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REGULATION OF BIOTECHNOLOGY

U.S. AND INTERNATIONAL DEVELOPMENTS

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TABLE OF CONTENTS

page

Part I Regulatory Status

Section 1 - Science, Products and Issues.....2

Section 2 - U.S. Regulatory Policy and Procedures.....9

Coordinated Framework for Regulation of Biotech..9

NIH.....13

FDA.....15

EPA.....16

USDA.....18

Section 3 - International Regulatory Policy and Procedures.....20

OECD.....20

State Department Working Group.....21

Developed Countries.....21

Developing Countries.....22

U.N Activities/International Center for Genetic Engineering and Biotechnology.....23

Part II A.I.D. and the Regulation of Biotechnology

General Discussion.....24

Section 1 - Technical Considerations in Biotechnology Project....26

Range of effort.....26

Organisms and system used.....26

End Product use.....27

Section 2 - Regulatory Approach in A.I.D.....28

Historical Perspective.....28

A.I.D.'s Regulatory Needs - suggested approaches..29

Collection of Information.....31

Assessment of Information.....31

Monitoring Activities.....32

Section 3 - Suggested Topics for the
Standing Committee on Biotechnology.....33

References.....34

Appendix 1 - Biotechnology Regulations - France and Japan.....36

Appendix 2 - The Role of the ICGEB and the
Informa Working Group (U.N.).....43

Appendix 3 - Project Information sheets for
Biotechnology Projects 48

Introduction

Biotechnology is rapidly becoming an element of development strategies around the world. The Agency for International Development (A.I.D.) is in the process of establishing a Standing Committee to address the issues surrounding this new area. The purpose of this report is to provide background information for the Committee.

The information in this report is drawn from many sources: textbooks, media reports, congressional records, and interviews. A complete list of references and contacts is provided in the Reference section.

An effort has been made to develop a balanced presentation of the current regulatory situation and suggestions have been made to stimulate discussion within the A.I.D. on this important topic. The opinions in this report are the author's. They do not represent those of A.I.D.

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Section 1 - Science, Products and Issues

Over the past several years, biotechnology has been the focus of an inordinate amount of activity and excitement. Although not a new area, advances in cell and molecular biology have radically expanded the array of products which can be designed. The method which has generated the most excitement and potential is recombinant DNA technology - the ability to manipulate the genetic make-up of an organism. Its potential has been toted as the solution to an enormous range of problems and although the potential is genuine, the enthusiasm has sometimes been premature. Currently biomedical products are appearing in the market and agricultural products are soon to follow.

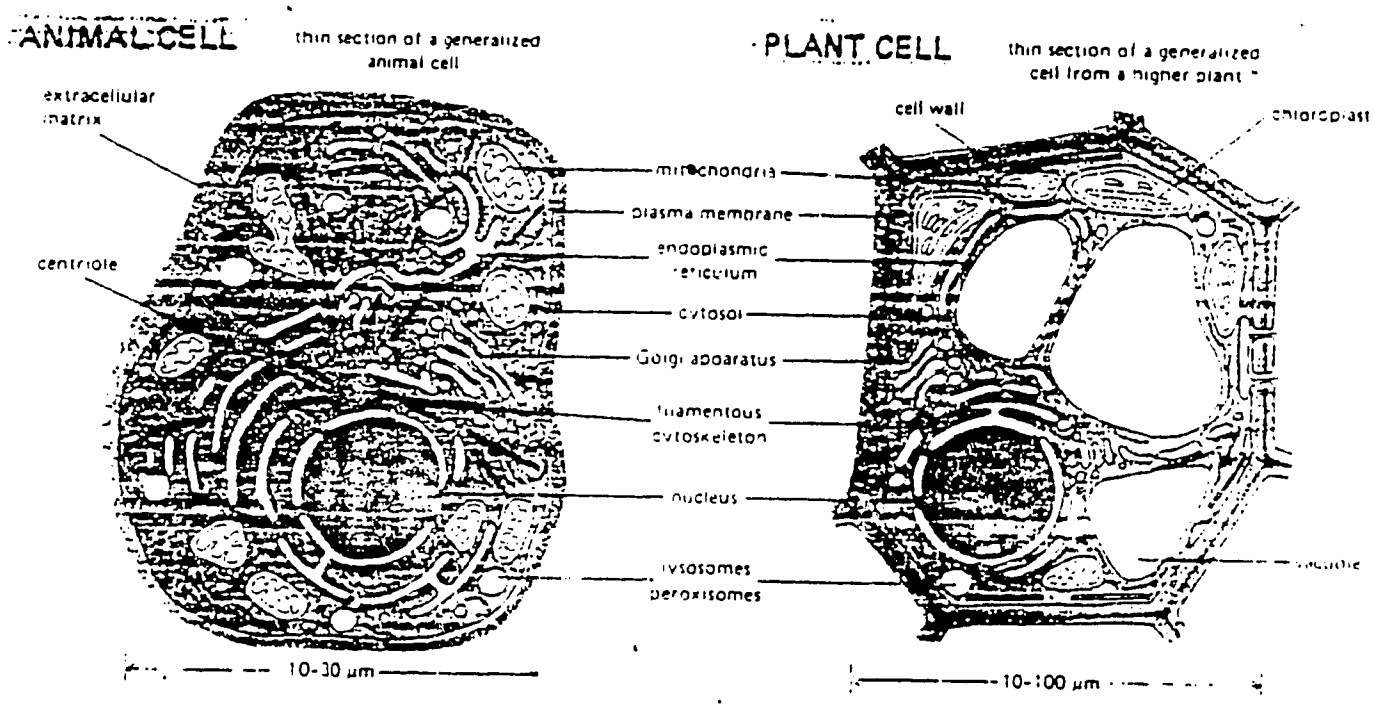
The products of biotech present a new type of beast - different from previous products and therefore raising new environmental and ethical concerns. To discuss these concerns and the policies which are evolving it is necessary first to have an understanding of the science and products which comprise biotechnology.

Classification and Cell Structure

The development of a classification system for all living organisms has been one of the primary activities of biology. The classification system describes all creatures into smaller and smaller groups based on specific characteristics. The characteristics become more limiting as the characterization proceeds from kingdom to species. The characteristic which distinguishes one species from another is the ability to inter breed and produce viable offspring. Genera are groups of related species. The classifications of two common organisms are presented below:(1)

Common name	Giraffe	Domestic cattle
kingdom-----	animal	animal
phyla--------	chordata	chordata
order---------	artiodactyla	artiodactyla
suborder-------	ruminantia	ruminantia
family----------	giraffidae	bovidae
genus----------	giraffa	bos
species----------	cameloparadalis	taurus

All organisms are composed of cells - the basic unit of life. There are unicellular organisms, viruses, bacteria, protozoa, and multicellular organisms, plants and animals. Despite the differences in these organisms there are basic similarities at the cellular level. Presented below are diagrams of an animal cell and a plant cell indicating the major structures:(2)

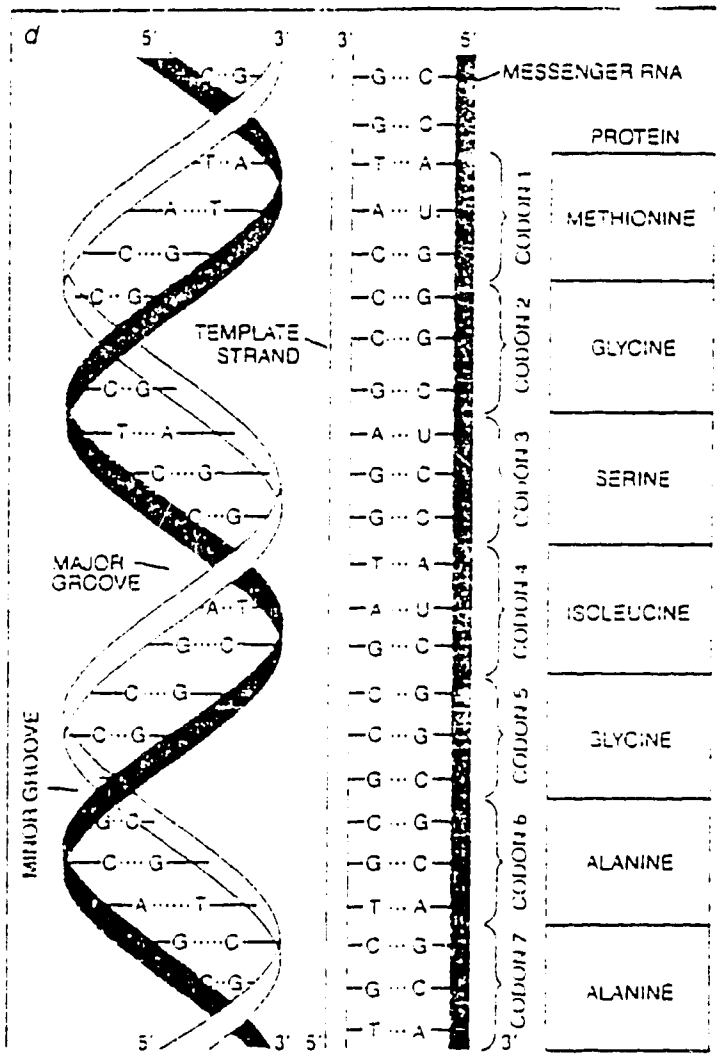


The nucleus is the that part of the cell where deoxyribonucleic acid (DNA) is found. DNA carries the genetic information of the cell and in higher organisms is packaged into chromosomes. The term genome is used to designate all of the genetic information found in the cell - e.g. the human genome is comprised of all DNA found in the chromosomes. DNA is a double stranded molecule made up of four nucleotides (or bases) organized in a linear sequence. The bases are adenine, thymidine, guanadine, and cytosine, represented by single letters, A,T,C,G.

