DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Proposed Actions Under the Guidelines

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules.

SUMMARY: On July 8, 1996, the NIH published a Notice of Intent to modify NIH's oversight of gene therapy. Specifically, the NIH proposed to: (1) Terminate the NIH Recombinant DNA Advisory Committee (RAC); (2) relinquish all approval responsibilities for recombinant DNA experiments involving human gene transfer to the Food and Drug Administration (FDA), which holds statutory authority for such approval; (3) establish the Office of Recombinant DNA Activities Advisory Committee (OAC); (4) limit the membership of OAC to 6–10 individuals, as compared to the 25 members appointed to the RAC; (5) regularly convene Gene Therapy Policy Conferences; and (6) continue the publicly available, comprehensive NIH database of human gene transfer clinical trials, including adverse events.

The NIH received 71 written comments in response to the Notice of Intent, reflecting a broad range of opinions. After careful consideration of these comments, the NIH Director revised the proposal put forward in the July 8, Notice of Intent. This revised proposal, described herein as the Notice of Proposed Actions, reflects both public opinion and the NIH Director's intent to increase the effectiveness and efficiency of public discussion of gene therapy. Specifically, because of the historical importance of the RAC as a public platform for discussion of the science, as well as the safe and ethical conduct of gene therapy research, the NIH Director proposes to: (1) Retain the 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) reduce the membership of RAC from 25 members to 15 members; (4) regularly convene Gene Therapy Policy Conferences; and (5) maintain public access to human gene transfer clinical trial information.

This notice sets forth proposed actions to be taken by the Director, National Institutes of Health (NIH), regarding enhanced mechanisms for scientific and ethical/societal oversight of human gene transfer research, under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) (59 FR 34496, amended 59 FR 40170, amended 60 FR 20726, amended 61 FR 1482, amended 61 FR 10004). These proposed actions reflect a revision of the proposal set forth in the July 8, 1996, Federal Register Notice of Intent. It is important to note that the proposal outlined in the July 8, 1996, Notice of Intent and the revised proposed actions described herein are applicable only to recombinant DNA experiments involving human subjects. NIH oversight of recombinant DNA research conducted in compliance with the NIH Guidelines (with the exception of human gene transfer research) remains unchanged.

DATES: Interested parties are invited to submit comments concerning this proposal. Comments received by December 2, 1996, will be reproduced and distributed to the Recombinant DNA Advisory Committee for consideration at its December 9, 1996, meeting. After consideration of this proposal and comments by the Recombinant DNA Advisory Committee, the Director of the National Institutes of Health will issue decisions in accordance with the NIH Guidelines.

ADDRESSES: Written comments and recommendations should be submitted to Debra Knorr, Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, or by FAX to 301–496–9839.

All comments received in response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX 301–496–9839.

SUPPLEMENTARY INFORMATION: In l990, the NIH reviewed and approved its first gene therapy experiment. In the ensuing six years, knowledge about and experience with somatic cell human gene therapy has grown substantially. As the field has matured, the NIH has sought to preserve both the effectiveness and efficiency of its oversight of human gene therapy research by periodically modifying the functions of the Recombinant DNA Advisory Committee (RAC).

When the NIH first published the Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Into the Genome of Human Subjects (Points to Consider) in the Federal Register in 1990, each human gene therapy experiment was reviewed by both the Human Gene Therapy Subcommittee (HGTS) and the RAC, and then approved by the NIH Director. In 1992, when the HGTS was merged with its parent committee (the Recombinant DNA Advisory Committee), the NIH adopted a semiannual reporting process for human gene transfer experiments. One year later, the NIH established an expedited review process for single patient protocols by allowing written RAC review of such protocols between the committee's quarterly meetings. In the following year, the NIH adopted an accelerated review process for certain categories of clinical trials that had been routinely reviewed by the RAC and determined not to represent any significant risk to human health and the environment. Under this mechanism, such protocols were subject to written review by several RAC members outside of the committee's quarterly meetings and NIH Office of Recombinant DNA Activities (ORDA) approval. In l995, another change relevant to RAC review occurred when the RAC approved consolidated review, in which all protocols determined not to represent a novel gene therapy delivery strategy or target disease were exempted from RAC review and approval and were approved solely by the Food and Drug Administration (FDA).

