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Part III

Department of Health and Human Services

National Institutes of Health

Recombinant DNA: Notice of Meeting and Proposed Actions; Notices

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Advisory Committee; Meeting

Pursuant to Public Law 92–463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee on February 10–11, 1992. The meeting will be held at the National Institutes of Health (NIH), Building 31C, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892, starting at approximately 9 a.m. on February 10, 1992, to adjournment at approximately 5 p.m. on February 11, 1992. The meeting will be open to the public to discuss the following proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (51 FR 16958):

Proposed Major Actions to the NIH Guidelines;

Five additions to appendix D of the NIH Guidelines Regarding Human Gene Therapy/Gene Transfer Protocols;

An amendment to appendix D–XV of the NIH Guidelines Regarding a Human Gene Therapy Protocol;

Amend section IV–B and add sections IV–C and IV–D to the Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Into the Genome of Human Subjects Regarding Reporting Requirements for Human Gene Transfer/Gene Therapy Protocols;

Amend sections III–A and IV–C of the NIH Guidelines regarding publishing notice of meetings and proposed actions in the Federal Register;

Amend introduction, section IV–B and V of the Points to Consider regarding review by the Human Gene Therapy Subcommittee;

Amend appendices B–I–B–1 and B–I–B–2 of the NIH Guidelines to include only pathogenic genera and species of the bacterial order, *Actinomycetales*, in the current list of microorganisms;

Amend Appendices B–I–C–1 and B–I–B–1 in the NIH Guidelines regarding *Mycobacterium* avium;

Other Matters To Be Considered by the Committee.

Attendance by the public will be limited to space available. Members of the public wishing to speak at this meeting may be given such opportunity at the discretion of the Chair. Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, Building 31, room 4B11, Bethesda, Maryland 20892, Phone (301) 496–9838, FAX (301) 496–9839, will provide materials to be discussed at this meeting, roster of committee members, and substantive program information. A summary of the meeting will be available at a later date.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) 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 not to be 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.

Dated: December 24, 1991.

Susan K. Feldman,

Committee Management Officer, NIH.

[FR Doc. 92–107 Filed 1–2–92; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Recombinant DNA Research: Proposed Actions Under the Guidelines

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice of proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (51 FR 16958).

SUMMARY: This notice sets forth proposed actions to be taken under the National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules. Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee (RAC) at its meeting on February 10–11, 1992. After consideration of these proposals and comments by the RAC, the Director of the National Institutes of Health will issue decisions in accordance with the NIH Guidelines.

DATES: Comments received by January 28, 1992, will be reproduced and distributed to the RAC for consideration at its February 10–11, 1992, meeting.

ADDRESSES: Written comments and recommendations should be submitted to Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, Building 231, room 4B11, National Institutes of Health, Bethesda, Maryland 20892, or sent by FAX to 301–496–9839.

All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, Building 31, room 4B11, National Institutes of Health, Bethesda, Maryland 20892, (301) 496–9838.

SUPPLEMENTARY INFORMATION: The NIH will consider the following actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules:

I. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Therapy Protocol/Dr. Nabel

In a letter dated October 18, 1991, Dr. Gary J. Nabel of the University of Michigan Medical School, Ann Arbor, Michigan, indicated his intention to submit a human gene therapy protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"Immunotherapy of Malignancy by In Vivo Gene Transfer into Tumors."

This request was published for comment in the Federal Register on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on November 21–22, 1991. Provisional approval was given with the following conditions: (i) Amend consent form regarding possibility of sensitization to the human antigen; (ii) expand the clinical protocol regarding the number of biopsies; (iii) make available the nucleotide sequence analysis of the total construct of the vector; and (iv) provide clarification concerning the status of DNA integration in tumor cells.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory

Committee for consideration during the February 10–11, 1992, meeting.

II. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Dr. Cornetta

In a letter dated October 10, 1991, Dr. Kenneth Cornetta of Indiana University, Indianapolis, Indiana, indicated his intention to submit a human gene transfer protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"Retroviral-Mediated Gene Transfer of Bone Marrow Cells During Autologous Bone Marrow Transplantation for Acute Leukemia."

