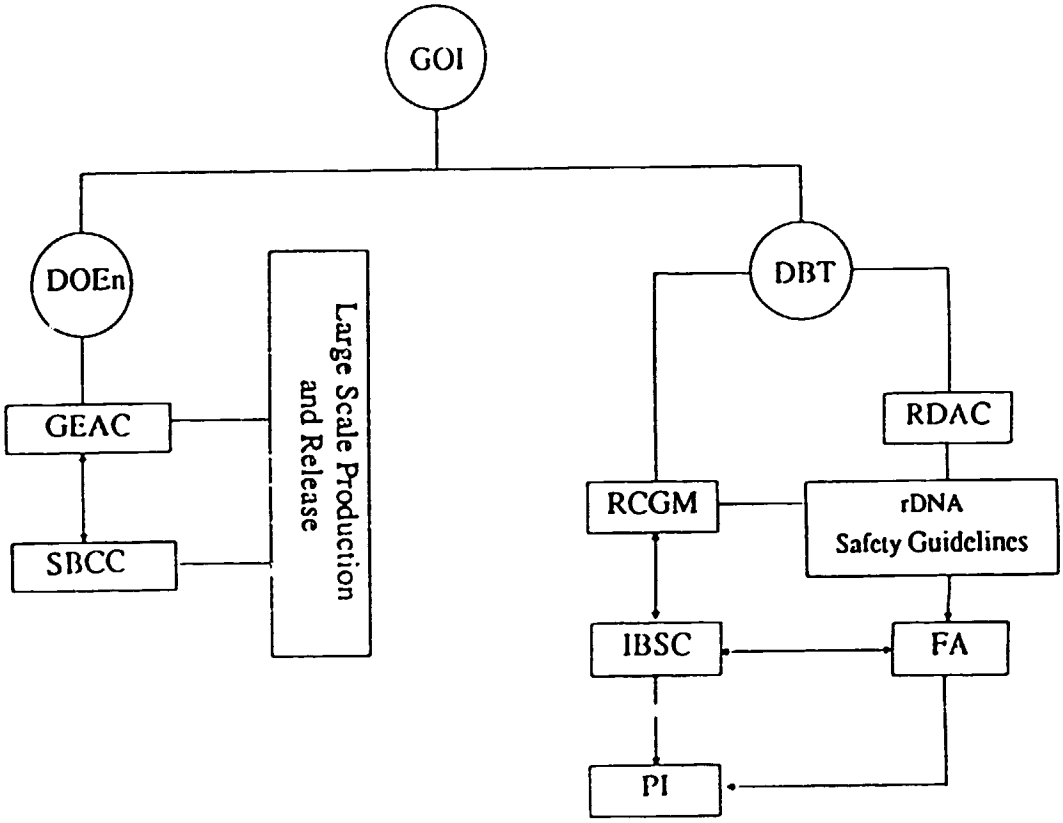
ii) Monitoring of large scale release of engineered organisms/products into environment, oversee field applications and experimental field trials.

iii) To provide information/data inputs to RCGM upon surveillance of approved projects under industrial production, and in case of environmental releases with respect to safety, risks and accidents.

Statutory rules and regulations to be operated by the GEAC would be laid down under the Environment Protection Act, 1986.

The following diagram reproduced from the Indian Government guidelines illustrates the interaction of the four levels of committee required under this structure.

INSTITUTIONAL MECHANISM FOR IMPLEMENTATION OF GUIDELINES
FRAMEWORK FOR IMPLEMENTATION



GOI	–	Government of India
DBT	–	Department of Biotechnology
RDAC	–	Recombinant DNA Advisory Committee
IBSC	–	Institutional Biosafety Committee
RCGM	–	Review Committee on Genetic Manipulation
DOEn	–	Department of Environment
GEAC	–	Genetic Engineering Approval Committee
SBCC	–	State Biotechnology Coordination Committee
PI	–	Principal Investigator (R&D/Industry/Others)
FA	–	Funding Agency (Govt./Private & Public Institutions)

Chapter IV of the Indian guidelines covers Containment facilities and Biosafety practices.

Section A covers the basic Laboratory and is divided into the following sections:

a) Code of Practice
b) Laboratory design and facilities
c) Laboratory equipment
d) Health and medical Surveillance
e) Training
f) Handling transfer to Shipment of Specimens
g) Emergency Procedures
h) Animal Facilities

Section B covers the same range of subjects for the Containment Laboratory intended for Risk Group III activities.

Section C covers the identical range for Maximum Containment Laboratories intended for high risk activities and Section D deals specifically with gene technology Laboratories.

Chapter V of the guidelines is divided into four sections all of which deal with various aspects of the Safety Considerations for Recombinant DNA.

a) Micro-organisms
b) Large Scale Operations
c) Plants & Agriculture
d) Environment

Of these only Section B - Large Scale Operations needs to be considered in this review.

In this context large scale is defined as work above 20 litre capacity.

The requirements of the guide lines for large scale work are as follows:

Physical Containment Conditions for Large Scale (20L) Fermentation Experiments and Production

A. Cultures of viable organisms containing recombinant DNA molecules shall be handled in a closed system (e.g. closed vessel used for the propagation and growth of cultures) or other primary containment equipment (e.g. biological safety cabinet containing a centrifuge used to process culture fluids) which is designed to reduce the potential for escape of viable organisms.

B. Cultures fluid shall not be removed from a closed system or other primary containment equipment unless the viable organism containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure

is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.

C. Sample collection from a closed system, the addition of materials to a closed system and the transfer of culture fluids from one closed system to another shall be done in a manner which minimises the release of aerosols and contamination of exposed surfaces.

D. Exhaust gases removed from a closed system or other primary containment equipment shall be treated by filters which have efficiencies equivalent to HEPA filters or by other equivalent procedures (e.g. incineration) to minimise the release of viable organisms containing recombinant DNA molecules to the environment.

E. A closed system or other primary containment equipment that has viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purposes unless it has been sterilised by a validated sterilisation procedure. A validated sterilisation procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.

F. Emergency plans as and when required shall include methods and procedures for handling large losses of cultures on an emergency basis as recommended by IBSC and approved by the competent authority.

The criteria for rDNA GLSP micro-organisms are exactly as developed by OECD.

Ireland

There have been no specific regulations since 1985 applicable to genetically modified organisms or products derived from them. The Irish rDNA Committee issued in 1987 a short explanatory booklet on working practices and procedures for research on industrial use and deliberate release of rDNA organisms, entitled "Guide to Recombinant DNA Regulation in Ireland".

Italy

No national guidelines have been developed in Italy for large scale industrial applications of Biotechnology.

It is understood that an initiative headed by the Istituto Superiore di Sanita is considering methods for the implementation of the European Directive.

Japan

In Japan the application of guidelines for large scale work involving rDNA organisms is controlled by four government agencies. The choice of agency depends on the type of work to be carried out. The four agencies are:

Ministry of Science and Technology
Ministry of International Trade and Industry
Ministry of Agriculture, Forestry and Fisheries
Ministry of Health and Welfare

Each Ministry has separately produced its own set of guidelines, all are similar in structure and closely follow the recommendations of OECD.

1) Ministry of Science and Technology

This department only deals with submissions at the experimental level. It published Guidelines for Recombinant DNA Experiments in 1987, having adopted the OECD recommendations in May 1986.

The M.S.T. guidelines apply to contained rDNA research whether privately or publicly funded.

There is a separate set of guidelines with a very similar content for Universities.

The department has added two additional requirements to the OECD guideline for GILSP.

1) Minimise release of organisms in Exhaust gases
2) Inactivate liquid wastes by validated means.

The term minimise for organisms in exhaust gases is generally accepted to mean that de-misting or passage through a water spray is acceptable.

Inactivation of waste streams by the use of disinfectants or treatment in a Company sewage treatment plant is also regarded as acceptable.

The Guidelines distinguish seven physical and two biological containment levels.

