

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****National Institutes of Health****Recombinant DNA Research: Proposed Actions Under the Guidelines**

**AGENCY:** National Institutes of Health (NIH), PHS, DHHS.

**ACTION:** Notice of Proposed Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496).

**SUMMARY:** This notice sets forth proposed actions to be taken under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496). Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee at its meeting on March 6-7, 1995. After consideration of these proposals and comments by the Recombinant DNA Advisory Committee, the Director of the National Institutes of Health will issue decisions in accordance with the NIH Guidelines.

**DATES:** Comments received by February 27, 1995, will be reproduced and distributed to the Recombinant DNA Advisory Committee for consideration at its March 6-7, 1995, meeting.

**ADDRESSES:** Written comments and recommendations should be submitted to Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, or sent by FAX to 301-496-9839.

All comments received in timely response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5 p.m.

**FOR FURTHER INFORMATION CONTACT:** Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, Suite 323, 6006 Executive Boulevard, MSC 7052, Bethesda, Maryland 20892-7052, Phone 301-496-9838, FAX to 301-496-9839.

**SUPPLEMENTARY INFORMATION:** The NIH will consider the following actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules:

**I. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Curiel and Alvarez**

In a letter dated January 5, 1995, Drs. David T. Curiel and Ronald D. Alvarez of the University of Alabama,

Birmingham, Alabama, submitted a human gene transfer protocol entitled: A Phase I Study of Recombinant Adenovirus Vector-Mediated Delivery of an Anti-erbB-2 Single-Chain (sFv) Antibody Gene for Previously Treated Ovarian and Extraovarian Cancer Patients to the Recombinant DNA Advisory Committee for formal review and approval.

**II. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Dr. Malech**

In a letter dated January 6, 1995, Dr. Harry L. Malech of the National Institutes of Health, Bethesda, Maryland, submitted a human gene transfer protocol entitled: Gene Therapy Approach for Chronic Granulomatous Disease to the Recombinant DNA Advisory Committee for formal review and approval.

**III. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Black and Fakhrai**

In a letter dated January 6, 1995, Drs. Keith L. Black and Habib Fakhrai of the University of California, Los Angeles, California, submitted a human gene transfer protocol entitled: Immunization of Glioblastoma Patients with TGF- $\beta$ 2 Antisense and Interleukin-2 (IL-2) Gene Modified Autologous Tumor Cells: A Phase I Study to the Recombinant DNA Advisory Committee for formal review and approval.

**IV. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Dr. Gansbacher**

In a letter dated January 6, 1995, Dr. Bernd Gansbacher of the Memorial Sloan-Kettering Cancer Center, New York, New York, submitted a human gene transfer protocol entitled: Phase I/II Study of Immunization with MHC Class I Matched Allogeneic Human Prostatic Carcinoma Cells Engineered to Secrete Interleukin-2 and Interferon- $\gamma$  to the Recombinant DNA Advisory Committee for formal review and approval.

**V. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Link and Moorman**

In a letter dated January 6, 1995, Drs. Charles J. Link and Donald Moorman of the Human Gene Therapy Research Institute, Des Moines, Iowa, submitted a human gene transfer protocol entitled: A Phase I Trial of In Vivo Gene Therapy with the Herpes Simplex Thymidine Kinase/Ganciclovir System for the Treatment of Refractory or Recurrent

Ovarian Cancer to the Recombinant DNA Advisory Committee for formal review and approval.

**VI. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Morgan and Walker**

In a letter dated January 9, 1995, Drs. Richard Morgan and Robert Walker of the National Institutes of Health, Bethesda, Maryland, submitted a human gene transfer protocol entitled: Gene Therapy for AIDS Using Retroviral Mediated Gene Transfer to Deliver HIV-1 Antisense TAR and Transdominant Rev Protein Genes to Syngeneic Lymphocytes in HIV Infected Identical Twins to the Recombinant DNA Advisory Committee for formal review and approval.

**VII. Addition to Appendix D of the NIH Guidelines Regarding a Human Gene Transfer Protocol/Drs. Economou, Glaspy, and McBride**

In a letter dated April 11, 1994, Drs. James Economou, John Glaspy, and William McBride of the University of California, Los Angeles, California, submitted a human gene transfer protocol entitled: A Phase I Testing of Genetically Engineered Interleukin-7 Melanoma Vaccines to the Recombinant DNA Advisory Committee for formal review and approval. At its June 9-10, 1994, meeting, the Recombinant DNA Advisory Committee deferred the protocol based on insufficient toxicology studies and failure to demonstrate biological efficacy. The Recombinant DNA Committee required a new submission for future review of the full Recombinant DNA Advisory Committee, not just the toxicology data.

In a letter dated January 17, 1995, Drs. James S. Economou, John A. Glaspy, and William H. McBride submitted a revised protocol to the Recombinant DNA Advisory Committee for formal review and approval at its March 6-7, 1995, meeting.

**VIII. Proposed Amendments to Appendix B of the NIH Guidelines Regarding Updating the Classification of Microorganisms/Fleming**

In a letter dated June 24, 1993, Dr. Diane Fleming, President of the Mid-Atlantic Biological Safety Association requested updating Appendix B, Classification of Microorganisms on the Basis of Hazard. The Mid-Atlantic Biological Safety Association submitted an updated list of the classification of microorganisms for the Committee to review which included the latest taxonomy and agent risk group classifications as defined by the Centers

for Disease Control and Prevention. This request was published for public comment in the **Federal Register** (August 18, 1994, 58 FR 44098).

During the September 9–10, 1993, meeting, the Recombinant DNA Advisory Committee recommended by consensus that the current classification of etiological agents described in the *Biosafety in Microbiological and Biomedical Laboratories*, 3rd edition, May 1993, U.S. Department of Health and Human Services, should be endorsed by the Committee. The Committee retains the option to adopt any modification to the CDC listing. The Committee recommended that the revised Appendix B, *Classification of Microorganisms on the Basis of Hazard*, submitted by Dr. Fleming should not be adopted until the Committee receives letters of concurrence from both the Centers for Disease Control and Prevention and the NIH Division of Safety.

In a telephone call on October 20, 1994, Dr. Fleming stated that Appendix B, *Classification of Microorganisms on the Basis of Hazard*, would be reviewed by experts from the Centers for Disease Control and Prevention and the American Society for Microbiology. The revised Appendix B was submitted to the Recombinant DNA Advisory Committee December 1–2, 1994, meeting for review and discussion. During the December 1994 meeting, the Committee recommended publishing the revised Appendix B in the **Federal Register** for public comment, with further review of this proposal and possible approval during the March 6–7, 1995, meeting.

The proposed Appendix B reads as follows:

**Appendix B. Classification of Etiologic Agents and Oncogenic Viruses on the Basis of Risk (See Appendix B–VI–A)**

Agents evaluated by the Centers for Disease Control (CDC) and the National Institutes of Health (NIH) and published in the *Morbidity and Mortality Weekly Report*, or in a revision of the CDC/NIH “*Biosafety in Microbiological and Biomedical Research Laboratories*” (BMBL), as agent summary statements shall automatically be added to this list. Revisions to lists of agents provided by the Subcommittee on Arbovirus Laboratory Safety (SALS) as taken from the BMBL (see Appendix B–VI–D) and provided here in Tables 3–6 shall be incorporated into this list. Appendix B shall undergo an annual review for the Office of Recombinant DNA Activities (ORDA) by a special committee of the American Society for Microbiology (ASM) to ensure that all such updates

have been incorporated. Additions or corrections to this list may also occur following a review by ORDA, the RAC, and/or by recommendation of the CDC.

*Appendix B–I. Points To Consider in Using Appendix B and in Assessing the Risk of Handling Microorganisms*

Appendix B is not to be used to replace a thorough assessment of the risk of working with a particular biohazardous agent. However, the information can be used to establish an initial, qualitative assessment of the risk of handling an agent. Such information would be appropriate for initial estimates of the design of facilities needed for the use of such agents or the requirements for their transport. Much of the information in the previous version of Appendix B, based upon a 1974 publication of the Centers for Disease Control (see Appendix B–VI–C), is updated and retained in this revision. Information on agent risk assessments found in the “Agent Summary Statements” of the CDC/NIH publication “*Biosafety in Microbiological and Biomedical Laboratories*” (See Appendix B–VI–D), information from the American Public Health Association publication, “*Control of Communicable Diseases of Man*” (See Appendix B–VI–B) and input from a special committee of the American Society for Microbiology provided additional information for the revised list of four risk groups found in Appendix B. The definition of each risk group and the relationship of the four risk groups to four biosafety levels (BL) is found in Tables 1 and 2 from the *Laboratory Biosafety Manual* of the World Health Organization (See Appendix B–VI–E). As a general principle, the greater the hazard posed by the microorganism, the higher the risk group placement. Use of the term “risk group” is recommended by the World Health Organization and is used here to indicate the result of a qualitative risk assessment based upon agent characteristics as described below. Risk Group designations are currently used in Canada for human and animal pathogens, and in the member nations of the European Union, which list only human pathogens in the Directive for protection of workers from exposure to biohazardous agents.

Specific strains of many species may fall into either a more or a less hazardous risk group depending upon the genetic background and natural history of the strain. Information on the parent or wild-type strain is used for the qualitative risk assessment list in Appendix B. Further information on a specific strain is to be used by the

Principal Investigator or supervisor for a quantitative risk assessment.

In assessing the risk of working with a specific strain, the following criteria should be considered: any organism directly isolated from a human or animal should be treated as a potentially pathogenic organism until proven otherwise; specific strains that are known to be more hazardous than the parent strain, such as those resistant to a limited number of drugs used for treatment, may need to be handled at a higher containment level than the parent strain. On the other hand, specific strains of Risk Group 2 microorganisms that are known to have minimal hazard risk to humans may be classified within Risk Group 1 and handled at BL1. Certain attenuated strains that are commonly used for live vaccines and specific attenuated strains with an extensive history of safe laboratory use without harmful effect may be placed in a lower risk group than the parent organism, as done by the CDC (See Appendices B–VI–C through –D). Where a strain is attenuated or has lost known virulence factors (i.e., genes) and is to be used as a product or part of a product or for prophylactic/therapeutic purposes, then the containment required by the classification of the parent strain need not apply when used for such purpose.

Appendix B–I–A. The list of biohazardous agents in Appendix B is meant to be based on the effect of a biological agent on a healthy worker. No account is taken of particular effects on those whose susceptibility may be affected by one or other reasons such as preexisting disease, medication, compromised immunity, pregnancy or breast feeding. Additional risk to workers should be considered as a part of the required (quantitative) risk assessment which takes into account the potential interactions of the agent-host-activity. Only agents known to infect humans are meant to be included in Appendix B. Lists of restricted animal pathogens, included in BMBL and previously included in Appendix B, should be obtained by contacting the USDA, Animal and Plant Health Inspection Service (APHIS).

Appendix B–I–B. Genetically modified organisms are not specifically covered by this list. The determination of the risk of a recombinant organism is a part of the required quantitative risk assessment of the specific strain to be carried out by the Principal Investigator/supervisor.

Appendix B–I–C. For agents where more than one species is known to be pathogenic for man, this appendix may include the genus name as well as

individual species which are known to be the most important in terms of human infectivity. When such a genus is listed in Appendix B, the species and strains known to be non-pathogenic are meant to be excluded from the list. For parasites, the stages of the life cycle which are not infectious for humans are excluded.

Appendix B-I-D. Those agents not listed in Risk Groups 2-4 are not automatically or implicitly classified in Risk Group 1; a risk assessment must be conducted. The list in Appendix B is meant to serve as a general guideline for the risk group classification of microorganisms. Further guidance for microorganisms which are not specifically listed may be obtained from the Centers for Disease Control and Prevention, Office of Health and Safety (404-329-3883).

Appendix B-I-E. The list provided in Appendix B reflects the state of knowledge at the time it was prepared. The nomenclature reflects and is meant to be in conformity with the latest international agreements on taxonomy and nomenclature of agents at this time. The list is as complete as possible but necessarily not exhaustive. Additional information to be used to update the list in a timely manner shall include new agent summary statements published by the Centers for Disease Control as well as taxonomic changes to human pathogens. An annual review to incorporate the new agents and to correct the taxonomy has been offered through the ASM.

#### Appendix B-II. Risk Assessment

Appendix B-II-A. It is the responsibility of the Principal Investigator/supervisor to assess the risk associated with the handling of potentially biohazardous microorganisms and to ensure that the appropriate biosafety practices are employed prior to conducting any experiments or operations. A rough, qualitative risk assessment is used for an initial agent classification. However, it is to be followed by a quantitative risk

assessment of the specific strain of the agent, the immune status of the host relative to the agent in question and potential agent-host-activity interactions, such as those caused by aerosol production. For example, although cultures of the organism may be handled at BSL-2 for Risk Group 2 agents such as the dengue virus, when used for animal inoculation or transmission work it is handled at BSL-3. Similarly, such work with monkey pox, VEE or yellow fever viruses are carried out under BSL-4 containment.

Appendix B-II-B. The quantitative risk assessment described above is to be used to determine the Biosafety Level (BL), as described in Appendices G and K, which identifies the appropriate facilities, equipment, and work practices to be used for specific procedures carried out by a healthy adult individual (assessed for health status) with a specific biohazardous agent (assessed for virulence factors including antibiotic resistance to drugs of treatment). Factors to be considered in determining the level of containment include agent factors such as: Virulence, pathogenicity, stability, route of spread, communicability, the operation(s), quantity, and availability of vaccine or treatment. The higher risk agents also require more stringent biosafety practices and facilities as reflected in the Biosafety Level to which work is to be assigned (See Table 2 for the relation between risk groups and biosafety level). Although risk assessment is ultimately a subjective process, the CDC/NIH Guidelines in BMBL (See Appendix B-VI-D) have provided information about microorganisms based on the hazard they present and guidance for defining safe conditions for their use. Further information on specific biohazardous microorganisms is available in the Agent Summary Statements of the primary reference (See Appendix B-VI-D), from a publication of the American Public Health Association "Control of Communicable Diseases in Man" (See Appendix B-VI-

B) and from the CDC, e.g., the Office of Safety and Health and the Special Pathogens Branch. Changes to the agent which enhance or remove virulence factors should be considered by the Principal Investigator/supervisor and/or a local Institutional Biosafety Committee (IBC) which has the authority to raise or lower the containment level used for that agent. Published regulations or guidelines from Federal, State or local governments must also be taken into account.

Appendix B-II-C. When laboratory work is conducted with biological agents for which epidemiology and etiology are unknown or incompletely understood, it will be presumed that the work presents a biohazard similar to related agents until further information can be provided. This method was used by the Subcommittee on Arbovirus Laboratory Safety in assessing the risk of work with arboviruses for which risk information is inadequate or unavailable (See Table C of Appendix B). It is assumed that information needed for risk evaluation will be obtained prior to the large-scale use of such an agent.

Appendix B-II-D. Special consideration will be given to large-scale (greater than 10 liters of culture) and aerosol producing operations which may pose additional significant risks and thus may require additional containment (See Appendix K).

#### Appendix B-III. Risk Groups: Classification of Infectious Substances and Oncogenic Viruses on the Basis of Risk

The characteristics used for the qualitative risk assessment of biohazardous agents into the four Risk Groups of human etiologic agents are defined in Table 1 below, with each higher number representing an increased hazard. The information and interpretations below are from the CDC/NIH, BMBL (See Appendix B-VI-D) and the World Health Organization Laboratory Biosafety Manual (See Appendix B-VI-E).

TABLE 1.—CLASSIFICATION OF BIOHAZARDOUS AGENTS BY RISK GROUP (SEE APPENDIX B-VI-E)

Risk Group 1 ....	(No or very low individual and community risk) An agent that is unlikely to cause human disease. Well characterized agents not known to cause disease in healthy adult humans and of minimal potential hazard to laboratory personnel and the environment.
Risk Group 2 ....	(Moderate individual risk, low community risk) Agents which can cause human disease but are unlikely to be a serious hazard to workers, the community or the environment; laboratory exposures may cause serious infection but effective treatment and preventive measures are available and the risk of spread of infection is limited.
Risk Group 3 ....	(High individual risk, low community risk) Agents which usually cause serious human disease but do not ordinarily spread from one infected individual to another. Effective treatment or preventive measures are available.
Risk Group 4 ....	(High individual and high community risk) Agents which can cause serious human disease and can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

TABLE 2.—RELATIONSHIP OF RISK GROUPS TO BIOSAFETY LEVELS, PRACTICES, AND EQUIPMENT  
(SEE APPENDIX B—VI—E)

Risk group	Biosafety level	Examples of laboratories	Laboratory practices	Safety equipment
1	Basic Biosafety Level 1 .....	Basic Teaching .....	GMT <sup>a</sup> .....	None, open bench work
2	Basic Biosafety Level 2 .....	Primary health svcs; primary level hospital; diagnostic, teaching and Public Health.	GMT plus protective clothing; biosafety sign.	Open bench plus BSC <sup>b</sup> for potential aerosols.
3	Containment-Biosafety Level 3 .	Special diagnostic .....	As level 2 plus special clothing, controlled access, directional air flow.	BSC and/or other primary containment for all activities.
4	Maximum Containment-Biosafety Level 4 .....	Dangerous pathogens units .....	As level 3 plus airlock entry, shower exit, special waste disposal.	Class III BSC or positive pressure suits, double-ended autoclave filtered air.

<sup>a</sup> GMT—good microbiological practices.

<sup>b</sup> BSC—biological safety cabinet.

#### Appendix B—III—A. Risk Group 1—Agents

Risk Group 1 agents are usually not placed on a list but are assumed to include all bacterial, fungal, viral, rickettsial, chlamydial, and parasitic agents which have been assessed for hazard and are not included in higher risk groups. Risk Group 1 agents can be used for undergraduate and secondary educational training and teaching laboratories and for other facilities in which work is conducted with defined and characterized strains of viable microorganisms not known to cause disease in healthy adult humans and of minimal potential hazard to personnel and the environment under ordinary conditions of use. These agents can be handled safely in the laboratory without special apparatus or equipment using techniques generally acceptable for nonpathogenic materials. Examples of agents in Risk Group 1 are: *Bacillus subtilis*, infectious canine hepatitis viruses; influenza reference strains A/PR/8/34, A/WS/33; agents listed in Appendix C—II of the NIH *Guidelines for Research Involving Recombinant DNA Molecules* (*Escherichia coli* K12, *Saccharomyces cerevisiae*, etc.); vectors such as Baculovirus. It is not appropriate to assume that an unassessed agent belongs in this risk group. Even vaccine strains which have undergone multiple *in vivo* passages would not be considered avirulent based only on the fact that they are vaccine strains.

#### Appendix B—III—A—1. Risk Group 1—Low-Risk Oncogenic Viruses (See Appendix B—VI—G)

Adenovirus 7—Simian virus 40 (Ad7—SV40)

Avian leukosis virus  
Bovine leukemia virus  
Bovine papilloma virus

Chick-embryo-lethal orphan (CELO) virus or fowl adenovirus—1  
Dog sarcoma virus  
Guinea pig herpes virus  
Lucke (Frog) virus  
Hamster leukemia virus  
Marek's disease virus  
Mason-Pfizer monkey virus  
Mouse mammary tumor virus  
Murine leukemia virus  
Murine sarcoma virus  
Polyoma virus  
Rat leukemia virus  
Rous sarcoma virus  
Shope fibroma virus  
Shope papilloma virus  
Simian virus 40 (SV—40)

#### Appendix B—III—B. Risk Group II—Agents

Agents of moderate potential hazard to healthy human adults and the environment. Such agents may produce disease of varying degrees of severity from accidental inoculation, injection or other means of cutaneous penetration but can usually be adequately and safely contained by ordinary laboratory techniques. Some agents may cause disease by contact or respiratory routes, but they are self-limiting and do not cause a serious illness, e.g. the common cold (rhinoviruses). Risk Group 2 agents are recommended for use only in those laboratories where staff are trained to handle microbes which pose this level of risk. Examples include *Streptococcus pneumoniae*, *Staphylococcus aureus*, poliovirus, etc.

#### Appendix B—III—B—1. Risk Group 2—Bacteria<sup>1</sup>

*Acinetobacter baumannii*  
*Actinobacillus spp.*  
*Actinomyces pyogenes*

<sup>1</sup> When "spp" follows the name of a genus, or "serotype" follows a species, only those species or serotypes known to be pathogenic to healthy human adults are meant to be included in this list.