This request was published for comment in the **Federal Register** on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on November 21–22, 1991. Provisional approval was given with the following conditions: (i) Amend the consent form regarding the possible benefit of the introduction of gene; (ii) amend the consent form regarding compensation to the patient related to the research aspects of the protocol; (iii) demonstrate that the transduced leukemic cells will survive the freezing process; and (iv) add a statistical section that addresses the interpretation of recurrent labeled bone marrow specimens.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the February 10–11, 1992, meeting.

III. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Dr. Economou

In a letter dated October 15, 1991, Dr. James S. Economou of the University of California, Los Angeles, indicated his intention to submit a human gene transfer protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"The Treatment of Patients with Metastatic Melanoma and Renal Cell Cancer Using In Vitro Expanded and Genetically-Engineered (Neomycin Phosphotransferase) Bulk, CD8(+) and/or CD4(+) Tumor Infiltrating Lymphocytes and Bulk, CD8(+) and/or CD4(+) Peripheral Blood Leukocytes in Combination with Recombinant Interleukin-2 Alone, or with Recombinant Interleukin-2 and Recombinant Alpha Interferon."

This request was published for comment in the **Federal Register** on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on November 21–22, 1991. Provisional approval was given with the following conditions: (i) All data concerning vector safety and testing must be submitted; (ii) patient eligibility will be limited to those with at least one lesion that can be biopsied post therapy; (iii) add the schedule for the post therapy assessment of cell trafficking; (iv) develop a statistical section for analysis of cell trafficking; (v) submit proportionality experiments demonstrating the limits of the ability to quantitate differences in ratio of the two vectors; (vi) submit data showing stable integration of the genetic markers in chronic cell cultures; (vii) modify the consent form so that the language concerning biopsies is moved from the biomodulator section to the viral marker section; and (viii) include a stopping rule in the protocol if the in vivo trafficking data is uninterpretable.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the February 10–11, 1992, meeting.

IV. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Therapy Protocol/Dr. Greenberg

In a letter dated October 8, 1991, Dr. Philip D. Greenberg of the University of Washington, Seattle, Washington, indicated his intention to submit a human gene therapy protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"A Phase I/II Study of Cellular Adoptive Immunotherapy Using Genetically Modified CD8+ HIV-Specific T Cells for HIV-Seropositive Patients Undergoing Allogeneic Bone Marrow Transplant."

This request was published for comment in the **Federal Register** on November 4, 1991 (56 FR 56415).

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on November 21–22, 1991. Approval was given with the following requested changes in the patient consent form: (i) Reword language regarding unforeseen problems; (ii) reword the language concerning the costs associated with the research aspects of the protocol and billing to the patients; (iii) clearly distinguish between the therapy and the gene modification portions of the protocol; (iv) use less technical terminology throughout the document; and (v) provide hard copies of the helper-virus assay and vector testing slides presented during the subcommittee meeting.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the February 10–11, 1992, meeting.

V. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Therapy Protocol/Dr. Freeman

In a letter dated May 10, 1990, Dr. Scott M. Freeman of the University of Rochester School of Medicine, Rochester, New York, indicated his intention to submit a human gene therapy protocol to the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee for formal review and approval. The title of this protocol is:

"Gene Transfer for the Treatment of Cancer."

This request was published for comment in the **Federal Register** on July 2, 1991 (56 FR 30398).

The protocol was reviewed during the Human Gene Therapy Subcommittee meeting on July 29–30, 1991. Provisional approval was given with the stipulation that the PA–1 ovarian cancer cell line be tested for potential pathogens as per FDA guidelines. Further, it was requested that there should be more preclinical studies on the MFG vector to assure that it does not contain replication competent retroviruses.

The Human Gene Therapy Subcommittee forwarded the protocol to the Recombinant DNA Advisory Committee for consideration during the October 7–8, 1991, meeting.

This request was published for comment in the **Federal Register** on September 3, 1991 (56 FR 43686).

The protocol was reviewed during the Recombinant DNA Advisory Committee meeting on October 7–8, 1991. The Recombinant DNA Advisory Committee passed a motion to defer approval of the protocol by a vote of 19 in favor, 0 opposed, and no abstentions. The protocol can be considered again when the following requests have been met: (i) Improvement of the animal model so that it has some relevance to the malignancy seen in patients; (ii) examination of the animal model for the tumor specificity of cytotoxic T lymphocytes; (iii) demonstration of the efficacy of this proposed treatment by measuring the tumor burden in patients and state whether this will be done by laparoscopy or imaging techniques or both; (iv) refinement of safety tests; and (v) elimination of every reference to

cancer vaccine in the patient consent form.

