Stanford University

2007

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Appendixes

FOREWORD

MESSAGE FROM THE VICE PROVOST AND DEAN OF RESEARCH
OF STANFORD UNIVERSITY

To: The Stanford Academic Community

This Biosafety Manual represents the institutional practices and procedures for the safe use and handling of biological materials and recombinant DNA at Stanford University. The Administrative Panel on Biosafety and the Biosafety Manager have revised this document based on the latest government regulatory requirements, guidelines and current professional standards. It is designed to inform the laboratory worker of good work practices and safe procedures which are found in most biosafety manuals; however, this manual also emphasizes the regulatory requirements that must be followed and the need for all related research to be conducted in a responsible manner.

The Environmental Health and Safety Office, through the Biosafety Manager, is responsible for monitoring individual principal investigators and laboratory facilities for adherence to the practices and procedures described in this manual. However, it is the responsibility of each principal investigator to ensure that all lab workers are familiar with the contents of this manual and that these workers and employees are trained to recognize potential related hazards prior to initiation of the research work. Your cooperation with the Administrative Panel on Biosafety and the Environmental Health and Safety Office is essential to comply with the regulatory requirements that our University must follow in order to continue the success of our research endeavors.

If you have any questions regarding this document, please call the Research Compliance Administrator at 723-4697 or the Biosafety Manager at 725-1473.

Sincerely,

Ann Arvin
Vice Provost and Dean of Research

1 INTRODUCTION

This revision of the Biosafety Manual was prepared under the auspices of the Administrative Panel on Biosafety (APB) by the Office of Environmental Health and Safety (EH&S) after careful review of pertinent federal and state government regulatory documents, along with reference guidelines from the Centers for Disease Control and the National Institutes of Health.

This manual will:

- Address the most commonly asked questions from faculty, staff and students on general Biosafety and rDNA issues;
- Provide information about safe work practices, safety equipment and personal protective equipment; and,
- Provide guidance for investigators who need to submit an application for review by the Administrative Panel on Biosafety.

Due to the ever-changing regulatory environment that we all live and work in, updates to this manual will be made as needed; these changes will be made on the EH&S Biosafety web site (http://www.stanford.edu/dept/EHS/prod/researchlab/bio/) as needed.

Please feel free to comment on this manual. If you have questions regarding this manual, please call the Biological Safety Manager at Environmental Health and Safety Department, 725-1473.

Sincerely,

Ann Arvin, M.D.
Vice Provost and Dean of Research

David Relman, M.D.
Chair, Administrative Panel on Biosafety

Lawrence Gibbs, C.I.H.
Associate Vice-Provost, Environmental Health and Safety

Ellyn Segal, Ph.D.
Biosafety Manager, Environmental Health and Safety

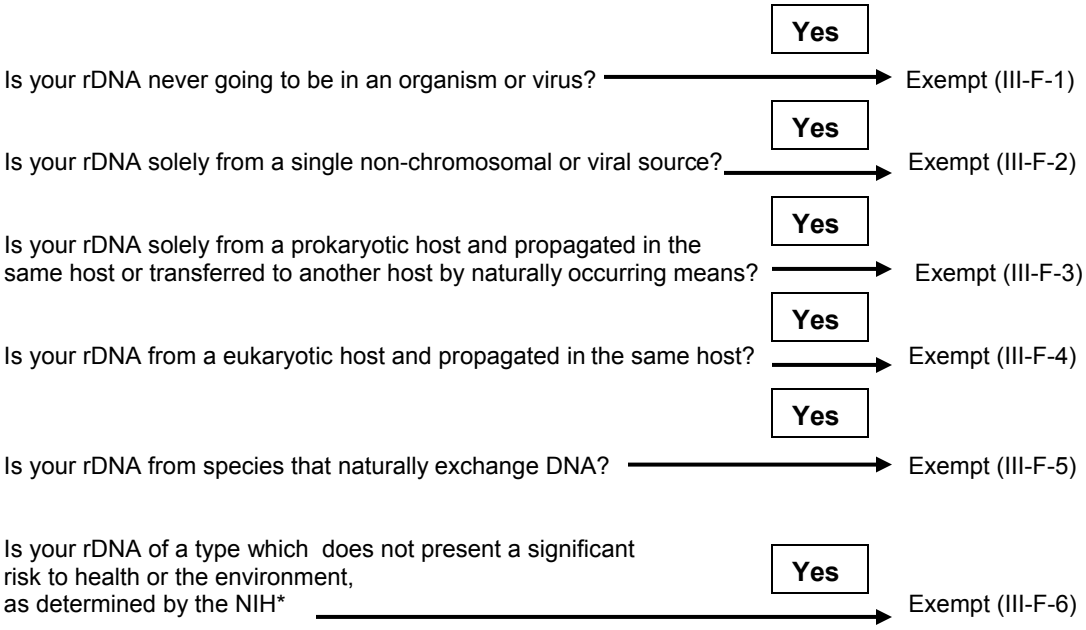
2 Recombinant DNA: Regulations and Guidelines

We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest….. It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Watson and Crick (1953), Nature 171, pg 737

The use of recombinant DNA (rDNA) is regulated by the National Institutes of Health (NIH); the guidelines can be found in the publication *Guidelines for Research Involving Recombinant DNA Molecules* (http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html). A copy of the current guidelines is in Appendix A. These guidelines are the official guide to all rDNA work done at Stanford. It is important to realize that following these guidelines is the responsibility of **all** investigators at Stanford University and not solely investigators that are funded by NIH.

The guidelines specify a number of different categories of rDNA molecules. One of the most important categories is the Exempt category. Experiments that qualify for this category do not need approval by the Stanford University Institutional Biosafety Committee (the Administrative Panel on Biosafety (APB), see Chapter 4). To determine if your experiments are exempt, you can check Category F in the NIH Guidelines; a short reference guide is presented here.



*The NIH has determined that rDNA from infectious agents of BL-2 or above is not exempt and must receive Biosafety approval. Additionally, certain **cloning vectors**, such as Adeno or Sindbis based vectors, or amphotrophic MMLV based vectors, are some examples of rDNA that are non-exempt.

If your experiment does not fall within the exempt categories, you **MUST** obtain APB approval.

Viral Vectors and Transgenes

All vectors are not the same. More importantly, the class of gene insert can change the Biosafety level of the construct. It is also important to realize that obtaining a cloning/ expression vector from a commercial source does not mean it is automatically exempt or a BSL-1. Table 1 lists many of the more common viral vectors in combination with different classes of inserts and their associated BSL level.

Table 1.

Gene transfer vector[a]	Host range[b]	Insert or gene function[c]	Laboratory containment level[d]
MMLV based- *gag, pol, env* deleted	Ecotropic	S, E, M, G, CC, T, MP, DR, R, TX O_v, O_c	BSL-1*
	Amphotropic, VSV-G pseudotyped	S, E, M, T, MP, DR	BSL-2
		O_v, O_c, R, G, CC	BSL-2+/BSL-3
		TX	BSL-3
Herpes virus based- nonlytic	Broad host range	S, E, M, MP, DR, T	BSL-2
		O_v, O_c, R, G, CC	BSL-2+
		TX	BSL-3
Lentivirus based- HIV, SIV, EIAV, FIV, etc.; *gag, pol, env, nef, vpr* deleted	Ecotropic, amphotropic, VSV-G pseudotyped	S, E, M, MP, DR,	BSL-2+/BSL-3, until
		O_v, O_c, R, G, CC, T	safety issues then BLS-2/ BSL-2+ may be appropriate
		TX	BSL-3
Adenovirus based- Serotype 2, 5, 7; E1 and E3 or E4 deleted	Broad host range, infective for many cell types	S, E, M, T, MP, DR	BSL-2
		O_v, O_c, R, G, CC	BSL-2+
		TX	BSL-3
Alphavirus based- SFV, SIN	Broad host range	S, E, M, T, MP, DR	BSL-2
		O_v, O_c, R, G, CC	BSL-2+
		TX	BSL-3
Baculovirus based	Broad mammalian host cell range	S, E, M, T, MP, DR	BSL-1*
		O_v, O_c, R, G, CC	BSL-2
		TX	BSL-2+/BSL-3
Parvovirus, AAV based- (rep^-, cap^-)	Broad host range, infective for many cell types including neurons	S, E, M, T, MP, DR	BSL-1*
		O_v, O_c, R, G, CC	BSL-2
		TX	BSL-2+/BSL-3
Poxvirus based- caarypox, vaccinia	Broad host range	S, E, M, T, DR, MP	BSL-2
		O_v, O_c, R, G, CC, TX	BSL-2+/BSL-3

[a]Refers to the parental or wild-type virus.

[b]Refers to the ability of vector to infect cells from a range of species. Ecotropic generlly means able to infect only cells of species originally isolated from or identified in. Please note that the ecotropic host for HIV and HSV would be human cells, but the ecotropic host for MMLV would be murine cells. Amphotropic and VSV-G pseudotyped virus host range includes human cells.

[c]General categories of cellular genes and functions: S, structural proteins: actin, myosin, etc.; E, enzymatic proteins: serum proteases, transferases, oxidases, phosphatases, etc.; M, metabolic enzymes: amino acid metabolism, nucleotide synthesis, etc.; G, cell growth, housekeeping; CC, cell cycle, cell division; DR, DNA replication, chromosome segregation, mitosis, meiosis; MP, membrane proteins, ion channels, G-coupled protein receptors, transporters, etc.; T, tracking genes such as GFP, luciferases, photoreactive genes; TX, active subunit genes for toxins such as ricin, botulinum toxin, Shiga, and Shiga-like toxins; R, regulatory genes, transcription, cell activators such as cytokines, lymphokines, tumor suppressors; O_v and O_c, oncogenes identified via transforming potential of viral and cellular analogs, or mutations in tumor suppressor genes, resulting in a protein that inhibits/moderates the normal cellular wild-type protein. This does not include SV40 T antigen. SV40 T antigen-containing cells should not be considered more hazardous than the intact virus. The prevalence of SV40 infection in the U.S. population due to contaminated polio vaccine does not seem to have caused an increased rate of cancers (Strickler et al., 1998). However, a cautionary note might be in order. More recent assessment of epidemiologic data suggests a possible causative role for SV40 in some human cancers (Butel and Lednicky, 1999).

[d]This is a general assessment of appropriate containment for construction and laboratory use of these vectors for nonproduction quantities only based on the 1999 CDC/NIH BMBL. It cannot cover every potential use within a research or laboratory setting; as information is gained an assessment may be changed. Local IBCs should use their best judgment with the available information to determine appropriate containment levels. BSL-1* refers to the containment level based on parent virus risk group. However, most procedures involving the handling and manipulation of the viral vectors are done at BSL-2 to protect cell cultures and viral stocks from contamination.

From Biological Safety Principles and Practices, 3rd ed., pg. 594, D.O. Fleming and D.L. Hunt, ed, ASM Press, 2000.

Human Gene Transfer

Protocols involving the use of rDNA for gene transfer into humans, whether done directly in the subject or in vitro and subsequently put into the subject, must be submitted to both the APB and Stanfords Institutional Review Board (IRB) for Medical Human Subjects. Current Federal Regulations call for submission of the protocol to the Recombinant Advisory Committee (RAC) and Food and Drug Administration (FDA) prior to submission to the local institutions panels. For additional information concerning Stanford University's IRB panels, please contact Alice Haskett at X3.5244 or access the panel's web site at http://researchcompliance.stanford.edu/

Transgenic Plants

Experiments to genetically engineer plants by recombinant DNA methods may require registration with the APB (see NIH rDNA guidelines). To prevent release of transgenic plant materials to the environment, the guidelines provide specific plant biosafety containment recommendations for experiments involving the creation and/or use of genetically engineered plants.

3 Infectious Agents: Regulations and Guidelines

The Sciences gain by mutual support. When, as the result of my first communications on the fermentations in 1857-1858, it appeared that the ferments, properly so-called, are living beings, that the germs of microscopic organisms abound in the surface of all objects, in the air and in water; that the theory of spontaneous generation is chimerical; that wines, beer, vinegar, the blood, urine and all the fluids of the body undergo none of their usual changes in pure air, both Medicine and Surgery received fresh stimulation.

Louis Pasteur**,** Germ Theory And Its Applications To Medicine And Surgery, 1878

Laboratories that work with infectious agents pose risks to people within and near them. Infections have been contracted in connection with laboratory work throughout the history of microbiology (a dubious distinction). Studies have illustrated that laboratory-acquired infections are not confined to any one kind of lab or group of people, and that the incidence of infection among untrained and ancillary workers is high averaging approximately one-third of all acquired infections.

Stanford University follows the categorizing of infectious agents into levels as described in *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), 4th ed., written and published by the Centers for Disease Control (CDC) and NIH. The BMBL describes combinations of microbiological practices, laboratory facilities, and safety equipment in combination with four biosafety levels for various agents infectious to humans. The descriptions of Biosafety Levels (BSL) 1 – 4 parallel those in the NIH Guidelines for Research Involving Recombinant DNA. Biosafety levels are also described for infectious disease activities that involve laboratory animals. It is important to note that the guidelines presented in the BMBL are considered minimal for containment, and will be customized as needed.

The BSL categories are divided up by risk of disease combined with availability of preventive and therapeutic treatments. The four groups are shown in Table 1. For the list of agents and their categories, see Appendix B or go to http://www.absa.org/riskgroups/index.htm

Table1. Basis for the Classification of Biohazardous Agents by Biosafety Level

BSL 1	Agents that are not associated with disease in healthy adult humans
BSL 2	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available
BSL 3	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk but low community risk)
BSL 4	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available (high individual risk and high community risk)

Biological Agents and Toxins Database

This is the Stanford University database of **all** biological agents and toxins that are used or stored here; this includes NIH/CDC exempt and non-exempt material and certain toxins. The Bio Database is an on-line comprehensive inventory for all biological agents present at Stanford University. Each Principal Investigator should enter their information in the database and will be able to access their information in the database for all future updates.

