Federal Register

Friday
October 31, 1997

Part II

Department of Health and Human Services

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines

AGENCY: Notice of Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) (59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782).

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Debra Knorr, Acting Director, Office of Recombinant DNA Activities (ORDA), Office of Science Policy, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX 301–496–9839. ORDA's web site is located at http://www.nih.gov/od/orda for further information about the office.

SUPPLEMENTARY INFORMATION: Today's actions are being promulgated under the NIH Guidelines for Research Involving Recombinant DNA Molecules. These Proposed Actions were published for comment in the **Federal Register** of July 8, 1996 (61 FR 7108), and August 20, 1997 (62 FR 44387). The Proposed Actions were reviewed and recommended for approval by the NIH Recombinant DNA Advisory Committee (RAC) at its meetings on December 9, 1996, March 6–7, 1997, and September 12, 1997.

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

I–A. Amendment to the Overall Procedures for Human Gene Transfer Protocols

I–A–1. Notice of Intent—July 1996

On July 8, 1996, the NIH Director published a Notice of Intent to Propose Amendments to the NIH Guidelines for Research Involving Recombinant DNA Molecules Regarding Enhanced Oversight of Recombinant DNA Activities (61 FR 35774). This Notice of Intent proposed modifications in the NIH oversight of human gene transfer research. Specifically, it was proposed that RAC would be terminated and that all approval responsibilities for recombinant DNA experiments involving human gene transfer would be relinquished to the Food and Drug Administration (FDA), which retains statutory authority for such approval. Under this revised structure, a newly created ORDA Advisory Committee (OAC) would preserve continued public accountability for recombinant DNA research. To ensure quality and efficiency of public discussion of the scientific merit and the ethical issues relevant to gene therapy clinical trials, it was proposed that the NIH Director implement a regular series of Gene Therapy Policy Conferences (GTPCs). Finally, the proposal assured the continuation of the publicly available comprehensive NIH database of clinical trials with human gene transfer, including reporting of adverse events.

In response to the Notice of Intent, NIH received 71 written comments (90 signatures) reflecting a broad spectrum of public opinion on the proposed changes. Comments were received from a variety of stakeholders, including individuals representing academia, industry, patient advocacy organizations, consumer advocacy organizations, professional scientific societies, ethicists, other Federal agencies, NIH-funded investigators, past and present RAC members, and private citizens. Careful consideration was given to each of the written comments that was submitted.

I–B. Proposed Actions—November 1996

On November 22, 1996, the NIH Director published the Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (61 FR 59725). These Proposed Actions were prepared in response to public opinion and in keeping with the NIH Director's intent to increase the usefulness and productivity of public discussion of human gene transfer research.

In the Proposed Actions, the NIH Director proposed to: (1) Retain RAC, while modifying its roles and responsibilities relevant to human gene therapy research, (2) continue RAC discussion of novel human gene transfer experiments, without RAC approval of individual human gene transfer experiments; (3) regularly convene GTPCs; and (4) maintain public access to human gene transfer clinical trial information. The following summarizes the roles and responsibilities of the NIH Director, RAC, ORDA, and local institutions under the Notice of Proposed Actions.

I–B–1. Proposed Roles and Responsibilities in Accordance With the NIH Guidelines

I–B–1–a. NIH Director

The roles and responsibilities of the NIH Director in accordance with the NIH Guidelines remain unchanged except for the following: (1) Approval of human gene transfer experiments by the NIH Director will be relinquished to FDA which already holds statutory authority for such approval under 21 CFR, Chapter I, Subchapter D. (2) GTPCs will be established and regularly convened by the NIH Director.

I–B–1–b. Recombinant DNA Advisory Committee (RAC)

The roles and responsibilities of RAC related to human gene transfer research remain the same except for the following: (1) RAC will identify novel human gene transfer experiments deserving of public discussion by the full RAC and will transmit its comments/recommendations on specific human gene transfer experiments or categories of human gene transfer experiments to the NIH Director, the principal Investigator, the sponsoring institution, and other Department of Health and Human Services (DHHS) components, as appropriate. (2) Novel scientific, safety, social, and ethical issues relevant to specific human applications of gene transfer will be identified by RAC, which will recommend to the NIH Director appropriate modifications to the Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider) that will provide guidance in the design and submission of human gene transfer clinical trials. (3) RAC will publicly review human gene transfer clinical trial data submitted to NIH/ORDA in accordance with the annual data reporting requirements contained in Appendix M–VII–B of the NIH Guidelines. (4) Broad scientific,safety, social, and ethical issues relevant to human gene transfer research will be identified by RAC and submitted to the NIH Director as recommendations for consideration as potential GTPC topics.

I–B–1–c. Gene Therapy Policy Conferences (GTPCs)

In order to enhance the depth and value of public discussion relevant to scientific, safety, social, and ethical implications of gene therapy research, the NIH Director will convene GTPCs at regular intervals. As appropriate, the NIH Director may convene a GTPC in conjunction with a regularly scheduled RAC meeting. GTPCs will be administered by NIH/ORDA. Conference participation will not involve a standing committee membership but rather will offer the unique advantage of assembling numerous participants who possess significant scientific, safety, social, and ethical expertise and/or interest that is directly applicable to a specific gene therapy research issue. At

least one member of RAC will serve as Co-chair of each GTPC and report the findings of each GTPC to RAC at its next scheduled meeting. The RAC representative for each GTPC will be chosen based on the participant's area of expertise relative to the specific gene therapy research issue to be discussed. GTPCs will have representation from other Federal agencies, including FDA and the Office for Protection from Research Risks (OPRR). GTPCs will focus on broad overarching policy and scientific issues related to gene therapy research. Proposals for GTPC topics may be submitted by members of RAC, representatives of academia, industry, patient and consumer advocacy organizations, other Federal agencies, professional scientific societies, and the general public. GTPC topics will not be limited to discussion of human applications of gene therapy research, i.e., they may include basic research on the use of novel gene delivery vehicles or novel applications of human gene transfer. GTPC findings will be transmitted to the NIH Director and will be made publicly available. The NIH Director anticipates that this public policy forum will serve as a model for interagency communication and collaboration, concentrated expert discussion of novel scientific issues and their potential societal implications, and enhanced opportunity for public discussion of the potential impact of such applications on human health and the environment.

I–B–1–d. The Office of Recombinant DNA Activities (ORDA)

ORDA is an organizational unit of the NIH Office of Science Policy within the Office of the Director. The roles and responsibilities of NIH/ORDA remain unchanged except for the following: (1) Serving as the focal point for public access to summary information pertaining to human gene transfer experiments. (2) Transmitting to the NIH Director comments/ recommendations arising from public RAC discussion of a novel human gene transfer experiment. RAC recommendations shall be forwarded to the Principal Investigator(s), the sponsoring institution, and other DHHS components, as appropriate. (3) Collaborating with Principal Investigators, IBCs, Institutional Review Boards (IRBs), and other DHHS components, to ensure human gene transfer experiment registration compliance. (4) Administering GTPCs as deemed appropriate by the NIH Director. (5) Publishing announcements of GTPCs and tentative agendas in the **Federal Register** at least 15 days in advance.

I–B–1–e. Institutional Biosafety Committees (IBCs)

The roles and responsibilities of IBCs related to human gene transfer experiments remain unchanged, except when the institution participates in or sponsors recombinant DNA research involving human subjects, the institution must ensure that: (a) The IBC has adequate expertise and training (using *ad hoc* consultants as deemed necessary), and (b) all aspects of Appendix M, Points to Consider, have been appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA.

I–C. Proposed Actions—December 1996 RAC Meeting

On November 22, 1996, the NIH Director published a Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (61 FR 59725). The Notice of Proposed Actions was prepared in response to public opinion and in keeping with the NIH Director's intent to increase the usefulness and productivity of public discussion of human gene transfer research. As a result of its December 9, 1996, deliberations of the Proposed Actions under the NIH Guidelines, RAC proposed the following modifications to the November 22, 1996, Notice of Intent:

I–C–1. Triggering Mechanism for RAC Discussion

A motion was made that: (1) The capacity for Principal Investigators and institutional representatives to request RAC discussion of an individual human gene transfer protocol should be deleted. (2) The NIH Director or an appropriate FDA representative may request RAC review of an individual protocol. (3) Rather than a majority vote, RAC recommendations for full review of an individual protocol should be changed to a minimum of three members. (4) The decision regarding necessity for RAC discussion should be made within 15 working days. The motion passed by a vote of 16 in favor, 0 opposed, and no abstentions.

