COUNCIL DECISION

of 15 December 1994

adopting a specific programme of research and technological development, including demonstration, in the field of biotechnology (1994 to 1998)

(94/912/EC)

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 130 i (4) thereof,

Having regard to the proposal from the Commission (1),

Having regard to the opinion of the European Parliament (2),

Having regard to the opinion of the Economic and Social Committee (3),

Whereas by Decision No 1110/94 EC (4), the European Parliament and the Council adopted a fourth framework programme for Community activities in the field of research, technological development and demonstration (RTD) for the period 1994 to 1998 specifying *inter alia* the activities to be carried out in the field of biotechnology; whereas this Decision takes account of the grounds set out in the preamble to that Decision;

Whereas Article 130i (3) of the Treaty stipulates that the framework programme shall be implemented through specific programmes developed within each activity under the framework programme and that each specific programme shall define the detailed rules for its implementation, fix its duration and provide for the means deemed necessary;

Whereas the amount deemed necessary for carrying out this programme is ECU 522 million; whereas the appropriations for each financial year shall be laid down by the budgetary authority, subject to the availability of resources within the financial perspectives and the conditions set out in Article 1 (3) of Decision No 1110/94/EC;

Whereas research in biotechnology may lead to improvements in agricultural and industrial efficiency and viability, to more protection of the environment and health and a better quality of consumer products;

Whereas agriculture should benefit from biotechnology spin-offs to maintain its productivity levels, whilst preferring technical solutions in order to diversify products, reduce environmental impacts, and favour partnerships with European enterprises;

Whereas this programme may make a significant contribution to the stimulation of sustainable growth, to the strengthening of competitiveness and to the development of employment in the Community, as indicated in the White Paper on 'Growth, competitiveness and employment';

Whereas the content of the fourth framework programme for Community RTD activities was established in accordance with the subsidiarity principle; whereas this specific programme specifies the content of the activities to be carried out in accordance with this principle in the field of biotechnology;

Whereas Decision No 1110/94/EC lays down that a Community action is justified if, *inter alia*, research contributes to the strengthening of the economic and social cohesion of the Community and the promotion of its overall harmonious development, while being consistent with the pursuit of scientific and technical quality; whereas this programme is intended to help meet these objectives;

Whereas the Community should only support RTD activities of high quality; whereas the implementation of this programme should be directed towards strategic and, where possible, measurable aims with a view to facilitating coordination with programmes in the Member States and evaluation of the present programme;

Whereas basic research in biotechnology must be encouraged throughout the Community because it provides a source of innovation offering a large range of scientific opportunities to meet the real needs of society;

Whereas the rules for the participation of undertakings, research centres (including the Joint Research Centre (JRC)) and universities and the rules governing the dissemination of research results specified in the measures provided for in Article 130j of the Treaty apply to this specific programme;

(1) OJ No C 228, 17. 8. 1994, p. 107.
(2) OJ No C 341, 5. 12. 1994.
(3) Opinion delivered on 14 September 1994 (not yet published in the Official Journal).
(4) OJ No L 126, 18. 5. 1994, p. 1.

Whereas provision should be made for measures to encourage the involvement of small and medium-sized enterprises (SMEs) in this programme, in particular through technology stimulation measures;

Whereas the Commission's efforts to simplify and accelerate the application and selection procedures and make them more transparent must be continued in order to promote the implementation of the programme and to facilitate the action which undertakings, particularly SMEs, research centres and universities have to undertake in order to participate in a Community RTD activity;

Whereas this programme will help to strengthen synergy between the RTD activities carried out in the field of biotechnology by research centres, universities and enterprises, in particular SMEs, in the Member States and between these and the corresponding Community RTD activities;

Whereas the nature of the activities to be undertaken in this programme requires close cooperation and coordination with activities undertaken under other specific research programmes; whereas such coordination and cooperation should achieve synergies especially in the fields of biomedicine and health, and agriculture and fisheries;

Whereas it may be appropriate to engage in international cooperation activities with international organizations and third countries for the purpose of implementing this programme;

Whereas this programme should also comprise support activities and activities for the dissemination and exploitation of RTD results, in particular towards SMEs, notably those in the Member States or regions which participate least in the programme (close coordination with Activity 3 of the framework programme being necessary to achieve synergies), and activities to stimulate the mobility and training of researchers within this programme to the extent necessary for proper implementation of the programme;

Whereas *ex ante* and *ex post* assessments should be made of possible socio-economic and ecological consequences and of any technological and biological risks and of the social desirability of the activities undertaken in this programme;

Whereas, in view of the rapid progress being made in biotechnology, the programme should also contribute to the development of ethical guidelines for the promotion of biotechnological research;

Whereas any projects aimed at modifying germ cells or any stage in the development of the human embryo must be excluded from the research funded by this programme;

Whereas progress with this programme should be continuously and systematically monitored with a view to adapting it, where appropriate, to scientific and technological developments in this area; whereas in due course there should be an independent evaluation of progress with the programme so as to provide all the background information needed in order to determine the objectives of the fifth RTD framework programme; whereas at the end of this programme there should be a final evaluation of the results obtained compared with the objectives set out in this Decision;

