

Drive, Room 4132, Bethesda, MD 20892, (301) 594-7241.

*Name of SEP:* Microbiological and Immunological Sciences.

*Date:* June 23, 1995.

*Time:* 8 a.m.

*Place:* Holiday Inn, Bethesda, MD.

*Contact Person:* Dr. Jean Hickman, Scientific Review Administrator, 6701 Rockledge Drive, Room 4178, Bethesda, MD 20892, (301) 594-7078.

*Name of SEP:* Behavioral and Neurosciences.

*Date:* June 28, 1995.

*Time:* 1 p.m.

*Place:* NIH, Rockledge II, Room 5198, Telephone Conference.

*Contact Person:* Dr. Peggy McCardle, Scientific Review Admin., 6701 Rockledge Drive, Room 5198, Bethesda, MD 20892, (301) 435-1258.

*Name of SEP:* Behavioral and Neurosciences.

*Date:* July 6, 1995.

*Time:* 12 noon.

*Place:* NIH, Rockledge II, Room 5198, Telephone Conference.

*Contact Person:* Dr. Peggy McCardle, Scientific Review Admin., 6701 Rockledge Drive, Room 5198, Bethesda, MD 20892, (301) 435-1258.

*Purpose/Agenda:* To review Small Business Innovation Research Program grant applications.

*Name of SEP:* Behavioral and Neurosciences.

*Date:* July 10, 1995.

*Time:* 8:30 a.m.

*Place:* Holiday Inn, Chevy Chase, MD.  
*Contact Person:* Dr. Peggy McCardle, Scientific Review Admin., 6701 Rockledge Drive, Room 5198, Bethesda, MD 20892, (301) 435-1258.

The meetings will be closed in accordance with the provisions set forth in secs. 552b(c)(4) and 552b(c)(6), Title 5, U.S.C. Applications and/or proposals and the discussions could reveal confidential trade secrets or commercial property such as patentable material and personal information concerning individuals associated with the applications and/or proposals, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

This notice is being published less than 15 days prior to the meeting due to the urgent need to meet timing limitations imposed by the grant review cycle.

(Catalog of Federal Domestic Assistance Program Nos. 93.306, 93.333, 93.337, 93.393-93.396, 93.837-93.844, 93.846-93.878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: April 21, 1995.

**Susan K. Feldman,**

*Committee Management Officer, NIH.*

[FR Doc. 95-10377 Filed 4-26-95; 8:45 am]

BILLING CODE 4140-01-M

### National Institute on Drug Abuse; Notice of Meeting

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the

National Advisory Council on Drug Abuse, National Institute on Drug Abuse on May 16-17, 1995.

On May 16, from 9 a.m. to 5 p.m., the meeting will be held at the National Institutes of Health, Building 1, Wilson Hall, 9000 Rockville Pike, Bethesda, Maryland 20892. This portion of the meeting will be open to the public for announcements and reports of administrative, legislative, and program developments in the drug abuse field. Attendance by the public will be limited to space available.

On May 17, from 9 a.m. to 1 p.m., the meeting will be held at the Parklawn Building, Conference Room E, 5600 Fishers Lane, Rockville, MD 20857. In accordance with provisions set forth in sec. 552b(c)(4) and 552b(c)(6), Title 5, U.S.C. and sec. 10(d) of Pub. L. 92-463, this portion of the meeting will be closed to the public for the review, discussion, and evaluation of grant applications. These applications and the discussions could reveal confidential trade secrets or commercial property such as patentable material and personal information concerning individuals associated with the applications, disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

A summary of the meeting and a roster of committee members may be obtained from Ms. Camilla L. Holland, NIDA Committee Management Officer, National Institutes of Health, Parklawn Building, Room 10-42, 5600 Fishers Lane, Rockville, Maryland 20857 (301/443-2755).

Substantive program information may be obtained from Ms. Eleanor C. Friedenber, Room 10-42, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857, (301/443-2755).

Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should contact the contact person named above in advance of the meeting.

(Catalog of Federal Domestic Assistance Program Numbers: 93.277, Drug Abuse Research Scientist Development and Research Scientist Awards; 93.278, Drug Abuse National Research Service Awards for Research Training; 93.279, Drug Abuse Research Programs.)

Dated: April 24, 1995.

**Susan K. Feldman,**

*Committee Management Officer, NIH.*

[FR Doc. 95-10378 Filed 4-26-95; 8:45 am]

BILLING CODE 4140-01-M

### National Library of Medicine; Notice of Meeting of the Biomedical Library Review Committee

Pursuant to Pub. L. 92-463, notice is hereby given of the meeting of the Biomedical Library Review Committee on June 14-15, 1995, convening at 8:30 a.m. in the Board Room of the National Library of Medicine, Building 38, 8600 Rockville Pike, Bethesda, Maryland.

The meeting on June 14 will be open to the public from 8:30 a.m. to approximately 11 a.m. for the discussion of administrative reports and program developments. Attendance by the public will be limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should contact Dr. Roger W. Dahlen at 301-496-4221 two weeks before the meeting.

In accordance with provisions set forth in secs. 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and sec. 10(d) of Pub. L. 92-463, the meeting on June 14 will be closed to the public for the review, discussion, and evaluation of individual grant applications from 11 a.m. to approximately 5 p.m., and on June 15 from 8:30 a.m. to adjournment. These applications and the discussion could reveal confidential trade secrets or commercial property, such as patentable material, and personal information concerning individuals associated with the applications, disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Dr. Roger W. Dahlen, Scientific Review Administrator, and Chief, Biomedical Information Support Branch, Extramural Programs, National Library of Medicine, 8600 Rockville Pike, Bethesda, Maryland 20894, telephone number: 301-496-4221, will provide summaries of the meeting, rosters of the committee members, and other information pertaining to the meeting.

(Catalog of Federal Domestic Assistance Program No. 93.879—Medical Library Assistance, National Institutes of Health.)

Dated: April 21, 1995.

**Susan K. Feldman,**

*Committee Management Officer, NIH.*

[FR Doc. 95-10379 Filed 4-26-95; 8:45 am]

BILLING CODE 4140-01-M

### 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 (59 FR 34496 and 59 FR 40170).

**SUMMARY:** This notice sets forth an action to be taken by the Director, National Institutes of Health (NIH), under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496 and 59 FR 40170).

**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, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838.

**SUPPLEMENTARY INFORMATION:** Today's action is being promulgated under the NIH Guidelines for Research Involving Recombinant DNA Molecules. This proposed action was published for comment in the **Federal Register** of February 8, 1995 (60 FR 7630), and reviewed and recommended for approval by the NIH Recombinant DNA Advisory Committee (RAC) at its meeting on March 6-7, 1995.

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

#### *A. Amendments to Sections I, III, IV, V, and Appendices C, F, G, I, and M of the NIH Guidelines Regarding Consolidated Review of Human Gene Transfer Protocols*

On July 18-19, 1994, the National Task Force on AIDS Drug Development held an open meeting for the purpose of identifying barriers to AIDS Drug Discovery that included a proposal to streamline the dual review process for human gene transfer experiments. Members of the Task Force recommended a consolidated review process to enhance interactions between the NIH and the Food and Drug Administration (FDA). As a result of the Task Force's deliberations, recommendations were adopted in order to eliminate any unnecessary overlap between the NIH and FDA review of human gene transfer proposals. Both Drs. Varmus and Kessler noted that their respective agencies would cooperate fully to effect the changes necessary to implement these recommendations.

The NIH and FDA proposed that the RAC become advisory to both the NIH Director and the FDA Commissioner with regard to the review of human gene transfer protocols. In the interest of maximizing the resources of both agencies and simplifying the method and period of review for research protocols involving human gene

transfer, the NIH and FDA should institute an interagency consolidated review process that incorporates the following principal elements:

(1) All human gene transfer protocols shall be submitted directly to the FDA. Submission will be in the format required by the FDA and the same format will be used by the RAC when public review is deemed necessary.

(2) Upon receipt, FDA review will proceed. The NIH/ORDA staff will simultaneously evaluate the protocol for possible RAC review.

(3) Factors which may contribute to the need for RAC review include: (a) New vectors/new gene delivery systems, (b) new diseases, (c) unique applications of gene transfer, and (d) other issues that require further public review.

(4) If either the NIH/ORDA or FDA decides that a proposal should be reviewed by the RAC, the proposal will be forwarded to the RAC primary reviewers immediately. Whenever possible, Principal Investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required. (RAC reviewed applications will be distributed to RAC members approximately four weeks prior to the next quarterly RAC meeting.)

(5) Semiannual data reporting procedures will remain the responsibility of NIH (ORDA). Semiannual data reports will be reviewed by the RAC in a public forum.

In a letter dated August 2, 1994, Dr. Nelson A. Wivel, Director, ORDA, NIH, provided the RAC with background information regarding the National Task Force on AIDS Drug Development meeting, and proposed amendments to Sections I, III, IV, V, and Appendices C, F, G, I, and M of the NIH Guidelines, to reflect the proposed consolidated review process. The revised review process was proposed as follows:

(1) Investigators will be required to submit all human gene transfer proposals directly to the FDA in the format required by the FDA; therefore, investigators will no longer be required to provide a separate submission to NIH/ORDA for RAC review. The FDA Division of Cellular and Gene Therapies will forward a copy of each submission to NIH/ORDA. Both the FDA Division of Cellular and Gene Therapies and NIH/ORDA will simultaneously evaluate each proposal for the necessity for RAC review. Whenever possible, the investigators will be notified within 15 working days following receipt of the submission regarding the necessity for RAC review.

(2) If either the NIH/ORDA or FDA decides that a proposal should undergo

RAC review, the proposal will be forwarded to the RAC primary reviewers immediately. Any protocol submitted less than 8 weeks before a RAC meeting will be reviewed at the following quarterly RAC meeting.

(3) The RAC will make recommendations regarding approval/disapproval of protocols, including any relevant stipulations, to the NIH Director. The NIH Director will review, approve, and transmit the RAC's recommendations/stipulations to the FDA Commissioner.

(4) The FDA will consider such recommendations/stipulations and will be responsible for completion of review. The RAC and NIH/ORDA will no longer have the responsibility for reviewing material submitted for Accelerated Review or for the review of minor modifications to human gene transfer protocols.

These proposed actions were discussed during the September 12-13, 1994, RAC meeting (published for public comments in the **Federal Register**, August 23, 1994 (59 FR 43426)). Dr. Philip Noguchi, Director, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, FDA, provided additional suggestions regarding the proposed review process including FDA adoption of the Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider), of the NIH Guidelines. The FDA will require investigators to submit the Points to Consider with their proposed experiments. A lengthy discussion ensued involving RAC members' concerns and suggestions regarding the consolidated review process.

Dr. Noguchi submitted the following compromise proposal regarding the NIH/FDA consolidated review of human gene transfer experiments:

(1) Appendix M, Points to Consider, will not be deleted from the NIH Guidelines. The NIH Guidelines will be modified to provide for submission of Appendix M, Points to Consider, directly to the FDA prior to IND submission. The FDA will update their guidance documents in a similar manner. When necessary, the RAC will continue to be responsible for modifying Appendix M, Points to Consider.

(2) The RAC, NIH/ORDA, and FDA will decide on the necessity for full RAC review. The submitted Appendix M, Points to Consider, will be publicly available for all human gene transfer

submissions even if RAC review is not required.

(3) The RAC and FDA will broaden their scope of review for human gene transfer proposals to jointly and prospectively address global issues on a regular basis, e.g., ethical consideration in the implementation of gene therapy patient registry, access for "orphan" genetic disease patients to therapies, criteria for prenatal gene therapy, and transgenic technology for xenotransplantation.

(4) The RAC, NIH/ORDA, and FDA will establish a working group to enhance data monitoring efforts.

(5) A RAC, NIH/ORDA, and FDA working group will be established to propose long-term consolidation. The working group will have input from public, academic, and corporate sources.

The RAC approved a motion to (1) accept the FDA proposal submitted by Dr. Noguchi; (2) adopt the Categories for Accelerated Review that were approved by the RAC at its March 3-4, 1994, meeting as guidelines for proposals that will not require RAC review; (3) establish a working group to examine the review process for human gene transfer protocols (in response to Dr. Varmus' request to establish such a group); (4) the RAC prefers that any stipulation requirements should be satisfactorily met prior to forwarding its recommendation for approval to the NIH Director; and (5) accept the proposed amendments to the NIH Guidelines to reflect this revised consolidated review process (including acceptance of a revised Appendix M and incorporation of minor editorial changes). The motion was approved by a vote of 15 in favor, 0 opposed, and 1 abstention.

On October 26, 1994, NIH/ORDA forwarded the revised actions to the NIH Director for approval and the FDA Commissioner for concurrence. FDA legal counsel expressed concern that implementation of these actions would require amendment to the FDA Investigational New Drug Application Regulations (21 CFR Part 312) to accommodate the release of proprietary information. To resolve this concern, a waiver for release of information from the FDA to the NIH was proposed. While the NIH Guidelines could require such a waiver for NIH-funded investigators, it would be voluntary for others submitting proposed human gene transfer experiments to the FDA. The NIH expressed concern that failure to comply with voluntary waiver procedures may result in the loss of critical information necessary to maintain: (1) The human gene therapy

database, (2) "real-time" reporting of serious adverse events, and (3) comprehensive overview (by category) by the RAC in a public forum. Public review and access to submission, review, and follow-up information is critical to the safe and focused advancement of human gene therapy research. As a result of these concerns, the NIH and FDA agreed on a compromise proposal that would accommodate the single submission format proposed at the July 18-19, 1994, meeting of the National Task Force on AIDS Drug Development, yet maintain public access to critical information and "real-time" reporting of adverse events. The compromise proposal involves simultaneous submission of human gene transfer protocols to both NIH and the FDA in a single submission format. This format includes (but is not limited to) the documentation described in Appendices M-I through M-V, of the NIH Guidelines. NIH/ORDA and the FDA will simultaneously evaluate the proposal regarding the necessity for RAC review.

