EUROPEAN COMMUNITIES

DIRECTORATE-GENERAL
FOR SCIENCE, RESEARCH
AND DEVELOPMENT
JOINT RESEARCH CENTRE

BRIC/1/86

March 1986.

THIRD DRAFT

Biotechnology Regulation
Interservice Committee

THE EUROPEAN COMMUNITY, AND THE REGULATION OF BIOTECHNOLOGY: AN INVENTORY

1. INTRODUCTION

Like most industrialized countries, the European Community has a variety of health and environmental protection laws that could be applied to biotechnological processes and products. For instance, Community legislation covers risks relating to food additives, pharmaceuticals, feedstuffs, cosmetics, and industrial chemicals. But these Community laws are usually limited by their application to commercial products only. They were not designed to monitor accidental release or the deliberate use of exotic or genetically modified organisms.

Other Community laws cover health and environmental risks to workers and the public from industrial processes or wastes. These laws are similarly limited by their application to chemicals; they, too, were not designed to anticipate, evaluate and control risks from genetically modified organisms.

CONTENTS

1.A. THE NATURE OF RISKS FROM MODERN BIOTECHNOLOGY

In the past fifteen years, new developments in techniques to recombine *in vitro* the DNA from different organisms, permit precise alteration, construction, recombination, deletion and translocation of genes to obtain a desired phenotype. These procedures are relatively simple to learn and apply. Consequently, they are potentially accessible to a wide range of industrial, agricultural and other organisations, large and small. Although the costs of research and development may in some areas have been enormous, in other areas the entry cost is negligible, the benefits enticing. It is therefore unsurprising that many hundreds of companies are already active in this field and commercialization of their products is progressing much more rapidly than was foreseen a few years ago.

Thus, although biotechnology is as old as human civilization, the scale of international trade and this rapidly accelerating industrial progress means that the application of these new techniques of genetic manipulation will increase the potential scale of their impacts by several orders of magnitude.

The "quality" of hazard posed by a particular application of biotechnology may be the same at all stages of development from research to large-scale production and use. However, the overall risks (intrinsic hazard + exposure to the hazard) could increase substantially with the scale of production and use.

In the case of fermentation technologies, the genetically modified microorganism is usually contained during the research or manufacturing process, and it is usually destroyed when its work has been accomplished. At this stage the risks would arise from accidental release of the microorganism and exposure of workers inside the plant, or people and the environment outside the plant. Further risks might arise from the generation of wastes.

In the case of genetically modified or exotic microorganisms intended for use in the environment, three categories of direct risks are involved:

1) Ecological disruption (for example, due to a lack of natural enemies);

2) Infectivity, pathogenicity or toxicity to nontarget organisms (plants, animals, humans); and

3) Exchange of genetic material with other organisms or disruption of ecosystems and consequent risks of (1) and (2).

1.B. THE EUROPEAN COMMISSION'S APPROACH TO BIOTECHNOLOGY REGULATION

The European Commission's interest in controlling the potential risks from biotechnology is obvious. Long experience in such fields as health care and environmental protection demonstrates that it is better to identify and evaluate potential risks as far as possible in advance of large-scale production, so that the appropriate measures to limit and control these risks can be taken. Such risk assessments should be followed up by monitoring and re-evaluation in the light of growing experience.

Clearly, as in the case of chemical-based industrial processes and products in the past, the onus must be laid upon the innovator or producer to carry out the initial risk assessment and to provide the regulatory authorities with data adequate for a risk assessment and monitoring.

Several important arguments underly the European Commission's commitment to providing adequate regulation of biotechnology:

1) The health and environmental impacts of biotechnology might easily cross national frontiers - national regulations cannot protect against risks from genetically modifed organisms;

2) EC regulation would offer the scale of the common market for biotechnological products, and thereby provide a more economically attractive environment for European industrial innovation in biotechnology;

3) Pooling the data relevant to the regulatory assessment of risks from biotechnological innovations at the European level would mean a more rapid accumulation of experience and hence the more timely and appropriate development and adaptation of regulations in the light of experience;

4) European Community regulation would mean a more efficient use of resources, both in the underlying research, and in the development and application of regulations.

The probability of such a risk occurring depends upon five factors :

1) The possibility of release into the environment;

2) The possibility that the organism will survive there;

3) The possibility that the organism will reproduce and multiply;

4) The possibility that the organism will make contact with a receptive environment (gene exchange, dissemination);

5) The possibility that the organism will be harmful.

Hence, the direct risks from a particular genetically modified organism are probably small, but, nevertheless, the consequences could be very large. They might give rise to problems comparable with those created in the past by incursions of natural pathogens into novel environments (for example, measles, typhoid, smallpox in North America, Dutch elm disease).

Indirect risks from modern, large-scale uses of genetically modified organisms also must be considered, such as the potential loss of native plant and animal species posed by large-scale industrialized agricultural practices. Such risks, however, may derive more from the scale of applications than the intrinsic harmfulness of the biotechnological product.

A useful point of common international reference on these issues will be provided by the publication later in 1986 of a report by an ad hoc group of experts, convened by the OECD. This report will be entitled:

"Recombinant DNA Safety Considerations: Safety Considerations for Industrial, Agricultural and Environmental Applications of Organisms Derived by Recombinant DNA Techniques".

The summary and recommendations are attached as an annex to this report.

Experts from most Community Member States and from the Commission were among those who approved unanimously the text at their final working meeting (Paris, 2-6 December, 1985).