Whereas on 23 April 1990 the Council aodpted Directive 90/219/EEC on the contained use of gentically modified micro-organisms [1] and Directive 90/220/EEC on the deliberate release into the environment of genetically modified organisms [2]; and whereas research financed by the Community must follow all the legislative provisons of the biotechnology regulatory framework concerning the protection of human health and the environment, the protection of workers exposed to biological agents at work, and the protection of animals used for experimental purposes or for other scientific purposes, current at the time of the programme's application;

Whereas this programme should set up a scientific basis to guide the formulation and technical adaptation of biotechnology regulations;

Whereas, to achieve this, there must be an informed public in society which, by making the content, goals and methods of biotechnology transparent, takes part in a competent manner in the discussion on issues as to the desirability of this programme;

Whereas activities undertaken within this programme will take account of common principles such as those embodied in international treaties for the protection of fundamental human rights and of the draft Bioethics Convention of the Council of Europe, once it is adopted;

Whereas the JRC may participate in indirect actions covered by this programme;

Whereas the Scientific and Technical Research Committee (Crest) has been consulted,

HAS ADOPTED THIS DECISION:

Article 1

A specific programme of research and technological development, including demonstration, in the field of

(1) OJ No L 117, 8. 5. 1990, p. 1.
(2) OJ No L 117, 8. 5. 1990, p. 15.

ANNEX I

SCIENTIFIC AND TECHNOLOGICAL OBJECTIVES AND CONTENT

This specific programme fully reflects the orientations of the fourth framework programme, in applying the selection criteria and in specifying its scientific and technological objectives.

Paragraph 4.A of Annex III, first activity of the fourth framework programme, is an integral part of this programme.

The Background

The Commission has presented in its White Paper on 'Growth, competitiveness and employment' an analysis of the potential of biotechnology revealing definite promise based on the omnipresence of bioprocesses and the competitiveness of sectors of application but identifying weaknesses on which Community efforts should have priority.

The economic sectors whose competitiveness significantly depends on biotechnology (pharmaceuticals, chemicals, agriculture, food) account for the employment of 16,4 million people in Europe and exports worth ECU 132,8 billion. Europe has up to approximately 3 000 companies involved in some aspect of modern biotechnology, including a number of world-class chemical and pharmaceutical companies. The sustained growth of these sectors depends on a strong and innovative science base; a highly trained and skilled workforce; the efficiency of technology transfer from the science base to industry; the rapidity with which novel and innovative techniques are incorporated into established practices; the adoption of a multidisciplinary approach to biotechnology-based processes; the validation of scientific principles to underpin a unified market for biotechnology-dervied products; and the harmonious application of bioprocesses as beneficial alternatives to promote the environment, human health and welfare. Progress along these lines will ensure that the estimated sales of non-food biotechnology products of up to ECU 40 billion by the year 2000 can be realized with prominent European participation and a high degree of social acceptance.

This situation is historically unique, as it brings biotechnology into the present reality of scientists, policy makers and industry, whereas earlier research programmes had been based on future promise.

Particularly relevant to bringing the life sciences to play an increasing role in society will be the arrival on the market, under the period covered by the fourth framework programme, of the first generation of transgenic plants endowed with useful new properties, of safer and more efficient vaccines deriving from rDNA work or of natural antimicrobial substances preventing microbial spoilage of food products.

While two other programmes, on biomedicine and health research and on agriculture and fisheries research, will promote the applications of biotechnology within their respective sectoral activities linked to the provision of goods and services, the biotechnology programme itself will create further opportunities by deliberately penetrating the heart of living systems. The flow of information between those three will be the key to success.

It will be the responsibility of the Community to promote under this programme further research work where society would expect the highest returns. This points to privileged areas for the exploitation of new knowledge, all of which experience in common an acute need for cross-linking connected topics and/or integrating large groups of experts on an international scale. Such an integrative approach must also be taken in order to:

— ensure safety when using living cells in the production process,

— give commensurate importance to the European contribution to international genome projects,

— promote reasonable development of agriculture, taking environmental protection into account, and taking appropriate account of animal protection, in so far as, for example, genetic modification of animals and crops or health is involved,

— overcome the purely academic distinctions between specialist areas such as neurobiology, endocrinology or immunology with a view to unravelling cellular and molecular interactions.

International collaboration with the Human frontier science programme will be strengthened, as will links with Eureka projects and national programmes within the Community.

Environmental impact and also, in principle, socio-economic aspects will be taken into account, on the basis of parameters which are as quantifiable as possible, in project selection and the evaluation of research objectives and in evaluating the results.

Translation of the programme's research findings should be viewed in connection with the socio-economic environment and the consequences which are therefore likely and hence calls for special attention. In special cases, demonstration projects must be set up. Dialogue between the research community and public opinion in connection with ethical and social issues and consequencs of biotechnological research and the application thereof will be launched or continued under the programme. As far as research is concerned, what is being sought is not only the obtaining of public 'acceptance' with regard to the consequences of research, but above all the creation of transparency to enable a well informed public to make a responsible judgment on biotechnology and its applications.

This programme will be implemented, as appropriate, in coordination with the specific programmes on: Information technologies; Standardization, measurement and testing, Environment and climate, Industrial and materials technologies, Non-nuclear energy; and Targeted socio-economic research.