These revisions to the consolidated review process were discussed during the March 6-7, 1995, RAC meeting (published for public comments in the **Federal Register**, February 8, 1995 (60 FR 7630)). The following motions were made in response to the February 24, 1995, comments submitted by Ms. Sheryl Osborne of Viagene, Inc., San Diego, California: (1) A motion to retain the current requirement for obtaining Institutional Review Board (IRB) approval prior to RAC submission. A friendly amendment was made and accepted that ORDA should notify the Director of the Office for Protection from Research Risks regarding the necessity for IRB adherence to the detailed questions contained in Appendices M-II through M-V of the NIH Guidelines (Informed Consent issues). The amended motion was approved by a vote of 17 in favor, 0 opposed, and 1 abstention. (2) A motion was made that the RAC should continue to review and approve Phase I follow-up studies, i.e., Phase II and Phase III trials. Such studies may be submitted through the Accelerated Review process; however, the RAC retains the option to require full RAC review. The motion passed by a vote of 18 in favor, 0 opposed, and no abstentions.

The RAC approved a motion to approve the proposed amendments to Sections I, III, IV, V, and Appendices C, F, G, I, and M of the NIH Guidelines regarding NIH and FDA consolidated review of human gene transfer protocols, by a vote of 18 in favor, 0 opposed, and no abstentions.

The actions are detailed in Section II—Summary of Actions. I accept these recommendations, and the NIH Guidelines will be amended accordingly.

## II. Summary of Actions

### A. Amendments to Section I, Scope of the NIH Guidelines

The amended version of Section I-A, Purpose, reads:

#### Section I-A. Purpose

The purpose of the NIH Guidelines is to specify practices for constructing and handling: (i) Recombinant deoxyribonucleic acid (DNA) molecules, and (ii) organisms and viruses containing recombinant DNA molecules.

Section I-A-1. 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 approvals, 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 (see exception in Section I-A-1-a).

Section I-A-1-a. In the interest of maximizing the resources of both the NIH and the Food and Drug Administration (FDA) and simplifying the method and period for review, research proposals involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) will be considered through a consolidated review process involving both the NIH and the FDA. Submission of human gene transfer proposals will be in the format described in Appendices M-I through M-V of the Points to Consider. Investigators must simultaneously submit their human gene transfer proposal to both the NIH and the FDA in a single submission format. This format includes (but is not limited to) the documentation described in Appendices M-I through M-V, of the Points to Consider. NIH/ORDA and the FDA will simultaneously evaluate the proposal regarding the necessity for RAC review.

### B. Amendments to Section III, Experiments Covered by the NIH Guidelines

The amended version of Section III beginning paragraphs reads:

This section describes five categories of experiments involving recombinant DNA: (i) Those that require Institutional Biosafety Committee (IBC) approval, RAC review, and NIH Director approval before initiation (see Section III-A), (ii) those that require NIH/ORDA and Institutional Biosafety Committee approval before initiation (see Section III-B), (iii) those that require Institutional Biosafety Committee approval before initiation (see Section III-C), (iv) those that require Institutional Biosafety Committee notification simultaneous with initiation (see Section III-D), and (v) those that are exempt from the NIH Guidelines (see Section III-E).

**Note:** If an experiment falls into either Section III-A or Section III-B and one of the other categories, the rules pertaining to Section III-A or Section III-B shall be followed. If an experiment falls into Section III-E and into either Sections III-C or III-D categories as well, the experiment is considered exempt from the NIH Guidelines.

Any change in containment level, which is different from those specified in the NIH Guidelines, may not be initiated without the express approval of NIH/ORDA (see Minor Actions, Section IV-C-1-b-(2) and its subsections).

The amended version of Section III-A reads:

Section III-A. Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation (see Section IV-C-1-b-(1)).

Section III-A-1. Major Actions Under the NIH Guidelines

Experiments considered as Major Actions under the NIH Guidelines cannot be initiated without submission of relevant information on the proposed experiment to the Office of Recombinant DNA Activities, National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838, the publication of the proposal in the **Federal Register** for 15 days of comment, review by the RAC, and specific approval by the NIH (see Appendix M for submission requirements on human gene transfer experiments). The containment conditions or stipulation requirements for such experiments will be recommended by the RAC and set by the NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D which may be obtained from the Office of Recombinant DNA Activities,

National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838.

Section III-A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V-B), if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by the RAC.

Section III-A-2. Human Gene Transfer Experiments

Investigators must simultaneously submit their human gene transfer proposal to both the NIH and the FDA in a single submission format. This format includes (but is not limited to) the documentation described in Appendices M-I through M-V, of the Points to Consider. The NIH/ORDA and the FDA will simultaneously evaluate the proposal regarding the necessity for RAC review.

Factors that may contribute to the necessity for RAC review include: (i) New vectors/new gene delivery systems, (ii) new diseases, (iii) unique applications of gene transfer, and (iv) other issues considered to require further public discussion. Among the experiments that may be considered exempt from RAC review are those determined by the NIH/ORDA and FDA not to represent possible risk to human health or the environment (see Appendix M-VII, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review). Whenever possible, investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required. In the event that NIH/ORDA or the FDA require RAC review of the submitted proposal, the documentation described in Appendices M-I through M-V of the Points to Consider, will be forwarded to the RAC primary reviewers for evaluation. RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed. The RAC and FDA prefer that information provided in response to Appendix M contain no proprietary data or trade secrets, enabling all aspects of the review to be open to the public. The RAC will recommend approval or disapproval of the reviewed proposal to the NIH Director. In the event that a proposal is contingently approved by the RAC, the RAC prefers that the conditions be satisfactorily met before the RAC's recommendation for approval is submitted to the NIH Director. The NIH Director's decision on the

submitted proposal will be transmitted to the FDA Commissioner and considered as a Major Action by the NIH Director.

The amended version of Section III-B reads:

Section III-B. Experiments That Require NIH/ORDA and Institutional Biosafety Committee Approval Before Initiation

Section III-B-1. Experiments Involving the Cloning of Toxin Molecules with LD<sub>50</sub> of Less than 100 Nanograms per Kilogram Body Weight

Deliberate formation of recombinant DNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD<sub>50</sub> of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, and Shigella dysenteriae neurotoxin). Specific approval has been given for the cloning in Escherichia coli K-12 of DNA containing genes coding for the biosynthesis of toxic molecules which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight. Specific experiments already approved under this section may be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838.

Section III-B-1-(a). Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH/ORDA. The containment conditions for such experiments will be determined by NIH/ORDA in consultation with ad hoc experts. Such experiments require Institutional Biosafety Committee approval before initiation (see Section IV-B-2-b-(1)).

The following section, Section III-C-7, is deleted:

Section III-C-7. Human Gene Transfer Experiments Not Covered by Sections III-A-2, III-B-2, III-B-3, and Not Considered Exempt under Section V-U

Certain experiments involving the transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into one or more human subjects that are not covered by Sections III-A-2, III-B-2, III-B-3, and that are not considered exempt under Section V-U must be registered with NIH/ORDA. The relevant Institutional Biosafety Committee and Institutional Review Board must review and approve all experiments in this category prior to their initiation.