Select Agents are also included within the database; while this subset of agents is associated with specific federal requirements, it is included within the database to facilitate data collection and reporting for Stanford research investigators. The information provided by Stanford faculty investigators will be protected except for legally mandated federal disclosures, will be used only by appropriate Stanford University personnel, and will not be available to the public.

To access the Bio Database, go to
http://www.stanford.edu/dept/EHS/prod/researchlab/bio/practical.html

Laboratory Requirements

Each BSL has its own corresponding requirements for the laboratory facilities; these are presented in Table 2.

Table 2. Summary of Laboratory Facilities for BSL 1 - 4

BSL	Agents	Practices	Safety Equipment (Primary Barriers)	Facilities (Secondary Barriers)
1	Not known to consistently cause disease in healthy adults	Standard Microbiological Practices	As needed to allow for good microbiological practices	Open bench top sink required
2	Associated with human disease, hazard =	BSL-1 practice plus:	Primary barriers = Class I or II BSCs or other physical	BSL-1 plus:

	percutaneous injury, ingestion, mucous membrane exposure	Limited access Biohazard warning signs "Sharps" precautions Biosafety manual defining any needed waste decontamination or medical surveillance policies	containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials; PPEs: laboratory coats; gloves; face protection as needed	Autoclave available
3	Indigenous or exotic agents with potential for aerosol transmission; disease may have serious or lethal consequences	BSL-2 practice plus: Controlled access Decontamination of all waste Decontamination of lab clothing before laundering Baseline serum	Primary barriers = Class I or II BCSs or other physical containment devices used for all open manipulations of agents; PPEs: protective lab clothing; gloves; respiratory protection as needed	BSL-2 plus: Physical separation from access corridors Self-closing, double-door access Exhausted air not recirculated Negative airflow into laboratory
4	Dangerous/exotic agents which pose high risk of life-threatening disease, aerosol-transmitted lab infections; or related agents with unknown risk of transmission	BSL-3 practices plus: Clothing change before entering Shower on exit All material decontaminated on exit from facility	Primary barriers = All procedures conducted in Class III BSCs or Class I or II BSCs in combination with full-body, air-supplied, positive pressure personnel suit	BSL-3 plus: Separate building or isolated zone Dedicated supply and exhaust, vacuum, and decon systems Other requirements outlined in the text

The physical requirements described above will be used in conjunction with additional protective mechanisms (see Chapter 7) to achieve personnel and environmental safety.

Tissue Culture, Human and Primate Tissue

The potential laboratory hazards associated with human cells and tissues include the bloodborne pathogens HBV, HCV, and HIV, as well as agents such as *Mycobacterium tuberculosis* that may be present in human lung tissues. Other primate cells and tissues also present risks to laboratory workers as do cells transformed with viral agents such as SV-40, EBV, or HBV, cells carrying viral genomic material and tumorigenic human cells. All are potential hazards due to the possibility of

self-inoculation.

Cultured cells which are known to contain or be contaminated with a biohazardous agent (e.g. bacteria or viral) are classified in the same BSL as the agent. Cell lines which do not contain known human or animal pathogens are designated BL-1. The following list contains cells that are to be handled using BSL-2 practices and containment.

1. Cells from blood, lymphoid cells, and neural tissue
2. All primary cell lines (human or primate)
3. Secondary (immortalized) cell lines originating from lymphoid cells or neural tissue
4. Cell lines exposed to or transformed by a human or primate oncogenic virus
5. Pathogen deliberately introduced or known endogenous contaminant
6. Fresh or frozen tissue explants

Additionally, all human blood, blood products, unfixed human tissue and certain body fluids should be handled with Universal Precautions and as BSL-2. All work should be performed in a biosafety cabinet, and all material should be treated as medical waste.

Take note that this list is not conclusive and individual cases will be determined as they occur.

4 Administrative Panel on Biosafety (APB)

Good sense is the most evenly distributed thing in the world, for all people suppose themselves so well provided with it that even those who are the most difficult to satisfy in every other respect never seem to desire more than they have. It is not likely that everyone is mistaken; rather this attitude reveals that the ability to judge and distinguish the true from the false, which is properly what one calls good sense or reason, is in fact naturally equally distributed among all people. Thus the diversity of our opinions does not result from some of us being more reasonable than others, but solely from the fact that we conduct our thoughts along different paths, and consider different things. . . .

René Descartes: *Discourse on Method* (1637)

The NIH as mandated the presence of an Institutional Biosafety Committee for all organizations that come under NIH regulations. At Stanford University, this committee is called the **Administrative Panel on Biosafety (APB);** the charge of the panel is as follows:

> The Administrative Panel on Biosafety reviews all University research and teaching activities involving the use of biohazardous agents and recombinant DNA molecules that require approval ("biosafety activities"), as defined below. Through these reviews, the Panel ensures that the activities described in the previous sentence and the related facilities are in compliance with applicable University policies and external regulations.
>
> The Panel advises the University and recommends policies to guide investigators and the Department of Environmental Health & Safety (EH&S) in carrying out the University's Biosafety Program in the acquisition, use, training, transfer, storage, disposal, and emergency response procedures for all biosafety activities. The Panel's objective shall be to ensure that such activities meet standards of good practices consistent with safety of personnel and the general public in ways that best facilitate relevant research or teaching activities of the University.
>
> The Panel is responsible for reviewing all University projects conducted by faculty, staff, students and/or visiting scientists which involve biosafety activities whether the activities are carried out on campus or off campus (usually under other Institutional Biosafety Committees). In addition, the Panel may be asked by the University administration to review research projects on behalf of other institutions with which Stanford has formal affiliation agreements. Under Stanford's current Cooperation Agreement with the Palo Alto Veteran's Administration Medical Center (PAVAMC), the Panel shall review all biosafety applications from Stanford researchers located at the PAVAMC and up to 5 biosafety applications per year from PAVAMC researchers not otherwise affiliated with Stanford University.
>
> All biosafety activities involving the use of Class 2 or 3 agents OR non-exempt recombinant DNA molecules as defined by the National Institutes of Health (NIH) shall be reviewed by the Panel regardless of the source of funding for the project. The Panel may approve research projects with or without modifications, or withhold approval of all or any portion of a project.
>
> The Panel shall function so as to discharge the University's obligations placed upon the Panel by current governmental requirements, including those described in the National Institutes of Health (NIH) Guidelines and Occupational Health & Safety Administration (OSHA) Regulations. To this end, the Panel shall assist Principal Investigators in meeting their responsibilities.

The Panel shall assess suspected or alleged violations of approved projects, external regulations, or University policies which involve biosafety activities. Activities in which serious or continuing violations occur may be suspended by the Panel. The Panel will immediately so notify the affected investigator(s), the relevant school dean, the Dean of Research, appropriate University officers, and others as required by University policies and external regulations.

Upon request, the Panel shall review and comment on proposed external regulations dealing with biosafety. When appropriate, the Panel will formulate draft policies and procedures for approval by the appropriate University bodies and promulgation by the Dean of Research.

Appeals
In cases of dispute with respect to procedures or decisions of the Panel, appeals may be made to the Dean of Research for mediation.

Membership
The Panel is appointed by the President and shall be made up of at least five members with expertise in general issues of laboratory biosafety, use of infectious materials, and recombinant DNA technology. Individuals on the Panel include faculty and staff, the Biosafety Officer (BSO), one student nominated by the ASSU Committee on Nominations who is either an upperclassman or preferably a graduate student with previous biosafety experience, two members from the local community not otherwise affiliated with the University, and any others invited to serve when their expertise is required.

Ex officio members (nonvoting) shall include representatives of the Dean of Research, the office of General Counsel, the Department of Environmental Health & Safety, and a veterinarian from the Department of Comparative Medicine.

The term of membership on the Panel is a 12-month renewable period beginning October 1 through September 30.

Reporting
The Panel reports to the President of the University through the Office of the Dean of Research. The Biosafety Officer is the institutional official responsible for the day-to-day operation of the biosafety program and reports to the Associate Vice-President, Environmental Health and Safety Office.

Meetings
The Panel shall meet as necessary, but no less than bi-monthly, to conduct its business. The Chair shall submit an annual report of Panel activities and deliberations to the Office of the President through the Office of the Dean of Research by October 1st of the following year.

Support
EH&S and the Office of the Dean of Research shall provide the necessary staffing and administrative assistance. EH&S shall provide technical expertise and advice as necessary for the Panel to fulfill its duties.

The APB Review Process

Applying to the APB is done by submitting an application (available on the web at: http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/APBform.pdf or in Appendix C) to the Biosafety Manager. Please note that there are separate forms for rDNA/biohazards and human gene therapy (an application for human subjects and biohazardous or rDNA use is at: http://humansubjects.stanford.edu/medical/forms.html or can be found in Appendix D). Upon receipt of the application, the Biosafety Manager will do an initial review of the proposal and

contact the PI with any questions. Additionally, an inspection of the laboratory facilities may take place. Once a month the APB meets and reviews applications submitted within the last month. At this time the proposal will either be accepted or will be sent back to the PI with comments and/or questions. Upon final approval written notification will be sent out to the PI with a copy to the Stanford Research Compliance Office.

Renewals and Amendments

Duration of approval for BSL- 2 projects corresponds is for three years. BSL-3 projects are approved for one year and must be renewed annually. Additionally human gene transfer projects can only be approved for one year. Renewal of projects can be done by submitting an APB Renewal/Update Form (at http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/new_APB_update_form.pdf or Appendix E). This form can also be used to amend existing projects; amendments are required for personnel changes, changes in the scope of the project or changes in the biohazardous agent (s).

Cross-Reference of Projects

Multiple projects that are similar to each other can be cross-referenced by using the Cross Reference Form (at http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/BioAgentsdoc.pdf) or Appendix F.

5 Training

Life happens – be prepared.
Fortune cookie, 2001

Stanford University offers numerous training courses and materials for employees of all levels and backgrounds. All employees (faculty, staff) and students that require Biosafety training can take it at http://axess.stanford.edu – Biosafety (EHS – 1500). This class will provide the **basic, tier one level** training in Biosafety.

For personnel who will be handling **bloodborne pathogens (BBP)** which includes but is not limited to Hepatitis B, Hepatitis C, and HIV, **tier two level training is mandatory** and is available at http://axess.stanford.edu . This course Bloodborne Pathogen Training EHS – 1600 is entirely web based and requires annual updates, (Biosafety – EHS1601) also available on the web. To help determine if a worker is at risk for contact with BBP, please use the questions listed below.

Will the person:

handle human blood products, such as whole blood, plasma, serum, platelets, or white cells?

handle human body fluids such as semen, cerebrospinal fluid, vaginal secretions, joint fluid, plueral fluid, peritoneal fluid, pericardial fluid, or amniotic fluid?

work with animals, such as primates that are infected with hepatitis B or other bloodborn pathogens OR perform tasks where such animals are housed?

handle unfixed human tissue or organs (including tissue cultyre)? (Tissues and organs soaked in chemical preservatives such as alcohol or formaldehyde are fixed)

work with hepatitis B virus or other bloodborn pathogens or with preparations, such as liquid solutions or powders containing the hepatitis B virus?

handle blood, blood products, body fluids or unfixed tissues or organs of animals infected with the hepatitis B virus or other bloodborn pathogens?

handle sharp instruments such as knives, needles, scalpels, or scissors which have been used by others working with human blood or other potentially infectious materials to include human organs, tissue or body fluids OR used by others working with similar body parts and fluids from animals infected with the hepatitis B virus or other bloodborn pathogens?

enter areas where other individuals work with human or animal blood, body fluid, tissues or organs which are infected with the hepatitis B virus or other bloodborn pathogens AND perform tasks where any of the forementioned body substances may come into contact with the laboratory workers unbroken skin, broken skin, or mucous membranes?

perform tasks which may potentially result in the lab workers exposed skin or mucous membranes coming in contact with human or animal blood, body fluids, organs, or tissues which are infected with the hepatitis B virus or other bloodborn pathogens?

If the answer to **ANY** of the above questions is yes, then the worker is considered to be at occupational risk of contracting Hepatitis B or other Bloodborn pathogens. All workers at risk must take the Bloodborne Pathogen Training. Registration and completion of the appropriate above mentioned courses are required within the first month of work at Stanford University. Additionally, all personnel listed on grant applications must be shown to have completed the appropriate training.

All personnel should be made aware that regardless of occupational risk or not, all employees are eligible to receive Hepatitis B vaccinations at no cost as part of the Stanford University HBV Immunization Program. A vaccination declination form must be signed whether or not the vaccine is accepted. Please see Chapter 6 for more information, or call the Stanford Biosafety Office, 725.1473; staff, faculty and students of the School of Medicine (SOM) can also contact the Director of the SOM Health and Safety Programs at 723.6336.

Tier III training is conducted by the PI or laboratory supervisor. This training will be a combination of the Stanford University Exposure Control Plan (see Chapter 6) and of individualized training suitable for each individual. In a laboratory environment the type of experiments being conducted, nature of the material used, and the equipment used would determine the required types of training. Written documentation of Tier III training must be recorded and retained by the PI.

6 Bloodborne Pathogens & Medical Surveillance

This is the story of Leeuwenhoek, the first of the microbe hunters. It is the tale of the bold and persistent and curious explorers and fighters of death who came after him……Some of them who were too bold have died – done to death by the immensely small assassins they were studying – and these have passed to an obscure small glory.

Paul De Kruif, Microbe Hunters (1926), Harcourt, Brace and Co., pub, pg. 3

In 1993 CAL/OSHA published the Bloodborne Pathogens Rule (Title 8 CCR GISO 5193); the fundamental premise of this rule is an approach to infection control termed *Universal Precautions. Universal Precautions* assumes that all human blood, blood products, and certain body fluids are contaminated with HIV, HBV, HCV, or other bloodborne pathogens and that these materials be handled accordingly.

