of Recombinant DNA Activities, National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892–7052, (301) 496–9838.

Section III–A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V–B), if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by the RAC.

Section III–A–2. Human Gene Transfer Experiments

Investigators must simultaneously submit their human gene transfer proposal to both the FDA and the NIH in a single submission format. This format includes (but is not limited to) the documentation described in Appendices M–I through M–V, of the Points to Consider. The NIH/ORDA and the FDA will simultaneously evaluate the proposal regarding the necessity for RAC review.

Factors that may contribute to the necessity for RAC review 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 review are those determined by the FDA and NIH/ORDA not to represent possible risk to human health or the environment (see Appendix M-VII, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review). Whenever possible, investigators will be notified within 15 working days following 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.

Section III-B is proposed to read:

Section III–B. Experiments That Require NIH/ORDA and Institutional Biosafety Committee Approval Before Initiation

Section III–B–1. Experiments Involving the Cloning of Toxin Molecules With LD_{50} of Less Than 100 Nanograms per Kilogram Body Weight

Deliberate formation of recombinant DNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD₅₀ of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, and Shigella dysenteriae neurotoxin). Specific approval has been given for the cloning in Escherichia coli K-12 of DNA containing genes coding for the biosynthesis of toxic molecules which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight. Specific experiments already approved under this section may be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, (301) 496-9838

Section III–B–1–(a). Experiments in this category cannot be initiated without submission of relevant information on the proposed experiment to NIH/ORDA. The containment conditions for such experiments will be determined by NIH/ORDA in consultation with *ad hoc* experts. Such experiments require Institutional Biosafety Committee approval before initiation (see Section IV–B–2–b–(1)).

Section III–C–7 is proposed to be deleted:

Section III–C–7. Human Gene Transfer Experiments Not Covered by Sections III–A–2, III–B–2, III–B–3, and Not Considered Exempt Under Section V–U

Certain experiments involving the transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into one or more human subjects that are not covered by Sections III–A–2, III–B–2, III–B–3, and that are not considered exempt under Section V–U must be registered with NIH/ORDA. The relevant Institutional Biosafety Committee and Institutional Review Board must review and approve all experiments in this category prior to their initiation.

Section IV-B-4-b, Submissions by the Principal Investigator to the NIH/ ORDA, is proposed to read:

Section IV-B-4-b-(3). Petition NIH/ORDA, with concurrence of the Institutional Biosafety Committee, for approval to conduct experiments specified in Sections III-A-1 and III-B of the NIH Guidelines;

In Section IV–B–4–e, Responsibilities of the Principal Investigator During the Conduct of the Research, the following section is added:

Section IV-B-4-e-(5). Comply with semiannual data reporting and adverse event reporting requirements for NIH and FDA-approved human gene transfer experiments (see Appendix M-VIII, Reporting Requirements—Human Gene Transfer Protocols).

Section IV-C-1-b-(1), Major Actions, the first paragraph is proposed to read:

To execute Major Actions, the NIH Director shall seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the Notice of Meeting and Proposed Actions shall be published in the **Federal Register** at least 15 days before the RAC meeting. The NIH Director's decision/recommendation (at his/her discretion) may be published in the Federal Register for 15 days of comment before final action is taken. The NIH Director's final decision/ recommendation, along with responses to public comments, shall be published in the **Federal Register**. The RAC and **Institutional Biosafety Committee Chairs** shall be notified of the following decisions:

Section IV-C-1-b-(1)-(e) is proposed to read:

Section IV-C-1-b-(1)-(e).
Recommendations made by the NIH
Director to the FDA Commissioner
regarding RAC-reviewed human gene
transfer experiments (see Appendix MVI-E, RAC Recommendations to the
NIH Director);

Except for renumbering, the rest of the Section IV–C–1–b–(1) would remain unchanged.

In Section IV-C-1-b-(2), Minor Actions, the following sections are proposed to be deleted:

Section IV-C-1-b-(2)-(a). Reviewing and approving certain experiments involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into one or more human subjects that qualify for the Accelerated Review process (see Section III-B-2);

Section IV-C-1-b-(2)-(b). Reviewing and approving minor changes to human gene transfer protocols under Section III-A-2 and III-B-2;