DPC

THE WHITE HOUSE

WASHINGTON

DOMESTIC POLICY COUNCIL

Tuesday, May 20, 1986

2:00 p.m.

Roosevelt Room

AGENDA

1. Organ Transplantation

2. Biotechnology

DOMESTIC POLICY COUNCIL

May 20, 1986

PARTICIPANTS

Attorney General Meese

Secretary Baldrige
Secretary Bowen
Secretary Herrington
Director Miller

John Svahn, Assistant to the President for Policy Development
Alfred H. Kingon, Cabinet Secretary
Ralph Bledsoe, Executive Secretary

For Presentation:

William Roper, Administrator for Health Care Financing, HHS
David Kingsbury, Assistant Director, National Science Foundation
John Cohrssen, Regulatory Counsel, Office of Science and Technology Policy

Additional Attendees:

Gwen King, Deputy Assistant to the President for Intergovernmental Affairs
John Tuck, Special Assistant to the President for Legislative Affairs
Thomas Gibson, Special Assistant to the President and Director of Public Affairs
Albert R. Brashear, Special Assistant to the President and Deputy Press Secretary
Beryl Sprinkel, Chairman, CEA
John P. McTague, Acting Science Advisor to the President, OSTP
Fred Khedouri, Deputy Chief of Staff to the Vice President

Lee Thomas, Administrator, Environmental Protection Agency
Gerald Riso, Assistant Secretary for Policy, Budget and Administration, Department of Interior
John Knapp, General Counsel, Department of Housing and Urban Development
T. Kenneth Cribb, Counselor to the Attorney General, Department of Justice
Becky Norton Dunlop, Special Assistant to the Attorney General for Cabinet Affairs, Department of Justice

THE WHITE HOUSE
WASHINGTON

CABINET AFFAIRS STAFFING MEMORANDUM

Date: 5/19/86 **Number:** 317, 121 **Due By:** -----

Subject: Domestic Policy Council Meeting - May 20, 1986

2:00 P.M. Roosevelt Room

	Action	FYI
ALL CABINET MEMBERS	☐	☐
Vice President	☑	☐
State	☑	☐
Treasury	☑	☐
Defense	☐	☐
Justice	☑	☐
Interior	☑	☐
Agriculture	☑	☐
Commerce	☑	☐
Labor	☑	☐
HHS	☑	☐
HUD	☑	☐
Transportation	☐	☐
Energy	☑	☐
Education	☑	☐
Chief of Staff	☐	☐
OMB	☑	☐
CIA	☐	☐
UN	☐	☐
USTR	☐	☐
EPA	☑	☐
GSA	☐	☐
NASA	☐	☐
OPM	☐	☐
SBA	☐	☐
VA	☐	☐

	Action	FYI
CEA	☑	☐
CEQ	☐	☐
OSTP	☑	☐
Poindexter	☑	☐
Svahn	☑	☐
Chew *(For WH Staffing)*	☑	☐
Executive Secretary for:		
DPC	☑	☐
EPC	☐	☑

REMARKS:

The Domestic Policy Council will meet on Tuesday, May 20, 1986 at 2:00 P.M. in the Roosevelt Room.

The agenda and background papers are attached.

RETURN TO:

☑ **Alfred H. Kingon**
Cabinet Secretary
456-2823
(Ground Floor, West Wing)

☐ **Don Clarey**
☐ **Rick Davis**
☐ **Ed Stucky**

Associate Director
Office of Cabinet Affairs
456-2800 (Room 235, OEOB)

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

MEMORANDUM FOR THE DOMESTIC POLICY COUNCIL

FROM: Otis R. Bowen, M.D. OPB.
Secretary
Department of Health and Human Services

ISSUE: Should heart transplants be covered under Medicare? If so, should conditions be placed on such coverage?

Background

The report of the Congressionally mandated Task Force on Organ Transplantation will be published in late May, and will focus public attention on the policy of the Department of Health and Human Services (HHS) with respect to human heart transplantation. The rapid increase in the number of heart transplants performed underscores the importance of this issue. In 1984 there were 373; 730 were performed in 1985; and in the first three months of 1986 there have already been 300 performed.

This issue has been the subject of study and deliberation within the Department since 1980. There has also been strong Congressional interest in the Department's position. In fact, Congressman Waxman held hearings on May 12 to discuss implementation of the National Organ Transplant Act of 1984. Additionally, Senator Hatch has scheduled hearings for May 21 to review the Task Force's recommendations and address future directions in Federal policy.

We have reached a point where we must consider the broad implications of covering heart transplants under Medicare. As a result of advances in medical technology and treatment and the success of efforts to promote organ donation, the frequency of transplantation is no longer limited by scarce medical resources and organ availability. In addition, heart transplantation results in increasingly successful outcomes. Should Medicare cover heart transplants, improvements in medical technology could lead to substantial Federal expenditures. The resource allocation, quality of care, policy implications and ethical issues are of sufficient importance to warrant Domestic Policy Council review.

Coverage Under Medicare

Medicare provides payment for items and services which are "reasonable and necessary for the diagnosis or treatment of illness or injury." Currently Medicare does not cover heart transplants on the basis that, until recently, there has not been adequate evidence of satisfactory surgical outcomes. HHS has no authority to consider aggregate budget impact in making Medicare coverage decisions.

When the findings of the National Heart Transplant Study were released in May, 1985, former Secretary Heckler announced to the press that heart transplantation could be considered to be technology appropriate for application only where a definite set of medical criteria had been met and only in centers where a critical mass of clinical expertise and experience had been acquired. The Public Health Service (PHS) and the Health Care Financing Administration (HCFA) have developed criteria for such centers should a decision be made to cover heart transplants under Medicare.

Coverage Under Other Governmental Programs

Under Medicaid only 25 States cover heart transplants, but they represent a majority of the Medicaid population. Many of the 25 States which do not now cover heart transplants might do so if Medicare decided to cover the procedure. Medicaid costs are estimated to range from $5 million in 1986 and up to $20 million in 1990.

The Indian Health Service does not have a transplant program and has not paid for any heart transplants. None are expected this year.

The Civilian Health and Medical Program of the Uniformed Services (CHAMPUS) does not now cover heart transplants. However, it is preparing a final rule which would extend coverage if patient and facility criteria were met. CHAMPUS estimates that coverage would involve 36-182 transplants per year. Costs are estimated to range from $3.5 to $17.8 million a year.

The Department of Defense (DOD) does not have an established national policy on heart transplants. However, the Uniformed Services have paid for 8 procedures.

The Veterans Administration (VA) provides coverage for heart transplants at selected centers for those veterans who meet established patient criteria. Between 1984 and March, 1986, the VA provided for 83 transplants.

Discussion

HHS believes that heart transplants can be considered non-experimental or "reasonable and necessary" when they are furnished to patients who meet certain criteria and are performed in facilities which meet certain criteria. It should be noted that the use of facility criteria to limit coverage differs from the usual process whereby coverage is extended to all facilities which meet statutory requirements.