I–C–2. Reporting Requirements

A motion was made to request that FDA report back to the RAC on how RAC recommendations on an individual protocol were implemented. RAC should require investigator to provide additional information if FDA is unable to provide the necessary information. The motion failed by a vote of 3 in favor, 7 opposed, and 4 abstentions.

Another motion was made to require investigators to submit a written report to the RAC that includes the following information: (1) How the investigator(s) responded to RAC's recommendations on the protocol (if applicable), and (2) any modifications to the protocol as required by FDA. The motion passed by a vote of 12 in favor, 1 opposed, and 1 abstention.

I–C–3. Relationship of RAC and GTPCs

A motion was made that the RAC, with the NIH Director's approval, should have the primary responsibility for: (1) planning GTPC agendas, and (2) summarizing GTPC recommendations in the form of a report back to the NIH Director. The close GTP/RAC relationship should not preclude other parties from suggesting GTPC topics and GTPCs should be convened in consultation with FDA and OPRR. The motion passed by a vote of 13 in favor, 0 opposed, and 2 abstentions.

I–C–4. Proposed Actions—Structural Changes

A motion was made to accept the overall structural changes put forward in the Proposed Actions as published in the November 22, 1996, **Federal Register** (61 FR 59725). However, RAC recommended that promulgation of the final actions should be postponed to the March 6–7, 1997, RAC meeting, in order to more fully address these unresolved issues. The structural changes endorsed by RAC were as follows: (1) Retain RAC, while modifying its roles and responsibilities relevant to human gene therapy research, (2) continue RAC discussion of novel human gene transfer experiments without RAC *approval* of individual human gene transfer experiments; (3) regularly convene GTPCs; and (4) maintain public access to human gene transfer clinical trial information. RAC members noted that several minor modification still remained unresolved, particularly with regard to the format for future discussion of gene therapy protocols and defining the role of RAC relative to GTPCs. The motion passed by a vote of 12 in favor, 0 opposed, and 2 abstentions.

I–D. Proposed Action—March 1997

On February 14, 1997, the NIH Director published a revised Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (62 FR 7108). The Notice of Proposed Actions was in response to public opinion and in keeping with the NIH Director's intent to increase the usefulness and productivity of public discussing of

human gene transfer research. During its March 6–7, 1997, meeting, RAC recommended the following changes to the February 14, 1997, Proposed Actions under the NIH Guidelines.

I–D–1. Relationship of RAC and GTPCs

A motion was made to include the following modifications will regard to the role of RAC relative to GTPCs: (1) One member of RAC will co-chair each GTPC. (2) GTPCs will be held in conjunction with RAC meetings when appropriate (preferably on the first day). (3) All RAC members will be invited to attend GTPCs. The motion passed by a vote of 8 in favor, 0 opposed, and no abstentions.

I–D–2. IBC Approval Requirements

A motion was made to modify IBC approval requirements for human gene transfer protocols under Section III–C–a of the NIH Guidelines. Specifically, RAC proposed that IBC approval must be obtained from each institution at which recombinant DNS material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application). The motion passed by a vote of 6 in favor, 0 opposed, and 2 abstentions.

I–D–3. NIH Human Gene Therapy Database

A motion was made to identify the objectives of the human gene transfer database. As a result of RAC's deliberation on this issue, the following five objectives were identified: (1) Maintain and institutional memory, (2) provide administrative details of protocol registration, (3) provide annual status reports of protocols, (4) facilitate risk assessment of individual applications of human gene transfer, and (5) enhance public awareness of relevant scientific, safety, social, and ethical issues. The motion passed by a vote of 7 in favor, 0 opposed, and 1 abstention.

I–E. Requirement for Submission of Appendix M to FDA

In a letter dated November 20, 1996, Dr. Andra Miller, Cytokine and Gene Therapy Branch, Center of Biologics Evaluation and Research, FDA, requested that the NIH Guidelines should be amended regarding procedures for simultaneous submission of Appendix M material to RAC and FDA. In her November 20, 1996, letter, Dr. Miller states:

''(1) Remove the requirement for submission of Appendix M to FDA. FDA does not accept Appendix M in place of an IND submission. FDA is not proposed to be and need not be included in the decisionmaking process to identify protocols to undergo full RAC review. Therefore, there is no reason for sponsors to submit Appendix M materials to FDA.

''(2) Explore the feasibility of a unified format for submission of protocols to RAC and FDA. This would relieve the sponsor of the burden of preparing duplicative submission to satisfy each agency.

''(3) Establish a mechanism for FDA staff to bring general issues of novelty and concern to RAC for discussion. This will provide a mechanism for public input toward the resolution of issues we all must consider and provide direction for policy development and growth in the field of gene therapy.''

On January 27, 1997, NIH and FDA staff met to consider amendments to the NIH Guidelines that incorporate the recommendations of both NIH and FDA with regard to simultaneous submission of human gene transfer protocols.

During its December 9, 1996, and March 6–7, 1997, meetings, RAC discussed the proposed changes to the NIH Guidelines submitted by Dr. Miller. The consensus of RAC was that the requirement for submission of responses to Appendix M to FDA should be removed since FDA does not accept responses to Appendix M in place of an Investigational New Drug (IND) application. However, RAC stated that all human gene transfer protocols should include discussion of issues raised in Appendix M–II through M–V of the NIH Guidelines in the clinical protocols. The proposed action was published in the **Federal Register** of August 20, 1997, for public comment. No comment was received from the public with regard to the proposed action.

During the September 12, 1997, RAC meeting, RAC approved the amendments to the NIH Guidelines to eliminate the requirement for submission of responses to Appendix M of the NIH Guidelines to FDA. The motion passed by a vote of 12 in favor, 0 opposed, and 0 abstentions.

I–F. Environmental Assessment—October 1997

As a prerequisite to amending the NIH Guidelines for the purpose of relinquishing the requirement for NIH Director approval of individual human gene transfer experiments, NIH prepared an Environmental Assessment for the Proposed Actions in accordance with requirements of the National Environmental Protection Act of 1969, 42 U.S.C. This Environmental Assessment that was completed in October 1997 included a finding of no significant impact on the environment. Copies of the Environmental Assessment are available from the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland, 20892–7010, (301) 496–9838.

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

II. Summary of Actions

NIH will take the following action under the NIH Guidelines for Research Involving Recombinant DNA Molecules:

Note: Editorial changes and updating of references have been incorporated to clarify the document.

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

Section I is amended to read:

''SECTION I. SCOPE OF THE NIH GUIDELINES

''Section I–A. Purpose''

[This section remains unchanged.]

''Section I–A–1. Any recombinant DNA experiment, which according to the NIH Guidelines requires approval by NIH, must be submitted to 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 NIH (whether the experiment is referred to that agency by 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 regarding requirement for human gene transfer protocol registration.)

''Section I–A–1–a. Experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) cannot be initiated without simultaneous submission to both NIH/ORDA and FDA of such information on the proposed experiment as is prescribed by those agencies. Submission of human gene transfer protocols to NIH shall be in the format described in Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, of the NIH Guidelines. Submission to NIH shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the NIH

Guidelines. Investigational New Drug (IND) applications shall be submitted to FDA in the format described in 21 CFR, chapter I, subchapter D, part 312, subpart B, section 23, IND Content and Format.

''If a determination is made that an experiment will undergo full RAC discussion, NIH/ORDA will immediately notify the Principal Investigator. RAC members may forward requests for additional information relevant to a specific protocol through NIH/ORDA to the Principal Investigator. In making a determination whether an experiment is novel and deserving of full RAC discussion, reviewers will examine the scientific rational, scientific content (relative to other proposals reviewed by RAC), whether the preliminary *in vitro* and *in vivo* safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. RAC's recommendation(s) on a specific human gene transfer experiment will be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate.

''Section I–B. Definition of Recombinant DNA Molecules''

[This section remains unchanged.]

''Section I–C. General Applicability

''Section I–C–1. The NIH Guidelines are applicable to:

Section I–C–1–a. All recombinant DNA research within the United States (U.S.) or its territories that is within the category of research described in either Section I–C–1–a–(1) or Section I–C–1–a–(2).

