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PROPOSAL FOR A MULTIANNUAL COMMUNITY
PROGRAMME OF RESEARCH AND DEVELOPMENT
IN BIOMOLECULAR ENGINEERING
(indirect action 1981-1985)

(presented by the Commission to the Council)

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A SUMMARY OF THE COMMUNITY PROGRAMME IN BIOMOLECULAR ENGINEERING

The present proposal concerns a Community Research and Development programme in the field of biomolecular engineering. It aims at the domestication of genes and of their products.

The programme is essentially motivated by the need to allow the optimal exploitation by man of the fundamentals of modern biology and to stimulate in the Community the developments in applied fields where nations such as the U.S.A. and Japan have gained a considerable advance. Two main themes form the basis of the integrated research proposed for Community action. The first one deals with the development of the second generation of enzyme reactors, that is to say, with the exploitation of complex enzymatic reactions for the synthesis of elaborated products important to European industries. The second concerns the application of genetic engineering methods to organisms of importance for European industries. Considerable attention is given, in this case, to the development of suitable host-vector systems and to the solution of the important practical problems which prevent the control of expression of foreign DNA.

The programme is composed of the six following integrated projects :

1. Development and evaluation of new reactors using immobilized multienzyme systems including those requiring multiphase environment and cofactor regeneration.

2. Development of bioreactors for industrial and human detoxification.

3. The transfer of genes from diverse sources to the bacterium Escherichia coli, Saccharomyces cerevisiae and other suitable micro-organisms.

4. Development of cloning vehicles.

5. Novel gene transfer in species important to biological industry.

6. Studies of strain stability and improved methods for detecting contamination.

These six projects represent a continuum of interest for industry and agriculture and fall into the area of mission oriented research. As such, they are concerned with recognising and investigating a series of " bottlenecks " which at present restrict the transfer of ideas and techniques in biomolecular engineering to industrial and agricultural problems.

The programme is to be implemented as an indirect action by means of cost-sharing contracts with both private and public organizations in the Member States. Full use will be made, in the case of patentable discoveries, of the Council regulation (EEC n° 2380/74) which adopts provision for the protection of intellectual property and a procedure of consultations will be established, with the help of a ACPM, for the continuous adaptation of the programme to the specific needs of European industry and of European Agriculture.

The global needs for the whole duration of the programme (1981-1985) are estimated to amount to 26 million EUA and 6 staff.

PROPOSAL FOR A MULTIANNUAL COMMUNITY PROGRAMME OF RESEARCH AND DEVELOPMENT IN BIOMOLECULAR ENGINEERING

(Indirect action : 1981-1985)

1. INTRODUCTION

1.1 Elaboration of the programme proposal

The basic principles underlying the present proposal have been previously defined by the Commission at the 1976 Milano Symposium "A science and technology policy for the European Community" and in document COM (77) 283 submitted to CREST on July 8, 1977.

A first description of a possible Community action in the field of Applied Molecular Biology (document XII/207/77) was thereafter submitted to CREST which, on December 7, 1977, requested the Commission to intensify during 1978 its studies relating to Molecular and Cellular Biology. Following this recommendation, the Commission expanded the dialogue established since 1975 with national experts and asked that two studies be executed :

- Genetic Manipulations in Applied Biology; study contract 346-77-7 ECI NL, with Professor A. RORSCH (Leiden University, the Netherlands); EUR 6078,1978.
- Production of Biological Catalysts, Stabilization and Exploitation; study contract 345-77-6 ECI F, with Professor D. THOMAS (Université de Technologie de Compiègne, France); EUR 6079, 1978.

These two studies, together with the initial document (XII/207/77) prepared by the Commission, provide a detailed appraisal of the present state of the arts in biomolecular engineering of the importance of the field in agricultural and industrial developments and of the research need to be carried out for allowing major break-throughs to occur. The three documents, which were extensively discussed with numerous national experts and analysed in study group meetings, constitute the basis of the present programme proposal in biomolecular engineering.

1.2 General purpose of the proposal

The Commission has defined (1) the general objectives of the Community research and technology policy. These are :

- long-term supply of resources (raw material, energy, agriculture and water) ;

(1) Doc. COM (77) 283 final, "The Common policy in the field of science and technology", 30/6/1977.

- promotion of internationally competitive economic developments;
- improvement of living and working conditions;
- protection of the environment and of nature.

The purpose of the present programme in biomolecular engineering is :

- to contribute to the improvement and exploitation of the modern techniques which allow the production of organisms with new genetic properties important for bio-industries;
- to stimulate the development and use of modern industrial production and detoxification methods which are based upon the utilization of immobilized enzymes , immobilized cells or specialised organisms for the catalysis of specific chemical reactions;
- to reduce, in this manner, the strong deficit in trade and in patents in biotechnology which presently characterizes the relationship between the Community of Member States and other industrial nations;
- to protect, in this manner, the environment of the Member States through the establishment of methods involving a decrease of waste products or leading to new detoxification procedures.

1.3 Conjectural risks associated with biomolecular engineering

The European biological industry has an excellent record with respect to safety and the purity of its products. Nevertheless conscious of the possible consequences for health and safety which may arise in the Member States from the expansion of research in biomolecular engineering, the Commission, in parallel to the preparation of the present proposal has taken initiative for evaluating possible risks associated with such development. A study contract (No. 430-78-5 ECI) has been prepared at the Microbiological Research Establishment, Porton Down, U.K. by Drs. K. Sargeant and C. Evans concerned with the setting of European standards and possible regulations as well as outlining research areas which need to be stimulated in order to provide industry with new ways of detecting contaminants and monitoring variability in industrial organisms (EUR 6349, 1979).

With reference specifically to conjectural risks associated with genetical engineering a proposal for a Council directive regulating recombinant DNA work (Doc. XII/698/78, Doc. XII/278/78 submitted to CREST in 1978) has been prepared.

1.4 The view of European industry

The Commission organized in Brussels, on September 18-19, 1979 a meeting of representatives from most of the major European Industries actively involved in research and development in biomolecular engineering.