For small-scale experiments (less than twenty litres), there are four physical containment levels: P1 to P4. However, P4 research has never taken place in Japan. For each of the containment levels, prescriptions are given for three aspects: "containment equipment", "special laboratory design", and "laboratory practices".
For large scale applications, there are three physical containment levels: LS-C, LS-1, and LS-2. Large-scale experiments are recombinant DNA experiments in which the volume of culture solution handled exceeds 20 litres. Prescriptions are given for "containment facilities and their design" and for "laboratory practices".

Besides these physical means of control there are two levels of biological containment, B1 and B2, based on the degree of safety of the host-vector systems.

There is neither a general notification requirement, nor a government review system for the experiments under the guidelines. Certain experiments, such as those conducted at the LS-C level, require "government supervision". The Guidelines do not define or clarify what government supervision entails.

Prior to the commencement of experiments a safety assessment is performed by the research laboratory on which basis the proper physical and biological containment levels are selected. Heads of research institutions assume responsibility for the safety of experiments performed by researchers at their institution. They approve or disapprove individual planned experiments. A Safety Committee, which has to be established at each research institution engaged in recombinant DNA research, advises the head of the institution on the acceptability of planned experiments.

The safety assessment focuses, where relevant, on issues such as the biological characteristics of the DNA donor cells, the newly acquired characteristics of the host after DNA insertion, the purity of the DNAs, the number of clones, and the culture scale.

LS-1 and LS-2 containment criteria are to be applied to experiments which would have called for P1 and P2 levels respectively, if carried out on a smaller scale. If the rDNA organisms are "verified" as extremely safe, the experiments may be conducted "under government supervision" at the LS-C level or with "special methods of containment" which are not included in one of the three LS levels.

The guidelines stress the individual responsibility and the necessity of continued training of researchers and laboratory supervisors. Laboratory supervisors and heads of research institutions are to be held explicitly responsible for knowledge of relevant rules and safety techniques and training of personnel. Research institutions are obliged to have a Safety Committee and a Safety Officer. For work with pathogenic micro-organisms, medical screening is required.

The Ministry of Science and Technology has a recombinant committee consisting of 15 members. Applications to the Committee require one to two months for processing. Approval is reasonably automatic providing that the applicant can show that the equipment has been correctly designed. No disagreements have occurred between the agency and industry.

The size limit for work controlled by this Ministry is 20 litres.

Providing that a company has a Biological Safety Committee and is working with E Coli, B Saccharomyces or B Subtillis, it does not need to apply for each separate experiment but is only required to report to the Committee on a yearly basis.

2.) Ministry of International Trade and Industry

MITI is divided into 3 divisions. Basic chemicals, chemical products and chemical fertilizers. The Ministry is responsible for the promotion of biotechnology in all three areas. Guidelines were issued in June 1986 which completely implement the OECD recommendations. These include sections on:

General Provisions
Evaluation of Recombinant's Safety
Equipment, Operations and Management
Management and responsibility systems

In the section which deals with GILSP the guidance calls for minimisation of release in exhaust gases and fermenter liquids to a level appropriate to the safety of the recombinant organism.

MITI has a Recombinant DNA Technology Committee consisting of 10 members.

Work is classified into safety categories as follows:

The "person in charge of a working organisation" is responsible for the evaluation of the safety of recombinant DNA organisms to be used in industrial processes. Relevant "items for evaluation" may include the taxonomy, genetic characteristics, and pathogenic and physiological traits of the recipient organism, the construction and the method of construction of the recombinant DNA molecule, the properties of DNA donor and vector donor, the gene expression characteristics of the recombinant DNA organism, and the similarity of the recipient organism and the recombinant DNA organism.

Based on this evaluation, the same person classifies the recombinant DNA organisms into one of the following safety categories:

- GILSP (Good Industrial Large Scale Practice);
- Category 1 (non-pathogenic organisms not included in GILSP);
- Category 2 (pathogenic; infections will not result in a serious outbreak);
- Category 3 (pathogenic organisms not included in Category 2).
- Recipient organisms which might be "significantly harmful to human health", and result in a disease for which no effective preventive nor therapeutic method is known, are to be assigned a classification separate from Category 3, and treated in a "special manner".

Each of the categories have corresponding rules of operation for cleaning and maintenance of equipment and apparatus; hygiene of personnel; and inoculation, transfer, sampling, waste treatment, storage and transportation of organisms.

None of the applications under the guidelines require mandatory notification or prior review by the government. In order to secure safety, the organiser of a working organisation can request MITI to confirm that his equipment, apparatus, operations and management are in accordance with the guidelines.

3) Ministry of Agriculture, Forestry and Fisheries

The sphere of activity of this Ministry is concerned only with environmental release.

4) The Ministry of Health and Welfare

The Ministry of Health and Welfare issued guidelines for recombinant DNA work in December 1986. The guidelines are divided into the following sections:

General principles
Facilities and equipment
Resource and organisation
Compliance points concerning operations
Addenda

The guidelines recognise GILSP. The attachments also quote from the OECD recommendations the characteristics for a GILSP organism, the characterisation of Categories 1, 2 and 3 organisms and the conditions for containment.

The Ministry deals with human drugs and food products and therefore has a wide range of interests. A study group on "The Safety of Food and rDNA" was set up early in 1987 to study the possible introduction of recombinant organisms in non pathogenic applications of single substances, amino acids, new substances and traditional products. GILSP is regarded as acceptable for single substances.

Whilst accepting the concept of GILSP the Ministry was cautious of the geographical conditions in Japan and the constraints which these impose on the social acceptance of biotechnology. The work on single substances is progressing smoothly but in order to obtain a socially acceptable technology, the Minister has recommended that the escape of micro-organisms be limited. Normally it is accepted that a water spray in the fermenter exhaust together with alkaline treatment of the spray water to pH 10 is a sufficient precaution to reduce organisms, odour and fermenter liquid carry-over.

At the request of the Minister, an Advisory Committee on Biotechnology has been set up to review applications. This committee which is quite separate from the study group, consists of 12 people. There is no large scale committee.

Netherlands

For work involving the contained use of micro-organisms the legal basis in the Netherlands is the Nuisance Act which only applies to Organisations or Institutions. For work involving release to the environment, the Netherlands government on 25th January 1990 issued a Decree under Section 24 of the Chemical Substances Act which would regulate such activities.

Attention must also be drawn to the Working Conditions Act which covers the working conditions of employees.

The Ad Hoc Recombinant DNA Advisory Committee provides the oversight of rDNA activities. This committee has laid down rules for laboratory work based largely on the USA guidelines and has also established guidelines mainly following OECD.

New Zealand

Until recently, there was a moratorium on all experimentation involving GMOs outside contained laboratory conditions. This moratorium was informal and was self-imposed by government departments and government-funded institutions (including Universities). In February 1986 the Minister of Science and Technology set up a working party on field-testing and release of GMOs. The working party addressed possible regulatory requirements and made a number of recommendations, the details of which are included in the working party's report of February 1987.

The Ministry for the Environment established a steering group to consider the whole field of new organisms including new imported species. This gave detailed consideration to the working party's report. In July 1988, a discussion document was released outlining the principles and processes proposed to govern new organism assessments. Submissions were received and consultation with the indigenous Maori people initiated.

As a result of this and other policy development work, the Government has decided to establish a new independent agency, the Hazards Control Commission (HCC) with responsibility for assessing and licensing the use of hazardous substances and new organisms, GMOs and new imported species.

In August 1988, it became apparent that new legislation was still some time away so an Interim Assessment Group (IAG) was established by the Minister for the Environment with the approval of the Ministers of Science and Technology, and Agriculture and Fisheries. The IAG is non-statutory and will operate until such time as new legislation is in place. Researchers in both private and public sectors are advised to submit their proposals to the IAG for assessment. The IAG has prepared draft national guidelines for large scale fermentations of GMOs and considers applications for the use of GMOs in agriculture, industry and the environment.