Measures intended to encourage the participation of SMEs, in particular technology stimulation measures and links between science parks and biotechnology SMEs, taking account of the needs of those from less advanced regions, as recommended by the White Paper on Growth, competitiveness and employment, will be implemented.

The Proposed RTD Activities

The centre of any biological process in nature or in systems domesticated by man really is the living cell, which functions as a minute factory.

Each cell consumes its raw materiass, converts energy, produces high value molecules as well as wastes, and has learned through evolution how to carry out those constructive processes in equilibrium with its environment. An infinite number of cells in living organisms bred for agricultural purposes, or in fermenters conducted for the industrial supply of valuable molecules, all behave as populations of clean productive units which can be exploited in a sustainable manner. In an attempt to focus biotechnology where it genuinely differs from alternative technologies, all efforts must start with a thorough understanding of how the cell manages to be so succesfully industrious.

I. OBJECTIVES REQUIRING CONCENTRATED MEANS

Area 1: Cell factories

Industrial and environmental exploitations of living cells would hardly be achievable without a global approach integrating contributions from biological disciplines, computer science and process engineering which they have to depend on. New interfaces between biotechnology and other advanced technologies offer opportunities for the integration of biology also with other sciences and technological fields. A multidisciplinary vision of cell factories must be promoted, with the intertwined participation of academic and industrial laboratories.

The primary objective is to reach an understanding of how living cells, micro-organisms as well as animal and plant cells, manage to be productive and how industry can use cellular processes and further design and operate safe, reproducible and sustainable bioprocesses.

Optimal use should be made of relevant biological knowledge generated from studies on: cell biology and signalling, cell multiplication, membrane structure and function, macromolecular interactions, protein folding and secretion, enzyme catalysis mechanisms and control of the enzymatic activity,

biotechnology, as set out in Annex I, is hereby adopted for the period from the date of adoption of this Decision to 31 December 1998.

Article 2

1. The amount deemed necessary for carrying out the programme is ECU 552 million, including a maximum of 7,5 % for staff and administrative expenditure.

2. An indicative breakdown of this amount is given in Annex II.

3. The budgetary authority shall lay down the appropriations for each financial year, subject to the availability of resources within the financial perspectives and in accordance with the conditions set out in Article 1 (3) of Decision No 1110/94/EC, taking into account the principles of sound management referred to in Article 2 of the Financial Regulation applicable to the general budget of the European Communities.

Article 3

1. The general rules for the Community's financial contribution are laid down in Annex IV to Decision No 1110/94/EC.

2. The rules for the participation of undertakings, research centres and universities and for the dissemination of results are specified in the measures envisaged under Article 130j of the Treaty.

3. Annex III sets out the specific rules for implementing this programme, supplementary to those referred to in paragraphs 1 and 2.

Article 4

1. In order to help ensure, *inter alia*, the cost-effective implementation of this programme, the Commission shall continually and systematically monitor, with appropriate assistance from independent, external experts, progress within the programme in relation to the objectives set out in Annex I, as amplified in the work programme. It shall in particular examine whether the objectives, priorities and financial resources are still appropriate to the changing situation. It shall, if necessary, in the light of the results of this monitoring process, submit proposals to adapt or supplement this programme.

2. In order to contribute towards the evaluation of Community activities, as required by Article 4 (2) of Decision No 1110/94/EC and in compliance with the timetable laid down in that paragraph, the Commission shall have an external assessment conducted by independent qualified experts of the activities carried out within the areas covered by this programme and their management during the five years preceding this assessment.

3. At the end of this programme, the Commission shall have an independent final evaluation carried out of the results achieved compared with the objectives set out in Annex III to Decision No 1110/94/EC and Annex I to this Decision. The final evaluation report shall be forwarded to the European Parliament, the Council and the Economic and Social Committee.

Article 5

1. A work programme shall be drawn up by the Commission in accordance with the objectives set out in Annex I and the indicative financial breakdown set out in Annex II, and shall be updated where appropriate. It shall set out in detail:

— the scientific and technological objectives and research tasks,

— the implementation schedule, including dates for calls for proposals,

— the proposed financial and managerial arrangements, including specific modalities for implementing technology stimulation measures for SMEs and other measures, including preparatory, accompanying and support measures,

— arrangements for coordination with other RTD activities carried out in this area, in particular under other specific programmes, and, where appropriate, for ensuring improved interaction with activities carried out in other frameworks, such as Eureka and COST,

— arrangements for the dissemination, protection and exploitation of the results of RTD activities carried out under the programme.

2. The Commission shall issue calls for proposals for projects on the basis of the work programme.

Article 6

1. The Commission shall be responsible for the implementation of the programme.

2. In the cases provided for in Article 7 (1), the Commission shall be assisted by a committee composed of representatives of the Member States and chaired by the representative of the Commission.

3. The representative of the Commission shall submit to the committee a draft of the measures to be taken. The committee shall deliver its opinion on the draft within a time limit which the chairman may lay down according

to the urgency of the matter. The opinion shall be delivered by the majority laid down in Article 148 (2) of the Treaty in the case of decisions which the Council is required to adopt on a proposal from the Commission. The votes of the representatives of the Member States within the committee shall be weighted in the manner set out in that Article. The chairman shall not vote.