''Section I–C–1–a–(1). Research that is conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH, including research performed directly by NIH. An individual who receives support for research involving recombinant DNA must be associated with or sponsored by an institution that assumes the responsibilities assigned in the NIH Guidelines.

''Section I–C–1–a–(2). Research that involves testing in humans of materials containing recombinant DNA developed with NIH funds, if the institution that developed those materials sponsors or participates in those projects. Participation includes research collaboration or contractual agreements, not mere provision of research materials.

''Section I–C–1–b. All recombinant DNA research performed abroad that is within the category of research described in either Section I–C–1–b–(1) or Section I–C–1–b–(2).

''Section I–C–1–b–(1). Research supported by NIH funds.

''Section I–C–1–b–(2). Research that involves testing in humans of materials containing recombinant DNA developed with NIH funds, if the institution that developed those materials sponsors or participates in those projects. Participation includes research collaboration or contractual agreements, not mere provisions of research materials.

''Section I–C–1–b–(3). If the host country has established rules for the conduct of recombinant DNA research, then the research must be in compliance with those rules. If the host country does not have such rules, the proposed research must be reviewed and approved by an NIH-approved Institutional Biosafety Committee or equivalent review body and accepted in writing by an appropriate national governmental authority of the host country. The safety practices that are employed abroad must be reasonably consistent with the NIH Guidelines.

''Section I–D. Compliance with the NIH Guidelines

''As a condition for NIH funding of recombinant DNA research, institutions shall ensure that such research conducted at or sponsored by the institution, irrespective of the source of funding, shall comply with the NIH Guidelines.

''Information concerning noncompliance with the NIH Guidelines may be brought forward by any person. It should be delivered to both NIH/ORDA and the relevant institution. The institution, generally through the Institutional Biosafety Committee, shall take appropriate action. The institution shall forward a complete report of the incident recommending any further action to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''In cases where NIH proposes to suspend, limit, or terminate financial assistance because of noncompliance with the NIH Guidelines, applicable DHHS and Public Health Service procedures shall govern.

''The policies on compliance are as follows:

''Section I–D–1. All NIH-funded projects involving recombinant DNA techniques must comply with the NIH Guidelines. Non-compliance may result in: (i) Suspension, limitation, or termination of financial assistance for the noncompliant NIH-funded research project and of NIH funds for other recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.

''Section I–D–2. All non-NIH funded projects involving recombinant DNA techniques conducted at or sponsored by an institution that receives NIH funds for projects involving such techniques must comply with the NIH Guidelines. Noncompliance may result in: (i) Suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.''

[Previously numbered Section I–D, General Definitions, will be renumbered to Section I–E.]

II–B. Amendments to Section II, Safety Considerations

The second paragraph of Section II–A–3 is amended to read:

''Section II–A–3. Comprehensive Risk Assessment

''* * * A final assessment of risk based on these considerations is then used to set the appropriate containment conditions for the experiment (see Section II–B, Containment). The containment level required may be equivalent to the Risk Group classification of the agent or it may be raised or lowered as a result of the above considerations. The Institutional Biosafety Committee must approve the risk assessment and the biosafety containment level for recombinant DNA experiments described in Sections III–A, Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation; III–B, Experiments that Require NIH/ORDA and Institutional Biosafety Committee Approval Before Initiation; III–C, Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/ORDA Registration Before Initiation; and III–D, Experiments that Require Institutional Biosafety Committee Approval Before Initiation * * *''

II–C. Amendments to Section III, Experiments Covered by the NIH Guidelines

Section III is amended to read:

''SECTION III. EXPERIMENTS COVERED BY THE NIH GUIDELINES

''This section describes six 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 II–B), (iii) those that require Institutional Biosafety Committee and Institutional Review Board approvals and NIH/ORDA registration before initiation (see Section III–C), (iv) those that require Institutional Biosafety Committee approval before initiation (see Section III–D), (v) those that require Institutional Biosafety Committee notification simultaneous with initiation (see Section III–E), and (vi) those that are exempt from the NIH Guidelines (see Section III–F).

''Note: If an experiment falls into Sections III–A, III–B, or III–C and one of the other sections, the rules pertaining to Sections II–A, II–B, or III–C shall be followed. If an experiment falls into Section III–F and into either Sections III–D or III–E 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 Section IV–C–1–b–(2) and its subsections, Minor Actions).

''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), Major Actions).

''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/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838, the publication of the proposal in the **Federal Register** for 15 days of comment, review by RAC, and specific approval by NIH. The containment conditions or stipulation requirements for such experiments will be recommended by RAC and set by NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D, Major Actions Taken under the NIH Guidelines, which may be obtained from the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010 (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, Footnotes and References of Sections I–IV), if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by RAC.

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

''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), Institutional Biosafety Committee).

''Section III–B–1. Experiments Involving the Cloning of Toxin Molecules with LD_{50} 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_{50} of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphteria 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/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 10892–7010, (301) 496–9838.

''Section III–C. Experiments That Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/ORDA Registration Before Initiation

''Section III–C–1. Experiments Involving the Deliberate Transfer of Recombinant DNA or DNA or RNA Derived From Recombinant DNA Into One or More Human Subjects

''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 review process involving both NIH/ORDA and RAC. Investigators shall submit relevant information on the proposed human gene transfer experiments to NIH/ORDA. Submission of human gene transfer protocols to NIH will be in the format described in Appendix M–I, Submission Requirements—Human Gene Transfer Experiments. Submission to NIH/ORDA shall be for registration purposes and will ensure continued public access to relevant human gene transfer information in compliance with the NIH Guidelines. Investigational New Drug (IND) applications should be submitted to FDA in the format described in 21 CFR, chapter I, subchapter D, part 312, subpart B, section 23, IND content and Format.

''Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution invovled in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant DNA material into target cells for human application).

''RAC prefers that submission to NIH/ORDA in accordance with Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, contain no proprietary data or trade secrets, enabling all aspects of the review to be open to the public. Following receipt by NIH/ORDA, relevant information shall be entered into the NIH human gene transfer database for registration purposes. Summary information pertaining to the human gene transfer protocol will be forwarded to RAC members. NIH/ORDA summary information shall include comparisons to previously registered protocols. Specific items of similarity to previous experiments include (but are not limited to): (i) Gene delivery vehicle, (ii) functional gene, (iii) marker gene, (iv) packaging cell (if applicable), (v) disease application, (vi) route of administration, and (vii) patient selection criteria.

''RAC members shall notify NIH/ORDA within 15 working days if the protocol has been determined to represent novel characteristics requiring further public discussion.

''Full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by: (i) Three or more RAC members, or (ii) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate.

''Note: For specific directives concerning the use of retroviral vectors for gene delivery, consult Appendix B–V–1, Murine Retroviral Vectors.''

[Previously numbered Section III–C, Experiments that Require Institutional Biosafety Committee Approval Before Initiation, will be renumbered to Section III–D. References in this section will be changed due to renumbering.]

[Previously numbered Section III–D, Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation, will be renumbered to Section III–E. References in this section will be changed due to renumbering.]

[Previously numbered Section III–E, Exempt Experiments, will be renumbered to Section III–F. References in this section will be changed due to renumbering.]

II–D. Amendments to Section IV, Roles and Responsibilities

Section IV is amended to read:

''SECTION IV. ROLES AND RESPONSIBILITIES

''Section IV–A. Policy

''The safe conduct of experiments involving recombinant DNA depends on the individual conducting such activities. The NIH Guidelines cannot anticipate every possible situation. Motivation and good judgment are the key essentials to protection of health and the environment. The NIH Guidelines are intended to assist the institution, Institutional Biosafety Committee, Biological Safety Officer, and the Principal Investigator in determining safeguards that should be implemented. The NIH Guidelines will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, it is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines as well as to their specifics. Each institution (and the Institutional Biosafety Committee acting on its behalf) is responsible for ensuring that all recombinant DNA research conducted at or sponsored by that institution is conducted in compliance with the NIH Guidelines. General recognition of institutional authority and responsibility properly establishes accountability for safe conduct of the research at the local level. The following roles and responsibilities constitute an administrative framework in which safety is an essential and integral part of research involving recombinant DNA molecules. Further clarifications and interpretations of roles and responsibilities will be issued by NIH as necessary.