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 NIH oversight of human gene transfer research. Specifically, it was proposed that the RAC would be terminated and that all approval responsibilities for recombinant DNA experiments involving human gene transfer would be relinquished to the FDA, which retains statutory authority for such approval. Under this revised oversight 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. 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.

I. Revised Proposal in Response to Public Comment

In response to the Notice of Intent, the 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 were submitted.

In response to public opinion and in keeping with the NIH Director's intent to increase the usefulness and productivity of public discussion of gene therapy, the NIH Director has revised the proposal set forth in the July 8, 1996, Notice of Intent. In this amended proposal, the NIH Director proposes to retain the RAC, while modifying its responsibilities relevant to human gene therapy research. In doing so, the NIH Director acknowledges the public's view that the RAC has historical importance as a societal platform for discussion of the science, as well as the safe and ethical conduct of gene therapy research. The NIH Director recognizes that this tradition is lacking in OAC and, therefore, decided to retain the RAC instead of replacing it with OAC. The NIH Director's intent to increase the effectiveness and efficiency of the RAC will be achieved by the continuing discussion of novel human gene transfer experiments without RAC approval of individual human gene transfer experiments. The membership of the RAC will be reduced from 25 to 15 individuals to increase efficiency while ensuring sufficient representation from scientific, ethical, and legal communities. In order to stimulate public discussion of the safety, scientific merit, and ethical nature of present and future opportunities in gene therapy research, the NIH Director proposes to regularly convene Gene Therapy Policy Conferences (GTPCs). Finally, recognizing the importance of public access to human gene transfer clinical trial information, the NIH will continue to maintain the gene therapy clinical trial database.

II. Analysis of Written Comments in Response to the Notice of Intent

The following analysis compares and contrasts, point by point, the proposal set forth in the July 8, 1996, Notice of Intent, the public response to each point, and the new proposal described herein as the Notice of Proposed Actions.

II–A. Notice of Intent

Terminate the RAC and establish the Office of Recombinant DNA Activities Advisory Committee (OAC).

Notice of Proposed Actions

Retain the RAC, while modifying its roles and responsibilities relevant to human gene therapy research.

Of the 71 comments submitted in response to the Notice of Intent, 10 did not specifically address NIH's proposal to terminate the RAC. Of the 61 responses which did address the proposal to terminate the RAC, 20 expressed support and 41 expressed opposition. Supporting and opposing comments were submitted by representatives of: Academia (5 supported, 15 opposed), industry (8 supported, 4 opposed), private citizens (4 supported, 6 opposed), current and previous RAC members (3 supported, 10 opposed), professional scientific societies (1 supported, 2 opposed), the ethics community (1 supported, 5 opposed), consumer advocacy organizations (0 supported, 4 opposed), patient advocacy organizations (0 supported, 6 opposed), and professional scientific societies (0 supported, 2 opposed).

Comments in support of termination of the RAC reflected an interest in making substantive changes in the role of the RAC. Most of these comments supported the proposed restructuring of the functions of the RAC and did not specifically endorse termination of RAC. Opposing comments focused on the historical importance of retaining the RAC as an internationally recognized forum for public discussion of the science, safety, and ethics of human gene therapy research. These authors articulated the critical role that the RAC plays in maintaining public confidence in human gene therapy research.

The importance of the continuation of the RAC, *per se,* was underscored by comments which specifically addressed the establishment of the OAC. Of the 53 comments which addressed this issue, 12 expressed support and 41 expressed opposition. The majority of comments submitted in opposition to the OAC stated that the proposed functions of the OAC could be accomplished by the RAC, or by a restructured version of the RAC. Several authors emphasized that, absent the historic credibility of the RAC, the OAC might suffer from an inability to attract and motivate the type of expertise and judgement needed for this important public forum.

II–B. Notice of Intent

Relinquish all approval responsibilities for recombinant DNA experiments involving human gene transfer to the Food and Drug Administration (FDA) which holds statutory authority for such approval.

Notice of Proposed Actions

Relinquish all approval responsibilities of the RAC to the Food and Drug Administration (FDA) which holds statutory authority for such approval, while maintaining RAC discussion of novel human gene transfer experiments.

Of the 71 comments submitted in response to the Notice of Intent, 24 respondents did not specifically address the proposal to eliminate RAC approval of human gene transfer experiments; 23 respondents were in support and 24 respondents were opposed to abolishing protocol approval. Supporting and opposing comments were submitted by representatives of academia (7 supported, 7 opposed), industry (11 supported, 0 opposed), private citizens (2 supported, 7 opposed), previous or current RAC members (4 supported, 5 opposed), professional scientific societies (4 supported, 1 opposed), the ethics community (2 supported, 4 opposed), patient advocacy organizations (0 supported, 2 opposed), and consumer advocacy organizations (0 supported, 4 opposed).

In discussing the responses to the proposal to eliminate RAC approval of human gene therapy protocols, it is important to note that the NIH Director's interest in relinquishing RAC approval recognizes FDA authority to approve human gene therapy research under its Investigational New Drug regulations. This proposal eliminates duplication of this effort by the NIH, which does not have such regulatory authority.

Respondents supporting elimination of RAC approval felt that the current status of human gene transfer research is such that NIH approval is no longer warranted and that it is appropriate that the FDA exclusively manage the approval process. This point of view was supported by authors who suggested that the efficient use of Federal resources is optimized by

eliminating duplicate approval by the NIH. Opposing points of view emphasized that the FDA does not routinely take moral and ethical considerations into account in their review and approval process. Other comments opposed to exclusive FDA approval expressed concern that without NIH authority to approve individual human gene transfer experiments, the FDA could ignore any recommendations coming from the NIH.

After careful consideration of these letters, the NIH Director proposes to retain this element of the Notice of Intent, i.e., eliminate NIH approval of individual protocols. Under this new proposal the RAC will continue to emphasize the ethical, social, and scientific issues arising from the public review and discussion of individual novel protocols. The NIH Director recognizes that opinions on the proposed elimination of NIH approval of human gene transfer experiments were diverse. The majority of comments submitted in opposition to this issue emphasized the critical role of the RAC in providing a forum for the public discussion of ethical issues relevant to human gene therapy research. The NIH Director maintains that the elimination of RAC approval will not hamper critical public discussion, nor will it result in any untoward effects on human health or the environment. NIH's mission is to sponsor and conduct medical research of the highest scientific merit to improve the health of the nation and the world. Many of the submitted comments confirmed the NIH Director's concern that NIH approval on the grounds of safety is often perceived as a scientific endorsement of early-phase clinical trials, some of which have inadequate study design and insufficient preclinical foundations.

II–C. Notice of Intent

Limit the membership of OAC to 6–10 individuals, as compared to the 25 members appointed to the RAC; membership would represent the scientific, ethical and public advocacy communities.

Notice of Proposed Actions

Reduce the membership of RAC from 25 members to 15 members representing the scientific, ethical, and public advocacy communities.

Of the 71 comments submitted in response to the Notice of Intent, only 6 comments submitted specifically addressed the composition of OAC; 2 expressed support and 4 expressed opposition. Supporting and opposing comments were submitted by representatives of academia (1 supported, 0 opposed), current RAC members (1 supported, 2 opposed) and private citizens (0 supported, 2 opposed). Although the vast majority of responses to the Notice of Intent did not address the proposed reduction in the size of the committee membership, those who were opposed expressed concern that a standing committee membership of 6–10 individuals could not adequately represent the four fields of expertise required under the committee charter. Other suggested that a minimum of 12–15 members would be sufficient.

In order to facilitate efficient review and discussion and in response to comments questioning the extent of the reduction, the NIH Director proposes to reduce the current RAC membership from 25 to 15 members, including the Chair. The appointment of the 15 member RAC will adhere to the RAC Charter such that they will be appointed by the DHHS Secretary or his/her designee. At least eight of these members shall be knowledgeable in the fields of molecular genetics, molecular biology, recombinant DNA research, or other related fields and at least four of these members 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 of Federal agencies shall continue to serve as non-voting members.

