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Genetic Engineering and Bio-technology Monitor

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This issue is devoted to international biosafety guidelines for the release of genetically engineered microorganisms and plants, and the Voluntary Code of Conduct for the Release of Organisms into the Environment.

Distributed free to a targeted audience in developing countries

CONTENTS

INTERNATIONAL BIOSAFETY GUIDELINES AND CODE OF CONDUCT FOR THE RELEASE OF GENETICALLY ENGINEERED MICROORGANISMS AND PLANTS

Introduction

Biotechnology-based industries are less energy intensive and environmentally friendly. The rapid advances in biotechnology and genetic eingineering have already resulted in a number of products of high commercial value in the fields of health care, agriculture and environment. The realization of the potential of these frontier technologies often entails production and release of GMOs into the environment. Several releases have already taken place in industrialized countries. With the increasing application of these novel technologies in industrialized nations and the prospective high demand for their application in developing countries, safety issues relating to them have come to the forefront and are receiving particular attention in recent years.

As part of the Informal Working Group (IWG comprising UNIDO, The United Nations Environment Programme (UNEP), the World Health Organisation (WHO) and the Food and Agriculture Organization of the United Nations (FAO), UNIDO has been interested in evolving biosafety guidelines and preparation of an international voluntary code of conduct on environmentally sound management and application of biotechnology. In that context it was timely that appropriate funding could be obtained through the Swedish Industrial Development Fund assistance. The project objective was therefore to provide the basis of uniform standards in risk assessment methodology and risk management and thus facilitate the acceptance, at the international level, of a code of conduct for the release of engineered microorganisms and plants to the environment. The outputs envisaged on the project are to evolve a set of documents consisting of:

1. A report on the harmonization of existing national biosafety guidelines into a minimally acceptable set of global biosafety guidelines;

2. A UNIDO position paper on a code of conduct for the release of genetically modified organisms and plants to the environment;

3. Terms of reference of an advisory group for referral purposes for countries without relevant safety guidelines;

4. A manual reviewing all aspects of biosafety, including a comparative analysis of existing guidelines.

Achievements

To achieve the outputs enumerated above, UNIDO organized an Expert Group Meeting in March 1991 consisting of scientific experts from developing and developed countries. The group prepared a draft code of conduct on the release of GMOs into the environment, along with a recommendation for the establishment of a biosafety information network and advisory service (BINAS). BINAS is essentially intended to serve as a referral mechanism to advise developing countries that do not have guidelines on biosafety matters. The draft was further examined by another group of experts with a greater representation from developing counries at a meeting convened in July 1991 at the International Centre for Genetic Engineering and Biotechnology (ICGEB) at Trieste (Italy). The final draft that emerged from this meeting was endorsed by the Informal Working Group (IWG) on Biosafety comprising UNIDO, UNEP, WHO and FAO.

The governments of member countries of UNIDO were kept informed at each stage of the code of conduct's development. To begin with, UNIDO informed the governments of its intention to develop harmonized guidelines and a code on the release of genetically modified organisms into the environment, with a note on the schedule of work of the project. Information and documentation on existing national regulations were sought from them on the subject. Subsequently, after the March 1991 meeting of the experts, a preliminary draft of a possible voluntary code of conduct was circulated to governments for information and comments. Finally, at the end of the Trieste meeting in July 1991, the code in its final form was brought to the attention of the member countries.

Basically, the code attempted to harmonize existing guidelines, capturing the minimum commonly accepted principles into an international framework in the form of a code of conduct for the release of genetically modified organisms. The code stipulates general principles, the obligations of governments, the proposer and the researcher intending to release the GMOs. The guidelines expressed in the code are meant to be user friendly and aimed at promoting the process of biotechnology progress. These can be modified or extended to suit specific situations, if the countries so desire.

The need for the code is evident. A few developed countries have already formulated special regulations on the release of organisms into the environment. However, there is a startling lacunae in this area in many countries, as is evident in a recent survey conducted by

UNIDO. The Preparatory Committee for the ICGEB requested UNIDO to collect existing information on biosafety guidelines in its member countries. Accordingly UNIDO prepared a set of 24 questions relating to regulations, guidelines and the need for an advisory referral system on biosafety and submitted the questionnaire to member countries. The feedback received revealed that most countries have no biosafety committees, regulatory requirements or approval bodies. It is of interest to note in this connection that even many industrialized nations have yet to develop guidelines on biotechnology safety. There is therefore a pressing need to formulate biosafety guidelines, risk assessment and a code of conduct for the release of organsims into the environment. It seems necessary to have international cooperation in forming a basic set of guidelines that countries can make use of in order to avail the advances in frontier technologies to their benefit. These guidelines will:

- serve to promote R&D and environmental applications of GMOs
- provide guidance to national authorities to take quick decisions on proposals for introduction
- help industry to commercialize GMO-based products
- bring transparency and avoid trade barriers
- facilitate consumer confidence and acceptance.

It is hoped that the biosafety guidelines and the code of conduct will contribute towards the above objectives.

The code has been brought to the attention of various fora, such as the third Preparatory Committee meeting of UNCED, the 17th Preparatory Committee meeting of the ICGEB, UNEP's Biodiversity Convention, the Intergovernmental Meeting on Ecologically Sustainable Development and the Pan-African Ministerial Symposium on Biotechnology and elicited favourable response from a number of quarters.

The salient paragraphs of the code have been annotated and brought to the attention of developed and developing countries through the permanent missions of UNIDO and the ICGEB member countries and is reproduced hereunder for a wider dissemination. The figures in boldface refer to the annotations, which are contained in the Appendix immediately following the code and its Annex.

An educational manual on biotechnology safety will be published by the end of 1992.

VOLUNTARY CODE OF CONDUCT FOR THE RELEASE OF ORGANISMS INTO THE ENVIRONMENT(1)

I.PREAMBLE

A Genetically modified microorganisms, plants and animals offer new technological possibilities to improve quality and production. Improved crops and food products, drugs and health care products, vaccines, feeds, industrial chemicals and products, new diagnostic agents and environmental agents are being developed via new biotechnological processes. Throughout the centuries, traditional breeding programmes have produced new and improved varieties and brought products to markets. The products of biotechnology can be considered to be part of this continuum.(2)

B The advent of new molecular and cellular techniques of genetic modification has led to the continuing emergence of the products (including organisms) of biotechnology that promise substantial benefits and improvements to the quality of life. These techniques are available now, but to be safely and effectively used they must be applied according to a number of principles, such as those described below, and with the support of an international biosafety information network and advisory service.(3)

C The proposed document contains all the elements of a code of conduct for the release of genetically modified organisms (GMOs) into the environment. It aims to set forth the minimum acceptable components necessary for international cooperation. While not calling for a change in national regulatory provisions, it is intended as a general model that could be adopted in countries having no regulations at present. Aiming to draw on existing experience rather than to frame new principles, it contains a list of selected reference documents in an annex.(4)

D Since newly introduced organisms have the potential for transfrontier impacts, there is a need to develop an international code of conduct/practice and establish a general framework and guidelines that will ensure their safety in research, development, production, trade and use. This would facilitate safe applications of biotechnology in an orderly manner. Alongside high expectations from the application of biotechnology, questions regarding public health and environmental safety, development and use need to be addressed.(5)

E Of particular relevance to international cooperation is the introduction of organisms to the environment. It is anticipated that the code will provide help to

governments in developing their own regulatory infrastructure and in establishing standards for the safe development, manufacture, use and release of GMOs to the environment, or in obtaining appropriate advice and support in those cases where a country recognises the need for improvement in its review, national assessment or decision making structures. The principles outlined in this document deal primarily with GMOs. They may not always provide an adequate framework to assess the risks posed by the introduction of other organisms, such as organisms not indigenous to the introduction site. Therefore there is a need for a similar effort to develop principles and codes of practice to deal with this category of introductions.(6)

Furthermore, the document is not intended to deal with issues related to the contained industrial application of GMOs. Whereas there is a substantial body of knowledge regarding contained uses of microorganisms, there is still the need to further address safety considerations that pertain to industrial uses of pathogenic organisms, to internationalize the principles underlying safety and to develop codes of conduct to deal with this category of applications.(7)

To ensure the safe management of biotechnology including research, development, use and associated environmental introductions of GMOs, member countries need:

- appropriate scientific and technical expertise;
- national assessment and decision making structure(s);
- specific scientific advisory bodies;
- mechanisms to gather information on local agronomic and
- environmental conditions;
- systems for the provision of information to, and education of the public.

(a) To respond to these needs, a number of approaches are available to member countries. In this regard, virtually all countries have quarantine procedures of similar mechanisms for managing the import of new plants, animals or microorganisms. An adaptation of these mechanisms through specific organism-related scientific advisory bodies could provide a means of handling new biotechnology products. In addition, such procedures could be extended to include the review of new domestically produced GMOs.

(b) Governments may in other cases require assistance in the form of information or advice in order to make a proper scientific assessment. Even where a researcher supplies full documentation, expert advice may be needed to enable an adequate assessment to be made.

(c) In the simplest case, support to access existing information may be all that is needed to assist the product assessment. Beyond this, there will be a wide range of needs.

(d) For some countries, the only need will be for expert advice to help in the assessment of a particular project or product. Other countries may wish to draw on external sources to provide all the skills needed to form a national review or risk assessment body; and yet other countries may request a full risk assessment team from another country, regional grouping or international body. Such advice could be provided through an external service, which should also encourage the development of international expertise by inviting qualified local scientists to participate in the review process.

(e) No matter which option is selected by a country, it is necessary to build confidence in the system established and the results obtained.

The United Nations (UN) is an obvious system through which to coordinate a worldwide effort to ensure that all such work is preceded by an appropriate assessment of risks. The subject receives continuous attention in the various UN agencies and more specifically from the Informal UNIDO/UNEP/WHO/FAO Working Group on Biotechnology Safety.(8)

II. CODE OF CONDUCT

A. Purpose and Objectives

1. The objective of the Code is to:

(a) outline the general principles governing standards of practice for all parties involved in the introduction of organisms or their products/metabolites to the environment. Some sections of the Code may also be applicable to other phases of research and development;(9)

(b) encourage and assist the establishment of appropriate national regulatory frameworks, particularly where no adequate infrastructure presently exists;

(c) ensure that appropriate national authorities and institutions, distributors and users are informed or have access to information, thereby facilitating the safe use and handling of biotechnology products;

(d) encourage international governmental and non-governmental institutions, including funding organizations that provide incentives for the use of new biotechnology for development purposes, to require researchers or producers to follow the principles set out in this document;

(e) stimulate the development of mechanisms for cooperation and consultation between governments to ensure safe research, development, use, including environmental application, compliance with international

transport laws, and movement in commerce of the products of biotechnology;

(f) assist countries to ensure the safety of research, development, use and introduction by providing mechanisms to obtain consultation and advice as needed;

(g) stimulate the development of mechanisms for obtaining and disseminating information in a timely and efficient manner.

2. The document addresses the shared responsibility of many sectors of society, including individual governments, regional, supranational and international organizations, scientific researchers, institutions and societies, trade associations, industry, including manufacturers, formulators and distributors, users, and non-governmental organizations, such as environmental groups, consumers and trade unions, and funding institutions.

3. The document is designed to help industries, organizations and scientists seeking to facilitate, develop and apply biotechnology for social and economic improvement to be aware that their judgements and actions involving GMOs, if taken with adequate review and notification, will ensure public health and environmental safety and thereby promote and not jeopardize the long-term development of the technology.(10)

4. The document emphasizes the need and responsibility of all national authorities and other parties involved to ensure that the public is well informed.

5. It is intended that the Code will be broad-based, sufficiently comprehensive and transparent so that it will be widely acceptable. It should be sufficiently flexible to allow evolution over time to accommodate new advances, expertise and requirements. In addition to the existing general regulations for agricultural and pharmaceutical products, experience will also demonstrate whether there is a need for amendments to the regulatory approach specifically aimed at biotechnology products.

B. Scope

1. The scope of this document covers GMOs at all stages of research, development, use and disposal, while focusing on release to the environment. It covers, but is not limited to, genetically modified plants, animals (including, for example, insects, molluscs and fish), and microorganisms and their products and by-products.

2. The document is addressed to all those researching, developing, regulating or using the products of biotechnology in all countries.

3. This covers safety issues regarding public health and the environment.

C. The Code

1. General Principles

(a) Regulatory oversight and risk assessment should focus on the characteristics of the product rather than the molecular or cellular techniques used to produce it. While knowledge of the techniques is useful as it relates to properties conferred to the GMO, it is the GMO or related product to which humans, animals and the environment are exposed.(11)

(b) A primary research goal should be to work with well-characterized nucleic acid sequences and to know to the extent feasible all sequences transferred to the modified organisms to be released to the environment.