The single strands of DNA are complementary - that is the nucleotides will pair with only one other specific nucleotide. Adenine base pairs with thymidine and guanadine with cytosine. This complementarity of DNA allows the DNA to serve as a template - the double strand opens and replicates, reproduces itself, or transcribes, is copied into ribonucleic acid (RNA) for protein production.

The information of the DNA is communicated to the RNA and protein through the linear sequence of all the components. Three DNA nucleotides are transcribed into three RNA nucleotides which code for one amino acid. Proteins are composed of amino acids. The sequence of DNA which codes for one protein is called a gene.

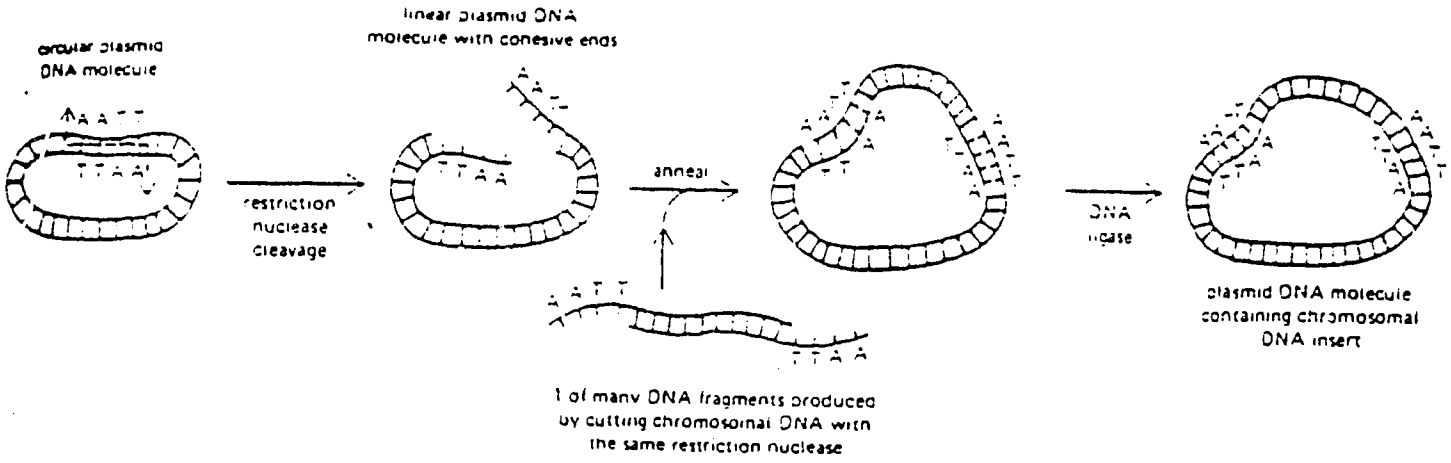
This system is presented schematically below.(3)



The elucidation of this genetic communication system is the basis for recombinant DNA technology. The first steps in rDNA technology (aka genetic engineering or cloning) were taken in bacterial systems. Bacteria were used to produce proteins of interest from other organisms. The gene of interest, i.e. coding for the a specific protein, is searched for, identified and placed in the bacteria.

A vehicle or vector is needed to carry the gene from its place of origin to the bacteria. For this purpose plasmids are used. These are circular, self-replicating pieces of DNA found in bacteria. Plasmids often code for antibiotic resistance which serves as a useful marker. The gene of interest is placed in the plasmid which is taken up by the bacteria - a process known as transformation. The bacteria then starts producing the plasmid and the protein of interest.

The schematic below presents the cloning process:(2)



The use of bacteria was the initial step in rDNA technology, first accomplished in 1973. Since that time numerable advances have been made in the technology. Intense research in the identification of new vectors and the regulatory mechanisms of gene expression have greatly expanded the ability to utilize rDNA.

Many new vectors have been identified which have broadened rDNA beyond bacteria. Viruses have proved particularly useful. Viruses invade cells and typically commandeer the host cell machinery to produce viral proteins. By disarming the virus, i.e. removing its potentially harmful genes, it can be used to carry non-viral genes. Viruses are being used to move genes in plants and animals. Cauliflower mosaic virus is one of the viruses which is being studied as a plant vector. Retroviruses have been identified as potential vectors for human gene therapy, where genetic disorders may be corrected with the insertion of the appropriate gene. Vaccinia virus is being used as a vector in designing new animal vaccines, with the potential of developing one vaccine providing protection for multiple diseases. (An excellent discussion of agriculturally useful vectors is presented in a paper by Phyllis Moses, National Academy of Science (4)).

Once a gene is moved from its original location to another it is placed under a different system of controls. All of the genes of a cell are not active at the same time, but rather expressed as they are needed. The regulation of this expression is a complex system - still the subject of much investigation. Some of the mechanisms of this process have been identified. Promoters and enhancers, known as regulatory sequences, are stretches of DNA which do not code for protein but are involved in the activation of a gene for expression. When these areas of DNA are activated, often by the reaction with another cellular component, a sequence of events begins which result in gene expression.

The discovery and understanding of regulatory processes has been incorporated into rDNA technology. Specific promoters are cloned into vectors in front of the gene in order to improve and/or control expression. For example, the promoter which regulates the heat shock proteins is a heat sensitive system. When this promoter is placed in front of a cloned gene the gene expression can be regulated by temperature.

In addition to rDNA techniques there are other methods which allow for the movement of DNA. These include cell fusion and recombinant RNA methods.

Products

The development of rDNA technology is reflected in the products. The original products available were proteins produced in bacterial systems. Once the genes are identified and moved into bacteria, the bacteria serves as a small factory producing the specified protein. Many proteins of importance have been very difficult to obtain because the traditional process of purification is tedious and results in very small yields. An additional problem with traditional purification methods is the possibility of contamination with an adventitious agent. (It has recently been determined that growth hormone was occasionally contaminated with the Krutzfeld-Jacob virus.) By moving a specific gene into a bacterial system an unlimited supply of the protein becomes available. Examples of such proteins include interferon, insulin, and growth hormone. The cloned DNA itself is also a useful product since it can be used as a probe in diagnostic procedures.

The next level of products available through rDNA uses the engineered organism as the product itself. The ability to move genes presented the opportunity to improve already beneficial organisms. Rhizobia which are capable of fixing nitrogen are being engineered to be more efficient and competitive. Presently a strain of rhizobium engineered to contain multiple copies of the nif gene, which codes for the enzyme nitrogenase, is being reviewed by EPA for field tests.

Additional areas of activity include the identification of genes responsible for increased stress tolerance. Once these genes are identified it is hoped that they can be successfully moved from one plant to another and appropriately expressed. Vaccines are being developed which use live viruses to carry the genes from the pathogen which trigger the host's immune response.

Issues

Ethical and environmental questions have evolved along with the advances in rDNA technology. The first flurry of questions appeared with the realization that scientists could manipulate DNA and therefore alter an organism's genetic composition. The questions were ethical and religious in nature. Should scientists play with genes? Could such a capability be used for destructive purposes - i.e. the "engineering of a super-race? In retrospect these questions sound rather dramatic but they are still the subject of controversy in some groups and the subject of discussion as technologies improve and human gene therapy enters the testing phase.

The scientific community raised their own questions when this new technology appeared. In 1975 scientists gathered at the Asilomar conference in California to discuss the enormous potential and unknown dangers that rDNA technology presented. The technology was in its infant stages at that time, so concerns were focused at the laboratory level. The scientists agreed to self-regulate their activities until their knowledge and experience grew. These discussions led to the establishment of the NIH regulatory system which is discussed later.

The questions surrounding rDNA have matured with the technology. Once products became a reality issues of safety and quality control became central. Before use of the initial products of rDNA, the proteins, e.g. insulin, it is necessary to ensure purity and lack of side reactions. Since these proteins are produced in microorganisms it is necessary to eliminate all bacterial contaminants. The use of genetically engineered organisms as products presents the next level of complexity - raising complicated environmental questions.

Many of the genetically engineered organisms developed as products need to be released into the environment to be useful. The first example of this is the ice-minus mutant, developed by deleting a single gene from the bacteria Pseudomonas syringae. This deletion presents one of the simplest approaches of genetic engineering - no new genetic information is added to an organism, nothing is moved around, the gene responsible for ice nucleation is simply removed.

Vaccine and drug development is an active area in the health applications of biotechnology. The testing of such items is a well developed field and it appears that there is considerable less controversy surrounding these applications of biotechnology than surrounding those concerning environmental release. However human gene therapy still remains to be addressed and it is likely that this subject will continue to generate substantial discussion.

A recent study (5) conducted by the Office of Technology Assessment (OTA) indicates that the 66% of the public surveyed feel they understand the meaning of genetic engineering and only 19% of those surveyed said that they had heard of any potential dangers from genetically engineered products. Additionally the survey asked participants to identify which applications of genetic engineering they would strongly support under risk-free conditions. In order of the application most strongly approved to that of the least strongly approved these are:

New treatment of cancer
New vaccines
Cures for human genetic diseases
Disease resistant crops
Frost resistant crops
More productive farm animals
Larger game fish

Placing an engineered organism into the environment raises many concerns. Some of these concerns which have been voiced by the environmental community include:

- the changes in the orginal organism may affect its interactions with other organisms; e.g. it may infect a broader range of hosts

- the genetic alterations may change a non-pathogenic organism into a pathogen or may lead to interactions with other organisms that would result in the development of pathogencity

- the application of a large number of engineered microorganisms to an area may alter the ecological balance

- the genetic alteration may give the organism a selective advantage, allowing it to expand its geographical range

Despite the intensity surrounding these issues a regulatory process has emerged. The fundamental step in the development of a regulatory system is definition. What is to be regulated? This has proved to be a complicated process in biotechnology, as advances and experience have generated new knowledge and possibilities. The definitions of some of the critical terms, recombinant DNA, foreign DNA, deliberate (environmental) release and recombinant organism, are still developing and each regulatory step includes a refinement or adjustment in these terms. Additionally, until recently different Federal agencies had different definitions. The current "accepted" definitions and the process used to arrive at them will be discussed in the following section.