VI. Amendment to Appendix D–XV of the NIH Guidelines Regarding a Human Gene Therapy Protocol/Drs. Blaese and Anderson

In a letter dated December 20, 1991, Drs. R. Michael Blaese and W. French Anderson of the National Institutes of Health, Bethesda, Maryland, requested an action item concerning a major amendment to the protocol entitled, "Treatment of Severe Combined Immunodeficiency Disease (SCID) due to Adenosine Deaminase (ADA) Deficiency with Autologous Lymphocytes Transduced with a Human ADA Gene."

This protocol was originally approved by the Recombinant DNA Advisory Committee at its meeting on July 31, 1990, and approved by the Director, NIH (September 12, 1990, 55 FR 37565).

The requested amendment would use as a supplemental therapy CD–34+ cells (the peripheral blood stem cell fraction) transduced with the gene coding for adenosine deaminase.

VII. Amending Section IV–B and Adding Sections IV–C and IV–D to the Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects Regarding Reporting Requirements for Human Gene Transfer/Gene Therapy Protocols

At the Human Gene Therapy Subcommittee meeting on July 30–31, 1991, the subcommittee formed a Working Group on Data Management. The working group was charged with developing a system for analyzing approved protocol results for the purpose of ensuring quality control in the approval process and to devise a follow-up procedure for analyzing already approved protocols. During the Human Gene Therapy Subcommittee meeting on November 21–22, 1991, a proposed reporting document was developed by the working group and submitted for review that would become Sections IV–C and IV–D of the Points to Consider.

Sections IV–C and IV–D of the *Points to Consider* will be an expansion of the *Reporting Requirement* section. It includes the requirements for the investigators to provide a detailed follow-up of approved human gene therapy/gene transfer protocols.

The Human Gene Therapy Subcommittee suggested minor changes to this section. The Recombinant DNA Advisory Committee will receive the following modified version of this proposed section from the Human Gene Therapy Subcommittee at the meeting of February 10–11, 1992. Section IV, Reporting Requirements, of the *Points to Consider* will be amended in Section IV–B, and two new sections, IV–C and IV–D, will be added.

Section IV–B of the *Points to Consider* currently reads:

"Section IV–B. Reports regarding the general progress of patients should be filed with both your local IRB and ORDA within 6 months of the commencement of the experiment and at six-month intervals thereafter. These twice yearly reports should continue for a sufficient period of time to allow observation of all major effects. In the event of a patient's death, a summary of the special post mortem studies and statement of the cause of death should be submitted to the IRB and ORDA, if available."

Reporting requirements will be more clearly defined in the new Sections IV–C and IV–D of the *Points to Consider* below. Therefore, Section IV–B will now read:

"Section IV–B. Reports regarding the general progress of patients should be filed with both your local IRB and ORDA. ORDA requests the first report after one year of the commencement of the experiment (See Section IV–C), and at yearly intervals thereafter (See Sections IV–D). These reports should continue for a sufficient period of time to allow observation of all major effects. In the event of a patient's death, a summary of the special post mortem studies and statement of the cause of death should be submitted to the IRB and ORDA, if available."

Two new sections, IV–C and IV–D will be added to the *Points to Consider*. The proposed sections read as follows:

"Section IV–C. Reporting Form "A". This information is being collected from each gene transfer protocol approved by the RAC that involves human subjects. The information on this form will be requested only with the first report.

"Section IV–C–1. General Information.

"Section IV–C–1–a. Indicate the: (1) Name of principal investigator, (ii) name of study, and (iii) date of report.

'Section IV–C–1–b. What is the current status of the study (i.e., is it open or closed)? If closed, include: (i) Date protocol closed; (ii) describe reason for closure; and (iii) submit summary.

"Section IV–C–2. Approval Process of Protocol.

"Section IV–C–2–a. Supply a copy of the latest version of the protocol including copies of sample case report forms or any other data collection forms that are being employed as part of this study.