Norway

In Norway, the Government has recently presented a proposal to Parliament with regard to biotechnology use and regulations. Currently, contained use and release of genetically modified micro-organisms (GMOs) may be regulated by the Pollution Control Act and the Product Control Act. Norway has no large-scale production involving GMOs. In research, the USA guidelines are followed.

The Norwegian Government, in its report to Parliament, recommends introduction of a general act on biotechnology, and elaboration of existing specific legislation in accordance with this act. The government proposes that deliberate release, as a rule, should be prohibited, but that dispensations may be given. It further recommends establishment of a permanent advisory board to assist Governmental agencies on issues relating to use of genetechnology.

The Norwegian Government has appointed a committee to review health hazards and safety measures with respect to recombinant DNA technology.

Organisation for Economic Co-operation and Development - OECD

OECD has made a major contribution to the debate on containment as well as other aspects of Biotechnology and it was due to OECD that the concept of GILSP, Good Industrial Large Scale Practice, was originally formalised.

In July 1983, at the recommendation of the committee for Scientific and Technological Policy, an Ad Hoc group of government experts was created. The work of the Ad Hoc group was concerned with a review of country positions on safety in the use of genetically modified organisms at the Industrial, Agricultural and Environmental levels, to identify criteria which have or may be adopted for monitoring or authorisation and explore ways for monitoring future production and care of rDNA organisms.

The Ad Hoc committee met on a number of occasions and finally in 1986 produced its Handbook - Recombinant DNA Safety Consideration.

OECD considered the safety considerations, risk assessment methods in terms of the properties of the donor and recipient organisms and the properties of the derived recombinant organisms.

The group considered the safety considerations associated with large scale industrial applications.

a) Infection hazard
b) Toxic allergenic or biological effects of the non viable cell
c) Toxic allergenic or biological effects of the product
d) Environmental effects.

The committee examined the principles of containment, biological and physical, examining the latter from the view of equipment, operating practices, techniques and facilities design.

The primary objective in the selection and implementation of containment was seen as to match an appropriate level of physical measures and associated safety procedures to the conclusions of the risk assessment.

Arising from these considerations it was felt that the following fundamental principles of good occupational safety and hygiene be applied.

i) To keep workplace and environmental exposure to any physical, chemical or biological agent to the lowest practicable level;

ii) To exercise engineering control measures at source and to supplement these with appropriate personal protective clothing and equipment when necessary;

iii) To test adequately and maintain control measures and equipment;

iv) To test when necessary for the presence of viable process organisms outside the primary physical containment;

v) To provide training of personnel;

vi) To establish biological safety committees or subcommittees as required;

vii) To formulate and implement local codes of practice for the safety of personnel.

The group also developed the concept of Good Industrial Large Scale Practice (GILSP) where it was recommended that for organisms considered to be of low risk, only minimal controls on containment procedures are necessary.

The following criteria for GILSP micro-organisms was suggested:

Host Organism	rDNA Engineered Organism	Vector/Insert
- Non-pathogenic;	- Non-Pathogenic	- Well characterised and free from known harmful sequences;
- No adventitious agents;	- As safe in industrial setting as host organism, but with limited survival without adverse consequences in environment	- Limited in size as much as possible to the DNA required to perform the intended function; should not increase the stability of the construct in the environment (unless that is a requirement of the intended function);
- Extended history of safe industrial use; **OR**		- Should be poorly mobilisable
- Built-in environmental limitations permitting optimal growth in industrial setting but limited survival without adverse consequences in environment		- Should not transfer any resistance markers to micro-organisms not known to acquire them naturally (if such acquisition could compromise use of drug to control disease agents).

It was also recognised that some industrial applications may use micro-organisms which did not correspond to these properties and that there was a need to match the physical containment with the assessment of potential risk. It was also

accepted that another consideration must be the nature of the product and the industrial process.

OECD developed a series of containment approaches for large scale applications other the GILSP. This development detailed requirements for three further categories of containment. These categories are reproduced in full from the OECD report, Appendix G.

EXAMPLES OF CONTAINMENT APPROACHES FOR LARGE SCALE INDUSTRIAL APPLICATIONS OTHER THAN GILSP (GOOD INDUSTRIAL LARGE SCALE PRACTICE)

A. Category 1

At this level of physical containment the following objectives should be achieved.

a) Viable organisms should be handled in a production system which physically separates the process from the environment;

b) Exhaust gases should be treated to minimise (i.e. to reduce to the lowest practicable level consistent with safety) the release of viable organisms;

c) Sample collection, addition of materials to the system and the transfer of viable organisms to another system should be done in a manner which minimises release;

d) Bulk quantities of culture fluids should not be removed from the system unless the viable organisms have been inactivated by validated means;

e) Closed systems should be located in an area controlled according to the requirements 6 (c) and (d) specified in the Table hereafter;

f) Effluent from the production facility should be inactivated by validated means prior to discharge.

B. Category 2

At this level of physical containment the following objectives should be achieved

a) Viable organisms should be handled in a production system which physically separates the process from the environment;

b) Exhaust gases should be treated to prevent the release of viable organisms;

c) Sample collection, addition of materials to a closed system and the transfer of viable organisms to another closed system should be done in a manner which prevents release;

d) Culture fluids should not be removed from the closed system unless the viable organisms have been inactivated by validated chemical or physical means;

e) Seals should be designed to prevent leakage or should be fully enclosed in ventilated housings;

f) Closed systems should be located in an area controlled according to the requirements 6 (a), (b), (c), and (d) specified in the Table hereafter;

g) Effluent from the production facility should be inactivated by validated chemical or physical means prior to discharge.

C. Category 3

At this level of physical containment the following objectives should be achieved:

a) Viable organisms should be handled in a production system which physically separates the process from the environment;

b) Exhaust gases should be treated to prevent the release of viable organisms;

c) Sample collection, addition of materials to a closed system and the transfer of viable organisms to another closed system should be done in a manner which prevents release;

d) Culture fluids should not be removed from the closed system unless the viable organisms have been inactivated by validated chemical or physical means;

e) Seals should be designed to prevent leakage or should be fully enclosed in ventilated housings;

f) Production systems should be located within a purpose built controlled area according to the requirements 6 (a) to (k) inclusive specified in the Table hereafter;

g) Effluent from the production facility should be inactivated by validated chemical or physical means prior to discharge.

EXAMPLES OF CONTAINMENT APPROACHES FOR LARGE SCALE INDUSTRIAL APPLICATIONS OTHER THAN GILSP (GOOD INDUSTRIAL LARGE SCALE PRACTICE)

Specifications	Containment Categories		
	1	2	3
1. Viable organisms should be handled in a system which physically separates the process from the environment (closed system)	Yes	Yes	Yes
2. Exhaust gases from the closed system should be treated so as to:	Minimise release	Prevent release	Prevent release
3. Sample collection, addition of materials to a closed system and transfer of viable organisms to another closed system, should be performed so as to:	Minimise release	Prevent release	Prevent release
4. Bulk culture fluids should not be removed from the closed system unless the viable organisms have been:	Inactivated by validated means	Inactivated by validated chemical or physical means	Inactivated by validated chemical or physical means
5. Seals should be designed so as to:	Minimise release	Prevent release	Prevent release
6. Closed systems should be located within a controlled area	Optional	Optional	Yes , and purpose-built
a) Biohazard signs should be posted	Option	Yes	Yes
b) Access should be restricted to nominated personnel only	Optional	Yes	Yes, via an airlock
c) Personnel should wear protective clothing	Yes work clothing	Yes	A complete change
d) Decontamination and washing facilities should be provided for personnel	Yes	Yes	Yes
e) Personnel should shower before leaving the controlled area	No	Optional	Yes
f) Effluent from sinks and showers should be collected and inactivated before release	No	Optional	Yes
g) The controlled area should be adequately ventilated to minimise air contamination	Optional	Optional	Yes
h) The controlled area should be maintained at an air pressure negative to atmosphere	No	Optional	Yes
i) Input air and extract air to the controlled area should be HEPA filtered	No	Optional	Yes
j) The controlled area should be designed to contain spillage of the entire contents of the closed system	No	Optional	Yes
k) The controlled area should be sealable to permit fumigation	No	Optional	Yes
7. Effluent treatment before final dishcharge	Inactivated by validated means	Inactivated by validated chemical or physical means	Inactivated by validated chemical or physical means

OECD continued its studies through the Ad Hoc committee and later commissioned the writer to carry out a study in member countries and to report on the implementation of GILSP.

