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Part IV

Department of Health and Human Services

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines; Notice
DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice of Actions Under the NIH Guidelines for Research Involving **Recombinant** DNA Molecules.

SUMMARY: This notice sets forth three actions to be taken by the Director, National Institutes of Health (NIH), under the NIH Guidelines for Research Involving **Recombinant** DNA Molecules (Federal Register, July 5, 1994, Part IV).

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Dr. Nelson A. Wivel, Director, Office of **Recombinant** DNA Activities (ORDA), Office of Science Policy and Technology Transfer, National Institutes of Health, Building 31, Room 4B11, Bethesda, Maryland 20892, (301) 496-9838.

SUPPLEMENTARY INFORMATION: Today three actions are being promulgated under the NIH Guidelines for Research Involving **Recombinant** DNA Molecules. These three proposed actions were published for comment in the Federal Register of May 11, 1994 (59 FR 24618), and reviewed and recommended for approval by the NIH **Recombinant** DNA Advisory Committee (RAC) at its meeting on June 9-10, 1994.

I. Background Information and Decisions on Actions Under the NIH Guidelines

A. Amendment to Appendix M-I-D of the NIH Guidelines Regarding Informed Consent for Human Gene Transfer Protocols

During the December 2-3, 1993, **Recombinant** DNA Advisory Committee meeting, Dr. Gary Ellis, Director of the Office for Protection from Research Risks (OPRR), NIH, Bethesda, Maryland, responded to the written comments submitted by Dr. Zallen, Chair of the Working Group on Informed Consent Issues. Dr. Ellis noted the **Recombinant** DNA Advisory Committee's concern regarding specific issues that should be addressed in human gene transfer protocol Informed Consent documents, i.e., request for autopsy, recommendations for male/female contraception, separate Informed Consent documents when the gene therapy aspects of the protocols are independent of an ongoing clinical protocol, commitment to long-term patient follow-up, and financial responsibility of the institution for all research-related costs. During his presentation, Dr. Ellis provided the **Recombinant** DNA Advisory Committee with background information regarding the roles of both OPRR and local Institutional Review Boards (IRB) in the review of research proposals

involving human subjects. Dr. Ellis recommended that the **Recombinant** DNA Advisory Committee draft a letter outlining its specific recommendations to OPRR for distribution and consideration by the local IRBs.

In a memorandum dated December 23, 1993, Dr. Ellis further clarified the avenues that should be pursued by the **Recombinant** DNA Advisory Committee with regard to translating its concern about the ``quality and content of informed consent documents into constructive changes in the informed consent process,'' specifically in relation to human gene transfer. Dr. Ellis recommended that the NIH Guidelines should be amended to introduce consistency in Informed Consent document language.

During the March 3-4, 1994, **Recombinant** DNA Advisory Committee meeting, Dr. Doris Zallen, Chair of the Working Group on Informed Consent, provided a summary of the proposed amendments to Appendix M-I-D, Informed Consent. Two versions of revised Appendix M-I-D were presented: (1) the version drafted by the working group, and (2) a modified version incorporating the modifications suggested by Mr. Alex Capron. The **Recombinant** DNA Advisory Committee recommended that the working group should develop a consolidated version of Appendix M-I-D which includes language from both proposed documents. The **Recombinant** DNA Advisory Committee suggested that questions should be prefaced with an explanation as to the necessity for the requested information.

On April 27, 1994, Dr. Zallen submitted revised amendments to Appendix M-I- D, Informed Consent, in response to the specific comments posed by the **Recombinant** DNA Advisory Committee at its March 3-4, 1994, meeting. The proposed amendments were reviewed by the **Recombinant** DNA Advisory Committee during the June 9-10, 1994, meeting. The **Recombinant** DNA Advisory Committee approved a motion to accept the proposed amendments with minor editorial changes to Appendix M-I-D, Informed Consent, by a vote of 13 in favor, 0 opposed, and no abstentions.

The amended version of Appendix M-I-D, Informed Consent, reads:

Appendix M-I-D. Informed Consent

In accordance with the requirements of DHHS regulations for the Protection of Human Subjects (45 CFR Part 46), investigators should indicate how subjects will be informed about the proposed study and the manner in which their consent will be solicited. They should also indicate how the Informed Consent document makes clear the special requirements of gene transfer research.

Appendix M-I-D-1. Communication About the Study to Potential Participants

Appendix M-I-D-1-a.

Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?

Appendix M-I-D-1-b.

How will the major points covered in Appendices M-I-A through M-I-C be disclosed to potential participants and/or their parents or guardians in language that is understandable to them?

Appendix M-I-D-1-c.

What is the length of time that potential participants will have to make a decision about their participation in the study?

Appendix M-I-D-1-d.

If the study involves pediatric or mentally handicapped

subjects, how will the assent of each person be obtained?

Appendix M-I-D-2. Informed Consent Document

``Investigators submitting human gene transfer proposals for **Recombinant** DNA Advisory Committee review must include the Informed Consent document as approved by the local Institutional Review Boards. A separate Informed Consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a 'marker' or to enhance the power of immunotherapy for cancer.

``Because of the relative novelty of the procedures that are used, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the Informed Consent process should include the following specific information in addition to any requirements of the DHHS regulations for the Protection of Human Subjects (45 CFR 46). Indicate if each of the specified items appears in the Informed Consent document or, if not included in the Informed Consent document, how those items will be presented to potential subjects. Include an explanation if any of the following items are omitted from the consent process or the Informed Consent document.

Appendix M-I-D-2-a. General Requirements of Human Subjects Research

Appendix M-I-D-2-a-(1). Description/purpose of the study. ``The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component.

Appendix M-I-D-2-a-(2). Alternatives. ``The Informed Consent document should indicate the availability of therapies and the possibility of other investigational interventions and approaches.

Appendix M-I-D-2-a-(3). Voluntary participation. ``The subjects should be informed that participation in the study is voluntary and that failure to participate in the study or withdrawal of consent will not result in any penalty or loss of benefits to which the subjects are otherwise entitled.

Appendix M-I-D-2-a-(4). Benefits. ``The subjects should be provided with an accurate description of the possible benefits, if any, of participating in the proposed study. For studies that are not reasonably expected to provide a therapeutic benefit to subjects, the Informed Consent document should clearly state that no direct clinical benefit to subjects is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

Appendix M-I-D-2-a-(5). Possible risks, discomforts, and side effects. ``There should be clear itemization in the Informed Consent document of types of adverse experiences, their relative severity, and their expected frequencies. For consistency, the following definitions are suggested: side effects that are listed as mild should be ones which do not require a therapeutic intervention; moderate side effects require an intervention; and severe side effects are potentially fatal or life-threatening, disabling, or require prolonged hospitalization.

``If verbal descriptors (e.g., `rare,' `uncommon,' or `frequent') are used to express quantitative information regarding risk, these terms should be explained.

``The Informed Consent document should provide information regarding the approximate number of people who have previously received the genetic material under study. It is necessary to warn potential subjects that, for genetic materials previously used in relatively few or no humans, unforeseen risks are possible, including ones that could be severe.

``The Informed Consent document should indicate any possible

adverse medical consequences that may occur if the subjects withdraw from the study once the study has started.

Appendix M-I-D-2-a-(6). Costs. ``The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the long-term follow-up to the protocol that are not covered by the investigators or the institution involved.

``Subjects should be provided an explanation about the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury.

Appendix M-I-D-2-b. Specific Requirements of Gene Transfer Research

Appendix M-I-D-2-b-(1). Reproductive considerations. ``To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, subjects should be given information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified.

``The inclusion of pregnant or lactating women should be addressed.

Appendix M-I-D-2-b-(2). Long-term follow-up. ``To permit evaluation of long-term safety and efficacy of gene transfer, the prospective subjects should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study. The Informed Consent document should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The principal investigator should request that subjects continue to provide a current address and telephone number.

``The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

Appendix M-I-D-2-b-(3). Request for autopsy. ``To obtain vital information about the safety and efficacy of gene transfer, autopsies are to be performed, if feasible. Subjects should be informed that at the time of death, no matter what the cause, permission for any autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance.

Appendix M-I-D-2-b-(4). Interest of the media and others in the research. ``To alert subjects that others may have an interest in the innovative character of the protocol and in the status of the treated subjects, the subjects should be informed of the following: (i) that the institution and investigators will make efforts to provide protection from the media in an effort to protect the participants' privacy, and (ii) that representatives of applicable Federal agencies (e.g., the National Institutes of Health and the Food and Drug Administration), representatives of collaborating institutions, vector suppliers, etc., will have access to the subjects' medical records.''

I accept this recommendation, and Appendix M-I-D, Informed Consent, of the NIH Guidelines will be added accordingly.