4. The Commission shall adopt the measures envisaged if they are in accordance with the opinion of the committee.

5. If the measures envisaged are not in accordance with the opinion of the committee, or if no opinion is delivered, the Commission shall, without delay, submit to the Council a proposal relating to the measures to be taken. The Council shall act by a qualified majority.

6. If, on the expiry of a period of three months from referral of the matter to the Council, the Council has not acted, the proposed measures shall be adopted by the Commission.

Article 7

1. The procedure laid down in Article 6 (2) to 6 (6) shall apply to:

— the preparation and updating of the work programme referred to in Article 5 (1),

— the content of the calls for proposals, and establishment of criteria and mechanisms for project approval and selection,

— the assessment of the RTD activities proposed for Community funding and the estimated amount of the Community contribution for each activity where this is equal to or more than ECU 0,5 million,

— any adjustment to the indicative breakdown of the amount as set out in Annex II,

— specific modalities for the financial participation of the Community in the different activities envisaged,

— the measures and terms of reference for programme evaluation,

— any departure from the rules set out in Annex III,

— participation in any project by legal entities from third countries and international organizations.

2. Where, pursuant to the third indent of paragraph 1, the amount of the Community contribution is less than ECU 0,5 million, the Commission shall inform the committee of the activities and of the outcome of their assessment.

3. The Commission shall regularly inform the committee of progress with the implementation of the programme as a whole.

Article 8

Participation in the area of prenormative research, biodiversity and social acceptance may be open on a project-by-project basis, without financial support from the Community, to legal entities established in third countries, where such participation contributes effectively to the implementation of the programme taking into account the principle of mutual benefit.

Article 9

This Decision is addressed to the Member States.

Done at Brussels, 15 December 1994.

For the Council

The President

A. MERKEL

transcriptional and post-translational events, genetic stability and interactions, microbial physiology and biodiversity, the control of metabolic fluxes and interactions, extremophily, extremotolerance, cellular stress reactions, antimicrobials, etc. also for the purpose of identifying and producing anti-metabolites and inhibitors of enzymes for industrial, pharmaceutical and medical use. Support will be given where the combination of this biology with engineering approaches is most likely to realize the biotechnological potentials of cell factories, particularly in fields such as: the fundamental aspects of fermentation, biotransformation, biocatalysis, bioremediation, biosensors and process control of technologies cell culture and co-culture, downstream processing, etc.

The research tasks will be concentrated on relevant generic topics of interest to industry and other end-users of biotechnology. A typical project will require the integration of biological and biochemical engineering disciplines and will be aimed at solving gaps in basic knowledge as well as technological barriers which prevent the full exploitation of the cell's capability as a factory for the conversion or production of useful biomolecules.

The biosafety of vector systems, cell lines an microbial cultures will be an important consideration of any project selected for this action.

In order to optimize Community resources and exploitation of research results, bioprocess engineering activities will be synergistically and closely coodinated with the contributions invited under the programme on Industrial technologies, or under the Agriculture and fisheries research programme which covers interrelated work applying processing, end-use and scaling-up technologies adapted to industrial conditions. The emphasis of cell factories is in the development and optimization of generic technologies potentially applicable to a large number of sectors.

Area 2: Genome analysis

Genome analysis is a field in which a global approach is essential. The coordination of European networks, supported by previous EC programmes in this area, has enabled these networks to participate succesfully in world-wide genome programmes, thus demonstrating a significant European added value. This effort will be continued and strengthened in the fourth framework programme through the further analysis and sequencing of model genomes, such as *Bacillus subtilis, Saccaromyces cerevisiae* and *Arabidopsis thaliana*. The mapping and sequencing projects will combine efforts to unravel new genes with studies on genetic function; they will make a new effort to encourage the development of novel software and other bioinformatic tools and, where appropriate, to integrate the development and extension of the methodological and instrumentation basis. Also relevant transcriptional and replicative mechanisms will be investigated, as well as higher levels of organization of the genomes, such as now made possible by the new knowledge of complete chromosome composition and structure becoming gradually available.

Methodologies and new tools for genome analysis should be established. These will render possible the association of detailed biological functions with newly unravelled genes from any appropriate model genome. A systematic approach to function search will be allowed through networks of specialized laboratories which on the basis of mutated, deleted or over-expressing strains carrying uncharacterized genes, will rely on standardized tests pointing the way towards the associated functions. Conversely, targeted approaches to biotechnologically important functions will be encouraged through the submission of proposals by consortia willing to screen, in yeast or other appropriate organisms, the collection of disrupted mutants against pre-defined phenotypic alterations with a view to identifying sets of genes coding for industrially relevant pathways. Special attention will be given to additional innovative approaches (i. e.: based on mRNAs, gene structure or promoter similarities, etc.) exploitable for harvesting the maximum biological benefits from existing genome projects. By briging the gap between sequencing activities and the functional characterization of sequences, another entry into the cell factory concept will be provided from the specific angle of the genetic control of metabolic pathways.

