

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### National Institutes of Health

#### Recombinant DNA Advisory Committee; Notice of Meeting

Pursuant to Public Law 92-463, notice is hereby given of a meeting of the Recombinant DNA Advisory Committee on September 2-3, 1999. The meeting will be held at the National Institutes of Health, Building 31C, 6th Floor, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892, starting on September 2, 1999, at approximately 9:00 a.m., and will recess at approximately 5:00 p.m. The meeting will reconvene on September 3, 1999, at approximately 8:30 a.m. and will adjourn at approximately 5:00 p.m. The meeting will be held to discuss Proposed Actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496) and other matters to be considered by the Committee. The Proposed Actions will follow this notice of meeting. The meeting will be open to the public. Attendance by the public will be limited to space available.

Debra W. Knorr, Deputy Director, 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, will provide a summary of the meeting and a roster of committee members upon request. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should contact Ms. Knorr in advance of the meeting. The Office of Recombinant DNA Activities (ORDA) web site is located at <http://www.nih.gov/od/orda> for further information about the office.

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that

every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: July 27, 1999.

**LaVerne Y. Stringfield,**

Director, Office of Federal Advisory Committee Policy, NIH.

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### National Institutes of Health

#### Office of Recombinant DNA Activities; Recombinant DNA Research; Proposed Actions Under the NIH 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 the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* (59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782, 62 FR 53335, 62 FR 56196, 62 FR 59032, 63 FR 8052, 63 FR 26018, 64 FR 25361). These proposed actions will be considered by the Recombinant DNA Advisory Committee (RAC) during its September 2-3, 1999, meeting. Public comments and any recommendations made by the RAC on these proposed actions will be considered by the NIH Director. Decisions regarding these proposed actions will be issued in accordance with the *NIH Guidelines*, as deemed appropriate by the NIH Director.

**DATES:** Interested parties are invited to submit comments concerning the proposed actions. Comments received by August 25, 1999, will be reproduced and distributed to the RAC for consideration at its September 2-3, 1999, meeting. After consideration of this proposal and comments by the RAC, the NIH Director will issue decisions in accordance with the *NIH Guidelines*.

**PUBLIC COMMENTS:** Interested parties are invited to comment on these proposed

actions. Written comments should be submitted to: Debra Knorr, RAC Executive Secretary, 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. Written comments received by August 25, 1999, will be reproduced and distributed to the committee members for their consideration during the September 2-3, 1999, RAC meeting. All comments received in response to this notice will be considered by the RAC 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.

**CONTACT INFORMATION:** For further information regarding these proposed actions please contact: The Office of Recombinant DNA Activities (ORDA), National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, Phone: 301-496-9838, Facsimile: 301-496-9839. Additional information is also available at ORDA's web site: <http://www.nih.gov/od/orda>.

**SUPPLEMENTARY INFORMATION:** The NIH has continually refined its oversight of human gene transfer research as the field has developed. In December 1996, the RAC review process was modified to consist of a rapid initial analysis of each human gene transfer experiment to determine which protocols present significant novel scientific, safety, ethical, legal and/or social issues and therefore warrant further RAC review and public discussion. In October 1997, the *NIH Guidelines* were amended to eliminate the requirement for approval by the RAC of individual protocols. The objectives of both of these actions were to streamline the review process and ensure that the roles and responsibilities of the NIH complement, rather than duplicate, those of other Federal agencies while preserving public confidence in the field.

At present, human gene transfer protocols must be approved by the local Institutional Biosafety Committee (IBC) and the local Institutional Review Board (IRB) prior to submission to the NIH Office of Recombinant DNA Activities (ORDA) for RAC review. Within 15 days of receipt of the complete submission to ORDA, investigators are informed of the RAC's decision as to whether a given protocol is novel and therefore warrants further review and public discussion. To provide adequate time for additional analysis of the protocol and public notice of the upcoming RAC review and discussion, a protocol must be received by ORDA at least eight weeks prior to

a RAC meeting. Over the past two years, approximately 10% of protocols were determined by the RAC to warrant further analysis and public discussion because they presented novel safety and/or ethical issues. Examples of novel characteristics included new disease indications, vulnerable patient populations, and new classes of viral vectors.