At the center of the regulatory discussion is the question : "How different are genetically engineered organisms ?" Mutation, the alteration of genetic make-up with time, is a natural process. Plant and animal breeding and selection of the optimal microorganism have all depended on changes at the genetic level. The difference is one of precision and knowledge. Whereas earlier genetic manipulations were performed at the level of the organism, the new manipulations are well defined and specific, performed at the molecular level.

Does this specificity mean that these "new" organisms are more or less predictable in the environment? Environmental groups are urging extreme caution in working with these unknowns, while U.S. industry and government suggest that the precision used in making these new organisms really make them more manageable and that testing should proceed. The result of these opposing positions has been serious delays in moving laboratory results to the field testing stage. Practically every government approval of a field test has been challenged by a law suit, either at the national or local level. In fact the entire Federal policy, the Coordinated Framework for Regulation of Biotechnology, has been challenged by a lawsuit (Jeremy Rifkin). The lawsuit has has been thrown out of court since there as yet has been no organism reviewed under the Framework. It is likely that with the first review the suit will reappear.

Section 2 - U.S. Regulatory Policy

Due the nature of biotechnology and the range of products it offers, numerous Federal agencies are involved with regulation. They are the National Institutes of Health (NIH), National Science Foundation (NSF), the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), Occupational Safety and Health Administration (OSHA), and United States Department of Agriculture (USDA). The major regulatory agencies are discussed individually in later sections. Presented here is a general discussion of the latest effort in coordination of policy. (The information in this section is derived from the Coordinated Framework for Biotechnology Regulation(6) and the most recent NIH Guidelines(7)).

Coordinated Framework for Regulation Biotechnology

The most recent U.S. regulatory policy on biotechnology was released in June 1986. This is the Coordinated Framework for Regulation of Biotechnology developed by the Biotechnology Science Coordinating Committee, a committee of the Domestic Policy Council Working Group on Biotechnology of the Office of Science and Technology Policy. The Framework was published last year in the Federal Register for comment and became effective immediately.

The basic premise of the Framework is that biotechnology does not require new statutes to ensure adequate regulation. Rather, "Existing statutes provide a basic network of agency jurisdiction over both research and products;..". With this premise at its center the Framework provides guidance on the following questions:

What products require regulation?
Who regulates what ?
How is regulation carried out?

To answer these questions the Framework takes the following approach:
- presentation of some common definitions to be used by all agencies when determining the level of regulation required
- discussion of the agencies specific jurisdiction and procedures to followed in cases of overlapping jurisdiction
- discussion of the review process within the various agencies to ensure a simlar approach and depth.

Definitions

To determine the level of regulation required, the Framework has established two working definitions, accepted by the agencies. The document emphasizes that this distinction does not imply that other modified organism should not be carefully reviewed and appropriate procedures followed. However the policy identifies the modified organisms which may pose potential hazards and therefore require detailed review.

These definitions determine what is a "new" organism and what is a potentially dangerous organism. To determine what is a "new" organism the Framework considers the source and nature of the transferred DNA. To require full

review, the policy has taken the genus subdivision as its boundary - intergeneric organisms require specific review. The definition provided within the document is as follows: Intergeneric organism - "organisms formed by deliberate combination of genetic materials from sources in different genera."

However, the Framework goes on to identify several exclusions to this rule. These exclusions are based on the nature of the DNA transferred. Even if the DNA is from another genus, full review is not required if the DNA "is well characterized and contains only non-coding regulatory regions."

The next term defined addresses the potential danger of the organism or the transferred DNA - pathogen, any agent capable of causing disease in other living organisms. "This includes microorganisms that belong to a pathogenic species or that contain genetic material from source organisms that are pathogenic." As with intergeneric organisms, there are also exceptions to this classification, such as "organisms generally recognized as non-pathogenic according to sources identified by a federal agency...".

These two BSCC definitions, intergeneric organism and pathogen, are the criteria for regulatory review. Although agreed upon by the agencies and now part of established policy there is still much discussion about these definitions. The environmental community questions the exemptions, for example, of intergeneric organisms containing non-coding regulatory sequence. This means that the transferred DNA does not code for a protein but plays a role in the expression of the protein gene it is associated with. Is the manipulation of this regulatory sequence so well understood to be deregulated ?

An important definition which is still under discussion and the subject of individual agency interpretation is "deliberate (environmental) release."

Jurisdiction

The Framework states: "To the extent possible, responsibility for a product will lie with a single agency. Where regulatory oversight or review for a particular product is to be performed by more than one agency, the policy establishes a lead agency.....". Jurisdiction is determined either by the source of funding or final product use.

The regulation of biotechnology encompasses both research and product use. Presented on the next pages are the charts from the Framework which indicate jurisdiction and lead agencies.

Chart I
Coordinated Framework - Approval of Commercial Biotechnology Products

Subject	Responsible Agencies
Foods/Food additives	FDA*, FSIS(1)
Human Drugs, Medical Devices, and Biologics	FDA
Animal Drugs	FDA
Animal Biologics	APHIS
Other Contained Uses	EPA
Plants and Animals	APHIS*, FSIS(1), FDA(2)
Pesticide Microorganism Released in the Environment	EPA*, APHIS(3)
Other Uses (Microorganisms):	
Intergeneric Combination	EPA*, APHIS(3)
Intrageneric Combination:	
Pathogenic Source Organism	
1) Agricultural Use	APHIS
2) Non-agricultural Use	EPA*(4), APHIS(3)
No Pathogenic Source Organisms	EPA Report
Nonengineered Pathogens:	
1) Agricultural Use	APHIS
2) Non-agricultural Use	EPA(4), APHIS(3)
Nonengineered Nonpathogens	EPA Report

Notes:
*Lead Agency
(1) FSIS, Food Safety and Inspection Service, under Assistant Secretary of Agriculture for Marketing and Inspection Services is responsible for food use
(2) FDA is involved when in relation to food use
(3) APHIS, Animal and Plant Health Inspection Service, is involved when microorganism is plant pest, animal pathogen or regulated article requiring a permit
(4) EPA requirements will only apply to environmental release under a "significant new use rule" that EPA intends to propose.

Chart II

Coordinated Framework - Biotechnology Research Jurisdiction

Subject	Responsible Agencies
Contained Research, No Release in Environment:	
1. Federally funded	Funding agency(1)
2. Non-Federally Funded	NIH or S&E voluntary review, APHIS(2)
Foods/Food Additives, Human drugs, Medical Devices, Animal Drugs:	
1) Federally Funded	FDA*, NIH guidelines & review
2) Non-Federally Funded	FDA*, NIH voluntary review
Plants, Animals and Animal Biologics:	
1) Federally Funded	Funding Agency(1)*, APHIS
2) Non-Federally Funded	APHIS*, S&E voluntary review
Pesticide Microorganisms:	
Genetically Engineered:	
Intergeneric	EPA*, APHIS(2), S&E voluntary review
Pathogenic Intrageneric	EPA*, APHIS(2), S&E voluntary review
Intrageneric nonpathogenic	EPA*, S&E voluntary review
Nonengineered:	
Nonindigenous Pathogens	EPA*, APHIS
Indigenous Pathogens	EPA*(3), APHIS
Nonindigenous Nonpathogen	EPA*
Other Uses (Microorganisms) Released in the Environment	
Genetically Engineered:	
Intergeneric Organisms:	
1) Federally Funded	Funding Agency*(1), APHIS(2), EPA (4)
2) Commercially Funded	EPA, APHIS, S&E voluntary review
Intrageneric Organisms:	
Pathogenic Source Organism:	
1) Federally Funded	Funding Agency*(1), APHIS(2), EPA(4)
2) Commercially Funded	APHIS(2), EPA(*If non-agricultural use)
Intrageneric Combination:	
No Pathogenic Source Organisms	EPA Report
Nonengineered	EPA Report*, APHIS(2)

Notes :

*Lead Agency; S&E-Science and Education, USDA

(1) Review and approval of research protocols conducted by NIH, S&E, or NSF

(2) APHIS issues permits for the importation and domestic shipment of certain plants and animals, plant pests and animal pathogens, and for the shipment or release in the environment of regulated articles

(3) EPA jurisdiction for research on a plot greater that 10 acres

(4) EPA reviews federally funded environmental research only when it is for commercial purposes.

Health and Human Services - National Institutes of Health (NIH)

Statute Providing Regulatory Authority - NIH is not a regulatory agency. It has developed "Guidelines" to be used by laboratories which it funds and this support is contingent on compliance with these Guidelines. Other public institutions and private research companies, not funded by NIH, follow these Guidelines on a voluntary basis.

Biotechnology originated in the laboratory, through basic research and it was there that the initial regulatory questions arose. The first set of NIH Guidelines for Recombinant DNA were released in 1976. At that time recombinant DNA was viewed simply as a research technique - the products had not yet appeared. The issues were concerned with laboratory safety and ensuring that the organisms under study remained in the laboratory. The focus of the guidelines was therefore on containment and laboratory practices.