(c) The level of potential risk identified based on the biological properties of the modified organisms and its receiving environment will determine the type and detail of the information required from the researcher/proposer.

(d) The safety precautions and monitoring procedures specified should be appropriate to the level of assessed risk.(12)

(e) National authorities, industry and researchers have a responsibility to disclose or make available safety information to the public. Acceptance of biotechnology products will be enhanced if the information is disclosed and made available to the public, especially the community where the test will occur. There is a need for openness in this process.(13)

(f) Unexpected or adverse public health or environmental impacts related to the release of a GMO should be reported to the appropriate national and international authorities.

(g) Key aspects of risk assessment should include the biological and reproductive properties of the organism, the characteristics imparted by the genetic modification and the relevant attributes of the site where the organism is to be used.

(h) Risk assessment/evaluation must be based on sound scientific principles, requiring participation of experts from appropriate disciplines.(14)

(i) Evaluations of risk should be conducted at each step of development from the research laboratory to small-scale and large-scale release for production and testing, and finally to commercial use. Evaluations at each stage should be built on those made at prior stages, and need not always be conducted *de novo*.

(j) The systems developed for review of proposal applications must remain flexible and capable of being adapted in accordance with the latest scientific information.

(k) While national authorities have primary responsibility for ensuring review and making decisions concerning biotechnology activities carried out within their countries, regional cooperation will be desirable and sometimes essential.

(l) Information on anticipated consequences, which may extend beyond the country immediately involved, will need to be provided. In this case formal notification and relevant information should be provided to the country or countries which may be affected.

2. Actions and Responsibilities for Governments

(a) Every member country should designate a national authority, or authorities, to be responsible for handling enquiries and proposals, i.e., all contacts concerning the use and introductions of GMOs. More than one authority may be appropriate to cover specific areas of use of biotechnology; for example, pharmaceuticals, foods, agriculture and pesticides.(15)

(b) As a starting point in implementing this code countries should examine their existing mechanisms for review and risk assessment to determine if they are suitable for ensuring the safe use of GMOs, both for human health and the environment.(16)

(c) Risk assessment and scientific reviews should be carried out by scientifically competent bodies independent of the researcher/proposer. Competent review bodies should be established on a national basis by the designated authority or authorities. Since risk assessment requires high level, multidisciplinary scientific competence, it may be necessary to call on expertise from outside the country. Nonetheless, decisions regarding the safety of GMOs are the responsibility of the country involved.

(d) Case-by-case evaluation should be the rule unless sufficient experience and an adequate body of knowledge is gathered to allow classifications and generalizations based on experience and conclusions regarding the behaviour of GMOs.(17)

(e) The national authority or authorities should establish mechanisms to facilitate the collection, storage and dissemination of data on local conditions, such as agronomic and environmental data.

(f) The national authority or authorities should ensure that for each proposed use or release there is appropriate compliance with the safety conditions set down as a result of the risk assessment. This should include any appropriate control or mitigation procedures as well as procedures for termination of the experiment and waste disposal.

(g) The national authority or authorities should ensure that the researcher/proposer has suitable monitoring protocols in place. In addition, the national authority may wish to undertake additional monitoring of the GMO, the site or the surrounding environment beyond that which is necessary as part of the experimental protocol.

(h) While ensuring maximum disclosure of information necessary for risk assessment and safety, the recognition of, and respect for, confidential business information is essential.

(i) When an introduction of an organism is planned, the national authority or authorities should ensure that the local community is informed prior to the release. In addition, the national authority or authorities in collaboration with its (their) scientific advisory bodies and the researcher/proposer should provide appropriate educational material.

(j) The national authority or authorities should ensure public access to information on which decisions regarding the use or release of organisms are taken.

(k) Member countries should establish mechanisms for exchanging information with other interested countries, particularly those in their geographic region.

(l) The designated authority or authorities should also be responsible for ensuring that the principles set out in this document are being implemented. As a confidence building procedure, countries may wish to seek outside review of their implementation of the principles set out in this document.

(m) When informed about an unexpected or adverse public health or environmental impact related to the release of a GMO, the national authority or authorities should report relevant information to the appropriate international organizations.(18)

3. Responsibilities of the Researcher/Proposer

(a) Researchers should take into account for environmental introduction of GMOs:

- the characteristics of the organism(s) used, including theintroduced gene, genetic materials and gene products;
- the characteristics of the site and the surroundingenvironment;
- appropriate conditions of the release, including confinement, control, mitigation, termination and disposal procedures as required.

(b) The researcher/proposer has the responsibility for conducting evaluations of potential risks at appropriate stages of research and development of an organism prior to its formal review or assessment.

(c) Records should be kept and securely maintained on all activities involving GMOs. Documentation should include the description and location of each activity, protocols for carrying them out, the results, monitoring data and any other pertinent information.

(d) The researcher/proposer should notify or obtain approval from the responsible national authority or authorities prior to the conduct of an activity involving the release of a GMO.

(e) If an unexpected or adverse public health or environmental impact occurs related to the release of a GMO the researcher/proposer should notify and provide relevant information to the appropriate national authority or authorities.

(f) The researcher/proposer should disclose all relevant information to the responsible national authority or authorities. Details of specific approvals and refusals of all trials and applications, including those in other countries, granted or denied, should be included in any new application.(19)

(g) When a country does not yet have a designated national authority or a suitable scientific review body, the researcher/proposer has an obligation to inform the government authorities in the areas having the closest corresponding responsibilities, for example, health ministries for pharmaceutical applications and agriculture ministries for crops and livestock. The researcher/proposer should suggest alternative review mechanisms to enable the government involved to obtain access to competent and independent scientists able to provide unbiased and scientifically sound risk assessment. In this case the risk assessment effort should include consultation with the appropriate international organizations.

A recommendation for a mechanism to this effect in the form of establishment of an international biosafety information network and advisory service is set out in the Annex below. Once this service or an equivalent international mechanism is in place, the researcher/proposer should, in consultation with the government involved, contact the service for appropriate advice.

D. Existing Regulatory Provisions and Guidelines

To facilitate international cooperation in biosafety and to help countries that do not have regulatory mechanisms, a list of a number of documents reflecting existing approaches is given in the Appendix.

ANNEX

RECOMMENDATION TO ESTABLISH AN INTERNATIONAL BIOSAFETY INFORMATION NETWORK AND ADVISORY SERVICE

Recognizing that an international mechanism is needed in the field of biosafety for advice to countries that may require it, it is proposed that the UN system shall establish an international biosafety information network and advisory service. This will handle requests for advice and questions about the assessment of proposals as rapidly as possible and also arrange for appropriate help. Such a service will be of particular help to developing countries. An important area of its activities will be concerned with the release of organisms into the environment.

A. Role of the Service

1. The service shall, on request, provide advice to assist in working towards the setting up of a designated national authority/authorities, in each country to provide a national point of contact. All contact shall be through, or at least with the knowledge of, such authority/authorities. The service may also help countries on request to ensure that they have the means to conduct assessments. The national authority/authorities will make requests for whatever assistance is desired. In some cases, the national authority/authorities may wish to request assistance directly from certain experts or from another country or group of countries; when this is the case, the service will play a coordinating and facilitating role. It will be responsible for ensuring that products or projects are assessed and that its decisions based on these assessments, and any others, are enforced.(20)

2. The service shall have access to sufficient multidisciplinary expertise to be accepted as competent to share information with national and international advisory and/or regulatory bodies. It shall have sufficient links with national authority/authorities and scientific advisory bodies. It shall gather information on what projects have been or are being assessed worldwide. Where possible, it should attempt to compile information on the assessment procedures used and the controls of experimental conditions imposed. Such information shall be made widely available in order to facilitate future assessments at the national, regional or international levels.(21)

3. The service shall provide assistance to national authority/authorities on request to facilitate the implementation of the principles set out in this document.

4. As requested, advice and technical assistance shall be provided on monitoring the environmental impacts associated with the use of organisms.

5. The primary function of the advisory service is to provide assistance to assess health and environmental safety of a proposed application. It is not to provide an assessment of need, cost effectiveness, or of risk/benefit.

6. The service shall take into account developments in new assessment methods or approaches, as well as the work of national, regional and international organizations aimed at harmonization.

B. Organization of the Service

1. *A scientific steering committee*. The function of the steering committee will be to facilitate access to the latest scientific and technological knowledge in the relevant fields. It will also provide overall guidance to

the service. It should be made up of a panel of recognized scientists selected to represent appropriate disciplines and regional perspectives.

2. *A small technical/administrative secretariat*. It will be responsible for the day-to-day operation of the service. Its duties will include the servicing of the steering committee, liaising with different authorities, collecting and distributing relevant information, and with the advice of the steering committee, setting up *ad hoc* panels of experts as needed.

3. UNIDO should take the lead, in consultation with the Informal UNIDO/UNEP/WHO/FAO Working Group and other international organizations, in setting up an international biosafety information network and advisory service.

4. As a starting point, the service should conduct an international survey to identify existing expertise in the various scientific disciplines required for the safety assessment of biotechnology use. At a minimum, this should result in the development of an international directory of experts with names, areas of expertise, telephone and telefax numbers.

5. Sufficient funding will be necessary to enable the service to carry out these duties. Expenditures will include those associated with meetings of the scientific steering committee, the salaries and operational expenditures for the secretariat, and travel-related expenditure for experts.

APPENDIX

AVAILABLE LIST OF AUTHORITATIVE STATUTES AND GUIDELINES

The following information has been compiled by the Informal UNIDO/UNEP/WHO/FAO Working Group to facilitate dissemination of information regarding international legislation in biosafety. The information on applicable statutes and guidelines has been provided by national and international regulatory authorities and is therefore illustrative and not comprehensive. It has been reproduced without formal editing.

The list will be expanded as additional information is received and its contents will be regularly updated to keep pace with evolving international and national biosafety legislation.

Guidelines, Recommendations and Rules on Genetic Engineering

Australia: Genetic Engineering

- Guidelines for the preparation and presentation of applications for general marketing of monoclonal antibodies for use in humans, May 1988.
- Procedures for the assessment of the planned release of recombinant DNA organisms, May 1987.
- Guidelines for small-scale genetic manipulation work, 1989.
- Guidelines for large-scale work with genetically manipulated organisms, 1990.
- Guidelines for the preparation and presentation of applications for general marketing of monoclonal antibodies for use in humans, May 1988; Australian Drug Evaluation Committee, Department of Community Services and Health, GPO Box 9848, Canberra, ACT 2601.
- Australian Code of Good Manufacturing Practice for Therapeutic Goods – Medicinal Products, draft of January 1990; Therapeutic Goods Administration, Department of Community Services and Health, P.O. Box 100, Woden, ACT 2606.
- NDF four guidelines for preparing applications for the general marketing or clinical investigational use of a therapeutic substance; Therapeutic Goods Administration, Department of Community Services and Health, P.O. Box 100, Woden, ACT 2606.
- Code of Good Manufacturing Practice for Therapeutic Goods, May 1983; National Biological Standards Laboratory, P.O. Box 462, Canberra. ACT 2601.
- Australian Code of Practice for the Care and Use of Animals for Scientific Purposes (1990); National Health and Medical Research Organisation and Australian Agricultural Council, Australian Government Publishing Service, Canberra, ISBN 0-644-03737-7.
- The NH and MRC statement on human experimentation and supplementary notes, 1987; National Health and Medical Research Council, Department of Community Services and Health, Canberra, ACT 2601.
- Ethical Aspects of Research on Human Gene Therapy. Report to the NH and MRC by the Medical Ethics Committee, 1987; National Health and Medical Research Council, Commonwealth of Australia, ISBN 0-644-06623-7.
- Laboratory Biosafety Guidelines, September 1986; AIDS Task Force, P.O. Box 100, Woden, ACT 2606, ISBN 0-644-05315-1.
- Infection Control Guidelines – Acquired Immune Deficiency Syndrome (AIDS) and Related Conditions; AIDS Task Force, P.O. Box 100, Woden, ACT 2606, Commonwealth of Australia, 1988, ISBN 0-644-05021-7.

- Requirements for Clearance of Agricultural and Veterinary Drugs – Regulatory Control of Veterinary Drugs, document PB 2374A, 1983; Department of Primary Industry, Pesticides Section, Australian Government Publishing Service, Canberra.

- Australian Standard 2243: Safety in Laboratories:
  Part 1, 1982 – General
  Part 3, 1985 – Microbiology; plus 1990 appendix

- Australian Standard 2252: Biological Safety Cabinets:
  Part 1, 1981 – Biological Safety Cabinets (class I)
  Part 2, 1985 – Laminar Flow Biological Safety Cabinets (class II) for Personnel and Product Protection, ISBN 0-7262-3627-6.

- Australian Standard 2647: "Biological Safety Cabinets: Installation and Use", 1983.

- Australian Standard 1095: Microbiological Methods for the Dairy Industry.

- Australian Standard 1132-1973: Methods for Testing of Air Filters for Use in Air Conditioning and General Ventilation, ISBN 0-7262-0095-6.

- Australian Standard 1386-1989: Cleanrooms and Clean Workstations, ISBN 0-7262-5689-7; 5691-9; 5692-7; 5693-5, 5694-3; 5695-1.

- Australian Standard 1766: Methods for the Micro-biological Examination of Food.

- Australian Standard 1807-1989: Cleanrooms, Workstations and Safety Cabinets – Methods of Testing.

- Australian Standard 2013-1989: Cleanroom Garments, ISBN 0-7262-5686-2 and 5687-0.

Information available from:

Secretary
Genetic Manipulation Advisory Committee
Department of Administrative Services
P.O. Box 2183
Canberra, ACT 2601

Austria

- NIH Guidelines translated and adapted for Austria.

- Act on Contained Use and Deliberate Release of Genetically Modified Organisms into the Environment (first draft April 1991).

Belgium: Applied and Existing Regulationsin connection with Genetic Engineering

- Waste Regulation, Decree of 5.7.1985 (B.S.14.12.1985)

- Waste Water Regulation, Decree of 26.3.1971 (B.S.1.5.1971)

- Air Regulation under Law of 28.12.1964 (B.S.14.1.1965)(controlled by the National Health Authority)

- Royal Regulation of 6 June 1960 on the Production, Distribution and Marketing of Drugs and their application, inclusive of all Additional Regulation until September 1988

- Regulation concerning plants at risk (Etablissement incommodes, dangereux, insalubres)

- Regional building regulations (also regulate waste water problems) (Code wallon d'urbanisme et d'amenagement du toirie)

- Construction regulations for construction companies in Brussels, 3000 pages volume (Union des entreprises de Bruxelles)

- Regulation for the protection of workers (Réglement général pour la protection du travail)

- General regulations concerning chemical plants, drugs group (Fédération des Industries Chimiques, Groupement Médicament)

Brazil

Biosafety Guidelines for the National Programme of Science and Technological Development (PADCT/Biotechnology). The programme is financed by an agreement between the Brazilian Government and the World Bank.

Canada: General Guidance Documents

- Guidelines for the Registration of Genetically Modified Micro-organisms (GMMs), in preparation for 1991. **Agriculture Canada**

- Guidelines for the Registration of Naturally Occurring Micro-organisms (NOMs), 1990. **Agriculture Canada**

- Requirements for Field Trials of Naturally Occurring Microbial Pest Control Agents, 1990. **Agriculture Canada**

- Guidelines for Field Trials of Genetically Modified Micro-organisms, Registration of Microbial Pesticides and Pest Control Agents, in preparation for 1991.

- Guidelines for the Handling of Recombinant DNA Molecules and Animal Viruses and Cells. MedicalResearch Council of Canada, 1989

- Guidelines for the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology. **Health and Welfare, 1990**

- Guidelines for the Regulation of Veterinary Biologics produced by Biotechnology

- Regulation of Plant Biotechnology, Part 2: Environmental release of genetically altered plant material

Applied and Existing Regulations in Connection with Genetic Engineering

- Health of Animals Act and Regulations
- Fertilizer Act and Regulations
- Pest Control Products Act and Regulations
- Guidelines for the Registration of Microbial Pesticides
- Feeds Act and Regulations
- Seeds Act and Regulations
- Canadian Environmental and Protection Act and Regulations
- Environmental Contaminants Act and Regulations
- Food and Drugs Act and Regulations
- Hazardous Products Act and Regulations

China

The Institute of Genetics and the Chinese Academy of Agricultural Sciences have advised that no guidelines have been established for surveillance of GMOs, as this field has as yet undergone little development in China. However, a quarantine system is operated by the Animal Drug Administrative Division of the Bureau of Animal Husbandry, Ministry of Agriculture in Beijing, which also handles the registration of veterinary products. Pharmaceuticals are registered by the State Pharmaceuticals Administration of China, also in Beijing. The Ministry of Labour administers laws relating to health and safety at work that would apply to the fabrication of biotechnology products. Patent protection is afforded to microorganisms and provides for plant variety rights.

Russian Federation: Genetic Engineering

Many guidelines covering the release of genetically modified organisms into the environment

CSFR: Applied and existing regulations in connection with Genetic Engineering

- Decree on Protection Against Pests, Plant Diseases and Weeds within Import (No.63/1964 of Col. in working of No.51/1977 of Col.)
- Act on Protection of Agricultural Soil Fund (No.53/1966 of Col. in working of the Act No.75/1976 of Col.)
- Act on Water Management State Administration (No.130/1974 of Ccl. and No.135/1974 of Col.)
- Water Act (No.138/1973 of Col.)
- Act on Provision Against Air Pollution (No.35/1967 of Col.)
- Decree on Creation and Protection of Healthy Living Conditions (No.45/1966 of Col.)
- Guidelines for the Handling of Recombinant DNA Act on Health Care (No.20/1966 of Col.)
- Labour Act (No.65/1965 of Col.)
- Act on Technical Standardization (No.96/1964 of Col.)
- Decree (No.62/1964 of Col.)
- Act on Plant Production (No.61/1964 of Col.)
- Act on State Technical Supervision Regarding Safety or Work
- Decree on Ground and Underground Waters
- Directives on Hygienic Services

Denmark: Genetic Engineering

Environment and Genetic Engineering Law, June 1986 (Act No. 288 of 4 June 1986)

Information available from:

The National Agency for Environmental Protection The Biotechnology Office
Strandgade 29
DK-1401 Copenhagen K

Att: Kaj Juhl Madsen

Finland: Applied and Existing Regulations in connection with Genetic Engineering

- The Law on Pesticides
- The Law on Infectious Diseases
- The Law on Water

- The Law on Air Protection
- The Law on Waste Management

France: Genetic Engineering

- Note No.86-32 of 19 September 1986 concerning installations classified under the protection of the environment (Ordonnance of 30 July 1985, chapter 58-11: installations necessitating microorganisms)
- Manual of good research practices and "field testing" (development under natural conditions, reproduced in a laboratory) of transgenic plants (class 1)

Germany: Genetic Engineering

- Law for the Rregulation of Genetic Engineering matters, 1990
- Gene Technology Record Keeping Ordinance, 1990
- Gene Technology Safety Ordinance, 1990
- Gene Technology Consultation Ordinance, 1990
- Procedural Ordinance relating to Gene Technology, 1990
- Environment and Genetic Engineering Law, June 1986 (Act No. 288 of June 1986)
- Rule for the *in vitro* Recombination of Genetic Material, 1986
- Rules and Regulations for Safety in Biotechnological Research and Production
- Genetic Engineering Safety Directive
- Directive concerning the Central Commission for Biological Safety
- Genetic Engineering Hearings Directive
- Genetic Engineering Procedures Directive
- Directive concerning written documentation about genetic works for research or for commercial purposes

Information available from:

Bundesministerium fuer Gesundheit (BMG)
Referat 333 Gentechnologie
Postfach 20 02 29
5300 Bonn 2

Tel: (0228) 941-0

Hong Kong

The Government of Hong Kong has neither guidelines nor laws for surveillance of GMOs. Vaccines and pharmaceuticals for human and veterinary use are controlled via the Pharmacy and Poisons Ordinance (Cap 138), and each consignment from overseas requires an import licence. All importations of biological materials, including live bacterial cultures and disease-causing organisms, require permits that are issued by the Port Health Office of the Department of Health.

Hungary

Two EC Directives have been translated and adapted to Hungarian law. These will be presented to Parliament for adoption by the end of 1991 (90/219/EEC and 90/229/EEC)

India: Genetic Engineering

- Recombinant DNA Advisory Committee, Department of Biotechnology: Safety Guidelines for the Genetic Engineering Research
- Recombinant DNA Safety Guidelines and Regulations
- Release Approval Committee: Environmental Protection Act Notification

Information available from:

Dr. K. Narayanaswami
Director
Department of Biotechnology
Block 2, 7th Floor, CGO Complex
Lodhi Road
New Delhi 110 003

Indonesia

At present there are no guidelines for GMOs, but the existing regulations, administered by the Ministry of Health for the safety of production and efficacy of products, could be used to control GMOs. The Ministry of Justice controls the patents on GMOs as well as plant variety rights. Quarantine is controlled by the Ministry of Agriculture and pollution is controlled the State Ministry for Population and Environment.

Ireland: Genetic Engineering

Guide to Recombinant DNA Regulation on Ireland, June 1987: Application of NIH Guidelines (May 1986, Definition of Recombinant DNA Molecules) and other existing regulations in connection with the release of genetically modified organisms, as:

- Water Pollution Act, 1977
- The Dangerous Substances Act, 1972

- Destructive Insects and Pests (Consolidation) Act, 1958

- Council Directive 77/95/EEC on Protective Measures against the Introduction into the Member States of Harmful Organisms of Plants or Plant Products

Japan: Genetic Engineering

- Guidelines for the Application of Recombinant DNA Organisms in Agriculture, Forestry, Fisheries, Food Industry and Other Related Industries, December 1986

- Guidelines for Recombinant DNA Experiments, 1983

- Guidelines for Manufacture of Drug Products by Application of Recombinant DNA Technology

- Guidelines for Industrial Application of Recombinant DNA Technology

- Guidelines for Fieldtesting of Genetically Engineered Plants

Information available from:

Mr. R. Higashiuchi
Deputy Director
Ministry of Health and Welfare
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Mr. H. Hiramatsu
Director
Bio-industry Office
Ministry of International Trade and Industry
Tokyo

Dr. T. Takahashi, M.D.
Director
Life Science Division
Science and Technology Agency
Tokyo

Dr. S. Tsuru
Secretariat
Council of Agriculture, Forestry and Fisheries
Tokyo

Prof. H. Uchida
Advisor
University of Tokyo
Tokyo

Korea

Although no guidelines for GMOs exist at present in Korea, the Director General for Livestock in the Ministry of Agriculture, Forestry and Fisheries will administer them once they are implemented. The same Ministry is responsible for all quarantine matters and for registering veterinary products. Pharmaceuticals are registered under the Pharmaceutical Laws administered by the Ministry of Health and Social Welfare. The Industrial Office of the Ministry of Trade and Industry oversees all patents, and it is considered that this power would enable plant varieties and GMOs to be protected.

Latin America

Guías para el Uso y la Regularidad de las Técnicas de Ingeniería Genética o Tecnología del ADN Recombinante (Guides for the Use and Safety of Genetic Engineering Techniques or Recombinant DNA Technologies). IICA, 1988, 151 pp.

Malaysia

There are no guidelines at present for GMOs, but the import of all biological materials to Malaysia is controlled by the Plant Quarantine Regulations (1981), administered by the Department of Agriculture. The Ministry of Health is responsible for the control and registration of all pharmaceuticals, drugs and vaccines. At present there are no regulations for health and safety at work, nor patent protection for GMOs or plant variety rights.

Netherlands: Genetic Engineering

- Resolution of 25 January 1990 for the Preparation of a General Directive Concerning the Existing Article 24 of the Law on Environmentally Hazardous Materials

- Guidelines for Environmental Applications with Genetically Modified Organisms

New Zealand: Genetic Engineering

- Recommendations for the control of field testing and release of genetically modified organisms in New Zealand, February 1987

- Until a relevant rule will be passed, the Interim Assessment Group for the Field Testing and Release of Genetically Modified Organisms (Section 33 of the Environment Act) will exercise this control function, 1990

Information available from:

Dr. Lin Roberts
Ministry for the Environment
84 Boulcott Street
PO Box 10362
Wellington

Norway

Environment and Genetic Engineering Law (in preparation for 1992)

Philippines

Executive Order No. 430, series of 1990, established by the National Biosafety Committee

Information available from:

The Chairman
National Biosafety Committee
Department of Science and Technology
Bicutan, Taguig
Metro Manila

Tel: 632 822 0961 to 67

Singapore

In Singapore, permits to import live organisms are issued by the Commissioner of Public Health through the Infectious Disease Act. The Ministry of Health administers the Medicines Act, which provides for the registration, safety and efficacy of pharmaceuticals, while the Veterinary Division of Primary Production deals with veterinary products. Safety at work is enforced by the Ministry of Health. Patent protection is based on the model of UK patent laws, but Singapore is currently preparing its own patent law for this area and for a Plant Variety Act.

Sweden

- AFS 1988:12. Occupational Guidelines for the Use of Microorganisms
- SFS 1988:534. Animal Protection Law. Gives the Government the right to ban or set criteria for developing or using genetically modified animals
- SFS 1989:492. Amendment to Plant Protection Law (1972:318). Gives the Government the right to ban or set criteria for developing or using genetically modified plants and genetically modified micro-organisms used in conjunction with plants
- SFS 1990:34. Governmental decree requiring a permit for growing genetically modified plants in greenhouse experiments or field tests. Administrative responsibility for issuing permits rests with the National Board of Agriculture after obligatory consultation with the Environmental Protection Agency and the Recombinant DNA Advisory Committee
- SFS 1991:114. Law on Selected Use of Genetic Screening in Healthcare
- SFS 1991:115. Human Embryo Research Law
- SFS 1991:116. Amendment to Law on Healthcare Worker Supervision (1980:11). Refers to specific rules regarding legal action if Law SFS 1991:115 is not followed
- Proposed law on pre-market risk assessment of biological pesticides (non-modified as well as genetically modified)

Switzerland: Genetic Engineering

- Ordinance on the prevention of major accidents, April 1991
- Federal Law Relating to the Protection of the Environment (revision in preparation)
- Guidelines for the safe use of genetically modified organisms, SKBS/SGGB 1991

Taiwan Provine of China

- Guidelines for Research Involving Recombinant DNA Molecules (1978)
- Law on Animal Drugs

Information available from:

Mr. Yong-Da Fan
Department of Biological Sciences
Council of National Sciences
Executive Academy
Building 21, 106 Section
2 Heping (East) Road
Taipei 10636

Thailand: Applied and existing regulations in connection with Genetic Engineering and Biotechnology

- Plant Quarantine Act B.E. 2507 (1964)
- Poisonous Article Act B.E. 2510 (1967) amended B.E. 2516 (1973)
- Animal Disease Control Act B.E. 2505 (1962)
- Animal Pathogen and Toxin Act B.E. 2525 (1985)
- National Environmental Quality and Protection Act B.E. 2518 (1975)
- Patent Law B.E. 2522 (1979)
- Copyright Law B.E. 2521 (1978)

United Kingdom: Genetic Engineering

Code: Genetic Manipulation Regulations (1989) (for revision); EC Directives 90/219 and 90/220 also apply.

Advisory/Regulatory Bodies: Health and Safety Executive (HSE); Advisory Committee on Genetic Modification (ACGM); Advisory Committee on Releases to the Environment (ACRE).

Coverage of Code: Construction of GMOs; use of a cell or organism constructed by genetic manipulation, including use at large-scale; intentional introduction of GMOs into the environment.

The regulations are supplemented by several Notes of Guidance:

1. Construction of recombinants containing potentially oncogenic nucleic acid sequences

2. Disabled host/vector systems

3. Intentional introduction of GMOs into the environment

4. Health surveillance

5. Eukaryotic viral vectors

6. Large-scale use of GMOs

7. Categorisation of genetic manipulation experiments

8. Laboratory containment facilities

9. Transgenic animals

10. Plants and plant pests

11. Genetic manipulation safety committees

Codes for related areas:

- Control of Substances Hazardous to Health (1988) Regulations
- Health and Safety (Dangerous Pathogens) Regulations (1990)
- Environment at Protection Act (1990)

Applied and Existing Regulations in Connection with Genetic Engineering

- Food Act, 1984 (In Scotland, the Food and Drugs (Scotland) Act, 1956)
- The Animal Health Act, 1981
- The National Biological Standards Board (Functions) Order, 1976
- The Biological Standards Act, 1975
- Health and Safety at Work etc. Act, 1974
- Agriculture Act, 1970
- Medicines Act, 1968
- The Plant Health Act, 1967

Information available from:

Health & Safety Executive
Branch MDA3
Baynards House
1, Chepstow Place
Westbourne Grove
London W2 4TF

Tel: 071-243-6000

USA: Genetic Engineering

- USDA Guidelines for Research with Genetically Modified Organisms Outside Contained Facilities, 1 February 1990
- Final Rule, 52 FR 22882-22914, 16 June 1987
- Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, 31.07.1990, Office for Science and Technology Policy in the White House (OSTP)
- NIH Guidelines for Research Involving Recombinant DNA Molecules, 1987
- Co-ordinated Framework for Regulation of Biotechnology: announcement of policy and notice for public comment (**Federal Register**, 26 June 1986, Part II)
- Animal and Plant Health Inspection Service: Plant Pests: Introduction of Genetically Engineered Organisms or Products

Applied and existing regulationsin connection with Genetic Engineering

- Toxic Substances Control Act (TSCA)
- Plant Pest Act
- Virus-Serum-Toxin Act
- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- Food, Drug, and Cosmetic Act
- ASEAN [Association of Southeast Asian Nations (Brunei Darussalam, Indonesia, Malaysia, Philippines, Singapore, Thailand)]
- ASEAN Guidelines for the Introduction of Biological Control Agents, 1989
- ASEAN Ministerial Understanding on Plant Quarantine Ring, 1982

European Community: Genetic Engineering

- Council Directive of 23 April 1990 on the Contained Use of Genetically Modified Micro-organisms (90/219/EEC)
- Council Directive of 23 April 1990 on the Deliberate Release of Genetically Modified Organisms into the Environment (90/229/EEC)
- Council Directive on the Protection of Workers from the Risks Related to Exposure to Biological Agents at the Work Place (90/.../EEC)

OECD (Organization for Economic Cooperation and Development): Genetic Engineering

- Recombinant DNA Safety Considerations: Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques, 1986
- Safety Considerations for the Use of Genetically Modified Organisms: Elaboration of Criteria and Principles for Good Industrial Large-scale Practice (GILSP) and Good Development Principles (GDP): Guidance for the Design of Small-scale Field Research with Genetically Modified Plants and Micro-organisms, 1991
- BIOTRACK: The Computerized OECD Pointer System on the Use of Genetically Modified Organisms, 1991
- International Survey on Biotechnology Use and Regulations, OECD Environment Monograph No. 39, 1990

Information available from:

Recombinant DNA Safety Considerations
OECD Publications
2 rue André-Pascal
F-75775 Paris

UNEP (United Nations Environment Programme)

Ecological Impacts of Introducing Novel Organisms into the Environment (1986)

WHO (World Health Organization)

- Strategies for Assessing the Safety of Foods Produced by Biotechnology, 1991
- Guidelines for Assuring the Quality of Medicinal Products Prepared by Recombinant DNA Technology. Technical Report Series, 1991
- Laboratory Biosafety Manual, 1983 (Second edition in press)

ANNOTATIONS

1. The Document was initially drafted by 20 experts representing academia, industry, governments from developed and developing countries and international organizations, at a meeting held at UNIDO headquarters, Vienna during 6-9 March 1991. The draft was further discussed and finalized at a meeting convened at the International Centre for Genetic Engineering and Biotechnology (ICGEB) during 8-10 July 1991 by some 30 experts with greater representation from the developing regions. Among the participants present at the meetings were representatives from Argentina, Austria, Belgium, Brazil, Canada, Costa Rica, China, Denmark, Germany, India, Italy, Kenya, Mexico, Philippines, Sudan, Thailand, UK, USA; industry (Ciba-Geigy AG and Monsanto) and international organizations (OECD, UNCED, UNIDO and WHO).

The objectives of the document are to define responsibilities and establish voluntary standards of conduct for all those involved in the safe handling and use of GMOs and to derive maximum benefits from their application to the environment without significant adverse effects on people and the environment. As these are in general on similar lines to those set forth to codes of conduct in other areas (e.g. FAO's International Code of Conduct on the Distribution and Use of Pesticides), the document was given its present title.

There was considerable discussion by the experts on this title. They were confident that all the major components of a code of conduct are contained in the document and felt that it serves as a basis for the development of more comprehensive application-specific codes.

2. The genetic modification may be induced in an organism through modern biotechnologies such as cell fusion and microinjection. The ability to create new genetic strains at will in a predictable manner with speed and precision is made possible by advances in recombinant DNA (rDNA) or "gene splicing" techniques. Using these techniques, scientists have made it possible to incorporate desirable hereditary traits into genomes of a variety of organisms such as microorganisms, plants and animals. Moreover, advances in this field provide an unlimited range of possibilities for the transfer of genetic material between life forms. Genetically modified organisms are finding numerous applications, among which are: control of pests and weeds; bioremediation; leaching of mineral ores; development of plants with increased pest and herbicide resistance, improved nutritive value and tolerance to drought and other environmental stresses; coal desulphurization and enhanced oil recovery.

3. During 1983 to 1989, the US Environmental Protection Agency (EPA) reviewed over 50 biotechnology products with a similar number of recombinant

plants proposed to the Department of Agriculture (USDA) for field testing. As of 1991, over 300 proposals for field testing of genetically modified organisms have been approved by regulatory authorities for testing, thus registering a five-fold increase in the USA alone. When combined with those approved in other OECD countries, the figure reaches about 500, the majority of which are crop plants for agricultural uses. Outside the OECD, there is only anecdotal information on releases of GMOs (personal communication from OECD).

4. Basically, the code attempts to bring about a certain degree of harmonization of available biosafety guidelines and lays down the minimum commonly accepted principles to be adopted in connection with the release of GMOs into the environment. It draws on existing directives and regulations and does not intend to develop new concepts. It stipulates general principles and obligations for those involved in release of GMOs and aims at promoting biotechnology innovations and their applications in an ecologically sustainable manner. It has been framed in such a manner that more specific guidelines could be built up from it for specific products or applications. Thus the document could serve as a basis for specific guidelines for the review of biotechnology products.

5. Concern for the accidental release of GMOs from the laboratory into the environment began in the 1970s and resulted in the Asilomar conferences in 1975, forming a basis for the development of safety guidelines. The phenomenal advances in recombinant DNA (rDNA) technology resulted in tailoring the genomes of organisms with desirable hereditary traits. The enormous potential that these organisms provide for the benefit of humankind and industry often warrants their release into the environment. Although to date no untowards effects are obvious from the over 500 field releases that have already taken place, public perceptions indicate caution against potential risks to the ecosystems and the environment and thus call for some type of oversight to ensure the safe application of GMOs.

Among the biosafety concerns expressed are that the GMOs may bring about harmful effects, such as the colonizing of natural habitats; interaction with native microbes in established ecosystems and thereby leading to their disruption; inducing non-conventional virus resistance mechanisms; and transferring traits such as herbicide resistance to weeds.

The GMOs are not bound by political boundaries but are governed by ecological barriers. In environmental applications a myriad of non-human species are exposed to the released organisms and the effects of such releases on the structure and function of the ecological communities are not entirely predictable. Therefore the consensus of regulatory authorities has in general been to strike a balance between risks and benefits, and formulate risk-based biosafety regulations with logical reasoning rather than by empirical methodology.

6. Many industrialized countries have instituted mechanisms for the regulation of biotechnology, although the approach to regulation varies from country to country. For example, in the USA different agencies are involved in regulation, such as the Environment Protection Agency (EPA), the Food and Drug Administration (FDA) and the Department of Agriculture (USDA), depending on the product and purpose of introduction. The regulatory policies appear less stringent compared to those of the EC, which has created a Community-wide body of regulatory legislation (Journal Officiel des Communautés Européenes, "Directives du Conseil, du 23 avril 1990, relative à la dissemination volontaire d'organismes génétiquement modifiés dans l'environnement", 90/220/CEE). The Community directives are mandatory for all Members as of October 1991. These restrictive regulations are likely to be reviewed as the countries gather more confidence based on global experiences on releases. In the UK, notification to the Health and Safety Executive (HSE) authority is required for release, including an assessment of risk by an HSE-approved method (GENHAZ, 1991). Many developed countries, such as Spain and Italy, have so far no biosafety regulations of their own and are apparently bound now by the EC directives.