A number of recommendations were made to the OECD committee including - That there is a general need for a better understanding of the way the concept can be applied and in particular, for further elaboration of the GILSP criteria. Arising from this programme OECD has now issued a second booklet - Safety Considerations for Biotechnology 1992 which summarises recent developments in the GILSP concept. The book takes each of the GILSP criteria in turn and then explains the criterion in detail.

SPAIN

No national guidelines have been developed concerning large-scale industrial application or introduction of genetically modified organisms into agriculture or into the environment. No specific regulation on the use of GMOs has been established in Spain.

Until recently, there was a self-control on all experimentation involving GMOs outside contained laboratory conditions. This control was informal and was self-imposed by government research departments and government-funded institutions (including Universities). In addition, general regulations concerning pathogenic organisms have been applied.

The Spanish Governmental Expert Committee has a mandate to evaluate whether there is a need to develop regulations in this field, or to implement the OECD Guidelines through the future EEC Directives.

Sweden

The use of biotechnology in general and genetic engineering in particular started in Sweden in the late seventies and in 1978 a committee was appointed to make a study of the necessity of measures and laws governing activities dealing with recombinant DNA-techniques. The report of the committee resulted in the elaboration of a Government Bill proposing social control of the use of recombinant DNA techniques. As a consequence, since 1980, it has been necessary to obtain authorisation to use certain recombinant DNA-techniques.

In the same year, 1980, an advisory committee for recombinant DNA-questions was established at the National Board for Occupational Safety and Health. The main task for the committee was to promote safety in the use of recombinant DNA techniques and to provide information concerning developments in this field.

In 1982 the Swedish Government appointed another committee, the Genetic-ethical Committee, in order to make an inquiry on ethical, humanitarian and social issues, arising from the use of recombinant DNA techniques. The committee was composed of representatives of the political parties of the parliament and included experts from various fields of science and society.

In addition to the ethical guidelines drawn up in the Genetic-ethical Committee, the Swedish Industrial Committee for Biotechnology has recognised the need for ethical guidelines concerning the development and industrial application of biotechnology. These guidelines should complement the existing and planned legislation.

Since companies in Sweden are responsible for the methods used and the products achieved by modern biotechnology, these must be safe and thoroughly tested. In the light of this responsibility, Swedish industry considers it very important that the public is not caused unnecessary worry and that it does not emotionally react against the use of modern biotechnology as a result of being provided with inadequate or false information.

In Sweden, work is presently being carried out on possible legislation concerning the use of biotechnology, especially gene technology. At the same time, a thorough review is being made of the possible application of safety guidelines. The general aim in Sweden is to keep the decision on legislation open until the countries of the European Communities have agreed on Community guidelines. For the time being, Sweden adheres to the guidelines which have been elaborated within the framework of OECD.

Switzerland

National guidelines have not yet been issued, although there is a common agreement by industrial users of gene technology to work according to the recommendations of the SKBS (NIH guidelines including the GILSP concept of OECD).

On the basis of the report by an ad hoc expert panel, the Federal Government took two decisions on 20 August 1986:

- to consider the SKBS as a consultative body for matters related to gene technology

- to establish a so-called "co-ordination service" in order to achieve a co--ordinated procedure to issue licenses for the commercial use of rDNA organisms based on existing regulations.

The SKBS and the co-ordination service have started to function. Thus far, no rDNA organisms have been subject to a license either in the field of industrial application or in connection with deliberate release into the environment.

Further interdepartmental studies are to begin in order to determine the future needs for legislative acts in the field of gene technology.

Turkey

In Turkey there has been a growing interest for biotechnology. Recombinant DNA experiments were initiated in the 1980s and have accelerated after 1985. Genetic manipulations are being performed in several Universities and in the Research Institute for Basic Sciences of the Turkish Scientific Research Council. Being aware of the increasing amount of safety and ethic problems arising from the increasing use of genetic engineering and modern biotechnology techniques, Turkey is preparing guidelines for experiments involving recombinant DNA techniques. In addition, Turkey aims at collaborating with other countries to adopt a common language and regulations.

The guidelines in preparation will cover the following areas of biotechnology:

(i) Microbiology;

(ii) Recombinant DNA technology; defining the aim of recombinant DNA technology, use of the organisms obtained by the recombinant DNA manipulations. Application to the industry, intentional distribution in the environment of the recombinant organisms.

(iii) Education of the personnel involved on safety rules and ethics of biotechnology;

(iv) Hybridoma technology; and conditions of hybridoma laboratory, working with tumour cells.

(v) Transgene technology: Working rules on germ and somatic cells. Limits of research in this area.

United Kingdom

The United Kingdom has a long history of the control of genetically manipulated micro-organisms.

Originally this control was vested in the Genetic Manipulation Advisory Group (GMAG) who issued a series of notes to aid practitioners and who also gave guidance and made site inspection as required.

Some years ago the duties of GMAG were taken over by the Advisory Committee on Genetic Modification (ACGM) which is an advisory committee to the Health and Safety Commission. Secretarial duties and enforcement are carried out by officers of the Health and Safety Executive using the legislative framework provided by the Health and Safety at Work Act.

The original GMAG notes were overhauled and brought up to date with current thinking by HSE. New regulations, The Genetic Manipulation Regulations 1989, were also approved.

Recently in order to satisfy the need to comply with European Directives 90/219/EEC and 90/220/EEC, the UK government has revised the legislation, this time the modification being a joint exercise between the Health and Safety Executive and the Department of the Environment who also have the responsibility for the implementation of Section Six of the Environmental Protection Act, which involves biotechnology.

As these paragraphs are written the new legislation is at the proposal stage and is open to comment in the form of a consultative document. It is proposed, however, to assume that the proposals will be accepted and will become law by the time the paragraphs are published. Readers should, however, be advised to check the detail of the final published legislation for complete accuracy.

The new legislation covering contained use will be known as "The Contained use of Genetically Modified Organisms Regulations and will consist of six parts.

1) Interpretation and general

2) Notification of and consent for activities involving genetic modification

3) Conduct of activities involving genetic modification

4) Disclosure of information notified and publicity

5) Additional duties to be placed on the executive

6) Miscellaneous and general

The main features of the contained use regulations are:

- human health and environmental risk assessment;
- the need to keep records of risk assessments;
- categorisation of work on the basis of risks to human health and safety and of damage to the environment, taking into account the nature of the organism and the type of activity;
- advance notification to the Health and Safety Executive of an intention to use premises for activities involving genetic modification for the first time and, in prescribed circumstances, specific consent from the Executive and for such use;
- notification to the Health and Safety Executive of individual activities involving genetic modification, in advance where specified, and, in prescribed circumstances, specific consent from the Executive before such activities can proceed;
- standards of occupational and environmental safety and levels of containment;
- notification of accidents and, where appropriate, the drawing up of emergency plans;
- provisions relating to confidentiality, disclosure of information and public registers;
- provision for fees for notification.

Part I of the regulation is mainly concerned with definition of these and it is interesting to note that operations are defined as Type A or B which are defined as:

"Type A operation" means any activity involving genetically modified micro-organisms for the purposes of teaching, research or development, or for non-industrial or non-commercial purposes on a scale at which the practices and conditions of the operations relative to the culture volume and numbers of organisms involved are such that -

(a) the system used to keep the organisms under containment reflects good micro biological practice and good occupational safety and hygiene; and

(b) it is possible easily to render the organisms inactive by standard laboratory decontamination techniques;

"Type B operation" means any activity involving the genetic modification of micro-organisms other than a Type A operation.