*C. Amendments to Section IV, Roles and Responsibilities*

In Section IV-B-4-b, Submissions by the Principal Investigator to the NIH/ORDA, the following sections are amended to read:

Section IV-B-4-b-(3). Petition NIH/ORDA, with concurrence of the Institutional Biosafety Committee, for approval to conduct experiments specified in Sections III-A-1 and III-B of the NIH Guidelines;

In Section IV-B-4-e, Responsibilities of the Principal Investigator During the Conduct of the Research, the following section is added:

Section IV-B-4-e-(5). Comply with semiannual data reporting and adverse event reporting requirements for NIH and FDA-approved human gene transfer experiments (see Appendix M-VIII, Reporting Requirements—Human Gene Transfer Protocols).

In Section IV-C-b-(1), Major Actions, the first paragraph is amended to read:

To execute Major Actions, the NIH Director shall seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the Notice of Meeting and Proposed Actions shall be published in the **Federal Register** at least 15 days before the RAC meeting. The NIH Director's decision/recommendation (at his/her discretion) may be published in the **Federal Register** for 15 days of comment before final action is taken. The NIH Director's final decision/recommendation, along with responses to public comments, shall be published in the **Federal Register**. The RAC and Institutional Biosafety Committee Chairs shall be notified of the following decisions:

Section IV-C-1-B-(1)-(e) is amended to read:

Section IV-C-1-b-(1)-(e). Recommendations made by the NIH Director to the FDA Commissioner regarding RAC-reviewed human gene transfer experiments (see Appendix M-VI-E, RAC Recommendations to the NIH Director);

Except for renumbering, the rest of the Section IV-C-1-B-(1) remains unchanged.

In Section IV-C-1-b-(2), Minor Actions, the following sections are deleted:

Section IV-C-1-b-(2)-(a). Reviewing and approving certain experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into one or more human subjects that qualify for the Accelerated Review process (see Section III-B-2);

Section IV-C-1-b-(2)-(b). Reviewing and approving minor changes to human

gene transfer protocols under Section III-A-2 and III-B-2;

The rest of the section has been renumbered.

Section IV-C-3, Office of Recombinant DNA Activities (ORDA), will be amended to read:

Section IV-C-3. Office of Recombinant DNA Activities (ORDA)

ORDA shall serve as a focal point for information on recombinant DNA activities and provide advice to all within and outside NIH including institutions, Biological Safety Officers, Principal Investigators, Federal agencies, state and local governments, and institutions in the private sector. ORDA shall carry out such other functions as may be delegated to it by the NIH Director. ORDA's responsibilities include (but are not limited to) the following:

Section IV-C-3-a. Evaluating human gene transfer protocols for the necessity for RAC review (see Appendix M-VI-A);

Section IV-C-3-b. Serving as the focal point for data management of NIH and FDA approved human gene transfer protocols (see Appendix M-VIII, Reporting Requirements—Human Gene Transfer Protocols);

Section IV-C-3-c. Administering the semiannual data reporting requirements (and subsequent review) for human gene transfer experiments, including experiments that are reviewed solely by the FDA (see Appendix M-VI, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review);

Section IV-C-3-d. Maintaining an inventory of NIH and FDA-approved human gene transfer experiments (including subsequent modifications);

Section IV-C-3-e. Reviewing and approving experiments in conjunction with ad hoc experts involving the cloning of genes encoding for toxin molecules that are lethal for vertebrates at an LD<sub>50</sub> of less than or equal to 100 nanograms per kilogram body weight in organisms other than *Escherichia coli* K-12 (see Section III-B-1 and Appendices F-I and F-II);

Section IV-C-3-f. Serving as the executive secretary of the RAC;

Section IV-C-3-g. Publishing in the **Federal Register**:

Section IV-C-3-g-(1). Announcements of RAC meetings and agendas at least 15 days in advance (NOTE—If the agenda for a RAC meeting is modified, ORDA shall make the revised agenda available to anyone upon request in advance of the meeting);

Section IV-C-3-g-(2). Proposed Major Actions (see Section IV-C-1-b-(1)) at least 15 days prior to the RAC meeting; and

Section IV-C-3-h. Reviewing and approving the membership of an institution's Institutional Biosafety Committee, and where it finds the Institutional Biosafety Committee meets the requirements set forth in Section IV-B-2 will give its approval to the Institutional Biosafety Committee membership;

*D. Amendments to Section V, Footnotes and References of Section I through IV*

The following sections are deleted:

Section V-U. Human studies in which the induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected, are not covered under Sections III-A-2, III-B-2, or III-B-3. Such studies may be initiated without RAC review and NIH approval if approved by another Federal agency.

Section V-V. For recombinant DNA experiments in which the intent is to modify stably the genome of cells of one or more human subjects (see Sections III-A-2, III-B-2, and III-B-3).

Section V-W has been renumbered to Section V-U:

Section V-U. In accordance with accepted scientific and regulatory practices of the discipline of plant pathology, an exotic plant pathogen (e.g., virus, bacteria, or fungus) is one that is unknown to occur within the U.S. (see Section V-R). Determination of whether a pathogen has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of plant diseases, crops, and ecosystems in the geographic area of the research.

*E. Amendments to Appendix C, Exemptions under Section III-E-6*

The following sections are amended to read:

Appendix C-I-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

#### Appendix C-II-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

#### Appendix C-III-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

#### Appendix C-IV-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

#### Appendix C-V-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

Appendix C-VI-A-1. The NIH Director, with advice of the RAC, may revise the classification for the purposes of these NIH Guidelines (see Section IV-C-1-b-(2)-(b)).

#### *E. Amendments to Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates*

The following sections are amended, due to reference changes, to read:

#### Appendix F-I. General Information

. . . The results of such tests shall be forwarded to NIH/ORDA, which will consult with ad hoc experts, prior to inclusion of the molecules on the list (see Section IV-C-1-b-(2)-(c)).

#### Appendix F-III. Cloning of Toxic Molecule Genes in Organisms Other Than *Escherichia coli* K-12

Requests involving the cloning of genes coding for toxin molecules for vertebrates at an LD<sub>50</sub> of <100 nanograms per kilogram body weight in host-vector systems other than *Escherichia coli* K-12 will be evaluated by NIH/ORDA in consultation with ad hoc toxin experts (see Sections III-B-1 and IV-C-1-b-(2)-(c)).

#### *F. Amendments to Appendix G, Physical Containment*

The following sections are amended, due to reference changes, to read:

#### Appendix G-II. Physical Containment Levels.

. . . Consideration will be given by the NIH Director, with the advice of the RAC, to other combinations which achieve an equivalent level of containment (see Section IV-C-1-b-(2)-(a)).

#### *G. Amendments to Appendix I, Biological Containment*

The following sections are amended, due to reference changes, to read:

#### Appendix I-II-A. Responsibility

. . . Proposed host-vector systems will be reviewed by the RAC (see Section IV-C-1-b-(1)-(f)). . . Minor modifications to existing host-vector systems (i.e., those that are of minimal or no consequence to the properties relevant to containment) may be certified by the NIH Director without prior RAC review (see Section IV-C-1-b-(2)-(f)). . . The NIH Director may rescind the certification of a host-vector system (see Section IV-C-1-b-(2)-(g)).

#### *H. Amendments to Appendix M, The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider)*

Appendix M is amended to read:  
Appendix M. The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider)  
Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant DNA research from the NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M.