''Section IV–B. Responsibilities of the Institution

''Section IV–B–1. General Information

''Each institution conducting or sponsoring recombinant DNA research which is covered by the NIH Guidelines is responsible for ensuring that the research is conducted in full conformity with the provisions of the NIH Guidelines. In order to fulfill this responsibility, the institution shall:

''Section IV–B–1–a. Establish and implement policies that provide for the safe conduct of recombinant DNA research and that ensure compliance with the NIH Guidelines. As part of its general responsibilities for implementing the NIH Guidelines, the institution may establish additional procedures, as deemed necessary, to govern the institution and its components in the discharge of its responsibilities under the NIH Guidelines. Such procedures may include: (i) Statements formulated by the institution for the general implementation of the NIH Guidelines, and (ii) any additional precautionary steps the institution deems appropriate.

''Section IV–B–1–b. Establish an Institutional Biosafety Committee that meets the requirements set forth in Section IV–B–2–a and carries out the functions detailed in Section IV–B–2–b.

''Section IV–B–1–c. Appoint a Biological Safety Officer (who is also a member of the Institutional Biosafety Committee) if the institution: (i) Conducts recombinant DNA research at Biosafety Level (BL) 3 or BL4, or (ii) engages in large scale (greater than 10 liters) research. The Biological Safety Officer carries out the duties specified in Section IV–B–3.

''Section IV–B–1–d. Appoint at least one individual with expertise in plant, plant pathogen, or plant pest containment principles (who is a member of the Institutional Biosafety Committee) if the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix P, Physical and Biological Containment for Recombinant DNA Research Involving Plants.

''Section IV–B–1–e. Appoint at least one individual with expertise in animal containment principles (who is a member of the Institutional Biosafety Committee) if the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix Q, Physical and Biological Containment for Recombinant DNA Research Involving Animals.

''Section IV–B–1–f. Ensure that when the institution participates in or sponsors recombinant DNA research involving human subjects: (i) The Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary), and (ii) all aspects of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subject (Points to Consider), have been appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application).

''Section IV–B–1–g. Assist and ensure compliance with the NIH Guidelines by Principal Investigators conducting research at the institution as specified in Section IV–B–4.

''Section IV–B–1–h. Ensure appropriate training for the Institutional Biosafety Committee Chair and members, Biological Safety Officer and other containment experts (when applicable), Principal Investigators, and laboratory staff regarding laboratory safety and implementation of the NIH Guidelines. The Institutional Biosafety Committee Chair is responsible for ensuring that Institutional Biosafety Committee members are appropriately trained. The Principal Investigator is

responsible for ensuring that laboratory staff are appropriately trained. The institution is responsible for ensuring that the Principal Investigator has sufficient training; however, this responsibility may be delegated to the Institutional Biosafety Committee.

''Section IV–B–1–i. Determine the necessity for health surveillance of personnel involved in connection with individual recombinant DNA projects; and if appropriate, conduct a health surveillance program for such projects. The institution shall establish and maintain a health surveillance program for personnel engaged in large scale research or production activities involving viable organisms containing recombinant DNA molecules which require BL3 containment at the laboratory scale. The institution shall establish and maintain a health surveillance program for personnel engaged in animal research involving viable recombinant DNA-containing microorganisms that require BL3 or greater containment in the laboratory. The Laboratory Safety Monograph discusses various components of such a program (e.g., records of agents handled, active investigation of relevant illnesses, and the maintenance of serial serum samples for monitoring serologic changes that may result from the employees' work experience). Certain medical conditions may place a laboratory worker at increased risk in any endeavor where infectious agents are handled. Examples cited in the Laboratory Safety Monograph include gastrointestinal disorders and treatment with steroids, immunosuppressive drugs, or antibiotics. Workers with such disorders or treatment should be evaluated to determine whether they should be engaged in research with potentially hazardous organisms during their treatment or illness. Copies of the Laboratory Safety Monograph are available from the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''Section IV–B–1–j. Report any significant problems, violations of the NIH Guidelines, or any significant research-related accidents and illnesses to NIH/ORDA within thirty days, unless the institution determines that a report has already been filed by the Principal Investigator or Institutional Biosafety Committee. Reports shall be sent to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''Section IV–B–2. Institutional Biosafety Committee (IBC)

''The institution shall establish an Institutional Biosafety Committee whose responsibilities need not be restricted to recombinant DNA. The Institutional Biosafety Committee shall meet the following requirements:

''Section IV–B–2–a. Membership and Procedures

''Section IV–B–2–a–(1). The Institutional Biosafety Committee must be comprised of no fewer than five members so selected that they collectively have experience and expertise in recombinant DNA technology and the capability to assess the safety of recombinant DNA research and to identify any potential risk to public health or the environment. At least two members shall not be affiliated with the institution (apart from their membership on the Institutional Biosafety Committee) and who represent the interest of the surrounding community with respect to health and protection of the environment (e.g., officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical occupational health, or environmental concerns in the community). The Institutional Biosafety Committee shall include at least one individual with expertise in plant, plant pathogen, or plant pest containment principles when experiments utilizing Appendix P, Physical and Biological Containment for Recombinant DNA Research Involving Plants, require prior approval by the Institutional Biosafety Committee. The Institutional Biosafety Committee shall include at least one scientist with expertise in animal containment principles when experiments utilizing Appendix Q, Physical and Biological Containment for Recombinant DNA Research Involving Animals, require Institutional Biosafety Committee prior approval. When the institution conducts recombinant DNA research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV–B–3, Biological Safety Officer). When the institution participates in or sponsors recombinant DNA research involving human subjects, the institution must ensure that: (i) The Institutional Biosafety Committee has adequate expertise and training (using ad hoc consultants and deemed necessary) and (ii) all aspects of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider), have been appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant DNA material into target cells from human application).

''Note: Individuals, corporations, and institutions not otherwise covered by the NIH Guidelines, are encouraged to adhere to the standards and procedures set forth in Sections I through IV (see Section IV–E, Voluntary Compliance. The policy and procedures for establishing an Institutional Biosafety Committee under Voluntary Compliance, are specified in Section IV–D–2, Institutional Biosafety Committee Approval).

''Section IV–B–2–a–(2). In order to ensure the competence necessary to review and approve recombinant DNA activities, it is recommended that the Institutional Biosafety Committee: (i) Include persons with expertise in recombinant DNA technology, biological safety, and physical containment; (ii) include or have available as consultants persons knowledgeable in institutional commitments and policies, applicable law, standards of professional conduct and practice, community attitudes, and the environment, and (iii) include at least one member representing the laboratory technical staff.

''Section IV–B–2–a–(3). The institution shall file an annual report with NIH/ORDA which includes: (i) A roster of all Institutional Biosafety Committee members clearly indicating the Chair, contact person, Biological Safety Officer (if applicable), plan expert (if applicable), animal expert (if applicable), human gene therapy expertise or ad hoc consultant (if applicable); and (ii) biographical sketches of all Institutional Biosafety Committee members (including community members).

''Section IV–B–2–a–(4). No member of an Institutional Biosafety Committee may be involved (except to provide information requested by the Institutional Biosafety Committee) in the review or approval of a project in which he/she has been or expects to be engaged or has a direct financial interest.

''Section IV–B–2–a–(5). The institution, that is ultimately

responsible for the effectiveness of the Institutional Biosafety Committee, may establish procedures that the Institutional Biosafety Committee shall follow in its initial and continuing review and approval of applications, proposals, and activities.

''Section IV–B–2–a–(6). When possible and consistent with protection of privacy and proprietary interests, the institution is encouraged to open its Institutional Biosafety Committee meetings to the public.

''Section IV–B–a–(7). Upon request, the institution shall make available to the public all Institutional Biosafety Committee meeting minutes and any documents submitted to or received from funding agencies which the latter are required to make available to the public. If public comments are made on Institutional Biosafety Committee actions, the institution shall forward both the public comments and the Institutional Biosafety Committee's response to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''Section IV–B–2–b. Functions

''On behalf of the institution, the Institutional Biosafety Committee is responsible for:

''Section IV–B–2–b–(1). Reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with the NIH Guidelines as specified in Section III, Experiments Covered by the NIH Guidelines, and approving those research projects that are found to conform with the NIH Guidelines. This review shall include: (i) Independent assessment of the containment levels required by the NIH Guidelines for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; and (iii) ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements required by the NIH Guidelines.

