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

In recognition of the social concern that surrounds the subject of human gene transfer, the RAC, NIH/ORDA, and the FDA, will cooperate with other groups in assessing the possible longterm 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. 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, (301) 496-9838 (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 $3\frac{1}{2}$ 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: