

Appendix C-II-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

Appendix C-III-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

Appendix C-IV-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

Appendix C-V-A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III-A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation.

Appendix C-VI-A-1. The NIH Director, with advice of the RAC, may revise the classification for the purposes of these NIH Guidelines (see Section IV-C-1-b-(2)-(b)).

E. Amendments to Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates

The following sections are amended, due to reference changes, to read:

Appendix F-I. General Information

. . . The results of such tests shall be forwarded to NIH/ORDA, which will consult with ad hoc experts, prior to inclusion of the molecules on the list (see Section IV-C-1-b-(2)-(c)).

Appendix F-III. Cloning of Toxic Molecule Genes in Organisms Other Than *Escherichia coli* K-12

Requests involving the cloning of genes coding for toxin molecules for vertebrates at an LD₅₀ of <100 nanograms per kilogram body weight in host-vector systems other than *Escherichia coli* K-12 will be evaluated by NIH/ORDA in consultation with ad hoc toxin experts (see Sections III-B-1 and IV-C-1-b-(2)-(c)).

F. Amendments to Appendix G, Physical Containment

The following sections are amended, due to reference changes, to read:

Appendix G-II. Physical Containment Levels.

. . . Consideration will be given by the NIH Director, with the advice of the RAC, to other combinations which achieve an equivalent level of containment (see Section IV-C-1-b-(2)-(a)).

G. Amendments to Appendix I, Biological Containment

The following sections are amended, due to reference changes, to read:

Appendix I-II-A. Responsibility

. . . Proposed host-vector systems will be reviewed by the RAC (see Section IV-C-1-b-(1)-(f)). . . Minor modifications to existing host-vector systems (i.e., those that are of minimal or no consequence to the properties relevant to containment) may be certified by the NIH Director without prior RAC review (see Section IV-C-1-b-(2)-(f)). . . The NIH Director may rescind the certification of a host-vector system (see Section IV-C-1-b-(2)-(g)).

H. Amendments to Appendix M, The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider)

Appendix M is amended to read:
Appendix M. The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects (Points to Consider)
Appendix M applies to research conducted at or sponsored by an institution that receives any support for recombinant DNA research from the NIH. Researchers not covered by the NIH Guidelines are encouraged to use Appendix M.

The acceptability of human somatic cell gene therapy has been addressed in several public documents as well as in numerous academic studies. In November 1982, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published a report, *Splicing Life*, which resulted from a two-year process of public deliberation and hearings. Upon release of that report, a U.S. House of Representatives subcommittee held three days of public hearings with witnesses from a wide range of fields from the biomedical and social sciences to theology, philosophy, and law. In December 1984, the Office of Technology Assessment released a background paper, *Human Gene Therapy*, which concluded: civic,

religious, scientific, and medical groups have all accepted, in principle, the appropriateness of gene therapy of somatic cells in humans for specific genetic diseases. Somatic cell gene therapy is seen as an extension of present methods of therapy that might be preferable to other technologies. In light of this public support, the Recombinant DNA Advisory Committee (RAC) is prepared to consider proposals for somatic cell gene transfer.

The RAC will not at present entertain proposals for germ line alterations but will consider proposals involving somatic cell gene transfer. The purpose of somatic cell gene therapy is to treat an individual patient, e.g., by inserting a properly functioning gene into the subject's somatic cells. Germ line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring.

In the interest of maximizing the resources of both the NIH and the Food and Drug Administration (FDA) and simplifying the method and period for review, research proposals involving the deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects (human gene transfer) will be considered through a consolidated review process involving both the NIH and the FDA. Submission of human gene transfer proposals will be in the format described in Appendices M-I through M-V of the Points to Consider. 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. 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