In an effort to optimize further and streamline this process, the NIH is proposing to modify further the requirements for protocol submission for RAC review. Specifically, clinical trial proposals may be submitted for RAC review before having been approved by the local IBC and IRB; however, clinical trial investigations may not be initiated until the RAC review process has been completed, IBC and IRB approvals have been obtained, and applicable regulatory authorization(s) have been obtained.

The above changes will allow investigators to receive RAC input at an earlier stage of protocol development and allow multiple levels of protocol review to occur simultaneously. This proposed action is intended to reduce the delays in initiating clinical trials that may result from the multiple, sequential reviews currently conducted by the local institutional review bodies and federal government agencies. The NIH is interested in exploring strategies to expedite further the process of public discussion by the RAC of novel protocols.

Other changes to the *NIH Guidelines* are presented in these Proposed Actions in order to clarify the process and requirements for protocol submission, review, and reporting. These Proposed Actions will preserve RAC's critical role in the review and public discussion of novel human gene transfer experiments in advance of clinical application.

## I. Proposed Actions

I-A. Proposed Amendments to Section I, *Scope of the NIH Guidelines*; Section III, *Experiments Covered by the NIH Guidelines*; Section IV, *Roles and Responsibilities*; 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)*; of the *NIH Guidelines Regarding Human Gene Transfer Experiments*.

Section I-A-1-a, *Scope of the NIH Guidelines*, currently reads:

"Experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) cannot be initiated without

simultaneous submission to both NIH/ORDA and FDA of such information on the proposed experiment as is prescribed by those agencies. Submission of human gene transfer protocols to NIH shall be in the format described in Appendix M-I, *Submission Requirements—Human Gene Transfer Experiments*, of the *NIH Guidelines*. Submission to NIH shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the *NIH Guidelines*. Investigational New Drug (IND) applications shall be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, *IND Content and Format*.

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

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

"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 and completion of the RAC review process. The RAC review process shall include an initial determination as to whether the submission has novel characteristics warranting full RAC review and public discussion. During the initial determination, RAC members shall notify NIH/ORDA of their recommendations regarding the necessity for full RAC review and public discussion. At any time during the review process, individual RAC members may contact NIH/ORDA to request additional information deemed important to the decision-making process. NIH/ORDA will immediately

notify the Principal Investigator(s) of RAC requests for additional information. The initial RAC review shall be completed and NIH/ORDA will notify the Principal Investigator of the results of this review within 15 working days of receipt of a complete submission. RAC review at a public meeting of an individual human gene transfer experiment can be: (1) initiated by the NIH Director, or (2) recommended to NIH/ORDA by: (a) three or more RAC members, or (b) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should have novel characteristics deserving of public discussion. Following that review and discussion, RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and/or other DHHS components, as appropriate. Submission of human gene transfer protocols to NIH shall be in the format described in Appendix M-I, *Submission Requirements—Human Gene Transfer Experiments*, of the *NIH Guidelines*." Investigational New Drug (IND) applications shall be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, *IND Content and Format*.

Section III, *Experiments Covered by the NIH Guidelines*, preamble, first paragraph, currently reads:

"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)."

Section III, *Experiments Covered by the NIH Guidelines*, preamble, first paragraph, is proposed to be amended to read:

"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 completion of the RAC review process 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)."

Section III-C, *Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/ORDA Registration Before Initiation*, currently reads:

"Section III-C, *Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/ORDA Registration Before Initiation*.

"Section III-C-1, *Experiments Involving the Deliberate Transfer of Recombinant DNA or DNA or RNA Derived from Recombinant DNA into One or More Human Subjects*.