Comparative methods will be exploited across different genomes including the human genome. These approaches will include the development of new mapping procedures based on the use of homologous DNA probes from model genomes, heterologous expression through cDNAs in bacteria or fungi and

development of new informatic software to improve detection of functional or structural homologies. The development and sharing of advanced technologies and a decentralized pool of exchangeable clones, probes and data will be organized.

With a view on possible medical applications, work on the human genome will be concentrated in the Biomedicine and health research programme. However, comparative approaches and related technology developments will include human DNA and, with respect to human cells, the same limitations will be applied, i.e. alteration of germ cells or any stage of embryo development with the aim of modifying human genetic characteristics in a hereditary manner is excluded from the programme objectives. The coordination with accompanying measures on the ethical, social and legal aspects, executed elsewhere in the programme, will be emphasized.

Area 3: Plant and animal biotechnology

(a) *Plant molecular and cellular biology*

Plant molecular and cellular biology, including protein engineering physiology and pathology, at the crossroads of agricultural, industrial and environmental issues, will be developed by stressing the need for an integrated research. Particular attention will be given to the molecular understanding and eventual modification of relevant plant processes as an approach leading to new tailor-made market-relevant agricultural or forestry products, and to production methods compatible with the environment, health and consumers' demand, which areas are included within the Agriculture and fisheries research programme. Identifying, characterizing and exploiting useful biological traits of agricultural and industrial relevance, in terms of quality improvement and greater environmental acceptability, and their corresponding genes would be the main target for such activity.

These include: pest an disease resistance; stress tolerance; quality, quantity and tissue specific expression of valuable plant metabolites such as starch, oils, valuable protein, fibres, pharmaceuticals in leaves, seeds, roots, etc., at the cell level; improved enzymes and macromolecules for processing; developmental pathways, reproduction and regeneration; improved enzymes and macromolecules for processing.

Underpinning science will have to be considered, such as that allowing control of stable heterologous expression and of stability of expression, cell structural analyses (to understand and regulate the traffic of molecules), or identification of nutritional and health properties of food and feed components (to fine tune molecular breeding objectives towards crops displaying healthy attributes), which is complementary to an important objective of the Agriculture and fisheries research programme. A typical project will attempt to achieve the appropriate level of integration of plant science with end-user technology, and of target-oriented research with those areas of eukaryotic biology where key knowledge is stemming from (genome analysis, structural analysis of macromolecules and enzymes, signalling pathways, bioinformatics, etc.).

(b) *Animal physiopathology*

Low resolution maps of a few farm species will be available shortly. Physical maps that are tightly related to the genetic maps must be estblished. Gene mapping will be very useful to select animals for traits which are under the control of many genes (quantitative trait loci or QTL) such as the resistance to diseases, to eliminate genes with harmful effects or to transfer new genes of interest from various strains of animals by appropriate breeding. European networks will be established or extended to map the genomes of animals, including fish, chosen for their importance in agricultural, industrial or fisheries sector. Such studies will greatly advance our knowledge on QTL analysis. Research activities related to animal disease resistance, developmental biology, and basic reproductive mechanisms of the farm animals will also be supported, due consideration being given to animal welfare and animal genetic diversity principles.

In so far as an understanding of certain severe human and animal diseases requires transgenic and other animal models to be developed, studies will be conducted to allow the development of new techniques to raise animal models with precise and predicted genetic characteristics designed to provide information of high quality and specificity in relation to pathological disorders. Research

will be encouraged where it produces evidence on the physiological roles of regulated/deregulated pathways, or genetically-encoded factors during the evolution of any particular disease.

An equally important objective will be the development of new methods for somatic gene therapy, particularly vectors to transfer genetic material capable of complementing weakened or missing gene functions potentially of medical importance. The programme will also consider other associated techniques to overcome barriers precluding the general applicability of somatic gene therapy protocols, with regard to recipient cells. Models which could be used for the evaluation of the method will also be considered.

Concerning the last two subjects which might impinge on future medical and veterinary applications, the emphasis of this programme will remain on the design and development of safe experimental tools giving rise to possible synergies with the Biomedicine and health or Agriculture and fisheries research programmes.

Area 4: Cell communication in neurosciences

Cellular biology, molecular biology inculding molecular genetics and biochemistry, pharmacology will be combined with genetic engineering in order to promote multidisplinary studies on cell physiology and cell communication of the nervous system including associated cells and with a view to promoting neurosciences using the support of these disciplines. Special attention will be paid to the physiology of the development of the nervous system, the management of information (intra- and intercellular events) by the nervous cells, possible cellular dysfunctions such as those associated with human and animal degenerative diseases, the design of neuro-drugs taking advantage of biotechnology (e.g. molecular modelling), the development of *in vitro* tests for the pharmaco/toxicology of such substances.

This programme will concentrate on approaches at molecular and cellular levels and the development of related tools.

The four actions described will be supported by specific measures designed to improve interactions between research and research teams, on the one hand, and practical applications and users, on the other. Ethical issues, questions concerning safety provisions, public information issues and — in particular with a view to the link between research and industry — training issues will play a role in this.