Since 1976 the NIH Guidelines have been revised and expanded several times and have become less restrictive as experience with rDNA has accumulated. The most recent publication was in May 1986. The NIH Guidelines have served as the foundation for the current regulatory policy and other agencies, e.g. USDA, have incorporated similar approaches. They have also served as a model for other countries, which have often simply adopted them.

As the first agency to grapple with rDNA, NIH established definitions, internal agency mechanisms, institutional mechanisms and containment conditions as the basis for regulatory procedures. The central definition for the NIH Guidelines is recombinant DNA molecules. These "are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above."

The NIH has also struggled with the definition of "deliberate release." A new definition is under discussion for "deliberate releases into the environment as the planned introduction of recombinant DNA-containing microorganisms, plants or animals." (8)

Containment is the result of specific barriers which can be of varying nature. In recombinant DNA work the barriers are both biological and physical. Biological barriers are those inherent to the organism. For example, due to biological requirements a bacteria may not be able to survive outside of the laboratory. Specific biological barriers exist which "limit either (i) the infectivity of a vector or vehicle (plasmid or virus) for specific hosts or (ii) its dissemination and survival in the environment." Physical barriers are those imposed on the research procedures. These include both research practices and physical structures.

The NIH Guidelines define laboratory practices and the containment level required. Four levels of physical containment have been described, identified as Biosafety level 1 (BL1) through (BL4), where BL4 is the most stringent level of containment. The Guidelines provides a classification of organisms and host vector systems as well.

The review structure established through the NIH Guidelines is composed of different levels of review, dependent on the nature of the experiment and the organisms involved. The review can range from the local level to the Director of NIH who has the final decision. To advise and assist in this process the Recombinant DNA Advisory Committee (RAC) was created. This committee contains scientists and non-scientists, with a total of 25 members. NIH has also established an Office of Recombinant DNA (ORDA) which coordinates all activities in this area.

On the local level, each institution where rDNA research is being carried out must have an Institutional Biosafety Committee (IBC). This committee is comprised of at least 5 members with expertise in rDNA. An additional 2 members must be unaffiliated with the institute, representing the communities interest. ORDA is responsible for the approval of the membership of IBCs.

The May 1986 NIH Guidelines have defined four classes of experiments:

1. Experiments which require specific RAC review and NIH and IBC approval before initiation of the experiment;

2. Experiments which require IBC approval before initiation of the experiment;

3. Experiments which require IBC notification at the time of initiation of the experiment; and

4. Experiments which are exempt from the procedures of the Guidelines.

For example, in category 2, experiments which require IBC approval before initiation, includes experiments using human of animal pathogens (Class 2, Class 3, Class 4, or Class 5 Agents as Host-Vector Systems).

As rDNA research has advanced, movement out of the laboratory and into the testing stage has occurred. For such experiments NIH requires that each experiment be reviewed by RAC and a final decision made by the Director. This procedure was adequate a few years ago, but the number of proposed field tests/environmental releases has grown dramatically and additional Federal agencies have become involved. It is the purpose of the Framework and the BSCC to coordinate these regulatory processes. NIH requests that institutions submitting release experiments for review indicate what other agency is involved in the review and then a decision is made as to whether both reviews are necessary.

Food and Drug Administration (FDA)

Statutes Providing Regulatory Authority - Public Health Service Act
Food, Drug and Cosmetic Act

The FDA does not view products developed through biotechnology as different from any other. "The agency believes that each product must undergo adequate and appropriate testing and review to ensure that it is safe and effective regardless of the technology employed."

The agency's established methods for approval of new drugs or food additives are applied to rDNA products. No new procedures are proposed. Therefore before marketing a new drug application (NDA), a biological product license, or a new animal drug application (NADA) must be approved. For new medical devices, a premarket approval application (PMA) is required. Each of these approvals requires specific information on the proposed new product.

The FDA has an established system of steps for the approval of new drugs. These include:

1. Phase I trials - drug toxicity assessed
2. Phase II trials - therapeutic efficacy is assessed, and
3. Phase III trials - the role of the new therapeutic approach is defined and it is compared with existing approaches.

The process is a long and costly one. To bring a new anti-cancer drug to market it is estimated that 6 -10 years of development are required at a cost of $60 - 100 million. (9)

Environmental Protection Agency (EPA)

Statutes Providing Regulatory Authority - Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)
- Toxic Substances Control Act (TSCA)

Recombinant DNA technology has developed many products/organisms which will useful as insecticides, fertilizers, or leaching agents. Such products fall under the jurisdiction of EPA and the products final use determine which statute and procedures are appropriate. EPA, under FIFRA and TSCA, is particularly concerned with "microorganisms that:

1. are used in the environment,
2. are pathogenic or contain material from pathogens, or
3. contain new combinations of traits....."

A biotechnology Science Advisory Committee is being established by the Agency to provide peer review of special cases and advise on technical matters.

FIFRA

Under FIFRA, EPA has authority to regulate the products of biotechnology used as pesticides. As with all pesticides, these must be registered with the agency. This process requires that a complete evaluation and review be conducted before registration by the agency. Testing of a pesticide requires a Experimental Use Permit (EPU), which under certain circumstances are waived.

EPA has determined that the EPU process is required for "any field testing of genetically altered or nonindigenous microbial pesticides". However, the agency has distinguished two levels of this process, requiring different types of information, based on the nature of the microorganism. Level 1, requires a limited amount of information, and is appropriate for microorganisms defined by EPA as less likely to pose environmental hazards. Level 2 review, full notification requirements, is concerned with "microbial pesticides formed by deliberately combining genetic material form organisms of different genera and genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organism."

TSCA

The products subject to TSCA cover a wide range: "all microorganisms produced for environmental, industrial, or consumer uses are potentially regulable under TSCA.". The exceptions include microbes used as food, food additives, drugs, cosmetics, medical devices, and pesticides as well as plants and animals. Under TSCA a Premanufacture Notification (PMN) requirements must be met for any "new" organism. EPA uses intergeneric as the definition of "new", supporting this decision with the following justifications:

- "the degree of human intervention involved
- the significant likelihood of creating new combination of traits
- the greater uncertainty regarding potential risks...."

EPA accepts the general exclusion, put forth in the framework, for intergeneric organisms generated using only well-defined regulatory sequences. EPA has developed a detailed list of information required for the PMN.

EPA is proposing to extend its jurisdiction under TSCA with the development of a Significant New Use Rule (SNUR). This will be an effort to include organisms that although not strictly "new", and therefore excluded under TSCA, may still present a potential hazard. Specifically, pathogens and microorganisms containing pathogenic material fall into this category. Other groups of microorganisms, nonindigenous and those which degrade structural components of nature (e.g. cellulose) are being considered for inclusion in the proposed SNUR. Until the SNUR is developed EPA expects voluntary compliance.

United States Department of Agriculture (USDA)

Statutes Providing Regulatory Authority
- Virus-Serum Toxin Act
- Federal Plant Pest Act
- Plant Quarantine Act
- Organic Act
- Federal Noxious Weed Act
- Federal Seed Act
- Plant Variety Protection Act
- Federal Meat Inspection Act
- Poultry Products Protection Act
- Food Security Act

USDA is in a unique position as an agency with both research and product regulatory responsibilities. (This has generated considerable discussion regarding USDA's objectivity in regulatory development.) In comparison, NIH serves solely as a research institution and defines regulation there and FDA serves solely as a regulatory agency for products used as foods, food additives, or drugs. USDA has established the Committee on Biotechnology in Agriculture "which will function as both a policy body in the USDA and a bridge between its research and regulating structures."

Regulation of Research

USDA is in the process of developing a regulatory system for research activities similar to that of NIH. At the local institutional level, this system will depend on Institutional Biosafety Committees (IBC). An Agriculture Biotechnology Recombinant DNA Advisory Committee (ABRAC) will serve as a final review for research believed to be potentially more hazardous.

As in the NIH system, containment levels and classification of experiments are defined. Containment levels have been identified for both laboratory studies (Biosafety Levels 1-4) and large scale research or production, 10 liters or greater, (Biosafety Levels 1-3, Large Scale). The four classes of experiments, which determine the containment and procedural requirements, are as follows:

1. Agricultural research that is exempt
2. Agricultural research that requires IBC notification at initiation
3. Agricultural research that requires IBC approval and USDA registration before initiation
4. Agricultural research that requires USDA and IBC approval before initiation: Release of organisms

Product Regulation

USDA has regulatory authority in one form or another over the movement into the U.S or interstate of veterinary biological products, plants and plant products, meat and poultry products, and seeds. Such movement requires a license or permit for which specific information has been identified.

USDA has also established a new category for regulation, as an extension of the Federal Plant Pest Act (FPPA) and Plant Quarantine Act (PQA). This class includes "introduction of organisms and products altered through genetic engineering which are plant pests or which there is reason to believe are plant pests." In this discussion USDA has defined introduction broadly as " to move into the United States, to release into the environment, or to move interstate, or any attempt thereat."

Section 3 - International Regulatory Policies

Organization of Economic Cooperation and Development (OECD)

The members of OECD are:

Austria	Belgium
Canada	Denmark
France	Federal Republic of Germany
Greece	Iceland
Ireland	Italy
Luxembourg	Netherlands
Norway	Portugal
Spain	Sweden
Switzerland	Turkey
United Kingdom	United States

In July of 1983 the Ad Hoc Group on Safety and Regulations in Biotechnology, of the Committee for Scientific and Technological Policy, began work on an international framework for regulation. In May 1986 a document was distributed entitled, "Recombinant DNA Safety Considerations - Safety Considerations for Industrial, Agricultural and Environmental Application of Organism Derived by Recombinant DNA Techniques." This document,(10) discusses general procedures and approaches to the use of recombinant DNA engineered organisms. "They are not standards for regulating applications or products, but a first step towards recommendations for eventual harmonization on these issues."