''Section IV–B–2–b–(2). Notifying the Principal Investigator of the results of the Institutional Biosafety Committee's review and approval.

''Section IV–B–2–b–(3). Lowering containment levels for certain experiments as specified in Section III–C–2–a, Experiments in which DNA from Human or Animal Pathogens (Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eurkaryotic Host-Vector Systems.

''Section IV–B–2–b–(4). Setting containment levels as specified in Sections III–C–4–b, Experiments Involving Whole Animals, and III–C–5, Experiments Involving Whole Plants.

''Section IV–B–2–b–(5). Periodically reviewing recombinant DNA research conducted at the institution to ensure compliance with the NIH Guidelines.

''Section IV–B–2–b–(6). Adopting emergency plans covering accidental spills and personnel contamination resulting from recombinant DNA research.

''Note: The Laboratory Safety Monograph describes basic elements for developing specific procedures dealing with major spills of potentially hazardous materials in the laboratory, including information and references about decontamination and emergency plans. The NIH and the Centers for Disease Control and Prevention are available to provide consultation and direct assistance, if necessary, as posted in the Laboratory Safety Monograph. The institution shall cooperate with the state and local public health departments by reporting any significant research-related illness or accident that may be hazardous to the public health.

''Section IV–B–2–b–(7). Reporting any significant problems with or violations of the NIH Guidelines and any significant research-related accidents or illnesses to the appropriate institutional official and NIH/ORDA within 30 days, unless the Institutional Biosafety Committee determines that a report has already been filed by the Principal Investigator. Reports to NIH/ORDA shall be sent to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''Section IV–B–2–b–(8). The Institutional Biosafety Committee may not authorize initiation of experiments which are not explicitly covered by the NIH Guidelines until NIH (with the advice of the RAC when required) establishes the containment requirement.

''Section IV–B–2–b–(9). Performing such other functions as may be delegated to the Institutional Biosafety Committee under Section IV–B–2, Institutional Biosafety Committee.

''Section IV–B–3. Biological Safety Officer (BSO)

''Section IV–B–3–a. The institution shall appoint a Biological Safety Officer if it engages in large scale research or production activities involving viable organisms containing recombinant DNA molecules.

''Section IV–B–3–b. The institution shall appoint a Biological Safety Officer if it engages in recombinant DNA research at BL3 or BL4. The Biological Safety Officer shall be a member of the Institutional Biosafety Committee.

''Section IV–B–3–c. The Biological Safety Officer's duties include, but are not limited to:

''Section IV–B–3–c–(1). Periodic inspections to ensure that laboratory standards are rigorously followed;

''Section IV–B–3–c–(2). Reporting to the Institutional Biosafety Committee and the institution any significant problems, violations of the NIH Guidelines, and any significant research-related accidents or illnesses of which the Biological Safety Officer becomes aware unless the Biological Safety Officer determines that a report has already been filed by the Principal Investigator;

''Section IV–B–3–c–(3). Developing emergency plans for handling accidental spills and personnel contamination and investigating laboratory accidents involving recombinant DNA research;

''Section IV–B–3–c–(4). Providing advice on laboratory security;

''Section IV–B–3–c–(5). Providing technical advice to Principal Investigators and the Institutional Biosafety Committee on research safety procedures.

''Note: See the Laboratory Safety Monograph for additional information on the duties of the Biological Safety Officer.

''Section IV–B–4. Plant, Plant Pathogen, or Plant Pest Containment Expert

''When the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix P, Physical and Biological Containment for Recombinant DNA Research Involving Plants, the institution shall appoint at least one individual with expertise in plant, plant pathogen, or plant pest containment principles (who is a member of the Institutional Biosafety Committee).

''Section IV–B–5. Animal Containment Expert

''When the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix Q, Physical and Biological Containment for Recombinant DNA Research Involving Animals, the institution shall appoint at least one individual with expertise in animal containment principles (who is a member of the Institutional Biosafety Committee).

''Section IV–B–6. Human Gene Therapy Expertise

''When the institution participates in or sponsors recombinant DNA research

involving human subjects, the institution must ensure that: (i) The Institutional Biosafety Committee has adequate expertise and training (using ad hoc consultants as deemed necessary) and (ii) all aspects of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider), have been appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA.

''Section IV–B–7. Principal Investigator (PI)

''On behalf of the institution, the Principal Investigator is responsible for full compliance with the NIH Guidelines in the conduct of recombinant DNA research.

''Section IV–B–7–a. General Responsibilities

''As part of this general responsibility, the Principal Investigator shall:

''Section IV–B–7–a–(1). Initiate or modify no recombinant DNA research which requires Institutional Biosafety Committee approval prior to initiation (see Sections III–A, III–B, III–C, and III–D, Experiments Covered by the NIH Guidelines) until that research or the proposed modification thereof has been approved by the Institutional Biosafety Committee and has met all other requirements of the NIH Guidelines;

''Section IV–B–7–a–(2). Determine whether experiments are covered by Section III–D, Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation, and ensure that the appropriate procedures are followed;

''Section IV–B–7–a–(3). Report any significant problems, violations of the NIH Guidelines, or any significant research-related accidents and illnesses to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/ORDA, and other appropriate authorities (if applicable) within 30 days. Reports to NIH/ORDA shall be sent to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838;

''Section IV–B–7–a–(4). Report any new information bearing on the NIH Guidelines to the Institutional Biosafety Committee and to NIH/ORDA (reports to NIH/ORDA shall be sent to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838);

''Section IV–B–7–a–(5). Be adequately trained in good microbiological techniques;

''Section IV–B–7–a–(6). Adhere to Institutional Biosafety Committee approved emergency plans for handling accidental spills and personnel contamination; and

''Section IV–B–7–a–(7). Comply with shipping requirements for recombinant DNA molecules (see Appendix H, Shipment, for shipping requirements and the Laboratory Safety Monograph for technical recommendations).

''Section IV–B–7–b. Submissions by the Principal Investigator to NIH/ORDA

''The Principal Investigator shall:

''Section IV–B–7–b–(1). Submit information to NIH/ORDA for certification of new host-vector systems;

''Section IV–B–7–b–(2). Petition NIH/ORDA, with notice to the Institutional Biosafety Committee, for proposed exemptions to the NIH Guidelines;

''Section IV–B–7–b–(3). Petition NIH/ORDA, with concurrence of the Institutional Biosafety Committee, for approval to conduct experiments specified in Sections III–A–1, Major Actions Under the NIH Guidelines, and III–B, Experiments that Require NIH/ORDA and Institutional Biosafety Committee Approval Before Initiation;

''Section IV–B–7–b–(4). Petition NIH/ORDA for determination of containment for experiments requiring case-by-case review; and

''Section IV–B–7–b–(5). Petition NIH/ORDA for determination of containment for experiments not covered by the NIH Guidelines.

''Section IV–B–7–b–(6). Ensure that all aspects of Appendix M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects, have been appropriately addressed prior to submission of human gene therapy experiments to NIH/ORDA.

''Section IV–B–7–c. Submissions by the Principal Investigator to the Institutional Biosafety Committee

''The Principal Investigator shall:

''Section IV–B–7–c–(1). Make an initial determination of the required levels of physical and biological containment in accordance with the NIH Guidelines;

''Section IV–B–7–c–(2). Select appropriate microbiological practices and laboratory techniques to be used for the research;

''Section IV–B–7–c–(3). Submit the initial research protocol and any subsequent changes (e.g., changes in the source of DNA or host-vector system), if covered under Sections III–A, III–B, III–C, or III–D (Experiments Covered by the NIH Guidelines), to the Institutional Biosafety Committee for review and approval or disapproval; and

''Section IV–B–7–c–(4). Remain in communication with the Institutional Biosafety Committee throughout the conduct of the project.

''Section IV–B–7–d. Responsibilities of the Principal Investigator Prior To Initiating Research

''The Principal Investigator shall:

''Section IV–B–7–d–(1). Make available to all laboratory staff the protocols that describe the potential biohazards and the precautions to be taken;

''Section IV–B–7–d–(2). Instruct and train laboratory staff in: (i) The practices and techniques required to ensure safety, and (ii) the procedures for dealing with accidents; and

''Section IV–B–7–d–(3). Inform the laboratory staff of the reasons and provisions for any precautionary medical practices advised or requested (e.g., vaccinations or serum collection).