*Aeromonas hydrophila*  
*Amycolata autotrophica*  
*Archanobacterium haemolyticum*  
*Arizona hinshawii*—all serotypes  
*Bacillus anthracis*\*<sup>2</sup>  
*Bartonella henselae*, *B. quintana*, *B. vinsonii*  
*Bordetella spp.* including *B. pertussis*\*  
*Borrelia recurrentis*, *B. burgdorferi*  
*Burkholderia was Pasteurella spp.*  
(except for those listed in Risk Group 3)  
*Burkholderia pseudomallei*\*  
*Campylobacter coli*, *C. fetus ssp. fetus*,  
*C. jejuni*  
*Chlamydia psittaci*\*, *C. trachomatis*\*, *C. pneumoniae*\*  
*Clostridium botulinum*\*, *Cl. chauvoei*,  
*Cl. haemolyticum*, *Cl. histolyticum*,  
*Cl. novyi*, *Cl. septicum*, *Cl. tetani*  
*Corynebacterium diphtheriae*, *C. pseudotuberculosis*, *C. renale*  
*Dermatophilus congolensis*  
*Edwardsiella tarda*  
*Erysipelothrix rhusiopathiae*  
*Escherichia coli*—all enteropathogenic, enterotoxigenic, enteroinvasive and strains bearing K1 antigen, including *E. coli* O157:H7  
*Haemophilus ducreyi*, *H. influenzae*  
*Helicobacter pylori*  
*Klebsiella spp.*  
*Legionella spp.* including *L. pneumophila*\*  
*Legionella-like organisms*  
*Leptospira interrogans*—all serotypes  
*Listeria spp.*  
*Moraxella spp.*  
*Mycobacterium spp.* (except those listed in Risk Group 3) including *M. avium* complex, *M. asiaticum*, *M. chelonae*, *M. fortuitum*, *M. kansasii*, *M. leprae*, *M. malmoense*, *M. marinum*, *M. paratuberculosis*, *M. scrofulaceum*, *M. simiae*, *M. szulgai*, *M. ulcerans*, *M. xenopi*

<sup>2</sup> \*Agents in Risk Group 2 which require special handling using BL 3 practices are noted with an asterisk.

- Mycoplasma* spp. except *M. mycoides* and *M. agalactiae* which are restricted animal pathogens (See Appendix B–V)
- Neisseria gonorrhoea*, \* *N. meningitidis*\*
- Nocardia asteroides*, *N. brasiliensis*, *N. otitidiscaviarum*, *N. transvalensis*
- Rhodococcus equi*
- Salmonella* spp. and serotypes including *S. arizonae*, *S. choleraesuis*, *S. enteritidis*, *S. gallinarum-pullorum*, *S. meleagridis*, *S. paratyphi*, A, B, C, *S. typhi*\*, *S. typhimurium*,
- Shigella* spp. \* and serotypes including *S. boydii*, *S. dysenteriae*, Type 1, *S. flexneri*, *S. sonnei*
- Sphaerophorus necrophorus*
- Staphylococcus aureus*
- Streptobacillus moniliformis*
- Streptococcus* spp. including *Streptococcus pneumoniae*, *S. pyogenes*
- Treponema pallidum*, *T. carateum*
- Vibrio cholerae*, *V. parahemolyticus*, *V. vulnificus*
- Yersinia enterocolitica*, *Y. pestis*\*
- Appendix B–III–B–2. Risk Group 2—Fungal Agents<sup>3</sup>
- Blastomyces dermatitidis*
- Cladosporium bantianum*, *C. (Xylohypha) trichoides*
- Cryptococcus neoformans*<sup>4</sup>
- Dactylaria galopava (Ochroconis gallopavum)*
- Epidermophyton* spp.
- Exophiala (Wangiella) dermatitidis*
- Fonsecaea pedrosoi*
- Microsporium* spp.
- Paracoccidioides braziliensis*
- Penicillium marneffeii*
- Sporothrix schenckii*
- Trichophyton* spp.
- Appendix B–III–B–3. Risk Group 2—Parasitic Agents
- Ancylostoma* spp., human hookworms including *A. duodenale*, *A. ceylanicum*
- Ascaris* spp. including *Ascaris lumbricoides suum*
- Babesia* spp. including *B. divergens*, *B. microti*
- Brugia* spp. filaria worms including *B. malayi*, *B. timori*
- Coccidia* spp.
- Cryptosporidium* spp. including *C. parvum*
- Cysticercus cellulosae* (hydatid cyst, larva of *T. solium*)
- Echinococcus* spp. including *E. granulosis*, *E. multilocularis*, *E. vogeli*
- Entamoeba histolytica*
- Enterobius* spp.
- Fasciola* spp. including *F. gigantica*, *F. hepatica*
- Giardia* spp. including *G. lamblia*
- Heterophyes* spp.
- Hymenolepis* spp. including *H. diminuta*, *H. nana*
- Isospora* spp.
- Leishmania* spp. including *L. braziliensis*, *L. donovani*, *L. ethiopia*, *L. major*, *L. mexicana*, *L. peruviana*, *L. tropica*
- Loa loa* filaria
- Microsporidium* spp.
- Micogleria fowleri*
- Necator* spp. human hookworm, including *N. americanus*
- Onchoerca* spp. filaria including, *O. volvulus*
- Plasmodium* spp. including simian species, *P. cynomologi*, *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax*
- Sarcocystis* spp. including *S. suis hominis*
- Schistosoma* spp. including *S. haematobium*, *S. intercalatum*, *S. japonicum*, *S. mansoni*, *S. mekongi*
- Strongyloides* spp. including *S. stercoralis*
- Taenia solium*
- Toxocara* spp. including *T. canis*
- Toxoplasma* spp. including *T. gondii*
- Trichinella spiralis*
- Trypanosoma* spp. including *T. brucei brucei*, *T. brucei gambiense*, *T. brucei rhodesiense*, *T. cruzi*
- Wuchereria bancrofti* (filaria)
- Appendix B–III–B–4. Risk Group 2—Viruses and prions (See Tables 3 and 4)
- Adenoviruses-human, all types
- Arboviruses (See Table 3)
- Arenaviruses (See Table 3)
- Bunyamwera virus
- Coronaviruses
- Coxsackie A and B viruses
- Creutzfeldt-Jacob disease agent (prion)
- Echoviruses—all types
- Encephalomyocarditis virus (EMC)
- Encephalomyelitis viruses<sup>5\*</sup> (See Table 3)
- Hepatitis A, B\*, C\*, D, E viruses
- Herpesviruses\* including Cytomegalovirus, Epstein Barr, Herpes simplex types 1 and 2 and Herpes zoster, except Herpesvirus simiae (Monkey B virus) which is in Risk Group 4
- Human Immunodeficiency Virus (HIV) all serotypes
- Human T-cell lymphotropic viruses\* (HTLV) types 1 and 2.
- Influenza viruses
- Kuru (prion)
- Lymphocytic choriomeningitis virus\* (except neurotropic strains)
- Lymphogranuloma venereum agent
- Measles virus
- Molluscum contagiosum virus
- Mumps virus
- Orf virus
- Papovaviridae including human papilloma viruses
- Parainfluenza virus
- Paravaccinia virus
- Polioviruses—all types, wild and attenuated
- Poxviruses<sup>6</sup>—all types such as Cowpox\*\*, Monkeypox\*\* or Vaccinia\*\*, Camelpox, Milker's node virus, Molluscum contagiosum virus, Orf, Rabbitpox, Tanapox and Yabapox, with the exception of Alastrim, Smallpox, and Whitepox (See Appendix B VI–H)
- Rabies virus<sup>7</sup>—all strains, including fixed/attenuated virus, except Rabies street virus
- Reoviruses all types
- Respiratory syncytial virus
- Rhinoviruses all types
- Rubella virus
- Simian viruses all types including simian immunodeficiency virus\*, except Herpesvirus simiae (Monkey B virus) and Marburg virus which are in Risk Group 4
- Transmissible Spongiform Encephalopathies (TME)-prions (Creutzfeldt-Jacob; Kuru)
- Vesicular Stomatitis Virus, lab adapted strains:VSV-Indiana, San Juan and Glasgow
- Appendix B–III–B–5. Risk Group 2—Moderate Risk Oncogenic Viruses (See Appendix B–VI–G)
- Adenovirus
- Adenovirus 2—Simian virus 40 (Ad2–SV40)
- Epstein-Barr virus (EBV)
- Feline leukemia virus (FeLV)
- Feline sarcoma virus (FeSV)
- Gibbon leukemia virus (GaLV)
- Herpesvirus (HV) ateles
- Herpesvirus (HV) saimiri
- Papovaviridae including human papilloma viruses
- Simian sarcoma virus (SSV)–1
- Yabapox virus
- Appendix B–III–C. Risk Group 3—Agents
- Indigenous or exotic agents which may cause serious or potentially lethal disease as a result of exposure by the inhalation route. Agents involving special hazards to laboratory personnel or agents derived from outside the

<sup>3</sup> When "spp" follows the name of a genus, or "serotype" follows a species, only those species or serotypes known to be pathogenic to healthy human adults are to be included in this list.

<sup>4</sup> Risk Group 2 agent for which droplets/aerosols are handled in a Biological Safety Cabinet (BSC).

<sup>5</sup> \*Risk Group 2 Viruses for which droplets/aerosols are handled with BL 3 practices.

<sup>6</sup> All types with double asterisk can be handled at BL2 in a BSC by immunized personnel.

<sup>7</sup> Rabies virus may be handled at BL 2 by immunized personnel using a BSC.

United States which require a permit for importation, unless they are specified for higher classification.

This risk group includes pathogens which require special conditions for containment. Agents in this group can be used in laboratories where staffs have levels of competency equal to or greater than one would expect in a college department of microbiology, and who have had special training in handling these or similar pathogens which cause potentially lethal disease. Workers are to be supervised by competent scientists trained and experienced in handling these biohazardous agents/materials. Examples include: *Brucella melitensis*, *Coxiella burnetii*, *Mycobacterium tuberculosis*, *Rickettsia rickettsii*, etc.

Appendix B-III-C-1. Risk Group 3—Bacterial Agents, including Chlamydia and Rickettsia

*Bartonella* spp.