1.C. THE PURPOSE OF THIS PAPER

At this time of rapid industrial innovation in the field of biotechnology, it is essential that the European Community respond quickly and effectively to the need for protection of human health and the environment and strengthening of the common market for these products. Responding to the same circumstances, there is a natural temptation for the individual member states each to embark on the preparation of domestic legislation. This could obviously lead to a proliferation of inconsistent national regulatory systems.

It is clearly incumbent upon the institutions of the European Community to anticipate and act to prevent such a situation from arising.

The following pages describe Community regulatory activities relating to biotechnology. In each area are presented :

- the objectives of the activity and background;

- the content of current directives, recommendations, etc;

- the current situation and potential initiatives;

- the committees which provide technical advice to the Commission in these areas.

2. REGULATIONS AND COMMUNITY ACTIONS

This section outlines the current Directives which may be of relevance to the regulation of biotechnology in the European Community.

The sequence of the sections follows the linear logic: from research, to production, to marketing, use of products, and finally waste treatment.

The scope of areas selected for discussion reflects the breadth of potential applications of biotechnology. Since the term itself is open to differing definitions, and its future technological development and commercialisation are not in detail predictable, the scope adopted in this report is fairly broad. Thus, for example, Directives are mentioned or described for fields which may not currently be the target of "biotechnology-based" product or process development, but which might become so.

2.A. RESEARCH

The initial creation and propagation of genetically modified organisms generally takes place in a research laboratory, and historically it was with this type of activity that regulatory debate on biotechnology first took place.

Title

Council Recommendation concerning the establishment of safety measures against the conjectural risks associated with rDNA work (82/472/EEC).

At the same period, the Commission services decided to draft a Council Directive concerning the establishment of safety measures against the conjectural risks associated with rDNA work.

After further widespread debate, and a general reduction in the assessed level of possible risks (in the light of experimental results, the absence of adverse incidents, and the development of fuller scientific understanding), the Commission in 1980 replaced its draft directive by the recommendation which was finally adopted by Council in June 1982 (82/472/EEC), concerning the registration of rDNA work.

The same text also formed the basis for the recommendation adopted in October 1984 by the Council of Europe

Contents

The recommendation to the Member States is that they adopt laws, regulations and administrative provisions requiring prior notification by laboratories of their intention to undertake rDNA work. Notification should be accompanied by safety-relevant details of the experimental protocol; a list of protective and supervisory measures to be applied; and a description of the training in rDNA work of those concerned with the execution, supervision, monitoring or safety of the experiment.

Current situation

In June 1983, the services of the Commission sent to national experts nominated by the delegation of CRM (Committee on Medical and Public Health Research of the European Community) a questionnaire designed for allowing an appraisal of the state of implementation in the Member States of the recommendation by Council concerning the registration of recombinant DNA work. The questionnaire also requested from the experts that they expressed their opinion on any modification of the recommendation, including its abrogation or its replacement by a Council directive, which they would consider necessary.

Synthesis of answers received

The answers received indicate that:

- The United Kingdom and Denmark are the only two Member States where a system of notification has been rendered compulsory to all laboratories;

- In the Federal Republic of Germany notification is compulsory for research work supported by the government. Research not funded by the federal government is submitted to a system of voluntary registration;

Objectives and background

Following the initial scientific successes of genetic engineering, recombining DNA from different organisms to create a novel genome, apprehension was expressed by some scientists about potentially serious and uncontrollable consequences of the creation and proliferation of new organisms. The Asilomar conference in 1975 was followed by voluntary adoption of severe constraints on the types of experiments pursued and the safety measures to be adopted. These included both physical containment, and (through the use of disabled host organisms unlikely to survive outside artificial conditions) biological containment.

In the USA, a detailed regulatory system was imposed on all laboratory rDNA work funded by the National Institutes of Health. This was supervised by the Recombinant DNA Advisory Committee ('NIH-RAC'). In the UK, following the establishment of a national consultative committee ('GMAG': Genetic Manipulation Advisory Group), an equally strict but more flexible system of regulation was imposed. Throughout the other Member States of the Community, consultative committees were constituted similarly to GMAG, and recommendations usually based on the American or British models were adopted.

In 1976, the European Science Foundation established an expert group, including a representative of the Commission, to examine in detail the question of the risks of rDNA work, to promote harmonisation of national legislation, and to formulate appropriate recommendations.

2.B. INDUSTRIAL PRODUCTION

The safety of the industrial use of organisms is secured by providing appropriate conditions of containment to prevent release of potentially hazardous agent into the outside environment and to protect the product. The primary objective in selecting containment is to match an appropriate level of physical measures and safety procedures to the conclusions of a risk assessment of the biotechnological process involved.

2.B.1. WORKER PROTECTION

Title

Directive 80/1107/EEC of 27 November 1980 concerns the protection of workers from the risks related to exposure to chemical, physical and biological agents at work.

Objectives

The Directives sets out two objectives:

- The elimination of exposure to chemical, physical and biological agents and the prevention of risks to workers' health and safety;

- The protection of workers who are likely to be exposed to these agents.

Contents

This Directive requires the Member States to take short and longer term measures, and it also foresees the adoption by Council of individual Directives laying down limit value(s) and other specific requirements for named agents.

In order that the exposure of workers to agents is avoided or kept at as low a level as is reasonably practicable, Member States should comply with a set of requirements, but in doing so they have to determine whether and to what extent each of these requirements is applicable to the agents concerned.

- The laboratories involved in recombinant DNA work in Belgium, France, Greece, Ireland, and the Netherlands are reported to comply to a system of voluntary registration.

- With few exceptions, the systems implemented in Belgium, Denmark, the Federal Republic of Germany, France, Greece, Ireland, the Netherlands, and the United Kingdom take into account all the specifications recommended by Council. Ireland, however, adopted a definition of recombinant DNA work different from the definition outlined in the recommendation;

- Specific safety regulations, compatible with the terms of the recommendation, are now being prepared in Italy;

- One suggestion (Ireland) was made for the abrogation of the recommendation; requests for its replacement by a directive were presented by Belgium and Greece. In Greece, however, where existing notification procedures are to be complemented by detailed guidelines, the view is held that a recommendation implemented by all Member States could be considered as adapted to the present situation. The answers received from the Netherlands express the view that the recommendation, considered as non-adapted, should not be abrogated or modified; it should, however, if not implemented by all Member States, be tranformed into a directive. No changes are suggested in the other Member States (DK, F, FRG, I, UK) where the recommendation is reported to be adapted to the current situation.

Advisory Committees

The Medical Research Committee advices the Commission on safety aspects of laboratory rDNA work.

The Management and Coordination Advisory Committee (Biotechnology) advises the Commission on the execution of its research programmes in biotechnology.

The DG V paper states that microorganisms can be classified into four groups:

Group 1: An organism that is most unlikely to cause human disease.

Group 2: An organism that may cause human disease and which might be a hazard to workers but is unlikely to spread in the community. It rarely produces infection and effective prophylaxis or effective treatment are usually available.

Group 3: An organism that may cause severe human disease and present a serious hazard to workers. It may present a risk of spread in the community but there is usually effective prophylaxis or treatment available.

Group 4: An organism that causes severe human disease and is a serious hazard to workers. It may present a high risk of spread in the community and there is usually no effective prophylaxis or treatment.

This classification is practically identical to that proposed by the Safety in Biotechnology working group of the European Federation of Biotechnology.

No particular measures are required for those organisms which are non-pathogenic and are classified in Group 1, but containment procedures are required for Groups 2, 3 and 4. A working paper has been drafted by the Commission services, setting out defined containment levels for each of the three hazard groups, and for animal room containment levels relating to work with vertebrates deliberately inoculated with organisms in each of the three hazard groups.

b) Monitoring, assessment, measurement, prevention

The Commission's proposal in 1982 for a Council Resolution (COM 82/690
final) establishing a second programme of action of the European Communities on safety and health at work in point 12 was to "Establish the principles and criteria for monitoring groups of workers likely to be at high risk to their health and safety, in particular maintenance and repair teams, workers undertaking sub-contract or temporary work, laboratory workers and those involved with biotechnology and other new technologies".

The Council deleted the reference to biotechnology and other new technologies. (OJ C 67, 8.3.84).

These requirements are:

- Limitation of use at the place of work;
- Limitation of the number of workers exposed;
- Prevention by engineering control;
- Establishment of limit values and of sampling and measuring procedures, and methods for evaluating results;
- Collective and individual protection measures, where exposure to agents cannot be avoided by the other means, as well as hygiene measures;
- Emergency procedures for abnormal exposures;
- Information for workers,
- Surveillance of the workers' health.

Current Situation

a) Containment

A study on the health risks of workers exposed to chemical and biological agents including dangerous pathogens has been carried out, under CEC contract, to collect and examine the available data with a view to identifying the hazards and drawing up conclusions and recommendations concerning them. Following a meeting in July 1985, DG V prepared a paper relating to the control of pathogenic organisms by containment, discussed in February 1986 by a specialist working group of the Advisory Committee named below, which will consider in May 1986 the recommendations of the group.

2.B.2. INDUSTRIAL PRODUCTION - CONTROL OF ACCIDENTS

Title

The Council Directive on the major accident hazards of certain industrial activities (82/501/EEC), known as the "Seveso" Directive, concerns the protection of the public and the environment from the accidental release of harmful material from the industrial use of biotechnological processes.

Objectives

The Directive was adopted in 1982, in response to a series of major industrial accidents in chemical plants in the European Community (Flixborough, Seveso). It set up 2-tier system that requires measures to be taken by industrial plant operators and governments to prevent major accidents and to limit the consequences of those that do occur.

Contents

The Directive imposes general requirements on industrial operators to avoid and control the impacts of major industrial accidents arising from certain specific activities, including most processing and storage by the chemical industry. Then, for a list of 178 dangerous substances, the Directive requires the industrial operator to carry out a detailed risk assessment and submit a notification to the competent authority of the member state setting out risks, controls, and emergency response procedures. In the case of an accident, the Directive requires member states and industrial operators to take further steps to control and repair the impacts of the accident and to inform the European Commission of what is done.

Current Situation

The Commission services are reviewing the applicability of the Directive to industrial processes using microorganisms and considering the need for either amending the Directive specifically to include certain dangerous organisms or adopting new legislation setting out approriate measures to prevent accidents and control their impacts.

Advisory Committee:

The Advisory Committee on Safety, Hygiene and Health protection at Work.

Contents

The "Sixth Amendment" is intended to ensure that all "new" Chemical substances placed on the EC market after a specified date are tested and assessed for their potential risks to people and the environment, - and appropriately labelled.

The manufacturers of new chemical substances must :

- Carry out a "base set" of tests to identify the potential risks of the chemical;

- Conduct a risk assessment;

- Adopt appropriate labelling according to EC standards;

- Notify this information to their national competent authority (who forwards the dossier to the Commission and thereby to the other member state), and

- Carry out further tests and provide futher information about risks according to certain criteria specified in the directive.

In essence, the directive establishes an information system based on the notification dossier which ensures that industries generate the information necessary to identify potential risks and that the EC and the member states receive the information necessary to monitor potential risks and ensure compliance with the directive.