The basis for requiring that heart transplants be performed only by providers with proven prior experience is to ensure high quality of care, given not only the complexity of the procedure, but the need for long term patient followup. The proposed patient selection criteria are based upon critical patient need and

current maximum likelihood of overall successful outcomes. The transplant must be a treatment of last resort and the patient must be without complicating conditions. The current proposed facility criteria require experience in and a commitment to heart transplantation and the facility must have a demonstrated record of successful outcomes. These criteria may be modified over time since progress can be expected in both techniques and survival rates.

It is likely that few Medicare beneficiaries will be candidates for this procedure because the advanced age and complicating conditions of most beneficiaries would generally make them unsuitable transplant recipients. Potential candidates from beneficiaries entitled to Medicare on the basis of disability are required by law to serve a 29-month waiting period before becoming entitled to Medicare benefits. We do not favor legislation that would either establish an entitlement for all end-stage cardiac disease patients or shorten the waiting period to qualify for disability.

The total cost for such transplants is estimated at $100,000 per case. It is estimated that the beneficiary's share would be $4000-5000.

Options

Option 1: Allow Medicare payment for heart transplants, but only in institutions that meet the facility criteria.--The application of these criteria would help assure that heart transplantation would be medically necessary and reasonable treatment because payment would be made only in facilities of demonstrated excellence. We anticipate that about 10 facilities would qualify during the first year and about 10 additional facilities during the next year. HCFA actuaries estimate that 65 transplants would be performed in FY 86 costing $5 million, rising to 143 transplants costing $25 million in FY 90. (The costs rise not only because of increases in medical costs between FY 86 and 90 but also because of the maintenance costs associated with transplanted patients over time and the larger number of facilities that would participate.)

Pros:

- o discourages inappropriate proliferation of facilities offering heart transplants, including those with substantial experience in open heart surgery but with little experience in managing treatment of post-transplant followup;
- o preserves equity by allowing all interested facilities to attempt to meet the special criteria;
- o ensures access to scarce donor organs to a few facilities of proven excellence;
- o optimizes the quality of services by using facilities with demonstrated records of good patient outcomes. Experienced facilities are associated with more favorable outcomes;

- o is consistent with the general approach taken by private insurers to set threshold criteria and would be supported by many recognized experts in the heart transplant field.

Cons:

- o many facilities that have performed at least one heart transplant would not meet the levels of experience and success required by the criteria;
- o any requirement that limits the availability of heart transplantation to less than all Medicare participating hospitals will be perceived as limiting access of some eligible and suitable candidates for the procedure;
- o would initially eliminate access to this procedure in significant geographic areas of the country that have no institutions that would currently qualify;
- o would require a mechanism to review facility applications;
- o could lead to transplants in less than optimal candidates as hospitals try to achieve sufficient experience and number of transplants to qualify as a transplant facility.

Option 2: Allow all Medicare participating hospitals to establish transplant programs without additional selection criteria, although the patient selection criteria would have to be used.—In the National Heart Transplant Study, Battelle projected that just under 200 facilities could be interested in qualifying in the next 5 years. Under this option medically reasonable and necessary heart transplantation may be performed in any Medicare certified hospital. HCFA actuaries estimate 190 transplants would be performed in FY 86, costing $20 million, rising to 787 transplants in FY 90 costing $135 million. (The costs rise not only because of increases in medical costs between FY 86 and 90 but also because of the maintenance costs associated with transplanted patients over time and the larger number of facilities that would participate.)

Pros:

- o is consistent with current policy on the provision of all other hospital services and procedures under Medicare;
- o preserves equity because no interested Medicare hospitals would be precluded from providing transplant services;
- o would probably be supported by the AHA and other hospital industry groups;
- o involves minimal added administrative cost and burden.

Cons:

- o permits proliferation of transplant institutions, raising questions about the quality of services, given the limited availability of donor organs and experienced teams;
- o because of the larger number of facilities, it is likely the experience level would be lower and could result in lower success and survival rates among recipients;
- o could lead to transplants for less than optimum candidates, increasing the likelihood of wasting scarce donor organs;
- o would allow participation even by facilities that may have substantial experience in open heart surgery but no experience in the complex medical management of post-transplant organ rejection.

Option 3: Continue present policy of non-coverage of heart transplants.--This option would have to be based on a determination that heart transplants are still experimental. The cost to the Medicare program would be $0.

Pros:

- o Avoids expenditures of limited Medicare funds;
- o Requires no administrative action.

Cons:

- o Congress could mandate coverage, and the legislative process could result in the establishment of a costly entitlement program.
- o HHS would have to continue to justify non-coverage when there appears to be a growing consensus that heart transplants under certain conditions represent the only acceptable therapy;
- o Some patients in need will not be transplanted without Medicare coverage.

Recommendation: O.R.B.

Of the three options described, we recommend Option 1. Under that option we would allow only those facilities which meet the facility criteria, either now or later, to participate. It should be noted that this option includes guidelines for patient selection criteria. While our preferred option may be controversial within the hospital community, it does represent a clear commitment to quality care. Also, the successful performance of heart transplants appears to rest upon the existence of a complex and extensive network of personnel and facilities, to a much greater degree than that for nearly any services currently covered by the Medicare program.

If the Domestic Policy Council agrees with this approach, we will work with other Federal programs to promote as much consistency in policy as possible, given differing legislative mandates.

In a meeting of the Working Group on Health Policy, all agencies concurred with our recommendation of Option 1, except the Council of Economic Advisors, which endorsed Option 2.

THE WHITE HOUSE

WASHINGTON

May 16, 1986

MEMORANDUM FOR THE DOMESTIC POLICY COUNCIL

FROM: RALPH C. BLEDSOE Ralph Bledsoe
Executive Secretary

SUBJECT: Meeting on May 20, 1986

Attached are an agenda and materials for the Domestic Policy Council meeting scheduled for Tuesday, May 20, 1986 at 2:00 p.m. in the Roosevelt Room. Two items will be covered.

The first agenda item, Organ Transplantation, will include a presentation and discussion of whether heart transplants should be covered under Medicare. This has been discussed within the Health Policy Working Group and a paper drafted by the Group is attached.

The second agenda item will include a discussion of biotechnology issues. The Working Group on Biotechnology is seeking approval from the DPC to publish a coordinated framework for the regulation of biotechnology. Future Working Group issues such as commercialization and international cooperation will also be discussed. A paper on the framework is attached, along with a draft Federal Register notice and Preamble.

attachment

THE WHITE HOUSE

WASHINGTON

DOMESTIC POLICY COUNCIL

Tuesday, May 20, 1986

2:00 p.m.