Micro-organisms are divided into Group I and Group II, broadly in accordance with the EEC Directive but with considerable amplification.

Part II of the regulations which deals with notifications states that a person shall not use any premises for activities involving GMO's for the first time or undertake any GMO work unless adequate risk assessment has been made. The person should then notify HSE for first time use 90 days in advance and may proceed for Group I work at the end of the 90 day period unless HSE objects in writing. For Group II work consent has to be given.

The following information should be supplied by first time users.

(a) the name and address of the person responsible for carrying out the activity and the names of persons responsible for supervision, monitoring and safety together with details of their training and qualifications;

(b) address of the premises where the activity is to be carried on and its grid reference and, where appropriate, a description of the sections of the installation;

(c) a description of the nature of the activity to be undertaken, the likely scale of the operation and in particular, in the case of micro-organisms, their classification (whether in Group I or Group II);

(d) a summary of the risk assessment undertaken in accordance with Regulation 7;

(e) the names and capacities of the members of the genetic modification safety committee;

(f) comments made by the genetic modification safety committee on the local arrangements for risk assessment;

(g) the names of the biological and deputy biological safety officers concerned with the intended activities (if any);

(h) the name of the supervisory medical officer (if any); and

(i) the arrangements for health surveillance (if any).

In the case of Type B operations using Group I organisms the following information is also required under the regulations.

(a) the name and address of the person responsible for carrying out the activity;

(b) address of the premises where the activity is to be carried out;

(c) the date of the notification referred to in regulation 8(1);

(d) the parental organism used, or where applicable the host-vector system used;

(e) the source and the intended function of the genetic material involved in the modification;

(f) the identity and characteristics of the genetically modified organism;

(g) the purpose of the activity including the expected results;

(h) where appropriate the culture volumes to be used or the scale of the activity; and

(i) details of waste treatment including levels of live genetically modified micro-organisms in the waste; and

(j) a summary of the risk assessment required in accordance with Regulation 7 and of the comments of the genetic modification safety committee on it.

Type A operation using Group II organisms require additionally the following extra information.

(a) a description of the sections of the installation involved and the methods for handling the organisms;

(b) a description of the predominant meteorological conditions and the potential sources of danger arising from the location of the installation;

(c) a description of the protective and supervisory methods to be applied throughout the duration of the activity; and

(d) in the case of micro-organisms, the containment level to which the micro-organism has been allocated in accordance with the risk assessment made in accordance with regulation 7(1 and in any case the safety precautions to be observed.

In the case of Type B operations involving Group II organisms, further information is required and activities can only commence if the consent of the Executive has been obtained. The additional information is as follows:

(i) the identity and characteristics of the genetically modified micro-organism,

(ii) the purpose of the contained use or the nature of the product,

(iii) the host-vector system to be used where applicable,

(iv) the culture volume to be used,

(v) behaviour and characteristics of the micro-organisms in the case of changes in the conditions of containment or release into the environment,

(vi) overview of the potential hazards associated with the release of the micro-organisms into the environment, and

(vii) substances which are or may be produced in the course of use of the micro-organisms other than the intended product;

(b) information about personnel -

(i) the maximum number of persons working in the installation, and

(ii) the number of persons who will work directly with the micro-organism;

(c) information about the installation -

(i) the activity in which the micro-organisms are to be used,

(ii) the technological processes used,

(iii) a description of the sections of the installation involved, and

(iv) the predominant meteorological conditions and specific hazards arising from the location of the installation;

(d) information about waste management -

(i) types, quantities and potential hazards arising from the use of the micro-organisms,

(ii) waste management techniques used including recovery of liquid or solid wastes and the inactivation techniques used, and

(iii) ultimate form and destination of inactivated wastes:

(e) information about accident prevention and emergency response plans -

(i) the sources of hazards and conditions under which accidents might occur,

(ii) the preventive measures applied such as safety equipment, alarm systems, containment methods and procedures and available resources,

(iii) a description of information necessary for the Executive to evaluate any emergency plan prepared in accordance with Regulation 13.

When consent is required the Executive must communicate its decision within 90 days.

Part III of the regulations deals with conduct of activities and requires the principles of occupational hygiene laid down by OECD to be observed. The section of the regulations also details the requirements of the emergency plan in the cases where this is required by the regulations. There is also a procedure for the notification of accidents.

Part IV of the regulations deals with confidentiality and in accordance with the duties laid down in Directive 90/219/EEC.

Part VI of the regulations deals with enforcement and fees.

United States of America

The present legislative procedure in the USA is described in detail in the Federal Register, June 26, 1986 - A Co-ordinated Framework for Regulation of Biotechnology - issued by the Office of Science and Technology Policy.

Specific departments in the US administration may be considered as follows:

Environmental Protection Agency

The EPA does not, at this time, have any additional relevant regulatory information to update the framework described in the 26 June 1986 Federal Register. EPA is currently in the process of drafting a proposed rule to regulate certain products of biotechnology under the Toxic Substances Control Act (TSCA). EPA is also drafting an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) for regulatory and registration activities with pesticides.

The proposed regulations under TSCAS include mechanisms and options for the reporting, review and regulation of the release of genetically engineered organisms into the environment that were developed for commercial purposes. Certain release activities performed at the research and development stage are also addressed in the proposed rule.

Subdivision M, which contains guidance on test methods and standards to be used in developing the necessary data to support the experimental use or registration of naturally occurring or genetically engineered microbial pesticides, has been updated.

Department of Agriculture

National guidelines and regulatory developments: Regulations for introductions involving genetically modified plant pests were promulgated 16 June 1987 and are described in detail below. Guidelines for agricultural research on genetically modified organisms are currently under development and unavailable for outside review at this time.

USDA Policy and Authority

In the Federal Register of 16 June 1986, the US Department of Agriculture (USDA) published a final policy statement on the regulation of biotechnology as a part of the federal co-ordinated framework for regulating the products of the new technology. USDA restated its conclusion that agricultural products developed by biotechnology would not differ fundamentally from those produced by conventional methods and that the existing statutes were adequate for regulating genetically engineered organisms and products.

USDA has broad regulatory authority to protect US agriculture against threats to animal health and to prevent the introduction and dissemination of plant pests. This authority has been applied to the regulation of genetically engineered veterinary biological products, plants, and micro-organisms.

Case-by-Case Reviews

In the area of animal health, the Virus-Serum-Toxin Act provides USDA with the authority to regulate all veterinary biological products that are imported into the United States, shipped or delivered for shipment interstate and intrastate, and that are exported. Since January 1986, USDA has issued four veterinary biological product licenses for modified live virus vaccines produced through recombinant DNA techniques, all for pseudo-rabies in swine.

Under the existing authority of the Federal Plant Pest Act and the Plant Quarantine Act, USDA published a new rule in Title 7 of the Code of Federal Regulations, Part 340 (7 CFR 340) which became effective 16 July 1987, establishing a permit requirement for the introduction of genetically engineering organisms that are plant pests or that USDA has reason to believe are plant pests. This final rule provides that an organism or product altered or produced through genetic engineering would be regulated if the donor organism, recipient organism, or vector or vector agent: (1) belongs to a plant pest group designated in the regulation, or is an unclassified organism; (2) meets the definition of "plant pest"; and (3) is "introduced", which means being imported, moved interstate, or released into the environment. USDA granted 21 permits between 16 July 1987 and 31 December 1988 under this rule for field tests of genetically engineered plants. Before the rule became effective, USDA issued opinion letters on the risk of plant pest introduction for nine proposals to field-test genetically engineered plants (January 1986 to July 1987).

Environmental Assessment

In accordance with the provisions of the National Environmental Policy Act and Departmental regulations, USDA conducts an environmental analysis prior to each license or field test of a genetically engineered veterinary biological product, and for each permit for a release into the environment of a genetically engineered plant or micro-organism subject to the provisions of 7 CFR 340. An announcement of the availability of the environmental assessment is published in the Federal Register. This procedure provides the public with documentation that the environmental impacts of releasing a genetically engineered organism into the environment have been thoroughly evaluated.