It was generally agreed that the programme represented a continuum of interest for industry and that the proposals fell into the area of mission oriented research. As such it was concerned with recognizing and investigating a series of "bottlenecks" which at present restrict the transfer of ideas and techniques in biomolecular engineering to industrial problems. The results arising from such a programme of mutually related projects were expected to be of direct use to industry in the mid-long term. The meeting expressed the strong view that the importance of the programme to European industry would necessitate a speedy route towards implementation. Projects have been modified in line with suggestions received at the meeting.

2. STATE OF THE ART AND POTENTIALITIES OF RESEARCH IN BIOMOLECULAR ENGINEERING

Modern biology is extremely diversified and probably represents the branch of the Natural Sciences with the largest number of sub-disciplines (biochemistry, genetics microbiology, cell biology, physiology, morphogenesis , systematics, plant and animal anatomy, ecology, ethology, paleontology ...) and the strongest potentialities for additional contributions to the welfare of man or to the protection of mankind from dangers affecting its requirements for survival and expansion. This increasing importance of biology, expressed nowadays through the terms of "new biology" and "biological revolution", essentially results from the entrance in classical biology, since the end of World-War II, of several scientific traditions, such as those of physics and chemistry, which not only lead to the description of life at the cellular and molecular level but also provide the necessary tools for domestication and transformation of the basic properties of living organisms important to man.

Although, because of lack of time, of investment and of concerted planning on a very large scale, the newly acquired biological knowledge has not yet really been applied in the daily life of man, it is already possible to define two of the foundation stones upon which important applications will be founded :

1) the development of enzyme technology, that is to say the use of biological units in chemical manufacturing (enzyme engineering);
2) the recently acquired capacity of man to break-down biological isolation and transfer genetic information between distantly related organisms (genetic engineering).

Enzyme engineering and genetic engineering are two very closely related fields of work which deal with the domestication of genes and of their products; they constitute different phases of attempts to exploit to a maximum the continuous flow of discoveries which are made by the molecular geneticist and by the enzymologist. For all practical purposes enzyme engineering and genetic engineering, as defined below, can be conveniently grouped under the heading "Biomolecular engineering".

2.1 Enzyme engineering

This field of work, often referred to as enzyme technology, is based upon the possibility to produce, isolate, purify and immobilize enzymes and to use their unique capabilities for the catalysis of extremely specific chemical reactions. Through the immobilization of enzymes or of cells on an appropriate matrix or through circulation of the substrate across a bed of immobilized enzyme, it is now possible to develop compact and specific molecular converters (bioreactors) able to yield on a large scale and with a minimum of energy losses or of insults to the environment, the range of complex products needed by man and obtained in the past by polluting and high-energy consuming man-made machines.

Already, and particularly in Japan and in the U.S.A., industrial applications are underway (for a detailed inventory see study contract 345-77-6 by D. THOMAS) which allow the production of L-amino acids (from acyl-DL-amino acids by aminocyclase), high fructose syrup (from corn starch by glycoamylase and glucose isomerase) and semi-synthetic

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penicillin (through the use of penicillin acylase and penicillin amidase) It has been calculated, in the case of fructose syrup, that the cost of the method presently in use in the United States is ten times lower than the conventional batch process using native enzymes. Many other industrial developments, and particularly those involving the synthesis of new products rather than simple degradation or transformation processes, are in sight. Research has shown for instance that it is possible, through enzymatic synthesis, to produce important polypeptide antibiotics and one may list, as other possible examples of applications for the future, the synthesis of steroids, vitamins and organic acids, the modification of petrochemicals and heterocyclic compounds, the synthesis or modification of flavours and fragrances, the removal of pesticide residues from food and water supplies, the production of novel food sources as single cell protein, continuous malting and nitrogen fixation with immobilized cells. Such achievements may be expected to occur if a strong research effort is carried out to develop stabilized multienzyme multiphasic systems able to perform very specific syntheses involving co-factor molecules and producing compounds with high added value.

In addition, biochemical engineering, through the construction of enzyme electrodes, enzyme membranes and paper-enzyme grafts, may also contribute significantly to the production of new analytical devices particularly well adapted for detection and measurement. An apparatus based on a glucose electrode is already commercialized in the United States and diagnostic papers, prepared by grafting enzymes on filter paper impregnated with appropriate indicators, are commercially available for urea and glucose.

2.2 Genetic engineering

Modern techniques, and most particularly the use of recently discovered enzymes, called restriction enzymes, now allow the arrangement of genetic material in combinations which at the moment do not exist under natural conditions. The general method involves the isolation of DNA from a donor organism, its fragmentation by restriction enzymes into groups of one or more genes, the coupling of selected fragments to a vector (usually a virus or a constituent of the cell to be used as host) and its introduction in a host-cell which may be propagated to form populations of identical cells called clones.

Provided that the genetic material transferred in this manner replicates and expresses itself in its new surroundings, there are theoretically no limits to the range of organisms with new properties which may be produced through the use of recombinant DNA technology. In some industrially important bacteria such as the Actinomycetes the use of suitable plasmids to act as vectors to bring about gene transfer between a number of different species has given rise to the possibility of producing new pharmaceutical products such as antibiotics. However, the cloning and expression of foreign DNA into widely unrelated host-organisms are often difficult to achieve. Yet, DNA sequences coding for human placental lactogen and human growth hormone have been cloned in Escherichia coli (a widely used experimental bacterium) and there are several instances (e.g. expression in E. coli of a chemically synthesized gene for the hormone somatostatin and of the yeast structural gene for the enzyme imidazole-glycerophosphate dehydratase) where it has been shown that the expression problem could be overcome.

The first efforts for practical achievement must be centred upon the specification of the genetic material to be transferred, its incorporation and multiplication in appropriate cells as well as the regeneration of protoplasts into mature organisms.

It is obvious, in view of these prospects and of these results, that recombinant DNA technology opens up new avenues for fundamental and applied work which will certainly lead to a great improvement in our knowledge of genetic structures and genetic functions and which, in the long run, could completely revolutionize certain production methods in industry. While growth hormone and insulin represent well known examples of products which could be elaborated at industrial level by manipulated bacteria, several other substances (calcitonin, prolactin, neurotransmitters, antibodies...) may also be produced in the same manner.

