This section describes five categories of experiments involving recombinant DNA: (i) Those that require Institutional Biosafety Committee (IBC) approval, RAC review, and NIH Director approval before initiation (see Section III–A), (ii) those that require NIH/ORDA and Institutional Biosafety Committee approval before initiation (see Section III–B), (iii) those that require Institutional Biosafety Committee approval before initiation (see Section III–C), (iv) those that require Institutional Biosafety Committee notification simultaneous with initiation (see Section III–D), and (v) those that are exempt from the NIH Guidelines (see Section III–E).

Note: If an experiment falls into either Section III–A or Section III–B and one of the other categories, the rules pertaining to Section III–A or Section III–B shall be followed. If an experiment falls into Section III–E and into either Sections III–C or III–D categories as well, the experiment is considered exempt from the NIH Guidelines.

Any change in containment level, which is different from those specified in the NIH Guidelines, may not be initiated without the express approval of NIH/ORDA (see Minor Actions, Section IV–C–1–b–(2) and its subsections).

The amended version of Section III–A reads:

Section III–A. Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation (see Section IV–C–1–b–(1)).

Section III–A–1. Major Actions Under the NIH Guidelines

Experiments considered as Major Actions under the NIH Guidelines cannot be initiated without submission of relevant information on the proposed experiment to the Office of Recombinant DNA Activities, National Institutes of Health, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892–7052, (301) 496–9838, the publication of the proposal in the **Federal Register** for 15 days of comment, review by the RAC, and specific approval by the NIH (see Appendix M for submission requirements on human gene transfer experiments). The containment conditions or stipulation requirements for such experiments will be recommended by the RAC and set by the NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D which 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–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 NIH and the FDA 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 NIH/ORDA and FDA 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 or 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.

The amended version of Section III–B reads:

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 LD_{50} 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)).

The following section, Section III–C–7, is 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.