Food and Drug Administration

The US National Academy of Sciences (NAS) report of August 1987 provides conclusions and policy recommendations on the use and governmental oversight of rDNA manipulations of organisms for field testing or commercial applications.

Several of the most significant of these are: (1) rDNA techniques constitute a powerful and safe new means for the modification of organisms; (2) genetically modified organisms will contribute substantially to improved health care, agricultural efficiency, and the amelioration of many pressing environmental problems that have resulted from the extensive reliance on chemicals in both agriculture and industry; (3) there is no evidence that unique hazards exist either in the use of rDNA techniques or in the movements of genes between unrelated organisms; (4) the risks associated with the introduction of rDNA-engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods; and (5) the assessment of risks associated with introducing rDNA organisms into the environment should be based on the nature of the organism, based on the environment into which the organisms are to be introduced, and independent of the method of engineering per se.

FDA's latest formal statement of policy is to be found in 51 Fed. Reg. 23309-13, June 26, 1986. With regard to FDA policy toward introduction of "genetically modified organisms into the environment", the assumptions underlying FDA's approaches are as set out in the NAS report.

In the Federal Register of 13th September 1990 Appendix K of the NIH guidelines was revised for GILSP

"Appendix K - Physical Containment for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules."

"This part of the Guidelines specifies physical containment guidelines for large-scale (greater than 10 litres of culture) research or production involving viable organisms containing recombinant DNA molecules. It shall apply to large-scale research or production activities as specified in Section III-B-5 of the Guidelines. It is important to note that this appendix addresses only the biological hazard associated with organisms containing recombinant DNA. Other hazards accompanying the large scale cultivation of such organisms (e.g. toxic properties of products; physical, mechanical and chemical aspects of downstream processing) are not addressed and must be considered separately, albeit in conjunction with this appendix."

"All provisions of the Guidelines shall apply to large-scale research or production with the following modifications:

Appendix K shall replace portions of Appendix G when quantities in excess of 10 litres of culture are involved in research or production. Appendix K-II applies to GLSP; Appendices G-I and G-II, as indicated in accompanying table, apply to Biosafety Levels (BL) BL1-LS, BL2-LS, and BL3-LS."

[Remainder of Introduction remains unchanged.]

"Appendix K-I - Selection of Physical Containment Levels.

The selection of the physical containment level required for recombinant DNA research or production involving more than 10 litres of culture is based on the containment guidelines established in Part I of the Guidelines. For purposes of large-scale research or production, four physical containment levels are established. The four levels set containment conditions at those appropriate for the degree of hazard to health or the environment posed by the organism, judged by experience with similar organisms unmodified by recombinant DNA techniques and consistent with good large scale practices. These are referred to as GLSP, BL1-LS, BL2-LS, and BL3-LS. The GLSP (Good Large-Scale Practice) level of physical containment is recommended for large-scale research or production involving viable, non-pathogenic, and non-toxigenic recombinant strains derived from host organisms that have an extended history of safe large scale use. Likewise, the GLSP level of physical containment is recommended for organisms such as those included in Appendix C that have built-in environmental limitations that permit optimum growth in the large scale setting but limited survival without adverse consequences in the environment. For those organisms that do not qualify for GLSP, the BL1-LS (Biosafety Level 1 - Large-Scale) level of physical containment is recommended for large-scale research or production of viable organisms containing recombinant DNA molecules that require BL1 containment at the laboratory scale. The BL2-LS (Biosafety Level 2 - Large-Scale) level of physical containment is required for large-scale research or production of viable organisms containing recombinant DNA molecules that require BL2 containment at the laboratory scale. The BL3-LS (Biosafety Level 3 - Large-Scale) level of physical containment is required for large-scale research or production of viable organisms containing recombinant DNA molecules that require BL3 containment at the laboratory scale. No provisions are made for large-scale research of production of viable organisms containing recombinant DNA molecules that require BL4 containment at the laboratory scale. If necessary, these requirements will be established by NIH on an individual basis."

"Appendix K-II - GLSP Level."

Appendix K-II-A. Institutional codes of practice shall be formulated and implemented to assure adequate control of health and safety matters."

"Appendix K-II-B. Written instructions and training of personnel shall be provided to assure that cultures of viable organisms containing recombinant DNA molecules are handled prudently and that the workplace is kept clean and orderly.

"Appendix K-II-C. In the interest of good personal hygiene, facilities (e.g. hand washir sink, shower, changing room) and protective clothing (e.g. uniforms, laboratory coats) shall be provided that are appropriate for the risk of exposure to viable organisms containing recombinant DNA molecules. In addition, eating, drinking, smoking, applying cosmetics and mouth pipetting shall be prohibited in the work area."

"Appendix K-II-D. Cultures of viable organisms containing recombinant DNA molecules shall be handled in facilities intended to safeguard health during work with micro-organisms that do not require containment."

"Appendix K-II-E. Discharges containing viable recombinant organisms shall be handled in accordance with applicable governmental environmental regulations."

"Appendix K-II-F. Addition of materials to a system, sample collection, transfer of culture fluids within/between systems, and processing of culture fluids shall be conducted in a manner that maintains employee exposure to viable organisms containing recombinant DNA molecules at a level that does not adversely affect the health and safety of employees."

"Appendix K-II-G. The facility's emergency response plan shall include provisions for handling spills."

"Appendix K-III-A. Spills and accidents which result in overt exposures to organisms containing recombinant DNA molecules are immediately reported to the laboratory director. Medical evaluation, surveillance, and treatment are provided as appropriate and written records are maintained.

"Appendix K-IV-M-8, The controlled area shall have a ventilation system that is capable of controlling air movement. The movement of air shall be from areas of lower contamination potential to areas of higher contamination potential. If the ventilation system provides positive pressure supply air, the system shall operate in a manner that prevents the reversal of the direction of air movement or shall be equipped with an alarm that would be actuated in the event that reversal in the direction of air movement were to occur. The exhaust air from the controlled area shall not be recirculated to other areas of the facility. The exhaust air from the controlled area may not be discharged to the outdoors without being HEPA filtered, subjected to thermal oxidation, or otherwise treated to prevent the release of viable organisms."

Following an announcement by President Bush on February 26th 1992, the Office of Science and Technology published in the Federal Register of February 27th 1992 an Announcement of Policy, the salient points of which are reproduced.

In 1986 the "Co-ordinated Framework" was issued to explain the proper allocation and co-ordination of oversight responsibilities under the several relevant statutes and among the several relevant federal agencies. The Co-ordinated Framework thus addressed who shall have oversight authority in each instance, but did not address how that authority should be exercised in the frequent situations in which a statute leaves the implementing agency latitude for discretion.

To fill that need, the present FEDERAL REGISTER notice sets forth the proper basis for agencies' exercise of oversight authority within the scope of discretion afforded by statute. It describes a risk-based, scientifically sound approach to the oversight of planned introductions of biotechnology products into the

environment that focuses on the characteristics of the biotechnology product and the environment into which it is being introduced, not the process by which the product is created. Exercise of oversight in the scope of discretion afforded by statute should be based on the risk posed by the introduction and should not turn on the fact that an organism has been modified by a particular process or technique.

In order to ensure that limited federal oversight resources are applied where they will accomplish the greatest net beneficial protection of public health and the environment, oversight will be exercised only where the risk posed by the introduction is unreasonable, that is, when the value of the reduction in risk obtained by additional oversight is greater than the cost thereby imposed. The extent and type of oversight measure(s) will thus be commensurate with the gravity and type of risk being addressed, the costs of alternative oversight options, and the effect of additional oversight on existing safety incentives.

These principles recognise the desirability of appropriate oversight of unreasonable risks, such as current restrictions on the introduction of dangerous pathogens; the principles also confirm the limited extent of current oversight of low-risk activities, such as the traditional breeding of farm animals and plants.