The document discusses the general issues of regulation - the potential uses of engineered organisms, potential risks, evaluation of the organism, and containment. The central premise of the document is that good industrial large scale practices (GILSP) are adequate for industrial uses of recombinant organisms. However, in the areas of environmental and agricultural use there is less experience and therefore a less developed procedure for risk assessment. In these areas it emphasizes that there is useful data available from studies in ecology, pathology, taxonomy, and physiology. The report discusses steps and information required for an assessment.

As with the U.S Coordinated Framework, the OECD policy emphasizes that new legislation is not required for regulation. In the final recommendations of the report its underlying policy is clearly stated:

> "There is no scientific basis for specific legislation for the implementation of rDNA techniques and application. Member countries should examine their existing oversight and review mechanisms to ensure that adequate review and control any be applied while avoiding undue burdens that may hamper technological developments in this field.
>
> Any approach to implementing guidelines should not impede future developments in rDNA techniques. Internal harmonization should recognize this need."

State Department Working Group - The Biotechnology Science Coordinating Committee has established a working group to discuss international regulation. This group has met met approximately three times and is focusing on the developed world. Specifically the group is discussing regulatory documents designed by the OECD and the European Community (EC). This attention to the developed world reflects the U.S. concern with trade barriers, which may restrict the growth of the new industry and the related topic of U.S. competitiveness, which is currently a central issue.

In the U.S Coordinated Framework for Regulation of Biotechnology the various agencies have indicated there acceptance of the OECD recommendations. NIH (7) has specifically described regulations applicable to funding overseas:

> "The Guidelines are also applicable to projects done abroad if they are supported by NIH funds. If the host country, however, has established rules for the conduct of recombinant DNA projects, then a certificate of compliance with those rules may be submitted to NIH in lieu of compliance with the NIH Guidelines. The NIH reserves the right to withhold funding if the safety practices to be employed abroad not reasonably consistent with NIH Guidelines."

A summary of some specific regulatory policies in developed countries is presented below.

West Germany - A five year moratorium on all experiments involving the environmental release of genetically engineered organisms has been recommended by a parliamentary commission. Also it has been suggested that all experiments on human embryos, capable of achieving full maturity, and genetic screening of newborn babies for untreatable genetic diseases be banned. The committee which made the proposals had conducted a two year study of the issues. The committee was comprised of representatives of the four main political parties, and representatives of the scientific, religious and industrial communities. The proposals were broadly endorsed by the members of the committee with one exception, the Green party, Germany's environmentalist party, which supports an even more extreme position.. The government's response to the proposals is expected in several months. (11)

England - Environmental testing of some products has begun.

France - Summary tables (12) of France's regulatory approach are presented in Appendix 1.

Japan - Biotechnology in Japan is the the subject of recent report prepared for the Department of Commerce. Included in this report (13) is a discussion of regulation indicating that numerous agencies have developed guidelines, typically based on those of NIH and OECD. A summary table from that report on regulation is presented in Appendix 1.

Information on Developing Countries Regulatory Policy

Information on the regulatory policy in developing countries is not readily available. This is due to the fact that such policies either do not exist or are in the formative stages.

Asia/Near East

Thailand - The Ministry of Science, Technology, and Energy has established Thai guidelines through its National Center for Genetic Engineering and Biotechnology. The guidelines in use presently are extremely broad - " which call attention to potential environmental hazards DNA urge individual grantees to make responsible decisions in the management of their NCGEB supported projects."

A committee has been established to develop more detailed guidelines. The Director of NCGEB believes that the Thai regulation will be less restrictive but derived from the NIH guidelines. A.I.D./Thailand's large Science and Technology and Development Program will most likely follow the NCGEB guidelines, but what their role will be in national policy is unclear. (14)

India - India is active in Biotechnology and in the process of developing regulations. No final document has appeared.

Phillipines - The Philippine Institute of Biotechnology will develop guidelines. (15)

Indonesia - The National Academy of Sciences has been active in the identification of priorities in Indonesia where biotechnology would be useful. Recently a workshop was conducted on this topic. There appears to be no regulatory structure in place yet.(16)

Latin America - Discussions have indicated that the development of regulations Latin America are not well advanced. A group from Brazil recently visited the U.S. to discuss biotechnology, including regulatory considerations.(17)

Africa - No information on regulation in Africa has been obtained.

UNIDO Biotechnology Centers (17) - The United Nations Industrial Development Organization (UNIDO) has supported the development of international centers in biotechnology which will "promote the development of and peaceful application of genetic engineering and biotechnology, especially for developing countries The center is known as the International Center for Genetic Engineering and Biotechnology (ICGEB). This activity is supported by 36 countries (excluding the United States). The center will have two locations, one in New Delhi, India and the other in Trieste, Italy. A director has been chosen Dr. Gonzales, of Illinois, and staff is being recruited.

While the center is in the process of being established a working group has been developed among U.N. agencies (World Health Organization WHO, UNIDO, and United Nations Environment Programme UNEP) to discuss the risks of biotechnology. Presented in Appendix 2 is a discussion, prepared for UNIDO (17), on the proposed role of the ICGEB and the informal working group in the development of international regulation.

Part II - Regulation of Biotechnology and A.I.D.

General Discussion

As A.I.D. begins to discuss its support of biotechnology and the regulatory considerations involved it is essential that certain observations be discussed. First among these is the nature of regulation in the United States. Although the Coordinated Framework for Regulation of Biotechnology was released in June 1986, the regulatory structure set forth in that document is far from established. The Framework has been challenged in court and debated within the environmental community. The first environmental release to be reviewed using the Framework has yet to be completed.

The U.S. Regulatory Framework is based on the history and authorities of six federal agencies. As discussed earlier, much of the effort of the BSCC has been to develop some concensus of definition and approach among these agencies. Each agency however still maintains its own procedures. Although the definitions and classifications, if acceptable, may serve as important starting point, the U.S. system is not readily transferable to the international arena. On the international level OECD's document presents a philosophical and "harmonizing" approach rather than the development of any specific regulations.

The review process in the U.S. is not running smoothly yet. Although some field testing of genetically engineered plants has been approved and is underway, those involving microorganisms are moving slowly. The now famous ice-minus bacteria spent almost five years in the regulatory matrix before field tests were finally begun in April 1987 (18).

The first case to be reviewed through the Coordinated Framework structure involves an improved rhizobium strain. Although EPA has stated that the tests proposed by Biotechnica, Inc. "will not pose unreasonable risks", the review has been extended for another 60 days (19). It is likely, given the number of requests for testing approval and the staffing problems of the agencies involved, that the review process will remain quite slow. Additionally, the U.S. regulatory process will most likely proceed on a case by case basis for quite some time.

Secondly, in biotechnology regulation the issues are basically worker safety and environmental questions. What effect will a released organism have on the environment? Are containment facilities and procedures adequate? A.I.D. has developed procedures in its project design, review and evaluation process to address environmental concerns. These mechanisms are in place but it would be difficult to simply incorporate biotechnology projects and provide adequate review.

This difficulty would arise due to the evolving nature of biotechnology and its regulations and the expertise required to identify the nature of the risk presented by the organism and procedures involved, as well as evaluating containment facilities. If an A.I.D. review process is developed based on the environmental system now in place, it is essential that expertise be brought in during the early phases of project design and review. A.I.D. is currently in the process of developing animal use guidelines. The process developed for this different type, but somewhat overlapping regulatory issue may be useful in the biotechnology discussions.

Finally, the complexity of biotechnology - both the science involved and the emerging industry present important issues. The most successful scientific feat in gene manipulation may not be the applicable in the developing world. Although the result is a scientific achievement it may not have any impact or even have a negative impact on a situation. An excellent example of this is the transfer of herbicide resistance from one organism to a plant. Such an "improved" plant is capable of withstanding increased amounts of herbicide, but is such a goal desirable in the developing world ?

In addition to presenting new approaches to difficult research problems, biotechnology presents an avenue for the stimulation of the private sector. In the United States the biotechnology industry has grown dramatically. Since 1978 there have been 287 new businesses started in the area. As the industry. has grown so has the industry's interest in new markets, including the developing world. A.I.D.'s support of joint ventures and limited R&D partnerships are beginning to include biotechnology activities. Regulatory responsibility and liability should be discussed in the design of such efforts.

Section 1 - Technical considerations in a biotechnology project

In considering a biotechnology project for support it is necessary to consider the following points:

1. What is the range of effort of the project ?
2. What organisms and systems are being used ?
3. What will be the end product use ?

Range of Effort

The first step in assessing the regulatory aspects of a biotechnology project is to determine what the project end point is. Although biotechnology has shortened the time span between bench research and product use the basic steps in the process remain the same. To develop a useful product includes the following steps:

1) Basic research
2) Contained testing
3) Field testing
4) Marketing and/or distribution

Dependent on project design, any one or all of these steps may be supported by A.I.D. Each one of these steps, in the United States, is subject to Federal regulation in some form or another. As discussed in Part 1, the Coordinated Framework defines jurisdiction. Typically the NIH Guidelines for Recombinant DNA would apply to the basic research, unless it was agricultural research. Steps 2,3 and 4 would be subject to USDA, EPA or FDA dependent on the final product use.