The acceptability of human somatic cell gene therapy has been addressed in several public documents as well as in numerous academic studies. In November 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report, *Splicing Life*, which resulted from a two-year process of public deliberation and hearings. Upon release of that report, a U.S. House of Representatives subcommittee held three days of public hearings with witnesses from a wide range of fields from the biomedical and social sciences to theology, philosophy, and law. In December 1984, the Office of Technology Assessment released a background paper, *Human Gene Therapy*, which concluded: civic,

religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene therapy of somatic cells in humans for specific genetic diseases. Somatic cell gene therapy is seen as an extension of present methods of therapy that might be preferable to other technologies. In light of this public support, the Recombinant DNA Advisory Committee (RAC) is prepared to consider proposals for somatic cell gene transfer.

The RAC will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cell gene therapy is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject's somatic cells. Germ line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring.

In the interest of maximizing the resources of both the NIH and the Food and Drug Administration (FDA) and simplifying the method and period for review, research proposals involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) will be considered through a consolidated review process involving both the NIH and the FDA. Submission of human gene transfer proposals will be in the format described in Appendices M-I through M-V of the Points to Consider. Investigators must simultaneously submit their human gene transfer proposal to both the NIH and the FDA in a single submission format. This format includes (but is not limited to) the documentation described in Appendices M-I through M-V of the Points to Consider. NIH/ORDA and the FDA will simultaneously evaluate the proposal regarding the necessity for RAC review.

Factors that may contribute to the necessity for RAC review include: (i) New vectors/new gene delivery systems, (ii) New diseases, (iii) unique applications of gene transfer, and (iv) other issues considered to require further public discussion. Among the experiments that may be considered exempt from RAC review are those determined by the NIH/ORDA and FDA not to represent possible risk to human health or the environment (see Appendix M-VII, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review). Whenever possible, investigators will be notified within 15 working days following

receipt of the submission whether RAC review will be required. In the event that NIH/ORDA and the FDA require RAC review of the submitted proposal, the documentation described in Appendices M-I through M-V of the Points to Consider, will be forwarded to the RAC primary reviewers for evaluation. RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed. The RAC and FDA prefer that information provided in response to Appendix M contain no proprietary data or trade secrets, enabling all aspects of the review to be open to the public. The RAC will recommend approval or disapproval of the reviewed proposal to the NIH Director. In the event that a proposal is contingently approved by the RAC, the RAC prefers that the conditions be satisfactorily met before the RAC's recommendation for approval is submitted to the NIH Director. The NIH Director's decision on the submitted proposal will be transmitted to the FDA Commissioner and considered as a Major Action by the NIH Director.

Public review of human gene transfer proposals will serve to inform the public about the technical aspects of the proposals as well as the meaning and significance of the research.

In its evaluation of human gene transfer proposals, the RAC, NIH/ORDA, and the FDA will consider whether the design of such experiments offers adequate assurance that their consequences will not go beyond their purpose, which is the same as the traditional purpose of clinical investigation, namely, to protect the health and well being of human subjects being treated while at the same time gathering generalizable knowledge. Two possible undesirable consequences of the transfer of recombinant DNA would be unintentional: (i) Vertical transmission of genetic changes from an individual to his/her offspring, or (ii) horizontal transmission of viral infection to other persons with whom the individual comes in contact.

Accordingly, Appendices M-I through M-V requests information that will enable the RAC, NIH/ORDA, and the FDA, to assess the possibility that the proposed experiment(s) will inadvertently affect reproductive cells or lead to infection of other people (e.g., medical personnel or relatives).

In recognition of the social concern that surrounds the subject of human gene transfer, the RAC, NIH/ORDA, and the FDA, will cooperate with other groups in assessing the possible long-term consequences of the proposal and related laboratory and animal

experiments in order to define appropriate human applications of this emerging technology.

Appendix M will be considered for revisions as experience in evaluating proposals accumulates and as new scientific developments occur. This review will be carried out periodically as needed.

#### Appendix M-I. Submission Requirements—Human Gene Transfer Proposals

Investigators must simultaneously submit the following material to both: (1) The Office of Recombinant DNA Activities (ORDA), National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838 (see exemption in Appendix M-IX-A); and (2) the Division of Congressional and Public Affairs, Document Control Center, HFM-99, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448. Proposals will be submitted in the following order: (1) Scientific abstract—1 page; (2) non-technical abstract—1 page; (3) Institutional Biosafety Committee and Institutional Review Board approvals and their deliberations pertaining to your protocol (the IBC and IRB may, at their discretion, condition their approval on further specific deliberation by the RAC); (4) Responses to Appendix M-II, *Description of the Proposal*—5 pages; (5) protocol (as approved by the local Institutional Biosafety Committee and Institutional Review Board)—20 pages; (6) Informed Consent document—approved by the Institutional Review Board (see Appendix M-III); (7) appendices (including tables, figures, and manuscripts); (8) curricula vitae—2 pages for each key professional person in biographical sketch format; and (9) three 3½ inch diskettes with the complete vector nucleotide sequence in ASCII format.

#### Appendix M-II. Description of the Proposal

Responses to this appendix should be provided in the form of either written answers or references to specific sections of the protocol or its appendices. Investigators should indicate the points that are not applicable with a brief explanation. Investigators submitting proposals that employ the same vector systems may refer to preceding documents relating to the vector sequence without having to rewrite such material.

#### Appendix M-II-A. Objectives and Rationale of the Proposed Research

State concisely the overall objectives and rationale of the proposed study. Provide information on the specific points that relate to whichever type of research is being proposed.

##### Appendix M-II-A-1. Use of Recombinant DNA for Therapeutic Purposes

For research in which recombinant DNA is transferred in order to treat a disease or disorder (e.g., genetic diseases, cancer, and metabolic diseases), the following questions should be addressed:

Appendix M-II-A-1-a. Why is the disease selected for treatment by means of gene therapy a good candidate for such treatment?

Appendix M-II-A-1-b. Describe the natural history and range of expression of the disease selected for treatment. What objective and/or quantitative measures of disease activity are available? In your view, are the usual effects of the disease predictable enough to allow for meaningful assessment of the results of gene therapy?

Appendix M-II-A-1-c. Is the protocol designed to prevent all manifestations of the disease, to halt the progression of the disease after symptoms have begun to appear, or to reverse manifestations of the disease in seriously ill victims?

Appendix M-II-A-1-d. What alternative therapies exist? In what groups of patients are these therapies effective? What are their relative advantages and disadvantages as compared with the proposed gene therapy?

##### Appendix M-II-A-2. Transfer of DNA for Other Purposes

Appendix M-II-A-2-a. Into what cells will the recombinant DNA be transferred? Why is the transfer of recombinant DNA necessary for the proposed research? What questions can be answered by using recombinant DNA?

Appendix M-II-A-2-b. What alternative methodologies exist? What are their relative advantages and disadvantages as compared to the use of recombinant DNA?

##### Appendix M-II-B. Research Design, Anticipated Risks and Benefits

###### Appendix M-II-B-1. Structure and Characteristics of the Biological System

Provide a full description of the methods and reagents to be employed for gene delivery and the rationale for their use. The following are specific points to be addressed:

Appendix M-II-B-1-a. What is the structure of the cloned DNA that will be used?