STATUTES PERTAINING TO BIOTECHNOLOGY PRODUCTS

Biotechnology is the use of various biological processes, both traditional and newly devised, to make products and perform services from living organisms or their components. See Report on National Biotechnology Policy (President's Council on Competitiveness: Feb. 1991), p.1. Because these diverse processes, products and services may find application in many areas, such as medicine and pharmaceuticals, agriculture, industry, and environmental protection, the attendant planned introduction of organisms or other biotechnology products into the environment may be subject to federal oversight under the one or more federal statutes relating to each such area. The Federal Register of November 14, 1985 (50 Fed. Reg. 47174) contains a matrix of the many federal authorities related to biotechnology products. There is no single, unified statute governing all introductions of biotechnology products into the environment, just as there is no single, unified statute governing the use of any other basic, multipurpose technology such as chemical engineering, civil engineering, or the use of fire or electricity. A single statute would quickly become obsolete, or an excessive constraint on innovation, as people devised new and useful ways to employ the technology, and would fail to address the important differences in the potential impacts of the technology when used in different ways.

Introductions into the environment of biotechnology products are therefore subject to government oversight pursuant to statutory authority corresponding to the particular type of introduction in question. The Federal Plant Pest Act governs the importation and movement of plant pests; the Federal Food, Drug and Cosmetic Act (FFDCA) governs foods, food additives, cosmetics, human and

veterinary drugs, and medical devices; the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) governs pesticides; the Toxic Substances Control Act (TSCA) governs chemicals; several statutes (the Clean Air Act, Clean Water Act, Oil Pollution Act, "Superfund" law, and Resource Conservation & Recovery Act) govern the use of pollution control techniques; and certain statutes govern projects that are federally funded. One or more of these laws may apply to introductions of biotechnology products for research or commercial purposes.

Each of these laws is administered by a federal agency. For example, the Food & Drug Administration (FDA) administers FFDCA; the Environmental Protection Agency (EPA)) administers FIFRA, TSCA, and the pollution-control statutes; and the Department of Agriculture (USDA) administers the Federal Plant Pest Act while also funding many research projects involving biotechnology.

Each statute directs the implementing executive branch agency to carry out certain responsibilities. The statutory provisions necessarily define the boundaries of the scope of discretion afforded to executive branch agencies to exercise oversight. Typically each statute leaves the agency discretion within those bounds in exercising oversight.

THE "CO--ORDINATED FRAMEWORK" AND THE NEED FOR A SCOPE DOCUMENT

In view of the diversity of federal statutes pertaining to biotechnology products, in 1986 the Co-ordinated Framework for the Regulation of Biotechnology was issued to describe the comprehensive Federal regulatory policy for ensuring the safety of biotechnology research and products. It explained that existing statutes provide a basic network of agency jurisdiction over both research and products, assuring reasonable safeguards for the public and the environment. It also explained the co-ordination among federal agencies to ensure that such safeguards would be generated by a smooth, understandable regulatory oversight process. The Co-ordinated Framework stated that "to the extent possible, responsibility for a product use will lie with a single agency." (51 Fed. Reg. 23363). The Framework was expected to evolve in light of experience, and modifications to the framework were anticipated. The Co-ordinated Framework for the Regulation of Biotechnology continues to be Federal Government policy today for the allocation of oversight responsibilities - which agencies shall have oversight responsibility for which biotechnology products.

But the Co-ordinated Framework did not fully address how oversight should be exercised within the scope of discretionary authority afforded by statute. The Co-ordinated Framework recognised that while the statutory bases for regulation among the involved agencies may differ, common principles should govern decisions on how to exercise discretionary oversight over introductions of biotechnology products.

RATIONALE FOR RISK-BASED APPROACH

The purpose of this statement is to guide the exercise of agencies' oversight, within the scope of authority afforded by statute, to ensure the safety of planed introductions of biotechnology products into the environment while not unduly inhibiting the benefits of such introductions. This approach, therefore, focuses on the characteristics and risk posed by an introduction, rather than on the process by which a product is created. This is the same fundamental, risk-based approach enunciated in the Proposed Scope in July 1990 (see 55 Fed. Reg. at 31119), and endorsed by the great majority of public comments on the Proposed Scope (see Appendix below). The risk-based approach is scientifically sound, properly protects public health and the environment against risk, and avoids hindering safe innovations. Citing these rationales, the first Principle of Regulatory Review for Biotechnology approved by President Bush in August 1990 requires the federal government to adhere to a risk-based approach. Likewise, the EPA Report on Risk Priorities issued in September 1990 and the Competitiveness Council Fact Sheet on Critical Technologies issued in April 1991 explain the imperative of following a risk-based approach. (See excerpts in Appendix, below.) This section briefly explains the reasoning behind this risk-based approach.

SCIENTIFIC PRINCIPLES FOR THE RISK-BALANCED APPROACH

Introductions of organisms into the environment may pose hazards to humans, wild or domesticated plants and animals, or to the environment generally (for example, algal blooms in ponds or disruptions of natural cycles). The risk posed by an introduction of biotechnology products into the environment is a function of the characteristics of the organisms or other products, the particular application (including confinement measures), and the environment itself. As stated in the Co-ordinated Framework, "Within agriculture, for example, introductions of new plants, animals and micro-organisms have long occurred routinely with only some of those that are not native or are pathogenic requiring regulatory approval." (51 Fed. Reg. 23303). Even many organisms that are pathogenic are routinely used with practices or under conditions that mitigate risk; much of the research within the discipline of plant pathology is in this category. Meanwhile, certain unmodified organisms are of such great risk that they are not allowed into the United States, such as the Foot and Mouth Disease Virus (FMDV).

Just as with traditional breeding techniques, the production of organisms using new molecular techniques of genetic manipulation may or may not pose risk, depending on the characteristics of the organism, the target environment, and the type of application. The National Research Council's extensive review of the potential risks of introductions of organisms made from new biotechnology processes (NRC, Field Testing Genetically Modified Organisms (1989) reached the conclusion that organisms that have been genetically modified are not per se of inherently greater risk than unmodified organisms. It elaborated:

1. The same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods. (p.15)

2. Information about the process used to produce a genetically modified organism is important in understanding the characteristics of the product. However, the nature of the process is not a useful criterion for determining whether the product requires less or more oversight (pp.14 and 15).

3. No conceptual distinction exists between genetic modification of plants and micro-organisms by classical methods or by molecular techniques that modify DNA and transfer genes (p.14).

4. Crops modified by molecular and cellular methods should pose risks no different from those modified by classical methods for similar traits. As the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants (p.3).

5. In many respects, molecular methods resemble the classical methods for modifying particular strains of micro-organisms, but many of the new methods have two features that make them even more useful than the classical methods. Precision allows scientists to make genetic modifications in microbial strains that can be characterised more fully, in some cases to the level of DNA sequence. This reduces the degree of uncertainty associated with any intended application. The new methods have greater power because they enable scientists to isolate genes and transfer them across natural barriers (p.123).

The process of modification is thus independent of the safety of the organism. Although the new biotechnology processes can be used to produce risky organisms, so can traditional techniques; it is the characteristics of the organism, the environment, and the application that determine risk (or lack thereof) of the introduction, not the technique used to produce the organism. Indeed, the new technologies of molecular modification may increase the potential for safe, planned introductions because they employ techniques that are more precise and more efficient than traditional cross-breeding, and that therefore yield a better-characterised and more predictable organism. On the other hand, their great power allows us to transfer genes more readily. This may result in organisms with new traits or combinations of traits.

From these scientific observations derive the following fundamental Scope principles:

1. A determination to exercise oversight within the scope of discretion afforded by statute should not turn on the fact that an organism has been modified, or modified by a particular process or technique, because such fact is not alone a sufficient indication of risk.

2. A determination to exercise oversight in the scope of discretion afforded by statute should be based on evidence that the risk presented by introduction of an organism in a particular environment used for a particular type of application is unreasonable.

3. Organisms with new phenotypic trait(s) conferring no greater risk to the target environment than the parental organisms should be subject to a level of oversight no greater than that associated with the unmodified organisms.