Organisms and systems to be used

An equally important consideration in biotechnoloy projects is the nature of the organisms being studied and used. These include the organisms used as the source for DNA, the organism which is the recipient, and the vector system used to transfer the DNA.

As emphasized throughout the Coordinated Framework, the use of pathogens for any of the above must be carefully scrutinized. Pathogencity, the ability to cause disease, is a broad characterization which determines the potential hazard of an organism or a gene. An additional hazardous group which may or may not be considered a pathogen subgroup, are the oncogenic (or tumor) viruses or the genes responsible for causing neoplastic transformation.

Neoplastic transformation is that process whereby a normal cell, with specific characteristics, including controlled growth is transformed into a cancer cell, with uncontrollable growth. Certain viruses, known as oncogenic or tumor viruses are associated with this process. Specific genes, oncogenes, are responsible for the transformation and typically these genes resemble normal cellular genes. The hypothesis is that transformation occurs as a result of the over expression of the normal cellular proteins responsible for the growth regulation. The relationship between oncogenes and cancer has been reinforced with the isolation of such genes from human tumors. The ability of oncogenes to shift from normal cellular genes to transforming agents is not understood. These genes present a possible illustration of a beneficial gene which becomes deleterious based on dosage.

The identification of an organism as pathogenic, either naturally occurring or recombinant, is a process which has been under study by many agencies for numerous years. In their recent guidelines EPA refers questions to appropriate sources, such as Pathogenesis of Invertebrate Microbial Diseases, Davidson, E. ed. The agency is developing an expanded list of resources and considering developing a list of pathogenic species.

In comparison NIH has identified five classes of microorganisms based on hazard. Class 5, the most hazardous group, includes animal disease organisms and vectors which are forbidden in the United States by law, e.g. Fowl plague virus. In class 4, oncogenic viruses are grouped according to risk, e.g. low risk - Murine leukemia virus and moderate risk - Feline leukemia virus. NIH has also developed an elaborate classification system for vectors.

The organisms used in a project should also be considered in context. This is of critical importance when overseas work is conducted. Despite the lack of pathogenicity or intergeneric DNA, the use of an exogenous organism in the proposed country may have far ranging effect.

End Product Use

The final goal of biotechnology research is to develop useful products. These products however may require special education for proper use or an increased sensitivity to quality control in the manufacturing process. Additionally the waste products in the manufacturing process often require specific handling measures. Liters and liters of recombinant organisms used to produce some protein must be disposed of properly. Regulations for such disposal have been designed in the United States.

Section 2 - Regulatory Approach at A.I.D

Historic Perspective

A.I.D.'s treatment of regulatory matters in projects which support genetic engineering activities has paralleled U.S. regulatory growth Projects initially have been subject to the standard environmental review and typically adherence to NIH Guidelines for Recombinant DNA has been suggested. A recent report (20) has been prepared which catalogues A.I.D.'s activities in this area and indicates that regulatory guidance is not treated uniformly throughout the Agency.

Two offices which have had considerably more experience with biotechnology regulation than other A.I.D. offices are the Office of the Science Advisor and the Office of Agriculture, S&T. The Science Advisor's program supports research grants throughout the world. The use of recombinant DNA technology has been a component of many of these grants and the office has included regulatory considerations in their list of project check points.

The office requires that the grantee certify that NIH or equivalent national guidelines are in place. Originally this was requested in the "Additional Information" form. A newer version of this form entitled "Special Concerns" goes beyond the NIH Guidelines and identifies the introduction of the products of genetic engineering as special concern which must be discussed. Both forms are attached in Appendix 3.

The Office of Agriculture recently began support of an animal vaccine project to develop an improved vaccine to rinderpest using genetic engineering. In the process of developing that project regulatory directions were outlined. Basically adherence to U.S. guidelines and written approvals from the host country government and A.I.D. are required. The language has been amended to all projects in the Office of Agriculture which support genetic engineering activities.

A.I.D.'s Regulatory Needs - suggested approaches

A.I.D. needs to address the question of guidelines and procedures in order to ensure that adequate precautions and safeguards are included in biotechnology programs. Presented and discussed below are some possible approaches which the Agency may pursue.

1. A.I.D. could cease to support biotechnology activities.

This possibilty would greatly simplify A.I.D.'s responsibilities, limiting the Agency to those projects which are already in place. However it does not take into consideration the enormous impact biotechnology may have on development. Developing countries are eager to become involved in this new area, problems that were previously unapproachable, though still complex can be attacked with the new methods, and industry supportive of biotechnology is beginning to see potential partners in the developing world. Although discouraging support in biotechnology is a simplistic approach to the complications posed by regulation of biotechnology, it is also naive and would exclude an area which offers unique potential. Even though biotechnology is very much a buzz word, its applications and impact are genuine.

2. A.I.D. could develop its own specific guidelines.

This approach presents an overwhelming and somewhat redundant task. The level of effort and expertise required would be difficult to find within the Agency and the U.S. scientific agencies have established definitions and methods which are likely to serve as a model system worldwide (if the NIH Guidelines are any indication). Although A.I.D.'s ties to the developing world presents expertise the Agency lacks the scientific character to adequately review and develop standard worldwide regulations for its programs. Additionally it would be inappropriate for A.I.D to establish such guidelines, given the current effort on both the national and international scence to develop "harmonization".

3. The establishment of regulation and review processes could be developed and conducted by outside expertise.

This approach would provide the Agency with the expertise it lacks and it could draw on established U.S. and international regulation. However it would also stunt the development of any internal expertise in biotechnology and it may result in a decentralized and diffuse approach, with each office developing its own resource contacts and process. Such a diffuse approach would be difficult to monitor.

This problem could be avoided with the establishment of one external group for the review of all biotechnology projects. However, given the nature of biotechnology regulation it may difficult to find such a group. (The establishment and maintenance of such a group would also be extremely costly.)

It is unlikely to assume that one of the U.S. scientific agencies, e.g. EPA would assume review responsibilities for A.I.D. projects. These agencies are already over burdened with U.S. project reviews and they are unfamiliar with the international considerations, especially those in the developing world.

4. Development of A.I.D. procedures based on host country and U.S. regulation, using in-house expertise with outside expertise for detailed review.

This process would allow for the development of some Agency expertise in the area, centralization and continuity of Agency experience in the area and utilization of the developed U.S. regulatory structure and expertise. It would appear to best fit A.I.D.'s needs while providing the Agency with an important role in the process but guided by the necessary scientific expertise. This approach can be considered a fusion of the approaches described in numbers 2 and 3 above.

What follows in the next few pages is a discussion of the requirements for establishing a regulatory procedure. using approach #4 as a possibility. (The same functions could be addressed using the other approaches, with the exception of #1, and may be carried out entirely within A.I.D. (#2) or outside of A.I.D. (#3).)

To adequately incorporate regulatory considerations into A.I.D. biotechnology projects three discrete stages can be envisioned:

1. the collection of complete and appropriate information concerning the proposed project,

2. an assessment of that information in terms of regulations required and

3. monitoring activities to ensure that facilities are sufficient and regulations are followed.

These stages indicate not only a temporal flow in the project process but also present increasingly difficult activities for A.I.D. The complexity and expense of regulation will increase as it proceeds from information gathering to monitoring. It will be essential to consider these expenses during the project design phase.

Collection of Project Information

As many A.I.D. staff are unfamiliar with genetic engineering, it is necessary to develop a standardized method of obtaining project information. The Science Advisor's forms are a useful model which can be expanded upon. An example of the type of information requested in presented in the "Biotechnology Information Form" in Appendix 3. The topics and questions are based on the current information requested by EPA and NIH during their review processes. As the U.S. agencies have not developed a finalized information list it will be necessary to work closely with these expert groups.

An additional use of the proposed form is to collect up to the date information on the regulatory policy of the host countries. A.I.D. is in a unique position to obtain this information from the developing world. It is likely that regulatory policies will evolve with time as the U.S. policy has and will continue to do, based on the expanding experience with recombinant organisms.

Assessment of Information

The assessment of the project information and host country regulations needs to be thoroughly understood and reviewed. As genetic engineering projects may contain many levels and types of experimentation, it will be difficult to depend solely on an in-house review. However the first step in the process will require that A.I.D. possess the ability to recognize certain general levels of experimentation and the risk involved.

Two specific methods may be used to develop this ability:

1. increased education of the A.I.D. staff in the biotechnology and
2. the establishment of a group within A.I.D. with a more significant understanding of biotechnology and the issues surrounding it.

The first of these methods has already started. There have been workshops both overseas and in Washington on the topic of biotechnology. Additionally the topic was addressed at last year's ADO conference and was also incorporated into the recent State of the Art training courses. Although all of these activities did not focus solely on regulation, the increased discussion of biotechnology is an important first step. Increased awareness about the subject should lead to consideration of the issues it raises - e.g. regulation.

The second method is also under discussion at the Agency. The establishment of an intra-agency committee is underway. This committee may serve as the Agency loci for the development of more advanced expertise in biotechnology or it may identify some alternative location for this expertise. Regardless, the A.I.D. expert group should contain agency-wide representation and technical competence.

This group can learn, through interaction with the U.S. scientific agencies and expertise, to identify the research and/or testing procedures which require special attention. The group can do a preliminary screening of biotechnology projects or simply provide a discussion group and training ground for the office representative who will be responsible the project review. It will ensure some uniformity in the Agency approach to biotechnology projects.

Once a project has been identified as requiring significant review, it is likely that an external review will be needed. Such an external review will define the necessary safeguards and procedures to be followed. Dependent on the potential risk involved, it may also be necessary to support a visit to the host country to evaluate facilities.