II. OBJECTIVES MAINLY ADDRESSED BY CONCERTATION

Four other activities will be approached mainly by concerted actions supplemented where appropriate by cost-shared actions. The objective in this case will be to share work and information in fast-moving fields, and to pool data or methods which may provide useful bases upon which science policy and regulatory measures could be developed further.

Area 5: Immunology; transdisease vaccinology

In immunology and immunotechnology, new biotechnology-derived substances in relation with the immune system (monoclonal and recombinant antibodies, immunotoxins, cytokines, growth factors, receptors, adhesion molecules etc.) may reveal a range of effects preventing or controlling major human and animal pathologies. Special attention will be given to the possiblity to initiate mechanistic studies of the interaction of these substances with the physiology of the organism, in order to develop new pharmacological concepts which should be relevant to specific interests of the Biomedicine and health research programme.

Research on transdisease vaccinology will be encouraged across Europe (live carriers and non-live carriers for vaccines, their ability to induce immunity to normal or pre-immunized organisms, their safety in normal, immunocompromized hosts and in other species likely to be in contact — antigen delivery systems, particularly those giving the possibility to administer a unique dose — mucosal and peroral vaccination — induction of T and/or B immune responses, and host-pathogen interactions, etc.). Model diseases of pathogenic and/or oncongenic origin used for the demonstration of the new methods will have to be chosen for their importance in human or veterinary medicine.

Area 6: Structural biology

The systematic determination of the three-dimensional structures of biomolecules will contribute to the knowledge of the relationships between primary structures and the tertiary structures of biologically active macromolecules and, even more, the quaternary structures of the multi-subunit complexes which mediate most biological activities. The accelerating accumulation of structural information underlines the need to store, retrieve and analyse this information (see Infrastructures).

The objective is the understanding of the structural basis of biomolecules and complexes (proteins, DNA, RNA, carbohydrates and lipids) which is essential to the discovery and refinement of new biochemical entities. The improvement of the resolution of the techniques and the growing size of structures that they can assess will be crucial. Such technical developments will allow work on subcellular structures, e.g. chromosomes, splicesomes, replisomes, with further implications for biological understanding.

Biological macromolecules that catalyze chemical reactions (enzymes, abzymes, ribozymes) are particularly of interest for industry. To obtain biomolecules with new properties, two different and complementary ways are to be considered. On the one hand there is the rational design of biomolecules which requires a detailed understanding of, and control over biomolecular conformation and reactivity (position of functional groups, folding properties). On the other hand there is *in vitro* directed molecular evolution whereby multiple rounds of selection, amplification and mutation, leading to biomolecules with the desired properties, are applied.

Finally, the emerging interface of biology and electronics will be stimulated with a view to allowing the integration of competences in structural biology, molecular engineering and nanolithographic patterning towards new possibilities of designing functional units which could incorporate modifications at the scale of the nanometre.

Area 7: Pre-normative research, biodiversity and social acceptance

Community efforts will be brought into closer harmony with national efforts when this leads to methods or data that would consolidate the rational basis of regulatory approaches and would support the development of internationally accepted standards and systems of risk assessment. This activity will have synergies with other programmes, e.g. Biomedicine and health, Industrial and materials technologies, Environment and climate, Agriculture and fisheries. This activity will be encouraged in three fields: the development of toxicological/pharmacological *in vitro* tests, the biosafety evaluation of biotechnology-derived products, and the development of processes solving environmental problems.

As far as *in vitro* testing is concerned, priority interest will be in neurobiology, immunology and developmental pharmaco/toxicology as well as in the development of cultures or co-cultures of cells maintaining their normal metabolism, with a clear view to providing methods and data usable as alternatives to animal testing and eventually made available for prevalidation studies, such as the Biomedicine and health research programme has planned.

As far as the biosafety evaluation of transgenic organisms and derived products is concerned, special emphasis will be given to the risks possibly associated with releases of genetically modified organisms, including recombinant life vaccines, into the environment and to the scientific support to the implementation of the Community's regulatory framework ensuring safety for man and the environment.

This should be approached at two levels. First at the basic level of molecular ecology and, second, at the level of prenormative research, which gathers data of particular usefulness to regulatory authorities when carrying out risk assessments under Community legislation.

Most of these studies, and particularly prenormative research, should be complemented by field tests in order to take into consideration environmental factors.

Microbial ecology does not only serve prenormative research but it is an indispensable element for studies on environmental biotechnology and microbial biodiversity.

In order to lead environmental biotechnology to useful results, knowledge acquired from microbial ecology, microbial diversity and bioprocessing (see cell factories) should be appropriately combined, aiming at the prevention, detection of hazardous compounds and the remediation of the environment.

Microbial diversity should be better understood, with particular attention to microbial characterization in the natural environment, isolation strategies and cultivation procedures, direct analysis of microbial communities through DNA sequencing and RNA analytical methods, biosystematics using molecular techniques and markers, screening strategies and conservation.

Plant and animal diversity studies will also be part of the more general approach which consists in using molecuar and cellular biology to bring about methological improvements for the conservation of genetic resources or/and for exploring unexploited diversity.

Particular emphasis will be put on analysing lateral issues such as public perception and the acceptance of biotechnology in general, in liaison with the horizontal activity on ethical, social and legal aspects of the life sciences and technologies.