II–D. Notice of Intent

Convene regular Gene Therapy Policy Conferences.

Notice of Proposed Actions

Convene regular Gene Therapy Policy Conferences.

Of the 71 comments submitted in response to the Notice of Intent, 33 specifically addressed NIH's proposal to convene GTPCs. These responses were equally divided, with 16 expressing support and 17 expressing opposition. Supporting and opposing comments were submitted by representatives of academia (3 supported, 5 opposed), industry (7 supported, 3 opposed), private citizens (4 supported, 1 opposed), current or previous RAC members (2 supported, 7 opposed), professional scientific societies (0 supported, 2 opposed), consumer advocacy organizations (0 supported, 2 opposed), patient advocacy organizations (0 supported, 1 opposed), and the ethics community (0 supported, 4 opposed).

Opposing comments did not question the concept of holding GTPCs, but rather suggested that the roles and responsibilities of the GTPCs could be accomplished through the RAC. Supporting comments were enthusiastic about a separate forum for public discussion of human gene therapy issues which would expand its discussions beyond individual protocols. Some responses put forth suggestions for future GTPCs, including discussion of controversial issues that arise as a consequence of human gene transfer clinical trials such as reproductive decisions, susceptibility to workplace dangers, and privacy questions. It was also suggested that GTPC topics should be actively solicited from industry and academia to facilitate development of new technologies.

After careful consideration of the comments submitted with regard to the proposed establishment of GTPCs, the NIH Director proposes to retain this element of the Notice of Intent and to establish GTPCs. However, it is important to note several clarifications of the previous proposal. GTPCs will focus on broad over-arching policy and scientific issues related to gene therapy research. The RAC will advise the NIH Director on GTPC topics. GTPC topics submitted by a member of the RAC, representatives of academia, industry, patient and consumer advocacy organizations, other Federal agencies, professional scientific societies, and the general public will be considered by the NIH Director. 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 gene transfer. A member of the RAC will co-chair each GTPC. This member will be selected by the RAC. All RAC members will be encouraged to attend these meetings. The NIH Director anticipates that GTPCs will serve as a model for interagency communication and collaboration, concentrated expert discussion of novel scientific issues, and enhanced opportunity for public understanding of specific gene therapy issues including ethical, legal, and social concerns.

II–E. Notice of Intent

Ensure public access to human gene transfer experiments information by maintaining the publicly available, comprehensive NIH database of human gene transfer clinical trials, including adverse events.

Notice of Proposed Actions

Ensure public access to human gene transfer experiments information by maintaining the publicly available, comprehensive NIH database of human

gene transfer clinical trials, including adverse events.

Of the 71 comments submitted in response to the Notice of Intent, 25 comments specifically addressed NIH's proposal to maintain its human gene transfer database; 20 expressed support and 5 expressed opposition. Supporting and opposing comments were submitted by representatives of academia (8 supported, 1 opposed), industry (4 supported, 2 opposed), private citizens (1 supported, 0 opposed), current or previous RAC members (5 supported, 2 opposed), the ethics community (1 supported, 0 opposed), and the European community (France) (1 supported, 0 opposed).

The overwhelming majority of comments expressed strong support for the NIH Director's proposal to maintain the human gene transfer database. Supporting comments emphasized the importance of maintaining public understanding of human gene therapy research. The majority of comments argued that the human gene transfer database is a vital tool for ensuring public confidence in this novel area of research. Many comments underscored the importance of capturing positive as well as negative data derived from gene therapy clinical trials. Other commentors felt that public access to such information avoids unnecessary duplication of effort and clearly identifies gaps in knowledge that are worthy of further preclinical and clinical investigation.

In response to these comments, the NIH Director will maintain public accountability for human gene therapy research through the publicly available, comprehensive database for human gene transfer clinical trials. Information entered into the database will be derived from the documentation submitted to NIH/ORDA in compliance with: (i) Appendix M–I, Submission Requirements—Human Gene Transfer Experiments and (ii) Appendix M–VII—Reporting Requirements—Human Gene Transfer Experiments, of 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) of the NIH Guidelines. In compliance with the NIH Guidelines, investigators will continue to be required to register human gene transfer experiments with NIH/ORDA to ensure continued public access to protocol information, ongoing data (including adverse and significant clinical events), and long-term follow-up data.