''Section IV–B–7–e. Responsibilities of the Principal Investigator During the Conduct of the Research

''The Principal Investigator shall:

''Section IV–B–7–e–(1). Supervise the safety performance of the laboratory staff to ensure that the required safety practices and techniques are employed;

''Section IV–B–7–e–(2). Investigate and report any significant problems pertaining to the operation and implementation of containment practices and procedures in writing to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/ORDA, and other appropriate authorities (if applicable) (reports to NIH/ORDA shall be sent to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838);

''Section IV–B–7–e–(3). Correct work errors and conditions that may result in the release of recombinant DNA materials; and

''Section IV–B–7–e–(4). Ensure the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., purity and genotypic and phenotypic characteristics).

''Section IV–B–7–e–(5). Comply with reporting requirements for human gene

transfer experiments conducted in compliance with the NIH Guidelines (see Appendix M–VII, Reporting Requirements—Human Gene Transfer Protocols).

''Section IV–C. Responsibilities of the National Institutes of Health (NIH)

''Section IV–C–1. NIH Director

''The NIH Director is responsible for: (i) Establishing the NIH Guidelines, (ii) overseeing their implementation, and (iii) their final interpretation. The NIH Director has responsibilities under the NIH Guidelines that involve ORDA and RAC. ORDA's responsibilities under the NIH Guidelines are administrative. Advice from RAC is primarily scientific, technical, and ethical. In certain circumstances, there is specific opportunity for public comment with published response prior to final action.

''Section IV–C–1–a. General Responsibilities

''The NIH Director is responsible for:

''Section IV–C–1–a–(1). Promulgating requirements as necessary to implement the NIH Guidelines;

''Section IV–C–1–a–(2). Establishing and maintaining RAC to carry out the responsibilities set forth in Section IV–C–2, Recombinant DNA Advisory Committee (RAC membership is specified in its charter and in Section IV–C–2);

''Section IV–C–1–a–(3). Establishing and maintaining NIH/ORDA to carry out the responsibilities defined in Section IV–C–3, Office of Recombinant DNA Activities;

''Section IV–C–1–a–(4). Conducting and supporting training programs in laboratory safety for Institutional Biosafety Committee members, Biological Safety Officers and other institutional experts (if applicable), Principal Investigators, and laboratory staff.

''Section IV–C–1–a–(5). Establishing and convening Gene Therapy Policy Conferences as described in Appendix L, Gene Therapy Policy Conferences.

''Section IV–C–1–b. Specific Responsibilities

''In carrying out the responsibilities set forth in this section, the NIH Director, or a designee shall weigh each proposed action through appropriate analysis and consultation to determine whether it complies with the NIH Guidelines and presents no significant risk to health or the environment.

''Section IV–C–1–b–(1). Major Actions

''To execute Major Actions, the NIH Director shall seek the advice of 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)–(a). Changing containment levels for types of experiments that are specified in the NIH Guidelines when a Major Action is involved;

''Section IV–C–1–b–(1)–(b). Assigning containment levels for types of experiments that are not explicitly considered in the NIH Guidelines when a Major Action is involved;

''Section IV–C–1–b–(1)–(c). Promulgating and amending a list of classes of recombinant DNA molecules to be exempt from the NIH Guidelines because they consist entirely of DNA segments from species that exchange DNA by known physiological processes or otherwise do not present a significant risk to health or the environment;

''Section IV–C–1–b–(1)–(d). Permitting experiments specified by Section III–A, Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation;

''Section IV–C–1–b–(1)–(e). Certifying new host-vector systems with the exception of minor modifications of already certified systems (the standards and procedures for certification are described in Appendix I–II, Certification of Host-Vector Systems). Minor modifications constitute (e.g., those of minimal or no consequence to the properties relevant to containment); and

''Section IV–C–1–b–(1)–(f). Adopting other changes in the NIH Guidelines.

''Section IV–C–1–b–(2). Minor Actions

''NIH/ORDA shall carry out certain functions as delegated to it by the NIH Director (see Section IV–C–3, Office of Recombinant DNA Activities). Minor Actions (as determined by NIH/ORDA in consultation with the RAC Chair and one or more RAC members, as necessary) will be transmitted to RAC and Institutional Biosafety Committee Chairs:

''Section IV–C–1–b–(2)–(a). Changing containment levels for experiments that are specified in Section III, Experiments Covered by the NIH Guidelines (except when a Major Action is involved);

''Section IV–C–1–b–(2)–(b). Assigning containment levels for experiments not explicitly considered in the NIH Guidelines;

''Section IV–C–1–b–(2)–(c). Revising the Classification of Etiologic Agents for the purpose of these NIH Guidelines (see Section V–A, Footnotes and References of Sections I–IV).

''Section IV–C–1–b–(2)–(d). Interpreting the NIH Guidelines for experiments to which the NIH Guidelines do not specifically assign containment levels;

''Section IV–C–1–b–(2)–(e). Setting containment under Sections III–C–1–d, Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems, and III–C–2–b, Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems;

''Section IV–C–1–b–(2)–(f). Approving minor modifications of already certified host-vector systems (the standards and procedures for such modifications are described in Appendix I–II, Certification of Host-Vector Systems);

''Section IV–C–1–b–(2)–(g). Decertifying already certified host-vector systems;

''Section IV–C–1–b–(2)–(h). Adding new entries to the list of molecules toxic for vertebrates (see Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates); and

''Section IV–C–1–b–(2)–(i). Determining appropriate containment conditions for experiments according to case precedents developed under Section IV–C–1–b–(2)–(c).

''Section IV–C–2. Recombinant DNA Advisory Committee (RAC)

''RAC is responsible for carrying out specified functions cited below as well as others assigned under its charter or by the DHHS Secretary and the NIH Director. RAC consists of 15 voting members including the Chair, appointed by the DHHS Secretary or his/her designee, at least 8 of whom are selected from authorities knowledgeable in the fields of molecular genetics, molecular biology, recombinant DNA research, or other scientific fields. At least 4 members of RAC shall be persons knowledgeable in applicable law, standards of professional conduct and practice, public attitudes, the environment, public health, occupational health, or related fields. Representatives from Federal agencies shall serve as non-voting members.

Nominations for RAC members may be submitted to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''All meetings of RAC shall be announced in the **Federal Register,** including tentative agenda items, 15 days before the meeting. Final agendas, if modified, shall be available at least 72 hours before the meeting. No item defined as a Major Action under Section IV–C–1–b–(1) may be added to an agenda following **Federal Register** publication.

''RAC shall be responsible for:

''Section IV–C–2–a. Advising the NIH Director on the following actions: (1) Adopting changes in the NIH Guidelines. (2) Assigning containment levels, changing containment levels, and approving experiments considered as Major Actions under the NIH Guidelines, i.e., the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture. (3) Promulgating and amending lists of classes of recombinant DNA molecules to be exempt from the NIH Guidelines because they consist entirely of DNA segments from species that exchange DNA by known physiological processes or otherwise do not present a significant risk to health or the environment. (4) Certifying new host-vector systems.

''Section IV–C–2–b. Identifying novel human gene transfer experiments deserving of public discussion by the full RAC;

''Section IV–C–2–c. Transmitting to the NIH Director specific comments/recommendations about: (i) A specific human gene transfer experiment, or (ii) a category of human gene transfer experiments;

''Section IV–C–2–d. Publicly reviewing human gene transfer clinical trial data and relevant information evaluated and summarized by NIH/ORDA in accordance with the annual data reporting requirements;

''Section IV–C–2–e. Identifying broad scientific, safety, social, and ethical issues relevant to gene therapy research as potential Gene Therapy Policy Conference topics;

''Section IV–C–2–f. Identifying novel social and ethical issues relevant to specific human applications of gene transfer and recommending appropriate modifications to the Points to Consider that will provide guidance in the preparation of relevant Informed Consent documents; and

''Section IV–C–2–g. Identifying novel scientific and safety issues relevant to specific human applications of gene transfer and recommending appropriate modifications to the Points to Consider that will provide guidance in the design and submission of human gene transfer clinical trials.