*Brucella* spp. including *B. abortus*, *B. canis*, *B. melitensis* (USDA restricted), *B. suis*

*Burkholderia (Pseudomonas) mallei*, *B. pseudomallei* (see Appendix B-VI-F)  
*Coxiella burnetii*

*Francisella tularensis*

*Mycobacterium bovis*, *M. tuberculosis*  
*Pasteurella multocida* type B—"buffalo"  
and others (see Appendix B-VI-F)

*Rickettsia akari*, *R. australis*, *R. canada*,  
*R. conorii*, *R. prowazekii*

*R. rickettsii*, *R. siberica*, *R.*

*tsutsugamushi*, *R. typhi (R. mooseri)*  
*Yersinia pestis* (antibiotic resistant strains)

Appendix B-III-C-2. Risk Group 3—Fungal Agents

*Coccidioides immitis* (sporulating cultures; contaminated soil)

*Histoplasma capsulatum*, *H. capsulatum* var. *duboisii*

Appendix B-III-C-3. Risk Group 3—Parasitic Agents

None

Appendix B-III-C-4. Risk Group 3—Viral Agents

Arboviruses<sup>8</sup> and certain other viruses assigned to Risk Group 3 (see Appendix B-VI-I and Tables 5 and 6).

Lymphocytic choriomeningitis virus (LCM) (neurotrophic strains)

Monkey pox virus—when used *in vitro* (see Appendix B-VI-H)

Rabies Street virus

Appendix B-III-D. Risk Group 4—Agents

Dangerous and exotic agents which pose a high individual risk of aerosol transmitted laboratory infections which result in a life-threatening disease, or related agents with unknown means of transmission. These agents require the most stringent conditions for their containment because they are extremely hazardous to laboratory personnel or may cause serious epidemic disease. These agents may only be used in special facilities where the staff has a level of competency equal to or greater than one would expect in a college department of microbiology, and who have had specific and thorough training in handling dangerous pathogens, including the specific techniques to be used. Such workers are to be supervised by competent scientists.

Appendix B-III-D-1. Risk Group 4—Bacterial Agents

None

Appendix B-III-D-2. Risk Group 4—Fungal Agents

None

Appendix B-III-D-3. Risk Group 4—Parasitic Agents

None

Appendix B-III-D-4. Risk Group 4—Viral Agents

Absettarov

Central European encephalitis viruses  
Crimean hemorrhagic fever (Congo)

Ebola fever virus

Guanarito

Hanzalova

Hemorrhagic fever agents and viruses as yet undefined

*Herpesvirus simiae* (Monkey B virus)

Hypr

Junin (BL3\* if vaccine is used)

Kumlinge

Kyasanur forest disease

Lassa

Machupo

Marburg

Omsk hemorrhagic fever

Russian spring-summer encephalitis  
Tick-borne orthomyxoviridae, Dhori & Thogoto

Appendix B-IV. Restricted Plant Pathogens

Non-indigenous pathogens of plants may require special laboratory design, operation and containment features not generally addressed in the CDC/NIH guidelines. Information on the importation, possession or use of these agents is to be obtained from the USDA, APHIS. Guidelines for handling recombinant plants are in Appendix P.

Appendix B-V. Restricted Animal Pathogens

Non-indigenous pathogens of domestic livestock and poultry may require special laboratory design, operation, and containment features not generally addressed in the CDC/NIH guidelines. The importation, possession or use of these agents is prohibited or restricted by law or by the U.S. Department of Agriculture regulations or administration policies. Animal pathogens other than those listed as zoonotic agents Appendix B may also be subject to USDA regulations. See Appendix Q for guidelines for recombinant animals.

Appendix B-V-A. Organisms which may not be studied in the United States except at Specified Facilities

Alastrim (see Appendix B-VI-H)

Small pox (see Appendix B-VI-H)

White pox (see Appendix B-VI-H)

Appendix B-VI. References of Appendix B

Appendix B-VI-A. For the purposes of these Guidelines, the list in Appendix B has been revised by using the Risk Group classification recommended by the World Health Organization (See Appendix B-VI-E), and adding information from agent summary statements of the CDC/NIH "Biosafety in Microbiological and Biomedical Laboratories" (See Appendix B-VI-D), from the APHA, "Control of Communicable Diseases of Man" (See Appendix B-VI-B), and from a special committee of the American Society for Microbiology. Information in Tables 1 and 2 came from the WHO reference (See Appendix B-VI-E) while that for Tables 3-6 and for Appendix B-V and B-VI was obtained directly from the CDC on computer disc. The original reference for this classification was the publication Classification of Etiologic Agents on the Basis of Hazard, 4th edition, July 1974 (See Appendix B-VI-C). A draft 1982 CDC document which included a more complete risk assessment of a larger group of human pathogens was also used (Dr. R. Knudsen, CDC, personal communication). For the purposes of these NIH Guidelines, these lists are revised by the NIH.

<sup>8</sup>The 171 arboviruses in Risk Group 3 are found in Appendix B-VI-I and Tables 5 and 6. Arboviruses indigenous to the United States are in Risk Group 3 except those listed in Risk Group 2 (Tables 3 and 4). West Nile and Semliki Forest viruses may be classified up or down depending on the conditions of use and geographical location of the laboratory.

Appendix B-VI-B. Benenson, Abram S. ed. 1990. Control of Communicable Diseases in Man. 15th edition. 532 pp. American Public Health Asso. Washington, D.C.

Appendix B-VI-C. Center for Disease Control, Office of Biosafety. 1974. Classification of Etiologic Agents on the Basis of Hazard, 4th Edition. U.S. Department of Health, Education and Welfare, Public Health Service.

Appendix B-VI-D. Centers for Disease Control and the National Institutes of Health (CDC/NIH), 1993. Biosafety in Microbiological and Biomedical Research Laboratories. pp 177. Government Printing Office. (#017-040-00523-7) Washington, D.C.

Appendix B-VI-E. World Health Organization Laboratory Biosafety Manual. 2nd Edition. WHO Albany, NY ORDER FROM: WHO Publication Centre, USA, (Q Corp) 49 Sheridan Avenue, Albany, NY 12210, tel 518-436-9686. Order # 1152213 (cost \$23.40 plus \$3.00 handling).

Appendix B-VI-F. A U.S. Department of Agriculture permit, required for import and interstate transport of pathogens, may be obtained from the U.S. Department of Agriculture, ATTN: Animal and Plant Health Inspection Service, Import-Export Products Office, Room 756, Federal Building, 6505 Belcrest Road, Hyattsville, Maryland 20782. Telephone; 301-436-7830 or 8499; FAX 301-436-8226

Appendix B-VI-G. National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses, U.S. Department of Health, Education, and Welfare Publication No. (NIH) 75-790, October 1974.

Appendix B-VI-H. All activities, including storage of variola and whitepox, are restricted to the single national facility (World Health Organization Collaborating Center for Smallpox Research, Centers for Disease Control and Prevention, Atlanta, Georgia).

Appendix B-VI-I. Tables 3-6 (See Appendix B-VI-D)

Appendix B-VI-I-A. Table 3. Arboviruses and Arenaviruses Assigned to Biosafety Level 2

Acado  
Acara  
Aguacate  
Alfuy  
Almpiwar  
Amapari  
Ananindeua  
Anhanga  
Anhembí  
Anopheles A  
Anopheles B

Apeu  
Apoi  
Aride  
Arkonam  
Aroa  
Aruac  
Arumowot  
Aura  
Avalon  
Abrás  
Abu Hammad  
Aabahoyo  
Bagaza  
Bahig  
Bakau  
Baku  
Bandia  
Bangoran  
Bangui  
Banzi  
Barmah Forest  
Barur  
Batai  
Batama  
Bauline  
Bebaru  
Belmont  
Benevides  
Benfica  
Bertioga  
Bimiti  
Birao  
Bluetongue  
Boraceia  
Botambi  
Boteke  
Bouboui  
Bujaru  
Bunyamwera  
Bunyip  
Burg E Arab  
Bushbush  
Bussuquara  
Buttonwillow  
Bwamba  
Cacao  
Cache Valley  
Caimito  
California enc.  
Calovo  
Candiru  
Cape Wrath  
Capim  
Caraparu  
Carey Island  
Catu  
Chaco  
Chagres  
Chandipura  
Changuinola  
Charleville  
Chenuda  
Chilibre  
Chobar gorge  
Clo Mor  
Colorado tick fever  
Corriparta  
Cotia  
Cowbone Ridge

Cuiro Village  
Cuiaba-D'aguilar  
Dakar Bat  
Dengue-1  
Dengue-2  
Dengue-3  
Dengue-4  
Dera Ghazi Khan  
East. equine enc.<sup>(d)</sup>  
Edge Hill  
Entebbe Bat  
Ep. Hem. Disease  
Erve  
Eubenangee  
Eyach  
Flanders  
Fort Morgan  
Frijoles  
Gamboa  
Gan Gan  
Gomoka  
Gossas  
Grand Arbaud  
Great Island  
Guajara  
Guama  
Guaratuba  
Guaroa  
Gumbo Limbo  
Hart Park  
Hazara  
Highlands J  
Huacho  
Hughes  
Icoaraci  
Ieri  
Ilesha  
Ilheus  
Ingwavuma  
Inkoo  
Ippy  
Irituia  
Isfahan  
Itaporanga  
Itaqui  
Jamestown Canyon  
Japanaut  
Jerry Slough  
Johnston Atoll  
Joinjakaka  
Juan Diaz  
Jugra  
Jurona  
Jutiapa  
Kadam  
Kaeng Khoi  
Kaikalur  
Kaisodi  
Kamese  
Kammavan pettai  
Kannaman galam  
Kao Shuan  
Karimabad  
Karshi  
Kasba  
Kemerovo  
Kern Canyon  
Ketapang  
Keterah

Keuraliba  
Keystone  
Kismayo  
Klamath  
Kokobera  
Kolongo  
Koongol  
Kotonkan  
Kowanyama  
Kunjin  
Kununurra  
Kwatta  
La Crosse  
La Joya  
Lagos Bat  
Landjia  
Langat  
Lanjan  
Las Maloyas  
Latino  
Le Dantec  
Lebombo  
Lednice  
Lipovnik  
Lokern  
Lone Star  
Lukuni  
M'poko  
Madrid  
Maguari  
Mahogany Hammock  
Main Drain  
Malakal  
Manawa  
Manzanilla  
Mapputta  
Maprik  
Marco  
Marituba  
Marrakai  
Matariya  
Matruh  
Matucare  
Melao  
Mermet  
Minatitlan  
Minnal  
Mirim  
Mitchell River  
Modoc  
Moju  
Mono Lake  
Mont. myotis leuk.  
Moriche  
Mosqueiro  
Mossuril  
Mount Elgon Bat  
Murutucu  
Mykines  
Navarro  
Nepuyo  
Ngaingan  
Nique  
Nkolbisson  
Nola  
Ntaya  
Nugget  
Nyamanini  
Nyando