Current Situation

Evidently, a different set of information is needed for the evaluation of risks from biological processes or living organisms than for non-living chemical substances. Rather than attempt to modify the Sixth Amendment to the information needs of both chemicals and biotechnology, it may be better to apply the approach of the Sixth Amendment - the information system - and develop a new Directive aimed at the use of genetically modified and exotic organisms.

Thus, it appears that new legislation may be necessary to establish a comparable notification system for the industrial and environmental use of genetically modified and exotic organisms. Because no Member State or any other country yet has legislation in this field, the Community has here an important opportunity to fix the parameters of the regulatory discussion for itself and to provide a model for other countries.

2.C. TESTING AND MARKETING

There is no doubt of the need to assess the potential impacts on human health and the environment from the use of genetically modified organisms in advance of production and marketing so that any necessary preventive measures can be taken. Evaluation of potential risks is only possible if the appropriate data are generated and made available to regulatory authorities. Clearly, this must be primarily the responsibility of the industries which develop the new processes and products.

From this point of view, regulation means setting up a framework for the generation of data about the hazards and exposure to biotechnological processes and products, risk assessment, and the transmission of this information to government and, to some extent, the public.

Title

Council Directive amending for the sixth time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (79/831/EEC) (the so-called "Sixth Amendment" on the testing and notification of new chemical substances).

Objectives and background

The Directive derives from the growing awareness during the 1970s of the role that chemical substances play in damage to human health and the environment. Only a tiny percentage of the some 55.000 chemicals currently on the world market have been extensively tested for their health and environmental effects; we have almost no knowledge of their synergistic effects.

A more comprehensive, preventive approach clearly was needed to supplement the restrictions on specific chemicals that were adopted in reaction to clear problems. Yet it would be impossible to mandate post hoc testing of all of these substances. So the decision was made to focus only on "new substances" - those marketed after a specific date - but to require testing and a comprehensive, initial risk assessment before sizable quantities of these new chemicals could be marketed. At the same time, the Community could ensure that the EC market remained open to these substances by creating a single, EC notification system, thereby overcoming the restrictions in the laws of several Member States which had been adopted beforehand.

2.D. PRODUCTS AND USES

Biotechnology's increasing significance is based upon recent and continuing rapid advances in understanding of biological processes. This understanding has widespread applications for the development:

- Of new processes (e.g. for the manufacture of existing or new products by biological or biomimetic methods);

- Of new uses (e.g. in industry, agriculture, health care, environmental management; based on the advances in understanding, and employing new or existing products);

- Of new products, including modified organisms and cells, molecules produced by them, and molecules designed to interact with existing or modified organisms and cells.

The novel character, potency, and potential for unintended and harmful effects are prima facie reasons for considering whether biotechnology demands new regulatory initiatives on the part of the public authorities.

In this section are considered the regulatory aspects of new products, produced by biotechnology, and of new uses, based upon advances in biological understanding.

The section is divided into the following sectoral areas of products and uses:

2.D.1. Pharmaceuticals and veterinary medicines

2.D.2. Foodstuffs

2.D.3. Chemical-Based Products

2.D.4. Agriculture

2.D.5. Cosmetics

2.D.6. Product liability

2.D.1. PHARMACEUTICALS

The pharmaceuticals sector is currently the sector towards which many of the innovations of biotechnology are directed. The novel character of some of the classes of product may demand corresponding regulatory initiatives[1].

Objective

The results of twenty years of harmonization of pharmaceutical regulations in Europe, governing both human and veterinary medicines, now comprise seven basic Directives, one Council Recommendation and various other texts[2]. These rules cover most medicines, but exclude immunological, blood and radioactive products and homeopathy.

Five important consequences have resulted for the movement of medicines within the Community:

a) The criteria of the quality, safety and efficacy of drugs have been progressively harmonized in Europe, as have certain aspects of procedures for marketing authorization (time-limits, giving of reasons, publication) or for manufacture (quality control, inspections);

---

[1] This sub-section is based upon a fuller paper, "Biotechnology and Rules Governing Pharmaceuticals in the European Community", prepared by the Commission services, published in January 1986, and available on request (in English or French) from DG III-A-3.

[2] Council Directive 65/65/EEC, OJ N° 22, 9.2.1965
Council Directive 75/318/EEC, OJ N° L147,9 6.1975
Council Directive 75/319/EEC, OJ N° L147,9.6.1975
Council Directive 78/25/EEC, OJ N° L11, 14.1.1978
Council Directive 81/851/EEC, OJ N° L317,6.11.1981
Council Directive 81/852/EEC, OJ N° L317,6.11.1981
Council Directive 83/570/EEC, OJ N° L332,28.11.1983
Council Recommendation 83/571/EEC, OJ N° L332, 28.11.1983

A booklet containing these may be bought from the Office for Official Publications of the European Communities, L-2985 Luxembourg - Catalogue N° CB-41-84-515

The relatively voluminous content of these proposals may be summarized as follows:

a) Prior Community consultation on high technology/biotechnology medicines (1st proposal)

It is proposed that competent authorities be obliged to consult through the Committee for Proprietary Medicinal Products or the Committee for Veterinary Medicinal Products, before they decide to authorize, refuse of withdraw any high technology medicine. The firm concerned is a direct party to this procedure which runs strictly parallel to the national examination procedure should be initiated systematically in the case of biotechnology, which the Community considers to be a priority, or at the request of the firms concerned, in the case of other high technology medicaments.

Furthermore, the Member States would be obliged to notify the Commission of any draft national regulations affecting the manufacture, marketing or use of biotechnological medicines, so as to give the Commission the opportunity to adopt regulations for the entire EC, thus preventing futher segmentation of the common market. This control over the proliferation of national regulations would be parallel to the information procedure on technical standards and regulations laid down by Directive 83/189/EEC.

b) Updating of requirements in respect of drug testing and simplification of the procedures for their subsequent review (2nd, 3rd and 4th proposals)

The present programme on the adoption, or amendment, of standards and protocols for drug testing requires the unanimous agreement of the Member States. The current delays of four to six years may well be lenghened with the recent enlargement of the Community. A veto by a national delegation can, in fact, prevent both the adoption of new provisions aimed at achieving increased protection of public health, and the removal of absolete requirements (e.g. in toxicology: reduction of the number of animals tested, gradual introduction of in vitro tests). The Commission is therefore proposing to the Member States that a simplified procedure be adopted for adapting Directives 75/318/EEC and 81/852/EEC to technical progress, a procedure which safeguards public health because it involves the agreement of a very large majority of the delegations.

At the same time, compliance with the principles of good laboratory practice (GLPs) will be explicitly required in the performance of safety tests.

b) The analytical and pharmacotoxicological tests and clinical trials with drugs, performed in accordance with the Community rules, need no longer be repeated within the Community;

c) The tests of manufacturing batches carried out in the produeing country are accepted by the other Member States;

d) The general requirements concerning labelling or package inserts have been harmonized;

e) A common list of colouring matters permitted for use in medicines has been adopted.

The five Commission proposals to promote high technology and biotechnology medicines

In 1983, the Commission requested the European pharmaceutical industry to pinpoint the chief obstacles to the development of biotechnology in this area. The replies were given in February 1984 by EFPIA in a major report entitled "The European Pharmaceutical Industry and the Development of Biotechnology"[3]
Simultaneously, the Commission consulted the various committees on which the competent national authorities were represented.

It was agreed that the Community pharmaceutical rules provide a generally valid basis for the assessment of drugs derived from biotechnology, although some adaptations were desirable. Furthermore, it was necessary to avoid freezing scientific progress in this sector by the introduction of new and massive bodies of legislation which concentrated exclusively on biotechnology. Other advanced technologies also offer new prospects for pharmaceutical research (e.g., new delivery systems, purification under conditions of microgravity, etc.).

Contents

In october 1984, the Commission submitted to the Council a report together with five proposals for legislative measures for high technology medicinal products, particularly those derived from biotechnology. (COM(84)437 and OJ N° C293, 5.11.84). The first proposal refers specifically to "high technology and biotechnology" drugs, whereas the other four measures cover all medicines, but are considered to be especially useful for these "high technology" drugs.

[3] EFPIA, 250 Avenue Louise, Bte 92, B-1050 Brussels

On 18 and 19 March 1985, the Commission arranged an important meeting on the theme of "Pharmacy/Biotechnology" concerning the joint actions to be implemented under existing Community pharmaceutical rules for medicines derived from biotechnology. The participants at the meeting agreed that any application concerning a biotechnological medicine cound be referred to the Committee for Proprietary Medicinal Products (CPMP) or the Committee for Veterinary Medicinal Products (CVMP) for opinion, upon the request of the company concerned, even before an initial national decision has been taken.
More recently, the Commission set up a Working Party on Biological products in collaboration with the CPMP and the CVMP, which will draft flexible guidelines for assessing medicaments derived from biotechnology, on the pattern of the documents entitled "Points to consider" published by the Food and Drug Administration.

During the Pharmacy/Biotechnology meeting, it was considered advisable to extend the Community pharmaceutical rules to biological medicines which are not yet covered by them, since biotechnology should permit the development of improved vaccines and new vaccines in many spheres in which prevention is still difficult or non-existent. The other immunological products and substitutes for blood products which could show rapid expansion will also be taken account of this work.

In response, the Commission intends to cover these aspects with new proposals for legislation on 1987.

The Commission is also paying close attention to the regulatory position of in vitro diagnostic agents, which are likely to make new progress thanks to biotechnology. The Community might have to step in, if national measures lead to further compartmentalization of the markets.

2.D.2. FOODSTUFFS

The increased understanding of human nutrition, the continuing analysis of consumers' changing preferences, requirements and constraints, and the continuing advances in the science and technology relevant to the processing and transformation of the materials used as foodstuffs - mainly of biological origin - all combine to create continuing innovation in the food and drink industry. Biotechnology offers a range of new product possibilities in this sector.

The protection of consumer safety, and integrity in product description and labelling, demand regulatory procedures which are adapted or developed as necessary to the challenges of continuing innovation.

c) Towards protection of pharmaceutical research and development over a minimum period of ten years
(5th proposal)

In all of the industrialized countries, companies have to test their new medicines over many years and then await a detailed examination of their licensing applications before being able to market their products. But firms that wish to market a copy aof a drug, especially a generic product, only have to demonstrate the quality of the copy and, if necessary, its bioequivalence in regard to the original product. Repetition, in animals or humans, of tests whose results are already known is not acceptable from the ethical point of view.

However, it is not fair if a copier can quickly place a drug on the market without contributing towards the heavy costs of all the experiments which led to the medicinal innovation.

The protection normally afforded by patent law is inadequate in this case, since the maximum period of protection of 20 years, is, in fact, reduced to less than 10 years when the duration of the tests and the licensing procedure is taken into account.