Only a few of the more advanced developing countries have biosafety guidelines and these appear to be directed to contained uses. As per the directive of the Preparatory Committee of ICGEB (ICGEB/Prep.Comm./14/3), a questionnaire was prepared by UNIDO and circulated to some 40 ICGEB member countries to elicit information on their biosafety guidelines. An analysis of the responses received from some of these countries revealed that safety guidelines relating to research exist in some form or other in several developing countries including, for example, Mexico, Brazil and India. In regard to regulations relating to the release of genetically engineered organisms, most developing countries have none. Among the developing countries the Philippines has adopted certain guidelines and in Thailand there is a regulatory scheme that is decentralized and informal. India has developed detailed safety guidelines concerning research and large-scale applications of GMOs and their products (see Appendix). Most developing countries that responded to the questionnaire have, however, stressed the need to have some regulatory infrastructure. Such a regulatory structure not only provides safety in the applications of GMOs, but also ensures access to products of research for industrial development.

7. See for example regulations of the UK, USA, EC and OECD in the Appendix on contained uses of microorganisms.

8. The following developments with regard to the Code of Conduct should be noted

In 1985 UNIDO, WHO and UNEP organized an Informal Working Group on Biotechnological Safety to consider biosafety in relation to research institutions, industry and the environment. At that time the Working

Group took into account the work of its member organizations in the field of biotechnology, including the proposed establishment of the ICGEB and pressed for an active role for the UN organization in the study of actual and conjectural hazards, in developing a risk assessment methodology and in developing biosafety guidelines as it pertains to biotechnology. The Working Group convened five meetings between 1986 to 1991 to plan its activities and review progress of its work. Among others, it recommended the promotion of an international code of conduct and the establishment of an advisory group under UN auspices to assist countries, on request, in the assessment of releases of genetically engineered and exotic organisms into the environment, the establishment of an international database for information on releases of GMOs, the preparation of a biosafety manual and the development of biosafety training programmes. The present voluntary code of conduct is thus a result of the above mandate assigned by the Working Group.

Concurrently, other UN Organizations felt the need for a regulatory framework for the release of GMOs into the environment. The *Ad Hoc* Working Group of Legal and Technical Experts on Biological Diversity recommended that the third session of UNEP's Biodiversity Convention meeting (UNEP/Bio.Div/INC.3/Inf.2, 1991) take note of the activities of UNCED with regard to the development of a Code of Conduct on the release of GMOs. The first meeting of the Preparatory Committee of the UNCED (A/CONF.151/PC/WG.1/L.8, 1990) directed its Secretariat to "follow closely the work undertaken by the UNIDO/UNEP/WHO/FAO Informal Working Group on Safety in Biotechnology" with a view to facilitating the preparation of an internationbal code of conduct. Harmonization of safety procedures into a set of internationally acceptable guidelines, possibly in the form of a code of conduct, is under consideration by the UNCED as part of its AGENDA 21 programme (A/CONF.151/PC/42/Add.5, 1991). The Code developed by the UNIDO/UNEP/WHO/FAO Working Group has been brought to the attention of the UNCED at the third session of its Preparatory Committee meeting (A/CONF.151/PC/WG.1, 1991).

Furthermore, the Preparatory Committee meeting of the ICGEB at its 14th session (ICGEB/Prep.Comm./14/14, 1990), recommended that the ICGEB should, being the only international and intergovernmental institution dealing with genetic engineering and biotechnology, play an important catalytic role in enhancing awareness and in promoting the adoption of common biosafety guidelines among its member states. The subsequent meeting of the ICGEB Preparatory Committee at its 16th session (ICGEB/Prep.Comm./16/16, 1991), took note of this document and felt that it provided a good basis for international cooperation and also contained the essential elements that could be adopted in national biosafety regulations.

9. The Code envisages a thorough knowledge on the part of the researcher of the characteristics of the product, such as the sequence of the gene introduced and the biological and reproductive properties of the organism. In addition, the risk assessment should be done from the laboratory stage onwards and the researcher/developer should be equipped to handle unexpected adverse developments with confinement, control, mitigation, termination and disposal procedures. The researcher/developer should be aware of other competent scientific peers including environmental scientists to suggest to his authorities, if need be, for independent risk assessment of his product.

10. Biotechnology started as one of the most highly regulated industries. However, because of its enormous potential, the experts felt that the guidelines in the document should be designed so as to promote the industry within the context of product quality and safety to health and the environment. The following developments justify this view.

The total global sales of biotechnology products for the year 1991 were US$ 150 billion. Predictions of the size of the world market for biotechnology in the agricultural and food processing sector alone range from US$ 10 to 100 billion by the year 2000. Among the examples of various developments in agro-biotechnology in the year 1991, were the successful field testing of cotton plants possessing the toxin gene from *Bacillus thuringiensis* which confers resistance to lepidopteran insects; genetically engineered corn resistant to corn borer pest; tomato plants resistant to tobacco mosaic virus; and tomatoes with an antisense gene that delays ripening, thus extending shelf life.

Cognizant of the fundamental importance to economic growth, most countries are evolving policies to promote the long-term development of the biotechnology industry. The US Administration for example, recently announced a 7 per cent increase in Federal research funding for biotechnology in 1993 over the previous year. Japan has targeted worldwide primacy in biotechnology by the year 2000 as an industrial priority. Among the developing countries, Argentina, Brazil, Chile, Costa Rica, Mexico and Venezuela are reviewing patent protection and economic policies to encourage biotechnology development. Malaysia, Singapore and Thailand emphasize biotechnology as a source of future economic development (G.S. Burrill and K.B. Lee, Jr. Biotech '92: Promise to Reality. An Industry Annual Report, Ernst and Young, 1991).

11. The regulatory oversight of different agencies differs with respect to their focus on the product or the process by which the product is made. The policy guidelines of the USA affirm the product-based oversight assessing them on their inherent characteristics and intended use. In the key issues document dealing with "Introduction of Recombinant DNA-Engineered Organisms into the Environment", the US National Academy of Sciences generally agrees that an assessment of risks for introducing GMOs should be based on the nature of the organism and the environment into which it is to be introduced, not the method by which it was produced (National Academy of Sciences (NAS),

1987, National Academy Press). The EC regulatory policy, however, considers both the product as well as the process by which it is produced as subject to regulation. The experts, in preparing this document, decided to focus their attention on the product to which eventually the environment will be exposed. Product focus also facilitates regulation by existing agencies and statutes, and may avoid the need for introducing biotechnology specific legislation. However, information on the specific process is helpful, if not essential, for risk assessment.

12. For example, the UK Advisory Committee on Dangerous Pathogens (ACDP), in a 1984 publication, categorized pathogens into four hazard groups according to hazards and categories of containment. Similarly, the rDNA safety guidelines adopted by India (Department of Biotechnology, Ministry of Science and Technology, Government of India, 1990), summarizes biosafety levels corresponding to P1 to P4 facilities for work with rDNA techniques for the four risk groups categorized on the basis of the pathogenicity of organisms being handled. The document also outlines model safety guidelines stipulating three categories of research activities based on the nature of the organisms. The OECD in its documents, rDNA Safety Considerations (1986) and GILSP and GDP (1991), gives examples of containment approaches for large- and small-scale industrial applications (Appendix G).

13. The importance of making risk analysis data on releases available to the public has been stressed by the experts. Transparent policies by all concerned would go a long way in gaining public acceptance, which is a key element for the ultimate success of commercial biotechnology. Regulatory bodies play a critical role in gaining public confidence and trust in a product, by making the public aware of its safety information. Also, it is advisable to inform the public of a potential test and where possible give them the opportunity to comment.

14. Consideration should be given to include environmentalists, ecologists and social scientists, apart from molecular biologists, medical and agricultural scientists.

15. The following examples with respect to the UK, USA and India are illustrative of the responsible authorities.

In the UK, the Health and Safety Commission and Executive (HSC and HSE) have the responsibility for health and safety of workers engaged in biotechnology. The Health and Safety at Work etc., Act 1974 (HSW Act) covers biotechnology, including the application of rDNA technology. The Genetic Manipulation Regulations were adopted in 1989 following a report published by the Royal Commission on Environmental Pollution. Three sets of regulations have been made that concern biotechnology under the HSW Act, namely the Control of Substances Hazardous to Health (COSHH) Regulations 1988; the Genetic Manipulation Regulations 1989; and the Health and Safety (Dangerous Pathogens) Regulations 1990. It is anticipated that the Genetic Manipulations Regulations 1989, will be revised and that new regulations covering both manipulated and release will be issued in 1992/93. An assessment of risks by an HSE approved method, establishment of a genetic modification safety committee at each centre undertaking genetic manipulation, and notification to the HSE of intention to work with or transport certain dangerous pathogens, are part of the requirements of these regulations. In addition, the Advisory Committee on Genetic Manipulation (ACGM) advises the HSC and HSE on aspects of work activities relating to genetic manipulation.

The USA has three regulatory bodies: the Environmental Protection Agency regulates biotechnology under the Toxic Substances Control Act (TSCA), administered by the Office of Toxic Substances (OTS) and the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) administered by the Office of Pesticide Programs (OPP). The US Department of Agriculture (USDA) has responsibility for the safety of crop plants, food and fibre products operating through its three wings, namely, the Agriculture Research Service (ARS); the Food Safety and Inspection Service (FSIS) and the Animal and Plant Health Inspection Service (APHIS). The Food and Drug Administration (FDA) regulates biotechnology under the authority of the Food, Drug and Cosmetic Act (FDCA) and the Public Health Services Act (PHSA). In addition, the Occupational Safety and Health Administration (OSHA) has the responsibility for the health and safety of workers in the biotechnology industry. The OSHA was part of the group that published guidelines in the Federal Register (1984) coordinated framework.

India established four types of committees, namely: (1) Institutional Biosafety Committees (at institutions where the research is undertaken); (2) the rDNA Advisory Committee; (3) a Review Committee on Genetic Manipulation, which is inter-departmental and inter-institutional; and (4) a Genetic Engineering Approval Committee under the Department of Environment as a statutory body for the 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.

16. The developed countries having regulations are listed in the Appendix. In many cases these regulations do not specifically deal with biotechnology as such. They are thought to be adequate to cover biotechnology applications, e.g., quarantine regulations for exotics, etc. Other developed countries, having no guidelines of their own, are generally following those of the OECD, USA or EC. Issues related to biosafety figure less prominently in most developing countries, since most do not engage in research involving genetic engineering techniques. Also, the infrastructure for regulation in most developing countries is generally weak although many have regulatory bodies for food, pharmaceuticals, pesticides and safety at the work place. Experience in regard to controlling or regulating environmental impacts is limited or non-existent. Technical expertise is

lacking in many developing countries for the adoption of safety measures, either in research, manufacture or in risk assessment. Under these conditions, adoption of the guidelines proposed in this document assumes importance.

17. Safety issues on the application of GMOs have been the subject of intense debate in scientific circles. W. J. Brill (**Science**, 227: 381-384, 1985), concluded that the products of modern biotechnology are a continuum of traditional technologies, where microorganisms, including pathogenic ones, have been added to soils and plants to find beneficial uses, thereby implying genetic engineering research does not involve excessive risks. The US National Academy of Sciences (NAS) in a pamphlet published in 1987, stated that the risk associated with the introduction of genetically engineered organisms carrying rDNA are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods. However, ecologists are of the view that the phenotype of a microorganism, especially its ecological traits and population dynamics, is not fully predictable from genotype alone. Therefore, risk assessment of release of GMOs should be conducted on a case-by-case basis (R. K. Colwell et al., **Science**, 229: 111-112, 1985; F. E. Sharples, **Science**, 235: 1329-1332, 1987). In a later publication of the NAS (**National Academy of Sciences, National Research Council, 1989**. Field Testing Genetically Modified Organisms into the Environment: Key Issues. National Academy Press, Washington, DC), certain criteria were suggested to define risk categories and ways to assess potential risks associated with the introduction of GMOs (small and intermediate scale). Among these are familiarity with the properties of the organism and the environment, ability to confine or control it effectively and probable environmental effects if the organism persists longer or spreads to non-target environments.

The Ecological Society of America, in a publication in 1989, focused on the ecological and evolutionary aspects of planned introductions of genetically engineered organisms, including microorganisms, plants and animals. The report (Tiedje et al., **Ecology**, 70: 297-315, 1989) divides attributes of organisms and environments into four categories: (1) genetic alteration; (2) parent (wild type) organism; (3) phenotypic attributes of engineered organism in comparison to parent organism; and (4) environment. The authors defined many specific attributes to each category and set up a scale on which to base the level of scientific consideration necessary for risk assessment. The authors suggested that the level of regulatory scrutiny be commensurate with the level suggested by the scientific attribute scales.

In several countries, since the knowledge base for assessing the implications of release needs to be constantly enlarged, a case-by-case and step-by-step approach is adopted. The step-by-step approach involves following the same GMO or GMO product at the level of research, field trial or field research and large-scale release. It is advisable to adequately address the risk assessment, evaluation and management at each step.