O'nyong-nyong  
Okhotskiy  
Okola  
Olifantsvlei  
Oriboca  
Ossa  
Pacora  
Pacui  
Pahayokee  
Palyam  
Parana  
Pata  
Pathum Thani  
Patois  
Phnom-Penh Bat  
Pichinde  
Pixuna  
Pongola  
Ponteves  
Precarious Point  
Pretoria  
Prospect Hill  
Puchong  
Punta Salinas  
Punta Toro  
Qalyub  
Quaranfil  
Restan  
Rio Bravo  
Rio Grande  
Ross River  
Royal Farm  
Sabo  
Saboya  
Saint Floris  
Sakhalin  
Salehabad  
San angelo  
Sandfly f. (Naples)  
Sandfly f. (Sicilian)  
Sandjimba  
Sango  
Sathuperi  
Sawgrass  
Sebokele  
Seletar  
Sembalam  
Serra do Navio  
Shamonda  
Shark River  
Shuni  
Silverwater  
Simbu  
Simian hem. fever  
Sindbis  
Sixgun City  
Snowshoe Hare  
Sokuluk  
Soldado  
Sororoca  
Stratford  
Sunday Canyon  
Tacaiuma  
Tacaribe  
Taggert  
Tahyna  
Tamiami  
Tanga  
Tanjong Rabok

Tataguine  
Tehran  
Tembe  
Tembusu  
Tensaw  
Tete  
Tett nang  
Thimiri  
Thottapalayam  
Tibrogargan  
Timbo  
Timboteua  
Tindholmur  
Toscana  
Toure  
Tribec  
Triniti  
Trivittatus  
Trubanaman  
Tsuruse  
Turlock  
Tyuleniy  
Uganda S  
Umatilla  
Umbre  
Una  
Upolu  
Urucuri  
Usutu  
Uukuniemi  
Vellore  
Venkatapuram  
Vinces  
Virgin River  
VS-Indiana  
VS-New Jersey  
Wad Medani  
Wallal  
Wanowrie  
Warrego  
West. equine enc.<sup>(d)</sup>  
Whataroa  
Witwatersrand  
Wonga  
Wongorr  
Wyeomyia  
Yaquina Head  
Yata  
Yogue  
Zaliv Terpeniya  
Zegla  
Zika  
Zingilamo  
Zirqa

Footnote:

<sup>d</sup>A vaccine is available and is recommended for all persons working with this agent.

#### Appendix B-VI-I-B

TABLE 4.—VACCINE STRAINS OF RISK GROUP 3 AND 4 VIRUSES WHICH MAY BE HANDLED AT BL2

Virus	Vaccine strain
Chikungunya .....	131/25
Junin .....	Candid #1

TABLE 4.—VACCINE STRAINS OF RISK GROUP 3 AND 4 VIRUSES WHICH MAY BE HANDLED AT BL2—Continued

Virus	Vaccine strain
Rift Valley fever .....	MP-12
Venezuelan equine encephalomyelitis.	TC-83
Yellow fever .....	17-D

Appendix B—VI—I—C. Table 5.

Arboviruses and Certain Other Viruses Assigned to Biosafety Level 3 (on the basis of insufficient experience)

Adelaide River  
 Agua Preta  
 Alenquer  
 Almeirim  
 Altamira  
 Andasibe  
 Antequera  
 Araguari  
 Aransas Bay  
 Arbia  
 Arboledas  
 Babanki  
 Batken  
 Belem  
 Berrimah  
 Bimbo  
 Bobaya  
 Bobia  
 Bozo  
 Buenaventura  
 Cabassue<sup>(c,d)</sup>  
 Cacipacore  
 Calchaqui  
 Cananeia  
 Caninde  
 Chim  
 Coastal Plains  
 Connecticut  
 Corfou  
 Dabakala  
 Douglas  
 Enseada  
 Estero Real  
 Fomede  
 Forecariah  
 Fort Sherman  
 Gabek Forest  
 Gadgets Gully  
 Garba  
 Gordil  
 Gray Lodge  
 Gurupi  
 Iaco  
 Ibaraki  
 Ife  
 Ingangapi  
 Inini  
 Issyk-Kul  
 Itaituba  
 Itimirim  
 Itupiranga  
 Jacareacanga  
 Jamanxi

Jari  
 Kedougou  
 Khasan  
 Kindia  
 Kyzylgach  
 Lake Clarendon  
 Llano Seco  
 Macaua  
 Mapuera  
 Mboke  
 Meaban  
 Mojui Dos Compos  
 Monte Dourado  
 Munguba  
 Naranjal  
 Nariva  
 Nasoule  
 Ndelle  
 New Minto  
 Ngari  
 Ngoupe  
 Nodamura  
 Northway  
 Odrenisrou  
 Omo  
 Oriximina  
 Ouango  
 Oubangui  
 Oubi  
 Ourem  
 Palestina  
 Para  
 Paramushir  
 Paroo River  
 Perinet  
 Petevo  
 Picola  
 Playas  
 Pueblo Viejo  
 Purus  
 Radi  
 Razdan  
 Resistencia  
 Rochambeau  
 Salanga  
 San Juan  
 Santa Rosa  
 Santarem  
 Saraca  
 Saumarez Reef  
 Sedlec  
 Sena Madureira  
 Sepik  
 Shokwe  
 Slovakia  
 Somone  
 Spipur  
 Tai  
 Tamdy  
 Telok Forest  
 Termeil  
 Thiafora  
 Tilligerry  
 Tinaroo  
 Tlacotalpan  
 Tonate<sup>(c,d)</sup>  
 Ttinga  
 Xiburema  
 Yacaaba

Yaounde  
 Yoka  
 Yug Bogkanova

Footnotes:

<sup>c</sup> SALS recommends that work with this agent should be conducted only in Biosafety Level 3 facilities which provide for HEPA filtration of all exhaust air prior to discharge from the laboratory.

<sup>d</sup> A vaccine is available and is recommended for all persons working with this agent.

Appendix B VI—I—D. Table 6.

Arboviruses and Certain Other Viruses Assigned to Biosafety Level 3

Aino  
 Akabane  
 Bhanja  
 Chikungunya<sup>(c,d)</sup>  
 Cocal  
 Dhori  
 Dugbe  
 Everglades<sup>(c,d)</sup>  
 Flexal  
 Germiston<sup>(c)</sup>  
 Getah  
 Hantaan  
 Israel Turkey mening.  
 Japanese enc.  
 Junin<sup>(c,d)</sup>  
 Kairi  
 Kimberley  
 Koutango  
 Louping Ill<sup>(a,c)</sup>  
 Mayaro  
 Middelburg  
 Mobala  
 Mopeia<sup>(c)</sup>  
 Mucambo<sup>(c,d)</sup>  
 Murray Valley enc.  
 Nairobi sheep disease<sup>(a)</sup>  
 Ndumu  
 Negishi  
 Oropouche<sup>(c)</sup>  
 Orungo  
 Peaton  
 Piry  
 Powassan  
 Puumala  
 Rift Valley fever<sup>(a,b,c,d)</sup>  
 Sagiyama  
 Sal Vieja  
 San Perlita  
 Semliki Forest  
 Seoul  
 Spondweni  
 St. Louis enc.  
 Thogoto  
 Tocio<sup>(c)</sup>  
 Turuna  
 Venezuelan equine<sup>(c,d)</sup> encephalitis  
 Vesicular Stomatitis (alagoas)  
 Wesselsbron<sup>(a,c)</sup>  
 West Nile  
 Yellow fever<sup>(c,d)</sup>  
 Zinga<sup>(b)</sup>

Footnotes:

<sup>a</sup> The importation, possession, or use of this agent is restricted by USDA regulation or

administrative policy (see Appendix B-VI-D).

<sup>b</sup>Zinga virus is now recognized as being identical to Rift Valley Fever virus.

<sup>c</sup>SALS recommends that work with this agent should be conducted only in Biosafety Level 3 facilities which provide for HEPA filtration of all exhaust air prior to discharge from the laboratory.

<sup>d</sup>A vaccine is available and is recommended for all persons working with this agent.

<sup>e</sup>This virus is presently being registered in the Catalogue of Arboviruses.

### **IX. Proposed Amendments to Sections I, III, IV, V, and Appendix M of the NIH Guidelines Regarding NIH and FDA Consolidated Review of Human Gene Transfer Protocols**

On July 18-19, 1994, the National Task Force on AIDS Drug Development held an open meeting for the purpose of identifying barriers to AIDS Drug Discovery that included a proposal to streamline the dual review process for human gene transfer experiments. Members of the Task Force recommended a consolidated review process to enhance interactions between the NIH and the Food and Drug Administration (FDA). As a result of the Task Force's deliberations, recommendations were adopted in order to eliminate any unnecessary overlap between the FDA and NIH review of human gene transfer proposals. Both Drs. Varmus and Kessler noted that their respective agencies would cooperate fully to effect the changes necessary to implement these recommendations.

The NIH and FDA proposed that the RAC become advisory to both the NIH Director and the FDA Commissioner with regard to the review of human gene transfer protocols. In the interest of maximizing the resources of both agencies and simplifying the method and period of review for research protocols involving human gene transfer, the FDA and NIH should institute an interagency consolidated review process that incorporates the following principal elements:

(1) All human gene transfer protocols shall be submitted directly to the FDA. Submission will be in the format required by the FDA and the same format will be used by the RAC when public review is deemed necessary.

(2) Upon receipt, FDA review will proceed. The NIH/ORDA staff will simultaneously evaluate the protocol for possible RAC review.

(3) Factors which may contribute to the need for RAC review include: (a) new vectors/new gene delivery systems, (b) new diseases, (c) unique applications of gene transfer, and (d) other issues that require further public review.

(4) If either the FDA or NIH/ORDA decides that a proposal should be reviewed by the RAC, the proposal will be forwarded to the RAC primary reviewers immediately. Whenever possible, Principal Investigators will be notified within 15 working days following receipt of the submission whether RAC review will be required. (RAC reviewed applications will be distributed to RAC members approximately four weeks prior to the next quarterly RAC meeting.)