2.3 Relationship between enzyme and genetic engineering

Biochemical engineering of course makes direct use of gene products for industrial purposes and the use of genetical techniques for strain improvement is well established. The success of strain selection and improvement programmes is a direct result of close cooperation between the biochemical engineer and the geneticist. In future this relationship will be even more important in formulating the specifications relating to the desired gene product or organisms (e.g. certain cell properties required for immobilization of whole cells, enzyme specificities in detoxification procedures).

2.4 Problems

Important obstacles still need to be overcome before biomolecular engineering can really be directed to contribute fully to the welfare of man. These barriers, which are defined in more detail in the description of the objectives of the present research proposal, are of various nature and may be classified in three different groups.

2.4.1 Technical

While the theory underlying projects for exchanging genetic information between unrelated organisms and building-up bio-reactors is, in most instances, known and understood, difficulties still persist at the level of application and realisation. The analysis, the control, the manipulation and the remodelling of molecular structures can only be achieved through the use of techniques having reached a high level of

precision and of accuracy. Such techniques are not always available and need to be developed through considerable efforts.
Important gaps in knowledge, particularly for the regulation of gene function and cell differentiation in genetic engineering work and for the control of the regeneration of co-factors and the immobilization of multienzymes and complex eukaryotic cells in biochemical engineering, still need to be filled before major breakthroughs can be made.

2.4.2 Structural and organizational

In most instances, the application of molecular and cellular biology to agriculture and industry implies a transfer of research efforts from well defined laboratory test systems to organisms important to man which, often refractory to investigation, have not been submitted in the past to the intensity of analyses performed on widely used laboratory species such as Escherichia coli, Drosophila melanogaster and Arabidopsis thaliana. In addition, the research necessary for the molecular domestication of nature requires the participation of specialists from different disciplines who combine expertise in the numerous facets (chemistry, microbiology, engineering, fermentation technology, genetics, cytology ...) of the project and are able to maintain the orientation of the project towards the specific objectives which serve agriculture and industry. Such coordination of efforts by multi-disciplinary teams is given high priority in the proposed programme.

2.4.3 Financial

Finally, applied molecular research is expensive and, to say nothing of the high cost of the biological and physical containments required by certain manipulations with recombinant DNA, is characterized by requirements in equipment, facilities and specialized staff which are heavier than in many other fields of biological research. The budget needed for initiating and bringing to term a detailed and important research action in molecular biology tends, nowadays, to exceed the possibilities of single institutes and, in certain cases, those of small nations.

3. THE NEED FOR EXPANSION OF RESEARCH EFFORTS IN BIOMOLECULAR ENGINEERING BY THE MEMBER STATES AND MOTIVATIONS FOR A COMMUNITY R AND D PROGRAMME

3.1 The need for an expansion of research efforts

Some of the most important problems to which the Member State are presently confronted are well known and concern :

- the production of goods (reduction of costs and improvement of quality);
- the supplies of energy;
- the preservation of the environment.

In view of the importance of these problems and of the potentialities of R and D in biomolecular engineering for their solution, research actions have been initiated in the Member States by private enterprises and by state supported laboratories. The main efforts essentially include applied projects in enzyme technology and bio-reactors by important European firms (for a detailed inventory of activities by private and national laboratories, see study contract 345-77-6 ECI F by D. THOMAS) and attempts by leading European Universities and National Institutes to shift from basic molecular work to research oriented towards industrial and agricultural needs. Up to now such efforts, in spite of their importance, have not led to a reduction of the Community deficit in trade and in the balance of patents for some of the essential goods and production methods which belong to biotechnology. Member States are for instance still completely self-insufficient with regard to their needs in soya beans and continue to import, annually, enormous amounts of plant proteins for animal foods. During the period 1969-1975 only 25 patents were delivered in Europe in the field of enzyme technology as compared to 40 in Japan and 65 in the U.S.A. Concerning the production of chemicals by fermentation, among 4539 applications for patents between 1965 and 1977, 67 % originated in Japan, 18 % in the U.S.A. and 15 % and E.E.C. Member States. The balance is slightly less unfavourable to the Community if one takes patents dealing with fermentation in general, that is to say including techniques, instruments and the production of compounds. Yet, for the period analysed in this case, (1970-1977), Japan exceeded the productivity of all Member States pooled together by a factor of 3. With regard to the very specific and sophisticated field of enzyme immobilization, which is proposed here for Community action, the patent department of the society Smith Kline-RIT has estimated as follows the distribution by nation of the last 194 patents delivered in 1977, 1978 and 1979.

Japan : 124; U.S.A. : 39; United Kingdom : 1; Italy : 3; France : 7; Federal Republic of Germany : 8; URSS : 9; Denmark : 1; not identified : 2.

A further interesting statistic which was provided by Beecham Pharmaceuticals UK Division is that if one considers the patents in this same area between 1967 and 1971, when much of the "prior art" of today's developments were emerging, 30 % came from the U.K. By 1975 not one of the patents recorded came from the U.K. Similar situations were found in the rest of Europe.

Clearly the high innate capability for innovation existing in Europe must be revitalized.

3.2 Motivation for a Community R and D programme in biomolecular engineering

Common action by the Member States in the field of research dealing with enzyme and genetical engineering is necessary at the moment because there is a need for :

- a pooling and cross-linking of competences and of potentialities;
- stimulation, planning and coordination of activities;
- integration of protection measures against bio-hazards;
- support for sectoral policies of the Commission.

3.2.1 Mobilization of competences and of potentialities: the task to be performed, namely the domestication of bio-molecules, requires considerable scientific and technical input and, therefore, the utilization of all potentialities in the Member States. Obviously, success will not be achieved if full use is not made of the few outstanding experts and of the rare facilities available in the Community for performing some of the highly specific and difficult research needed. Only few centers exist, or are under construction, in the Community which are equipped and organized for the execution of specific tasks required for modern applications in biology, such as recombinant DNA work under high levels of containment or the large scale supply of microbial products. These centers should be mobilized and organized in a cooperative system in order to achieve better overall efficiency and to reach the critical mass necessary for optimum productivity.

