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 Proposals

Investigators must simultaneously submit the following material to both: (1) the Office of Recombinant DNA Activities (ORDA), National Institutes of Health. Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892–7052 (see exemption in Appendix M-IX-A); 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-1 page; (2) nontechnical abstract—1 page; (3) Institutional Biosafety Committee and Institutional Review Board approvals and their deliberations pertaining to your protocol (the IBC and IRB may, at their discretion, condition their approval on further specific deliberation by the RAC); (4) Responses to Appendix M-II, Description of the Proposal—5 pages; (5) protocol (as approved by the local Institutional Biosafety Committee and Institutional Review Board)-20 pages; (6) Informed Consent document-approved by the Institutional Review Board (see Appendix M-III); (7) appendices (including tables, figures, and manuscripts); (8) curricula vitae-2 pages for each key professional person in biographical sketch format; and (9) three 3 1/2 inch diskettes with the complete vector nucleotide sequence in ASCII format.

## Appendix M–II. Description of the Proposal

Responses to this appendix should be provided in the form of either written answers or references to specific sections of the protocol or its appendices. Investigators should indicate the points that are not applicable with a brief explanation. Investigators submitting proposals that employ the same vector systems may refer to preceding documents relating to the vector sequence without having to rewrite such material.

Appendix M–II–A. Objectives and Rationale of the Proposed Research

State concisely the overall objectives and rationale of the proposed study.

Provide information on the specific points that relate to whichever type of research is being proposed.

Appendix M–II–A–1. Use of Recombinant DNA for Therapeutic Purposes

For research in which recombinant DNA is transferred in order to treat a disease or disorder (e.g., genetic diseases, cancer, and metabolic diseases), the following questions should be addressed:

Appendix M–II–A–1–a. Why is the disease selected for treatment by means of gene therapy a good candidate for such treatment?

Appendix M–II–A–1–b. Describe the natural history and range of expression of the disease selected for treatment. What objective and/or quantitative measures of disease activity are available? In your view, are the usual effects of the disease predictable enough to allow for meaningful assessment of the results of gene therapy?

Appendix M–II–A–1–c. Is the protocol designed to prevent all manifestations of the disease, to halt the progression of the disease after symptoms have begun to appear, or to reverse manifestations of the disease in seriously ill victims?

Appendix M–II–A–1–d. What alternative therapies exist? In what groups of patients are these therapies effective? What are their relative advantages and disadvantages as compared with the proposed gene therapy?

Appendix M–II–A–2. Transfer of DNA for Other Purposes

Appendix M–II–A–2–a. Into what cells will the recombinant DNA be transferred? Why is the transfer of recombinant DNA necessary for the proposed research? What questions can be answered by using recombinant DNA?

Appendix M–II–A–2–b. What alternative methodologies exist? What are their relative advantages and disadvantages as compared to the use of recombinant DNA?

Appendix M–II–B. Research Design, Anticipated Risks and Benefits

Appendix M–II–B–1. Structure and Characteristics of the Biological System

Provide a full description of the methods and reagents to be employed for gene delivery and the rationale for their use. The following are specific points to be addressed:

Appendix M–II–B–1–a. What is the structure of the cloned DNA that will be used?

Appendix M–II–B–1–a–(1). Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete nucleotide sequence analysis or a detailed restriction enzyme map of the total construct.

Appendix M–II–B–1–a–(2). What regulatory elements does the construct contain (e.g., promoters, enhancers, polyadenylation sites, replication origins, etc.)? From what source are these elements derived? Summarize what is currently known about the regulatory character of each element.

Appendix M–II–B–1–a–(3). Describe the steps used to derive the DNA construct.

Appendix M–II–B–1–b. What is the structure of the material that will be administered to the patient? Appendix M–II–B–1–b–(1). Describe

the preparation, structure, and composition of the materials that will be given to the patient or used to treat the patient's cells: (i) If DNA, what is the purity (both in terms of being a single DNA species and in terms of other contaminants)? What tests have been used and what is the sensitivity of the tests? (ii) If a virus, how is it prepared from the DNA construct? In what cell is the virus grown (any special features)? What medium and serum are used? How is the virus purified? What is its structure and purity? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials (for example, VL30 RNA, other nucleic acids, or proteins) or contaminating viruses (both replication-competent or replicationdefective) or other organisms in the cells or serum used for preparation of the virus stock including any contaminants that may have biological effects? (iii) If co-cultivation is employed, what kinds of cells are being used for cocultivation? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials? Specifically, what tests are being conducted to assess the material to be returned to the patient for the presence of live or killed donor cells or other non-vector materials (for example, VL30 sequences) originating from those cells? (iv) If methods other than those covered by Appendices M-II-B-1 through M-II-B-3 are used to introduce new genetic information into target cells, what steps are being taken to detect and eliminate any contaminating materials? What are possible sources of contamination? What is the sensitivity of tests used to monitor contamination?

Appendix M–II–B–1–b–(2). Describe any other material to be used in