(5) Semiannual data reporting procedures will remain the responsibility of NIH (ORDA). Semiannual data reports will be reviewed by the RAC in a public forum. In a letter dated August 2, 1994, Dr. Nelson A. Wivel, Director, ORDA, NIH, provided the RAC with background information regarding the National Task Force on AIDS Drug Development meeting, and proposed amendments to Sections I, III, IV, V, and Appendix M of the NIH Guidelines, to reflect the proposed consolidated review process. The revised review process was proposed as follows:

(1) Investigators will be required to submit all human gene transfer proposals directly to the FDA in the format required by the FDA; therefore, investigators will no longer be required to provide a separate submission to NIH/ORDA for RAC review. The FDA Division of Cellular and Gene Therapies will forward a copy of each submission to NIH/ORDA. Both the FDA Division of Cellular and Gene Therapies and NIH/ORDA will simultaneously evaluate each proposal for the necessity for RAC review. Whenever possible, the investigators will be notified within 15 working days following receipt of the submission regarding the necessity for RAC review.

(2) If either the FDA or NIH/ORDA decides that a proposal should undergo RAC review, the proposal will be forwarded to the RAC primary reviewers immediately. Any protocol submitted less than 8 weeks before a RAC meeting will be reviewed at the following quarterly RAC meeting.

(3) The RAC will make recommendations regarding approval/disapproval of protocols, including any relevant stipulations, to the NIH Director. The NIH Director will review, approve, and transmit the RAC's recommendations/stipulations to the FDA Commissioner.

(4) The FDA will consider such recommendations/stipulations and will be responsible for completion of review. The RAC and NIH/ORDA will no longer have the responsibility for reviewing material submitted for Accelerated

Review or for the review of minor modifications to human gene transfer protocols.

These proposed actions were discussed during the September 12-13, 1994, RAC meeting (published for public comments in the **Federal Register**, August 23, 1994 (59 FR 43426)). Dr. Philip Noguchi, Director, Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, FDA, provided additional suggestions regarding the proposed review process including FDA adoption of the Appendix M, 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 Subject (Points to Consider), of the NIH Guidelines. The FDA will require investigators to submit the Points to Consider with their proposed experiments. A lengthy discussion ensued involving RAC members' concerns and suggestions regarding the consolidated review process.

Dr. Noguchi submitted the following compromise proposal regarding the NIH/FDA consolidated review of human gene transfer experiments:

(1) Appendix M, Points to Consider, will not be deleted from the NIH Guidelines. The NIH Guidelines will be modified to provide for submission of Appendix M, Points to Consider, directly to the FDA prior to IND submission. The FDA will update their guidance documents in a similar manner. When necessary, the RAC will continue to be responsible for modifying Appendix M, Points to Consider.

(2) The FDA, NIH/ORDA, and RAC will decide on the necessity for full RAC review. The submitted Appendix M, Points to Consider, will be publicly available for all human gene transfer submissions even if RAC review is not required.

(3) The RAC and FDA will broaden their scope of review for human gene transfer proposals to jointly and prospectively address global issues on a regular basis, e.g., ethical consideration in the implementation of gene therapy patient registry, access for "orphan" genetic disease patients to therapies, criteria for prenatal gene therapy, and transgenic technology for xenotransplantation.

(4) The FDA, NIH/ORDA, and RAC will establish a working group to enhance data monitoring efforts.

(5) An FDA, NIH/ORDA, and RAC working group will be established to propose long-term consolidation. The working group will have input from

public, academic, and corporate sources.

The RAC approved a motion made by Dr. Miller and seconded by Dr. Zallen to accept the following: (1) the FDA proposal submitted by Dr. Noguchi; (2) adopt the Categories for Accelerated Review that were approved by the RAC at its March 3-4, 1994, meeting, as guidelines for proposals that will not require RAC review; (3) establish a working group to examine the review process for human gene transfer protocols (in response to Dr. Varmus' request to establish such a group); (3) the RAC prefers that any stipulation requirements should be satisfactorily met prior to forwarding its recommendation for approval to the NIH Director; and (4) accept the proposed amendments to the NIH Guidelines to reflect this revised consolidated review process (including acceptance of a revised Appendix M and incorporation of minor editorial changes).

The motion was approved by a vote of 15 in favor, 0 opposed, and 1 abstention.

On October 26, 1994, NIH/ORDA forwarded these actions to the NIH Guidelines (incorporating the modifications accepted by the RAC), to the NIH Director for approval and the FDA Commissioner for concurrence. FDA legal counsel expressed concern that implementation of the proposed actions would require amendments to the FDA Investigational New Drug Application Regulations (21 CFR Part 312) to accommodate the release of proprietary information. To resolve this concern, a waiver for the release of information from the FDA to the NIH was proposed. While the NIH Guidelines could require such a waiver for NIH-funded investigators, it would be voluntary for others submitting proposed human gene transfer experiments to the FDA.

The NIH expressed concern that failure to comply with the voluntary waiver procedures may result in the loss of critical information necessary to maintain: (1) The human gene therapy database, (2) "real-time" reporting of serious adverse events, (3) comprehensive overview (by category) by the RAC in a public forum. Public review and access to submission, review, and follow-up information is critical to the safe and focussed advancement of human gene therapy research.

As a result of these concerns, NIH and FDA agreed on a compromise proposal that would accommodate the single submission format proposed at the July 18-19, 1994, meeting of the National

Task Force on AIDS Drug Development, yet maintain public access to critical information and "real-time" adverse event reporting. The compromise proposal involves simultaneous submission of a 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 Appendix 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.

Section I-A, Purpose, is proposed to read:

#### Section I-A. Purpose

The purpose of the NIH Guidelines is to specify practices for constructing and handling: (i) recombinant deoxyribonucleic acid (DNA) molecules, and (ii) organisms and viruses containing recombinant DNA molecules.

Section I-A-1. Any recombinant DNA experiment, which according to the NIH Guidelines requires approval by the NIH, must be submitted to the NIH or to another Federal agency that has jurisdiction for review and approval. Once approvals, or other applicable clearances, have been obtained from a Federal agency other than the NIH (whether the experiment is referred to that agency by the NIH or sent directly there by the submitter), the experiment may proceed without the necessity for NIH review or approval (see exception in Section I-A-1-a).

Section I-A-1-a. 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 FDA and the NIH. 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 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. NIH/ORDA and the FDA will simultaneously evaluate the proposal regarding the necessity for RAC review.

Section III beginning paragraphs is proposed to read:

This section describes five categories of experiments involving recombinant DNA: (i) those that require Institutional Biosafety Committee 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).

Section III-A is proposed to read: 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 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<sub>50</sub> 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<sub>50</sub> 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 M-VI-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;

The rest of Section IV-C-1-b-(2) would be renumbered.

Section IV-C-3, Office of Recombinant DNA Activities (ORDA), is proposed to read:

Section IV-C-3. Office of Recombinant DNA Activities (ORDA)

ORDA shall serve as a focal point for information on recombinant DNA activities and provide advice to all within and outside NIH including institutions, Biological Safety Officers, Principal Investigators, Federal agencies, state and local governments, and institutions in the private sector. ORDA shall carry out such other functions as may be delegated to it by the NIH Director. ORDA's responsibilities include, but are not limited to the following:

Section IV-C-3-a. Evaluating human gene transfer protocols for the necessity for RAC review (see Appendix M-VI-A);

Section IV-C-3-b. Serving as the focal point for data management of FDA and NIH approved human gene transfer protocols (see Appendix M-VIII, Reporting Requirements—Human Gene Transfer Protocols);

Section IV-C-3-c. Administering the semiannual data reporting requirements (and subsequent review) for human gene transfer experiments, including experiments that are reviewed solely by the FDA (see Appendix M-VI, Categories of Human Gene Transfer Experiments that May Be Exempt from RAC Review);

Section IV-C-3-d. Maintaining an inventory of NIH- and FDA-approved human gene transfer experiments (including subsequent modifications);

Section IV-C-3-e. Reviewing and approving experiments in conjunction with *ad hoc* experts involving the cloning of genes encoding for toxin molecules that are lethal for vertebrates at an LD<sub>50</sub> of less than or equal to 100 nanograms per kilogram body weight in organisms other than *Escherichia coli* K-12 (see Section III-B-1 and Appendices F-I and F-II);

Section IV-C-3-f. Serving as the executive secretary of the RAC;

Section IV-C-3-g. Publishing in the **Federal Register**:

Section IV-C-3-g-(1). Announcements of RAC meetings and agendas at least 15 days in advance (Note—If the agenda for a RAC meeting is modified, ORDA shall make the revised agenda available to anyone upon request in advance of the meeting);

Section IV-C-3-g-(2). Proposed Major Actions (see Section IV-C-1-b-(1)) at least 15 days prior to the RAC meeting; and

Section IV-C-3-h. Reviewing and approving the membership of an institution's Institutional Biosafety Committee, and where it finds the Institutional Biosafety Committee meets the requirements set forth in Section IV-B-2 will give its approval to the Institutional Biosafety Committee membership,

In Section V, Footnotes and References of Sections I through IV, the following sections are proposed to be deleted:

Section V-U. Human studies in which the induction or enhancement of an immune response to a vector-encoded 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 expected, are not covered under Sections III-A-2, III-B-2, or III-B-3. Such studies may be initiated without RAC review and NIH approval if approved by another Federal agency.

Section V-V. For recombinant DNA experiments in which the intent is to modify stably the genome of cells of one or more human subjects (see Sections III-A-2, III-B-2, and III-B-3).

Section V-W would be renumbered to Section V-U:

Section V-U. In accordance with accepted scientific and regulatory practices of the discipline of plant pathology, an exotic plant pathogen (e.g., virus, bacteria, or fungus) is one that is unknown to occur within the U.S. (see Section V-R). Determination of whether a pathogen has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of plant diseases, crops, and ecosystems in the geographic area of the research.

In Appendix C, Exemptions under Section III-E-6, the following sections are proposed to read:

Appendix C-I-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-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)). \* \* \*

In Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates, the following sections are proposed to be amended due to reference changes:

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 LD<sub>50</sub> 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)).

In Appendix G, Physical Containment, the following section is proposed to be amended due to a reference change:

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)).

In Appendix I, Biological Containment, the following section is proposed to be amended due to a reference change:

#### 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)).\* \* \*

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), is proposed 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 FDA and the NIH. 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 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. 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.

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 long-term 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 (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) non-technical 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 your 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 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:

Appendix M-II-B-1-a. What is the structure of the cloned DNA that will be used?