3.2.2 Stimulations, planning and coordination of activities : the launching of large scale actions in the fields of enzyme technology and genetic engineering and the execution of the preparatory research still required for operational exploitation needs a careful distribution of tasks in space and in time. It is obvious, for instance, that several industrial objectives will not be reached unless certain organic substances are made available, through enzyme technology, which in turn will depend upon the construction, by means of genetic engineering, of novel genotypes in microorganisms, plants or animal cells. Hence, many laboratories of different profiles in the Community will reach a stage of interdependance and will have to orchestrate their activities. An integrated Community action specifically designed for fulfilling the needs of European industries and of European agriculture and for combining in a comprehensive programme some of the recently initiated research activities in the Member States should provide the stimulus to industrial innovation and the means for a succesful competition with foreign countries.

3.2.3 Integration of protection measures against bio-hazards : in the long term, the applications of molecular biology to agriculture and industry and the attempts which man is now making for assuming the responsibility for life on this planet will unavoidably transform life in society and may induce significant changes in our environment. A Community R and D action in the field of biomolecular engineering, if well integrated and carefully planned, should facilitate the uniform and harmonious development in Europe of the regulations and protection devices which should always be associated with large and economically important transformations. In addition, and as mentioned above, the adoption of a Community programme in biomolecular engineering should allow centralization of certain phases of conjecturally dangerous activities, for instance the mass production of certain forms of recombinant DNA material, at the rare locations in the Community where adequate protection can be provided against conjectural risk. In this connexion, and the same holds true for several different R and D activities in molecular biology, the case appears overwhelming for having, at the same locations, research groups who not only investigate the potentialities of modern techniques and approaches but are also looking at the possible hazards (for instance microbial contamination of industrial products and the immunological reactions to workers handling large quantities of microbial protein) that these techniques and approaches might pose, either singly or together.

3.2.4 Support to the sectoral policies of the Commission : the stimulation of new developments in the fields of genetic and biochemical engineering will support, as outlined in section 3.1, the present sectoral policies of the Commission which concern the optimization of food production, the competitivity of European industries and the improvement of life in society. Strongly complementary to the programmes which are presently carried out by the Commission for coordinating and stimulating research directly applied to agriculture, life in society, health protection, preservation of the environment and use of solar energy, the present proposal is an approach, through the engineering and domestication of bio-molecules, to the solution of these Community problems. The programme suggested is not an alternative to the present R and D activities of the Commission, but, on the contrary, constitutes the necessary matrix from which new biological material, such as novel forms of recombinant DNA and immobilized multi-enzymic systems, and new production concepts may be placed at the disposal of research centres and of industries in the European Community.

4. PROCEDURES FOR IMPLEMENTING THE RESEARCH PROGRAMME

4.1 Type of action

Stimulation and integration of research efforts are needed for achieving the goals which are set in the programme. Therefore, it shall be executed as an indirect action by means of cost-shared contracts concluded with public or private organizations in the Member States. Participation by non-Member States could be envisaged at a later stage through the mechanism of COST.

4.2 Duration

This first programme in biomolecular engineering is proposed for a period of five years (1981-1985). A gradual adaptation to new research requirements will be carried out, if necessary, during its execution.

4.3 Organization of the research

Each of the 6 projects making up the programme is to be executed by a research group which could consist of 3 to 12 research units, depending upon the complexity of the project and of the conditions to be fulfilled for its execution. (For example, the lower limit proposed here could reflect the effort expended in project 6). A research unit is composed of individuals working at the same site and includes, on an average :

- 3 scientific investigators
- 2 technicians
- 1 laboratory helper
- secretarial assistance

(The number of research units and their composition are used as the basis of budgetary estimation made under 4.5 below.

4.4. Management principles

The management of the research programme will be carried out by the services of the Commission with the help of an Advisory Committee for programme management in biomolecular engineering. The task of this Committee will essentially consist in advising the Commission on all matters related to :

- the selection, after a general call for tenders , of the research units which will participate in one or more of the six projects outlined in annex I;
- the integration of these research units in research groups (one per project) responsible for the execution of the programme through a rational distribution of tasks and of responsibilities;
- the nomination of project coordinators to be chosen on the basis of their scientific and organisational capabilities;

- the coordination of activities of the six research groups and particularly between those working on closely related subjects and the continuous transfer of information within and between groups;

- the regular evaluation of progress accomplished by the research groups in the light of the objectives of the programme and, if neccessary, modification of approaches and of orientations, on the basis of the results obtained and of new requirements from agriculture and industries;

- the establishment, for defining new research objectives and for maximum exploitation of the results obtained by the research groups, of a continuous dialogue with representatives of agriculture and industry. It is suggested in this connexion, and in view of the fact that research workers from industrial laboratories rarely benefit from the current national and international fellowship schemes that publicly supported laboratories participating in the Commission programme open their doors widely to industrial research scientits and invite them to participate, for short periods of time, in the work of the research groups. New techniques and methods, such as those dealing with molecular cloning or somatic cell hybridisation could be transferred in this manner to the European industries which would thus be stimulated to consider new approaches in R and D and to report regularly on their difficulties and needs to the laboratories participating in the Commission programme;

- the organisation of summer schools specifically intended for researchers from private industry which would allow a continuous transfer of information;

4.5 Ways and means

The Commission proposes that the ceiling of its participation to the programme for the period 1981-1985 be fixed at 26 MEUA.

These funds are to be used for partial financing (50 % as a rule) of the six research projetcs listed in Annex I as well as to cover the costs of management and coordination of the programme and the costs of a very limited number of Commission personnel.