The external expert group should also review, if available, the host country regulations as compared to U.S. regulations and determine if they are equivalent. On this point, A.I.D. needs to determine what its overall policy will be. Considered in this decision must be a balance between the respect for the host country's policies and the application of safe procedures. One possibility is that the most stringent of the regulations in place, either the host country or U.S., be the one utilized.

Monitoring Activities

A description of regulatory issues should be included in all project reports. Additionally, based on the risk involved, the project site should be visited as needed. This need will be determined by the external expertise group, who will also suggest appropriate individuals. In its review of the project the external expertise group may require that specific information be supplied during the progress of the project.

Site visits by the expert group will also allow the A.I.D. field staff to become more familiar with the requirements and regulations. For smaller projects, such as the Science Advisor's program, perhaps an annual regional trip by an expert group would suffice to review several projects.

The process may seem cumbersome but it is crucial that A.I.D. support only safe research and testing. The unknown quality of the products of genetic engineering and the constantly expanding nature of biotechnology makes this a complicated process. However, with time the process will simplify as greater and greater experience with engineered organisms is acquired and as countries establish their regulatory procedures.

Section 3 - Suggested Topics for the Standing Committee on Biotechnology

Specific topics which need to be addressed by the Committee are:

1. What is the definition of biotechnology in A.I.D. ?

- A working definition is needed for project classification. Such a discussion should take into consideration the discussions happening in other Federal agencies. OTA will be devoting an entire chapter in one of its next reports on the issue of definitions.
-Additionally, an Agency definition is needed in order that field personnel may compare their host country's definition with that of A.I.D. Often host countries' definitions of biotechnology are extremely broad.

2. What is the best method of interaction with the BSCC and the U.S. regulatory agencies ?

3. How can A.I.D. interact with the ICGEB ?

- The ICGEB, although only moving slowly toward establishment, will be an important resource for information on biotechnology in the developing world. Several of the countries which A.I.D. works with, e.g. India, are strong supporters of the center. However, there is some ambiguity concerning the U.S. interest and involvement in the center which needs to be resolved before official communication can commence. A.I.D. needs to clearly define its relationship to the center.

4. What is the best method for ensuring that the field is informed of developments in biotechnology ?

- The field needs to know what is happening, in biotechnology in general and specifically in regulation. One possibility may be a regular, perhaps monthly, newsletter.

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Appendix 1
Biotechnology Regulations - France and Japan

TABLE 1
SUMMARY OF BIOTECHNOLOGY REGULATIONS
FRANCE

Legislation/Regulation/ Guidelines	Description	Products/Processes Affected	Notes
Licensing and Other Pre-Marketing Requirements			
A. Laboratory Research and Development			
1. Recombinant DNA Research Guidelines (Regles concernant les experiences de recombinaisons genetiques *in vitro* normes adoptees par la Commission Nationale de Classement du Ministere de la Recherche et de la Technologie, December, 1984)	1. Guidelines cover all government-funded recombinant DNA research; physical and biological containment specified; delegation of review responsibilities given to local committees.		1. These Guidelines represent a revision of the 1980 guidelines of the Control Commission. DGRST approval of certain types of experiments must be obtained from the Control Commission, review of other approved experiments conducted by local safety committees; voluntary compliance of guidelines by industry
2. Agreement Between Research Institutes and the Delegation Generale a la Recherche Scientifique et Technique (DGRST)	2. A formal agreement requiring institutions to notify the DGRST of certain recombinant DNA experiments		
B. Pharmaceuticals			
1. Public Health Code, Articles L 596-605, of February 1, 1959, as modified by the Decree of September 23, 1967 (APPENDIX L)	1. Establishes requirements for the manufacture and sale of general pharmaceuticals and special medications		1. Manufacturers must be authorized to sell their products; authorization requires verification of product safety and efficacy. EC protocols for analytical, toxicological, and pharmaceutical tests and clinical trials were adopted in 1975
C. Others			
1. Public Health Code, Book Five, Articles L 658, parts 1-10 (as found in Article 2 of the Law No. 75-604 of July 10, 1975) (APPENDIX M)	1. Establishes requirements for the manufacture and sale of cosmetics and personal hygiene products		1. Manufacturers must maintain data which demonstrates product safety, contents must be identified and disclosed to authorities.
2. Decree of 15 April 1912 (modified under the decree of 12 February 1973 under the Law of 1 August 1905 (Loi du 1er aout 1905 sur la repression des fraudes en ce qui concerne les produits chimiques dans l'alimentation humaine et les materiaux et objets au contact des denrees, produits et boissons destines a l'alimentation de l'homme et des animaux ainsi que les procedes et les produits utilises pour le nettoyage de ces materiaux et objets). (APPENDIX N)	2. Regulates processing techniques and chemical additives in food and feed additives		2. Only authorized chemical additives can be added to food/feed stuffs

TABLE 2
SUMMARY OF BIOTECHNOLOGY REGULATIONS
FRANCE

Legislation/Regulation/ Guidelines	Description	Products/Processes Affected	Notes
D. Chemicals			
1. Chemicals Control Law (Law No. 77-771 of 12 July 1977) (APPENDIX O)	1. Regulates commercial manufacturing or importation of chemicals, either in natural state or industrially produced.		1. Does not apply to chemicals used for research purposes, pesticides, food additives and pharmaceuticals, predates the EEC 6th Amendment; after review of data on use, toxicology, and manufacturing, the product may be placed on a list of products found dangerous to man or the environment.
2. Decree No. 79-35 of 15 January 1979 on the Control of Chemical Products. (APPENDIX O)	2. Describes technical data to be submitted with a notice of a new chemical		
3. Agricultural Chemicals Control Law (Loi No. 525 du 2 Novembre 1943 relative a l'organisation du controle des produits antiparasitaires a usage agricole) (APPENDIX P)	3. Regulation of sales and distribution of agrichemicals; requires toxicological testing of product.		
Post Marketing Requirements			
A. Worker Health and Safety			
1. French Labour Code, Articles L.231-5,7 (APPENDIX Q)	1. Regulations in the workplace where potentially hazardous materials are manufactured.		
2. French Labour Code, Articles L.232-1 (APPENDIX Q)	2. Health regulations in the workplace.		
B. Environment			
1. Law on Installations Classified for Purposes of Environmental Protection (Law No. 76-663 of 19 July 1976) (APPENDIX R)	1. Regulation of factories, buildings, etc. where location may threaten, or be a danger to, the neighborhoods, public health, environment, agricultural activities, etc.		1. A building operator must apply for an authorization if such danger or threat is to be prevented.
2. Administration and Classification of Waters and the Control of Water Pollution Law (Decret No 67-1094 du 15 decembre	2. Regulates industrial activities relating to water pollution.		

TABLE 3
SUMMARY OF BIOTECHNOLOGY REGULATIONS
FRANCE

Legislation/Regulation/ Guidelines	Description	Products/Processes Affected	Notes
1967 sanctionnant les infractions a la loi No 641245 du 16 decembre 1964 relative au regime et a la repartition des eaux et a la lutte contre leur pollution).			
3. Waste Disposal and Recovery of Materials Law (Law No 75-633 of 15 July 1975) (APPENDIX S)	3. Regulates the handling and disposal of industrial wastes.	3. Decree No. 77 of 19 August 1977 identifies five major classes of hazardous waste: 27 proscribed substances; radioactive waste; paint, oil, and hydrocarbon sludges; waste from certain technologies, and metal finishing.	3. Wastes from laboratories, pharmaceutical, and chemical companies are listed in the decree.
D. Export/Import			
1. Administrative actions, including list of export items requiring licenses (Ministry of Economics and Finance).		1. An export license is required for biotechnology products used in biological warfare; an export license is not needed for antibiotics, other medicinal products, and cultures of non-pathogenic organisms.	
E. Patents			
1. Patent Law of 2 January 1968 (Law No 68-1 amended 13 July 1978 as Law No. 78-742). (APPENDIX T)	1. Microorganisms *per se*, and microorganisms produced by a defined process are protected, some plant species can be patented.	1. Three main categories of microorganisms include: natural, pure cultures from naturally occurring organisms, and microorganisms produced by classical or genetic engineering methods.	1. France is a member of the European Patent Convention (EPC).
2. Law on the Protection of New Plant Varieties (Law No. 70-489 of 11 June 1970).	2. Covers sexually and asexually produced plants of all species; samples are to be left in a collection; confers the right to produce, import, and sell all or part of the registered plant.	2. Plant species specifically provided for under the law are excluded from patent protection.	2. France has ratified the 1961 UPOV Convention Text, and is a signatory of the 1978 Text.

TABLE 4

GENERAL RULES REGARDING RECOMBINANT DNA EXPERIMENTS IN VITRO

Chapter I—List of Experiments Requiring the Prior Approval by the Commission

I.1 Cloning genes coding for toxin molecules.

I.2 Transfer of genes coding for resistance to antibiotics into organisms which do not naturally possess such resistance. Experiments utilizing vector systems, B1 or B2, or the introduction of resistant genes into eukaryotic cells in culture are not included in this category.

I.3 Experiments utilizing DNA from non-defective genomes of organisms recognized as pathogens to man or animal, and classified under the classification 2, 3, 4, and 5 according to the NIH regulations.

I.4 Introduction into human cells of recombinant DNA molecules containing complete genes of potentially oncogenic viruses or transformed genes.

I.5 Introduction into animal cells of unidentified DNA molecules extracted from either cancer cells or in vitro transformed cells.

I.6 Utilization of complete viral genomes, or sub-genomic fragments that are potentially oncogenic, as vectors for the introduction of recombinant DNA into animal cells.