Appendix M-II-B-1-a-(1). Describe the gene (genomic or cDNA), the bacterial plasmid or phage vector, and the delivery vector (if any). Provide complete nucleotide sequence analysis or a detailed restriction enzyme map of the total construct.

Appendix M-II-B-1-a-(2). What regulatory elements does the construct contain (e.g., promoters, enhancers, polyadenylation sites, replication origins, etc.)? From what source are these elements derived? Summarize what is currently known about the regulatory character of each element.

Appendix M-II-B-1-a-(3). Describe the steps used to derive the DNA construct.

Appendix M-II-B-1-b. What is the structure of the material that will be administered to the patient?

Appendix M-II-B-1-b-(1). Describe the preparation, structure, and composition of the materials that will be given to the patient or used to treat the patient's cells: (i) If DNA, what is the purity (both in terms of being a single DNA species and in terms of other contaminants)? What tests have been used and what is the sensitivity of the tests? (ii) If a virus, how is it prepared from the DNA construct? In what cell is the virus grown (any special features)? What medium and serum are used? How is the virus purified? What is its structure and purity? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials (for example, VL30 RNA, other nucleic acids, or proteins) or contaminating viruses (both replication-competent or replication-defective) or other organisms in the cells or serum used for preparation of the virus stock including any contaminants that may have biological effects? (iii) If co-cultivation is employed, what kinds of cells are being used for co-cultivation? What steps are being taken (and assays used with their sensitivity) to detect and eliminate any contaminating materials? Specifically, what tests are being conducted to assess the material to be returned to the patient for the presence of live or killed donor cells or other non-vector materials (for example, VL30 sequences) originating from those cells? (iv) If methods other than those covered by Appendices M-II-B-1 through M-II-B-3 are used to introduce new genetic information into target cells, what steps are being taken to detect and eliminate any contaminating materials? What are possible sources of contamination? What is the sensitivity of tests used to monitor contamination?

Appendix M-II-B-1-b-(2). Describe any other material to be used in

preparation of the material to be administered to the patient. For example, if a viral vector is proposed, what is the nature of the helper virus or cell line? If carrier particles are to be used, what is the nature of these?

#### Appendix M-II-B-2. Preclinical Studies, Including Risk-Assessment Studies

Provide results that demonstrate the safety, efficacy, and feasibility of the proposed procedures using animal and/or cell culture model systems, and explain why the model(s) chosen is/are most appropriate.

##### Appendix M-II-B-2-a. Delivery System

Appendix M-II-B-2-a-(1). What cells are the intended target cells of recombinant DNA? What target cells are to be treated *ex vivo* and returned to the patient, how will the cells be characterized before and after treatment? What is the theoretical and practical basis for assuming that only the target cells will incorporate the DNA?

Appendix M-II-B-2-a-(2). Is the delivery system efficient? What percentage of the target cells contain the added DNA?

Appendix M-II-B-2-a-(3). How is the structure of the added DNA sequences monitored and what is the sensitivity of the analysis? Is the added DNA extrachromosomal or integrated? Is the added DNA unrearranged?

Appendix M-II-B-2-a-(4). How many copies are present per cell? How stable is the added DNA both in terms of its continued presence and its structural stability?

##### Appendix M-II-B-2-b. Gene Transfer and Expression

Appendix M-II-B-2-b-(1). What animal and cultured cell models were used in laboratory studies to assess the *in vivo* and *in vitro* efficacy of the gene transfer system? In what ways are these models similar to and different from the proposed human treatment?

Appendix M-II-B-2-b-(2). What is the minimal level of gene transfer and/or expression that is estimated to be necessary for the gene transfer protocol to be successful in humans? How was this level determined?

Appendix M-II-B-2-b-(3). Explain in detail all results from animal and cultured cell model experiments which assess the effectiveness of the delivery system in achieving the minimally required level of gene transfer and expression.

Appendix M-II-B-2-b-(4). To what extent is expression only from the desired gene (and not from the

surrounding DNA)? To what extent does the insertion modify the expression of other genes?

Appendix M-II-B-2-b-(5). In what percentage of cells does expression from the added DNA occur? Is the product biologically active? What percentage of normal activity results from the inserted gene?

Appendix M-II-B-2-b-(6). Is the gene expressed in cells other than the target cells? If so, to what extent?

##### Appendix M-II-B-2-c. Retrovirus Delivery Systems

Appendix M-II-B-2-c-(1). What cell types have been infected with the retroviral vector preparation? Which cells, if any, produce infectious particles?

Appendix M-II-B-2-c-(2). How stable are the retroviral vector and the resulting provirus against loss, rearrangement, recombination, or mutation? What information is available on how much rearrangement or recombination with endogenous or other viral sequences is likely to occur in the patient's cells? What steps have been taken in designing the vector to minimize instability or variation? What laboratory studies have been performed to check for stability, and what is the sensitivity of the analyses?

Appendix M-II-B-2-c-(3). What laboratory evidence is available concerning potential harmful effects of the transfer (e.g., development of neoplasia, harmful mutations, regeneration of infectious particles, or immune responses)? What steps will be taken in designing the vector to minimize pathogenicity? What laboratory studies have been performed to check for pathogenicity, and what is the sensitivity of the analyses?

Appendix M-II-B-2-c-(4). Is there evidence from animal studies that vector DNA has entered untreated cells, particularly germ-line cells? What is the sensitivity of these analyses?

Appendix M-II-B-2-c-(5). Has a protocol similar to the one proposed for a clinical trial been conducted in non-human primates and/or other animals? What were the results? Specifically, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals?

##### Appendix M-II-B-2-d. Non-Retrovirus Delivery/Expression Systems

If a non-retroviral delivery system is used, what animal studies have been conducted to determine if there are pathological or other undesirable consequences of the protocol (including insertion of DNA into cells other than

those treated, particularly germ-line cells)? How long have the animals been studied after treatment? What safety studies have been conducted? (Include data about the level of sensitivity of such assays.)

##### Appendix M-II-B-3. Clinical Procedures, Including Patient Monitoring

Describe the treatment that will be administered to patients and the diagnostic methods that will be used to monitor the success or failure of the treatment. If previous clinical studies using similar methods have been performed by yourself or others, indicate their relevance to the proposed study. Specifically:

Appendix M-II-B-3-a. Will cells (e.g., bone marrow cells) be removed from patients and treated *ex vivo*? If so, describe the type, number, and intervals at which these cells will be removed.

Appendix M-II-B-3-b. Will patients be treated to eliminate or reduce the number of cells containing malfunctioning genes (e.g., through radiation or chemotherapy)?

Appendix M-II-B-3-c. What treated cells (or vector/DNA combination) will be given to patients? How will the treated cells be administered? What volume of cells will be used? Will there be single or multiple treatments? If so, over what period of time?

Appendix M-II-B-3-d. How will it be determined that new gene sequences have been inserted into the patient's cells and if these sequences are being expressed? Are these cells limited to the intended target cell populations? How sensitive are these analyses?

Appendix M-II-B-3-e. What studies will be conducted to assess the presence and effects of the contaminants?

Appendix M-II-B-3-f. What are the clinical endpoints of the study? Are there objectives and quantitative measurements to assess the natural history of the disease? Will such measurements be used in patient follow-up? How will patients be monitored to assess specific effects of the treatment on the disease? What is the sensitivity of the analyses? How frequently will follow-up studies be conducted? How long will patient follow-up continue?

Appendix M-II-B-3-g. What are the major beneficial and adverse effects of treatment that you anticipate? What measures will be taken in an attempt to control or reverse these adverse effects if they occur? Compare the probability and magnitude of deleterious consequences from the disease if recombinant DNA transfer is not used.

Appendix M-II-B-3-h. If a treated patient dies, what special post-mortem studies will be performed?

#### Appendix M-II-B-4. Public Health Considerations

Describe any potential benefits and hazards of the proposed therapy to persons other than the patients being treated. Specifically:

Appendix M-II-B-4-a. On what basis are potential public health benefits or hazards postulated?

Appendix M-II-B-4-b. Is there a significant possibility that the added DNA will spread from the patient to other persons or to the environment?

Appendix M-II-B-4-c. What precautions will be taken against such spread (e.g., patients sharing a room, health-care workers, or family members)?

Appendix M-II-B-4-d. What measures will be undertaken to mitigate the risks, if any, to public health?

Appendix M-II-B-4-e. In light of possible risks to offspring, including vertical transmission, will birth control measures be recommended to patients? Are such concerns applicable to health care personnel?

#### Appendix M-II-B-5. Qualifications of Investigators and Adequacy of Laboratory and Clinical Facilities

Indicate the relevant training and experience of the personnel who will be involved in the preclinical studies and clinical administration of recombinant DNA. Describe the laboratory and clinical facilities where the proposed study will be performed. Specifically:

Appendix M-II-B-5-a. What professional personnel (medical and nonmedical) will be involved in the proposed study and what is their relevant expertise? Provide a two-page curriculum vitae for each key professional person in biographical sketch format (see Appendix M-I, Submission Requirements).

Appendix M-II-B-5-b. At what hospital or clinic will the treatment be given? Which facilities of the hospital or clinic will be especially important for the proposed study? Will patients occupy regular hospital beds or clinical research center beds? Where will patients reside during the follow-up period? What special arrangements will be made for the comfort and consideration of the patients. Will the research institution designate an ombudsman, patient care representative, or other individual to help protect the rights and welfare of the patient?

#### Appendix M-II-C. Selection of the Patients

Estimate the number of patients to be involved in the proposed study. Describe recruitment procedures and patient eligibility requirements, paying particular attention to whether these procedures and requirements are fair and equitable. Specifically:

Appendix M-II-C-1. How many patients do you plan to involve in the proposed study?

Appendix M-II-C-2. How many eligible patients do you anticipate being able to identify each year?

Appendix M-II-C-3. What recruitment procedures do you plan to use?

Appendix M-II-C-4. What selection criteria do you plan to employ? What are the exclusion and inclusion criteria for the study?

Appendix M-II-C-5. How will patients be selected if it is not possible to include all who desire to participate?

#### Appendix M-III. Informed Consent

In accordance with the Protection of Human Subjects (45 CFR Part 46), investigators should indicate how subjects will be informed about the proposed study and the manner in which their consent will be solicited. They should indicate how the Informed Consent document makes clear the special requirements of gene transfer research. If a proposal involves children, special attention should be paid to the Protection of Human Subjects (45 CFR Part 46), Subpart D, Additional Protections for Children Involved as Subjects in Research.