B. Amendment to Appendix M-VI of the NIH Guidelines Regarding Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments

On April 29, 1994, Dr. Nelson Wivel of the Office of **Recombinant** DNA Activities, National Institutes of Health, Bethesda, Maryland, requested that Appendix M-VI, Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments, be amended to

clarify submission requirements.

The Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments currently reads:

``Appendix M-VI-D. Regardless of the method of review, the Points to Consider is the standard of review for all gene transfer protocols.''

The proposed amendment reads:

``Appendix M-VI-D. Regardless of the method of review, the Points to Consider is the standard of review for all gene transfer protocols; therefore, submission of the response to the Points to Consider is required.''

The proposed amendment was reviewed by the **Recombinant** DNA Advisory Committee during the June 9-10, 1994, meeting. The **Recombinant** DNA Advisory Committee approved a motion to accept the proposed amendment to Appendix M-VI, Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments, by a vote of 13 in favor, 0 opposed, and no abstentions.

I accept this recommendation, and Appendix M-VI, Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments, of the NIH Guidelines will be amended accordingly.

C. Deletion of Appendix L of the NIH Guidelines Regarding Release into the Environment

On April 29, 1994, Dr. Nelson Wivel of the Office of **Recombinant** DNA Activities, National Institutes of Health, Bethesda, Maryland, requested that Appendix L, Release into the Environment of Certain Plants, be deleted from the NIH Guidelines based on the following: (1) Section I of the NIH Guidelines allows experiments to proceed that are reviewed and approved by another Federal agency that has jurisdiction for review and approval without the necessity for NIH review or approval (52 FR 31849); (2) the **Recombinant** DNA Advisory Committee has not reviewed any deliberate release experiment involving **recombinant** DNA since 1984; (3) at its May 30-31, 1991, meeting, the **Recombinant** DNA Advisory Committee recommended that Section III-A-2 be deleted from the NIH Guidelines; and (4) experiments involving deliberate release into the environment are currently reviewed within the framework of existing Federal regulations, as administered by the Environmental Protection Agency and the U.S. Department of Agriculture.

Section I of the NIH Guidelines was amended on August 24, 1987, such that any **recombinant** DNA experiment (other than human gene transfer) may proceed without **Recombinant** DNA Advisory Committee and NIH approval if it has been reviewed and approved by another Federal agency that has jurisdiction over such a proposal. The amended version (52 FR 31849) of Section I reads as follows:

Section I-A. Purpose

``* * *Any **recombinant** DNA experiment, which according to the NIH Guidelines requires approval by the NIH, must be submitted to the NIH or to another Federal agency that has jurisdiction for review and approval. Once approval, or other applicable clearances, have been obtained from a Federal agency other than the NIH (whether the experiment is referred to that agency by the NIH or sent directly there by the submitter), the experiment may proceed without the necessity for NIH review or approval* * *.''

On December 6, 1990, the **Recombinant** DNA Advisory Committee Planning Subcommittee recommended that the requirement for **Recombinant** DNA Advisory Committee review of experiments involving deliberate environmental release of organisms containing **recombinant** DNA be eliminated from the NIH Guidelines. This recommendation reflected the fact that the Federal regulatory agencies, the U.S. Department of Agriculture and the Environmental Protection Agency, are responsible for the review and approval of environmental release experiments. The **Recombinant** DNA Advisory Committee reviewed the request and recommended that the following sections be deleted from the NIH Guidelines (Actions Under the Guidelines, Federal Register, July 5, Part III):

Section III-A-2.

Deliberate release into the environment of any organism containing **recombinant** DNA except those listed below. The term ``deliberate release'' is defined as a planned introduction of **recombinant** DNA-containing microorganisms, plants, or animals into the environment.

Section III-A-2-a. Introductions conducted under conditions considered to be accepted scientific practices in which there is adequate evidence of biological and/or physical control of the **recombinant** DNA-containing organisms. The nature of such evidence is described in Appendix L.

Section III-A-2-b. Deletion derivatives and single base changes not otherwise covered by the NIH Guidelines.

Section III-A-2-c. For extrachromosomal elements and microorganisms (including viruses), rearrangements and amplifications within a single genome. Rearrangements involving the introduction of DNA from different strains of the same species would not be covered by this exemption.''