"Research proposals involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects (human gene transfer) will be considered through a review process involving both NIH/ORDA and RAC. Investigators shall submit relevant information on the proposed human gene transfer experiments to NIH/ORDA. Submission of human gene transfer protocols to NIH will be in the format described in Appendix M-I, *Submission Requirements—Human Gene Transfer Experiments*. Submission to NIH/ORDA shall be for registration purposes and will ensure continued public access to relevant human gene transfer information in compliance with the *NIH Guidelines*. Investigational New Drug (IND) applications should be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format.

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

recombinant DNA material into target cells for human application).

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

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

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

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

Section III-C-1 is proposed to be amended to read:

"Section III-C, *Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and RAC Review Before Initiation*.

"Section III-C-1. *Experiments Involving the Deliberate Transfer of Recombinant DNA or DNA or RNA Derived from Recombinant DNA into One or More Human Subjects*.

"Investigators shall not initiate any human gene transfer experiments until the RAC review process has been completed as described in the *NIH Guidelines* (see 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)*); Institutional Biosafety Committee approvals have been obtained from each institution at which recombinant DNA material will be administered to human subjects (rather than from each site involved in manufacturing gene transfer products); Institutional Review Board approval(s) have been obtained; and applicable regulatory authorization(s) have been obtained.

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

"The RAC review process shall include an initial determination as to whether the submission has novel characteristics warranting full RAC review and public discussion. During the initial determination, RAC members shall notify NIH/ORDA of their recommendations regarding the necessity for full RAC review and public discussion. At any time during the review process, individual RAC members may contact NIH/ORDA to request additional information deemed important to the decision-making process. NIH/ORDA will immediately notify the Principal Investigator(s) of RAC requests for additional information. The initial RAC review shall be completed and NIH/ORDA will notify the Principal Investigator of the results of this review within 15 working days of receipt of a complete submission. RAC review at a public meeting of an individual human gene transfer experiment can be: (1) Initiated by the NIH Director, or (2) recommended to NIH/ORDA by: (a) Three or more RAC members, or (b) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should have novel characteristics

deserving of public discussion. Following that review and discussion, RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and/or other DHHS components, as appropriate.

“Investigational New Drug (IND) applications should be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format.

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

“Section IV-B-1-f, under *Roles and Responsibilities*, of the Institution currently reads in part:

“\* \* \* and (ii) all aspects of Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)*, have been appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application).”

“Section IV-B-1-f is proposed to be amended to read in part:

“\* \* \* 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 the initiation of any human gene transfer experiments. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (rather than from each site involved in manufacturing gene transfer products).”

“Section IV-B-2-a-(1) under *Roles and Responsibilities*, Institutional Biosafety Committee (IBC), Membership and Procedures, currently reads in part:

“\* \* \* and (ii) all aspects of Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)*, have been

appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application).”

“Section IV-B-2-a-(1) is proposed to be amended to read:

“\* \* \* 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 the initiation of any human gene transfer experiments. Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (rather than from each site involved in manufacturing gene transfer products).”

“Section IV-B-6 under *Roles and Responsibilities*, Institutional Biosafety Committee (IBC), Human Gene Therapy Expertise, currently reads in part:

“\* \* \* and (ii) all aspects of Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)*, have been appropriately addressed by the Principal Investigator prior to submission to NIH/ORDA.”

“Section IV-B-6 is proposed to be amended to read:

“\* \* \* 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 the initiation of human gene transfer experiments.”

“Section IV-B-7-b-(6) under *Roles and Responsibilities*, Principal Investigator, currently reads:

“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 (Points to Consider)*, have been appropriately addressed prior to submission of human gene therapy experiments to NIH/ORDA.”

“Section IV-B-7-b-(6) is proposed to be amended to read:

“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 (Points to Consider)*, have been appropriately addressed prior to submission of human gene transfer experiments to NIH/ORDA, and provide a letter signed by the Principal Investigator(s) (PI) on institutional letterhead acknowledging that the documentation being submitted to NIH/ORDA complies with the requirements set forth in Appendix M, *Points to Consider*; that an exact duplicate of this submission has been sent to the Institutional Biosafety Committee; and that the proposed study will not be initiated until: (1) The RAC review process has been completed, (2) final approval(s) have been obtained from the IBC(s) at each clinical trial site(s), (3) final approval(s) have been obtained from the IRB(s), and (4) applicable regulatory authorization(s) have been obtained.”