Appendix M-II-B-1-a-(1). Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete nucleotide sequence analysis or a detailed restriction enzyme map of the total construct.

Appendix M-II-B-1-a-(2). What regulatory elements does the construct contain (e.g., promoters, enhancers, polyadenylation sites, replication origins, etc.)? From what source are these elements derived? Summarize what is currently known about the regulatory character of each element.

Appendix M-II-B-1-a-(3). Describe the steps used to derive the DNA construct.

Appendix M-II-B-1-b. What is the structure of the material that will be administered to the patient?

Appendix M-II-B-1-b-(1). Describe the preparation, structure, and composition of the materials that will be given to the patient or used to treat the patient's cells: (i) If DNA, what is the purity (both in terms of being a single DNA species and in terms of other contaminants)? What tests have been used and what is the sensitivity of the tests? (ii) If a virus, how is it prepared from the DNA construct? In what cell is the virus grown (any special features)? What medium and serum are used? How is the virus purified? What is its structure and purity? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials (for example, VL30 RNA, other nucleic acids, or proteins) or contaminating viruses (both replication-competent or replication-defective) or other organisms in the cells or serum used for preparation of the virus stock including any contaminants that may have biological effects? (iii) If co-cultivation is employed, what kinds of cells are being used for co-cultivation? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials? Specifically, what tests are being conducted to assess the material to be returned to the patient for the presence of live or killed donor cells or other non-vector materials (for example, VL30 sequences) originating from those cells? (iv) If methods other than those covered by Appendices M-II-B-1 through M-II-B-3 are used to introduce new genetic information into target cells, what steps are being taken to detect and eliminate any contaminating materials? What are possible sources of contamination?

What is the sensitivity of tests used to monitor contamination?

Appendix M-II-B-1-b-(2). Describe any other material to be used in preparation of the material to be administered to the patient. For example, if a viral vector is proposed, what is the nature of the helper virus or cell line? If carrier particles are to be used, what is the nature of these?

Appendix M-II-B-2. Preclinical Studies, Including Risk-Assessment Studies

Provide results that demonstrate the safety, efficacy, and feasibility of the proposed procedures using animal and/or cell culture model systems, and explain why the model(s) chosen is/are most appropriate.

Appendix M-II-B-2-a. Delivery System

Appendix M-II-B-2-a-(1). What cells are the intended target cells of recombinant DNA? What target cells are to be treated *ex vivo* and returned to the patient, how will the cells be characterized before and after treatment? What is the theoretical and practical basis for assuming that only the target cells will incorporate the DNA?

Appendix M-II-B-2-a-(2). Is the delivery system efficient? What percentage of the target cells contain the added DNA?

Appendix M-II-B-2-a-(3). How is the structure of the added DNA sequences monitored and what is the sensitivity of the analysis? Is the added DNA extrachromosomal or integrated? Is the added DNA unrearranged?

Appendix M-II-B-2-a-(4). How many copies are present per cell? How stable is the added DNA both in terms of its continued presence and its structural stability?

Appendix M-II-B-2-b. Gene Transfer and Expression

Appendix M-II-B-2-b-(1). What animal and cultured cell models were used in laboratory studies to assess the *in vivo* and *in vitro* efficacy of the gene transfer system? In what ways are these models similar to and different from the proposed human treatment?

Appendix M-II-B-2-b-(2). What is the minimal level of gene transfer and/or expression that is estimated to be necessary for the gene transfer protocol to be successful in humans? How was this level determined?

Appendix M-II-B-2-b-(3). Explain in detail all results from animal and cultured cell model experiments which assess the effectiveness of the delivery system in achieving the minimally

required level of gene transfer and expression.

Appendix M-II-B-2-b-(4). To what extent is expression only from the desired gene (and not from the surrounding DNA)? To what extent does the insertion modify the expression of other genes?

Appendix M-II-B-2-b-(5). In what percentage of cells does expression from the added DNA occur? Is the product biologically active? What percentage of normal activity results from the inserted gene?

Appendix M-II-B-2-b-(6). Is the gene expressed in cells other than the target cells? If so, to what extent?

Appendix M-II-B-2-c. Retrovirus Delivery Systems

Appendix M-II-B-2-c-(1). What cell types have been infected with the retroviral vector preparation? Which cells, if any, produce infectious particles?

Appendix M-II-B-2-c-(2). How stable are the retroviral vector and the resulting provirus against loss, rearrangement, recombination, or mutation? What information is available on how much rearrangement or recombination with endogenous or other viral sequences is likely to occur in the patient's cells? What steps have been taken in designing the vector to minimize instability or variation? What laboratory studies have been performed to check for stability, and what is the sensitivity of the analyses?

Appendix M-II-B-2-c-(3). What laboratory evidence is available concerning potential harmful effects of the transfer (e.g., development of neoplasia, harmful mutations, regeneration of infectious particles, or immune responses)? What steps will be taken in designing the vector to minimize pathogenicity? What laboratory studies have been performed to check for pathogenicity, and what is the sensitivity of the analyses?

Appendix M-II-B-2-c-(4). Is there evidence from animal studies that vector DNA has entered untreated cells, particularly germ-line cells? What is the sensitivity of these analyses?

Appendix M-II-B-2-c-(5). Has a protocol similar to the one proposed for a clinical trial being conducted in non-human primates and/or other animals? What were the results? Specifically, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals?



#### Appendix M-II-B-2-d. Non-Retrovirus Delivery/Expression Systems

If a non-retroviral delivery system is used, what animal studies have been conducted to determine if there are pathological or other undesirable consequences of the protocol (including insertion of DNA into cells other than those treated, particularly germ-line cells)? How long have the animals been studied after treatment? What safety studies have been conducted? (Include data about the level of sensitivity of such assays.)

#### Appendix M-II-B-3. Clinical Procedures, Including Patient Monitoring

Describe the treatment that will be administered to patients and the diagnostic methods that will be used to monitor the success or failure of the treatment. If previous clinical studies using similar methods have been performed by yourself or others, indicate their relevance to the proposed study. Specifically:

Appendix M-II-B-3-a. Will cells (e.g., bone marrow cells) be removed from patients and treated *ex vivo*? If so, describe the type, number, and intervals at which these cells will be removed.

Appendix M-II-B-3-b. Will patients be treated to eliminate or reduce the number of cells containing malfunctioning genes (e.g., through radiation or chemotherapy)?

Appendix M-II-B-3-c. What treated cells (or vector/DNA combination) will be given to patients? How will the treated cells be administered? What volume of cells will be used? Will there be single or multiple treatments? If so, over what period of time?

Appendix M-II-B-3-d. How will it be determined that new gene sequences have been inserted into the patient's cells and if these sequences are being expressed? Are these cells limited to the intended target cell populations? How sensitive are these analyses?

Appendix M-II-B-3-e. What studies will be conducted to assess the presence and effects of the contaminants?