The Bloodborne Pathogens Standard (29 CFR, Bloodborne Pathogens. - 1910.1030) applies to all occupational exposure to blood or other potentially infectious materials. **Blood** means human blood, human blood components, and products made from human blood. **Bloodborne Pathogens** means pathogenic microorganisms that are present in human blood and can cause disease in humans. These pathogens include, but are not limited to, hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Additionally, "**Other Potentially Infectious Materials"** (OPIM) are included under this standard. OPIM means (1) The following human body fluids: semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, pericardial fluid, peritoneal fluid, amniotic fluid, saliva in dental procedures, any body fluid that is visibly contaminated with blood, and all body fluids in situations where it is difficult or impossible to differentiate between body fluids; (2) Any unfixed tissue or organ (other than intact skin) from a human (living or dead); and (3) HIV-containing cell or tissue cultures, organ cultures, and HIV- or HBV-containing culture medium or other solutions; and blood, organs, or other tissues from experimental animals infected with HIV or HBV.

The following are specific actions Stanford University has taken to minimize exposures to bloodborne pathogens:

Bloodborne Pathogens Exposure Control Plan – describes how to eliminate or minimize exposure of all Stanford University personnel to human/primate blood or blood products that might contain bloodborne pathogens. All work at Stanford University that has the potential to contain bloodborne pathogens will be carried out using Universal Precautions. Universal precautions is an approach to infection control whereby all human/primate blood and other human/primate body fluids, tissues and cells are treated

as if known to be infectious for HIV, HBV, HCV, and other bloodborne pathogens (BBP's).

Each principle investigator (PI)/supervisor will complete an Exposure Plan based on the nature of the work being carried out in their facilities. The PI/supervisor will indicate procedures and materials in the laboratory that have the possibility of exposing personnel to BBP's. Once completed, the plan will remain on file in a central location within the laboratory/work place.

A copy of the Stanford University Bloodborne Pathogens Exposure Control Plan is in Appendix G. It can also be accessed on the web at:
http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/bloodborn_pat_exp_control.pdf

Hepatitis B vaccine program - the vaccine is offered free of charge to all Stanford University personnel considered 'at risk' due to occupational exposure. While Stanford University encourages employees to be vaccinated, accepting vaccination is not a condition of employment. Employees that are offered the vaccine are required to either accept the vaccine or sign a declination form. Stanford University students (including post doctoral fellows, graduate students, and medical students) are to go to Vaden for vaccination, while faculty and staff use Employee Health. For additional information of the vaccine program and a copy of the Hepatitis B Vaccination Declaration, see Appendix H or access the web at:
http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/Hepat_BVacc_Decl.pdf

Bloodborne Pathogen Training program - All Stanford University faculty, staff, and students who have potential exposure to blood or blood products will be trained annually (see Chap. 5).

Vaccinations

Vaccinations are available for many etiologic agents used in the laboratory. The Biosafety Officer in conjunction with the Administrative Panel on Biosafety (APB) will make the recommendation for the use of vaccinations on a case- by- case basis.

Medical surveillance

Medical surveillance may be required for both those workers who use biohazardous agents as well as any animal handler who must tend to animals inoculated with etiologic agents. Some animals may be infected with agents not related to the research, such as sheep whose body fluid may contain *Coxiella burnetii*, the causative agent for Q-fever. The Department of Comparative Medicine will work with the Biosafety Officer and EH&S to identify animal handlers who may be at risk for occupational exposure to infectious microorganisms in the course of their duties.

Procedures for receiving a medical examination:

A. Each University School/Department shall administer the Medical Surveillance program for its employees. The supervisor shall identify employees who may be at risk for occupational exposure to biological agents. The Biosafety Officer can assist the supervisor if a medical examination is appropriate.

B. The Department/School will schedule a medical appointment with:
Stanford University Occupational Health Clinic
Environmental Safety Facility (ESF)
480 Oak Road, Room B15
Stanford, CA 94305-8007
Phone: (650) 725-5308
www.stanford.edu/dept/EHS/prod/researchlab/IH/SUOHC/index.html

C. Upon completion of the medical examination, the participant will be notified by the examining physician to review the results. Appropriate referrals will be made at this time in the event of abnormal findings. EH&S will receive one copy of the medical clearance form from the Occupational Health Clinic. This form will describe the participant's ability to work with biological agents, work in the particular environment or other condition that initiated the examination. The Occupational Health Clinic will also send a copy of the clearance form to the requesting department.

D. If there is a restriction indicated on the clearance form that inhibits an individual's ability to complete a job, then the supervisor shall notify the Biosafety Officer to discuss a remedial course of action.

E. Medical records will be kept at the Occupational Health Clinic for the duration of the individual's participation in the Medical Surveillance Program at Stanford University. A copy of the medical surveillance clearance form will be kept by the department and at EH&S.

7 Safety

Biosafety is a two-way path involving the creation of a safe working environment for all personnel and ensuring that the work being done does not impact the environment. It is essential to understand that the most important factor in biosafety is the laboratory worker. Good work practice, facility design, training, and protective clothing all fall to the wayside in the presence of a worker who is ignorant or uncaring of proper work procedures.

There are obvious dangers to working with infectious agents. Pathogens can infect a host through a number of routes, and it is important to be aware that a laboratory-acquired infection may not follow the same route as a naturally occurring one. The following are some of the more common accidents that can result in infection, listed in decreasing order of occurrence (Collins, pg. 30):

Spills and splashes
Needle and syringe sticks
Sharp objects (including glass)
Animal bite or scratch
Mouth pipetting

Universal Precautions

The concept of Universal Precautions is to treat all human/primate blood and other body fluids, tissues and cells as if they were known to be infectious for BBP's. Along with frequent handwashing, no mouth pipetting, no food or drink in the lab and proper disposal of medical waste are the inclusions of engineering controls and Personal Protective Equipment (PPE). Engineering controls include items such as biosafety cabinets, ventilation systems, closed top centrifuge rotors, etc. – these are the primary methods to control exposure. PPE such as gloves, lab coats, face shields, must be selected and used as appropriate.

Safety Engineered and Needleless Sharps

Over the last few years manufacturers have developed “engineered sharps”; these are commonly used items (e.g. scalpels, syringes, needles) that have various mechanical devises to vastly decrease the occurrence of injuries due to sharps. CAL-OSHA requires any laboratory using human or primate blood, blood products, cell lines, tissues or other potentially infectious materials to use needleless systems/and or engineered sharps. If a PI/supervisor decides that a non-compliant sharps is necessary for a certain procedure, the reason must be documented. For additional information and resources on obtaining engineered sharps, see: http://www.stanford.edu/dept/EHS/prod/researchlab/bio/useful.html

Biosafety Cabinets

Biological safety cabinets (BSC) are designed to provide three types of protection:

Personnel protection from material inside the cabinet
Protection for the material inside of the cabinet
Protection for the environment from the material inside of the cabinet

There are three types of BSCs, Class I, II, and III. Class I are designed to provide personnel and environmental protection only. The material (research experiment) inside the cabinet is not protected and thus subject to contamination. The use of Class I BSC is not advised at Stanford; talk to Biosafety if you feel you need to purchase one.

Class II cabinets meet requirements for the protection of personnel, product and the environment. There are four types of Class II cabinets (A, B1, B2, and B3), each differentiated according to the method by which air volumes are recirculated or exhausted.

Class II, type A: The Class II, type A biosafety cabinet does not have to be vented, which makes it suitable for use in laboratory rooms which cannot be ducted. This cabinet is acceptable for use of low to moderate risk agents in the absence of volatile toxic chemicals and volatile radionuclides.

Class II, type B1: The Class II, type B1 biosafety cabinet must be vented. 30% of the air is exhausted from the cabinet while 70% is recirculated back into the room. This cabinet may be used with etiologic agents treated with minute quantities of toxic chemicals and trace amounts of radionuclides required as an adjunct to microbiological studies if work is done in the directly exhausted portion

of the cabinet, or if the chemicals or radionuclides will not interfere with the work when recirculated in the downflow air.

Class II, type B2: The Class II, type B2 biosafety cabinet must be totally exhausted. 100% of the air from the cabinet is exhausted through a dedicated duct. This cabinet may be used with etiologic agents treated with toxic chemicals and radionuclides required as an adjunct to microbiological studies.

Class II, type B3: The Class II, type B3 biosafety cabinet must be vented. 70% of the air is exhausted from the cabinet while 30% is recirculated. This cabinet may be used with etiologic agents treated with minute quantities of toxic chemicals and trace quantities of radionuclides that will not interfere with work if recirculated in the downflow air.

Class III cabinets are gas-tight, designed for use with high-risk (BSL-4) agents. There are no Class III cabinets at Stanford University.

Stanford University has taken a strong stance against the use of gas burners or alcohol flames in biosafety cabinets. The use of such devices cannot only be extremely dangerous but can also inactivate manufacturers warranties. There are many alternatives to the use of burners; microincinerators, disposable tissue culture supplies, etc. Please consult with the Biosafety Manager if you have any questions.

All purchases of BSCs at Stanford University must first be approved by the Biosafety Manager. Call X5.1473 for more information.

Installation and Maintenance of BSCs

Installation of cabinets must be done by certified professionals. Stanford University has a contract with a certified company for installation, cabinet certification (must be done annually), decontamination and any other needs that may arise. Arrangements and payment for any of the above work must be schedualed by the PI or the Department. For more information please see http://www.stanford.edu/dept/EHS/prod/researchlab/bio/index.html

Signs and Hazard Communication

All laboratories that are approved by the Stanford APB must have a sign on the outside of the door indicating that biohazardous material is used within the room. Investigators who are using BSL2 or 3 agents are required by NIH to post a sign on the door that incorporates the universal biohazard symbol on the outer laboratory door. The sign must include information regarding the agent name and specific requirements for entry, the PI's name and spaces for two phone numbers of laboratory staff in case contact must be made. Biohazard signs are available through EH&S.

The Bloodborne Pathogen Standard also requires that red-orange coded biohazard labels be placed on storage freezers, refrigerators, any laboratory equipment used with BSL2 or 3 agents, shipping containers, medical waste containers or any surface which may be reasonably anticipated to encounter surface contamination from biohazardous materials. These labels are available through EH&S.

Spill Response

The following procedures are provided as a guideline to biohazardous spill cleanup. If the spill is considered too large or too dangerous for laboratory personnel to safely clean up, secure the entire laboratory and call EHS immediately for assistance.

1. **Inside the Biosafety Cabinet**

    1. Wait at least five minutes to allow the BSC to contain aerosols.
    2. Wear laboratory coat, safety glasses and gloves during cleanup.
    3. Allow BSC to run during cleanup.
    4. Apply disinfectant and allow a minimum of 20 minutes contact time.
    5. Wipe up spillage with disposable disinfectant-soaked paper towels.
    6. Wipe the walls, work surfaces and any equipment in the cabinet with disinfectant-soaked paper towels.

7. Discard contaminated disposable materials using appropriate biohazardous waste disposal procedures.
8. Place contaminated reusable items in biohazard bags or autoclavable pans with lids before autoclaving.
9. Expose non-autoclavable materials to disinfectant (20 minutes contact time) before removal from the BSC.
10. Remove protective clothing used during cleanup and place in a biohazard bag for removal
11. Run BSC 10 minutes after cleanup before resuming work or turning BSC off.

2. In the laboratory, outside the Biosafety Cabinet

1. Evacuate Room – insure all personnel are accounted for and that doors are closed. Allow spill to settle (30 min.).

2. Put on appropriate PPE, including lab coat, shoe covers, gloves and eye/face protection.

3. Initiate cleanup with disinfectant as follows:

1. Place paper towels or other absorbent material over spill area
2. Carefully pour disinfectant around the edges of the spill and then onto the paper towels. Avoid splashing or generating aerosol droplets.
3. Allow disinfectant to remain in contact with spill for at least 20 minutes
4. Apply more paper towels to wipe up spill
5. Clean spill area with fresh towels soaked in disinfectant.
6. Place all towels or absorbent materials using appropriate biohazardous waste disposal procedures.
7. Remove protective clothing and segregate for disposal or cleaning.
8. Wash hands with soap prior to leaving area.

3. **Inside a centrifuge**

1. Clear area of all personnel.
2. Wait 30 minutes for aerosol to settle before attempting to cleanup spill.
3. Wear a laboratory coat, safety glasses and gloves during cleanup.
4. Remove rotors and buckets to nearest BSC for cleanup.
5. Thoroughly disinfect inside of centrifuge.
6. Discard contaminated disposable materials using appropriate biohazardous waste disposal procedures.

4. **Outside the laboratory**

1. To prevent a spill, transport labeled biohazardous material in an unbreakable, well-sealed primary container placed inside of a second unbreakable, lidded container (cooler, plastic pan or pail) labeled with the biohazard symbol.

2. Should a spill occur in a public area, do not attempt to clean it up without appropriate PPE.
3. Secure the area, keeping all people well clear of the spill.
4. Call EHS at 724.0448 to assist in cleanup.
5. Stand by during spill response and cleanup activity and provide assistance only as requested or as necessary.

8 Select Agents

First of all searchers, of all men that ever lived, ahead of the prophet Pasteur who blazed the trail for him, Koch had really made sure that one certain kind of microbe causes one definite kind of disease, that miserably small bacilli may be the assassins of formidable animals.

Paul De Kruif, Microbe Hunters (1926), Harcourt, Brace and Co., pub, pg 116

Select Agents are a collection of designated infectious agents and toxins that, by their nature, have the potential to pose a severe threat to public health and safety; this threat has resulted in the creation of a number of legislative acts.