Consequently, the solution suggested by the Commission chiefly consists of obliging the copier:

- Either to try to obtain the originating firm's consent to allow reference to be made to the original tests (for a financial consideration);

- Or to wait for 10 years from the date of the marketing authorization of the original medicine before being able to submit a dossier in simplified form retaining mainly the quality of the copy.

Current Situation

On 27 March 1985, the Economic and Social Committee expressed a very favourable opinion on these five proposals. The European Parliament similarly gave a favourable view on 16 January 1986.

The Council is expected to approve this series of five measures in 1986.

Examples of "horizontal" measures include Directives on labelling, additives, and methods of analysis for the monitoring of foodstuffs. "Vertical" measures include Directives on sugar, jams, cocoa and chocolate.

Current Situation

A first meeting with Member States experts has been held to consider the need to adapt some existing Directives to take account of any possible hazards which might be presented by the incorporation of biotechnologically-derived ingredients or additives in foodstuffs. A preliminary reaction would indicate that no adaptations would appear to be necessary in the legal text, but some protocols of assessment would need to be modified. The question is being left under review on a case-by-case basis.

Committees

Scientific Committee for food

Commission decision of 16 April 1974.

Objectives and background

The Commission has over the past twenty years introduced, and the Council has approved, a large number of measures aimed at eliminating technical obstacles to trade in foodstuffs, as in other industrial products, arising from differences between the legislative, regulatory and administrative measures applied in the Member States[4].

The basic general Council Resolutions are as follows:

1. That of 28 May 1969:

   - Establishing a programme to eliminate technical obstacles to trade in general;

   - The same, with particular reference to foodstuffs;

   - Concerning mutual recognition of controls;

   - Concerning the adaptation of directives to technical progress.

2. That of 17 December 1973, concerning industrial policy (which contained a calendar for the elimination of obstacles to trade in both industrial goods and foodstuffs).

   Mention should also be made of the recent document: "Completion of the Internal Market: Community Legislation on Foodstuffs", a communication from the Commission to the Council: COM(85)603 Final of 08.11.85.

Content of current measures

These may be grouped into two classes: "horizontal" measures, applying across many categories and "vertical" specific to a particular foodstuff. They include Council Directives, Commission Directives and other Community instruments. Several subjects are under discussion in the Council.

---

[4] A comprehensive list of Community legislation and related documentation up to 1 June 1982 is given in Documentation Bulletin B6 of the Commission, "L'Elimination des Entraves Techniques aux Echanges des Denrées Alimentaires". A separate 7-page note updates this to 1 March 1985. A new edition (1986) will be published shortly.

2.D.4. AGRICULTURE

The biological basis of all agricultural activity implies corresponding widespread potential for biotechnological innovation, wherever a deeper understanding of biological processes and the development of suitably designed bio-active products allows for more cost-effective production methods.

Not included here are fertilisers (grouped with chemicals, see preceding section 2.D.3.) and veterinary medicines (grouped with pharmaceuticals, see section 2.D.1.).

Objectives

The general aim of the several Directives referred to below is to establish a common European system of regulation for the products concerned, thereby opening the European market to all such products as meet the requirements of these Directives, and to provide harmonised high standards for the protection of the health and interests of the consumers, the health of agricultural animals, and the environment.

The regulations established or proposed in the field of harmonisation of legislation concerning products used for veterinary purposes (excluding medicaments), in animal nutrition or for plant protection have as their aim the admission only of products of proven efficacy, and whose use, in the conditions defined, carries no dangers for human or animal health, or for the environment.

Given the wide range of objectives pursued by the use of the products in question, the regulations established or proposed in this field are specific in the sense that they always relate to groups of products linked by a common objective. One may cite by way of example: the Directives or proposed Directives concerning additives to animal feedstuffs, substances of thyrostatic, oestrogenic, androgenic or gestagenic effect, medicated feedstuffs, EEC type approval of plant protection products, etc.

The regulations in question are therefore established is such a way that all the factors involved by the circulation or use of these products (both in terms of efficacy and in terms of risk to human or animal health, or to the environment) are taken into consideration in the context of the objectives pursued, whatever their source or the production technique.

It follows from this situation that if "horizontal" measures had to be taken for the products of biotechnology, they should be limited, so far as concerns products used for veterinary purposes (excluding medicaments), in animal nutrition and for plant protection, to dispositions concerning research and production.

2.D.3 CHEMICAL-BASED PRODUCTS

Biotechnology can sometimes provide an alternative and more economic method for the production of chemical products. Molecules of biological origin may themselves be classed as chemical products; whether this might be extended to include complex assemblies of diverse molecules such as constitute plasmids, viruses or whole viable organisms, remains to be studied.

Objectives

The aim of Community regulation of chemical products is the provision of a harmonised common market for trade in all chemical products meeting the requirements of the corresponding Directives, with a high standard of safety for the protection of product users, the general public and the environment.

Content of current measures

The basic Directive 67/548/EEC concerning the classification, packaging and labelling of dangerous substances has been discussed under section 2C, Testing and Marketing.

The characteristics of certain chemical substances and preparations have led to specific Directives concerning the products in the specific areas mentioned in the following lists:

Current Situation

The impact of biotechnologically-derived products and products components on the substance of the existing Directives is kept under review.

Content

This Directive covers all products meeting the requirements for admission as additives in animal nutrition. These include natural products, synthetic products and products of bacterial fermentation. The requirements concerned are established by the Directive and specified in the "Guidelines". Other articles govern labelling provisions.

Annex 1 lists additives permitted throughout the Community, Annex 2 those whose use may be permitted nationally for a limited period.

Current situation

The guidelines are currently being updated by the Scientific Committee on Animal Nutrition. In particular, it is envisaged that dispositions will be introduced concerning the declaration of any genetic modification undergone by the microorganisms used for the production of additives, and the possible tests to which such products should be submitted.

The Directive on certain (protein or related) products

Objectives

The objective of this Directive are to ensure that certain novel substances in animal nutrition have nutritional value because they supply nitrogen or protein; in normal use, have no unfavourable influence on human or animal health or the environment; and no effect prejudicial to the consumer through altering the characteristics of the animal products.

Content

This Directive covers biotechnology products meeting the requirements for admission as feedstuffs or feedstuff constituents for animals. These requirements are established by the Directive and specified in the Guidelines which are the object of Council Directive 83/228/EEC. The case of microorganisms subjected to genetic manipulations is included.

Regarding the selection of plants and animals modified by genetic engineering, their utilisation does not present any problems greater than those resulting from classical methods of selection.

Content of Current Measures

In general, the provisions concern:

- The character of the product;

- Criteria for admission and/or examination;

- Control of compliance with the rules;

- Exception provisions;

- Procedural provisions. Under certain of these, management powers have been delegated by Council to the Commission, to act by means of regulatory committees (called standing committees)on which the Member States are represented.

Animal feedstuffs

Title

Council Directive concerning additives in animal feedstuffs (70/524/EEC)
Council Directive concerning certain products used in animal feedstuffs (82/471/EEC)

The Directive on additives

Objectives

The objectives of this Directive are to ensure that all additives used have some beneficial effect; no harmful effects on animal or human health, nor prejudicial alteration of the animal product characteristics; that they are controllable in the fedstuffs; have no prophylactic or therapeutic effects at the levels used; and do not have to be reserved for medical or veterinary use for serious reasons concerning human or animal health (e.g. spread of antibiotic resistance in infective organisms).

Vegetable seed and plant varieties

Title

Council Directives concerning the common catalogue of varieties of agricultural plant species (70/457/EEC); and the marketing of vegetable seed (70/458/EEC).

Objective and content

These Directives concern the admission to the common catalogues of varieties whose seeds or plants may be marketed in the EEC. A variety should be distinct, stable, and sufficiently homogeneous, harmless to other cultivated species. The origin of the variation may be artificial or natural. A Standing Committee elaborates the criteria and methods of examination.

Title

Council Directive concerning pedigree breeding cattle(77/504/EEC).

Objective and content

This Directive authorises free trade within the Community of pedigree breeding cattle, their sperm and fertilised ova, permits the establishment of genealogical records, and recognises the organisations responsible for them.

With the help of the standing zootechnical committee, there are established methods for evaluating genetic value and performance of cattle, recognition criteria for the breeders' organisations, criteria for record-keeping and information to be entered on genealogical certificates.

Title

Council Directive concerning the prohibition of certain substances having hormonal effect and substances having thyrostatic effect (81/602/EEC).

Plant protection products

Title

Council Directive concerning the prohibition of the marketing and use of phytopharmaceutical products containing certain active substances (79/117/EEC)

Objective

The objective of this Directive is to prohibit the use of products - even where appropriate for the end in view - if they present or risk presenting effects harmful to human or animal health, or unacceptable unfavourable effects on the environmant.

Content

This Directive already covers all microorganisms and viruses having an anti-parasite effect. Moreover, the Directive allows for the prohibition, if need be, of a phytopharmaceutical product resulting from biotechnology, which present unacceptable risks for public health or the environment.

The standing phytosanitary committee is consulted regarding modification of the list of prohibited substances and for authorising the temporary use of a product. The annex lists forbidden substances and describes authorised uses. There are two groups of substances: A, mercuric compounds; B, persistent organochlorine compounds.

Current situation

The Commission has prepared a draft directive concerning the type approval of phytopharmaceutical products which could circulate freely in the Community (OJ 212 of 9.9.1976, P.3.).

This proposal envisages the establishment, once it is agreed, of "Guidelines" for the control of the general requirements of the Directive. Draft "Guidelines" have been elaborated, not only for chemical products but also for biological pesticides.

In principle, these "Guidelines" should also be applicable for the evaluation of biological pesticides resulting from genetic manipulation; this question is currently under examination by the Scientific Committee on Pesticides.

2.D.5 COSMETICS

Cosmetics containing ingredients that have been produced by biotechnological agents are already on the market in one country, at least. This could be major area of rapid growth in products.

Title

Council Directive on the approximation of the laws of the Member States relating to cosmetic products (76/768/EEC).

Objectives

The Directive intends both to establish an European system of cosmetics regulation, thereby opening the European market to all cosmetics that meet the requirements of the directive, and to provide harmonised, high standards for the protection of the users of cosmetics.

Contents

The Directive regulates the contents, labelling and packaging of cosmetics. It forbids the use of certain substances in cosmetics, regulates the use of certain other substances, and permits the temporary use of certain substances that are already in use in one or more Member States. It also contains a "positive list" of substances that are definitively permitted.

Cosmetics that comply with the Directive may be freely traded in the European Community. Member states may permit the use of non-EC-approved substances for up to 3 years. A committee is established to decide what substances should be regulated, and to adapt the Directive to technical progress.

The Commission is aided by a Scientific Advisory Committee for Cosmetics.

Current Situation

The Directive will be reviewed for its applicability to biotechnological products.

Objective and content

Under Article 2, the Member States ensure the prohibition (except as under Articles 4 and 5), of

a) The administration to an agricultural animal, by any means, of substances having thyrostatic effect and of substances having oestrogenic, androgenic or gestogenic effect;

b) The marketing or slaughter of animals to which such substances have been administrated;

c) The marketing of the meat of such animals referred to under b);

d) The transformation of meat as referred to under c) and of products based upon or with such meats.