Appendix M-II-B-3-f. What are the clinical endpoints of the study? Are there objectives and quantitative measurements to assess the natural history of the disease? Will such measurements be used in patient follow-up? How will patients be monitored to assess specific effects of the treatment on the disease? What is the sensitivity of the analyses? How frequently will follow-up studies be conducted? How long will patient follow-up continue?

Appendix M-II-B-3-g. What are the major beneficial and adverse effects of

treatment that you anticipate? What measures will be taken in an attempt to control or reverse these adverse effects if they occur? Compare the probability and magnitude of deleterious consequences from the disease if recombinant DNA transfer is not used.

Appendix M-II-B-3-h. If a treated patient dies, what special post-mortem studies will be performed?

#### Appendix M-II-B-4. Public Health Considerations

Describe any potential benefits and hazards of the proposed therapy to persons other than the patients being treated. Specifically:

Appendix M-II-B-4-a. On what basis are potential public health benefits or hazards postulated?

Appendix M-II-B-4-b. Is there a significant possibility that the added DNA will spread from the patient to other persons or to the environment?

Appendix M-II-B-4-c. What precautions will be taken against such spread (e.g., patients sharing a room, health-care workers, or family members)?

Appendix M-II-B-4-d. What measures will be undertaken to mitigate the risks, if any, to public health?

Appendix M-II-B-4-e. In light of possible risks to offspring, including vertical transmission, will birth control measures be recommended to patients? Are such concerns applicable to health care personnel?

#### Appendix M-II-B-5. Qualifications of Investigators and Adequacy of Laboratory and Clinical Facilities

Indicate the relevant training and experience of the personnel who will be involved in the preclinical studies and clinical administration of recombinant DNA. Describe the laboratory and clinical facilities where the proposed study will be performed. Specifically:

Appendix M-II-B-5-a. What professional personnel (medical and nonmedical) will be involved in the proposed study and what is their relevant expertise? Provide a two-page curriculum vitae for each key professional person in biographical sketch format (see Appendix M-I, *Submission Requirements*).

Appendix M-II-B-5-b. At what hospital or clinic will the treatment be given? Which facilities of the hospital or clinic will be especially important for the proposed study? Will patients occupy regular hospital beds or clinical research center beds? Where will patients reside during the followup period? What special arrangements will be made for the comfort and consideration of the patients. Will the research institution designate an ombudsman, patient care representative,

or other individual to help protect the rights and welfare of the patient?

#### Appendix M-II-C. Selection of the Patients

Estimate the number of patients to be involved in the proposed study.

Describe recruitment procedures and patient eligibility requirements, paying particular attention to whether these procedures and requirements are fair and equitable. Specifically:

Appendix M-II-C-1. How many patients do you plan to involve in the proposed study?

Appendix M-II-C-2. How many eligible patients do you anticipate being able to identify each year?

Appendix M-II-C-3. What recruitment procedures do you plan to use?

Appendix M-II-C-4. What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?

Appendix M-II-C-5. How will patients be selected if it is not possible to include all who desire to participate?

#### Appendix M-III. Informed Consent

In accordance with 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 indicate how the Informed Consent document makes clear the special requirements of gene transfer research. If a proposal involves children, special attention should be paid to the Protection of Human Subjects (45 CFR Part 46), Subpart D, Additional Protections for Children Involved as Subjects in Research.

#### Appendix M-III-A. Communication About the Study to Potential Participants

Appendix M-III-A-1. 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-III-A-2. How will the major points covered in Appendix M-II, *Description of Proposal*, be disclosed to potential participants and/or their parents or guardians in language that is understandable to them?

Appendix M-III-A-3. What is the length of time that potential participants will have to make a decision about their participation in the study?

Appendix M-III-A-4. If the study involves pediatric or mentally handicapped subjects, how will the assent of each person be obtained?

#### Appendix M-III-B. Informed Consent Document

Investigators submitting human gene transfer proposals must include the Informed Consent document as approved by the local Institutional Review Board. 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-III-B-1. General Requirements of Human Subjects Research

##### Appendix M-III-B-1-a. Description/Purpose of the Study

The subjects should be provided with a detailed explanation in nontechnical 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-III-B-1-b. Alternatives

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

##### Appendix M-III-B-1-c. 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-III-B-1-d. 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-III-B-1-e. 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 lifethreatening, 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-III-B-1-f. Costs

The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the longterm followup 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-III-B-2. Specific Requirements of Gene Transfer Research

##### Appendix M-III-B-2-a. 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-III-B-2-b. 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 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-III-B-2-c. 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-III-B-2-d. 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.

#### Appendix M-IV. Privacy and Confidentiality

Indicate what measures will be taken to protect the privacy of patients and their families as well as to maintain the confidentiality of research data.

Appendix M-IV-A. What provisions will be made to honor the wishes of individual patients (and the parents or guardians of pediatric or mentally handicapped patients) as to whether, when, or how the identity of patients is publicly disclosed?

Appendix M-IV-B. What provisions will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual patients?

#### Appendix M-V. Special Issues

Although the following issues are beyond the normal purview of local Institutional Review Boards, investigators should respond to the following questions:

Appendix M-V-A. What steps will be taken, consistent with Appendix M-IV, Privacy and Confidentiality, to ensure that accurate and appropriate information is made available to the public with respect to such public concerns as may arise from the proposed study?

Appendix M-V-B. Do you or your funding sources intend to protect under patent or trade secret laws either the products or the procedures developed in the proposed study? If so, what steps will be taken to permit as full communication as possible among investigators and clinicians concerning research methods and results?

#### Appendix M-VI. RAC Review—Human Gene Transfer Protocols

##### Appendix M-VI-A. Categories of Human Gene Transfer Experiments That Require RAC Review

Factors that may contribute to the necessity for RAC review include, but are not limited to: (i) New vectors/new gene delivery systems, (ii) new diseases, (iii) unique applications of gene transfer, and (iv) other issues considered to require further public discussion. Whenever possible, investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required. In the event that RAC review is deemed necessary by the NIH and FDA, the proposal will be forwarded to the RAC primary reviewers for evaluation. In order to maintain public access to

information regarding human gene transfer protocols, NIH/ORDA will maintain the documentation described in Appendices M-I through M-V (including protocols that are not reviewed by the RAC).

##### Appendix M-VI-B. RAC Primary Reviewers' Written Comments

In the event that NIH/ORDA or the FDA recommend RAC review of the submitted proposal, the documentation described in Appendices M-I through M-V will be forwarded to the RAC primary reviewers for evaluation.

The RAC primary reviewers shall provide written comments on the proposal to NIH/ORDA. The RAC primary reviewers' comments should include the following:

Appendix M-VI-B-1. Emphasize the issues related to gene marking, gene transfer, or gene therapy.

Appendix M-VI-B-2. State explicitly whether Appendices M-I through M-V have been addressed satisfactorily.

Appendix M-VI-B-3. Examine the scientific rationale, scientific context (relative to other proposals reviewed by the RAC), whether the preliminary in vitro and in vivo data were obtained in appropriate models and are sufficient, and whether questions related to safety, efficacy, and social/ethical context have been resolved.

Appendix M-VI-B-4. Whenever possible, criticisms of Informed Consent documents should include written alternatives for suggested revisions for the RAC to consider.