18. Among the international organizations to be notified, UNEP, UNIDO, FAO and WHO may be included, as they are directly concerned with the environment, industry, agriculture and health respectively.

19. There was considerable discussion among experts involved in the preparation of the document on the sensitive issue of whether the proposer should approach another country for field trials of his product when permission for such a trial has been refused in the country of its origin. The experts concluded that refusal of a trial of a product in the country of its origin does not preclude application for its testing in another country. The product may be of value to effectively tackle a country-specific problem, which may be illustrated by the following example. If a biological molluscicide is developed in a country to exterminate a snail population which is a vector for schistosomiasis, the country may refuse field trials of the product if it does not have the parasitic infection. Nevertheless, the product may be of great value to another country where the disease is prevalent. Another reason could be that the country that developed the product, may have a safety problem to apply it, while another country may not. For example, a test for an engineered plant may not be advisable in an area where it has many relatives with which it may cross fertilize, where as it could be safely applied in a different area where no such relatives exist.

The applicant should however, submit all the relevant data, including detailed reasons for refusal in the country of its origin, when applying for such tests in another country.

20. The potential for the application of genetically modified organisms for ecologically sustainable industrial development and its contribution to rapid economic growth, prompt developing countries to react favourably to proposals for their release into the environment. The adoption of the Voluntary Code of Conduct for the Release of Organisms into the Environment and the involvement of the ICGEB in the field of biosafety are likely to result in a number of requests by these countries for data on regulations and field releases of transgenic organisms. Furthermore, international assistance will be sought by these countries in forming national and institutional biosafety committees and in framing appropriate national biosafety regulations. The Biosafety Information Network and Advisory Service is designed to deal with such requests.

21. Under the Service, it is envisaged to identify biosafety experts from governments, industry and academia involved in work in the areas of industrial applications, health care, agriculture and the environment, who could be called upon by regulatory authorities when evaluating risks associated with a particular application of GMOs. Procedures will be worked out to provide timely and effective advisory services and assistance to countries, on request, for the

drawing up of safety regulations and for making decisions relating to the safety of applications of GMOs and their products for industrial development. This may involve risk assessment of proposals for the release of GMOs, the monitoring of releases, containment in cases where it is warranted and mitigation of adverse effects, if any.

The Service also envisages the establishment of contacts with governments, industry, scientists, regulators and international agencies and organizations to build up in-house databases on biological containment, releases of transgenic organisms and national biosafety regulations. These databases will be regularly updated and will be linked with the information resources of other international agencies and organizations. The Service, by setting-up a computer gateway, will enable scientists, regulators and industrialists in developing countries to access the UNIDO and ICGEB databases as well as others, such as those run by the OECD (BIOTRACK) and the Information Resource for the Release of Organisms into the Environment (IRRO).

REGULATORY ISSUES

BIA comments on proposed GMO regulations

The BioIndustry Association, through its Regulatory Affairs Working Party, has welcomed scientifically-based regulation, but argues that the proposed regulations for genetically modified organisms (GMOs) drafted by the UK Department of the Environment (DoE) and the Health and Safety Executive (HSE) are too rigid. Neither the Department of Trade and Industry nor the Biotechnology Unit of the Laboratory of the Government Chemist had an input into these regulations, the BIA notes. The proposed regulations are designed to implement the European Community Directive on GMO experiments and, specifically, deliberate releases of GMOs into the nevironment. "The UK regulations should be clear, practical, user-friendly and technically sound," says the BIA. "The present draft regulations, however, are unclear on many points. To ensure greater clarity and transparency, the BIA is calling for a new round of consultation – and is offering to mobilise experts to help with the process."

The BIA is alarmed about the cost implications for the industry. Among the Associations's concerns are the following:

- the financial and administrative implications of keeping records for 10 years and for conducting retrospective risk assessments have not been considered;
- the proposed fees for consent and enforcement are both variable and excessive, potentially placing the UK industry at a competitive disadvantage (in The Netherlands, no charges are proposed for consents to release GMOs);
- the potential leakage of commercially sensitive information to competitors;
- the timing of consent limits should be more appropriate to time constraints characteristic of each area of work (e.g. growing seasons in plant breeding);
- there are inconsistencies between the approaches adopted by the DoE and HSE;
- the area on transgenic animals is not fully addressed.

The BIA favours the HSE being used as the regulatory agency for the regulations, arguing that the existing structure has worked well over the last 15 years. It also strongly supports the continued operation of the Advisory Committee for Release into the Environment (ACRE) and the Advisory Committee on Genetic Manipulation (ACGM). Details from: BioIndustry Association, 1 Queen Anne's Gate, London SW1H 9BT or on 071 222 2809. (Source: **Biotechnology Bulletin**, February 1992)

Biotechnology approval lags behind FDA

Of the 132 US biomedical products in development, only four biopharmaceuticals are expected to receive US Food and Drug Administration approval in 1992. This prediction comes from a forecast of biomedical product market approval dates completed by Consulting Resources Corporation, Lexington, Mass., and Decision Resources Inc., Burlington, Mass.

Products expecting FDA clearance in 1992 include Centocor's Myoscint, a diagnostic imaging MAB used to diagnose and assess risk in heart attack patients, and Chiron's interleukin-2 (IL-2), used to treat cancer patients.

A host of other products are waiting in the wings, destined for approval in the mid- to late 1990's. Among the more near-term products are: two recombinant versions of factor VIII, one sponsored by Miles and the other by Baxter International and Genentech's recombinant soluble CD4 for AIDS treatment.

Mid-decade approvals are expected for atrial natriuretic peptide produced by California Biotechnology and Genentech's tumour necrosis factor (TNF). Consulting Resources also predicts that a vaccine for the AIDS (HIV) virus could be approved by late 1996.

Some of the longer-term biomedical products expected to receive FDA approval between 1997 and 2000 include: Relaxin (Genentech), stem cell growth factor (Amgen), insulin-like growth factor (Chiron), and Genetics Institute's bone growth factors.

The successful launching of biotechnology products in the 1990's is largely dependent upon the efficiency with which FDA handles the ever increasing load of product license applications (PLAs). Recent proposals have been made to expedite the drug-review procedure through utilization of outside contractors and increased reliance on computers. (Source: **Chemical Marketing Reporter**, 16 March 1992)

US biotechnology regulatory "scope" set

A process to set the scope of regulating the deliberate release of biotechnology products is complete. Late in February, President George Bush's Office of Science and Technology Policy (OSTP), Washington, DC) issued a final policy statement emphasizing the Administration's belief that the regulatory oversight of biotechnology products "should be based on risk, not on the fact that an organism has been modified by a particular process or technique."

Reactions to the policy statement are mixed, with nearly everyone finding enough ambiguity in the final document to allay some of the anxieties that have persisted during the two years in which this policy has gestated. Virtually everyone is eager for the next promised document, called the road map, that is intended to help researchers and company officials navigate biotechnology products that are headed for deliberate-release tests through agencies with overlapping regulatory jurisdictions.

Some observers are saying that the new policy statement on scope represents a triumph for biotechnology industries. Others are less enthusiastic, arguing that major responsibilities for regulating biotechnology products remain with statute-bound agencies and thus could still prove immensely challenging. Yet others blame the long wait for this policy statement on heedless wrestling within the Administration between pragmatists and political ideologists, and they point out that scope's true scope is a good deal more limited than its proponents claim. In any case, with the publication of scope, an unofficial, nearly two-year moratorium on the release of biotechnology regulatory proposals appears to have ended.

The 1992 version of scope refers broadly to biotechnology as the "use of various biological processes, both traditional and newly devised, to make products and perform services." Later, in delineating scope principles, the document declares that regulatory oversight "should not turn on the fact that an organism has been modified by a particular process or technique, but should be based on evidence that the risk presented by introduction of an organism in a particular environment is unreasonable." An unreasonable risk arises, says the document, when "the value of the reduction in risk obtained by additional oversight is greater than the cost" of oversight.

However scope ends up being used, it remains a policy statement - not a law or a rule. (Extracted from: **Bio/Technology**, Vol. 10, April 1992)

Key passages in the "scope" document

Scientific Principles for the Risk-Based 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 Coordinated Framework, 'Within agriculture, for example, introductions of new plants, animals and microorganisms, have long occurred routinely with only some of those that are not native or are pathogenic requiring regulatory approval'".

"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."

Risk-Based Approach Ensures Safety

"In order to protect the public and the environment, the scope of oversight should help focus agency efforts at reduction of the most important risks (and least costs so that society's resources are kept available to combat the next highest risks)."

Risk-Based Approach Avoids Discouraging Useful Innovation

"The distribution of oversight burden across technologies is in many ways as important as the total amount of burden: if oversight is aimed at one type of technology, the burden will be skewed against the technology and hinder its development. ... This uneven regulation encourages the continued use of older products and technologies while discouraging risk and potential risk reduction."

Final Statement on Scope

"Within the scope of oversight, 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..."

"Federal government regulatory oversight should focus on the characteristics and risk of the biotechnology product – not the process by which it was 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." (Source: **Genetic Engineering News**, 15 March 1992)

Proposal to study transgenic catfish in outdoor ponds

A rescued version of the US Agricultural Biotechnology Research Advisory Committee (ABRAC) of the US Department of Agricutlure (USDA), Washington, DC) recently gave limited approval to a proposal to study transgenic catfish in outdoor ponds. The panel however, criticized principal investigator Rex Dunham of Auburn University (Auburn, Al.) with more intensity than expected, arguing that his experiments were not well designed and that only the rigour of his confinement precautions qualified the proposal for approval.

Yet there still is no mandate for any federal review of such experiments, nor is there a requirement that anyone, including USDA officials, heed ABRAC's advice. The whole topic resides in a "regulatory never-never land," according to some observers.

Dunham and his collaborators approached USDA in October 1991, seeking approval to release 100,000 transgenic catfish fry into specially designed outdoor ponds on the Auburn campus. The fish carry a growth-hormone gene from rainbow trout. Dunham is trying to learn whether the transgenic fish grow faster and more efficiently than ordinary catfish, which are farmed intensively through the southern United States.

After hearing an advisor of fisheries experts panel's advice as well as a lengthy description of the proposal by Dunham, a majority of ABRAC members also concluded that the experiment could go ahead "because the confinement design and protocols are sufficient to prevent escape of the fish into the environment." However, several ABRAC members criticized the proposed experiments, suggesting that they might not qualify for federal support if judged by peer reviewers. (Extracted from: **Bio/Technology**, Vol. 10, May 1992)

Cutting out a genetic engineering hazard

The release of genetically manipulated organisms outdoors will be made considerably less risky thanks to a technique developed by genetic engineers in the USA. The procedure, which snips out unwanted genes, could allay fears that redundant characteristics introduced into modified organisms will not spread when they are released to other microbes, insects and plants.

Almost all genetically modified organisms receive at least two foreign genes when they are transformed. One confers a desirable trait, such as making a plant grow quickly. The other is a marker gene, which enables biotechnologists to screen out those cells that have been successfully modified from those that have not.

The most common form of marker gene makes the recipient cells or organisms resistant to a herbicide or an antibiotic. When the treated cells are exposed to the appropriate herbicide or antibiotic, only the transformed cells will survive.

But once researchers have established which cells were modified, the antibiotic gene serves no further purpose. In fact, it becomes an impediment when scientists seek approval for the release of modified organisms. Officials monitoring the release of genetically modified organisms may fear that the gene conferring resistance will spread, perhaps to harmful bacteria or to insect pests.

David Ow and Emily Dale of the Plant Gene Expression Center at the US Department of Agriculture in Albany, California, have devised a way to snip out the marker gene without harming the gene that confers the desired trait. They apply it to plants but say that it could easily be adapted for snipping genes out of bacterial, yeast and mammalian cells, or even human ones selected for use in gene therapy. (Extracted from **New Scientist**, 1 February 1992)

COUNTRY NEWS

Australia

Risk assessment for contained and released use of GMOs

The Genetic Manipulation Advisory Committee (GMAC) in its annual report of July 1990 to June 1991 outlines its procedures for risk assessment relating to contained and released use of genetically manipulated organisms. New developments it states, "pose some uncertainties and require continued monitoring."

New level of low risk at large scale contained use defined

The new guidelines for Large Scale Work with genetically manipulated organsims, published in December 1990, include a new level of procedures and requirements for systems of low risk. The parent organism "must have an extended history of safe industrial use and a non-hazardous insert or be incapable of establishing viable populations in the environment."