	Approximate number of research units	Total cost M EUA/5 years	Maximum EC contribution M EUA/5 years
Contractual research	43	47	23.5
Management and coordination			
Expenditure for experts fees, meetings, workshops, etc.			0.7
Commission personnel (3 A, 1 B, 2 C)			1.8
Total			26.00

5. DISSEMINATION OF INFORMATION AND RELATIONSHIP TO THE PROTECTION OF INTELLECTUAL PROPERTY

The services of the Commission are conscious, in relation to the execution of the present programme proposal, of the triple necessity to :

- protect intellectual property and to prevent the premature disclosure of patentable discoveries : Protection
- to assist scientists of the Community in the detection of such patentable discoveries and, when needed, to provide help for the attribution of ownership for patentable inventions : Assistance
- to promote, whenever needed, a continuous exchange of information and competences between all scientists working under different aspects of the field : Diffusion

The services of the Commission propose to fulfill these needs through the following initiatives :

Protection

To prevent the premature disclosure of information which, in the interest of the contractor ought to remain secret, it is proposed to apply, for the execution of the programme, the Council regulation (EEC N° 2380/74) which adopts provisions for the dissemination of information relating to research programmes for the European Economic Community. A set ofgeneral rules based on the Council Regulation has been drawn up (XII/105/76) and is used in other programmes of the Commission. In particular, attention is drawn to the first paragraph of article B1, where it is stipulated that the invention, patentable or not, shall belong to the contractor if he so desires. This means that confidentiality can be assured, with regard to patentable invention, at least until the first filing of a patent application. With regard to non patentable invention, it is clear that the Commission also has to respect the ownership and the corresponding rights of the contractor.However it should be noted that the meeting of industrial representatives mentioned in 1.4. above expressed the view that the few problems in this area which might arise by rigidly applying the dispositions in XII/105/76 were soluble on the basis that contracts in these cases be negotiated individually within the framework of the Council Regulation.

Assistance

- Patentability of inventions

  The Commission will assess systematically, through the most appropriate means, the patentability of the inventions made and reported by the contractors. Where requested, it will also provide assistance and guidance to the contractors at the time of filing applications for a patent and, if necessary, will make arrangements with competent national institutions, through contractual dispositions or otherwise, for seeking permanent advice on certain problems dealing with the exploitation of inventions and the protection of Community interests.

- Exploitation, industrialization and marketing of inventions

Whilst the exploitation, industrialization and marketing of any invention made by the contractor is in the first place an obligation of the contractor, the Commission can formulate opinions and advice upon the various steps and procedures to be followed by the contractor.

Diffusion

It is essential, for the proper execution of the programme and its harmonious evolution, that a continuous flow of information circulates between the contractors, the Commission and third parties (for example the industries not directly involved in contracts). This transfer of information is particularly necessary for :

- defining the specific objectives of the research programme and the approaches and means needed for reaching these objectives;
- evaluating research data and results.

To this effect :

- the Commission will establish permanent relationships with representatives of industries in the Member States and will seek permanent guidance and advice for the preparation of programmes and the evaluation of results. One way to build the relationship (and this is obviously the only official and formal way) could consist in the participation at each meeting of the ACPM of national experts mandated by the Member States to express the views of industries. But this can only be suggested by the Commission, as the membership in the ACPM delegations is totally under the responsibility of the Member States. Other possibilities, such as unofficial advisory expert groups, will be used. Moreover, one could also envisage that certain specific assessment tasks be conducted, through contractual arrangements, with the collaboration of institutions having unique competences in certain areas of the programme. For instance, EMBO could act as a consultant for assessing applications dealing with recombinant DNA work in microorganisms.
- the Commission will encourage, through symposia, summer-schools, travel grants and research grants, the establishment of permanent contact between its contractors and researchers from non-participating industries. In particular, efforts will be carried out for promoting the transfer of skills, methods and biological material and for reviewing continuously the specific needs of European industries.

DETAILED DESCRIPTION OF THE RESEARCH PROGRAMME

Aims of the programme

Enzyme technology has demonstrated its economic and industrial potentialities by the successful development, specially in Japan and the U.S.A. of the "first generation" of immobilized enzymes which concern simple degradative enzymes which by hydrolysis or oxidation yield products with rather limited added value such as amino-acids, sugars, alcoholic beverages, fruit juices or cheeses. The long term objectives of this part of the programme is to prepare European science and European industries to develop a "second generation" of enzyme reactors which would effect a range of detoxification procedures and catalyse the synthesis of fine chemicals of high added value. A number of suggestions as to which end products should be studied can be found in the report of THOMAS (EUR, 6079) but at this stage the choice should not be restricted since it is recognized that the major outcome of the work would be the description and analysis of model systems and innovative developments. Industry would, of course, be consulted in the final choice as envisaged in section 4.4.

The present situation of this field in Europe is particularly favourable for launching a successful research and development action. On the one hand, enough knowledge has been accumulated in the past to expect new research investment to be beneficial, and, on the other hand, it is clear that without a vigorous additional research stimulus, the European industries will not be able to compete successfully with Japanese and American industries.

The general goal of the research proposed for genetic engineering is, in the long run, the improvement of microbial and plant cell productivity and the supply to the biochemist and chemical engineer of new gene products.

The short-term objectives are, however, more restricted and deal, in most cases, with the execution of the preparatory work which must be carried out before any new important achievement may be considered to be within reach. In general, these short-term objectives may be defined as follows :

- specification, in organisms important to biological industry of the genetic elements which are to be submitted to recombinant DNA work;
- development of transfer methods (including uptake and choice vehicles) adapted to the material at hand;
- control of expression after incorporation and selection;
- in the case of recombinant DNA work with multicellular organisms, regeneration of recipient cells into adult organisms.

Research projects selected

Project 1. Development and evaluation of new reactors using immobilized multienzyme systems including those requiring multiphase environment and cofactor regeneration.

This project is designed to promote the development of new solutions to the technical and theoretical bottlenecks which hamper the development of large scale industrial application of the second generation of sophisticated enzyme reactors. The key points where such research is needed are identified and justified as follows :

- while a variety of reactors have been developed for different forms of single immobilized enzymes in monophasic systems, only preliminary studies are available concerning the reaction kinetics and reactor geometries of multienzymes and multiphasic reactors. Therefore, additional kinetic studies and optimization of the flux of matter in multienzyme reactors will be promoted ;

- few satisfactory procedures exist yet for the immobilization of multienzymes and for cofactor regeneration for biosynthetic enzymes. In particular the development of appropriate new supports and new procedures for fixation as well as for compartmentation of multienzyme reactors is required. Simultaneously, there is an obvious need for the development of new efficient systems for cofactor regeneration to be used in the new enzyme reactors ;

- when operating "in vivo", many enzymes of industrial potentialities are embedded in hydrophobic lipidic membranes. To use such enzymes, it is necessary to study the stabilization of lipid-requiring enzymes and to develop new multiphasic reactors where enzymatic reactions take place at a hydroorganic interphase ;

- little is known about the stabilization of subcellular organelles, some of which catalyze extremely complex multienzymatic reactions of great economic importance such as the transformation of carbon dioxide into carbohydrate at the expense of light energy carried by isolated chloroplasts. Therefore, attempts aiming at the immobilization of subcellular organelles, such at mitochondria, chloroplasts and peroxisomes and of membrane-bound enzymatic complexes such as microsomes, thylakoids, inner mitochondrial or plasma membranes must be promoted.