Roosevelt Room

AGENDA

1. Organ Transplantation

2. Biotechnology

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

May 16, 1986

MEMORANDUM FOR THE DOMESTIC POLICY COUNCIL

FROM: THE BIOTECHNOLOGY WORKING GROUP David T. Kingsbury

SUBJECT: **The Coordinated Framework for the Regulation of Biotechnology**

Issue: Approval is requested for the publication in the Federal Register of the Coordinated Framework for the Regulation of Biotechnology

Background: Biotechnology may be defined to include the use of a variety of biological processes to manufacture commerical products. Technological innovation is achieved two ways: by improving the biological organism involved in a commercial process; or, through the addition of unique, new traits to an organism to be used in a process. In traditional biotechnology, for example, selective breeding techniques improved the quality of food products. Modern biotechnology relies on the improved precision afforded by the sophisticated genetic manipulation techniques to enhance the desirable characteristics of an organism.

Microorganisms are broadly used, but not always commonly recognized, as a major industrial tool for pharmaceutical, chemical, agricultural, and many other purposes. For slightly over a decade, industry has developed products, such as pharmaceuticals, that resulted from the large-scale fermentation of microorganisms that had been genetically modified. In these cases, the microorganisms themselves were not the products, but rather were the means of production of the end product.

Recently, it became clear that a new generation of products would use the living organisms as the final product, and that some, such as microbial pesticides, would be applied in the environment. Accordingly, health and environmental concerns were raised, and proper answers to questions regarding regulation of the emerging industry were becoming critical to its survival.

Considering both health and environmental concerns, and the continued vitality of the emerging industry, the Cabinet Council on Natural Resources and the Environment (CCNRE--later the DPC) took action to establish a sound and consistent regulatory framework involving all agencies with jurisdiction over some aspect of the biotechnology industry:

o The CCNRE established a Biotechnology Working Group in April 1984.

o The Working Group, upon CCNRE approval, published in the Federal Register a proposed coordinated regulatory framework for comment in December 1984.

o To ensure consistent biotechnology science policy among the agencies, the Biotechnology Science Coordinating Committee (BSCC) was chartered in October 1985 under the Federal Coordinating Council for Science, Engineering and Technology (FCCSET) upon approval by the DPC.

o At the direction of the Working Group, the BSCC developed the unifying definitions and uniform scientific principles essential for the final coordinated regulatory framework.

Development of the proposed coordinated framework for the regulation of biotechnology proceeded upon a determination that existing statutory authority was sufficient to regulate biotechnology. The proposed framework encompasses guidelines of a crosscutting nature that interpret regulatory practices and responsibilities across a broad spectrum of statutes and agencies (e.g., Food, Drug, and Cosmetic Act, Toxic Substances Control Act, Federal Insecticide, Fungicide and Rodenticide Act, Federal Plant Pest Act).

Industry is awaiting the publication of the policy which it believes will provide a necessary climate of regulatory certainty. There has been continuing Congressional interest, often expressed by hearings, on the safe use of biotechnology and the ability of the Administration to competently assure adequate regulatory protection of risks to health and the environment.

Discussion: It is critical for Administration policy to maintain a proper balance between the public concerns for health and environmental safety while maintaining sufficient regulatory flexibility to avoid impeding the growth of an infant industry. The policy needs to be able to evolve in a manner corresponding to rapid technological advancements that are taking place. Of great concern is that we not place ourselves at a competitive disadvantage with other nations, particularly since the underlying biological research that forms the foundation of the industry was funded by U.S. agencies. There has been a rapid growth in biotechnology industries in many foreign countries, most notably Japan, Germany, France, and the United Kingdom. Moreover, in the past three years, the Soviet Union has become a significant force in the area of large-scale fermentation. The policy addresses these concerns in a balanced manner.

The final coordinated framework for the regulation of biotechnology refines the proposed framework based upon consideration of the co ents received and the unifying definitions proposed by the BSCC. The framework:

- o More precisely defines those organisms that are believed to pose such risk as to require federal review, and excludes classes of organisms which are not considered to possess characteristics that impart a sufficient degree of risk to trigger regulation by a federal agency;

- o Contains the regulatory policies of FDA, EPA, OSHA and USDA, and the research policies of NIH, NSF, EPA, and USDA.

- o Identifies a single agency as responsible for a particular class of products or for categories of research experiments, to the extent possible; identifies a lead agency when statutory requirements involve more than one agency, and establishes consolidated or coordinated reviews.

The Working Group recognizes that in this emerging technological area, there are many concerns about hypothetical environmental consequences from the introduction of modified organis . Any proposal will be subject to debate. Because this policy relies upon sound scientific evidence in addressing those areas that require regulatory intervention, the Working Group and the BSCC are confident that the approach is reasonable, workable, and defensible scientifically.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

COORDINATED FRAMEWORK FOR REGULATION OF BIOTECHNOLOGY:

AGENCY: Executive Office of the President, Office of Science and Technology Policy

ACTION: Announcement of Policy; Notice for Public Comment

SUMMARY: This Federal Register notice announces the policy of the federal agencies involved with the review of biotechnology research and products. As certain concepts are new to this policy, and will be the subject of rulemaking, the public is invited to comment on these aspects which are specifically identified herein.

DATE: Comments must be received on or before [insert date 60 days after date of FR Notice].

Public Participation: The Domestic Policy Council Working Group on Biotechnology through the Office of Science and Technology Policy, is seeking advice on certain refinements published herein to the previously published proposed coordinated framework for regulation of biotechnology. These new aspects include the Biotechnology Science Coordinating Committee's (BSCC's) definitions for an "intergeneric organism (new organism)" and for "pathogen." These definitions are critical to the coordinated framework for the regulation of biotechnology because they establish the types or the organisms subject to certain kinds of review.

It is the intention of the Domestic Policy Council Working Group on Biotechnology, the Biotechnology Science Coordinating Committee (BSCC), the Department of Agriculture (USDA), the Environmental Protection Agency (EPA), the Food and Drug

Administration (FDA), the National Institutes of Health (NIH), the National Science Foundation (NSF), and the Occupational Safety and Health Administration (OSHA) that the policies contained herein be effective immediately. In consideration of comments, modifications, if any, may be published either in a separate notice or as part of proposed rulemaking by the involved agencies.

Information submitted to an agency that is trade secret information or confidential business information should be clearly marked so that it can be accorded the protection provided to such by each respective agency.

ADDRESS: Comments specific to the BSCC definitions or overall comments to the Coordinated Framework for the Regulation of Biotechnology statements should be addressed to:

BSCC: Docket #BSCC 0001, Office of Science and Technology Policy, Executive Office of the President, NEOB-Room 5005, Washington, D.C. 20506

Comments relating to the policy statements of a particular agency should be sent directly to the agency contact identified at the beginning of the respective agency policy statement.

FOR FURTHER INFORMATION CONTACT: Dr. David T. Kingsbury, Assistant Director for Biological, Behavioral, and Social Sciences, National Science Foundation, 1800 G Street, N.W., Washington, D.C. 20550, (202-357-9854).