III. Proposed Roles and Responsibilities in Accordance With the NIH Guidelines

III–A. The NIH Director

The roles and responsibilities of the NIH Director remain unchanged except for relinquishing approval of human gene transfer experiments. The NIH Director is responsible for: (1) Establishing the NIH Guidelines and overseeing their implementation. (2) Promulgating requirements as necessary to implement the NIH Guidelines. (3) Establishing and maintaining the RAC. (4) Establishing and maintaining ORDA.

III–B. The Recombinant DNA Advisory Committee

The RAC will remain a chartered public advisory committee to the NIH Director regarding recombinant DNA research conducted in compliance with the NIH Guidelines. The RAC will conduct quarterly meetings. RAC members will continue to be appointed by the DHHS Secretary or his/her designee for 4-year terms. RAC membership will be reduced from 25 to 15 members. At least eight of these members shall be knowledgeable in the fields of molecular genetics, molecular biology, recombinant DNA research, or other related fields and at least four of these members 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 of Federal agencies shall continue to serve as non-voting members.

The RAC will be responsible for: (1) Identifying novel human gene transfer experiments deserving of public discussion by the full RAC and transmitting comments/recommendations about specific human gene transfer experiments or categories of human gene transfer experiments to the NIH Director. (2) Identifying novel 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. (3) 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. (4) Publicly reviewing human gene transfer clinical trial data captured by NIH/ORDA in accordance with the annual data reporting requirements. (5) Identifying broad scientific and ethical/social issues relevant to gene therapy research as potential Gene Therapy Policy Conference topics.

The RAC will advise 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.

III–C. Gene Therapy Policy Conferences (GTPCs)

In order to enhance the depth and value of public discussion relevant to scientific, safety, and ethical/societal implications of gene therapy research, the NIH Director will convene Gene Therapy Policy Conferences (GTPC) at regular intervals. As appropriate, the NIH Director will convene GTPC immediately following scheduled RAC meetings. GTPC will be administered by the 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 the RAC will serve as Co-chair of each GTPC and report the findings of the GTPC to the full committee 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. GTPC will also have representation from other Federal agencies, including the FDA. GTPCs will focus on broad over-arching policy and scientific issues related to gene therapy research. Proposals for GTPC topics may be submitted by members of the 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 gene transfer. The findings of the GTPC 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 communications 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.

III–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. 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's responsibilities include (but are not limited to) the following: (1) Serving as the focal point for public access to summary information pertaining to human gene transfer experiments. (2) Serving as the focal point for data management of human gene transfer experiments. (3) Administering the annual data reporting requirements (and subsequent review) for human gene transfer experiments. (4) 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, sponsoring institution, and other Department of Health and Human Services (DHHS) components, as appropriate. (5) Collaborating with Principal Investigators, Institutional Biosafety Committees, Institutional Review Boards, and other DHHS components, to ensure the safe conduct of recombinant DNA research. (6) Administering Gene Therapy Policy Conferences as deemed appropriate by the NIH Director. (7) 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 nanograms per kilogram body weight in organisms other than *Escherichia coli* K–12. (8) Serving as the executive secretary of the RAC. (9) Reviewing and approving the membership of Institutional Biosafety Committees. (10) Changing containment levels for experiments that are specified in Section III, Experiments Covered by the NIH Guidelines (except when a Major Action is involved). (11) Assigning containment levels for experiments not explicitly considered in the NIH Guidelines. (12) Interpreting the NIH Guidelines for experiments to which the NIH Guidelines do not specifically assign containment levels. (13) Approving minor modifications and decertifying host-vector systems. (14) Preparing minutes of RAC meetings and gene therapy policy conferences.

III–E. Local Institutions

The roles and responsibilities of local institutions, Institutional Biosafety Committees, Biosafety Officers, Principal Investigators, Animal Facility Directors, and Greenhouse Supervisors relevant to recombinant DNA research conducted in compliance with the NIH Guidelines, remains unchanged.

IV. Proposed Actions

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

[Note: Editorial changes and updating of references are proposed to clarify the document in addition to the Proposed Actions regarding the Notice of Intent.]