- on the other hand, because of the high cost of enzyme purification there is a growing interest for the immobilization of whole microbial cells. The know-how already developed from immobilization studies of relatively simple bacterial cells should now permit tackling studies of immobilization of more complex eukaryotic cells, especially plant cells, which contain the genetic information for the synthesis of a variety of chemicals of unique industrial potentialities. The immobilization of yeast cells is also a great potential interest because of the recent

demonstration of the possibility of using yeast as a vehicle for the expression of exogenous eukaryotic genes previously amplified in bacteria. Research on the fixation of intact eukaryotic plant and yeast cells and of their permeation to appropriate substrates and products must thus be encouraged.

Project 2. Development of bioreactors for industrial and human detoxification

This project has been chosen as a very practical way for placing the European industries in a position to compete with Japan and the U.S.A. for the exploitation of the "second generation" of enzyme technology. In order to overcome some of the difficulties which have limited the development of the "first generation" of enzyme applications in Europe (namely, the scarcity of biological-minded industrial traditions, the difficulties of identification of good new industrial projects and the present reluctance to invest in long term research), projects of high social relevance such as the development of bioreactors for industrial and human detoxification must be promoted. If successful, these procedures will increase the efficiency and reduce the present cost of classical detoxification procedures.
Since a large potential market exists, it is likely that the industries once they have acquired the basic know-how with the help of public funds, will then be in position to develop without further stimulous a variety of more or less related new enzymatic reactors. The development of new enzyme reactors for detoxification requires coordinated research actions at the following levels :

- development of bio-compatible insoluble matrices for multienzymes with special reference to thrombocompatibility, immunocompatibility, biodegradability and absence of toxicity.

- development of carriers provided with specific tropisms for targeting exogenously administrated enzymes.

- development of systems for enzymatic detoxification of poisons of industrial, agricultural, environmental or pharmaceutical origins susceptible to enzymatic modification. In addition to specific enzymes the use of microorganisms (including mixed cultures and genetically engineered strains) with high degradative capacities would be valuable.

Project 3. The transfer of genes from diverse sources to the bacterium Escherichia coli, the yeast Saccharomyces cerevisiae and other suitable microorganisms

Human proteins prepared on a large scale would have a wide potential market and great pharmaceutical and medical interest. The therapeutist needs hormones to replace endocrine organ failure, while the clinical chemist requires relatively large amounts of the specific proteins he wants to assay.

While growth hormone and insulin represent well known examples, the industrial production of many other human polypeptides would also be desirable. These proteins include hormones (calcitonin, parathormone, prolactin, erythropeitin, TSH, LH, FSH, ...), growth factors (somatomedins, nerve growth factor, ...), neurotransmitters (gastrin, endophins, ...) and proteins involved in host defence (interferon, antibodies).

Chemical synthesis of these proteins has been considered feasible on an industrial basis only in the case of relatively short polypeptides such as ACTH. The use of genetic recombinants could provide a general solution to this problem because no technical obstacle impedes the cloning of any structural gene in plasmid-carrying E. coli and because methods available to screen and identify bacterial clones containing any gene coding for a protein for which an antibody is available. In fact, DNA sequences coding for human placental lactogen and human growth hormone have already been cloned.

The problem of expression of eukaryotic genes in prokaryotes has not been solved in a general way. The orientation in this project will have special reference to :

- overcoming the expression barriers for particular proteins, e.g. for the development of virus vaccines;

- the chemical construction of "synthetic genes";

- development of mutational tools (e.g. site specific mutagenesis) which can be applied, for example, to produce harmless vaccines or stabilized enzymes ;

- modification to inhibit the degradation of enzymes in a foreign environment by such techniques as repression of proteolytic activity of the host cell or by tagging the desired protein to another which is excreted extracellularly.

- development of "libraries" of expressed genetic information and rapid screening techniques for their identification.

Other well-studied microorganisms may be more suitable than E. coli For example, the use of yeast may allow the removal of possible obstacles to expression when cloning DNA from other eukaryotic sources. In addition, yeast cells have been safely used industrially for many years and hence may be more acceptable as a host for large scale exploitation.

Project 4. Development of cloning vehicles

Although cloning of foreign genes in the bacterium Escherichia coli is now routinely performed in many laboratories, very little has yet been done on the cloning of other organisms which are likely to be of

greater importance for European industry. The first step is the development of practically applicable vectors in such bacteria (e.g. Actinomycetes, Pseudomonads, Bacilli),fungi (e.g. Penicillium) and algae by using plasmids, viruses and mitochondrial DNA.

With regard to plant cells, the project will essentially concentrate on the use of potential vehicles such as the Agrobacterium plasmids, plant DNA viruses, like CoMV for which some reseach has been initiated, chloroplasts and mitochondria.

Project 5. Novel gene transfer in species important to biological industry

The long term goal is for industry to cultivate cells with new or improved properties both in terms of cells or organisms themselves as well as valuable primary or secondary metabolities produced by them. However, the use of genetically altered, hybrid microbial, plant or mammalian cells in industrial production methods, requires a genetic stability of the cultivated material which is of a different order than is achieved by sole cloning. Thus the stability, regulation and expression of these transferred genes will need to be studied. In addition,even if cloning of DNA from economically important organisms were successfullyy undertaken outside of the organism (e.g. in E.coli) there are likely to be many problems when attempts are made to reincorporate the cloned DNA into the original organism, a requirement which is expected to arise when the procedures for cultivation, extraction,safety,etc.. have been characterized and optimised in the original strain.