Jerry D. Jennings
Executive Director,
Office of Science and Technology Policy

May __, 1986

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Table of Contents

A. INTRODUCTION

This notice describes the comprehensive federal regulatory policy for ensuring the safety of biotechnology research and products. Specifically addressed are agency policies that formed part of the previously proposed Coordinated Framework for the Regulation of Biotechnology, published in the Federal Register December 31, 1984 (49 FR 50856, hereinafter "the December 84 Notice"). These agency policies build upon experience with agricultural, pharmaceutical, and other commercial products developed by traditional genetic modification techniques.

Existing statutes provide a basic network of agency jurisdiction over both research and products; this network forms the basis of this coordinated framework and helps assure reasonable safeguards for the public. This framework is expected to evolve in accord with the experiences of the industry and the agencies, and, thus, modifications may need to be made through administrative or legislative actions.

The application of traditional genetic modification techniques is relied upon broadly for enhanced characteristics of food (e.g., hybrid corn, selective breeding), manufactured food (e.g., bread, cheese, yogurt), waste disposal (e.g., bacterial sewage treatment), medicine (e.g., vaccines, hormones), pesticides (e.g. Bacillus thuringiensis) and other uses. Federal agencies implement an array of laws which seek to ensure the safety of these products. A concise index of these U.S. laws was published in the Federal Register November 14, 1985 (50 FR 47174, hereinafter "the November 85

Notice"). These laws are product-specific because they regulate certain product uses, such as foods or pesticides. This approach provides the opportunity for similar products to be treated similarly by particular regulatory agencies.

Biotechnology also includes recently developed and newly emerging genetic manipulation technologies, such as recombinant DNA (rDNA), recombinant RNA (rRNA) and cell fusion, that are sometimes referred to as genetic engineering. While the recently developed methods are an extension of traditional manipulations that can produce similar or identical products, they enable more precise genetic modifications, and therefore hold the promise for exciting innovation and new areas of commercial opportunity.

Concerns were raised as to whether products resulting from the recently developed techniques would pose greater risks than those achieved through traditional manipulation techniques. For example, what might be the possible environmental consequences of the many anticipated agricultural and environmental applications that will take place outside the physical constraints of a contained facility? In particular, the environmental application of genetically engineered microorganisms may elicit concern because they are of microscopic size, and some may be able to reproduce, proliferate, and become established.

The underlying policy question was whether the regulatory framework that pertained to products developed by traditional genetic manipulation techniques was adequate for products obtained with the new techniques. A similar question arose regarding the

sufficiency of the review process for research conducted for agricultural and environmental applications.

The Administration, recognizing its responsibility to confront these concerns, formed an interagency working group under the former White House Cabinet Council on Natural Resources and the Environment in the spring of 1984. The working group sought to achieve a balance between regulation adequate to ensure health and environmental safety while maintaining sufficient regulatory flexibility to avoid impeding the growth of an infant industry.

Upon examination of the existing laws available for the regulation of products developed by traditional genetic manipulation techniques, the working group concluded that, for the most part, these laws as currently implemented would address regulatory needs adequately. For certain microbial products, however, additional regulatory requirements, available under existing statutory authority, needed to be established.

The existing health and safety laws had the advantage that they could provide more immediate regulatory protection and certainty for the industry than possible with the implementation of new legislation. Moreover, there did not appear to be an alternative, unitary, statutory approach since the very broad spectrum of products obtained with genetic engineering cut across many product uses regulated by different agencies.

Because of the rapid growth in the scientific knowledge base, the working group felt strongly that the federal agencies needed to have an interagency mechanism for sharing scientific information

related to biotechnology, particularly information on research and product applications submitted to the agencies.

The December 84 Notice described the regulatory framework envisioned by the working group, and recognizing the evolutionary nature of its development, asked for comments. In summary, the Notice stated that the Food and Drug Administration (FDA) would regulate genetic engineering products no differently that those achieved through traditional techniques. The Environmental Protection Agency (EPA) described existing and proposed new policies for regulating pesticidal and nonpesticidal microorganisms. The Department of Agriculture (USDA) stated that under its different legislative authorities it could broadly regulate genetically engineered plants and animals, and plant and animal pathogens. The Notice also proposed an interagency science coordinating mechanism.

Many comments were received in response to the Notice. These contributed to the refinement of both the regulatory requirements and the interagency science coordination mechanism.

The interagency coordination mechanism, the Biotechnology Science Coordinating Committee (BSCC), discussed in more detail in section C. of this Preamble, came into being while the agencies were still in process of refining their regulatory proposals. Consequently, the BSCC was able to play a helpful role in the formulation of two basic principles: (1) agencies should seek to adopt consistent definitions of those genetically engineered organisms subject to review to the extent permitted by their

respective statutory authorities; and, (2) agencies should utilize scientific reviews of comparable rigor.

The regulatory framework anticipates that future scientific developments will lead to further refinements. Experience with earlier basic scientific research has shown that as the science progressed and became better understood by the public, regulatory regimens could be modified to reflect more complete understanding of the potential risks involved. Similar evolution is anticipated in the regulation of commercial products as scientists and regulators learn to predict more precisely particular product use that require greater or lesser controls or even exemption from any federal review.

This framework has sought to distinguish between those organisms that require a certain level of federal review and those that do not. This follows a traditional approach to regulation. Within agriculture, for example, introductions of new plants, animals and microorganisms have long occurred routinely with only some of those that are not native or are pathogenic requiring regulatory approval. It should be noted that microorganisms play many essential and varied roles in agriculture and the environment and that for decades agricultural scientists have endeavored to exploit their advantages through routine experimentation and introduction into the environment; and as a rule these agricultural and environmental introductions have taken place without harm to the environment.

B. THE COORDINATED FRAMEWORK FOR THE REGULATION OF BIOTECHNOLOGY

General Comments

This notice includes separate descriptions of the regulatory policies of FDA, EPA, OSHA and USDA and the research policies of the National Institutes of Health (NIH), NSF, EPA and USDA. The agencies will seek to operate their programs in an integrated and coordinated fashion and together should cover the full range of plants, animals and microorganisms derived by the new genetic engineering techniques. To the extent possible, responsibility for a product use 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, and consolidated or coordinated reviews. While this preamble seeks to convey an overview of the coordinated framework, it must be noted that the regulatory requirements are highly technical; reliance only on the simplified summary statements herein could be misleading and, thus, the agency policy statements must be consulted for specific details. In the event that questions arise regarding which federal agency has jurisdiction, an information contact is provided at the beginning of this notice.