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

Section I is proposed to be 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 the NIH, must be submitted to the NIH or to another Federal agency that has jurisdiction for review and approval. Once approvals, or other applicable clearances, have been obtained from a Federal agency other than the NIH (whether the experiment is referred to that agency by the NIH or sent directly there by the submitter), the experiment may proceed without the necessity for NIH review or approval. (See exception in Section I–A–1–a regarding requirement for human gene transfer protocol registration.)

''Section I–A–1–a. In the interest of maximizing the resources of both the NIH and the Food and Drug Administration (FDA) and simplifying the method and period for review, research proposals involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) will be considered through a consolidated submission process involving both the NIH and the FDA. An investigator shall simultaneously submit a human gene transfer experiment to both the NIH and the FDA in a single submission format. This format shall include (but is not limited to) the documentation described in Appendices M–I through M–V, of 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). Submission to the NIH Office of Recombinant DNA Activities (ORDA) shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the NIH Guidelines. The RAC will receive periodic updates regarding recent submissions to NIH/ORDA. 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 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 the RAC), whether the preliminary *in vitro* and *in vivo* data were obtained in appropriate models and are sufficient, and whether questions related to safety, efficacy, and social/ethical context have been resolved. RAC recommendations on a specific human gene transfer experiment will be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and, as appropriate, to other Department of Health and Human Services (DHHS) components.

''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 the NIH, including research performed directly by the 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 provision 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. The policies on noncompliance 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.

''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 remainder of Section I is proposed to be renumbered to reflect above changes.]

IV–B. Proposed Amendments to Section II, Safety Considerations

The second paragraph of Section II–A–3 is proposed to be 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 * * *.''

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

Section III is proposed to be 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 III–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 III–A, III–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 expressed 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 the RAC, and specific approval by the NIH. The containment conditions or stipulation requirements for such experiments will be recommended by the RAC and set by the NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D, 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 the 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, diphtheria toxin, and *Shigella dysenteriae* neurotoxin). Specific approval has been given for the cloning in *Escherichia coli* K–12 of DNA containing genes coding for the biosynthesis of toxic molecules which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight. Specific experiments already approved under this section may be obtained from the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838.

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

''Experiments in this category cannot be initiated without simultaneous submission of relevant information on the proposed experiment to both NIH/ORDA and the FDA in a single submission format. This format shall include (but is not limited to) the documentation described in Appendices M–I through M–V, of 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). Prior to initiation of a human gene transfer experiment, the Principal Investigator must obtain both Institutional Biosafety Committee and Institutional Review Board approvals. These local committee approvals and relevant protocol documentation shall be submitted to NIH/ORDA for registration purposes and determination regarding the necessity of full RAC discussion. The 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 review to be open to the public. Full RAC review of an individual human gene transfer experiment can be recommended by: (i) A majority of the RAC, (ii) other Federal agencies, (iii) the Principal Investigator, or (iv) the sponsoring institution. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. Recommendations for full RAC review of individual human gene transfer experiments will be transmitted to the NIH Director, who will determine whether an individual human gene transfer experiment shall be discussed by the full RAC and determine the priority of the discussions if more than one experiment is awaiting discussion. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and, as appropriate, other Department of Health and Human Services (DHHS) components.

''Institutional Biosafety Committee approval must be obtained from any institution responsible for constructing or handling the recombinant DNA material to be used in the experiments. Specifically: (1) any institution involved in the production of the vectors for human application, (2) any institution at which there is *ex vivo* transduction of the recombinant DNA material into target cells for human application, and (3) any institution at which the recombinant DNA material will be directly administered to human subjects.

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

''Submission to NIH/ORDA shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the NIH Guidelines. 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. The 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 recommended by: (i) a majority of the RAC, (ii) other Federal agencies, (iii) the Principal Investigator, or (iv) the sponsoring institution. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. Recommendations for full RAC review of individual human gene transfer experiments will be transmitted to the NIH Director, who will determine whether an individual human gene transfer experiment shall be discussed by the full RAC and determine the priority of the discussions if more than one experiment is awaiting discussion.

If a determination is made that an experiment shall undergo discussion by the full RAC, 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. Relevant documentation will be included in the material for the RAC meeting at which the experiment is scheduled to be discussed. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and, as appropriate, other Department of Health and Human Services (DHHS) components.

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

''Section III–D. Experiments That Require Institutional Biosafety Committee Approval Before Initiation''

[This section remains unchanged except for renumbering and reference changes due to renumbering.]

''Section III–E. Experiments That Require Institutional Biosafety Committee Notice Simultaneous With Initiation''

[This section remains unchanged except for renumbering and reference changes due to renumbering.]

''Section III–F. Exempt Experiments''

[This section remains unchanged except for renumbering and reference changes due to renumbering.]

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

Section IV is proposed to be 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 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 the 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 also 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 also 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. 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–g. 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.

''Note: 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. Institutional Biosafety Committee approval must be obtained from each institution that will handle recombinant DNA material that is to be administered to human subjects.

''Section IV–B–1–h. 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–i. 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).

''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–E–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.

''Note: 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. Institutional Biosafety Committee approval must be obtained from each institution that will handle recombinant DNA material that will be administered to human subjects.

''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), plant expert (if applicable), and animal expert (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–2–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 (Class 2, Class 3, Class 4, or Class 5 Agents is Cloned into Nonpathogenic Prokaryotic or Low er Eukaryotic 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 be 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 also 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 also 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. Institutional Biosafety Committee approval must be obtained from each institution that will handle recombinant DNA material that is to be administered to human subjects.

''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 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 the 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), the Institutional Biosafety Committee, NIH/ORDA, and other appropriate authorities (if applicable) (reports to the 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 annual data reporting and adverse event reporting requirements for human gene transfer experiments (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

the RAC. ORDA's responsibilities under the NIH Guidelines are administrative. Advice from the 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 the 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 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 containment 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 M, Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects.

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

''Section IV–C–1–b–(1)–(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 the 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)

''The 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. The RAC consists of 15 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 the 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 the RAC 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 the 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.

''The RAC shall be responsible for:

''Section IV–C–2–a. Advising the NIH Director on the actions listed in Sections IV–C–1–b, NIH Director—Specific Responsibility;

''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 specific comments/recommendations about: (i) a specific human gene transfer experiment, or (ii) a category of human gene transfer experiments, to the NIH Director;

''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; and

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

''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, as appropriate, other Department of Health and Human Services (DHHS) components.

''Section IV–C–3–e. Collaborating with Principal Investigators, Institutional Biosafety Committees, Institutional Review Boards, and other DHHS components (including the 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;

''Section IV–C–3–f. Administering Gene Therapy Policy Conferences as deemed appropriate by the NIH Director;

''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 nanograms 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–I, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates-General Information, and Appendix F–II, Cloning of Toxin Molecules Genes in *Escherichia coli* K–12);

''Section IV–C–3–h. Serving as the executive secretary of the 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 do so by following 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, an 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 Sections IV–E–2 through IV–E–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–E–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–5–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 the 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 the 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, section 5.65 (d) and (e).

''Section IV–D–5–b. Presubmission Review

''Any institution not otherwise covered by the NIH Guidelines, which is considering submission of data or information voluntarily to NIH, may request presubmission 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 presubmission 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 Code of Federal Regulations, 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 on 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.''

IV–E. Proposed Amendments to Appendix A, Exemptions Under Section III–E–5—Sublists of Natural Exchanges

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

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

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

IV–G. Proposed Amendments to Appendix I, Biological Containment

After the first paragraph in Section I–II–A, Responsibility, the following Note is proposed to be 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 to the content of the notice (see Section IV–D–3, Certification of Host-Vector Systems—Voluntary Compliance).''

IV–H. Proposed 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 proposed to be amended to read:

''Appendix M. 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)

''Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant DNA research from the NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M (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: civic, religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene therapy of somatic cells in humans for specific genetic diseases. Somatic cell gene therapy is seen as an extension of present methods of therapy that might be preferable to other technologies. In light of this public support, the Recombinant DNA Advisory Committee (RAC) is prepared to consider proposals for somatic cell gene transfer.