Appendix M-VI-B-5. Primary reviews should state whether the proposal is: (i) acceptable as written, (ii) expected to be acceptable with specific revisions or after satisfactory responses to specific questions raised on review, or (iii) unacceptable in its present form.

##### Appendix M-VI-C. Investigator's Written Responses to RAC Primary Reviewers

Appendix M-VI-C-1. Written responses (including critical data in response to RAC primary reviewers' written comments) shall be submitted to NIH/ORDA greater than or equal to 2 weeks following receipt of the review.

##### Appendix M-VI-D. Oral Responses to the RAC

Investigators shall limit their oral responses to the RAC only to those questions that are raised during the meeting. Investigators are strongly discouraged from presenting critical data during their oral presentations that was not submitted greater than or equal to 2 weeks in advance of the RAC meeting at which it is reviewed.

##### Appendix M-VI-E. RAC Recommendations to the NIH Director

The RAC will recommend approval or disapproval of the reviewed proposal to the NIH Director. In the event that a proposal is contingently approved by the RAC, the RAC prefers that the conditions be satisfactorily met before the RAC's recommendation for approval is submitted to the NIH Director. The NIH Director's decision on the submitted proposal will be transmitted to the FDA Commissioner and considered as a *Major Action* by the NIH Director.

##### Appendix M-VII. Categories of Human Gene Transfer Experiments That May Be Exempt From RAC Review

A proposal submitted under one of the following categories may be considered exempt from RAC review unless otherwise determined by NIH/ORDA and the FDA on a case-by-case basis (see Appendix M-VI-A, Categories of Human Gene Transfer Experiments That Require RAC Review).

**Note:** In the event that the submitted proposal is determined to be exempt from RAC review, the documentation described in Appendices M-I through M-V will be maintained by NIH/ORDA for compliance with semiannual data reporting and adverse event reporting requirements (see Appendix M-VIII, Reporting Requirements—Human Gene Transfer Protocols). Any subsequent modifications to proposals that were not reviewed by the RAC must be submitted to NIH/ORDA in order to facilitate data reporting requirements.

##### Appendix M-VII-A. Vaccines

This category includes recombinant DNA vaccines not otherwise exempt from RAC review (see Appendix M-IX-A for exempt vaccines).

##### Appendix M-VII-B. Lethally Irradiated Tumor Cells/No Replication-Competent Virus

This category includes experiments involving lethally irradiated tumor cells and: (1) vector constructs that have previously been approved by the RAC (or with the incorporation of minor modifications), or (2) a different tumor cell target.

##### Appendix M-VII-C. New Site/Original Investigator

This category includes the following: (1) initiation of a protocol at an additional site other than the site that was originally approved by the RAC, and (2) the investigator at the new site is the same as the investigator approved for the original study.

**Appendix M-VII-D. New Site/New Investigator**

This category includes the following: (1) initiation of a protocol at an additional site other than the site that was originally approved by the RAC, and (2) the investigator at the new site is different than the investigator approved for the original site.

**Appendix M-VII-E. "Umbrella" Protocols**

This category includes initiation of a RAC-approved protocol at more than one additional site (the Principal Investigator may be the same or different than the Principal Investigator approved for the original site).

**Appendix M-VII-F. Modifications Related to Gene Transfer**

This category includes experiments involving a modification to the clinical protocol that is not related to the gene transfer portion of study.

**Appendix M-VII-G. Gene Marking Protocols**

This category includes human gene marking experiments involving vector constructs that have previously been approved by the RAC and: (1) minor modifications to the vector constructs, or (2) a different tumor cell target.

**Appendix M-VIII. Reporting Requirements—Human Gene Transfer Protocols****Appendix M-VIII-A. Semiannual Data Reporting**

Investigators who have received approval from the FDA to initiate a human gene transfer protocol (whether or not it has been reviewed by the RAC) shall be required to comply with the semiannual data reporting requirements. Semi-annual Data Report forms will be forwarded by NIH/ORDA to investigators. Data submitted in these reports will be evaluated by the RAC, NIH/ORDA, and the FDA and reviewed by the RAC at its next regularly scheduled meeting.

**Appendix M-VIII-B. Adverse Event Reporting**

Investigators who have received approval from the FDA to initiate a human gene transfer protocol (whether or not it has been reviewed by the RAC) must report any serious adverse event immediately to the local IRB, IBC, NIH Office for Protection from Research Risks, NIH/ORDA, and FDA, followed by the submission of a written report filed with each group. Reports submitted to NIH/ORDA shall be sent to the Office of Recombinant DNA

Activities, National Institutes of Health, 6006 Executive Boulevard, Suite 323, Bethesda, Maryland 20892-7052, (301) 496-9838.

**Appendix M-IX. Footnotes of Appendix M**

Appendix M-IX-A. Human studies in which the induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected, may be initiated without RAC review if approved by another Federal agency.

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.

Effective Date: April 17, 1995.

**Harold Varmus,**

Director, National Institutes of Health.

[FR Doc. 95-10381 Filed 4-26-95; 8:45 am]

BILLING CODE 4140-01-P

**Public Health Service****National Institutes of Health; Notice of Meeting of the Panel to Assess the NIH Investment in Research on Gene Therapy**

Notice is hereby given that the Panel to Assess the NIH Investment in Research on Gene Therapy, a fact-finding group reporting to the Advisory

Committee to the Director (ACD), National Institutes of Health (NIH), will meet in public session at the William H. Natcher Building (Building 45) Conference Center, Board Room, National Institutes of Health, Bethesda, Maryland 20892, on May 15-16, 1995. The meeting will begin at approximately 9:00 a.m. to recess on May 15, and from approximately 9:00 a.m. to 1:00 p.m. on May 16.

The goal of the Panel is to make recommendations to the ACD about the scientific areas that NIH should emphasize and the funding mechanisms that should be employed in order best to advance the development of gene therapy. The purpose of the meeting is to provide the Panel with an opportunity to hear presentations regarding the current and anticipated research activities relevant to gene therapy that are supported by the various components of NIH, and to discuss how to proceed with its assessment of NIH's investment in gene therapy.

Individuals who plan to attend and need special assistance, such as sign language interpretation or other special accommodations, should contact the person named below in advance of the hearing.

Attendance may be limited to seat availability. If you plan to attend the meeting as an observer or if you wish additional information, please contact Ms. Janice Ramsden, National Institutes of Health, Shannon Building, Room 235, 1 Center Drive MSC 0159, Bethesda, Maryland 20892-0159, telephone (301) 496-0959, fax (301) 496-7451, by May 10.

**Ruth L. Kirschstein,**

Deputy Director, NIH.

[FR Doc. 95-10382 Filed 4-26-95; 8:45 am]

BILLING CODE 4140-01-P

**DEPARTMENT OF THE INTERIOR****Bureau of Land Management**

[AZ-020-05-1330-00]

**Notice of Availability of the Cyprus Tohono Corporation Proposed Mine Expansion Final Environmental Impact Statement, Phoenix District, Arizona**

AGENCY: Bureau of Land Management, Interior.

ACTION: Final environmental impact statement.

SUMMARY: In compliance with the Federal Land Policy and Management Act of 1976, section 102(2)(c) of the National Environmental Policy Act of