While in part certain USDA and EPA requirements are new, the underlying regulatory regimens are not new. Members of the agricultural and industrial communities are familiar with the general requirements under these laws which include the Federal Plant Pest Act, the Plant Quarantine Act, the Toxic Substances Control Act (TSCA), and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Because this comprehensive regulatory framework uses a mosaic of existing federal law, some of the statutory nomenclature for certain actions may seem inconsistent. Certain laws, such as USDA's Federal Plant Pest Act, require a "permit" before a microorganism pathogenic to plants may be transported or imported. Under other laws such as FIFRA, the agencies "license" or "approve" the use of particular products. TSCA requires a "premanufacturing notification (PMN)". There are also some variations among the agencies in the use of the phrase "genetic engineering." Regardless of the nomenclature, the public should be aware that the reviews conducted by each of the regulatory agencies are intended to be of comparable rigor. Agencies have agreed to have scientists from each other's staff participate in reviews. Each regulatory review will require that the safety, or safety and efficacy, of a particular agricultural or industrial product be satisfactorily demonstrated to the regulatory agency prior to commercialization.

The National Environmental Policy Act (NEPA) imposes procedural requirements on all federal agencies to prepare an analysis prior to making a decision to take any action that may significantly affect the environment. Depending on the characteristics of a proposal, an environmental assessment, or a broader environmental impact statement may need to be prepared in connection with the release of genetically manipulated organisms. EPA's actions under most of its environmental statutes have been considered to be the functional equivalent of NEPA compliance.

For the handling of microorganisms, agencies of the Department

of Health and Human Services have established recommendations for the safe use of infectious agents. The CDC/NIH publication, Biosafety in Microbiological and Biomedical Laboratories, describes combinations of standard and special microbiological practices, safety equipment and facilities which are recommended for working with a variety of infectious agents in research laboratories, academic and industrial. The USDA also has issued guidance on other infectious agents.

The NIH has published guidelines for the contained use of rDNA organisms in the NIH Guidelines for Research Involving Recombinant DNA Molecules, Federal Register, May 7, 1986 (51 FR 16958, NIH guidelines). The guidelines recommend physical containment at specific levels for different experiments, and exempt other experiments from containment requirements. However, they recommend Biosafety Level 1, the least stringent level of physical containment, for some "exempt" experiments. For large-scale exempt experiments, the NIH guidelines recommend "Biosafety Level 1-Large-Scale" although following review by the Institutional Biosafety Committee, "some latitude" in the application of these requirements is permitted.

The appropriate large-scale containment requirements for many low risk rDNA derived industrial microorganisms will be no greater than those appropriate for the unmodified parental organisms. This concept is discussed further in the Organization for Economic Cooperation and Development (OECD) document, described in the International Aspects section below.

OSHA in its Federal Register Notice of April 12, 1984 (50 FR 14468) stated that its authority under the Occupational Safety and Health Act of 1970 (29 U.S.C. et seq.) provides an adequate and enforceable basis for protecting the safety and health of employees in the field of biotechnology and that no additional regulation is necessary. After consideration of comments on the April 1984 notice, OSHA is publishing this policy statement in final form without change.

Product Regulation

Agencies involved with regulating agriculture, foods, medical devices, drugs, biologics and pesticides have had extensive experience with products that involve living organisms in their manufacture and/or ultimate use including releases into the environment for these purposes. By the time a genetically engineered product is ready for commercialization, it will have undergone substantial review and testing during the research phase, and thus, information regarding its safety should be available. The manufacture by the newer technologies of food, the development of new drugs, medical devices, biologics for humans and animals, and pesticides, will be reviewed by FDA, USDA and EPA in essentially the same manner for safety and efficacy as products obtained by other techniques. The new products that will be brought to market will generally fit within these agencies' review and approval regimens.

The regulatory scheme for products is described in Chart I Coordinated Framework -- Marketing Approval of Biotechnology Products.

CHART I -- COORDINATED FRAMEWORK -- APPROVAL OF COMMERCIAL BIOTECHNOLOGY PRODUCTS

Subject	Responsible Agency(ies)
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 Microorganisms Released in the Environment	
All	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

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* LEAD AGENCY

[1] FSIS, Food Safety and Inspection Service, under the Assistant Secretary of Agriculture for Marketing and Inspection Services is responsible for food use.

[2] FDA is involved when in relation to a food use.

[3] APHIS, Animal and Plant Health Inspection Service, is involved when the 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.

Jurisdiction over the varied biotechnology products is determined by their use, as has been the case for traditional products. The detailed description of the products and their review are found in the individual agency policy statements contained in this Federal Register Notice. The following is a brief summary of jurisdiction as described in Chart I.

Foods, food additives, human drugs, biologics and devices, and animal drugs are reviewed or licensed by the FDA. Food products prepared from domestic livestock and poultry are under the jurisdiction of the USDA's Food Safety Inspection Service (FSIS).

Animal biologics are reviewed by the Animal and Plant Health Inspection Service, (APHIS). APHIS also reviews plants, seeds, animal biologics, plant pests, animal pathogens and "regulated articles", i.e., certain genetically engineered organisms containing genetic material from a plant pest or an animal pathogen. An APHIS permit is required prior to the shipment (movement) or release into the environment of regulated articles, or the shipment of a plant pest or animal pathogen.

"Other contained uses" refers to the closed system uses of those microorganisms, subject to TSCA, that are intergeneric combinations, i.e., deliberately formed microorganisms which contain genetic material from dissimilar source organisms. These are subject to EPA's PMN requirement. EPA is considering promulgating a rule to exempt certain classes of microorganisms from this requirement.

Microbial pesticides will be reviewed by EPA, with APHIS

involvement in cases where the pesticide is also a plant pest, animal pathogen, or regulated article requiring a permit. (FDA may become involved in implementing pesticide tolerances for foods.)

"Other uses (microorganisms)" include uses involving release into the environment. For these, jurisdiction depends on the characteristics of the organism as well as its use. "Intergeneric combination" microorganisms will be reported to EPA under PMN requirements, with APHIS involvement in cases where the microorganism is a also a "regulated article" requiring a permit.

"Intrageneric combinations" are those microorganisms formed by genetic engineering other than intergeneric combinations. For these, when there is a pathogenic source organism, and the microorganism is used for agricultural purposes, APHIS has jurisdiction. If the microorganism is used for nonagricultural purposes, then EPA has jurisdiction, with APHIS involvement in cases where the microorganism is also a regulated article requiring a permit. Intrageneric combinations with no pathogenic source organisms are under EPA jurisdiction although EPA will only require an informational report.

Nonengineered pathogenic microorganisms that are used for an agricultural use will fall under APHIS jurisdiction. Those that are for a nonagricultural use come under EPA jurisdiction, with APHIS involvement in cases where the microorganism is also a plant pest or animal pathogen requiring a permit. Nonengineered nonpathogenic microorganisms are under EPA jurisdiction which will require only an informational report.

Research

The coordinated framework for the regulation of biotechnology establishes requirements for the conduct of research.