"Section IV–C–2–b. Indicate the dates of the following approvals: Institutional Review Board, Institutional Biosafety Committee, Human Gene Therapy Subcommittee, Recombinant DNA Advisory Committee, and Food and Drug Administration.

"Section IV–C–2–b–(1). Note major changes suggested by each committee and the responses to those suggestions.

"Section IV–C–2–c. Have there been any amendments to the protocol?

"Section IV–C–2–d. Describe your proposed standard quality control measures.

"Section IV–D. Reporting Form "B". An annual update of the following information will be required. Each question may not be applicable to each protocol.

"Section IV–D–1. General Information.

"Section IV–D–1–a. Indicate the: (i) Name of principal investigator, (ii) name of study, and (iii) date of report.

"Section IV–D–1–b. What is the current status of the study (i.e., is it open or closed)? If closed, include: (i) Date protocol closed; (ii) describe reason for closure; and (iii) submit summary.

"Section IV–D–1-c. Have there been any amendments to the protocol? If so, indicate the dates of the following approvals: Institutional Review Board (IRB) and Office of Recombinant DNA Activities (ORDA).

"Section IV–D–1–d. Have there been any adverse reactions reported? If so, describe. What dates were they reported to the IRB and ORDA?

"Section IV-D–2. Measurements of Gene Transfer Success *In Vitro*.

"Section IV–D–2–a. Describe what you are doing currently and how this compares with what you proposed.

"Section IV–D–2–b. What material are you administering to the patients via what route? is this different from what you proposed?

"Section IV–D–2–c. What *in vitro* evidence is there for the efficacy of the genetic manipulation prior to administration of the material, i.e., the efficiency of gene transfer and the manufacture of the desired product? How do your results compare with anticipated results?

"Section IV–D–2–d. Have there been any unexpected results of the ongoing quality control measures? In particular, has there been any incidence of replication competent virus or vector rearrangement? Are these tests performed for each lot of materials administered?

"Section IV–D–2–e. Are there problems that have occurred that you did not anticipate prior to starting the

protocol? What are these? Have they resulted in a change in your procedures?

"Section IV–D–3. Measure of Gene Transfer Success *In Vivo*.

"Section IV–D–3–a. Positive effects.

"Section IV–D–3–a–(1). In the patients treated, has there been any evidcnce of activity of the transferred gene? what is the documentation for this? How does this compare with what you anticipated?

"Section IV–D–3–a–(2). Has the patients' condition improved?

"Section IV–D–3–a–(3). Is there significant variation between patients. If so, how is this explained?

"Section IV–D–3–b. Negative effects.

"Section IV–D–3–b–(1). Is there any evidence of adventitial spread of transduced material? Was any tumor/normal tissue obtained after transduced material was administered? Was a post mortem obtained? Was there any sign of gonadal transfer of genetic material? By what criteria?

"Section IV–D–3–b–(2). Is there any evidence of generation of replication competent virus related to gene transfer procedure in patients?

"Section IV–D–3–b–(3). What toxicity was seen? Local, at injection site, systemic, any evidence of allergy/hypersensitivity/autoimmunity to the administered products?

"Section IV–D–3–b–(4). Is there evidence of deterioration of the disease state in relation to therapy?

"Section IV–D–3–b–(5). Is there any evidence of effects on other genes?

"Section IV–D–3–b–(6). Are there problems that have occurred that you did not anticipate prior to starting the protocol? What are these? Have they resulted in a change in your procedures?

"Section IV–D–4. Patient Accrual Data.

"Section IV–D–4–a. How many patients were considered for entry on study?

"Section IV–D–4–b. For those who were rejected, what were the reasons?

"Section IV–D–4–b–(1). Unavailability of tissue for transduction?

"Section IV–D–4–b–(2). Lack of ability to transduce tissue?

"Section IV–D–4–b–(3). Was that transduced tissue unable to be used? If not, give reason.

"Section IV–D–4–b–(4). Patient/physician refusal to participate?

"Section IV–D–4–b–(5). Other reasons not accepted in protocol?

"Section IV–D–4–c. How many patients were actually entered?

"Section IV–D–4–c–(1). Upon review, were all these patients eligible? If not, give reasons why not.

"Section IV–D–4–d. Provide a coded list of patients on study along with their on-study dates, off-study dates, and reason for being taken off study.