Area 8: Infrastructures

The development of user driven centres for bioinformatics, information infrastructures and resources as a service and support to wider scale research by the Community or its Member States should be encouraged. This should include the collection, annotation, maintenance and distribution at a European scale of sequence and bioresource database, the coordination of national and specialized nodes of biocomputing and the development of biological collections. The services shall aim to support and underpin the overall objectives of the Biotechnology programme, particularly in the areas of genome sequencing, structural biology and biodiversity. Special attention shall be paid to ensure that these services match the research needs, including those of large industry and SMEs.

Necessary actions should be taken as to ensure proper publicity and wide spread distribution of collections and information contained in databases. In the case of biological collections, coupling of specimen distribution channels and related information systems will be fostered in order to ease access to repository catalogues and eventual ordering and delivery.

Large scientific and technical communities should be able to have simple and, as far as possible easy access to deposit and retrieve information from diverse sources of data, including bibliographic indexes. To achieve these objectives, the following facilities should be provided by the information services: user-friendly interfaces; cross-reference and navigation mechanisms between data entries; interconnection of diverse national and Community-wide databases via European networks; extensive use of standards and, when necessary, definition of new exchange formats. Close cooperation with existing R&D programmes in the field of Information Technologies should be encouraged in order to benefit from their findings and achievements.

Research activities on novel bioinformatics techniques will be supported whenever they could contribute to improve the service aspect of the mentioned tasks.

III. OBJECTIVES TREATED BY MEANS OF HORIZONTAL ACTIVITIES

Demonstration activities in biotechnology

New biotechnologies stemming from forefront European research encounter specific difficulties and socio-economic barriers which preclude their full exploitation in the market place. European biotechnology researchers continuously produce a rich flow of opportunities that can benefit society in many different ways. However, a variety of techno-ecnomic uncertainties, inherent to the adoption of these complex interdisciplinary processes (which are not easily understood by the technology users, or even, in some way or another, feared by the public), hamper the full exploitation of research efforts and increase the time and risks involved in the market penetration of well established, new

biotechnological concepts. Community support to carefully selected biotechnology demonstration activities will encourage European concerns to deploy the costly, critical-mass, interdisciplinary resources needed for overcoming those hurdles and will, therefore, facilitate the adoption of new biotechnologies by potential users in industry and services, as well as the end consumers. To this end, when appropriate, platforms of technology-users, including industry platforms for small and medium-sized enterprises ('extended audiences') might be created in order to maximize both the impacts of the demonstration projects and the awareness about the techno-economic potential of the new technology subject to the demonstration.

Biotechnology demonstrations can be linked to any scientific and technological research area considered within this specific programme and will be developed in close cooperation and synergy with the Agriculture and fisheries, and the Biomedicine and health research programmes, integrating resources from all disciplines relevant to project implementation. A high thematic flexibility is needed for the bottom-up identification of demonstration activities from which the highest impact is to be expected, both in strengthening the competitiveness of European industries, and in promoting an objective public understanding of biotechnology. Particular focus areas might include, amongst others: novel cell technology and biochemical engineering approaches with the potential to maximize benefits from the cell factories; new vaccines; use of transgenic plants and animal models; bio-remedial application of micro-organisms for the removal of toxic wastes.

Ethical, social and legal aspects (ESLA)

The participation of the Community in a dialogue embracing all relevant socio-political and bioethical positions, taking into account cultural differences and existing national policies will be encouraged and, where appropriate, deliberately organized. Whilst recognizing existing national and international points of view, scientific studies will focus on transdisciplinary approaches of selected topics, of high relevance and possible impact within the biotechnology programme, and on the applications of their results (e.g. genome research, biodiversity, intellectual property, in particular research exemption for patents, introduction of new biotechnology products for industry and environment, transgenic animals, neurosciences). Where appropriate, these activities will also contribute to identifying areas for the application of common principles and for agreeing their best possible interpretation. The continuous updating of scientific data in support regulatory processes will be facilitated.

Public perception

Specialized working groups will be established to prepare *ad hoc* initiatives, like workshops, conferences, reports and surveys important for the public perception of biotechnology. Appropriate and timely information about research objectives, scientific breakthroughs, knowledge and added value/benefits obtained, and obstacles are the key elements for the public perception of biotechnology which must be reviewed in an open discussion about possible applications and implications of the results of this new technology. It is important that in addition to information dissemination, in particular through conferences and surveys, it could be demonstrated that suggestions and concern expressed from the public side are considered in strategic planning.

Socio-economic impacts

An important factor for the competitiveness of European industry and employment will be the adoption of up-to-date and sustainable production systems. Consequently the opportunities offered by biotechnology will be promoted. In large industrial areas (agro-industry, pharmacy, fine chemicals etc.) while new products and productions tend to be based on biotechnological research (for example new pharmaceuticals), the actual production will rely in general on traditional technologies. Efforts will be made to assess these indirect effects of the biotechnology research programme, by which new tools and methods get amalgamated with an existing background of established practices, to the benefit of industrial branches already in place. At the same time, questions will be asked on the rise of new industrial sectors based on opportunities offered to research SMEs, and on the specific related handicaps/chances experienced in Europe.