Approximately ten years ago the NIH issued the NIH guidelines describing the manner in which research with organisms derived by rDNA techniques should be conducted. Since then the guidelines have been modified many times with gradual relaxation of these requirements. The guidelines prescribe the conditions under which institutions which receive NIH funds must conduct experiments. For a very small category of NIH funded experiments including environmental release, the guidelines require that the Director, NIH, approve each experiment on an individual basis. For each of these experiments, the RAC conducts a scientific review with an opportunity for public comment, and makes a recommendation to the NIH Director. As research experiments have expanded out of the biomedical area to environmental applications both agricultural and nonagricultural, other agencies have become involved, with shifting of responsibility for research approval to NSF (described in the November 85 Notice), USDA's S&E, and EPA. These other agencies' policies build, in part, on the NIH guidelines and NIH experience.

The S&E guidelines for agricultural research published separately for comment in this issue of the Federal Register have adopted the NIH guidelines with certain modifications including expansion of the scope to manipulation techniques other than rDNA; the table included with the S&E guidelines shows where particular elements of the NIH guidelines are used.

It should be noted that not all experiments involving the environmental release of genetically engineered organisms require prior federal approval. In plant applications there is a substantial body of research indicating that such experiments are of low risk. For certain categories of microorganisms modified by traditional genetic modification techniques, there is also a substantial body of research indicating low risk for environmental experiments.

Chart II -- Coordinated Framework -- Biotechnology Research Jurisdiction shows which agency has responsibility for a particular experiment. If more than one agency has potential jurisdiction, one agency has been designated as the lead agency and it is marked with an asterisk on Chart II. The lead agency designation depends on which research agency is funding the research (e.g. NIH, S&E, or NSF) or which regulatory agency reviews specific purpose research (e.g. pesticides). In the chart and in this discussion, the authority refers to approval of the actual execution of experiments and not to their funding.

CHART II--COORDINATED FRAMEWORK--BIOTECHNOLOGY RESEARCH JURISDICTION

Subject	Responsible Agency(ies)
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, Biologics, 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]
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 Nonpathogen	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-agricul. use)
Intrageneric Combination	
No Pathogenic Source Organisms	EPA Report
Nonengineered Pathogens	EPA Report*, APHIS[2]

* LEAD AGENCY

[1] Review and approval of research protocols conducted by NIH, S&E, 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 than 10 acres.

[4] EPA reviews federally funded environmental research only when it is for commercial purposes.

For contained federally funded research for for biomedical and agricultural purposes, research approval will granted by the funding agency. The NIH guidelines relate primarily to biomedical experiments and only to those using rDNA techniques. Research on foods/food additives, human drugs, medical devices and biologics will continue to rely on the NIH guidelines, with NIH approval required for certain experiments such as human gene therapy, and FDA permission for clinical trials.

Fashioned after the NIH guidelines, the S&E guidelines apply to agricultural research on plants, animals, and microorganisms and provide guidance for laboratory and field testing of organisms derived using rDNA manipulation and other technologies. Adherence to the appropriate set of guidelines is required for institutions receiving financial support from NIH, S&E, or NSF. These guidelines specify what type of review procedures are required for specific categories of experiments. Some experiments require individual approval by the respective agency providing institutional support. For those experiments that require agency approval, advisory committees at NIH, S&E, and NSF, composed primarily of nongovernment scientists, may be asked to provide expert review. In addition, research on plants, animals, and animal biologics will come under APHIS permit requirements if a regulated article, plant pest, animal pathogen is involved. An APHIS permit is required prior to the shipment (movement) or release of a regulated article, or the importation or shipment of a plant pest or regulated article used in any research experiment.

EPA has authority for all environmental research on microbial pesticides regardless of whether research is federally funded or not. EPA will regulate research under a two level review system based upon its evaluation of the potential risks posed by various types of microorganisms with lesser notification required for level I reporting and full review for level II.

For the "other uses" category from Chart II (research involving nonpesticide microorganisms released into the environment), jurisdiction for release may be under S&E, NSF, APHIS, or EPA depending primarily upon the source of the funding, but also upon the purpose of the research and the characteristics of the genetically engineered microorganism. Thus, federally funded research conducted for an agricultural use will require adherence to S&E guidelines and approval of certain experiments by S&E or NIH depending on which is the funding agency. EPA will review commercial research. APHIS's jurisdiction applies to issuing permits for regulated articles, plant pests, or animal pathogens.

For nonengineered pathogens EPA will require an informational report, with APHIS involvement for the review of plant pests or animal pathogens.

There may be situations where one agency may choose to defer to, or ask advice from, another agency. If experiments requiring NIH, NSF or S&E review/approval are submitted for review to another agency, then NIH, NSF, or S&E may determine that such review serves the same purpose, and based upon that determination, notify the submitter that no NIH, NSF, or S&E review will take place, and the experiment may proceed upon approval from the other agency.

C. INTERAGENCY COORDINATION MECHANISMS

The Domestic Policy Council Working Group on Biotechnology

The Domestic Policy Council Working Group on Biotechnology has been responsible for this coordinated framework for the regulation of biotechnology; it also considers policy matters related to agency jurisdiction, commercialization, and international biotechnology matters. The Working Group monitors developments in biotechnology and is ready to identify problems and make appropriate recommendations for their solution.

Although at the present time existing statutes seem adequate to deal with the emerging processes and products of modern biotechnology, there always can be potential problems and deficiencies in the regulatory apparatus in a fast moving field. The Working Group will be alert to the implications these changes will have on regulation, and in a timely fashion will make appropriate recommendations for administrative or legislative action.

The Domestic Policy Council Working Group on Biotechnology is a continuation of a similar group established under the former Cabinet Council on Natural Resources and the Environment. The chair is the Director, Office of Science and Technology Policy, who is now assisted by the Assistant Director for Biological, Behavioral and Social Sciences of the National Science Foundation, with staff support provided by the Office of Science and Technology Policy.

The Biotechnology Science Coordinating Committee (BSCC)

The BSCC is responsible for coordination and consistency of scientific policy and scientific reviews. The BSCC, established October 31, 1985 as part of the Federal Coordinating Council for Science, Engineering and Technology (FCCSET), consists of senior policy officials of agencies involved in the oversight of biotechnology research and products. FCCSET is a statutory interagency coordinating mechanism managed by the Office of Science and Technology Policy, Executive Office of the President, with a mission to coordinate federal science activities among federal agencies. The November 85 Notice described the structure and activities of the BSCC.

One of the primary activities of the BSCC has been the development of definitions because a common scientific approach is essential to a coordinated federal regulatory framework. The underlying scientific issue, therefore, was defining those organisms subject to certain types of agency review.

The definitions are included in the following section of this preamble and have been incorporated, with modification, into the individual policy notices of the involved agencies. Explanatory material is also included in the agency policy statements. As mentioned elsewhere, the BSCC is seeking comments on these definitions.