FINAL STATEMENT ON SCOPE

Statutory provisions necessarily define the boundaries of the scope of discretion afforded to executive branch agencies to exercise oversight. Within the scope of authority provided by statute, federal agencies shall exercise oversight of planned introductions of biotechnology products into the environment only upon evidence that the risk posed by the introduction is unreasonable. A risk is unreasonable where the full value of the reduction in risk obtained by oversight exceeds the full cost of the oversight measure. This formulation ensures that limited federal oversight resources will be applied where they will accomplish the most net beneficial protection of public health and the environment while allowing useful, safe innovations to proceed. Evidence of risk must incorporate information about the characteristics of the organism or other biotechnology product, the target environment, and the type of application.

Federal government regulatory oversight should focus on the characteristics and risks of the biotechnology product - not the process by which it is created. Products developed through biotechnology processes do not per se pose risks to human health and the environment; risk depends instead on the characteristics and use of individual products. Where oversight is warranted, the extent and type of oversight measure(s) must be commensurate with the gravity and type of risk being addressed, must maximise the net benefits of oversight by choosing the oversight measure that achieves the greatest risk reduction benefit at the least cost, and must consider the effect that additional oversight could have on existing safety incentives.

The risk-based approach taken in this Final Statement on Scope is the same as the approach enunciated in the July 1990 Proposed Scope, which provided that "To the extent permitted by law, planned introductions into the environment ...should not be subject to oversight... unless information concerning the risk posed by the introduction indicates that oversight is necessary." (55 Fed. Reg. at 31120) As detailed below, the Final Statement on Scope also retains the "criteria for evaluating risk" suggested in the Proposed Scope. The principal differences between today's Final Statement on Scope and the Proposed Scope are (i) the recognition that there are a variety of oversight measures that agencies might employ, not simply a binary choice between "oversight" and "no oversight", and therefore the provision that agencies choose from among the menu of measures those oversight measures that achieve risk reduction at net benefit and least cost;

and (ii) the removal of the examples of "categories for exclusion" in the Proposed Scope, because, as described below under "Implementation", these categories were not explained in the basis of risk and ignored the need for each agency to have the flexibility to fashion its implementation in the context of its statutory program. These differences are warranted in the interest of sound public policy, and reflect the numerous public comments (summarised in the Appendix) recommending such revisions.

IMPLEMENTATION

EXERCISING DISCRETION WITHIN THE SCOPE OF STATUTORY AUTHORITY

As described above, this Final Statement on Scope guides agencies' exercise of oversight within the scope of discretion provided by statute. Nothing in this document displaces agencies' duties under applicable statutes, nor does this document provide the basis for additional authority not available to agencies under applicable law. Rather, this document guides the exercise of discretion within the range of authority left to agencies under their statutes. Each agency will need to implement these guidelines in a manner appropriate to each statutory framework, and to exercise its oversight authority consistent with the risk-based principles of this Final Statement on Scope.

This Final Statement on Scope governs all oversight within the scope of agency discretion afforded by statute of planned introductions of biotechnology products into the environment. It does not relate only to new regulatory initiatives or new categories of organisms introduced into the environment. In addition, the term "planned introduction" as used here includes introductions in the course of research and in commercial and other applications. It is not limited to initial small-scale field trials.

In applying the risk-based approach there will of course be areas in which regulatory interventions are frequent, and areas in which such interventions are legally authorised but are less common because the industry operates safely and the occasions for regulation and enforcement are fewer. Such safety could be the result of long-standing industry practices, and of industry's pragmatic understanding that government intervention - whether through federal or state law or otherwise - would occur if safety rules were violated. Although federal oversight for such activities may be legally available, it may be observed that where an industry operates in a safe manner, little or no oversight is commonly exercised. One example of such a safe equilibrium may be traditional agriculture operating with safe organisms following accepted practices and precautions. This is consistent with recommendations made by the National Research Council in the publication Field Testing Genetically Modified Organisms, 1989, p.66.

EVALUATING RISKS

Products developed through biotechnology processes do not per se pose risks to human health and the environment; risk depends instead on the characteristics and use of individual products. Such determinations should be based on risk factors or criteria like the ones listed below pertaining to the organism's ecological niche, potential for gene exchange, ability to monitor and to mitigate persistence and spread and potential consequences of dissemination into the greater environment. These factors for evaluation of risk are largely derived from the work of the Ecological Society of America. (See J. Tiedje, R. Colwell, Y. Grossman, et al., 79 Ecology 298 (April 1989)).

For the organism:

Fitness; infectivity, virulence, pathogenicity, toxicity; host range; the type of substrate or resources utilised; the purity of the formulation; environmental limits to growth or reproduction (habitat, micro habitat); susceptibility to control by antibiotics, biocides, by substrate, or by mechanical means; whether and how introduced traits are expressed.

For the target environment:

Selection pressure for the introduced trait; presence of wild, weedy or feral relatives within dispersal capability of the organism or its genes; presence of vectors or agents of dissemination or dispersal (e.g. mites, insects, rodents, birds, humans, machines, wind, water); direct involvement in basic ecosystem process (e.g. nutrients cycling); whether there are alternative hosts or partners (e.g. the organism is involved in symbiosis or mutualism); range of environments for testing or use in light of potential geographic range; effectiveness of confinement, monitoring and mitigation plans.

The scope principles do not dictate precisely how information or risk should be evaluated. Different ways of making the risk determination are possible. One means of judging the risk posed by an introduction is to compare its risk to an introduction of a comparable organism or biotechnology product previously used in introductions in a comparable target environment. An organism or other biotechnology product can be comparable to a previously used organism or product regardless of the process by which that organism has been modified or product produced. An introduction should be subject to no greater degree of oversight than was a comparable organism or product previously used in past safe introductions in a comparable target environment. Effective confinement techniques in appropriate cases can also reduce the potential risk of an introduction, and accordingly, the need for oversight.

Unreasonable risk is the threshold for exercising oversight within the scope of discretion afforded by statute. The term does not denote a fixed absolute number. Rather, a risk is "unreasonable" where the environmental benefits achieved by oversight measures to reduce the risk are greater than the social cost of those oversight measures.

ASSESSING OVERSIGHT OPTIONS

Agencies have a wide variety of oversight options with which to fashion their oversight programs consistent with the risk-based approach enunciated here. The term "federal oversight" includes a range of possible Federal activities related to planned introductions: issuance of suggested industry practices, development of guidelines for certain introductions, and requirements for notification, labelling, prior review or approval of certain introductions. This range of federal oversight activity might be undertaken from a Federal agency. It could involve, for example, a research institution establishing an "institutional safety committee" for review of certain planned introduction experiments.

This menu of oversight options means that agencies can choose oversight measures to be commensurate with the gravity and type of risk being addressed, and fashioned to maximise the net benefits to society and the environment, taking into account the costs of oversight.

In determining the risk reduction that may be achieved by a contemplated oversight measure, it is important to recognise that persons introducing biotechnology products into the environment often face other institutional incentives to ensure that such introductions are safe. Such existing safety incentives may include oversight already being exercised under another regulatory authority, state laws, and marketplace incentives for safety created by the interests of workers and consumers in obtaining products that are safe. Safety can also be promoted by generally accepted research practices, professional and industrial association standards, and other safety oriented guidelines and procedures. It is important to take account of the interplay between the new oversight measure and the pre-existing incentive systems. In some circumstances the effect of a new oversight measure may complement existing safety incentives, but in others its effect may be dampened or undercut by its (unintended) displacement of existing safety incentives. For example, imposing new safety standards may in certain circumstances simply displace existing safety incentives provided by state law or by market price differentials for accepting risk. Agencies should account for these potential incentive effects in their calculation of the net benefits of potential oversight measures. Further, agencies should affirmatively design oversight measures to work in concert with pre-existing safety systems, such as by strengthening the information base on which marketplace incentives depend. In appropriate cases agencies might forego additional oversight where existing incentives adequately address the risks posed.