Methods of achieving transfer can be summarised as follows :

- vehicle transfer (a) among prokaryotes, (b) from prokaryotes to eukaryotes and (c) from eukaryotes to eukaryotes.
- somatic cell hybridization
- other means of transfer (e.g. hybridoma,use of whole chromosones) that appear to be promising for the future.

Finally,in specific reference to plant cells, particular attention will be devoted to :

- the exploitation,for the production of valuable metabolites in fermentors, of the enormous phenotypic variability which is spontaneously expressed in in vitro cultures.

- regeneration in vitro, that is to say the production of adult organisms from isolated cells cultured in vitro which obviously constitute one of the first conditions for the success of any project based upon recombinant DNA technology or somatic hybridization for the improvement of cultivated plants. What is needed and will be stimulated by all means in this connexion is the development of methods allowing in species important to European industry the regeneration of host cells (protoplast,microspores...) into mature organisms or into suitable stem lines for large scale cultivation.

Project 6. Studies of strainstability and improved methods for detecting contamination

It is well known that phenotypic and genotypic changes in industrially important microorganisms can have severe detrimental effects on the fermentation and hence on the subsequent use of the product. It has also been pointed out by Sargeant and Evans (EUR 6349) that this

variability constitutes a potential source of hazard in biotechnological operations. In addition, the possibility of having even small numbers of harmful microorganisms contaminating the product is also of concern.

However, on the whole, process checks via strict fermentation controls operated by industry are at present a sufficient safeguard. Nevertheless, with an expanding programme in biotechnology and particularly with the use of engineered cells some small support for research in this area is considered desirable. Should there be a requirement to set up agreed Community standards and procedures for new fermentation products this type of study would provide valuable background information.

The importance of strain stability for industry (and the possibility of added problems with engineered strains) cannot be overemphasized. This part will closely complement work undertaken in project 3 and 5.

DRAFT COUNCIL DECISION

ADOPTING A MULTIANNUAL RESEARCH AND DEVELOPMENT PROGRAMME FOR THE EUROPEAN ECONOMIC COMMUNITY IN THE FIELD OF BIOMOLECULAR ENGINEERING

(Indirect action 1981 - 1985)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 235 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Having regard to the opinion of the Social and Economic Committee ;

Whereas Article 2 of the Treaty establishing the European Economic Community assigns to the Community the task of promoting throughout the Community a harmonious development of economic activities, a continuous and balanced expansion and an accelerated raising of the standard of living ;

Whereas in its Resolution of 14 January 1974 on a first action programme of the European Communities in the field of science and technology, the Council stated that the whole range of available ways and means should be used as appropriate, including indirect action ;

Whereas a Community research programme in the field of biomolecular engineering could contribute effectively to the achievement of the above-mentionned objectives and, particularly, to the development of new technologies leading to :

- the development of improved agricultural and bio-industrial products,
- the determination of more efficient and less harmful production methods,
- reduced of energy consumption and improvements in the balance of payments.

Whereas the Treaty establishing the European Economic Community has not provided the necessary powers ;

Having considered the opinion of the Scientific and Technical Research Committee (CREST) concerning the proposal from the Commission ;

HAS DECIDED AS FOLLOWS :

Article 1

The European Economic Community shall carry out over a period of five years from 1 January 1981 a programme of research and development in the field of biomolecular engineering as described in Annex A.

Article 2

The total amount required for the duration of the programme is estimated at 26 million EUA, as defined in Article 10 of the Financial Regulation of 21 December 1977, and the staff allocation at 6 servants.
These figures are merely intended as a guide.

Article 3

The Commission shall be responsible for the implementation of the Research and Development Programme. To assist it in this task there is hereby established an Advisory Committee for the Management of the Research and Development Programme in the field of Biomolecular Engineering. The terms of reference and the composition of this Committee shall be as set out in Annex B.

Article 4

During the third year the programme shall be reviewed ; this review may result in a revision of the programme in accordance with the appropriate procedures after the Advisory Committee on Programme Management has been consulted. The European Parliament shall be informed of the results of that review.

Article 5

The information resulting from the execution of the programme shall be disseminated in accordance with Council Regulation (EEC) No 2350/74 of 17 September 1974 adopting provisions for the dissemination of information relating to research programmes for the European Economic Community (1).

Done at

For the Council

The President

(1) OJ No L 255, 20/9/1974, p.1.

DESCRIPTION OF RESEARCH AREA

The programme aims at the removal of obstacles which prevent the applications of modern genetic and biochemical methods to industry and to agriculture.
It focusses essentially upon development of the second generation of enzyme reactors, that is to say the possibility of exploiting complex enzymatic reactions for the synthesis of elaborated new products, and upon the improvement of techniques which allow directed gene transfer and the modification of the genetic properties of commercially important organisms. It comprises the six integrated projects :

1. Development and evaluation of new reactors using immobilized multienzyme systems including those requiring multiphase environment and cofactor regeneration.

2. Development of bioreactors for industrial and human detoxification.

3. The transfer of genes from diverse sources to the bacterium Escherichia coli, Saccharomyces cerevisiae and other suitable micro-organisms.

4. Development of cloning vehicles.

5. Novel genes transfer in species important to biological industry.

6. Studies of strain stability and improved methods for detecting contamination.

TERMS OF REFERENCE AND COMPOSITION OF THE ADVISORY COMMITTEE FOR THE MANAGEMENT OF THE RESEARCH AND DEVELOPMENT PROGRAMME IN THE FIELD OF BIOMOLECULAR ENGINEERING

1. Without prejudice to the Commission's responsibility for the execution of the programmes, the Committee has the task of contributing, in its advisory capacity to the optimal implementation of the research and development programme in the field of Biomolecular Engineering, and, in particular to :

   - the selection, after a general call for tenders , of the research units which will participate to one or more of the six projects outlined in annex 1;

   - the integration of these research units in research groups (one per project) responsible for the execution of the programme through a rational distribution of tasks and of responsibilities;

   - the nomination of project- coordinators to be chosen on the basis of their scientific and organisational capabilities;

   - the coordination of activities of the six research groups and particularly between those working on closely related subjects and the continuous transfer of information within and between groups;

   - the regular evaluation of progress accomplished by the research groups towards the objectives of the programme and, if necessary, on the basis of the results obtained and of new requirements from agriculture and from industries, the modification of approaches and of orientations;

   - the establishment, for defining new research objectives and for maximum exploitation of the results obtained by the research groups, of a continuous dialogue with representatives of agriculture and industry.