"Section IV–D–4–e. Are your patient accrual goals being met in a timely fashion? If not, why not.

"Section IV–D–5. Have any publications (abstracts or articles) resulted from this work? If so, provide reprints.

VIII. Amend Introduction, Section IV–B and V of the Points to Consider Regarding Review by the Human Gene Therapy Subcommittee; Amend Sections III–A and IV–C of the NIH Guidelines Regarding Publishing Notice of Meetings and Proposed Actions in the Federal Register

At the Human Gene Therapy Subcommittee meeting on July 30–31, 1991, the subcommittee requested that the Working Group on the Future Role of the Recombinant DNA Advisory Committee prepare a report about the feasibility of merging the Human Gene Therapy Subcommittee and the Recombinant DNA Advisory Committee.

This request was published for comment in the **Federal Register** on November 4, 1991 (56 FR 56415).

The Human Gene Therapy Subcommittee received a report from this working group during its meeting on November 21–22, 1991 which recommended that: (i) All eligible Human Gene Therapy Subcommittee members be added to the Recombinant DNA Advisory Committee as full voting members; or (ii) all of the Human Gene Therapy Subcommittee members be added to the Recombinant DNA Advisory Committee as non-voting members; or (iii) joint meetings would be held in which the subcommittee would vote on the proposed action first, followed by the full Recombinant DNA Advisory Committee.

During the meeting, the following motion passed by a vote of 11 in favor, 2 opposed, and no abstentions:

"We move to recommend to the Recombinant DNA Advisory Committee, that its subcommittee, the Human Gene Therapy Subcommittee, be merged into the parent committee. The number of meetings per year of the Recombinant DNA Advisory Committee would increase to four per year. There would be a transition period of one year in which the Recombinant DNA Advisory Committee would begin to review proposed actions as the sole review group with the following provisions: (i) The Human Gene Therapy Subcommittee would codify a set of guidelines for shortening the review process, and (ii) the eligible members of the Human Gene Therapy Subcommittee would be brought onto the Recombinant DNA Advisory Committee as full voting members in keeping with the nomination process for Federal Advisory Committees."

The Human Gene Therapy Subcommittee forwarded the proposal to the Recombinant DNA Advisory Committee for consideration during the February 10–11, 1992, meeting.

In a letter dated December 23, 1991, Dr. Nelson Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Maryland, is making a request to enable the above transition to proceed more efficiently. His letter states:

"* * * the Office of Recombinant DNA Activities (ORDA) is requesting that the following amendments be made to: (i) Sections III–A, IV–C–1–b–(1), IV–C–2, IV–C–3–b–(1), and IV–C–3–b–(2) to have the 30 day notice for Notice of Meeting and Proposed Actions be changed to a 15 day notice; and (ii) the *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects* in the sections of Introduction, IV–B, V, and the *NIH Guidelines*, Appendix D–XV, to have the Human Gene Therapy Subcommittee reviewing the human gene protocols changed to the Recombinant DNA Advisory Committee.

"ORDA is proposing that if the RAC votes to approve the recommendation to merge the HGTS with the parent committee and to increase the number of meetings per year, that the following changes must be made to amend the *National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules:*

"I. Notice of Meeting and Proposed Actions.

"The *NIH Guidelines* states that a 30 day Notice of Meeting and Notice of Proposed Action be published in the **Federal Register** for public comment. Under the Federal Advisory Committee Act, only a 15 day notice is required. The recommendation being forwarded by the HGTS to the RAC for approval would require an increase in the number of meetings per year. To more efficiently process the required paperwork prior to each meeting, the 30 day notice needs to be changed to a 15 day notice. It is proposed that the following changes be made:

'Section III–A. Experiments that Require RAC Review and NIH and IBC Approval Before Initiations.

'Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH, the publication of the Proposal in the **Federal Register** for

fifteen days of comment, review by the RAC, and specific approval by NIH.

'Section IV–C–1–b–(1). Major Actions. To execute major actions the Director, NIH, must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the **Federal Register** at least 15 days before the meeting, and the Director, NIH, will also publish the proposed action the **Federal Register** for comment at least 15 days before the meeting. In addition, the Director's proposed decision, at his/her discretion, may be published in the **Federal Register** for 15 days of comment before final action is taken.