Research to develop genetically modified organisms for environmental and agricultural applications (as for research on traditionally modified organisms) generally proceeds in a step-wise manner from highly contained facilities to progressively lesser

degrees of containment as the investigator determines the safety and efficacy of experimental applications; these are conducted sequentially under controlled laboratory conditions, greenhouse testing, small field trials, and full field trials. The BSCC recognizes the need for further work to define the nature and extent of physical and biological barriers that limit or manage environmental release of modified organisms during greenhouse testing and field research.

The BSCC is authorized to hold public meetings in order to discuss public concerns about scientific and other issues. Accordingly, the BSCC will hold its first public meeting shortly after publication of this notice for discussion of the scientific aspects of this notice and the receipt of comments from the public. The public meeting will be held in July 1986. Details regarding time and location will be separately announced in the Federal Register.

D. BSCC DEFINITIONS

Any proposal to regulate the research and products or genetic manipulation techniques quickly confronts the issue of what organisms should be considered appropriate for certain types of review. The BSCC formulated definitions are effective immediately but are open to comment; the text following the definition of "pathogen" contains details of the request for comments.

Organisms meeting two different sets of criteria are proposed. First are organisms formed by deliberate combination of genetic material from sources in different genera. It was recognized,

however, that in certain precisely constructed "intergeneric organisms" the genetic material is not considered to pose an increased risk to human health or the environment; thus, such combinations are excluded from the definition. A detailed explanation of the scientific basis for these exclusions is found in the footnote after the definition of pathogen. The BSCC specifically requests comments on whether also to consider for exclusion those organisms that exchange DNA by known physiological processes, as explained in the text immediately following the definition of "intergeneric organism (new organism)."

The second definition is "pathogen." This includes microorganisms that belong to a pathogenic species or that contain genetic material from source organisms that are pathogenic. In certain precisely constructed modified organisms, the genetic material from a pathogenic donor is not considered to pose an increased risk to human health or the environment; and, therefore, such combinations are excluded from the definition.

The BSCC definitions of "intergeneric organism (new organism)" and "pathogen" describe the combinations genetic material that would cause a modified organism to come under review. This does not mean to suggest that the behavior of a genetically manipulated organism exempted from these definitions is wholly predictable (since any biological organism is never 100% predictable), but that the probability of any incremental hazard compared to the unmodified organism host is low. This does not mean that any product manufacture or research experiment using an organism

exempted from the definition should be conducted without adherence to proper manufacturing standards or research guidelines.

Given the statutory differences in the laws that they administer, the agencies adopted the principles underlying the definitions in ways consistent with their legislation. EPA, APHIS, and S&E are using the definitions to identify levels of review for microbial products within their jurisdiction. EPA, APHIS, FDA, S&E, and NSF are using the definitions as factors to consider in the review of products or experiments.

The BSCC is attempting to define what constitutes "release into the environment." The BSCC is establishing a working group on greenhouse containment and small field trials in order to develop scientific recommendations. The concept of "containment" has traditionally been used to describe physical conditions which severely limit release (for example, a contained laboratory fermentation facility). Containment can also be "biologic" because the ability of an organism to reproduce, exchange genetic information, or become established can be effectively limited biologically. Thus, the BSCC's exploration of the conditions that constitute release into the environment will consider circumstances of both physical and biological containment for particular organisms and the circumstances of their release. While the concept of physical containment may imply the high containment conditions found in certain laboratories and greenhouses, in agricultural practice many simpler effective barriers are routinely used; these include microplots for soil bacteria and fungi, paddocks for

noninfective animals, and removing or covering the reproductive parts of plants and animals.

Release into the environment, for the time being, will have somewhat varying definitions for the regulatory and research review of the different agencies. There may be minor differences between agricultural and nonagricultural approaches and between macro- and microorganisms.

Intergeneric Organism (New Organism)

Those organisms deliberately formed to contain an intergeneric combination of genetic material; excluded are organisms that have resulted from the addition of intergeneric material that is well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators and ribosome binding regions.

"Well-characterized and contains only non-coding regulatory regions" means that the producer of the microorganism can document the following:

a. the exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. the regulatory region and any inserted flanking nucleotides do not code independently for a protein, peptide or functional RNA molecules;

c. the regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

Pathogen

A pathogen is a virus or microorganism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, microorganisms).

A microorganism (including viruses) will be subject to regulatory policies regarding pathogens if:

a. the microorganism belongs to a pathogenic species, according to sources identified by the agency, or from

information known to the producer that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as non-pathogenic according to sources identified by a federal agency, or information known to the producer and the appropriate federal agency (an example of a nonpathogenic strain of a species which contains pathogenic strains is Escherichia coli K-12; examples of nonpathogenic species are Bacillus subtilis, Lactobacillus acidophilus, and Saccharomyces species); or

b. the microorganism has been derived from a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item a. above. Excepted are genetically engineered organisms developed by transferring a well-characterized, non-coding regulatory region from a pathogenic donor to a non-pathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. the exact nucleotide base sequence of the regulatory region and any inserted flanking nucleotides;

b. the regulatory region and any inserted flanking nucleotides do not code independently for a protein, peptide, or functional RNA molecules; and,

c. the regulatory region solely controls the activity of other sequences that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

This definition excludes organisms such as competitors or colonizers of the same substrates, commensal or mutualistic microorganisms, or opportunistic pathogens.

The footnote contains the scientific basis for exempting non-coding regulatory regions from the definitions of intergeneric organisms and pathogen.*

[footnote]

* The BSCC has based the exemption of intergeneric transfers or regulatory regions on their lack of coding capacity for the production of proteins, peptides or functional RNA molecules. It has been recommended by other members of the scientific community that there should be additional exemptions such as ribosomal proteins, ribosomal RNAs and transfer RNAs. The BSCC has chosen to examine these suggestions in more detail during the next few months. At the present the BSCC has excluded:

1. Origins of replication;
2. Ribosome binding sites;
3. Promoters;
4. Operators; and,
5. Terminators.

The basis for these exemptions is as follows. Each of these regulatory elements has no coding capacity for the production of any gene product and therefore does not promote the production or any new material. What these elements are responsible for is the initiation and modulation of nucleic acid synthesis at the specific region where they appear in the chromosome.

Bacterial genes are precisely regulated and this regulation is based on a series of regulatory elements. The principal regulatory unit is the operon. Operons are controlled primarily, but not exclusively, through the regulation of the rate of initiation of messenger RNA synthesis. This regulation is based on the interaction of two short nucleotide sequences in the DNA, the promoter, which is the site of RNA polymerase binding and the operator, which follows closely and acts as an off-on switch for the movement of the polymerase into the structural gene which follows. The function of the operator is to bind a cellular repressor protein which is synthesized in response to changing nutritional stimuli. Terminator regions are short nucleotide sequences which signal the termination of mRNA synthesis by the polymerase. They act as a signal for the dissociation of the polymerase from the DNA.

