Dated: August 11, 1997.

LaVerne Y. Stringfield,

Committee Management Officer, NIH.

[FR Doc. 97–22029 Filed 8–19–97; 8:45 am]

BILLING CODE 4140–01–P

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 (NIH Guidelines).

SUMMARY: This notice sets forth proposed actions to be taken under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782). Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee (RAC) at its meeting on September 12, 1997. After consideration of these proposals and comments by the RAC, the NIH Director will issue decisions in accordance with the NIH Guidelines.

DATES: Interested parties are invited to submit comments concerning this proposal. Comments received by September 5, 1997, will be reproduced and distributed to the RAC for consideration at its September 12, 1997, meeting. After consideration of this proposal and comments by the RAC, the NIH Director 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, Phone 301–496–9838, FAX 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. The Office of Recombinant DNA Activities web site is located at Http://www.nih.gov/od/orda for further information about the office.

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

A. Amendment to the Submission Requirements—Human Gene Transfer Experiments Under Appendix M of the NIH Guidelines

During the June 12–13, 1997, RAC meeting, the following motions were approved by the Committee:

(1) A motion was made to eliminate the point-by-point responses to Appendix M–II, Description of the Proposal; however, the questions raised in Appendix M–II must be addressed in the clinical protocol. The motion passed by a vote of 8 in favor, 0 opposed, and 1 abstention.

(2) A motion was made that the RAC should not review any gene transfer protocol until the investigator has provided ORDA with evidence of protocol submission to the Institutional Biosafety Committee (IBC). IBC notification is needed in order to avoid the circumstances in which the RAC might review a protocol that has not been submitted to the IBC. The motion passed by a vote of 8 in favor, 1 opposed, and no abstentions.

(3) A motion was made to delete prior IBC and Institutional Review Board (IRB) approvals, responses to Appendix M–II through M–V, and vector sequence diskettes from Appendix M–I, Submission Requirements—Human Gene Transfer Experiments. The RAC accepted the submission requirements as follows:

''Appendix M–I, Submission Requirements—Human Gene Transfer Experiments''

''Investigators must submit the following material to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, 301–496–9838 (see exemption in Appendix M–IX–A, Footnotes of Appendix M). Proposals will be submitted in the following order: (1) Scientific abstract; (2) non-technical abstract; (3) protocol (including discussion of issues in Appendix M–II through M–V); (4) Informed Consent document prepared for IRB submission (see Appendix M–III, Informed Consent); (5) letter stating that submission has been made to the IBC; (6) appendices (including tables, figures, and manuscripts); and (7) curricula vitae for each key professional person in biographical sketch format.''

The motion passed by a vote of 7 in favor, 0 opposed, and 1 abstention.

B. Amendment to Institutional Biosafety Committee (IBC) Approvals of Experiments Involving Transgenic Rodents Under Section III of the NIH Guidelines

Section III–C–4, Experiments Involving Whole Animals, of the NIH Guidelines stipulates that all transgenic animal experiments are subject to IBC approval before initiation. In correspondence dated April 22, 1997, Dr. George Gutman, an IBC representative of the University of California, Irvine, California, inquired whether experiments involving the production or use of transgenic mice under Biosafety Level 1 containment could be initiated simultaneously with IBC notification. Current requirements under the NIH Guidelines require that IBC approval be obtained prior to initiation of such experiments. The RAC discussed this issue during its June 1997 meeting, recommending that this requirement be changed to initiation simultaneous with IBC notification. The RAC agreed that the requirement of IBC approval prior to initiation is unnecessary and recommended that the NIH Guidelines should be amended such that: (1) The generation of transgenic rodents at the Biosafety Level 1 containment (not all animals) can be initiated simultaneous with IBC notification, and (2) the purchase and use of transgenic rodents should be exempt from the NIH Guidelines.