'Section IV–C–2. Recombinant DNA Advisory Committee. * * * All meetings of the RAC will be announced in the **Federal Register**, including tentative agenda items, 15 days in advance of the meeting with final agendas (if modified) available at least 72 hours before the meeting.

'Section IV–C–3–b–(1). Announcements of RAC meetings and agendas at least 15 days in advance;

'Section IV–C–3–b–(2). Proposed major actions of the type falling under Section IV–C–1–b–(1) at least 15 days prior to the RAC meeting at which they will be considered; and * * *'

"II. Review of Human Gene Therapy/Transfer Protocols.

"The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA into the Genome of Human Subjects document (**Federal Register** of March 1, 1990) and the *NIH Guidelines* need to be amended to reflect exclusive review of protocols by the Recombinant DNA Advisory Committee. The *Points to Consider* will be amended as follows:

'Introduction. RAC consideration of each proposal will be on a case-by-case basis and will follow publication of a precis of the proposal in the **Federal Register**, and an opportunity for public comment.

'Section IV–B. If the change has been approved by the relevant IRB, and IBC, then the Chair of the Recombinant DNA Advisory Committee may give approval. It is expected that the Chairs will consult with one or more members of the committee, as necessary.

'Section V. Minor Modifications. A minor change in protocol approved by the Recombinant DNA Advisory Committee is a change that does not significantly alter the basic design of a protocol and that does not increase risk to the subjects.' "

IX. Amend Appendices B–I–B–1 and B–I–B–2 of the NIH Guidelines regarding the Bacterial Order, Actinomycetales

In a written request dated April 15, 1991, Dr. Diane O Fleming of Merck & Co., Inc., Somerset, New Jersey, requested that only pathogenic genera and species of the bacterial order, *Actinomycetales*, be included in Appendix B–I–B–1 of the *NIH Guidelines*.

It was proposed that the following pathogens be included in the list of Bacterial Agents in appendix B–I–B–1 of the *NIH Guidelines* as follows:

Actinomadura madurae
Actinomadura pelletieri
Actinomyces bovis
Actinomyces israelii
Nocardia asteroides
Nocardia brasiliensis

In appendix B–I–B–2, the entry under *Actinomycetes* would be deleted.

This request was reviewed at the Recombinant DNA Advisory Committee meeting on May 30–31, 1991. Following a discussion there was agreement that the *Actinomyces* should be reclassified as bacteria and removed from the list of fungi. However, there was disagreement about the number of species to be listed as pathogens. The number was thought to be considerably larger than the six species proposed for inclusion. Dr. Fleming was asked to consult with leading experts in the field and return with a revised list of pathogens, to be reviewed at the Recombinant DNA Advisory Committee meeting on October 7–8, 1991.

This request was published for comment in the **Federal Register** on September 3, 1991 (56 FR 43686).

During the October 7–8, 1991, Recombinant DNA Advisory Committee meeting, a motion was passed by a vote of 19 in favor, 0 opposed, and no abstentions to create an *ad hoc* working group within the Recombinant DNA Advisory Committee with outside consultants to provide an amended list of pathogens.

X. Amend Appendices B–I–C–1 and B–I–B–1 in the NIH Guidelines regarding Mycobacterium avium

In a letter dated December 18, 1991, Dr. William R. Jacobs, Jr., of the Albert Einstein College of Medicine, Bronx, New York, requested lowering the classification of *Mycobacterium avium* from a Class III bacterial agent to a Class II bacterial agent. *M. avium* would move from appendix B–I–C–1 to appendix B–I–B–1 in the *NIH Guidelines*.

XI. Other Matters To Be Considered by the Committee

Attendance by the public will be limited to space available. Members of the public wishing to speak at this meeting may be given such opportunity at the discretion of the Chair.

Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, National Institutes of Health, Building 31, room 4B11, Bethesda, Maryland 20892, Phone (301) 496–9838, FAX (301) 496–9839, will provide materials to be discussed at this meeting, a roster of committee members, and substantive program information. A summary of the meeting will be available at a later date.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) 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 not to be 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.

Dated: December 24, 1991.

Jay Moskowitz,

Associate Director for Science Policy and Legislation, NIH.

[FR Doc. 92–108 Filed 1–2–92; 8:45 am]

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