Procedures for Submission of Human Gene Transfer Protocols

May 11, 1998

To: Chairs, Institutional Biosafety Committees
Contact Persons, Institutional Biosafety Committees
Principal Investigators, Human Gene Transfer Protocols
Sponsors, Human Gene Transfer Protocols

From: Debra Knorr, Acting Director
Office of Recombinant DNA Activities (ORDA)

Subject: Procedures for Submission of Human Gene Transfer Protocols

Procedures for submission of human gene transfer protocols are outlined in *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), National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* published in the *Federal Register* on July 5, 1994 (59 FR 34496), and amended August 5, 1994 (59 FR 40170), April 27, 1995 (60 FR 20726), January 19, 1996 (61 FR 1482), March 12, 1996 (61 FR 10004), January 31, 1997 (62 FR 4782), October 14, 1997 (62 FR 53335), October 29, 1997 (62 FR 56196), October 31, 1997 (62 FR 59032), February 17, 1998 (63 FR 8052), and May 11, 1998 (63 FR 26018). The *NIH Guidelines* can be obtained through this office or at the ORDA's Internet site http://www4.od.nih.gov/oba/ which includes the Human Gene Therapy Protocol List, Principal Investigator List, Data Management Reports, Minutes of the Recombinant DNA Advisory Committee meetings, and ORDA News.

The October 31, 1997 and February 17, 1998, *Federal Register* actions revised the submission requirements for human gene transfer proposals. Please note that 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). 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. The May 11, 1998, *Federal Register* actions allow electronic submission of human gene transfer protocols to ORDA.

The *NIH Guidelines* read:

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, MSC 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.

With regard to reporting requirements, the *NIH Guidelines* read:

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 toNIH/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.

Please refer to the *NIH Guidelines* for more detailed information.