Based on these amendments to the NIH Guidelines, that have previously been recommended by the **Recombinant** DNA Advisory Committee, and the fact that the principles of planned introduction are now in place which provide a risk-assessment method by other Federal regulatory agencies, the Office of **Recombinant** DNA Activities requests that Appendix L be deleted from the NIH Guidelines.

Appendix L will be deleted as follows:

Appendix L. Release into the Environment of Certain Plants

Appendix L-I. General Information

Appendix L specifies conditions under which certain plants as specified below, may be approved for release into the environment. Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, review by the RAC Plant Subcommittee, and specific approval by the NIH Director. Such experiments also require the approval of the Institutional Biosafety Committee before initiation.

Appendix L-II. Criteria Allowing Review by the RAC Plant Subcommittee Without the Requirement for Full RAC Review

``In consultation with the RAC Plant Subcommittee and without the requirement for full RAC review (Institutional Biosafety Committee review and approval is necessary), NIH/ORDA may approve the growing of plants containing **recombinant** DNA in the field under the following conditions: (i) the plant species is a cultivated crop of a genus that has no species known to be a noxious weed; (ii) the introduced DNA consists of well-characterized genes containing no sequences harmful to humans, animals, or plants; (iii) the vector consists of DNA from exempt host-vector systems (see Appendix C), from plants of the same or closely related species, from nonpathogenic prokaryotes or nonpathogenic lower eukaryotic plants, from plant pathogens only if sequences resulting in production of disease symptoms have been deleted, or chimeric vectors constructed from sequences of exempt host-vector systems (see Appendix C) or from sequences from plant pathogens in which the disease symptoms have been deleted. The DNA may be introduced by any suitable method. If sequences resulting in production of disease symptoms are retained for purposes of introducing the DNA into the plant, greenhouse-grown plants must be shown to be free of such sequences before such plants, their derivatives, or seed can be used in field tests; (iv) plants are grown in controlled access fields under specified conditions appropriate for the plant under study and the geographical location. Such conditions should include provisions for using good cultural and pest control practices, for physical isolation from plants of the same species outside of the experimental plot in accordance with pollination characteristics of the species, and the prevention of plants containing **recombinant** DNA from becoming established in the environment. Review by the

Institutional Biosafety Committee should include an appraisal by scientists knowledgeable of the crop, its production practices, and the local geographical conditions. Procedures for assessing alterations in and the spread of organisms containing **recombinant** DNA must be developed. The results of the outlined tests must be submitted for review and approval by the Institutional Biosafety Committee. Copies of such results must be submitted to the Office of **Recombinant** DNA Activities, National Institutes of Health, Building 31, Room 4B11, Bethesda, Maryland 20892, (301) 496-9838.''

The proposed amendment was reviewed by the **Recombinant** DNA Advisory Committee during its June 9-10, 1994, meeting. The **Recombinant** DNA Advisory Committee approved a motion to accept the deletion of Appendix L, Regarding Release into the Environment, by a vote of 13 in favor, 0 opposed, and no abstentions.

I accept this recommendation, and Appendix L, Regarding Release into the Environment, of the NIH Guidelines will be deleted accordingly.

II. Summary of Actions

A. Amendment to Appendix M-I-D of the NIH Guidelines Regarding Informed Consent for Human Gene Transfer Protocols

Appendix M-I-D will read as follows:

Appendix M-I-D. Informed Consent

In accordance with the requirements of DHHS regulations for the Protection of Human Subjects (45 CFR Part 46), investigators should indicate how subjects will be informed about the proposed study and the manner in which their consent will be solicited. They should also indicate how the Informed Consent document makes clear the special requirements of gene transfer research.

Appendix M-I-D-1. Communication About the Study to Potential Participants

Appendix M-I-D-1-a

Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?

Appendix M-I-D-1-b

How will the major points covered in Appendices M-I-A through M-I-C be disclosed to potential participants and/or their parents or guardians in language that is understandable to them?

Appendix M-I-D-1-c

What is the length of time that potential participants will have to make a decision about their participation in the study?

Appendix M-I-D-1-d

If the study involves pediatric or mentally handicapped subjects, how will the assent of each person be obtained?

Appendix M-I-D-2. Informed Consent Document

``Investigators submitting human gene transfer proposals for **Recombinant** DNA Advisory Committee review must include the Informed Consent document as approved by the local Institutional Review

Boards. A separate Informed Consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a `marker' or to enhance the power of immunotherapy for cancer.