''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. Serving as the focal point for public access to summary information pertaining to human gene transfer experiments;

''Section IV–C–3–b. Serving as the focal point for data management of human gene transfer experiments;

''Section IV–C–3–c. Administering the annual data reporting requirements (and subsequent review) for human gene transfer experiments (see Appendix M–VII, Reporting Requirements—Human Gene Transfer Protocols);

''Section IV–C–3–d. Transmitting comments/recommendations arising from public RAC discussion of a novel human gene transfer experiment to the NIH Director. RAC recommendations shall be forwarded to the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate.

''Section IV–C–3–e. Collaborating with Principal Investigators, Institutional Biosafety Committees, Institutional Review Boards, and other DHHS components (including FDA and Office for Protection from Research Risks), to ensure human gene transfer experiment registration compliance in accordance with Appendix M–I, Submission Requirements, Human Gene Transfer Experiments of the NIH Guidelines.

''Section IV–C–3–f. Administering Gene Therapy Policy Conferences as deemed appropriate by the NIH Director (see Appendix L, Gene Therapy Policy Conference).

''Section IV–C–3–g. 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_{50} of less than or equal to 100 nanagrams per kilogram body weight in organisms other than Escherichia coli K–12 (see Section III–B–1, Experiments Involving the Cloning of Toxin Molecules with LD_{50} of Less than 100 Nanograms Per Kilogram Body Weight, Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Verebrates);

''Section IV–C–3–h. Serving as the executive secretary of RAC;

''Section IV–C–3–i. Publishing in the **Federal Register**:

''Section IV–C–3–i–(1). Announcements of RAC meetings and tentative 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–i–(2). Announcements of Gene Therapy Policy Conferences and tentative agendas at least 15 days in advance;

''Section IV–C–3–i–(3). Proposed Major Actions (see Section IV–C–1–b–(1), Major Actions) at least 15 days prior to the RAC meeting; and

''Section IV–C–3–j. 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, Institutional Biosafety Committee (IBC), giving its approval to the Institutional Biosafety Committee membership.

''Section IV–C–4. Other NIH Components

''Other NIH components shall be responsible for certifying maximum containment (BL4) facilities, inspecting them periodically, and inspecting other recombinant DNA facilities as deemed necessary.

''Section IV–D. Voluntary Compliance

''Section IV–D–1. Basic Policy—Voluntary Compliance

''Individuals, corporations, and institutions not otherwise covered by the NIH Guidelines are encouraged to follow the standards and procedures set forth in Sections I through IV. In order to simplify discussion, references hereafter to 'institutions' are intended to encompass corporations and individuals who have no organizational affiliation. For purposes of complying with the NIH Guidelines, and individual intending to carry out research involving recombinant DNA is encouraged to

affiliate with an institution that has an Institutional Biosafety Committee approved under the NIH Guidelines.

''Since commercial organizations have special concerns, such as protection of proprietary data, some modifications and explanations of the procedures are provided in Section IV–D–2 through IV–D–5–b, Voluntary Compliance, in order to address these concerns.

''Section IV–D–2. Institutional Biosafety Committee Approval—Voluntary Compliance

''It should be emphasized that employment of an Institutional Biosafety Committee member solely for purposes of membership on the Institutional Biosafety Committee does not itself make the member an institutionally affiliated member. Except for the unaffiliated members, a member of an Institutional Biosafety Committee for an institution not otherwise covered by the NIH Guidelines may participate in the review and approval of a project in which the member has a direct financial interest so long as the member has not been, and does not expect to be, engaged in the project. Section IV–B–2–a–(4), Institutional Biosafety Committee, is modified to that extent for purposes of these institutions.

''Section IV–D–3. Certification of Host-Vector Systems—Voluntary Compliance

''A host-vector system may be proposed for certification by the NIH Director in accordance with the procedures set forth in Appendix I–II, Certification of Host-Vector Systems. In order to ensure protection for proprietary data, any public notice regarding a host-vector system which is designated by the institution as proprietary under Section IV–D, Voluntary Compliance, will be issued only after consultation with the institution as to the content of the notice.

''Section IV–D–4. Requests for Exemptions and Approvals—Voluntary Compliance

''Requests for exemptions or other approvals as required by the NIH Guidelines should be submitted based on the procedures set forth in Sections I through IV. In order to ensure protection for proprietary data, any public notice regarding a request for an exemption or other approval which is designated by the institution as proprietary under Section IV–D–5–a, Voluntary Compliance, will be issued only after consultation with the institution as to the content of the notice.

''Section IV–D–5. Protection of Proprietary Data—Voluntary Compliance

''Section IV–D–a. General

''In general, the Freedom of Information Act requires Federal agencies to make their records available to the public upon request. However, this requirement does not apply to, among other things, 'trade secrets and commercial or financial information that is obtained from a person and that is privileged or confidential.' Under 18 U.S.C. 1905, it is a criminal offense for an officer or employee of the U.S. or any Federal department or agency to publish, divulge, disclose, or make known 'in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, (or) processes * * * of any person, firm, partnership, corporation, or association.' This provision applies to all employees of the Federal Government, including special Government employees. Members of RAC are 'special Government employees.'

''In submitting to NIH for purposes of voluntary compliance with the NIH Guidelines, an institution may designate those items of information which the institution believes constitute trade secrets, privileged, confidential, commercial, or financial information. If NIH receives a request under the Freedom of Information Act for information so designated, NIH will promptly contact the institution to secure its views as to whether the information (or some portion) should be released. If NIH decides to release this information (or some portion) in response to a Freedom of Information request or otherwise, the institution will be advised and the actual release will be delayed in accordance with 45 Code of Federal Regulations, § 5.65 (d) and (e).

''Section IV–D–5–b. Pre-submission Review

''Any institution not otherwise covered by the NIH Guidelines, which is considering submission of data or information voluntarily to NIH, may request pre-submission review of the records involved to determine if NIH will make all or part of the records available upon request under the Freedom of Information Act.

''A request for pre-submission review should be submitted to NIH/ORDA along with the records involved to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838. These records shall be clearly marked as being the property of the institution on loan to NIH solely for the purpose of making a determination under the Freedom on Information Act. NIH/ORDA will seek a determination from the responsible official under DHHS regulations (45 CFR part 5) as to whether the records involved, (or some portion) will be made available to members of the public under the Freedom of Information Act. Pending such a determination, the records will be kept separate from NIH/ORDA files, will be considered records of the institution and not NIH/ORDA, and will not be received as part of NIH/ORDA files. No copies will be made of such records.

''NIH/ORDA will inform the institution of the DHHS Freedom of Information Officer's determination and follow the institution's instructions as to whether some or all of the records involved are to be returned to the institution or to become a part of NIH/ORDA files. If the institution instructs NIH/ORDA to return the records, no copies or summaries of the records will be made or retained by DHHS, NIH, or ORDA. The DHHS Freedom of Information Officer's determination will represent that official's judgment at the time of the determination as to whether the records involved (or some portion) would be exempt from disclosure under the Freedom of Information Act if at the time of the determination the records were in NIH/ORDA files and a request was received for such files under the Freedom of Information Act.''

II–E. Amendments to Appendix A, Exemptions Under Section III–E–5—Sub-lists of Natural Exchanges

Appendix A, first paragraph, is amended to reflect renumbering of a previous section.

II–F. Amendments to Appendix C, Exemptions Under Section III–E–6

Appendix C is amended to reflect renumbering of a previous section.

II–G. Amendments to Appendix I, Biological Containment

After the first paragraph in Section I–II–A, Responsibility, the following Note is added:

''**Note.** A host-vector system may be proposed for certification by the NIH Director in accordance with the procedures set forth in Appendix I–II, Certification of Host-Vector Systems. In order to ensure protection for

proprietary data, any public notice regarding a host-vector system which is designated by the institution as proprietary under Section IV–D, Voluntary Compliance, will be issued only after consultation with the institution as as to the content of the notice (see Section IV–D–3, Certification of Host-Vector Systems-Voluntary Compliance).''