"The Antiterrorism and Effective Death Penalty Act of 1996," which became effective on April 15, 1997, established the first list of Select Agents and required registration for transfer of said agents. The "Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act (USA PATRIOT Act) of 2001" established provisions that regulate the possession, usage, or transfer of hazardous agents, and required the Department of Health and Human Services to issue rules to implement these provisions. The Patriot Act specifically addressed the issue of possession of Select Agents by certain “Restricted Persons” (Section 817(b) and criminalized possession of select agents except for bonafide purposes. Additionally, the “Public Health Security and Bioterrorism Preparedness and Response Act of 2002” expanded the list of select agents, required registration for possession of select agents and required security measures to prevent access to agents.

The list of Select Agents is constantly changing. The present list of Select Agents is in Appendix I; the list can also be found in its most updated form at
http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/select_agent_list.pdf

Stanford University is currently not registered for possession of Select Agents. If a PI decides that a viable Select Agent is required, contact the Biosafety Manager at 5.1473. If a PI requires the use of a toxin(s) that are listed as a Select Agent, only amounts below the non-exempt limit shall be ordered and/or used. The policy for possession of exempt quantities of Select Agents Toxins is as follows:

SU Requirements for Possession of Exempt Quantities of CDC Select Agent Toxins

A) Purpose of Document:

This document outlines Stanford University's institutional requirements on possession of exempt quantities of Center for Disease Control (CDC) Select Agent (SA) Toxins. (To review the federal legislation on Select Agents (42 CFR Part 73), go to http://www.cdc.gov/od/sap/docs/42cfr73.pdf . These requirements have been established to ensure:

- safe laboratory handling, use, and storage procedures,
- effective tracking and security of the regulated toxins, and
- compliance with federal regulations

B) Exempt Quantities of CDC Select Agent Toxins:

Per the federal regulations each Principle Investigator (PI) may possess a specified amount of toxin without triggering CDC registration and other stringent requirements. Below is the list of SA Toxins and the allowable maximum exempt quantities (per PI).

Toxin	Max. allowable per PI for exemption
Abrin	100 mg
Botulinum neurotoxins	0.5 mg
Clostridium perfringens epsilon toxin	100 mg
Conotoxins	100 mg
Diacetoxyscirpenol	1000 mg
Ricin	100 mg
Saxitoxin	100 mg
Shigatoxin and Shiga-like ribosome inactivating proteins	100 mg
Staphylococcal enterotoxins	5 mg
Tetrodotoxin	100 mg
T– 2 toxin	1000 mg

Additionally, the following toxins are exempt:

1. Any agent or toxin that is in its naturally occurring environment provided it has not been intentionally introduced, cultivated, collected, or otherwise extracted from its natural source.
2. Non-viable select agent organisms or nonfunctional toxins

It is important to ensure that the total amount of toxin per PI in a laboratory is maintained below these limits at all times for exemption from registration and the attendant restrictive requirements. Due to the severe penalties associated with non-compliance with the SA rules, it is imperative that each laboratory using and storing toxins maintains current inventory information for these substances. **(Failure to register a Select Agent is now a criminal offense, punishable by up to five years in prison and/or $500,000 in fines. (Public Health Security & Preparedness Response Act of 2002, s. 231(c))**.

C) SU Requirements for Possession of Exempt Quantities of CDC Select Agent Toxins

The Principle Investigator is responsible for ensuring the following:

1) **Standard Operating Procedures (SOPs):** Prepare written SOPs for toxin-involved research processes.
2) **Personnel Training:** Provide initial lab-specific safety training to staff on toxin-involved processes, with updates as necessary. Ensure documented training is maintained for at least one year (per Cal-OSHA 8CCR 3203). Training topics should include:
   - toxin-associated hazards
   - engineering controls used to minimize exposure (i.e., fume hood use)
   - personal protective equipment to be used when handling toxin (PPE)

- safe handling and storage
- proper decontamination and disposal
- administrative requirements (recordkeeping, inventory, security).

3) **Proper PPE:** Appropriate personal protection is to be provided (i.e., gloves, safety goggles, lab coat or disposable lab coat). NOTE: If respirators are necessary, contact EH&S at 725-0448 for necessary respirator use approval and compliance documentation.
4) **Engineering Controls:** Proper use of fume hood, biosafety cabinet or glove box with toxin-associated procedures.
5) **Inactivation:** Use accepted inactivation procedures described on the EH&S Biosafety website (click here) prior to disposal of remaining stock and/or empty containers.
6) **Disposal:** After inactivation, dispose of residual wastes (liquids/ solids) as follows:
   - **Liquids*:** Collect inactivated materials in a non-leaking container constructed of compatible material, and manage as hazardous waste per Stanford Hazardous Waste Management procedures. (click here).
   - **Stock Vials and other materials*:*** Deface container labeling. Collect in non-leaking container and manage as hazardous waste (see above link for proper disposal).

   **** NOTE:*** *Such inactivated toxin liquid waste shall be managed as hazardous waste unless the material is between 5.5-11.0 pH AND the final NaOCl concentration is less than 1% (wt/wt).*
7) **Storage/Security:** Items must be:
   - Stored with compatible materials within secondary containment; AND
   - Provided one layer of physical security (i.e., toxin secured within a locked freezer, or secured within a permanently fixed lockbox)
8) **List of PI-Approved Users:** A documented list to be maintained of PI-approved toxin users (including those having access to toxin materials). The lab must keep track of who uses the stock (and who has access to the freezer), but it is not necessary to record each use. Before becoming an Approved User, the PI must ensure that each person has received training under section C (2) above.
9) **Inventory Maintenance:** Inventory of toxins (like other laboratory hazardous materials) **must be kept current in the on-line Stanford Chemical Inventory Maintenance System** (SCIMS). To help PIs ensure inadvertent breaching of exempt quantity levels, inventories are to be promptly updated after every container of CDC toxin is:
   - acquired (by purchase/ intra-campus transfer)
   - depleted (by consumption/ intra-campus transfer); OR
   - inactivated
10) **Documented Security Inspection:**
    a. Self-Inspections: Are to be conducted using the laboratory safety inspection checklist at: http://www.stanford.edu/dept/EHS/prod/training/checklist/labcheck.pdf Inspections must be performed initially and at least quarterly thereafter; documentation of inspections must be kept for one year or the duration of SA possession, whichever is longer. Inspection items include:
       - Review of Approved Users List to verify authorized access to toxins.
       - Verification of appropriate labeling, storage, secondary containment, security measures
       - Comparison of physical inventory with what is accounted for on SCIMS.

    b. In addition, EH&S will provide periodic laboratory visits to review compliance with institutional requirements on possession of select agent toxins.

D) Possession of Select Agent Toxins Above Exempt Quantities:

- For possession of select agent toxin quantities above exempt quantities, prior approval from the Vice Provost and Dean of Research and Graduate Policy must be obtained and registration by the Centers for Disease Control approved.

For any questions regarding CDC Select Agent possession at Stanford University, contact Environmental Health and Safety- Biosafety Program at 725-1473.

9 Transportation

Beam me up, Scotty

Captain James T. Kirk, Star Trek

If only it could work that way….However, until we have a transporter, transportation of biohazardous goods requires a bit more planning and training.

Transport of biohazardous goods within Stanford University requires the use of proper secondary containment. Secondary containers can be a variety of items but they all must be leak-proof and have tight fitting covers. All containers must be labeled with a Biohazard sticker or label.

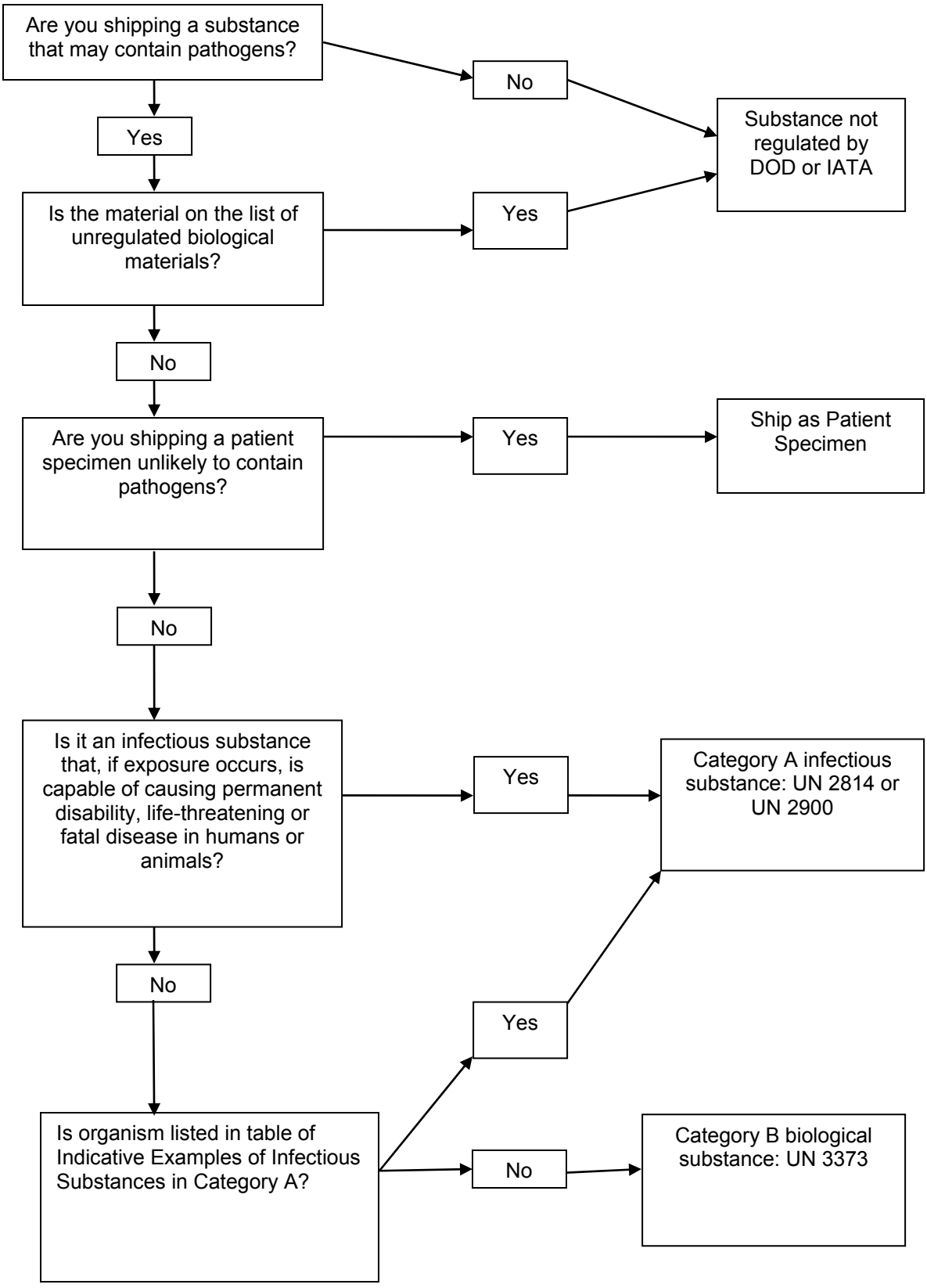
Transport of biohazardous goods off Stanford University requires training and certification prior to shipping. Federal (FAA, 49 CFR) and international agencies (ICAO (the branch of the United Nations that governs all international civil aviation matters), IATA (International Air Transport Association)) have in place numerous regulations for shipping of dangerous goods by surface or air. Training is mandatory for shippers (the person sending out the package) and handlers (the people who transport the package) and is based on these regulations. Non-conformance of these regulations can result in a fine and/or imprisonment.

What is a Dangerous (Biohazardous) Good?

According to the regulations, Dangerous Goods "are articles or substances which are capable of posing a significant risk to health, safety or to property when transported". For Biological material, the flow chart shown below indicates which materials are regulated and which are not.

Note: Dry Ice is considered a Dangerous Good. Training and certification is required, and the package must be labeled and shipped accordingly!

A flow chart for classification of Infectious Substances



For training to become certified for shipping of biological goods, go to:

http://www.stanford.edu/dept/EHS/prod/researchlab/bio/practical.html

Export Controls Related to Biologicals and Toxins

The Commerce Department, along with other federal agencies, regulates shipping of biologicals and toxins outside the U.S. When these substances derive from or are involved in "fundamental research" as defined by the export control regulations, they may be eligible for the "No License Required" (NLR) provisions of the Export Administration Regulation or other special treatment. To document NRL or other export exemptions, all faculty **must** have on file the following document (No License Required justification). See Stanford University Export Control Information for additional details.

Importation of Biohazardous Goods onto Stanford University

The Federal Government, in its shipping and transportation standards, defines etiologic agents as microorganisms that cause disease in humans including the following: bacteria, bacterial toxins, viruses, fungi, rickettsia, protozoans, and parasites. These disease-causing microorganisms may also be referred to as infectious agents or infectious substances and the materials, such as body fluids and tissues that contain them, are referred to as infectious materials. Organisms such as mosquitoes that might transmit infectious diseases to other humans are called vectors. When a package of infectious material is being imported into the United States, it must have an importation permit approved by the CDC.

It is important to obtain a CDC permit PRIOR to requesting an etiologic specimen from a source outside the United States. The Stanford University Administrative Panel on Biosafety will request that the Principal Investigator indicate the source of any agents used in experiments at Stanford during the application process. If the investigator intends to obtain the agent from outside the United States, a copy of the CDC permit will be requested by the APB as part of the APB review of the application.

Items Requiring Permits

Etiologic agents: It is impractical to list all of the several hundred species of etiologic agents. In general, an import permit is needed for any infectious agent known to cause disease in man. This includes, but is not limited to, bacteria, viruses, rickettsia, parasites, yeasts, and molds. In some instances, agents which are suspected of causing human disease also require a permit.