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

''In the interest of maximizing the resources of both the NIH and the Food and Drug Administration (FDA) and simplifying the method and period for review, research proposals involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) will be considered through a consolidated review process involving both the NIH and the FDA. Investigators shall simultaneously submit their human gene transfer proposal to both the NIH and the FDA. Submissions shall include (but are not limited to) the documentation described in Appendices M–I through M–V of the Points to Consider.

''Factors that may contribute to public discussion of a human gene transfer experiment by the 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 recommended by: (i) A majority of the RAC, (ii) other Federal agencies, (iii) the Principal Investigator, or (iv) the sponsoring institution. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. Recommendations for full RAC review of individual human gene transfer experiments will be transmitted to the NIH Director. The NIH Director will determine whether an individual human gene transfer experiment shall be discussed by the full RAC and will determine the priority of the discussions if more that one experiment is awaiting discussion. 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). The 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 should 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) should: (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, the meaning and significance of the research, significant safety issues, and ethical/societal 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.

''RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and, as appropriate, other Department of Health and Human Services (DHHS) components. In its evaluation of human gene transfer proposals, the 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 requests information that will enable the RAC, NIH/ORDA, and the FDA, to assess the possibility that the proposed experiment(s) will inadvertently affect reproductive cells or lead to infection of other people (e.g., medical personnel or relatives).

''In recognition of the social concern that surrounds the subject of human gene transfer, the RAC, NIH/ORDA, and the FDA, will cooperate with other groups in assessing the possible long-term consequences of the proposal and related laboratory and animal experiments in order to define appropriate human applications of this emerging technology.

''In order to enhance the depth and value of public discussion relevant to scientific, safety, and ethical/societal implications of gene therapy research, the NIH Director will convene Gene Therapy Policy Conferences (GTPC) as deemed appropriate. GTPC will be administered by the NIH/ORDA. These conferences 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. GTPC topics for discussion may be submitted by a member of the RAC, other Federal agencies, Principal Investigators, industry representatives, patient advocacy groups, or individuals who represent the general public interest through NIH/ORDA to the NIH Director. GTPC topics may include areas such as basic research on the use of novel gene delivery vehicles, novel applications of gene transfer, and relevant ethical/societal implications of a particular application of gene transfer technology. The findings of the GTPC 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 communications 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.

''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 simultaneously submit the following material to both: (1) 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); and (2) the Division of Congressional and Public Affairs, Document Control Center, HFM–99, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852–1448. Proposals will be submitted in the following order: (1) Scientific abstract; (2) non-technical abstract; (3) Institutional Biosafety Committee and Institutional Review Board approvals and their deliberations pertaining to your protocol; (4) Responses to Appendix M–II through M–V, Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues; (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); (8) curricula vitae—2 pages for each key professional person in biographical sketch format; and (9) two 3½ inch diskettes with the complete vector nucleotide sequence in ASCII format.

''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 the RAC). The 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 recommended by: (i) A majority of the RAC, (ii) other Federal agencies, (iii) the Principal Investigator, or (iv) the sponsoring institution. 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 will examine the scientific rationale, scientific context (relative to other proposals reviewed by the RAC), whether the preliminary *in vitro* and *in vivo* data were obtained in appropriate models and are sufficient, and whether questions related to safety, efficacy, and social/ethical context have been resolved. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and, as appropriate, other Department of Health and Human Services (DHHS) components.

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

''Appendix M–VII–A. Annual Data Reporting

''Investigators shall comply with the 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 the RAC and NIH/ORDA, and reviewed at a future RAC meeting.

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

''Investigators who have received approval from the FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local Institutional Review Board, Institutional Biosafety 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 M–VIII. Footnotes of Appendix M

''Appendix M–VIII–A. Human studies in which the induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected, are exempt from Appendix M–I, Submission Requirements, and Appendix M–VIII, 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 not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined to be not cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in

the Catalog of Federal Domestic Assistance are affected.

Dated: November 15, 1996.

Harold Varmus,

Director National Institutes of Health.

[FR Doc. 96–29891 Filed 11–21–96; 8:45 am]

BILLING CODE 4140–01–P