I.7 Use of non-certified host vector systems for cloning in microorganisms of rDNA molecules when the host or the vector are derived from microorganisms recognized as pathogens.

I.8 Experiments utilizing culture volumes larger than 20 liters.

I.9 Transfer of genes cloned or not into prokaryotic or eukaryotic organisms non-certified HB1 and HB2 leading to the establishing of new organism strains capable, or potentially capable, of autonomous reproduction following their deliberate release in the environment.

The projects pertaining to the categories described above will be examined on a case-by-case basis.

Source: Ministere de la Recherche et de la Technologie, Commission de Classement Recombinaisons Genetiques *In Vitro*, 1984

TABLE 5

GENERAL RULES REGARDING RECOMBINANT DNA EXPERIMENTS IN VITRO

CHAPTER II—Experiments That Can be Performed After Notifying the Classifying Commission

The experiments described in this section which do not enter into the experiment list described in Chapter I can be taken after simple notification to the Commission. These are:

II.1 Propagation into prokaryotic systems, certified as B1 or B2, of DNA molecules which do not pertain to the categories described in Chapter I. These experiments can be undertaken in labs classified as L1. However, when the source of DNA to be propagated is derived from messenger RNA or transformed cancerous cells the level of biological containment must be B1 or B2.

II.2 Utilization of host-vector systems consisting of cells in culture and vectors, either non-viral or containing defective viral genomes, for the propagation of DNA molecules not pertaining to the categories described in Chapter I.

For experiments classified in Chapter II, the laboratories can ask for an authorization to undertake all the experiments defined under this category provided that they will maintain with the Comité d'hygiène et de Securite (e.g., the local safety and hygiene commission which is maintained by every French company or lab) a list of all the experiments which have been undertaken.

Source: Ministere de la Recherche et de la Technologie, Commission de Classement Recombinaisons Genetiques *In Vitro*, 1984

TABLE 6

Major Japanese Government Ministries and Agencies involved in Biotechnology

Laws and Regulations

Cabinet	MESC	STA	MITI	MHW	MAFF
Patent	-	-	+	-	-
Standards	-	-	+	-	-
rec DNA guidelines	+	+	+	+	+
seed protection	-	-	-	-	-
Pharmaceutical, approval	-	-	-	-	-

MITI = Ministry of International Trade and Industry
MAFF = Ministry of Agriculture, Forestry and Fisheries
MESC = Ministry of Education, Science and Culture
MHW = Ministry of Health and Welfare
STA = Science and Technology Agency

Appendix 2
The Role of ICGEB and the Informal Working Group
U.N. (17)

The Role of the ICGEB and the Informal Working Group

The ICGEB could play a major role in addressing the unanswered questions about the nature and extent of any risks presented by genetic engineering and how to deal with those risks. Before the ICGEB is operating organizations such as UNIDO, WHO and UNEP have begun to address the most pressing safety issues. However, the Centre should take the lead once it is able, and the international organizations should provide expertise, advice, and assistance. The following are actions that should be undertaken:

1. Act as a forum for information exchange and debate;
2. Study potential risks and make findings regarding actual hazards or areas where additional research is needed;
3. Develop risk assessment methodology;
4. Conduct risk assessment;
5. Develop safety guidelines for the various categories of applications of genetically engineered organisms;
6. Assist other countries, especially less developed countries, in adapting these guidelines to their own special needs; and
7. Train scientists, technicians, workers, and other support staff to handle genetically engineered organisms safely.

Forum For Information Exchange

It should be recognized that the execution of some of these activities would involve the use of consultants or groups of experts under the direction of the Centre or the international organizations.

The ICGEB should act as a forum for information exchange and debate on biotechnology safety issues. This is a natural consequence of being an international centre and a catalyst for the development of biotechnology.

The Informal Working Group has acted in this capacity and should continue to do so. Even after the Centre initiates its own efforts, the international organizations should continue exchanging information about the activities of its member agencies in the area of biotechnology safety and should take steps to coordinate those activities with each agency and with the Centre.

Risk Identification and Assessment

For the ICGEB to be involved with safety issues in a major way, it should identify and study potential risks in order to determine actual hazards. This activity would naturally lead to risk assessment, to the extent possible, and to further development of risk assessment methodology. It would also lead to the identification of issues where further research on risk and risk assessment methodology is needed. With the experience gained in risk assessment and given the scientific facilities and talent of the Centre, it would be appropriate for the ICGEB to conduct risk assessment experiments.

Safety Guidelines

A major activity for the Informal Working Group should be to begin work immediately on the safety guidelines that will govern laboratory-scale research at the Centre. It should look initially to existing statutes and guidelines of the countries that will host the ICGEB and affiliated centres. After the Centre becomes operational, it might modify these guidelines, based on its experience.

Additional types of guidelines, such as those covering large-scale applications, environmental applications, or the handling of biowastes, could be developed in stages by the Centre as it gains experience in those areas and is able to commit the necessary resources. Ultimately, the Centre's guidelines could serve as a model for any country where genetic engineering is conducted. A related role for the Centre would be to assist other countries, especially less developed countries, in adapting the guidelines to their own special needs.

Care should be taken in the development of guidelines meant to serve as models so that all interested parties have an opportunity to participate in the process and the final guidelines represent consensus practices. In addition, such guidelines should be based upon sufficient data and rigorous scientific analysis. The ability of the Centre to persuade countries to follow its recommendations with regard to safety will

depend ultimately upon the quality of its work and the cogency of its reasoning.

Training

Safety training is an activity most appropriate for the ICGEB, and a major effort should be made. Such training should be incorporated into the scientific training already being planned for the Centre.

Appendix 3
Project Information Sheets

ADDITIONAL INFORMATION — SC1

Please also provide the additional information requested below:

___ Proposals Involving Human Experimentation. Please include a statement similar to the following from your institution's ethics committee:

"The Human Experimentation Plan for this proposal has been reviewed and approved by:

_____ _____."
Institution Ethics Committee (Date)

___ Proposals Involving Research on Recombinant DNA. Please submit certification by appropriate institutional committees (in each country involved) that the proposed research meets NIH DNA guidelines or, in the case of foreign countries, national guidelines essentially equivalent to the NIH guidelines. Please specify your plans for containment.

___ Proposals Involving Potential Environmental Hazards. Please submit certification by appropriate institutional committees (in each country involved) that the proposed research does not present unacceptable environmental hazards. Please specify your environmental safeguards and plans for containment. All release of exotic and/or genetically engineered organisms most definitely fits within this category.

___ U.S. Principal Investigator (Only). Please include your institution's DUNS (Data Universal Numbering System) number.

PROPOSALS RECEIVED WITH COMPLETE DOCUMENTATION -- INCLUDING ALL CVs, LETTERS OF COLLABORATION AND REQUIRED CERTIFICATIONS -- WILL BE CONSIDERED FIRST.

REMINDER: PLEASE BE SURE TO INCLUDE OUR IDENTIFICATION NUMBER ON THE FRONT OF EVERY DOCUMENT SUBMITTED. THANK YOU.

1125A
May 1986

May 1987

SPECIAL CONCERNS — SC 1

Agency policy requires that the following issues be addressed where appropriate. Our reviewers have checked those which they already think may apply. Please discuss your technical and administrative safeguards to meet the safety, ethics and/or legal concerns raised. Projects cannot be funded until these issues are adequately addressed.

___ HUMAN SUBJECTS: Research involving human subjects requires initial approval and continuing review by the appropriate medical ethics committee of all applicant organizations. The proposal must include their formal certification that the protocol has been reviewed and accepted. (Reference: U.S. Code of Federal Regulations, Title 45, Part 46.)

___ RECOMBINANT DNA: Research proposal must include certification by appropriate institutional commitees and/or national entities that the proposed research meets National Institute of Health DNA guidelines (or, in the case of foreign countries, equivalent national guidelines). Describe plans for containment in considerable detail.

___ ENVIRONMENT: Please address any potential of this research (or its success) to affect the environment. Please specify any plans for containment or planned prior research to assure environmental safety. The introduction of exotic organisms, toxic chemicals, radiation or the products of genetic engineering are special concerns. (Reference: U.S. Environmental Protection Act.)

___ ENDANGERED SPECIES: Please provide full scientific names of all species to be used, and specify safeguards to protect those which have been officially declared endangered (Reference: U.S. Endangered Species Act and the International Convention on the Export of Endangered Species, etc.).

___ LABORATORY ANIMALS: Specify safeguards to assure humane treatment of research animals. (Reference: U.S. National Research Council "Guide for the Care and Use of Laboratory Animals" and various U.S. Animal Welfare Acts, etc.). If your institution requires a committee review, please include a copy of their certification.

A.I.D. Biotechnology Projects - Required Information

Parental Organisms (donor and recipient)
- taxonomy
- source
- reproductive cycle
- habitat - geographic distribution
- pathogenicity, infectivity, virulence
- host range
- capacity for genetic transfer
- laboratory conditions specified for working with the organism

Modified organism
- new trait obtained
- amount and type of inserted/deleted genetic material
- vector construction
- stability
- test data - potential for survival

Production Process
- conditions for growth
- sites
- amount to be manufactured
- processing, storage, disposal of wastes

Containment
- physical containment facilities available
- emergency backup systems

Field Trials
- purpose and intended effect
- site of application - geographic, physical, chemical and biological
- introduction protocols
- emergency procedures

Monitoring
- detection procedures (including their limitations)
- sampling procedures
- periodicity

Host Country Regulations
- Ministries/departments responsible for regulation
- applicable regulations
- review procedures and notifications required
- monitoring requirements