Low risk small scale under review by local biosafety committees

Included in the new guidelines for Small Scale Contained Use are a category of low risk work now completely under review of Local Institutional Biosafety Committees, and a higher risk category A, which requires direct GMAC assessment and advice.

Revision of the procedure for the assessment of GMO releases

The Genetic Manipulation Advisory Committee (GMAC) is currently working on the revision of the procedure for the assessment of planned release of recombinant DNA organisms. Topics to be discussed include the transfer of genetic material into human subject for disease treatment (considered as a form of release) and work on germ-line cells. The assessment of planned release proposals involves consideration by two sub-committees of GMAC concerned with genetics of the construct and the environmental implications for its release. A new draft law on GMO releases is currently being discussed at the national level in Australia between the ministries responsible.

Examples of planned releases approved by GMAC are:

- Field trials of a live Salmonella vaccine to prevent death during live sheep export;
- Commercial evaluation of melibiose utilizing baker's yeast.

Details: GMAC, GPO Box 2183, 5th floor, East 111 Alinga Street, Canberra, ACT 2601. (Source: **EBIS**, Vol. 2, No. 1, 1992)

European Community

Little ventured on Europe's biotechnology

Uncertainties over patent rights and safety regulations are deterring investors from putting money into biotechnology companies. Venture capital organizations in Europe invested £62 million in biotechnology in 1991, down from £101 million in 1989, according to figures published by the European Venture Capital Association and KPMG, the management consultancy firm. In the United Kingdom, venture capitalists invested £15 million in biotechnology in 1991, down from £35 million in 1989.

Garry Watts, KPMG's biotechnology specialist, describes the area as "potentially a very high reward industry." But the patent situation in Europe is "a muddle", says Watts, who believes that the European biotechnology industry is under pressure from the Far East, where safety regulations are not as strict.

Innovators wanting to launch new companies in any area of high technology are finding it increasingly difficult to raise venture capital. KPMG's report **Venture Capital in Europe**, shows that the amount of money invested in high technology has declined by 22 per cent over the past two years, from a peak of £693 million in 1989.

While the amount of venture capital invested in Europe increased from £2,888 million in 1990 to £3,242 million in 1991, less of the money went into high-technology companies.

John Hustler, head of venture capital at KPMG, says that venture capital organizations have moved away from investing in new companies and high technology. They now put more money into management buy-outs and expansion schemes.

The growth of the European venture capital business also makes it harder for investors to analyse proposals from small companies, the source of most hi-tech projects.

Hustler says that universities turn increasingly to venture capital organizations when they want to commercialize their research, but academics rarely have the makings of successful entrepreneurs. One sign of the universities' growing interest in commercialization is the increase in their patent activities in biotechnology. One option that KPMG is developing with some universities is for them to establish their own companies to bring their products to market, perhaps partly owned by a commercial organization. The exploitation company would ferret out promising research in the university and act as a "marriage broker", bringing academic researchers into contact with entrepreneurs who would then, if appropriate, sell the idea to venture capital funds. (Source: **New Scientist**, 11 July 1992)

Regulatory environment rapidly evolves in Europen Community

The development and approval of biotechnology products for medical use is increasingly challenging and complex, with the range of product development, regulatory, marketing, legal and patent issues expanding on a worldwide basis.

The regulatory environment is evolving rapidly, with great attention focusing on changes in regulatory procedures within Europe and the USA. There are also international efforts to harmonize data requirements between the European Community (EC), Japan and the USA.

Current EC regulations

European Community approval of biotechnology-based products for human administration is currently controlled by EC Council Directive 87/22/EEC, which became effective on 1 July 1987. Known as the "high-tech directive", it provides the basis for the current EC concertation procedure, designed to accelerate approvals of two "lists" (A and B) of products that constitute significant advances.

List A products are medicinal products developed by means of the following biotechnology processes: recombinant DNA (rDNA) technology; controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells; and hybridoma and monoclonal antibody products.

List B products are other high technology medicinal products that, in the opinion of a regulatory agency, constitute a significant therapeutic interest. These include products manufactured by other biotechnology processes; medicinal products administered by means of new delivery systems; medicinal products based on radioisotopes; and medicinal products manufactured using processes that demonstrate a significant technical advance.

The procedure is mandatory for List A products, including any biotechnology products and optional for List B products. To date, all biotechnology submissions have been List A products.

Concertation procedures

The concertation procedure involves reviews of applications by EC member States coordinated by the Committee on Proprietary Medicinal Products (CPMP). The CPMP is composed of two representatives of each EC member State. The approach allows the members to exchange views and harmonize opinion at the community level before any national decision is reached about the product's approval. The CPMP opinion is not binding on the member States.

The procedure has fixed timetables for review and assessment of products. The timetable for a product is set when the application is filed with the first member State. The applicant should be in communication with the rapporteur country well in advance of submission.

Acceptance of an application as valid after a 10-working day (14-calendar-day) administrative review makes that member State the rapporteur. Applications to all other member States should be made within three weeks after the first application.

The rapporteur country should provide its assessment report to other member States within 45 days; each member State should provide its comments within 60 days thereafter. Thus, the review by all individual countries should be complete within 119 days, with a possible 90-day extension.

When comments from all member States are received, the CPMP and working parties – six sub-committees focusing on different aspects of the evaluation (e.g., efficacy and safety) – are given 45 days to review them and the rapporteur's assessment. The conclusions of these reviews are provided to the applicant, who has 90 days to respond (this time can be extended at the applicant's request).

The CPMP and member States assess the response. Within 135 days the CPMP meets, conducts a hearing, reaches a decision and issues its opinion to all member States. Each member State then has up to 30 days to provide its decision on approval of the product to the CPMP.

In theory, the entire process from submission to approval of a product by all member States should take 239 to 419 days, depending on how much time is taken for each activity.

Good Clinical Practice

Good Clinical Practice (GCP) has been enshrined in Community legislation by Directive 91/507/EEC. The GCP guideline adopted in July 1991 includes requirements for informed consent of the subjects, review of the protocol by an ethics committee, Standard Operating Procedures and extensive record keeping. The company retains all responsibility for the clinical trial, its outcome and, of course, responsibility for the eventual product.

Proposed EC regulations

The future operating procedures for product approvals in the EC are under discussion based on proposed Regulation 90/C330/01, which describes centralized procedures for the authorization and supervision of medicinal products for human and veterinary use and establishes a European Agency for the Evaluation of Medicinal Products. EC regulations take effect in member States without implementation through national legislation.

Approval of some regulations require unanimity; others, a qualified majority (weighted based on population considerations). France has taken the position that approval of this regulation would require unanimity.

If ratified in its current form, the proposed Council Regulation would bring broad changes. Biotechnology products would undergo a centralized assessment evolving from the concepts included in the present concertation procedure. According to the proposal, applications for biotechnology products would be submitted directly to the new Agency. The application would then be referred to the CPMP or CVMP (Committee on Veterinary Medicinal Products) for review.

For each application, an individual would be appointed as rapporteur with overall responsibility for coordination of the product review. Experts appointed by the appropriate committee would help the rapporteur evaluate individual parts of the file. The appointment would be made from lists of experts provided by the member States. The experts would report directly to the committee rather than to their individual national authorities.

Working under the CPMP or CVMP and consulting its expert advisory panels, the rapporteur would prepare an assessment report for the product, including

a review of the summary of product characteristics and proposed labeling and packaging inserts.

Draft reports would be presented to the appropriate committee for its scientific opinion. The committee's opinion, unlike those rendered during the current concertation procedure, should be binding on all EC members. The overall time allowed for the Agency to prepare an opinion is 210 days, but the clock would stop during any time requested by the applicant to reply to questions posed by the committee.

In practice, the minimum time to achieve a favourable opinion may be several months longer. If a company appealed or objected to the opinion, the time scale increases to about 16 months.

Although the European Parliament provided a favourable opinion on the proposals in June 1991, the member States may not provide final opinions until July 1992. A qualified majority can approve the directive and establish the Agency.

Most member States favour the use of a centralized procedure to review biotechnology products. This would ensure that the small available number of well-qualified people participate in evaluation of key product submissions. Implementation of the system would probably not take place before mid-1994.

Germany has publicly stated opposition to a centralized agency whose decisions are binding on each member State. The European Parliament may not vote on the proposal before the end of 1992. The new procedure could reduce the time to a central opinion from the present typical range of 12 to 18 months to less than one year, potentially including an opinion binding on all member States.

Biotechnology products have received rapid reviews through the existing concertation procedure. The only product that has experienced regulatory difficulties in Europe is bovine somatotropin, which has political difficulties similar to those in the USA.

Biosafety research in the European Communities

The Commission of the European Communities has implemented within the framework of BAP (Biotechnology Action Programme: 1985-1989) a research effort on biosafety, which involved the work of 58 laboratories organised through the Community in 16 international projects. These projects were aimed at the study of the problems associated with the release of genetically modified microorganisms, plants and recombinant vaccines with the view to ensuring their safe use and identifying possible risks.

The final report on these studies was published by the Commission (I. Economidis (Ed.), **Biotechnology R&D in the EC: Risk Assessment, Part I: Achievements; Part II: Detailed Results**). The information this report makes available to the international community of scientists and regulators covers a range of results and data on the development of specific monitoring techniques, the behaviour of genetically modified organisms (GMOs) in model ecosystems and small field trials and on the genetic stability and gene transfer from GMOs released into the environment.

The assessment of possible risks associated with the release of GMOs is continued and amplified by BRIDGE (Biotechnology, Research for Innovation, Development and Growth in Europe: 1990-1993). Last summer, the Commission launched a call for proposals, which attracted 41 projects involving 186 laboratories. After four evaluation sessions in which 26 experts from the member States participated, the Commission, in agreement with the Consultative Committee CAN-BRIDGE, which advises the Commission during the implementation of the programme, decided to support 15 projects grouping 78 participants.

These projects cover the following issues:

- **1. Horizontal Gene Transfer**
  Plant-bacterial plant pathogen interaction;
  Plant-fungal plant pathogen interaction;
  Plant-microbe interactions;
  Soil microbial inoculants.

- **2. Soil Microbial Ecology**
  Biological containment;
  Effect of selection on gene stability and transfer.

- **3. Bioremediation**
  PCB-degrading bacteria;
  Fate of GEMs in pollution hot spots;
  GEMs with high ecological predictability.

- **4. Tools**
  High resolution automated microbial identification (T-project);
  Molecular taxonomy of fungi (concerted action).

- **5. Transgenic plants**
  Baculoviruses for insect control;
  Environmental assessment of live recombinant vaccines;
  Genes involved in latency and reactivation of pseudorabies viruses;
  Biosafety of genetically engineered retroviruses.

Research in these areas was to start by 1 October 1991; the first results are to be discussed by *ad hoc* groups in late 1992.

In order to complement BRIDGE, the Commission of the European Communities has proposed that a new programme ("Biotechnology") be implemented during the period 1991-1994. "Biotechnology" will cover three main areas: molecular approaches, cellular and organism approaches and ecology and population biology.

Although biosafety is a horizontal concern that takes into consideration the findings of every other biological

sector (promoters, position effects for gene expression, cell-cell interactions) it falls essentially within the area of ecology and population biology. The research will aim at understanding in molecular terms the mechanisms of microbial genetics and of behavioural physiology, which are important for a proper management of natural ecosystems. As far as the release of GMOs is concerned, the programme will extend the ongoing research efforts of BRIDGE to transgenic fish and to insects.

The Commission hopes, through its biosafety research:

- to reassure the public on all matters related to the safety of GMOs for man and his environment;
- to help regulatory authorities with tools and data important for the authorization of field trials and application permits; and
- to stimulate the acquisition of fundamental knowledge important for environmental studies.

(Source: **BFE**, Vol. 8, No. 12, December 1991)

EC/US environmental bilateral in biotechnology

The Permanent Technical Working Group on Biotechnology and the Environment (set up in September 1990) met in Brussels on 27 March 1992. This was the fourth meeting of these bilateral consultations, whose objective is to exchange information and experience and develop closer cooperation between the USA and the EC. A first tangible result is the publication of a joint EC/US document on methods for the detection of microorganisms in the environment. The report (EUR 14158) is available at ECU 12 from the Office of Official Publications of the European Communities, L-2985 Luxemburg. A new joint document on vectors used in genetic modification was discussed. Information was exchanged on regulation.