Biological materials: Unsterilized specimens of human and animal tissue (including blood), body discharges, fluids, excretions or similar material, when known or suspected of being infected with disease transmissible to man require a permit under these provisions in order to be imported.

Animals: Any animal known or suspected of being infected with any disease transmissible to man. Importation of turtles of less than 4 inches in shell length and all non-human primates requires an importation permit issued by the Division of Quarantine. Telephone (404) 639-1437 for further information.

Insects: Any living insect, or other living arthropod, known or suspected of being infected with any disease transmissible to man. Also, if alive, any fleas, flies, lice, mites, mosquitoes, or ticks, even if uninfected. This includes eggs, larvae, pupae, and nymphs as well as adult forms.

Snails: Any snails capable of transmitting schistosomiasis. No mollusks are to be admitted without a permit from either Centers for Disease Control or the Department of Agriculture. Any shipment of mollusks with a permit from either agency will be cleared immediately.

Bats: All live bats. Bats may also require a permit from the U.S. Department of Interior, Fish and Wildlife Services.

If you are not certain if the agents you intend to use require a CDC importation permit, please call the Biosafety Officer at 725.1473 who will assist you in making the determination.

***A permit request form can be obtained by contacting the CDC automated fax service. Call (1.888.232.3299), have your own fax number ready and request document # 101000*.**

Import Permits for Etiologic Agents
CDC-Office of Health and Safety
Biosafety Branch

Letters of Authorization

After a review of an "Application to Import an Etiological Agent" the issuing officer may issue a "Letter of Authorization" rather than an importation permit. The Letter of Authorization is issued for materials that are judged to be non-infectious, but which might be construed to be infectious by U.S. Customs inspection personnel.

Letters of Authorization may be issued for items such as formalin fixed tissues, sterile cell cultures, clinical materials such as human blood, serum, plasma, urine, cerebrospinal fluid, and other tissues or materials of human origin when there is no evidence or indication that such materials contain an infectious agent.

A copy of a Letter of Authorization should be attached to the package, and also should be furnished to the courier or importation broker. Letters of Authorization are in effect for two years.

Other Permits

United States Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) permits are required for infectious agents of livestock and biological materials containing animal, particularly livestock material.

Tissue (cell) culture techniques customarily use bovine material as a stimulant for cell growth, tissue culture materials, and suspensions of cell growth. Tissue culture materials, and suspensions of cell culture grown viruses or other etiologic agents containing growth stimulants of bovine or other livestock origin are, therefore, controlled by the USDA due to the potential risk of introduction of exotic animal diseases into the U.S. Further information may be obtained by calling the USDA/APHIS at (301) 436-7885.

United States Department of Interior (USDI) permits are required for certain live animals and all live bats. Call (600) 358-2104 for further information.

Exports of Infectious Materials

The export of infectious material may require a license from the Department of Commerce. Call (202) 482-0896 for further information.

Further Information from the CDC

Centers for Disease Control and Prevention
Public Inquiries/OHS
Mailstop F05
1600 Clifton Road
Atlanta, GA 30333
U.S.A
http://www.cdc.gov/od/ohs/feedback.htm

10 Waste & Decontamination

Think Red. Not just because it's the Stanford color. Think Red bags. Red sharps containers. Red is the color of Biosafety and thus red is the color for biohazardous waste.

Waste

Biohazardous waste includes all laboratory waste that may contain any biohazardous material or were in contact with said material. Additionally, any blood or components of blood or body fluids are to be disposed of as biohazardous waste. All biohazardous waste must be disposed of in red bags marked with the biohazard symbol; these bags must be secondarily contained in a puncture resistant outer container and covered with a lid. Biohazard stickers must be present on all four sides of the container and the top of the lid.

In accordance with the California Medical Waste Management Act, Health and Safety Code, Chapter 6.1, medical waste is defined as including, but not limited to the following:

1. Human or animal specimens or cultures from medical and pathological laboratories
2. Cultures and stocks of infectious agents from research and industrial laboratories
3. Wastes from the production of bacteria, viruses, or the use of spores, discarded live and attenuated vaccines, and culture dishes and devices used to transfer, inoculate, and mix cultures

Additionally, medical waste can include:

A. Waste containing any biological specimens sent to the laboratory for analysis
B. Human specimens or tissues removed at surgery or autopsy, which are suspected by the attending physician and surgeon or dentist of being contaminated with infectious agents known to be contagious to humans

C. Animal parts, tissues, fluids, or carcasses suspected by the attending veterinarian of being contaminated with infectious agents contagious to humans

D. Waste, which at the point of transport from the generator's site, at the point of disposal, or thereafter, contains recognizable blood, fluid blood products, containers, or equipment containing blood that is fluid, or blood from animals known to be infected with diseases which are communicable to humans

E. Waste containing discarded materials contaminated with excretion, exudate, or secretions from humans who are required to be isolated by the infection control staff, the attending physician and surgeon, the attending veterinarian, or local health officer, to protect others from highly communicable diseases or isolated animals known to be infected with diseases which are highly communicable to humans

Please note, however, that the California Medical Waste Management Act has as exceptions to the definition of medical waste:

A. Waste generated in food processing or biotechnology that does not contain an infectious agent (defined as BL-3 or above).

B. Waste generated in biotechnology that does not contain human blood or blood products or animal blood or blood products suspected of being contaminated with infectious agents known to be communicable to humans

C. Urine, feces, saliva, sputum, nasal secretions, sweat, tears or vomitus, unless it contains fluid blood.

These exemptions would include tissue culture materials that are not known or suspected of being infected. The biotechnology exemption permits the above items to be disposed of as non-redbag (non-biohazardous) waste. Note that these materials should be inactivated with an appropriate disinfectant to avoid contamination elsewhere in the laboratory.

Sharps Waste

Sharps waste means any device having rigid corners, edges or protuberances capable of cutting or piercing, including, but not limited to, all of the following:

A. Hypodermic needles and attachments (syringes or tubing), and blades

B. Broken glass/plastic items, such as Pasteur pipettes and blood vials contaminated with medical waste

C. Teeth, both intact and fragmented

It is extremely important to remember NOT to clip, bend, shear or separate needles from syringes and do not recap needles – these are the times that you are most likely to get injured.

All sharps waste must be placed in an approved sharps container that is constructed of rigid, hard plastic and labeled with the universal biohazard symbol. Do not overfill the container. The lid of the sharps container must be shut and the container labeled with the room number prior to disposal.

Mixed Waste

Waste can often involve a mixture of medical and non-medical waste. Mixed waste is categorized as medical waste EXCEPT for the following:

A. A mixture of medical waste and hazardous chemical waste is categorized as hazardous chemical waste and is subject to the statutes and regulations applicable to hazardous chemical waste.

B. A mixture of medical waste and radioactive waste is categorized as radioactive waste and is subject to the statutes and regulations applicable to radioactive waste.

A mixture of medical waste, hazardous chemical waste, and radioactive waste is categorized as radioactive waste and is subject to the statutes and regulations applicable to radioactive waste.

Mixed chemical and biohazardous sharps waste will be placed into a sharps container that is labeled as chemical sharps waste. Any mixed chemical and biohazardous waste must be properly identified and labeled with a Hazardous Waste Tag. Tags and information are available from EH&S, 723.5069. Information on the Chemical Waste Pickup program, including on- line request for pickup, can be found at:
http://www.stanford.edu/dept/EHS/prod/enviro/waste/index.htm

All mixed radioactive-biohazardous waste must be properly segregated prior to disposal. Mixed radioactive and biohazardous non-sharps waste will be packed in a yellow bag labeled with the

universal radiation symbol and/or radiation symbol. Mixed radioactive and medical sharps waste will be placed in a sharps container labeled with the universal radiation label. Mixed radioactive waste is picked up by Radiation Safety waste technicians and transported to the EH&S radioactive waste accumulation area for packaging and disposal. Call 725-1408 for pick up and information regarding mixed radioactive-biohazardous waste.

Animal Carcasses

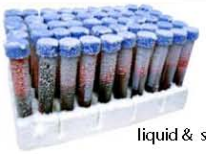
After proper euthanasia of laboratory animals (Department of Laboratory Animal Medicine Euthanasia Procedures), animal carcasses shall be placed in red bags labeled with the universal biohazard symbol and brought to the Research Animal Facility pathological waste freezer

Autoclave Waste

Any research biohazardous laboratory waste which will be autoclaved shall be placed in an autoclavable red bag. This bag shall have the Universal Biohazard Symbol on the outside. The top of the bag shall be secured with indicator tape that will change color after the attainment of sterilization. Be sure that the autoclavable red bag can withstand the autoclave cycle without melting. Autoclaved bags shall be placed in a red bag for disposal as medical waste.

STANFORD UNIVERSITY
ENVIRONMENTAL HEALTH & SAFETY

Biohazardous and Medical Waste Disposal Guidelines

ITEMS REQUIRING DISPOSAL	PROPER DISPOSAL METHOD
SHARPS  All: Blades (scalpels, razors), Pasteur pipets, Hypodermic needles with attached: •Syringes (barrels and plungers) •Tubing. **Never remove needles from syringes!**	→ Sharps Container  → Biohazard waste
CULTURES AND DISPOSABLES  Contaminated: Petri dishes, Disposable culture & tissue flasks, Materials (paper towels, kim wipes, etc.) → Red bag in hard-sided leak proof container with biohazard symbols on all sides and top  → Biohazard waste	
Contaminated liquid waste in container → Container with liquid removed → Decontaminate liquid → Dispose liquid into sewer using running water  **See below for disposing of blood and body fluids.**	
If culture is NOT Biohazardous (BSL-1) → Regular trash 	
PIPETS  Contaminated: Pipete Tips, Disposable Pipets → Red bag in hard-sided leak proof container with biohazard symbols on all sides and top  → Biohazard waste	
Non-contaminated: Pipete Tips, Disposable Pipets → Regular trash 	
GLASS  Contaminated: Broken and unbroken glass → Sharps container  → Biohazard waste	
Non-contaminated: Broken and unbroken glass → Broken glass container  → Recycling	
BLOOD & BODY FLUIDS  All: human blood, animal blood, blood elements, body fluids, liquid & semi-liquid materials → Dilute with bleach 1:10 (final concentration = 0.5% sodium hypochlorite) → Dispose into sewer using running water 	
or Autoclave (do not add bleach if autoclaving) 	
ANIMAL BODIES  All: Animal carcasses & body parts → Double red bag  → Research Animal Facility (RAF) refrigerators	
Radioactive carcasses → Double red bag → RAF radioactive refrigerators	
CHEM AND RAD  All: Biohazardous material with chemical contamination → Call EH&S Chem Waste 5.7520	
Biohazardous material with radioactive contamination → Call EH&S Radiation Waste 3.3765	

Do not use needle clippers or cardboard pipet envelopes for sharps disposal.

For biohazardous waste, do not use orange or clear autoclave bags.

For additional information contact Biosafety Office 725.1473

Autoclave Waste

Any research biohazardous laboratory waste which is generated and which must be autoclaved shall be placed in an autoclavable red bag. This bag shall have the Universal Biohazard Symbol on the outside. The top of the bag shall be secured with indicator tape that will change color after the attainment of sterilization. Be sure that the autoclavable red bag can withstand the autoclave cycle without melting. Autoclaved bags in the School of Medicine shall be placed in a red bag for disposal as medical waste. Call 723-6336 or 725-1473 if you have any questions.

Decontamination

Chemical and Gas

Place an absorbent material (paper towel, bench diaper) over the contaminated surface, then add liquid disinfectant; this will prevent spread of contamination. Allow sufficient contact time after applying the disinfectant. If the contact time is too brief, the surface will not be thoroughly disinfected. When cleaning a spill of concentrated material or if the disinfectant must act on an uneven surface, allow extra time for the disinfectant to act. Avoid using concentrated or undiluted solutions of your disinfectant to "speed up" the inactivation process. The surface that is being disinfected may be adversely affected by strong chemicals. This is especially significant when working with bleach, which is a very strong corrosive. Some disinfectants will leave a residue of chemicals behind. Rinse the cleaned area with distilled water to avoid adverse effects on your experiment. This is especially important in tissue culture rooms where a cell line can be wiped out by disinfectant residue left on equipment.

The following disinfectants, their efficancies, contact times and recommended dilutions follow:

Quaternary Ammonium Compounds are commonly used in floor cleaning solutions. Quaternary ammonium compounds are effective in inactivating most vegetative bacteria, fungi, and lipid containing viruses. Quaternary ammonium compounds are NOT effective when used to disinfect *Mycobacterium tuberculosis* (TB), bacterial spores, and many viruses such as HBV.
Recommended contact time: 10 minutes
Recommended Working Dilution: 0.1-2.0%
Recommended for: cleaning optical instruments and administrative areas in the vicinity of a laboratory.

Ethanol is commonly used on equipment whose surfaces are susceptible for corrosion if other disinfectants are applied. Ethyl alcohol is effective in inactivating most vegetative bacteria, fungi, and lipid containing viruses. Ethanol is NOT effective when used to disinfect HBV, *Mycobacterium tuberculosis* (TB) and bacterial spores.
Recommended contact time: 10 minutes
Recommended Working Dilution: 70-85%
Recommended for: Stainless steel surfaces. CAUTION: Do not use 70% ethanol to clean a Class II, type A recirculating biosafety cabinet. The vapors from ethanol are flammable and the lower explosive limit (LEL) for ethanol is easily attained.

Phenolics are commonly used to decontaminate surfaces such as lab bench tops. Phenolics are effective in inactivating vegetative bacteria, fungi, TB, lipid containing viruses and have some effect on HBV. However, phenolics will not inactivate bacterial spores.
Recommended contact time: 10 minutes
Recommended Working Dilution: 1.0-5.0%
Recommended for: an alternative to bleach as a broad -spectrum disinfectant for bench tops, floors, and metal surfaces. Phenolics will not corrode metal surfaces as readily as bleach.