``Because of the relative novelty of the procedures that are used, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the Informed Consent document should include the following specific information in addition to any requirements of the DHHS regulations for the Protection of Human Subjects (45 CFR 46). Indicate if each of the specified items appears in the Informed Consent document or, if not included in the Informed Consent document, how those items will be presented to potential subjects. Include an explanation if any of the following items are omitted from the consent process or the Informed Consent document.

Appendix M-I-D-2-a. General Requirements of Human Subjects Research

Appendix M-I-D-2-a-(1). Description/Purpose of the Study

``The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component.

Appendix M-I-D-2-a-(2). Alternatives

``The Informed Consent document should indicate the availability of therapies and the possibility of other investigational interventions and approaches.

Appendix M-I-D-2-a-(3). Voluntary Participation

``The subjects should be informed that participation in the study is voluntary and that failure to participate in the study or withdrawal of consent will not result in any penalty or loss of benefits to which the subjects are otherwise entitled.

Appendix M-I-D-2-a-(4). Benefits

``The subjects should be provided with an accurate description of the possible benefits, if any, of participating in the proposed study. For studies that are not reasonably expected to provide a therapeutic benefit to subjects, the Informed Consent document should clearly state that no direct clinical benefit to subjects is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

Appendix M-I-D-2-a-(5). Possible Risks, Discomforts, and Side Effects

``There should be clear itemization in the Informed Consent document of types of adverse experiences, their relative severity, and their expected frequencies. For consistency, the following definitions are suggested: side effects that are listed as mild should be ones which do not require a therapeutic intervention; moderate side effects require an intervention; and severe side effects are potentially fatal or life-threatening, disabling, or require prolonged hospitalization.

``If verbal descriptors (e.g., `rare,' `uncommon,' or `frequent') are used to express quantitative information regarding risk, these terms should be explained.

``The Informed Consent document should provide information regarding the approximate number of people who have previously received the genetic material under study. It is necessary to warn potential subjects that, for genetic materials previously used in

relatively few or no humans, unforeseen risks are possible, including ones that could be severe.

``The Informed Consent document should indicate any possible adverse medical consequences that may occur if the subjects withdraw from the study once the study has started.

Appendix M-I-D-2-a-(6). Costs

``The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the long-term follow-up to the protocol that are not covered by the investigators or the institution involved.

``Subjects should be provided an explanation about the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury.

Appendix M-I-D-2-b. Specific Requirements of Gene Transfer Research

Appendix M-I-D-2-b-(1). Reproductive Considerations

``To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, subjects should be given information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified.

``The inclusion of pregnant or lactating women should be addressed.

Appendix M-I-D-2-b-(2). Long-Term Follow-Up

``To permit evaluation of long-term safety and efficacy of gene transfer, the prospective subjects should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study. The Informed Consent document should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The principal investigator should request that subjects continue to provide a current address and telephone number.

``The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

Appendix M-I-D-2-b-(3). Request for Autopsy

``To obtain vital information about the safety and efficacy of gene transfer, subjects should be informed that at the time of death, no matter what the cause, permission for an autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance.

Appendix M-I-D-2-b-(4). Interest of the Media and Others in the Research

``To alert subjects that others may have an interest in the innovative character of the protocol and in the status of the treated subjects, the subjects should be informed of the following: (i) that the institution and investigators will make efforts to provide protection from the media in an effort to protect the participants' privacy, and (ii) that representatives of applicable Federal agencies (e.g., the National Institutes of Health and the Food and Drug Administration), representatives of collaborating

institutions, vector suppliers, etc., will have access to the subjects' medical records.''

B. Amendment to Appendix M-VI of the NIH Guidelines Regarding Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments

Appendix M-VI, Procedures to be Followed for Expedited Review of Single Patient Human Gene Transfer Experiments, will read as follows:

``Appendix M-VI-D. Regardless of the method of review, the Points to Consider is the standard of review for all gene transfer protocols; therefore, submission of the Points to Consider is required.''

C. Deletion of Appendix L of the NIH Guidelines Regarding Release into the Environment

Appendix L, Release into the Environment of Certain Plants, be deleted in full: To see the full text of Appendix L, reference the background information and decisions on actions under the NIH Guidelines (Section I-C).

OMB's ``Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA **recombinant** molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Effective Date: July 28, 1994.
Harold Varmus,
Director, National Institutes of Health.
[FR Doc. 94-19078 Filed 8-4-94; 8:45 am]
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