Following the official bilateral meeting, a workshop on Regulatory and Technical Issues Associated with Field Tests of Genetically Modified Organisms took place at the University of Leuven on 30 and 31 March 1992. The workshop brought together the US regulatory authorities for approving releases (EPA and USDA) and the EC competent authorities implementing Directive 90/220/EEC on the deliberate release of GMOs, and their experts to discuss regulatory and technical issues associated with field tests of GMOs. Specific case studies were examined. (Source: **EBIS**, Vol. 2, No. 2, 1992)

Germany

Experience with the gene technology law

On 12 February 1992, the Committee for Research, Technology and Technology Impact Assessment and the Committee for Health of the Bundestag, under the chairmanship of Wolf-Michael Catenhusen, conducted a public hearing on how the gene technology law, which came into force in July 1990, was being implemented. Twenty-one experts from government administrations (including the EC), enforcement authorities, industry, trade unions, universities and ecological institutes were invited to answer some 70 questions ranging from safety issues, length and cost of administrative procedures to international comparisons with other EC countries and the USA.

While general satisfaction was expressed both with the existence and the spirit of the gene technology law, criticism focused on the over-bureaucratic "Durchführungsverordnungen" (implementing regulations), which entered into force shortly after the gene law itself. The enforcement of these provisions is not carried out federally, but by 50 different regional authorities.

Long delays and compliance costs and the heavy obligations of documentation even for routine experiments without regard to the actual risk involved, were considered severe shortcomings.

Scientists registering S1 laboratories had to provide the same detailed information about laboratory installations as those working with S3; the forms to be filled in were basically the same for experiments with S1 and S4 organisms.

While there was general agreement between researchers and industry that work with S3 organisms should be subject to tight safety provisions (which, however, only concern 3 per cent of the experiments undertaken), the equally strict provisions for S1 and S2 organisms (96 per cent of experiments), were considered to be bureaucratic, stifling research and even dangerous, since students in particular, would get a wrong perception of risk.

Professor Winnacker of the Genzentrum of the University of Munich pointed out that while several hundred deliberate releases of recombinant organisms have been carried out worldwide, only one field trial has ever taken place in Germany (with petunias). Hardly any work on gene therapy is undertaken and no non-German company had invested in Germany in gene technology research or production.

The hearing ended with a call for concrete proposals from experts on those aspects of the gene law which would require adaptation, particularly with regard to scientific progress, and on how a more risk-based approach could be implemented. (Source: **EBIS**, Vol. 2, No. 2, 1992)

Japan

Deliberate release of GMOs report

The Central Council for Environmental Pollution Control of the Japanese Environment Agency set up an Expert Committee on Biotechnology in June 1989.

After 16 meetings, the Committee has produced a report on environmental protection for the deliberate release of genetically modified organisms into the environment. The report, some 50 pages of English translation, reviews the developments that have taken place in the USA and the EC, particularly taking account of the OECD deliberations. It considers likely impacts and the risks for the environment presented by the technology, and the need for the public to have a full and correct understanding of it. The Expert Committee concluded that it had found a wide disparity of views among its members. Debate on an appropriate institutional framework will be continued, taking into account the findings of the report and of advances in related science and technology. Details may be had by contacting the Environment Agency Global Environment Department, Planning Division, 1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100, Japan. (Source: **EBIS**, Vol. 2, No. 2, 1992)

The Netherlands

GMO safety

The Dutch government is cracking down on safety in GMO research. Environment minister, Hans Alders, has announced a major review of all "companies and research laboratories" working with GMOs.

The inspection will be comprehensive, for the Ministry intends to investigate every single company and every single laboratory. The inspections will not be completed for at least two years.

The government is acting in direct response to a study from Leiden University. The study, which focused on safety in GMO research, concluded that 7 per cent of all experiments are "illegal", because they do not conform to safety regulations designed to prevent the spread of GMOs in the environment.

The report blamed local government shortcomings for the breaches. Under the Dutch regulations, local authorities are responsible for GMO experiment licences, and for on-site inspections. Because this system has failed, the Ministry will now carry out the inspections itself.

The GMO-by-mail fracas has grown from warning in another report. The Dutch postal service carries some 3,000 GMO packages every year. Most of those packages are inadequately sealed, according to a report from the National Environment Research Institute (RIVM). At least 15 times a year, some of those packages break, exposing both the postman and the environment to the genetically-engineered contents. (Source: **Chemistry & Industry**, 6 April 1992)

Switzerland

"Yes" to genetic engineering

Through a referendum on 17 May 1992, the citizens of Switzerland voted genetic technology onto their constitution for the first time in the federation's history. Swiss companies involved in biotechnology have perceived the "yes" vote in the current referendum as an endorsement of genetic engineering. However, a subsequent referendum could place a complete ban on transgenic animals and on all releases of transgenic plants in Switzerland. Under the Swiss democratic system, the people are sovereign and through frequent referenda make known their views on how the federation's constitution should change. In due time, parliamentary process translates those wishes into law. Since 1874, the year it was established, the Swiss constitution has been changed 117 times to adapt to a variety of social and technical developments. Now it is the turn of genetic engineering.

It will probably take several years for the results of the May referendum to be translated into Swiss law. However, industry is concerned that, in enacting the Beobachter Initiative, the Swiss government should learn from experiences in the UK and Germany where the need to enact the directives of the European Community on genetically engineered products resulted in regulations that were more restrictive or cumbersome than necessary.

The new initiative calls for a complete ban on transgenic animals, a total ban on the release of transgenic plants and a ban on patenting living genetically engineered products. It also calls for the inclusion of non-governmental organizations on expert committees to regulate products manufactured through genetic engineering. And it wants manufacturers to demonstrate not only efficacy, safety and quality, but to also demonstrate socio-economic need and the absence of alternative production methods. (Extracted from: **Bio/Technology**, Vol. 10, June 1992)

United Kingdom

BIA and ABPI criticise EC implementation proposals

The BioIndustry Association and the Association of the British Pharmaceutical Industry (ABPI) have both told the government that its proposals for implementation of the EC directives on genetically modified organisms (GMOs) are badly drafted and could reduce the competitiveness of the UK biotechnology industry.

In its comments on the proposed GMO regulations, the ABPI notes that in their present format they "could have major implications for the pharmaceutical industry in the UK". Specifically, it is concerned about what it sees as the over cautious provisions relating to companies engaged in low-risk, high volume contained use production.

The ABPI also has reservations over aspects of confidentiality and public access to information of commercial importance and believes a number of proposals go beyond the requirements of the relevant EC directives. As such, it says they could disadvantage UK-based industry.

On the question of consents for release, it criticizes the costs involved, put at between £2,000 and 4,000 per consent, and the renewal period of three months, which it says is far too short in the context of large-scale culture of GMOs. It suggests a more practical renewal period would be four years.

Current sales by UK biotechnology companies are estimated at £350 million, of which 45 to 55 per cent is exported. Estimates are that sales will grow at the rate of 20 to 30 per cent per year. The world market, in contrast, is put at ECU 5.1 billion and is estimated to reach ECU 83.3 billion by the year 2000. (Extracted from: **European Chemical News**, 10 February 1992)

Rules in a mess

Draft regulations governing the development and release of genetically modified organisms in the UK were so complex and confusing that they require a comprehensive overhaul, according to the Department of the Environment. The department, which is working out a new "user-friendly" version, had hoped to issue the final regulations in May 1992, but now says that the final draft will be completed several weeks behind schedule. Industry complained that the text of the draft regulations was confusing, contradictory and unwieldy. (Source: **New Scientist**, 23 May 1992)

United States of America

Washington takes a stand on biotechnology

The White House has published long awaited guidelines for agencies that regulate the release of biotechnology products into the environment. These stress that all products, whether traditionally grafated hybrid plants, or genetically manipulated, pest resistant crops, must be treated in the same way.

Instead of assuming that all products of genetic engineering are dangerous until proven otherwise, the agency will have to base the need for regulation on the risk a product poses to the environment irrespective of the method of production.

The guidelines embody the findings of the National Research Council, published in 1989. That report said organisms that have been genetically modified do not pose an inherently greater risk than unmodified ones. It added that no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques.

The guidelines read that the Environmental Protection Agency and the US Department of Agriculture can go ahead with the publication of regulations governing the release of biotechnology products into the environment.

Without these regulations, the biotechnology industry could not be sure how the agencies would treat their applications for, say, field trials, or whether genetic engineering would push up the cost of testing before bringing a product to market.

Both the Association of Biotechnology Companies and the Industrial Biotechnology Association welcome the guidelines and the emphasis on risk rather than the method of production.

At the same time as publishing the guidelines, the White House called on the agencies to clarify which of them is responsible for regulating different products. Currently, companies need to seek approval from both the USDA and the EPA in some cases. That job is supposed to be completed within weeks rather than months. (Source: **New Scientist**, 7 March 1992)

US regulation of biotechnology products for human use

US regulation of biotechnology products for human use is under the jurisdiction of the FDA Center for Biologic Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). Most biotechnology products have been classified as biologics and are handled by the CBER. Veterinary products, such as bovine somatotropin, are covered by the Center for Veterinary Medicine.

The new biotechnology techniques are considered to be extensions, or refinements, of older techniques and subject to the same regulatory paradigms, procedures and jurisdictions. Thus, recombinant insulin was handled by CDER, as was insulin produced by extraction.

Scientific considerations dictate the course of FDA's review. Regulatory scrutiny is commensurate with perceived risk of the product. For example, conventional hepatitis B vaccine is derived from pooled plasma of patients with chronic hepatitis and undergoes an exhaustive inactivation. It generally causes the FDA more concern than the rDNA-derived sub-unit vaccine produced in recombinant yeast.

All pharmaceutical products are now designated "routine" or "expedited" by the FDA for review priority, replacing the 1 to 4 rating system previously used. It is expected that a disproportionate share of biotechnology products will be designated to receive expedited review.

Although products are generally treated on a first received, first reviewed basis, a product such as an AIDS vaccine would be given top priority.

There is a statutory requirement that drugs be reviewed within 180 days. This is rarely met, in part because the "clock" stops whenever the FDA is waiting for responses to questions.

Because the number of biotechnology products in development has increased considerably (over 250 products with over 1,000 clinical trials under way), the FDA has re-allocated substantial resources to this field.

In the past, Center responsibility for review of "combination products" (e.g., an immunoconjugate) would be uncertain. Under regulations implemented in November 1991, one Center will have primary jurisdiction for each product. Inter-centre agreements assign jurisdiction by product class, describing product characteristics and indications where collaboration in the review process may be appropriate. For products not clearly categorized by the agreements, companies may request specific assignment to a specific centre.

Companies are advised to talk to FDA early and often, particularly if they have no previous regulatory experience. Companies should provide FDA with concrete proposals for a product's development. The FDA's "Points to Consider" documents provide technical advice on a number of discrete areas of rapidly evolving technology and product classes. The most recent of these deals with somatic cell human gene therapy.

There is a broad consensus within the USA that biotechnology products do not pose different risks from similar products of other techniques and should therefore not be subjected to special procedures or requirements. Regulatory programmes should be structured to accommodate rapid scientific advances by employing, where possible, performance-based standards over design standards. FDA, in association with the President's Council on Competitiveness, announced a series of recommendations to improve the regulatory process in November 1991:

External Review of Drugs: FDA would contract with outside organizations, chosen and paid by FDA, to review applicants. There would be a 120-day deadline for completion of the contractor's review and a goal for total review time (including FDA's time) of 180 days.

Accelerated Approval Regulation: FDA would approve some drugs on the basis of "surrogate" endpoints rather than definitive evidence that a drug treated a disease. Post-marketing studies would then be required.

FDA-Proposed Management Reforms: Would include computerization of drug applications to speed reviews, imposition of user fees to fund additional reviewers, and improvement of internal systems of accountability.

Expanded Use of Advisory Committees: Would involve expert advisory committees earlier in drug review decisions and depend to a greater extent on the committee's judgement about the course of the drug's testing.

IRB Review of INDs: Institutional Review Boards would be given increased authority to approve early testing of drugs in humans. The exclusive jurisdiction of IRBs in Phase I drug testing is likely to be restricted to certain classes of products and selected institutions that have well-established expertise.

International Harmonization: FDA would continue to work towards a number of "harmonized" procedures with foreign countries (e.g., common application format, greater acceptance of foreign testing data, shared inspections and common requirements for animal testing). The ultimate goal would be "reciprocity" with other countries.

The recommendations also covered other areas not directly related to product approvals.

Implementation of these proposals is either under way or will begin within the next few months. They are expected to have a significant impact on the regulatory process beginning almost immediately. For example, FDA recently authorized 50 additional positions for review of biotechnology submissions. (Source: **Genetic Engineering News**, 1 April 1992. Article by Kenneth D. Brown).