#### Appendix M-III-A. Communication About the Study to Potential Participants

Appendix M-III-A-1. Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?

Appendix M-III-A-2. How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in language that is understandable to them?

Appendix M-III-A-3. What is the length of time that potential participants will have to make a decision about their participation in the study?

Appendix M-III-A-4. If the study involves pediatric or mentally handicapped subjects, how will the assent of each person be obtained?

#### Appendix M-III-B. Informed Consent Document

Investigators submitting human gene transfer proposals must include the Informed Consent document as approved by the local Institutional Review Board. A separate Informed Consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a 'marker' or to enhance the power of immunotherapy for cancer.

Because of the relative novelty of the procedures that are used, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the Informed Consent document should include the following specific information in addition to any requirements of the DHHS regulations for the Protection of Human Subjects (45 CFR 46). Indicate if each of the specified items appears in the Informed Consent document or, if not included in the Informed Consent document, how those items will be presented to potential subjects. Include an explanation if any of the following items are omitted from the consent process or the Informed Consent document.

#### Appendix M-III-B-1. General Requirements of Human Subjects Research

##### Appendix M-III-B-1-a. Description/Purpose of the Study

The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component.

Appendix M-III-B-1-b. Alternatives  
The Informed Consent document should indicate the availability of therapies and the possibility of other investigational interventions and approaches.

##### Appendix M-III-B-1-c. Voluntary Participation

The subjects should be informed that participation in the study is voluntary and that failure to participate in the study or withdrawal of consent will not result in any penalty or loss of benefits to which the subjects are otherwise entitled.

Appendix M-III-B-1-d. Benefits  
The subjects should be provided with an accurate description of the possible benefits, if any, of participating in the proposed study. For studies that are not reasonably expected to provide a therapeutic benefit to subjects, the

Informed Consent document should clearly state that no direct clinical benefit to subjects is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others.

#### Appendix M-III-B-1-e. Possible Risks, Discomforts, and Side Effects

There should be clear itemization in the Informed Consent document of types of adverse experiences, their relative severity, and their expected frequencies. For consistency, the following definitions are suggested: side effects that are listed as mild should be ones which do not require a therapeutic intervention; moderate side effects require an intervention; and severe side effects are potentially fatal or life-threatening, disabling, or require prolonged hospitalization.

If verbal descriptors (e.g., "rare," "uncommon," or "frequent") are used to express quantitative information regarding risk, these terms should be explained.

The Informed Consent document should provide information regarding the approximate number of people who have previously received the genetic material under study. It is necessary to warn potential subjects that, for genetic materials previously used in relatively few or no humans, unforeseen risks are possible, including ones that could be severe.

The Informed Consent document should indicate any possible adverse medical consequences that may occur if the subjects withdraw from the study once the study has started.

#### Appendix M-III-B-1-f. Costs

The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the long-term follow-up to the protocol that are not covered by the investigators or the institution involved.

Subjects should be provided an explanation about the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury.

#### Appendix M-III-B-2. Specific Requirements of Gene Transfer Research

##### Appendix M-III-B-2-a. Reproductive Considerations

To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, subjects should be given information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified.

The inclusion of pregnant or lactating women should be addressed.

#### Appendix M-III-B-2-b. Long-Term Follow-Up

To permit evaluation of long-term safety and efficacy of gene transfer, the prospective subjects should be informed that they are expected to cooperate in long-term follow-up that extends beyond the active phase of the study. The Informed Consent document should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The investigator should request that subjects continue to provide a current address and telephone number.

The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed.

#### Appendix M-III-B-2-c. Request for Autopsy

To obtain vital information about the safety and efficacy of gene transfer, subjects should be informed that at the time of death, no matter what the cause, permission for an autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance.

#### Appendix M-III-B-2-d. Interest of the Media and Others in the Research

To alert subjects that others may have an interest in the innovative character of the protocol and in the status of the treated subjects, the subjects should be informed of the following: (i) that the institution and investigators will make efforts to provide protection from the media in an effort to protect the participants' privacy, and (ii) that representatives of applicable Federal agencies (e.g., the National Institutes of Health and the Food and Drug Administration), representatives of collaborating institutions, vector suppliers, etc., will have access to the subjects' medical records.

#### Appendix M-IV. Privacy and Confidentiality

Indicate what measures will be taken to protect the privacy of patients and their families as well as to maintain the confidentiality of research data.

Appendix M-IV-A. What provisions will be made to honor the wishes of individual patients (and the parents or

guardians of pediatric or mentally handicapped patients) as to whether, when, or how the identity of patients is publicly disclosed.

Appendix M-IV-B. What provisions will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual patients?

#### Appendix M-V. Special Issues

Although the following issues are beyond the normal purview of local Institutional Review Boards, investigators should respond to the following questions:

Appendix M-V-A. What steps will be taken, consistent with Appendix M-IV, Privacy and Confidentiality, to ensure that accurate and appropriate information is made available to the public with respect to such public concerns as may arise from the proposed study?

Appendix M-V-B. Do you or your funding sources intend to protect under patent or trade secret laws either the products or the procedures developed in the proposed study? If so, what steps will be taken to permit as full communication as possible among investigators and clinicians concerning research methods and results?

#### Appendix M-VI. RAC Review—Human Gene Transfer Protocols

##### Appendix M-VI-A. Categories of Human Gene Transfer Experiments That Require RAC Review

Factors that may contribute to the necessity for RAC review include, but are not limited to: (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. 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 RAC review is deemed necessary by the NIH and FDA, the proposal will be forwarded to the RAC primary reviewers for evaluation. In order to maintain public access to information regarding human gene transfer protocols, NIH/ORDA will maintain the documentation described in Appendices M-I through M-V (including protocols that are not reviewed by the RAC).

##### Appendix M-VI-B. RAC Primary Reviewers' Written Comments

In the event that NIH/ORDA and/or the FDA recommend RAC review of the submitted proposal, the documentation described in Appendices M-I through

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 vector-encoded 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

expected, may be initiated without RAC review if approved by another Federal agency.

#### **X. Discussion on Adenoviral Vector Toxicology**

On January 19, 1995, Dr. Philip Noguchi, Food and Drug Administration, Rockville, Maryland, requested the Recombinant DNA Advisory Committee discuss adenoviral vector toxicology. In his letter, he states: "The RAC has correctly identified an emerging issue in terms of preclinical toxicities of adenoviral vectors given parenterally. From the FDA's point of view, the area of biotoxicology is an evolving one that has been one of FDA's main tools for determining dosing in gene therapy clinical trials. For gene therapies, most preclinical toxicology studies to date with retroviral and adenoviral vectors have not revealed toxicities of the magnitude seen recently. While the newest results are indeed significant, from the FDA's point of view, animal toxicity is the primary means of estimating safe starting doses in human trials. Thus, lack of overt or major preclinical toxicity is not comforting, but instead raises the specter of unanticipated adverse events in humans. The unexpected adverse event in a cystic fibrosis patient given an adenoviral vector is a case in point. The FDA would like to have one of its toxicologists present a fifteen minute overview of our current philosophy and testing requirements. This would be followed by a short presentation by a patient who will give a perspective on safety concerns in the real world of cancer therapy."

#### **XI. Discussion on Adenoviral Vector Toxicology**

On January 19, 1995, Dr. Philip Noguchi, Food and Drug Administration, Rockville, Maryland, requested the Recombinant DNA Advisory Committee to discuss transgenic xenotransplantation. In his letter, he states:

"Millions of Americans suffer tissue loss or end-stage organ failure, leading to over eight million surgical procedures annually. Current therapies include organ transplantation, surgical reconstruction using human tissues, and use of mechanical devices such as kidney dialysis machines. These treatments have significantly reduced the morbidity and mortality associated with tissue loss and end-stage organ failure. Transplantation as curative or

live-saving therapy, however, is greatly hampered by a critical donor shortage. For example, over 40,000 patients die from liver failure annually yet only 4,000 donors are available annually to address this need for lifesaving organs. The number of patients who die while on waiting lists for organ transplantation is increasing while the availability of donor organs is decreasing. Novel combination products used as bridging mechanisms may extend patients' lives and increase the number of patients on organ transplant waiting lists. The unmet demand for clinically needed human tissues coupled with the scientific and biotechnological progress during the past decade have also provided the impetus for new therapies involving xenogeneic cells, tissues, and organs.

"The FDA has become aware through the press and personal contacts that some Institutional Review Boards are reviewing proposals for xenotransplantation. Although it appears that most of the current proposed protocols seek to use nonhuman primate donors with conventional patient immunosuppression, a growing number of academic and commercial groups are exploring the use of transgenic animals in which human genes are introduced into the animal in an attempt to lower or mask immunogenicity. This latter category is a form of human gene transfer, since the transplanted transgenic organs contain human genes and/or human gene products. The RAC review process has served society well in the measured public introduction of gene therapies into clinical experimentation. We suggest that this exciting new area, in which genetic engineering is further extended to the manipulation and construction of new therapeutic entities, would likewise benefit from regular scientific, legal and ethical review in a public forum.

"Some issues for public discussion might include: (1) Preclinical: What kind of animal model testing would be needed before initiation of transgenic xenotransplantation? What would be the most appropriate animal model? What degree of scientific rationale is necessary? (2) Recipient issues: Should categories of patients be defined for first experimentation? Those who are acutely dying with no immediate human organ available? Those whose priority is so low that the patient would die before receiving an organ? What kinds of patient screening and follow-up would

be needed? (3) Hazards: What type of donor screening should be conducted? What new hazards might be created with transgenic transplantation, i.e., activation of a latent human virus in the animal organ? How could these concerns be addressed, i.e. specific scientific studies? (4) Informed consent and study results: What new elements of informed consent would be required? How can the field be monitored for success and failure? Should the local IRBs take the lead in primary monitoring of patient safety? Would the data monitoring efforts used for gene therapies be useful in this new field?

"Obviously, we do not expect that definitive answers to these questions and issues would be forthcoming at the meeting, but we would like to broach the subject so that future discussions can be planned. We suggest that the RAC might wish to augment its current panel with one or more ad hoc consultants with specific expertise in transplantation."

OMB's "Mandatory Information Requirements for Federal Assistance Program Announcements" (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

**Suzanne Medgyesi-Mitschang,**

*Acting Deputy Director for Science Policy and Technology Transfer.*

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