A motion was made that these proposed changes to the NIH Guidelines should be published in the **Federal Register** for consideration at the September 12, 1997, RAC meeting. The proposed action would allow: (1) The generation of transgenic rodents that require Biosafety Level 1 containment to be included under Section III–D, Experiments that Require IBC Notice Simultaneous with Initiation; and (2) the purchase and use of transgenic rodents should be exempt from the NIH Guidelines. The motion passed by a vote of 9 in favor, 0 opposed, and no abstentions.

C. The Dissociation of Simultaneous Submission of Responses to Appendix M of the NIH Guidelines to NIH/ORDA and the Food and Drug Administration (FDA)

In a letter dated November 20, 1996, Dr. Andra Miller, Food and Drug Administration, requested that the NIH Guidelines should be amended

regarding procedures for simultaneous submission of Appendix M material to the RAC and FDA. In her November 20, 1996, letter, Dr. Miller states:

''* * * To remove the requirement for submission of Appendix M to the FDA. The FDA does not accept Appendix M in place of an IND submission. The FDA is not proposed to be and need not be included in the decision making process to identify protocols to undergo full RAC review. Therefore, there is no reason for sponsors to submit Appendix M materials to the FDA.''

During its December 9, 1996, and March 6–7, 1997, meetings, the RAC discussed this issue. The consensus of the RAC was that the requirement for submission of responses of Appendix M to the FDA should be removed, since FDA does not accept responses to Appendix M in place of an Investigational New Drug (IND) application. However, the RAC stated that all human gene transfer protocols should include discussion of issues raised in Appendix M–II through M–V of the NIH Guidelines in the clinical protocols.

The NIH will consider the following proposed actions under the NIH Guidelines:

A. Proposed Amendments to Section I–A. Purpose

Section I–A–1–a is proposed to be amended to read:

''Section I–A–1–a''

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

B. Proposed Amendments to 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–2 is proposed to be amended to read:

''Section III–A–2. Human Gene Transfer Experiments''

''Investigators must submit their human gene transfer proposal to the NIH in a single submission format. This format includes (but is not limited to) the documentation described in Appendix M–I, Submission Requirements—Human Gene Transfer Experiments. The NIH/ORDA in consultation with the RAC, will evaluate the proposal regarding the necessity for RAC review.

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

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

C. Proposed Amendments to Section III–C–4. Experiments Involving Whole Animals

(Section III–C are experiments that require Institutional Biosafety Committee approval before initiation.)

Section III–C–4–c is proposed to be amended to read:

''Section III–C–4–c. Exceptions under Section III–C–4.

''Section III–C–4–c–(1). Experiments involving the generation of transgenic rodents that require BL1 containment are described under Section III–D–3, Experiments Involving Transgenic Rodents.

''Section III–C–4–c–(2). The purchase and use of transgenic rodents is exempt from the NIH Guidelines under Section III–E, Exempt Experiments (see Appendix C–VI, The Purchase and Use of Transgenic Rodents).''

D. Proposed Amendments to Section III–D. Experiments That Require Institutional Biosafety Committee Notice Simultaneous With Initiation

Section III–D–3 is proposed to be amended to read:

''Section III–D–3. Experiments Involving Transgenic Rodent''

''This section covers experiments involving the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic rodents). Only experiments that require BL1 containment are covered under this section; experiments that require BL2. BL3, or BL4 containment are covered under Section III–C–4, Experiments Involving Whole Animals.''

E. Section IV–C–1–b–(1)–(e). Responsibilities of the NIH Director

Section IV–C–1–b–(1)–(e) is proposed to be deleted.

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

(The rest of Section IV–C–b–(1) will be renumbered.)

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

A new section, Appendix C–VI, is proposed to read:

''Appendix C–VI. The Purchase and Use of Transgenic Rodents''

''The purchase and use of transgenic rodents for experiments that require BL1 containment are exempt from the NIH Guidelines.''

(The old Appendix C–VI, Footnotes and References of Appendix C, will be renumbered to Appendix C–VII through Appendix C–VII–E.)

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

The preamble of Appendix M is proposed to be amended to read:

''Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant DNA research from the NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M.