“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)*, preamble, paragraphs 4 through 7 are proposed to be deleted from the preamble and incorporated with modification into a reorganized Appendix M-I, *Submission, Review, and Reporting Requirements—Human Gene Transfer Experiments*.

“Research proposals involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects (human gene transfer) will be considered through a review process involving both NIH/ORDA and the RAC. Investigators shall submit their relevant information on the proposed human gene transfer experiments to NIH/ORDA. Submission of human gene transfer protocols to NIH will be in the format described in Appendix M-I, *Submission Requirements—Human Gene Transfer Experiments*. Submission to NIH shall be for registration purposes and will ensure continued public access to relevant human gene transfer information conducted in compliance with the *NIH Guidelines*. Investigational New Drug (IND) applications should be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format.

“Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution

involved in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant DNA material into target cells for human application).

"Factors that may contribute to public discussion of a human gene transfer experiment by RAC include: (i) New vectors/new gene delivery systems, (ii) new diseases, (iii) unique applications of gene transfer, and (iv) other issues considered to require further public discussion. Among the experiments that may be considered exempt from RAC discussion are those determined not to represent possible risk to human health or the environment. Full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by: (i) Three or more RAC members, or (ii) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. If the Director, NIH, determines that an experiment will undergo full RAC 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 RAC), whether the preliminary *in vitro* and *in vivo* safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate. Relevant documentation will be included in the material for the RAC meeting at which the experiment is scheduled to be discussed. RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed (see Section IV-D-5, *Protection of Proprietary Data*). RAC prefers that information provided in response to Appendix M contain no proprietary data or trade secrets, enabling all aspects of the review to be open to the public.

"**Note:** Any application submitted to NIH/ORDA shall not be designated as 'confidential' in its entirety. In the event that a sponsor determines that specific responses to one or more of the items

described in Appendix M should be considered as proprietary or trade secret, each item should be clearly identified as such. The cover letter (attached to the submitted material) shall: (1) Clearly indicate that select portions of the application contain information considered as proprietary or trade secret, (2) a brief explanation as to the reason that each of these items is determined proprietary or trade secret."

Appendix M, *Points to Consider*, Preamble, paragraphs 8 and 9, currently reads:

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

"In its evaluation of human gene transfer proposals, RAC will consider whether the design of such experiments offers adequate assurance that their consequences will not go beyond their purpose, which is the same as the traditional purpose of clinical investigation, namely, to protect the health and well being of human subjects being treated while at the same time gathering generalizable knowledge. Two possible undesirable consequences of the transfer of recombinant DNA would be unintentional: (i) Vertical transmission of genetic changes from an individual to his/her offspring, or (ii) horizontal transmission of viral infection to other persons with whom the individual comes in contact. Accordingly, Appendices M-I through M-V request information that will enable RAC and NIH/ORDA to assess the possibility that the proposed experiment(s) will inadvertently affect reproductive cells or lead to infection of other people (e.g., medical personnel or relatives)."

Appendix M, *Points to Consider*, Preamble, paragraphs 8 and 9, are proposed to be amended to read:

"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 NIH/ORDA and the RAC (described below in Appendix M-I). In its evaluation of human gene transfer proposals, RAC will consider whether the design of such experiments offers adequate assurance that their

consequences will not go beyond their purpose, which is the same as the traditional purpose of clinical investigation, namely, to protect the health and well being of human subjects being treated while at the same time gathering generalizable knowledge. Two possible undesirable consequences of the transfer of recombinant DNA would be unintentional: (i) Vertical transmission of genetic changes from an individual to his/her offspring, or (ii) horizontal transmission of viral infection to other persons with whom the individual comes in contact. Accordingly, Appendices M-I through M-V request information that will enable RAC and NIH 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 its evaluation of human gene transfer proposals, RAC will also consider whether a proposed human gene transfer experiment presents novel characteristics warranting further review by the full RAC and public discussion (as discussed in Appendix M-I below). Public discussion of human gene transfer experiments (and access to relevant information) shall serve to inform the public about the technical aspects of the proposals, meaning and significance of the research, and significant safety, social, and ethical implications of the research. The process of RAC review and public discussion is intended to foster the safe and ethical conduct of human gene transfer experiments and facilitate public understanding of this novel area of biomedical research."

Appendix M-I, currently entitled *Submission Requirements—Human Gene Transfer Experiments*, currently reads:

"Appendix M-I, Submission Requirements—Human Gene Transfer Experiments.

"Investigators must submit the following material (see exemption in Appendix M-VIII-A, *Footnotes of Appendix M*) to the Office of Recombinant DNA Activities, National Institutes of Health/MS-7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, Phone 301-496-9838, FAX 301-496-9839. Investigators may submit this material electronically and can obtain specific instructions from the ORDA home page (<http://www.nih.gov/od/orda>) regarding electronic submission requirements. For all submissions, whether printed or electronic, ORDA will confirm receipt within three working days after receiving the submission. Investigators

should contact ORDA if they do not receive this confirmation.

"Proposals in printed form and/or in an electronic version shall be submitted to NIH/ORDA in the following order: (1) Scientific abstract; (2) non-technical abstract; (3) Responses to Appendix M–II through M–V, *Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues* (the pertinent responses can be provided in the protocol or as an appendix to the protocol); (4) clinical protocol as approved by the local Institutional Biosafety Committee and Institutional Review Board; (5) Informed Consent document as approved by the Institutional Review Board (see Appendix M–III, *Informed Consent*); (6) appendices (including tables, figures, and manuscripts); (7) curricula vitae—no more than two pages for each key professional person in biographical sketch format; and (8) all submissions must include Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) approvals and their deliberations pertaining to your protocol. IBC approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant DNA material into target cells for human application). Because these written IBC and IRB approvals require appropriate signatures, investigators cannot submit them electronically. Investigators should submit these signed approvals either by mail or by facsimile transmission.

"Investigational New Drug (IND) applications shall be submitted to the FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, *IND Content and Format*. Submissions to the FDA should be sent to the Division of Congressional and Public Affairs, Document Control Center, HFM–99, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852–1448.

"**Note:** NIH/ORDA will accept submission material at any time. However, if a protocol is submitted less than eight weeks before a scheduled RAC meeting and subsequently is recommended for public discussion by the full RAC, the public discussion of that protocol will be deferred until the next scheduled RAC meeting. This eight-week period is needed to ensure adequate time for review by the committee members."

Appendix M–VI, *RAC Review—Human Gene Transfer Experiments*, currently reads (and is proposed to be incorporated in Appendix M–I):

"Appendix M–VI, *RAC Review—Human Gene Transfer Experiments*.

"In order to maintain public access to information regarding human gene transfer protocols, NIH/ORDA will maintain the documentation described in Appendices M–I through M–V (including protocols that are not reviewed by RAC). RAC prefers that information provided in response to Appendix M, *Points to Consider*, contain no proprietary data or trade secrets, enabling all aspects of the discussion to be open to the public.

"Appendix M–VI–A, *RAC Members' Written Comments*.

"Following receipt by NIH/ORDA, summary information on each human gene transfer protocol will be forwarded to RAC members. Each RAC member shall notify NIH/ORDA within 15 working days regarding the necessity for full RAC discussion. Full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by: (i) Three or more RAC members, or (ii) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. If the Director, NIH, determines that an experiment will undergo full RAC discussion, NIH/ORDA will immediately notify the Principal Investigator. RAC members may forward individual requests for additional information relevant to a specific protocol through NIH/ORDA to the Principal Investigator. In making a determination whether an experiment is novel, and thus deserving of full RAC discussion, reviewers shall examine the scientific rationale, scientific context (relative to other proposals reviewed by RAC), whether the preliminary *in vitro* and *in vivo* safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate."