Iodine containing compounds or iodophors are commonly used to decontaminate metal surfaces or equipment. Iodophors are effective in inactivating vegetative bacteria, fungi, TB and lipid containing viruses and have some effect on HBV. However, iodophors will not inactivate bacterial spores.
Recommended contact time: 10 minutes
Recommended Working Dilution: 25-1600 ppm, 0.47%
Recommended for: biosafety cabinets, dental equipment, bench tops, floors and lab equipment in general.

Chlorine compounds such as bleach are commonly used in the lab because of the relative ease in accessibility and low cost. Chlorine (hypochlorite) compounds are effective in inactivating vegetative bacteria, fungi, lipid and non-lipid viruses, *Coxiella burnetii* and TB.
Chlorine compounds have some effect in inactivating bacterial spores.
Recommended contact time: 10 minutes
Recommended Working Dilution: 500 ppm (1:10 dilution of household bleach, 5% hypochlorite ion)
Recommended for: floors, spills (inactivating liquid specimens), bench tops and contaminated clothing. Do not use bleach on electronic equipment, optical equipment or unpainted stainless steel. Undiluted bleach and other disinfectants must not go down the drain.

Paraformaldehyde and formaldehyde are often used to decontaminate large pieces of laboratory equipment, such as biosafety cabinets (but only by professionals!). Paraformaldehyde/formaldehyde will inactivate vegetative bacteria, fungi, lipid and non-lipid viruses, HBV, TB, *Coxiella burnetii*, and bacterial spores. However, paraformaldehyde and formaldehyde are registered carcinogens in the State of California and are very toxic to use without the accessibility of a vented fume hood and/or personal protective equipment. DO NOT USE PARAFORMALDEHYDE OR FORMALDEHYDE IN THE LAB TO DECONTAMINATE EQUIPMENT. The approved biosafety cabinet contractor will use paraformaldehyde to decontaminate your biosafety cabinet prior to changing the HEPA filters. Be sure to avoid the biosafety cabinet while this operation is in effect!

Glutaraldehyde is often used to disinfect hospital instruments. Glutaraldehyde will inactivate vegetative bacteria, fungi, lipid and non-lipid viruses, HBV, TB, *Coxiella burnetii*, and bacterial spores. However, glutaraldehyde is very toxic to use without the accessibility of a vented fume hood and/or personal protective equipment. DO NOT USE GLUTARALDEHYDE IN THE LAB TO DECONTAMINATE EQUIPMENT.

Ethylene Oxide is often used to disinfect hospital instruments. Ethylene Oxide will inactivate vegetative bacteria, fungi, lipid and non-lipid viruses, HBV, TB, *Coxiella burnetii*, and bacterial spores. However, Ethylene oxide is a registered carcinogen in the State of California and is very toxic to use without mechanically generated ventilation exhaust and personal protective equipment. DO NOT USE ETHYLENE OXIDE IN THE LAB TO DECONTAMINATE EQUIPMENT.

Anyone working with prions or other Spongiform encephalopathies that may be present in brain tissue must call the Biosafety Manager, 725.1473. The recommended disinfectant is 1.0N NaOH and autoclaving of reusable instruments is recommended. Slow viruses such as Kuru are included in this group.

Autoclaves

A steam autoclave is a device designed to sterilize cultures, media, surgical instruments and medical waste. Autoclaves will sterilize on the basis of:

- length of time in the cycle
- temperature

- contact
- pressure
- steam

An autoclave is suitable for the treatment of certain types of medical waste but not all types. The following items of medical waste must not be autoclaved:

A. Items of medical waste which are mixed with volatile chemical solvents or radioactive materials (this waste must be handled as either chemical waste or radioactive waste).
B. Pathological waste (pathological waste is handled as follows: animal carcasses are placed in a red bag and taken to the pathological waste freezers in the Research Animal Facility; human body parts are placed in a red bag and disposed of as medical waste without autoclaving.).

The following items of medical waste can be autoclaved:

A. Microbiological waste such as cultures of human or animal specimens from medical or pathological laboratories
B. Cultures and stocks of microbiological specimens
C. Waste contaminated with biohazardous materials such as contaminated paper towels or contaminated surgical gloves

Unless otherwise stated, autoclaving materials prior to medical waste disposal is not necessary; however, if desired, autoclaving is an acceptable method for decontamination of materials prior to disposal.

Considerations for effective autoclaving:

A. Do not overload the autoclave bag. The autoclave steam and heat cannot penetrate to the interior of an overloaded bag. The outer contents of the bag will be sterilized but the inner part of the bag will essentially be unaffected by the autoclave cycle.
B. Do not put sharp objects, such as broken glass that can puncture
C. Do not overload the autoclave.
D. Do not mix autoclave bags and other items to be autoclaved in the same autoclave cycle. Liquid media requires a shorter cycle, often 15-20

minutes while autoclavable medical waste requires a minimum of 30 minutes in order to be effectively sterilized.

E. To help insure non-variability of sterilization, try to use a consistent loading pattern of materials within the autoclave (amount of material and location within autoclave).

F. Validate autoclave effectiveness once every month (test strips are a recommended method and easily available).

Safety considerations for autoclave attendants:

A. Wear personal protective equipment to include heat-resistant gloves, goggles or safety glasses and a lab coat

B. Use caution when opening the autoclave door. Allow superheated steam to exit.

C. Use caution when handling a bag in case sharp objects have been inadvertently placed in the bag. Never lift a bag from the bottom of the bag to load into the chamber. Handle the bag from the top.

D. Watch out for pressurized containers. Superheated liquids may spurt from sealed containers. Never seal a container of liquid with a cork that may cause a pressurized explosion inside the autoclave.

E. Agar plates will melt and the agar will become liquefied. Avoid coming in contact with this molten liquid. Use a secondary tray to catch any potential leakage from the bag that would otherwise leak into the autoclave.

F. Glassware may crack or shatter if cold liquid comes in contact with this superheated glassware. If glass breaks in the autoclave, use tongs, forceps, or other mechanical means to recover the fragments; make certain that the autoclave has been cooled down to avoid surface burns.

G. Use an absorbent liner for glass vessels containing liquid. Never put autoclave bags or glassware directly in contact with the bottom of the autoclave.

To autoclave waste, follow the below procedures:

1. place waste as generated in an autoclavable red bag
2. put autoclave tape loosely around the top of the bag and place the bag in a secondary container such as an autoclave pan

3. set the cycle for 30 minutes, 121 degrees at 20 PSI
4. after autoclaving, the autoclaved red bag must be disposed of as red bag waste

Note that sterilizer purchases must be approved by the Biosafety Officer. A variety of factors must be taken into consideration prior to purchasing an autoclave; additional information concerning autoclave purchases is available on the web at: http://www.stanford.edu/dept/EHS/prod/researchlab/bio/practical.html

11 Lab Deactivation & Equipment Disposal

….those who pass their lives shut up in houses and offices are not often strong. Their muscles are not thick and hard, and their blood is not rich. But, worse than that, they make their brains and their nerves work too hard; they fatigue their heads and become irritable, or nervous, as it is called, being excited to gayety or anger without sufficient cause. Sometimes, indeed, their brains become altogether deranged, and are no longer able to act properly; the persons are then insane, or lunatic. It is by no means true, however, that the professions and sedentary occupations furnish all of the cases of insanity….

Paul Bert, First Steps in Scientific Knowledge (1886), J.B. Lippincott, pub, part VI, pg 65.

Laboratories which utilize biological materials must notify the Biosafety Manager prior to terminating work to ensure that the laboratory has been decontaminated and that the biological material has been secured or properly disposed of. If the Principal Investigator intends to cease work, he or she must notify the Biosafety Manager at least 60 days prior to the set departure date. This will allow the Biosafety Manager to consult with the Principal Investigator and perform a walkthrough of the lab to provide recommendations on the most expeditious way to prepare for the move and the final termination of the biohazardous work in the lab. A final Lab Deactivation Inspection will be scheduled accordingly.

Lab close out procedures

A. Biosafety cabinets must be decontaminated with paraformaldehyde and the outer surfaces cleaned with a suitable disinfectant. BSC paraformaldehyde decontamination must be done by a certified professional. Currently Stanford University contracts with an outside vendor for this; please call 1.510.845.5591 to schedual an appointment. The Principal Investigator should present a receipt verifying that the paraformaldehyde decontamination procedure has been completed by the contracted biosafety cabinet certifier.

B. Storage freezers should be emptied and the surfaces should be decontaminated with a suitable disinfectant. The former contents must be decontaminated by autoclaving or disposed of in a red bag. Cryostats and liquid nitrogen storage equipment must also be emptied. If the Principal Investigator intends to stay at Stanford but not continue the APB approved project, then only the biological agents that were approved for use on the application need to be disposed.

C. Account for all specimens stored outside the lab room. Specimens stored in a cold room or an incubator in an adjacent tissue culture room should be autoclaved or disposed of in a red bag.

D. Medical waste such as used sharps containers or red bags must be disposed of and the storage areas for the medical waste cleaned with a suitable disinfectant.

E. Any biohazard labels must be removed from surfaces. The outer surface of all equipment and any work surface must be decontaminated with a suitable disinfectant.

F. The Biohazard sign must be removed from door. The Life Safety Box should be amended to reflect the non-use of biohazardous agents if the Principal Investigator intends to stay at Stanford.

Disposal of Used Lab Equipment

Used laboratory equipment, such as incubators, refrigerators and freezers must be thoroughly decontaminated prior to disposal or release to surplus property. Laboratory equipment that was used in conjunction with biological research may have residual contamination resulting from chemicals and/or radioactive materials.

A. wear appropriate personal protective equipment. At a minimum wear gloves, lab coat, safety glasses with side shields or goggles and a face mask if chemical fumes are anticipated

B. remove all specimens and/or laboratory materials

C. remove all labels or stickers from the front of the equipment

D. clean the surface of the equipment for any radioactive contamination (if applicable). Schedule a wipe test with Health Physics to ensure that the equipment is free from residual radioactive contamination. Call Health Physics, 723.3201 for more information.

E. be sure that the equipment surface can be safely cleaned with a chemical disinfectant. Make sure that the equipment was not used to store water reactive chemicals, corrosives or strong oxidizers that may incompatibly react during the decontamination process.

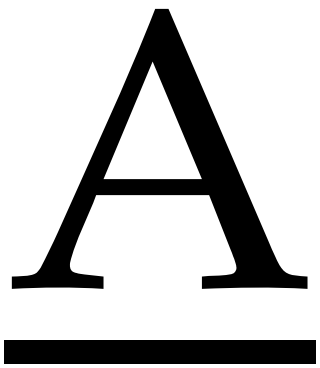
F. apply a chemical disinfectant to the surface of the equipment and allow the disinfectant time to inactivate potential contamination

G. insure that the surface is rinsed to remove the disinfectant

H. put the cleaning waste (paper towel, sponge) in a red bag and treat as biohazardous waste

Do not open internal compartments of equipment for decontamination. If the internal compartments of a piece of equipment are grossly contaminated with biohazardous material, label or tag the equipment as potentially biohazardous. Notify the Biosafety Manager and a decision will be made whether the equipment is safe for disposal.

When the equipment is ready for pick up, prepare a certificate with your department's letterhead addressed to the Director of Surplus Property, Material Management stating that you have decontaminated the equipment designated for removal in accordance with these guidelines (Section IV of the Stanford University Biosafety Manual). You need not send a copy to the Biosafety Manager or EH&S. Please call the Biosafety Manager at 5.1473 if you have any questions.



NOTICE PERTINENT TO THE APRIL 2002 REVISIONS OF THE *NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (NIH GUIDELINES)*

ROLES AND RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR (PI)

Under the amendment to Section IV-B-7, which was published in the *Federal Register* on November 19, 2001 (66 FR 57970, *specifically*: 57975) and became effective on December 19, 2001, a PI may delegate the reporting responsibilities set forth in Appendix M-I-C, *Reporting Requirements*, to another party, with written notification of the delegation to OBA.

A letter from each PI indicating to whom they have delegated the reporting requirements set forth in Appendix M-I-C must be on file with OBA.

This delegation of reporting responsibility may, if appropriate, be extended to include the material submitted under Appendix M-I-A, *Requirements for Protocol Submission*, of the *NIH Guidelines*. To that end, a letter from the PI should be submitted to OBA, either directly by the investigator or as part of the material submitted under Appendix M-I-A.

Summary of Amendments [Major Actions]

Page 10	Section I-E: Additions to General Definitions. New sections -- I-E-8, I-E-9, I-E-10
Page 36	Appendix B-I [Lines 5-8]: New – General definition of an *E. coli* strain as a RG1 agent
Page 97-98	Appendix M-I-C-3: Annual Reports. New – (Harmonized submission requirements)
Page 98	Appendix M-I-C-4: Safety Reporting. New appendix – (Harmonized reporting requirements)
Page 99	Appendix M-I-C-5: Confidentiality. New appendix
Page 99	Appendix M-I-D: Safety Assessment. New appendix
Page 106	Appendix M-IV: Privacy; deleted "…and Confidentiality" from heading; clarification of protection measures.

