M–V will be forwarded to the RAC primary reviewers for evaluation.

The RAC primary reviewers shall provide written comments on the proposal to NIH/ORDA. The RAC primary reviewers' comments should include the following:

Appendix M–VI–B–1. Emphasize the issues related to gene marking, gene transfer, or gene therapy.

Appendix M–VI–B–2. State explicitly whether Appendices M–I through M–V have been addressed satisfactorily.

Appendix M–VI–B–3. Examine the scientific rationale, scientific context (relative to other proposals reviewed by the RAC), whether the preliminary *in vitro* and *in vivo* data were obtained in appropriate models and are sufficient, and whether questions related to safety, efficacy, and social/ethical context have been resolved.

Appendix M–VI–B–4. Whenever possible, criticisms of Informed Consent documents should include written alternatives for suggested revisions for the RAC to consider.

Appendix M–VI–B–5. Primary reviews should state whether the proposal is: (i) acceptable as written, (ii) expected to be acceptable with specific revisions or after satisfactory responses to specific questions raised on review, or (iii) unacceptable in its present form.

Appendix M–VI–C. Investigator's Written Responses to RAC Primary Reviewers

Appendix M–VI–C–1. Written responses (including critical data in response to RAC primary reviewers' written comments) shall be submitted to NIH/ORDA greater than or equal to 2 weeks following receipt of the review.

Appendix M–VI–D. Oral Responses to the RAC

Investigators shall limit their oral responses to the RAC only to those questions that are raised during the meeting. Investigators are strongly discouraged from presenting critical data during their oral presentations that was not submitted greater than or equal to 2 weeks in advance of the RAC meeting at which it is reviewed.

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 transmitted to the FDA Commissioner and considered as a Major Action by the NIH Director.

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 FDA on a case-by-case basis (see Appendix M–VI–A, Categories of Human Gene Transfer Experiments that Require RAC Review).

Note: In the event that the submitted proposal is determined to be exempt from RAC review, the documentation described in Appendices M–I through M–V will be maintained by NIH/ORDA for compliance with semiannual 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.

Appendix M–VII–A. Vaccines

This category includes recombinant DNA vaccines not otherwise exempt from RAC review (see Appendix M–IX– A for exempt vaccines).

Appendix M–VII–B. Lethally Irradiated Tumor Cells/No Replication-Competent Virus

This category includes experiments involving lethally irradiated tumor cells and: (1) Vector constructs that have previously been approved by the RAC (or with the incorporation of minor modifications), or (2) a different tumor cell target.

Appendix M–VII–C. New Site/Original Investigator

This category includes the following: (1) Initiation of a protocol at an additional site other than the site that was originally approved by the RAC, and (2) the investigator at the new site is the same as the investigator approved for the original study.

Appendix M–VII–D. New Site/New Investigator

This category includes the following: (1) Initiation of a protocol at an additional site other than the site that was originally approved by the RAC, and (2) the investigator at the new site is different than the investigator approved for the original site.

Appendix M–VII–E. "Umbrella" Protocols

This category includes initiation of a RAC-approved protocol at more than

one additional site (the Principal Investigator may be the same or different than the Principal Investigator approved for the original site).

Appendix M–VII–F. Modifications Related to Gene Transfer

This category includes experiments involving a modification to the clinical protocol that is not related to the gene transfer portion of study.

Appendix M–VII–G. Gene Marking Protocols

This category includes human gene marking experiments involving vector constructs that have previously been approved by the RAC and: (1) Minor modifications to the vector constructs, or (2) a different tumor cell target.

Appendix M–VIII. Reporting Requirements—Human Gene Transfer Protocols

Appendix M–VIII–A. Semiannual Data Reporting

Investigators who have received approval from the FDA to initiate a human gene transfer protocol (whether or not it has been reviewed by the RAC) shall be required to comply with the semiannual data reporting requirements. Semi-annual Data Report forms will be forwarded by NIH/ORDA to investigators. Data submitted in these reports will be evaluated by the RAC, NIH/ORDA, and the FDA and reviewed by the RAC at its next regularly scheduled meeting.

Appendix M–VIII–B. Adverse Event Reporting

Investigators who have received approval from the FDA to initiate a human gene transfer protocol (whether or not it has been reviewed by the RAC) must report any serious adverse event immediately to the local IRB, IBC, NIH Office for Protection from Research Risks, FDA, and NIH/ORDA, 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, 6006 Executive Boulevard, Suite 323, Bethesda, Maryland 20892-7052, (301) 496-9838.

Appendix M–IX. Footnotes of Appendix M

Appendix M–IX–A. Human studies in which the induction or enhancement of an immune response to a vectorencoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not