Appendix M–VII, *Reporting Requirements—Human Gene Transfer Protocols* currently reads (and is proposed to be incorporated in Appendix M–I):

"Appendix M–VII, *Reporting Requirements—Human Gene Transfer Protocols*.

"Appendix M–VII–A, *Investigational New Drug Application Reporting*.

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

"Appendix M–VII–B, *Annual Data Reporting and Gene Therapy Database*.

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

"Appendix M–VII–C, *Adverse Event Reporting*.

"Investigators who have received approval from 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/MS-7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838."

Appendix M–VIII, *Footnotes of Appendix M*, is proposed to be renumbered to Appendix M–VII.

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

"Appendix M–I. Submission, Review, and Reporting Requirements—Human Gene Transfer Experiments.

"Appendix M–I–A. Submission Requirements.

"Investigators must submit the following material (see exemption in Appendix M–VI–A, *Footnotes of Appendix M*) to the Office of



Recombinant DNA Activities, National Institutes of Health/MS-7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, Phone 301-496-9838, FAX 301-496-9839.

Investigators may submit this material electronically. ORDA will confirm receipt within three working days after receiving the submission. Investigators should contact ORDA if they do not receive this confirmation. Additional information regarding RAC activities is located on the ORDA home page (<http://www.nih.gov/od/orda>).

"Proposals in printed form and/or in an electronic version shall be submitted to NIH/ORDA in the following order: (1) Cover letter on institutional letterhead that has been signed by the Principal Investigator(s) at the proposed clinical trial site(s). The cover letter must acknowledge that the documentation submitted to NIH/ORDA complies with the requirements set forth in Appendix M-I of the *NIH Guidelines* and that an exact duplicate of this documentation has been submitted to the IBC at the proposed clinical trial site(s). The cover letter must acknowledge that the proposed study will not be initiated until: (a) The RAC review process has been completed; (b) final approval(s) have been obtained from the IBC(s) at each clinical trial site(s); (c) final approval(s) have been obtained from the IRB(s); and (d) all applicable regulatory authorization(s) have been obtained. (2) Scientific abstract. (3) Non-technical abstract. (4) The proposed clinical protocol, including tables, figures, and relevant manuscripts. (5) Responses to Appendix M-II through M-V, *Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues*. Responses to Appendices M-II through M-V may be provided either as an appendix to the clinical protocol or within the clinical protocol. If responses to Appendices M-II through M-V are included within the clinical protocol, each response must be accompanied by its corresponding reference to Appendix M-II through M-V. (6) Proposed Informed Consent document (see Appendix M-III, *Informed Consent*). (7) Curricula vitae of the principal investigator(s) at the proposed clinical trial site(s) (no more than two pages for each key professional person in biographical sketch format).

"**Note:** NIH/ORDA will accept submission material at any time. However, if a protocol is submitted less than eight weeks before a scheduled RAC meeting and subsequently is recommended for public discussion by the full RAC, the public discussion of that protocol will be deferred until the next scheduled RAC meeting. This

eight-week period is needed to ensure adequate time for review by the committee members as well as public notice and comment.

"Investigational New Drug (IND) applications shall be submitted to the FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, *IND Content and Format*. Submissions to the FDA should be sent to the Division of Congressional and Public Affairs, Document Control Center, HFM-99, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

"Appendix M-I-B. RAC Review Requirements.

"Appendix M-I-B-1. Initial RAC Review

"Human gene transfer experiments submitted to NIH/ORDA must meet the requirements set forth in Appendix M-I, *Submission, Review, and Reporting Requirements—Human Gene Transfer Experiments*, and should not contain proprietary data or trade secrets, enabling all aspects of the review to be open to the public. Investigators shall not initiate the proposed study prior to completion of the RAC review process.

"The RAC review process shall include an initial determination as to whether the submission has novel characteristics warranting full RAC review and public discussion. During the initial determination, RAC members shall notify NIH/ORDA of their recommendations regarding the necessity for full RAC review and public discussion. At any time during the review process, individual RAC members may contact NIH/ORDA to request additional information deemed important to the decision-making process. NIH/ORDA will immediately notify the Principal Investigator(s) of RAC requests for additional information. The initial RAC review shall be completed and NIH/ORDA will notify the Principal Investigator of the results of this review within 15 working days of receipt of a complete submission. RAC review at a public meeting of an individual human gene transfer experiment can be: (1) Initiated by the NIH Director, or (2) recommended to NIH/ORDA by: (a) Three or more RAC members, or (b) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should have novel characteristics deserving of public discussion. Following that review and discussion, RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring

institution, and/or other DHHS components, as appropriate.

"An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. In making a determination whether an experiment is novel, reviewers shall examine the scientific rationale, scientific context (relative to other proposals reviewed by RAC). Factors that may warrant 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.

"Appendix M-I-B-2. Full RAC Review and Public Discussion

"RAC meetings will be open to the public except where trade secrets and proprietary information are reviewed. Relevant documentation will be included in the material for the RAC meeting at which the experiment is scheduled to be discussed. Following RAC review and public discussion, RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and/or other DHHS components, as appropriate.

"**Note:** To enable all aspects of the review process to be open to the public, information provided in response to Appendix M should not contain proprietary data or trade secrets and any application submitted to NIH/ORDA shall not be designated as 'confidential' in its entirety. In the event that an investigator determines that specific responses to one or more of the items described in Appendix M should be considered as proprietary or trade secret, each item should be clearly identified as such. The cover letter (attached to the submitted material) shall: (1) Clearly indicate the information that is considered as proprietary or trade secret, (2) an explanation as to the reason that each of these items is determined proprietary or trade secret.

"Appendix M-I-C. Reporting Requirements.

"Appendix M-I-C-1. Initiation of the Clinical Investigation.

"The Principal Investigator(s) shall submit the following to NIH/ORDA within 15 working days of initiation of a human gene transfer experiment: (1) A copy of the Informed Consent document approved by the IRB, (2) a copy of the protocol approved by the IBC and IRB, and (3) a copy of the final IBC

approval(s) at the clinical trial site(s); (4) a copy of the final IRB approval(s); (5) a brief written report that includes the following information: (a) how the investigator(s) responded to RAC's recommendations on the protocol (if applicable), and (b) any modifications to the protocol as required by FDA.

"Appendix M-I-C-2. Annual Reporting.

"Investigators shall comply with annual data reporting requirements. Annual data report forms will be forwarded by NIH/ORDA to investigators. Information submitted in these annual reports will be evaluated by NIH/ORDA and the RAC, and possibly considered at a future RAC meeting. Information obtained through the annual data reporting process will be included in the NIH/ORDA clinical trials database to: (1) Provide clinical trial information; (2) provide administrative details of protocol registration; (3) provide annual status reports of protocols; (4) facilitate risk assessment of individual applications of human gene transfer; and (5) enhance public awareness of relevant scientific, safety, social, and ethical issues.

"Appendix M-I-C-3. Serious Adverse Event Reporting.

"Investigators who have received authorization from 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/MS-7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, (301) 496-9838."

Appendix M-III-B currently reads in part:

"Investigators submitting human gene transfer proposals must include the Informed Consent document as approved by the local Institutional Review Board. A separate. \* \* \*"

Appendix M-III-B is proposed to read:

"Investigators submitting human gene transfer proposals must include a copy of the proposed Informed Consent document. A separate \* \* \*"

## **II. 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 (Points to Consider), of the NIH Guidelines, Regarding Prenatal Gene Transfer Research**

II-A. Background Information.