Effective June 24, 1994, Published in Federal Register, July 5, 1994 (59 FR 34496)
Amendment Effective July 28, 1994, Federal Register, August 5, 1994 (59 FR 40170)
Amendment Effective April 17, 1995, Federal Register, April 27, 1995 (60 FR 20726)
Amendment Effective December 14, 1995, Federal Register, January 19, 1996 (61 FR 1482)
Amendment Effective March 1, 1996, Federal Register, March 12, 1996 (61 FR 10004)
Amendment Effective January 23, 1997, Federal Register, January 31, 1997 (62 FR 4782)
Amendment Effective September 30, 1997, Federal Register, October 14, 1997 (62 FR 53335)
Amendment Effective October 20, 1997, Federal Register, October 29, 1997 (62 FR 56196)
Amendment Effective October 22, 1997, Federal Register, October 31, 1997 (62 FR 59032)
Amendment Effective February 4, 1998, Federal Register, February 17, 1998 (63 FR 8052)
Amendment Effective April 30, 1998, Federal Register, May 11, 1998 (63 FR 26018)
Amendment Effective April 29, 1999, Federal Register, May 11, 1999 (64 FR 25361)
Amendment Effective October 2, 2000, Federal Register, October 10, 2000 (65 FR 60328)
Amendment Effective December 28, 2000 Federal Register, January 5, 2001 (66 FR 1146)

Amendment Effective December 11, 2001 Federal Register, December 11, 2001 (66 FR 64051)
Amendment Effective December 19, 2001 Federal Register, November 19, 2001 (66 FR 57970)
Amendment Effective January 10, 2002 Federal Register, December 11, 2001 (66 FR 64052)
Amendment Effective January 24, 2002 Federal Register, November 19, 2001 (66 FR 57970)

NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (NIH GUIDELINES)

April 2002

VISIT THE OBA WEB SITE AT:
http://www4.od.nih.gov/oba
FOR CURRENT INFORMATION ON GUIDELINES, PROTOCOLS, PRINCIPAL INVESTIGATORS, MEETINGS, AND INFORMATION ABOUT UPCOMING GENE THERAPY POLICY CONFERENCES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (NIH GUIDELINES)

These *NIH Guidelines* supersede all earlier versions and shall be in effect until further notice.

TABLE OF CONTENTS

LIST OF TABLES

SECTION I. SCOPE OF THE *NIH GUIDELINES*

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 NIH, must be submitted to 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 NIH (whether the experiment is referred to that agency by 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 regarding requirement for human gene transfer protocol registration.)

Section I-A-1-a.
For experiments involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I-E-7) until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*);
Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained; Institutional Review Board approval has been obtained; and all applicable regulatory authorization(s) have been obtained.

For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I-E-7) at the clinical trial site until the following documentation has been submitted to NIH OBA: (1) IBC approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; and (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

Section I-B. Definition of Recombinant DNA Molecules

In the context of the *NIH Guidelines*, recombinant DNA molecules are defined as either: (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above.

Synthetic DNA segments which are likely to yield a potentially harmful polynucleotide or polypeptide (e.g., a toxin or a pharmacologically active agent) are considered as equivalent to their natural DNA counterpart. If the synthetic DNA segment is not expressed *in vivo* as a biologically active polynucleotide or polypeptide product, it is exempt from the *NIH Guidelines*.

Genomic DNA of plants and bacteria that have acquired a transposable element, even if the latter was donated from a recombinant vector no longer present, are not subject to the *NIH Guidelines* unless the transposon itself contains recombinant DNA.

Section I-C. General Applicability

Section I-C-1. The *NIH Guidelines* are applicable to:

Section I-C-1-a.

All recombinant DNA research within the United States (U.S.) or its territories that is within the category of research described in either Section I-C-1-a-(1) or Section I-C-1-a-(2).

Section I-C-1-a-(1).
Research that is conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH, including research performed directly by NIH. An individual who receives support for research involving recombinant DNA must be associated with or sponsored by an institution that assumes the responsibilities assigned in the *NIH Guidelines*.

Section I-C-1-a-(2).
Research that involves testing in humans of materials containing recombinant DNA developed with NIH funds, if the institution that developed those materials sponsors or participates in those projects. Participation includes research collaboration or contractual agreements, not mere provision of research materials.

Section I-C-1-b.
All recombinant DNA research performed abroad that is within the category of research described in either Section I-C-1-b-(1) or Section I-C-1-b-(2).

Section I-C-1-b-(1). Research supported by NIH funds.

Section I-C-1-b-(2).
Research that involves testing in humans of materials containing recombinant DNA developed with NIH funds, if the institution that developed those materials sponsors or participates in those projects. Participation includes research collaboration or contractual agreements, not mere provision of research materials.

Section I-C-1-b-(3).
If the host country has established rules for the conduct of recombinant DNA research, then the research must be in compliance with those rules.
If the host country does not have such rules, the proposed research must be reviewed and approved by an NIH-approved Institutional Biosafety Committee or equivalent review body and accepted in writing by an appropriate national governmental authority of the host country.
The safety practices that are employed abroad must be reasonably consistent with the *NIH Guidelines*.

Section I-D. Compliance with the *NIH Guidelines*

As a condition for NIH funding of recombinant DNA research, institutions shall ensure that such research conducted at or sponsored by the institution, irrespective of the source of funding, shall comply with the *NIH Guidelines*.

Information concerning noncompliance with the *NIH Guidelines* may be brought forward by any person. It should be delivered to both NIH/OBA and the relevant institution. The institution, generally through the Institutional Biosafety Committee, shall take appropriate action.
The institution shall forward a complete report of the incident recommending any further action to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985, 301-496-9838/301-496-9839 (fax) (for non-USPS mail, use zip code 20817).

In cases where NIH proposes to suspend, limit, or terminate financial assistance because of noncompliance with the *NIH Guidelines*, applicable DHHS and Public Health Service procedures shall govern.

The policies on compliance are as follows:

Section I-D-1. All NIH-funded projects involving recombinant DNA techniques must comply with the *NIH Guidelines*. Non-compliance may result in:
(i) suspension, limitation, or termination of financial assistance for the noncompliant NIH-funded research project and of NIH funds for other recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.

Section I-D-2.
All non-NIH funded projects involving recombinant DNA techniques conducted at or sponsored by an institution that receives NIH funds for projects involving such techniques must comply with the *NIH Guidelines*. Noncompliance may result in: (i) suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.

Section I-E. General Definitions
The following terms, which are used throughout the *NIH Guidelines*, are defined as follows:

Section I-E-1. An "institution" is any public or private entity (including Federal, state, and local government agencies).

Section I-E-2. An "Institutional Biosafety Committee" is a committee that: (i) meets the requirements for membership specified in Section IV-B-2, *Institutional Biosafety Committee (IBC)*, and (ii) reviews, approves, and oversees projects in accordance with the responsibilities defined in Section IV-B-2, *Institutional Biosafety Committee (IBC)*.

Section I-E-3. The "Office of Biotechnology Activities (OBA)" is the office within the NIH that is responsible for: (i) reviewing and coordinating all activities relating to the *NIH Guidelines*, and (ii) performing other duties as defined in Section IV-C-3, *Office of Biotechnology Activities (OBA)*.

Section I-E-4.
The "Recombinant DNA Advisory Committee" is the public advisory committee that advises the Department of Health and Human Services (DHHS) Secretary, the DHHS Assistant Secretary for Health, and the NIH Director concerning recombinant DNA research. The RAC shall be constituted as specified in Section IV-C-2, *Recombinant DNA Advisory Committee (RAC)*.

Section I-E-5.
The "NIH Director" is the Director of the National Institutes of Health, or any other officer or employee of NIH to whom authority has been delegated.

Section I-E-6.
"Deliberate release" is defined as a planned introduction of recombinant DNA-containing microorganisms, plants, or animals into the environment.

Section I-E-7.
“Enrollment” is the process of obtaining informed consent from a potential research participant, or a designated legal guardian of the participant, to undergo a test or procedure associated with the gene transfer experiment.

Section I-E-8.
A “serious adverse event” is any event occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, upon the basis of appropriate medical judgment, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Section I-E-9.
An adverse event is “associated with the use of a gene transfer product” when there is a reasonable possibility that the event may have been caused by the use of that product.

Section I-E-10.
An “unexpected serious adverse event” is any serious adverse event for which the specificity or severity is not consistent with the risk information available in the current investigator’s brochure.

SECTION II. SAFETY CONSIDERATIONS

Section II-A. Risk Assessment

Section II-A-1. Risk Groups

Risk assessment is ultimately a subjective process. The investigator must make an initial risk assessment based on the Risk Group (RG) of an agent (see Appendix B, *Classification of Human Etiologic Agents on the Basis of Hazard*). Agents are classified into four Risk Groups (RGs) according to their relative pathogenicity for healthy adult humans by the following criteria: (1) Risk Group 1 (RG1) agents are not associated with disease in healthy adult humans. (2) Risk

Group 2 (RG2) agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available.
(3) Risk Group 3 (RG3) agents are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available.
(4) Risk Group 4 (RG4) agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available.

Section II-A-2. Criteria for Risk Groups

Classification of agents in Appendix B, *Classification of Human Etiologic Agents on the Basis of Hazard*, is based on the potential effect of a biological agent on a healthy human adult and does not account for instances in which an individual may have increased susceptibility to such agents, e.g., preexisting diseases, medications, compromised immunity, pregnancy or breast feeding (which may increase exposure of infants to some agents).

Personnel may need periodic medical surveillance to ascertain fitness to perform certain activities; they may also need to be offered prophylactic vaccines and boosters (see Section IV-B-1-f, *Responsibilities of the Institution, General Information*).

Section II-A-3. Comprehensive Risk Assessment

In deciding on the appropriate containment for an experiment, the initial risk assessment from Appendix B, *Classification of Human Etiologic Agents on the Basis of Hazard*, should be followed by a thorough consideration of the agent itself and how it is to be manipulated. Factors to be considered in determining the level of containment include agent factors such as:
virulence, pathogenicity, infectious dose, environmental stability, route of spread, communicability, operations, quantity, availability of vaccine or treatment, and gene product effects such as toxicity, physiological activity, and allergenicity.
Any strain that is known to be more hazardous than the parent (wild-type) strain should be considered for handling at a higher containment level.
Certain attenuated strains or strains that have been demonstrated to have irreversibly lost known virulence factors may qualify for a reduction of the containment level compared to the Risk Group assigned to the parent strain (see Section V-B, *Footnotes and References of Sections I-IV*).

A final assessment of risk based on these considerations is then used to set the appropriate containment conditions for the experiment (see Section II-B, *Containment*).
The containment level required may be equivalent to the Risk Group classification of the agent or it may be raised or lowered as a result of the above considerations.
The Institutional Biosafety Committee must approve the risk assessment and the biosafety containment level for recombinant DNA experiments described in Sections III-A, *Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation*; III-B, *Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval Before Initiation*; III-C, *Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and NIH/OBA Registration Before Initiation*; III-D, *Experiments that Require Institutional Biosafety Committee Approval Before Initiation*.

Careful consideration should be given to the types of manipulation planned for some higher Risk Group agents. For example, the RG2 dengue viruses may be cultured under the Biosafety Level (BL) 2 containment (see Section II-B); however, when such agents are used for animal inoculation or transmission studies, a higher containment level is recommended.
Similarly, RG3 agents such as Venezuelan equine encephalomyelitis and yellow fever viruses should be handled at a higher containment level for animal inoculation and transmission experiments.

Individuals working with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or other bloodborne pathogens should consult the applicable Occupational Safety and Health Administration (OSHA) regulation, 29 CFR 1910.1030, and OSHA publication 3127 (1996 revised).
BL2 containment is recommended for activities involving all blood-contaminated clinical specimens, body fluids, and tissues from all humans, or from HIV- or HBV-infected or inoculated laboratory animals. Activities such as the production of research-laboratory scale quantities of HIV or other bloodborne pathogens, manipulating concentrated virus preparations, or conducting procedures that may produce droplets or aerosols, are performed in a BL2 facility using the additional practices and containment equipment recommended for BL3. Activities involving industrial scale volumes or preparations of concentrated HIV are conducted in a BL3 facility, or BL3 Large Scale if appropriate, using BL3 practices and containment equipment.

Exotic plant pathogens and animal pathogens of domestic livestock and poultry are restricted and may require special

laboratory design, operation and containment features not addressed in *Biosafety in Microbiological and Biomedical Laboratories* (see Section V-C, *Footnotes and References of Sections I through IV*). For information regarding the importation, possession, or use of these agents see Sections V-G and V-H, *Footnotes and References of Sections I through IV*.

Section II-B. Containment

Effective biological safety programs have been operative in a variety of laboratories for many years. Considerable information already exists about the design of physical containment facilities and selection of laboratory procedures applicable to organisms carrying recombinant DNA (see Section V-B, *Footnotes and References of Sections I-IV*). The existing programs rely upon mechanisms that can be divided into two categories: (i) a set of standard practices that are generally used in microbiological laboratories; and (ii) special procedures, equipment, and laboratory installations that provide physical barriers that are applied in varying degrees according to the estimated biohazard. Four biosafety levels are described in Appendix G, *Physical Containment*. These biosafety levels consist of combinations of laboratory practices and techniques, safety equipment, and laboratory facilities appropriate for the operations performed and are based on the potential hazards imposed by the agents used and for the laboratory function and activity. Biosafety Level 4 provides the most stringent containment conditions, Biosafety Level 1 the least stringent.

Experiments involving recombinant DNA lend themselves to a third containment mechanism, namely, the application of highly specific biological barriers. Natural barriers exist that limit either: (i) the infectivity of a vector or vehicle (plasmid or virus) for specific hosts, or (ii) its dissemination and survival in the environment. Vectors, which provide the means for recombinant DNA and/or host cell replication, can be genetically designed to decrease, by many orders of magnitude, the probability of dissemination of recombinant DNA outside the laboratory (see Appendix I, *Biological Containment*).

Since these three means of containment are complementary, different levels of containment can be established that apply various combinations of the physical and biological barriers along with a constant use of standard practices. Categories of containment are considered separately in order that such combinations can be conveniently expressed in the *NIH Guidelines*.