2. The Committee formulates opinions, prepared by the secretariat and submitted to approval by the Committee. Every Committee member can ask that his view be recorded in these opinions. These opinions are transmitted to the Commission and a copy to the Council. CREST and its Sub-Committee will be informed periodically on the work of the Committee.

3. The Committee includes :

   - representing the Member States, three members appointed by each government for the duration of the programme on the grounds of their competence in the matter; if it considers it necessary, each delegation may be accompanied by experts;

   - representing the Commission, three officials appointed by that institution.

Exceptionally, with the agreement of all the parties represented, special derogations may be made to these conditions.

4. In the case of those representing the Member States, a member's term of office comes to an end in the event of his death or resignation, or if the government which appointed him asks that he be replaced. His successor is appointed for the remainder of the initial term of office.

5. The Committee appoints its own chairman, on a proposal from the Commission delegation and for a period of one year.

6. Secretarial services for the Committee will be provided by the Commission.

X

X X

FINANCIAL RECORD

1. BUDGET CHAPTER :

   - Post : line 3368

   - Title : Biomolecular Engineering

1.1 TITLE OF ACTION :

Programme of research and development in the European Communities on biomolecular engineering (1981-1985)

2. JURIDICAL BASIS

Article 235 of EEC Treaty
Council Decision

3. DESCRIPTION OF ACTION

3.1 Description

Biomolecular engineering
Research programme carried out, by means of cost-sharing contracts with research organizations in the Member States, along the six following research projects :

1. Development and evaluation of new reactors using immobilized multienzyme systems including those requiring multiphase environment and cofactor regeneration.

2. Development of bioreactors for industrial and human detoxification

3. The transfer of genes from diverse sources to the bacterium Escherichia coli, the yeast Saccharomyces cerevisiae and other suitable microorganisms.

4. Development of cloning vehicles.

5. Novel gene transfer in species important to biological industry.

6. Studies of strain stability and improved methods for detecting contamination.

3.2. Objectives

To accelerate the production of data, biological materials and methods in genetic engineering which are necessary for the domestication and the transformation of the basic properties of living organisms useful to man and to place such data, materials and methods at the disposal of industries and agricultural research centres.

4. JUSTIFICATION OF ACTION

There is a need to promote in the Community, through oriented research, the exploitation of basic discoveries in modern biology and to increase in this manner, by an integrated effort, the capacity of the Member States to compete with the outside world in areas dealing with the elaboration of improved agricultural and bio-industrial products. The proposed activities are not only intended to contribute to the reduction of deficits in trade and in patents but should also lead, in the long run, to the decrease of energy consumption and the diminuation of waste products. Finally, it should allow the uniform and harmonious development throughout the Community of the regulations and protection devices which should always be associated, from the start, with new and economically important exploitation methods. Considering the present gap which separates the Community of Member States from countries with advanced technology and the partitions which too often isolate in Europe basic research from industrial research, these resutts can only be obtained through a global and continuously renewed analysis of the Community needs and through the stimulation of Community activities which allow the pooling together of competences and of research tools.

5. FINANCIAL INCIDENCE OF ACTION ON INTERVENING SUPPLIES

(including costs for staff and expenses for administrative and technical management).

5.1 Total cost during the entire term envisaged .....49.5 MEUA

5.2 Participation to funding

- on Community budget .....26.0 MEUA
- by national administrations
- by other sectors at national level } .....23.5 MEUA

5.3 Multiannual schedule

5.3.1.1. Commitment

in MEUA

Expenditures	1981	1982	1983	1984	1985
Staff	0.32	0.34	0.36	0.38	0.40
Administ. and Technical Manag.	0.12	0.13	0.14	0.15	0.16
Contracts	19.74	3.76	-	-	-
TOTAL	20.18	4.23	0.50	0.53	0.56

5.3.1.2. Payment

in MEUA

Expenditures	1981	1982	1983	1984	1985	1986
Staff	0.32	0.34	0.36	0.38	0.40	-
Administ. and Technical Manag.	0.12	0.13	0.14	0.15	0.16	-
Contracts	1.65	4.00	4.70	4.94	5.41	2.8
TOTAL	2.09	4.47	5.20	5.47	5.97	2.8

(Financial record)

5.3.2. Methods of calculation

a) Personnel expenditure

Minimal needs were assessed on the basis of the officials required for the programme :

3 category A officials

1 category B officials

2 category C officials

These needs take into account the necessity to carry out the administrative and scientific management of approximately 50 contracts and to promote the coordination and stimulation of 6 distinct research groups. The ratio of the number of national researchers estimated for implementing the programme to the number of category A officials (C.N/A.C.) amounts to 50/1. Needs for B and C personnel have been evaluated in proportion.

b) Expenditure for adminstrative and technical operations

They cover travel, mission and meeting expenses as well as the cost of scientific and technical assistance whenever it proves necessary for the implementation of the programme.

c) Expenditure in respect of contracts

Since the nature of the work and the qualification of the contracting parties vary, it is impossible to introduce a standard method of calculation. The average cost of 57.000 EUA in 1979 per scientist / year with a annual increase of 6.5% of the cost of the research and a contribution from the Commission of 50 % to the cost of this research were used as a basis for estimation. However, the Advisory Committee on Programme Management (ACPM) will always be consulted on the allocation of funds.

6. FINANCIAL INCIDENCE ON RUNNING SUPPLIES FOR PERSONNEL AND MANAGEMENT :

(see point 5 above)

7. FINANCING OF EXPENDITURES

Funds to be included in future budgets

(Financial record)

8. FINANCIAL IMPLICATIONS IN RESPECT OF REVENUE :

- Community tax on income of officials
- Contribution of officials to pension scheme

9. TYPE OF CONTROL FORESEEN :

- Scientific controls : ACPM

  Officials appointed by DG XII

- Administrative controls :

  . Budget implementation : Directorate General for Financial Control

  . Regularity of expenditure : Directorate General for Financial control and Contract Department of DG XII.