Replication of DNA in every biological system that has been examined is initiated at a specific site or group of sites in the chromosome. Those sites have broad specificity and a DNA molecule without the appropriate site will not be replicated. The sites which are critical to the initiation of replication are known as origins of replication. These regions are short nucleotide sequences which serve as initiation sites for specific enzyme action during the DNA replication process. For example, in order for mammalian DNA to replicate in bacteria, it must be associated with a bacterial origin of replication and vice versa.

Ribosome binding sites are short nucleotide segments at the beginning of messenger RNA molecules which signal the attachment of ribosomes for the initiation of protein synthesis. Functioning in this role they are not translated into the protein or peptide being processed.

The BSCC is requesting comments on these definitions during the period of sixty days following the date of this notice and specifically seeks comments addressing the following:

1. The suitability and applicability of these definitions to applications involving release into the environment, contained industrial large-scale applications, foods/food additives, drugs, medical devices, and other possible products.

2. Whether combinations of genetic material from organisms that exchange DNA by known physiological processes should be excluded from the definition of intergeneric organisms: i.e., should organisms be excluded which contain intergeneric combinations of certain specified rDNA molecules that consist entirely of DNA segments from different genera that exchange DNA by known physiological processes? As certain rDNA organisms are exempted under Section III-D-4 of the NIH guidelines, the question was raised whether these organisms when used in the environment should be similarly exempted from federal product review. This exemption would not, however, exclude from review such "natural exchangers" that are also pathogens or plant pests. In the event that the exclusion of such different species that exchange DNA by known physiological processes is accepted as appropriate, a list of such species combinations that has been maintained and updated by the Office of Recombinant DNA Activities of the National Institutes of Health will be updated, in light of environmental use.

3. What are the most appropriate definitions of "release into the environment" for macro- and microorganisms.

E. INTERNATIONAL ASPECTS

The United States seeks to promote international scientific cooperation and understanding of scientific considerations in biotechnology on a range of technical matters. These activities add to scientific knowledge and ultimately contribute to protection of health and the environment.

The United States also seeks to reduce barriers to international trade. U.S. agencies apply the same regulation and approval procedures on domestic and foreign biotechnological products. We are seeking recognition among nations of the need to harmonize, to the maximum extent possible, national regulatory oversight activities concerning biotechnology. Barriers to trade in biotechnological products should be avoided as nations join together in working toward this mutual goal.

The U.S. agencies that have published separate policy statements as part of this notice are committed to the policy described in this section on international harmonization and have incorporated by reference the language in this International Aspects section as part of their respective agency policy statements.

Organization for Economic Cooperation and Development (OECD)

The approach of the comprehensive framework contained in this notice takes into account, inter alia, the broad goals described by an Ad Hoc Group of Government Experts convened by OECD in their recent report entitled, "RECOMBINANT DNA SAFETY CONSIDERATIONS, Safety Considerations for Industrial, Agricultural and

Environmental Applications of Organisms Derived by Recombinant DNA Techniques." The United States is pleased to have had the opportunity for its experts to work with those of other governments in the preparation of this report. The report includes the following concepts:

Summary of Major Points

Recombinant DNA techniques have opened up new and promising possibilities in a wide range of applications and can be expected to bring considerable benefits to mankind. They contribute in several ways to the improvement of human health and the extent of this contribution is expected to increase significantly in the near future.

The vast majority of industrial rDNA large-scale applications will use organisms of intrinsically low risk which warrant only minimal containment, Good Industrial Large-Scale Practice (GILSP).

When it is necessary to use rDNA organisms of higher risk, additional criteria for risk assessment can be identified and furthermore, the technology of physical containment is well known to industry and has successfully been used to contain pathogenic organisms for years. Therefore, rDNA microorganisms of higher risks can also be handled safely under appropriate physical and/or biological containment.

Assessment of potential risks of organisms for environmental or agricultural applications is less developed than the assessment of potential risks for industrial applications. However, the means for assessing rDNA organisms can be approached by analogy with the existing data base gained from the extensive use of traditionally modified organisms in agriculture and the environment generally. With step-by-step assessment during the research and development process, the potential risk to the environment of the applications of rDNA organisms should be minimized.

I. General Recommendations

1. Harmonization of approaches to rDNA technology can be facilitated by exchanging: principles or guidelines for national regulations; developments in risk analysis; and practical experience in risk management. Therefore, information should be shared as freely as possible.

2. There is no scientific basis for specific legislation

for the implementation of rDNA technology and applications. Member countries should examine their existing oversight and review mechanisms to ensure that adequate review and control may be applied while avoiding any undue burdens that may hamper technological developments in this field.

3. Any approach to implementing guidelines should not impede future developments in rDNA technology. International harmonization should recognize this need.

4. To facilitate data exchange and minimize trade barriers between countries, further developments such as testing methods, equipment design, and knowledge of microbial taxonomy should be considered by both national and international levels. Due account should be taken of ongoing work on standards within international organizations such as: World Health Organization; Commission of the European Communities; International Standards Organization; Food and Agricultural Organization; and, Microbial Strains Data Network.

5. Special efforts should be made to improve public understanding of various aspects of rDNA technology.

6. For rDNA applications in industry, agriculture and the environment, it will be important for OECD Member countries to watch the development of these techniques. For certain industrial applications and for environmental and agricultural applications of rDNA organisms, some countries may wish to have a notification scheme.

7. Recognizing the need for innovation, it is important to consider appropriate means to protect intellectual property and confidentiality interests while assuring safety.

II. Recommendations Specific for Industry

1. The large-scale industrial application of rDNA technology should wherever possible utilize microorganisms that are intrinsically of low risk. Such microorganisms can be handled under conditions of Good Industrial Large-Scale Practice (GILSP).

2. If, following assessment using the criteria outlined in the document, a rDNA microorganism cannot be handled merely by GILSP, measures of containment corresponding to the risk assessment should be used in addition to GILSP.

3. Further research to improve techniques for monitoring and controlling non-intentional release of rDNA organisms should be encouraged in large-scale industrial applications requiring physical containment.

III. Recommendations Specific for Environmental and Agricultural Applications

1. Considerable data on the environmental and human health effects of living organisms exist and should be used to guide risk assessments.

2. It is important to evaluate rDNA modified organisms for potential risk, prior to applications in agriculture and the environment. However, the development of general international guidelines governing such applications is premature at this time. An independent review of potential risks should be conducted on a cases-by-case basis prior to application. Case-by-case means an individual review of a proposal against assessment criteria which are relevant to the particular proposal; this is not intended to imply that every case will require review by a national or other authority since various classes of proposals may be excluded.

3. Development of organisms for agricultural or environmental applications should be conducted in a stepwise fashion, moving, where appropriate, from the laboratory to the growth chamber and greenhouse, to limited field testing and finally, to large-scale field testing.

4. Further research to improve the prediction, evaluation, and monitoring of the outcome of applications of rDNA organisms should be encouraged.

JUN 12 1986

DPC

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Mary: Please keep a close hold on this list.

Thanks.

THE WHITE HOUSE
WASHINGTON

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