On July 31, 1998, Dr. W. French Anderson, University of Southern California, Los Angeles, California, and Dr. Esmail Zanjani, Veterans Hospital, Reno, Nevada, submitted the following two "pre-protocols" for *in utero* gene transfer entitled: (1) *In Utero* Gene Transfer for the Treatment of ADA-Deficient SCID and (2) *In Utero* Gene Transfer for the Treatment of a-Thalassemia. These two "pre-protocols" provided the catalyst for the RAC recommendation to the NIH Director made at its September 1998 meeting that a Gene Therapy Policy Conference (GTPC) should be held on the topic of prenatal gene transfer. On January 7-8, 1999, NIH convened the GTPC entitled: Prenatal Gene Transfer: Scientific, Medical, and Ethical Issues. This meeting provided a public forum for the presentation and discussion of relevant scientific data and policy issues by members of the scientific, biomedical, ethical, and legal communities and the public. The anticipated outcome of the GTPC is two-fold: (1) Development of a policy paper that will highlight the conclusions of the working groups and conference participants, and (2) a comprehensive list of issues that should be further deliberated by the RAC at subsequent meetings. To achieve this goal, RAC members and ad hoc experts were assigned to one or more of the following working groups based on their individual areas of expertise: Working Group I—Preclinical Research Issues; Working Group II—Clinical Research Issues; and Working Group III—Ethical, Legal, and Societal Issues.

At the March 11-12, 1999, RAC meeting, the RAC discussed three working group reports and issued a consensus statement that reads:

The RAC continues to explore the issues raised by the potential of *in utero* gene transfer research. However, at present, the members unanimously agree that it is premature to undertake any human *in utero* gene transfer experiment.

Rationale: Significant additional preclinical and clinical studies addressing vector transduction efficacy, biodistribution, and toxicity are required before a human *in utero* gene transfer protocol should proceed. In addition, a more thorough

understanding of the ontogeny of human organ systems, such as the immune and nervous systems, is needed to better define the potential efficacy and risks of human *in utero* gene transfer. Prerequisites for considering any specific human *in utero* gene transfer procedure include an understanding of the pathophysiology of the candidate disease and a demonstrable advantage to the *in utero* approach. Once the above criteria are met, the committee would be willing to consider well rationalized *in utero* gene transfer protocols."

Appendix M, *Points to Consider*, Preamble, to include a new paragraph after paragraph 3, is proposed to read:

The RAC continues to explore the issues raised by the potential of *in utero* gene transfer research. However, at present, the RAC concludes that it is premature to undertake any human *in utero* gene transfer experiment. Significant additional preclinical and clinical studies addressing vector transduction efficacy, biodistribution, and toxicity are required before a human *in utero* gene transfer protocol should proceed. In addition, a more thorough understanding of the ontogeny of human organ systems, such as the immune and nervous systems, is needed to better define the potential efficacy and risks of human *in utero* gene transfer. Prerequisites for considering any specific human *in utero* gene transfer procedure include an understanding of the pathophysiology of the candidate disease and a demonstrable advantage to the *in utero* approach. Once the above criteria are met, the RAC would be willing to consider well rationalized *in utero* gene transfer protocols."

## **III. Discussion of Three Novel Human Gene Transfer Protocols**

During the September 2-3, 1999, RAC meeting, three novel human gene transfer protocols will be discussed: (1) Limb girdle muscular dystrophy using adeno-associated viral vector delivery of sarcoglycan genes, (2) hemophilia A using systemic retroviral vector delivery of a gene encoding factor VIII, and (3) gyrate atrophy using retroviral vector delivery of a gene encoding ornithine aminotransferase.

## **IV. Discussion on Expediting RAC Public Review Process of Human Gene Transfer Experiments**

The NIH is interested in exploring strategies to expedite further the process of public discussion by the RAC of novel protocols.

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 5, 1999.

**Lana R. Skirboll,**

*Associate Director for Science Policy,  
National Institutes of Health.*

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