''The acceptability of human somatic cell gene therapy has been addressed in several public documents as well as in numerous academic studies. In November 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report, Splicing Life, which resulted from a two-year process of public deliberation and hearings. Upon release of that report, a U.S. House of Representatives subcommittee held three days of public hearings with witnesses from a wide range of fields from the biomedical and social sciences to theology, philosophy, and law. In December 1984, the Office of Technology Assessment released a background paper, Human Gene Therapy, which concluded: civic, religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene therapy of somatic cells in humans for specific genetic diseases. Somatic cell gene therapy is seen as an extension of present methods of therapy that might be preferable to other technologies. In light of this public support, the Recombinant DNA Advisory Committee (RAC) is prepared to consider proposals for somatic cell gene transfer.

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

''Research proposals involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) will be considered through a review process involving both the NIH/ORDA and the RAC. Public review of human gene transfer protocols will serve to inform the public about the technical aspects of the proposals as well as the meaning and significance of the research. Investigators must submit human gene transfer protocols to the NIH/ORDA in the format described in Appendix M–I. Submission Requirements—Human Gene Transfer Experiments. NIH/ORDA and the RAC will evaluate the proposal regarding the necessity for RAC review.

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

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

''In its evaluation of human gene transfer proposals, the RAC and NIH/ORDA 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 and NIH/ORDA to assess the possibility that the proposed experiment(s) will inadvertently affect reproductive cells or lead to infection of other people (e.g., medical personnel or relatives).

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

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

Appendix M–I is proposed to be amended to read:

''Appendix M–I. Submission Requirements—Human Gene Transfer Proposals''

''Investigators must submit the following material to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, 301–496–9838 (see exemption in Appendix M–IX–A, Footnotes of Appendix M). Proposals will be submitted in the following order: (1) Scientific abstract; (2) non-technical abstract; (3) clinical protocol (including discussion of all issues raised in Appendix M–II through

M–V); (4) Informed Consent document prepared for IRB submission (see Appendix M–III, Informed Consent); (5) letter stating that submission has been made to the IBC; (6) appendices (including tables, figures, and manuscripts); and (7) curricula vitae for each key professional person in biographical sketch format.

''**Note:** Final IBC and IRB approvals should be submitted to NIH/ORDA upon receipt of the following: (1) NIH notification of exemption from full RAC discussion, or (2) subsequent to full RAC discussion (if applicable). Human gene transfer protocols shall not be initiated prior to submission of final IBC and IRB approvals to the NIH/ORDA.''

Appendix M–VI–A is proposed to be amended to read:

''Appendix M–VI–A. Categories of Human Gene Transfer Experiments That Require RAC Review''

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

Appendix M–VI–B is proposed to be amended to read:

''Appendix M–VI–B. RAC Primary Reviewers' Written Comments''

''In the event that NIH/ORDA or the RAC recommends RAC review of the submitted proposal, the documentation described in Appendix M–I will be forwarded to the RAC primary reviewers for evaluation.''

Appendix M–VI–E is proposed to be amended to read:

''Appendix M–VI–E. RAC Recommendations to the NIH Director''

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

Appendix M–VII is proposed to be amended to read:

''Appendix M–VII. Categories of Human Gene Transfer Experiments That May Be Exempt from RAC Review''

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

Note: For proposals that are exempt from RAC review, the documentation described in Appendix M–I will be maintained by NIH/ORDA for compliance with annual data reporting and adverse event reporting requirements (see Appendix M–VIII, Reporting Requirements—Human Gene Transfer Protocols). Any subsequent modifications to proposals that were not reviewed by the RAC must be submitted to NIH/ORDA in order to facilitate data reporting requirements.''

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: August 4, 1997.

Lana R. Skirboll,

Associate Director for Science Policy, National Institutes of Health.

[FR Doc. 97–22030 Filed 8–19–97; 8:45 am]

BILLING CODE 4140–01–P