ANNEX II

INDICATIVE BREAKDOWN OF THE AMOUNT DEEMED NECESSARY

	ECU million
Objectives requiring concentrated means	
Area 1. Cell factories	121,5
Area 2. Genome analysis	88
Area 3. Plant and animal biotechnology	133
Area 4. Cell communication in neurosciences	33
Objectives mainly addressed by concertation	
Area 5. Immunology, transdisease vaccinology	39
Area 6. Structural biology	55
Area 7. Prenormative research, biodiversity, social acceptance	52,5
Area 8. Infrastructures	30
Total	552 (1) (2)

(1) Of which:
— a maximum of 3,5 % for expenditure on staff and 4,0 % for administrative expenditure;
— ECU 5,0 million for the dissemination and optimization of results;
— up to 5 % for specific measures in respect of SMEs.

(2) Up to 6 % of the funds will be allocated to horizontal demonstration activities; up to 3 % of the funds will be allocated to horizontal activities on ethical, social and legal aspects and on public perception and socio-economic impact studies; up to 7 % of the funds will be allocated to horizontal training activities.

This breakdown does not exclude the possibility that a project could relate to several areas.

ANNEX III

SPECIFIC RULES FOR IMPLEMENTING THE PROGRAMME

The programme will be executed through indirect action, whereby the Community makes a financial contribution to RTD activities out by third parties or by JRC institutes in association with third parties:

1. Shared-costs actions of the following types:

   (a) RTD projects (including demonstration projects) carried out by undertakings, research centres and universities, including, where appropriate, basic research of an industrial relevance; consortia for integrated projects with a common objective may be encouraged.

   Demonstration activities, as defined in Annex III of the framework programme, are intended to overcome the obstacles hindering the utilization of new technologies and to build the bridge between technology producers and users. Feasibility studies and awards to those who get involved in these technologies may also be included.

   Community funding will normally not exceed 50 % of the cost of the project, with progressively lower participation the nearer the project is to the market place. Those universities and other institutions which do not have analytical budget accountancy will be reimbursed on the basis of 100 % of the additional costs.

   (b) Thematic networks, bringing together primary producers, manufacturers, end-users, universities and research centres on a generic technology, in order to facilitate the incorporation and transfer of knowledge and mobility of researchers, and to ensure that greater account is taken of market needs.

   Community funding will normally not exceed ECU 20 000, in average per partner and per year, covering up to 100 % of the additional costs for the coordination of the action. Members of a network could also apply for research projects under normal procedures.

   (c) Technology stimulation to encourage and facilitate participation of SMEs in RTD activities:

      (i) by granting awards for carrying out the exploratory phase of an RTD activity, including the search for partners, during a period of up to 12 months. The award will be granted following the selection of an outline proposal to be submitted normally by at least two non-affiliated SMEs from two different Member States. The award will cover up to 75 % of the cost of the exploratory phase, without exceeding ECU 45 000 or ECU 22 500 in the exceptional case of a single applicant SME; and

      (ii) by supporting cooperative research projects, whereby SMEs having similar technical problems but not having adequate own research facilities, engage other legal entities to carry out RTD on their behalf. Community funding for cooperative research projects, involving normally at least four non-affiliated SME's from at least two different Member States, will normally cover 50 % of the cost of the research.

      Following an initial call, in both cases proposals may be submitted at any time during the period covered by the work programme being implemented.

2. Preparatory, accompanyig and support measures, such as:

   — studies in support of this programme and in preparation for future activities,

   — support for exchanges of information, conferences, seminars, workshops or other scientific or technical meetings, including intersectoral or multidisciplinary coordination meetings,

   — use of external expertise, including access to scientific databases,

   — scientific publications and activities for the dissemination, promotion and exploitation of results, in coordination with the activities carried out under the third activity; the factors liable to encourage

use of results will be taken into account from the outset and throughout the duration of RTD projects, the partners in which will constitute a key network for diffusion and exploitation of results,

— analysis of possible socio-economic consequences and technological risks associated with the programme, which will also contribute to the programme 'Targeted socio-economic research',

— training actions for research covered by this programme in order to enhance employment skills and to facilitate technology transfer to industry,

— technology stimulation to encourage and facilitate participation of SMEs in RTD activities: by mobilizing all above means (publications, interactions with industry platforms, specific training, fact-finding studies, partnering events, etc.) to identify and possibly overcome some of the handicaps hindering a high level of participation of SMEs in the conduct of biotechnological research and innovation, with emphasis on procedures at the interface of RTD activities and firms involved or interested in projects,

— independent evaluation of the management and execution of the programme and of the implementation of the activities,

— measures in support of the operation of networks for increasing awareness and providing decentralized assistance to SMEs, in coordination with the Euromanagement auditing activity of RTD.

Community funding may cover up to 100 % of the costs of these measures.

3. Concerted actions, consisting of the coordination of RTD projects already funded by public authorities or private bodies. The Member States will help the Commission to identify relevant laboratories or institutes, in order to ensure that no major activities are left out of this concertation process.

The concerted action option can also be used under the programme as a way of establishing the feasibility and defining the content of proposals for shared-cost research activities.

Community funding will cover up to 100 % of the costs of the concertation.