II–H. Addition of Appendix L, Gene Therapy Policy Conferences, to the NIH Guidelines

Appendix L is to read:

''Appendix L. Gene Therapy Policy Conferences (GTPCs)

''In order to enhance the depth and value of public discussion relevant to scientific, safety, social, and ethical implications of gene therapy research, the NIH Director will convene GTPCs at regular intervals. As appropriate, the NIH Director may convene a GTPC in conjunction with a RAC meeting. GTPCs will be administered by NIH/ORDA. Conference participation will not involve a standing committee membership but rather will offer the unique advantage of assembling numerous participants who possess significant scientific, ethical, and legal expertise and/or interest that is directly applicable to a specific gene therapy research issue. At least one member of RAC will serve as Co-chair of each GTPC and report the findings of each GTPC to RAC at its next scheduled meeting. The RAC representative for each GTPC will be chosen based on the participant's area of expertise relative to the specific gene therapy research issue to be discussed. All RAC members will be invited to attend GTPCs. GTPCs will have representation from other Federal agencies, including FDA and OPRR. GTPCs will focus on broad overarching policy and scientific issues related to gene therapy research. Proposals for GTPC topics may be submitted by members of RAC, representatives of academia, industry, patient and consumer advocacy organizations, other Federal agencies, professional scientific societies, and the general public. GTPC topics will not be limited to discussion of human applications of gene therapy research, i.e., they may include basic research on the use of novel gene delivery vehicles, or novel applications of human gene transfer. The RAC, with the Director's approval, will have the primary responsibility for planning GTPC agendas. GTPC findings will be transmitted to the NIH Director and will be made publicly available. The NIH Director anticipates that this public policy forum will serve as a model for interagency communication and collaboration, concentrated expert discussion of novel scientific issues and their potential societal implications, and enhanced opportunity for public discussion of specific issues and potential impact of such applications on human health and the environment.''

II–I. Amendments to Appendix M, Points To Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules Into One or More Human Subjects

Appendix M is amended to read:

''Appendix M. Points To Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules Into 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 NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M (see Section I–C, General Applicability).

''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 that 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, RAC is prepared to consider proposals for somatic cell gene transfer.

''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.

''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 review process involving both NIH/ORDA and RAC. Investigators shall submit their relevant information on the proposed human gene transfer experiments to NIH/ORDA. Submission of human gene transfer protocols to NIH will be in the format described in Appendix M–I, Submission Requirements—Human Gene Transfer Experiments. Submission to NIH shall be for registration purposes and will ensure continue public access to relevant human gene transfer information conducted in compliance with the NIH Guidelines. Investigational New Drug (IND) applications should be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format.

''Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application).

''Factors that may contribute to public discussion of a human gene transfer experiment by RAC 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 discussion are those determined not to represent possible risk to human health or the environment. Full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by: (i) Three or more RAC members, or (ii) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. If the Director, NIH, determines that an experiment will undergo full RAC discussions, NIH/ORDA will immediately notify the Principal Investigator. RAC members may forward individual requests for additional information relevant to a specific protocol through NIH/ORDA to the Principal Investigator. In making a

determination whether an experiment is novel, and thus deserving of full RAC discussion, reviewers will examine the scientific rationale, scientific context (relative to other proposals reviewed by RAC), whether the preliminary *in vitro* and *in vivo* safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate. Relevant documentation will be included in the material for the RAC meeting at which the experiment is scheduled to be discussed. RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed (see Section IV–D–5, Protection of Proprietary Data). RAC prefers 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.

''Note: Any application submitted to NIH/ORDA shall not be designated as 'confidential' in its entirety. In the event that a sponsor determines that specific responses to one or more of the items described in Appendix M should be considered as proprietary or trade secret, each item should be clearly identified as such. The cover letter (attached to the submitted material) shall: (1) Clearly indicate that select portions of the application contain information considered as proprietary or trade secret, (2) a brief explanation as to the reason that each of these items is determined proprietary or trade secret.

''Public discussion of human gene transfer experiments (and access to relevant information) shall serve to inform the public about the technical aspects of the proposals, meaning and significance of the research, and significant safety, social, and ethical implications of the research. RAC discussion is intended to ensure safe and ethical conduct of gene therapy experiments and facilitate public understanding of this novel area of biomedical research.

In its evaluation of human gene transfer proposals, RAC 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 request information that will enable RAC and NIH/ORDA 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).

''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 Experiments

''Investigators must submit the following material to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838 (see exemption in Appendix M–VIII–A, Footnotes of Appendix M). Proposals shall be submitted to NIH/ORDA in the following order: (1) Scientific abstract; (2) non-technical abstract; (3) Institutional Biosafety Committee and Institutional Review Board approvals and their deliberations pertaining to your protocol (Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application)); (4) Responses to Appendix M–II through M–V, Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues (the pertinent responses can be provided in the protocol or as an appendix to the protocol); (5) clinical protocol (as approved by the local Institutional Biosafety Committee and Institutional Review Board); (6) Informed Consent document—approved by the Institutional Review Board (see Appendix M–III, Informed Consent); (7) appendices (including tables, figures, and manuscripts); and (8) curricula vitae—2 pages for each key professional person in biographical sketch format. Investigational New Drug (IND) applications shall be submitted to FDA in the format described in 21 CFR, chapter I, subchapter D, part 312, subpart B, section 23, IND Content and Format. Submissions to FDA should be sent to 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.

''Appendix M–II. Description of the Proposal''

[This section remains unchanged]

''Appendix M–III. Informed Consent''

[This section remains unchanged]

''Appendix M–IV. Privacy and Confidentiality''

[This section remains unchanged]

''Appendix M–V. Special Issues''

[This section remains unchanged]

''Appendix M–VI. RAC Review—Human Gene Transfer Experiments

''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 RAC). RAC prefers that information provided in response to Appendix M, Points to Consider, contain no proprietary data or trade secrets, enabling all aspects of the discussion to be open to the public.

''Appendix M–VI–A. RAC Members' Written Comments

''Following receipt by NIH/ORDA, summary information on each human gene transfer protocol will be forwarded to RAC members. Each RAC member shall notify NIH/ORDA within 15 working days regarding the necessity for full RAC discussion. Full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by: (i) Three or more RAC members, or (ii) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. If the Director, NIH, determines that an experiment will undergo full RAC discussion, NIH/ORDA will immediately notify the Principal Investigator. RAC members may forward individual requests for additional information relevant to a specific protocol through NIH/ORDA to the Principal Investigator. In making a determination whether an experiment is novel, and thus deserving of full RAC

discussion, reviewers shall examine the scientific rationale, scientific context (relative to other proposals reviewed by RAC), whether the preliminary *in vitro* and *in vitro* safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring insititution, and other DHHS components, as appropriate.

''Appendix M–VII. Reporting Requirements—Human Gene Transfer Protocols

''Appendix M–VII–A. Investigational New Drug Application Reporting

''Upon receipt of notification of permission to proceed with an Investigational New Drug application for a human gene transfer protocol, the Principal Investigator(s) shall submit a written report that includes the following information: (1) How the investigator(s) responded to RAC's recommendations on the protocol (if applicable), and (2) any modifications to the protocol as required by FDA.

''Appendix M–VII–B. Annual Data Reporting and Gene Therapy Database

''Investigators shall comply with annual data reporting requirements. Annual Data Report forms will be forwarded by NIH/ORDA to investigators. Data submitted in these reports will be evaluated by RAC and NIH/ORDA, and reviewed at a future RAC meeting. Information obtained through annual data reporting will be included in a human gene transfer database that will be administered by NIH/ORDA. The purpose of this human gene transfer database is to: (1) Maintain an institutional memory, (2) provide administrative details of protocol registration, (3) provide annual status reports of protocols, (4) facilitate risk assessment of individual applications of human gene transfer, and (5) enhance public awareness of relevant scientific, safety, social, and ethical issues.

''Appendix M–VII–C. Adverse Event Reporting

''Investigators who have received approval for FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local Institutional Review Board, Institutional Boisafety Committee, Office for Protection from Research Risks (if applicable), 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/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

''Appendix VIII. Footnotes of Appendix M

''Appendix VIII–A. Human studies in which induction or enhancement of an immune response to a vector-encoded microbialimmunogen 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 exempt from Appendix M–I, Submission Requirements, and Appendix M–VII, Reporting Requirements—Human Gene Transfer Experiments.''

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and Federal research program in which recombinant DNA molecule techniques could be used, it has been determined not to be cost effective or in the public interst 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: October 22, 1997.

Harold Varmus,

Director, National Institutes of Health.

[FR Doc. 97–28921 Filed 10–30–97; 8:45 am]

BILLING CODE 4140–01–M