Under Article 3, the Member States forbid the marketing of stilbenes and their derivatives, salts and esters, as well as thyrostatics, with a view to their adminsitration to animals of any species.

Article 4 allows for the use in therapeutic treatment of the products referred to in Article 2.

Articles 5 envisages a Council Decision at the earliest possible date (see below, Council Directive of 31.12.85) concerning the administration to agricultural animals of products for the purpose of fattering.

Title

Council Directive prohibiting the use in livestock farming of certain substances having a hormonal action (31.12.1985).

Objective and content

This Directive was established as foreseen in Article 5 of Directive 81/602/EEC (see above). Other than for therapeutic purposes it maintains the ban established by Article 2 of that Directive.

2.D.6 PRODUCT LIABILITY

The recent adoption of Community legislation on product liability has great implications for the producers of new biotechnology products.

Title

Council Directive on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products (85/374/EEC)

Objective

The Directive was adopted last year after 9 years of discussion in the Council. It imposes strict liability on producers of defective products, for the protection of consumers from defective moveable goods.

Contents

It declares that producers and importers shall be jointly and severally liable for damage caused by defective products. A product is defective when it does not provide the safety which a person is entitled to expect. Primary agricultural products and game are excluded from the definition of "products", although the Member States are permitted to overrule this exception.

The producer shall not be liable if is proved that the state of scientific and technical knowledge at the time when the product was put into circulation was not such as to enable the existence of the defect be discovered, but the impact of this clause on consumer protection and the functioning of the common market must be reviewed by the Commission in 10 years.

The Directive must be implemented by the Member States by mid-1988.

Current Situation

Since mid-1988 is the deadline for formal implementation of the Directive, there is ample time to consider its applicability to biotechnological products.

2.E WASTE MANAGEMENT

Waste management is an issue that affects :

- Industrial processes using biological agents (industrial and agricultural wastes);
- Products (industrial and municipal wastes), and
- Waste treatment facilities (sewage plants, toxic waste treatment facilities).

Title

Council Directive on toxic and dangerous waste (78/319/EEC)
Council Directive on the supervision and control within the EEC of the transfrontier shipment of hazardous waste (84/631/EEC).

2.E.1 The Directive on toxic and dangerous waste

Objectives

The Directive was adopted after an earlier directive laid down a broad framework of control for waste management generally, including toxic waste. It responded to legislation that had been adopted in several member states, and provided a common approach procedures, and the basis of a system of information exchange about toxic waste management by the member states.

Contents

The Directive declares that toxic and dangerous waste may be stored, treated or deposited only by authorised undertakings. It provides for toxic waste management planning and permit systems and defines "toxic and dangerous waste" by means of an annexed list of substances. In particular, the directive lays down general requirements for the appointment of competent authorities to implement the directive, permit procedures for their management, recordkeeping, labelling of transport, inspection powers, separation and packaging, the allocation of costs, and a three-yearly situation reports by the member states to the European Commission.

Current Situation

The Commission has begun a review of the applicability of the Directive to wastes arising from industrial biotechnological processes.

2.E.2. The Directive on transfrontier shipment of hazardous wastes

Objective and background

The Directive was adopted in 1984, soon after the disappearance and rediscovery of a number of drums of contaminated earth from the region around the chemical plant in Seveso, Italy, where an industrial process accident caused the emission of clouds of dioxin to the surrounding area. It partially applies the OECD Council recommendation on a notification system for the international transport of hazardous wastes.

Contents

The Directive lays down a notification system by means of a consignment note for the transport of hazardous wastes from one EC member state to another or to a country outside the EC. Hazardous wastes include those defined by the directive, toxic and dangerous wastes (with certain exceptions) and PCBs.

Wastes must be properly packaged and labelled for transport. Every 2 years, the member states must submit a report to the Commission on the implementation of the directive.

Current Situation

The Directive must be reviewed in terms of its applicability to wastes from biotechnological industrial processes or products and in relation to the 1978 directive on toxic and dangerous wastes.

2.E.3 Other issues

Research is needed on the potential risks to human health and the environment from biotechnological consumer products that could enter the urban waste stream, and on the implication of the use of microorganisms for waste treatment, such as in sewage processing, the detoxification of PCBs. etc.

2.E WASTE MANAGEMENT

Waste management is an issue that affects :

- Industrial processes using biological agents (industrial and agricultural wastes);

- Products (industrial and municipal wastes), and

- Waste treatment facilities (sewage plants, toxic waste treatment facilities).

Title

Council Directive on toxic and dangerous waste (78/319/EEC)
Council Directive on the supervision and control within the EEC of the transfrontier shipment of hazardous waste (84/631/EEC).

2.E.1 The Directive on toxic and dangerous waste

Objectives

The Directive was adopted after an earlier directive laid down a broad framework of control for waste management generally, including toxic waste. It responded to legislation that had been adopted in several member states, and provided a common approach procedures, and the basis of a system of information exchange about toxic waste management by the member states.

Contents

The Directive declares that toxic and dangerous waste may be stored, treated or deposited only by authorised undertakings. It provides for toxic waste management planning and permit systems and defines "toxic and dangerous waste" by means of an annexed list of substances. In particular, the directive lays down general requirements for the appointment of competent authorities to implement the directive, permit procedures for their management, recordkeeping, labelling of transport, inspection powers, separation and packaging, the allocation of costs, and a three-yearly situation reports by the member states to the European Commission.