Physical containment conditions within laboratories, described in Appendix G, *Physical Containment*, may not always be appropriate for all organisms because of their physical size, the number of organisms needed for an experiment, or the particular growth requirements of the organism. Likewise, biological containment for microorganisms described in Appendix I, *Biological Containment*, may not be appropriate for all organisms, particularly higher eukaryotic organisms. However, significant information exists about the design of research facilities and experimental procedures that are applicable to organisms containing recombinant DNA that is either integrated into the genome or into microorganisms associated with the higher organism as a symbiont, pathogen, or other relationship. This information describes facilities for physical containment of organisms used in non-traditional laboratory settings and special practices for limiting or excluding the unwanted establishment, transfer of genetic information, and dissemination of organisms beyond the intended location, based on both physical and biological containment principles. Research conducted in accordance with these conditions effectively confines the organism.

For research involving plants, four biosafety levels (BL1-P through BL4-P) are described in Appendix P, *Physical and Biological Containment for Recombinant DNA Research Involving Plants*. BL1-P is designed to provide a moderate level of containment for experiments for which there is convincing biological evidence that precludes the possibility of survival, transfer, or dissemination of recombinant DNA into the environment, or in which there is no recognizable and predictable risk to the environment in the event of accidental release. BL2-P is designed to provide a greater level of containment for experiments involving plants and certain associated organisms in which there is a recognized possibility of survival, transmission, or dissemination of recombinant DNA containing organisms, but the consequence of such an inadvertent release has a predictably minimal biological impact. BL3-P and BL4-P describe additional containment conditions for research with plants and certain pathogens and other organisms that require special containment because of their recognized potential for significant detrimental impact on managed or natural ecosystems.

BL1-P relies upon accepted scientific practices for conducting research in most ordinary greenhouse or growth chamber facilities and incorporates accepted procedures for good pest control and cultural practices. BL1-P facilities and procedures provide a modified and protected environment for the propagation of plants and microorganisms associated with the plants and a degree of containment that adequately controls the potential for release of biologically viable plants, plant parts, and microorganisms associated with them. BL2-P and BL3-P rely upon accepted scientific practices for conducting research in greenhouses with organisms infecting or infesting plants in a manner that minimizes or prevents inadvertent contamination of plants within or surrounding the greenhouse. BL4-P describes facilities and practices known to provide containment of certain exotic plant pathogens.

For research involving animals, which are of a size or have growth requirements that preclude the use of conventional primary containment systems used for small laboratory animals, four biosafety levels (BL1-N through BL4-N) are described in Appendix Q, *Physical and Biological Containment for Recombinant DNA Research Involving Animals*. BL1-N describes containment for animals that have been modified by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic animals) and experiments involving viable recombinant DNA-modified microorganisms and is designed to eliminate the possibility of sexual transmission of the modified genome or transmission of recombinant DNA-derived viruses known to be transmitted from animal parent to offspring only by sexual reproduction.
Procedures, practices, and facilities follow classical methods of avoiding genetic exchange between animals. BL2-N describes containment which is used for transgenic animals associated with recombinant DNA-derived organisms and is designed to eliminate the possibility of vertical or horizontal transmission. Procedures, practices, and facilities follow classical methods of avoiding genetic exchange between animals or controlling arthropod transmission. BL3-N and BL4-N describe higher levels of containment for research with certain transgenic animals involving agents which pose recognized hazard.

In constructing the *NIH Guidelines*, it was necessary to define boundary conditions for the different levels of physical and biological containment and for the classes of experiments to which they apply. These definitions do not take into account all existing and anticipated information on special procedures that will allow particular experiments to be conducted under different conditions than indicated here without affecting risk. Individual investigators and Institutional Biosafety Committees are urged to devise simple and more effective containment procedures and to submit recommended changes in the *NIH Guidelines* to permit the use of these procedures.

SECTION III. EXPERIMENTS COVERED BY THE *NIH GUIDELINES*

This section describes six categories of experiments involving recombinant DNA: (i) those that require Institutional Biosafety Committee (IBC) approval, RAC review, and NIH Director approval before initiation (see Section III-A), (ii) those that require NIH/OBA and Institutional Biosafety Committee approval before initiation (see Section III-B), (iii) those that require Institutional Biosafety Committee and Institutional Review Board approvals and RAC review before research participant enrollment (see Section III-C), (iv) those that require Institutional Biosafety Committee approval before initiation (see Section III-D), (v) those that require Institutional Biosafety Committee notification simultaneous with initiation (see Section III-E), and (vi) those that are exempt from the *NIH Guidelines* (see Section III-F).

Note:
If an experiment falls into Sections III-A, III-B, or III-C and one of the other sections, the rules pertaining to Sections III-A, III-B, or III-C shall be followed.
If an experiment falls into Section III-F and into either Sections III-D or III-E 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/OBA (see Section IV-C-1-b-(2) and its subsections, *Minor Actions*).

Section III-A.
Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation

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 Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax), the publication of the proposal in the *Federal Register* for 15 days of comment, review by RAC, and specific approval by NIH.
The containment conditions or stipulation requirements for such experiments will be recommended by RAC and set by NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D, *Major Actions Taken under the NIH Guidelines*, which may be obtained from the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

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, *Footnotes and References of Sections I-IV*), if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by RAC.

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

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

Section III-B-1. Experiments Involving the Cloning of Toxin Molecules with LD_{50} of Less than 100 Nanograms per Kilogram Body Weight

Deliberate formation of recombinant DNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD_{50}
of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, and *Shigella dysenteriae* neurotoxin). Specific approval has been given for the cloning in *Escherichia coli*
K-12 of DNA containing genes coding for the biosynthesis of toxic molecules which are lethal to vertebrates at 100 nanograms to 100 micrograms per kilogram body weight. Specific experiments already approved under this section may be obtained from the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

Section III-C.
Experiments that Require Institutional Biosafety Committee and Institutional Review Board Approvals and RAC Review Before Research Participant Enrollment

Section III-C-1.
Experiments Involving the Deliberate Transfer of Recombinant DNA, or DNA or RNA Derived from Recombinant DNA, into One or More Human Research Participants

For an experiment involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human research participants (human gene transfer), no research participant shall be enrolled (see definition of enrollment in Section I-E-7) until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*).

In its evaluation of human gene transfer proposals, the RAC will consider whether a proposed human gene transfer experiment presents characteristics that warrant public RAC review and discussion (See Appendix M-I-B-2). The process of public RAC review and discussion is intended to foster the safe and ethical conduct of human gene transfer experiments.
Public review and discussion of a human gene transfer experiment (and access to relevant information) also serves to inform the public about the technical aspects of the proposal, meaning and significance of the research, and any significant safety, social, and ethical implications of the research.

Public RAC review and discussion of a human gene transfer experiment may be: (1) initiated by the NIH Director; or (2) initiated by the NIH OBA Director following a recommendation to NIH OBA by: (a) three or more RAC members; or (b) a Federal agency other than NIH.
After a human gene transfer experiment is reviewed by the RAC at a regularly scheduled meeting, NIH OBA will send a letter, unless NIH OBA determines that there are exceptional circumstances, within 10 working days to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate, summarizing the RAC recommendations.

For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I-E-7) at the clinical trial site until the following documentation has been submitted to NIH OBA:
(1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

In order to maintain public access to information regarding human gene transfer protocols (including protocols that are not publicly reviewed by the RAC), NIH OBA will maintain the documentation described in Appendices M-I through M-V. The information provided in response to Appendix M should not contain any confidential commercial information or trade secrets, enabling all aspects of RAC review to be open to the public.

Note: For specific directives concerning the use of retroviral vectors for gene delivery, consult Appendix B-V-1, *Murine Retroviral Vectors.*

Section III-D.
Experiments that Require Institutional Biosafety Committee Approval Before Initiation

Prior to the initiation of an experiment that falls into this category, the Principal Investigator must submit a registration document to the Institutional Biosafety Committee which contains the following information: (i) the source(s) of DNA; (ii) the nature of the inserted DNA sequences; (iii) the host(s) and vector(s) to be used; (iv) if an attempt will be made to obtain expression of a foreign gene, and if so, indicate the protein that will be produced; and (v) the containment conditions that will be implemented as specified in the *NIH Guidelines*. For experiments in this category, the registration document shall be dated, signed by the Principal Investigator, and filed with the Institutional Biosafety Committee.
The Institutional Biosafety Committee shall review and approve all experiments in this category prior to their initiation. Requests to decrease the level of containment specified for experiments in this category will be considered by NIH (see Section IV-C-1-b-(2)-(c), *Minor Actions*).

Section III-D-1.
Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems
(See Section II-A, Risk Assessment)

Section III-D-1-a.
Experiments involving the introduction of recombinant DNA into Risk Group 2 agents will usually be conducted at Biosafety Level (BL) 2 containment.
Experiments with such agents will usually be conducted with whole animals at BL2 or BL2-N (Animals) containment.

Section III-D-1-b.
Experiments involving the introduction of recombinant DNA into Risk Group 3 agents will usually be conducted at BL3 containment.
Experiments with such agents will usually be conducted with whole animals at BL3 or BL3-N containment.

Section III-D-1-c.
Experiments involving the introduction of recombinant DNA into Risk Group 4 agents shall be conducted at BL4 containment. Experiments with such agents shall be conducted with whole animals at BL4 or BL4-N containment.

Section III-D-1-d.
Containment conditions for experiments involving the introduction of recombinant DNA into restricted agents shall be set on a case-by-case basis following NIH/OBA review. A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V-G and V-M, *Footnotes and References of Sections I-IV*). Experiments with such agents shall be conducted with whole animals at BL4 or BL4-N containment.

Section III-D-2.
Experiments in Which DNA From Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems

Section III-D-2-a. Experiments in which DNA from Risk Group 2 or Risk Group 3 agents (see Section II-A, *Risk Assessment)*
is transferred into nonpathogenic prokaryotes or lower eukaryotes may be performed under BL2 containment.
Experiments in which DNA from Risk Group 4 agents is transferred into nonpathogenic prokaryotes or lower eukaryotes may be performed under BL2 containment after demonstration that only a totally and irreversibly defective fraction of the agent's genome is present in a given recombinant. In the absence of such a demonstration, BL4 containment shall be used.
The Institutional Biosafety Committee may approve the specific lowering of containment for particular experiments to BL1. Many experiments in this category are exempt from the *NIH Guidelines* (see Section III-F, *Exempt Experiments*).
Experiments involving the formation of recombinant DNA for certain genes coding for molecules toxic for vertebrates require NIH/OBA approval (see Section III-B-1, *Experiments Involving the Cloning of Toxin Molecules with LD_{50} of Less than 100 Nanograms Per Kilogram Body Weight*) or shall be conducted under NIH specified conditions as

described in Appendix F, *Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates*.

Section III-D-2-b.
Containment conditions for experiments in which DNA from restricted agents is transferred into nonpathogenic prokaryotes or lower eukaryotes shall be determined by NIH/OBA following a case-by-case review (see Section V-L, *Footnotes and References of Sections I-IV*).
A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V-G, *Footnotes and References of Sections I-IV*).

Section III-D-3.
Experiments Involving the Use of Infectious DNA or RNA Viruses or Defective DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems

Caution:
Special care should be used in the evaluation of containment levels for experiments which are likely to either enhance the pathogenicity (e.g., insertion of a host oncogene) or to extend the host range (e.g., introduction of novel control elements) of viral vectors under conditions that permit a productive infection. In such cases, serious consideration should be given to increasing physical containment by at least one level.

Note:
Recombinant DNA or RNA molecules derived therefrom, which contain less than two-thirds of the genome of any eukaryotic virus (all viruses from a single Family (see Section V-J, *Footnotes and References of Sections I-IV*) being considered identical (see Section V-K, *Footnotes and References of Sections I-IV*), are considered defective and may be used in the absence of helper under the conditions specified in Section III-E-1, *Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus*.

Section III-D-3-a. Experiments involving the use of infectious or defective Risk Group 2 viruses (see Appendix B-II, *Risk Group 2 Agents*) in the presence of helper virus may be conducted at BL2.

Section III-D-3-b. Experiments involving the use of infectious or defective Risk Group 3 viruses (see Appendix B-III-D, *Risk Group 3 (RG3) - Viruses and Prions*) in the presence of helper virus may be conducted at BL3.

Section III-D-3-c. Experiments involving the use of infectious or defective Risk Group 4 viruses (see Appendix B-IV-D, *Risk Group 4 (RG4) - Viral Agents*) in the presence of helper virus may be conducted at BL4.

Section III-D-3-d. Experiments involving the use of infectious or defective restricted poxviruses (see Sections V-A and V-L, *Footnotes and References of Sections I-IV*) in the presence of helper virus shall be determined on a case-by-case basis following NIH/OBA review.
A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V-G, *Footnotes and References of Sections I-IV*).

Section III-D-3-e.
Experiments involving the use of infectious or defective viruses in the presence of helper virus which are not covered in Sections III-D-3-a through III-D-3-d may be conducted at BL1.

Section III-D-4. Experiments Involving Whole Animals

This section covers experiments involving whole animals in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic animals) and experiments involving viable recombinant DNA-modified microorganisms tested on whole animals. For the latter, other than viruses which are only vertically transmitted, the experiments may *not* be conducted at BL1-N containment. A minimum containment of BL2 or BL2-N is required.

Caution
- Special care should be used in the evaluation of containment conditions for some experiments with transgenic animals.
For example, such experiments might lead to the creation of novel mechanisms or increased transmission of a recombinant pathogen or production of undesirable traits in the host animal. In such cases, serious consideration should be given to increasing the containment conditions.

Section III-D-4-a.

Recombinant DNA, or DNA or RNA molecules derived therefrom, from any source except for greater than two-thirds of eukaryotic viral genome may be transferred to any non-human vertebrate or any invertebrate organism and propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study (see Section V-B, *Footnotes and References of Sections I-IV*). Animals that contain sequences from viral vectors, which do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, may be propagated under conditions of physical containment comparable to BL1 or BL1-N and appropriate to the organism under study.
Experiments involving the introduction of other sequences from eukaryotic viral genomes into animals are covered under Section III-D-4-b, *Experiments Involving Whole Animals*. For experiments involving recombinant DNA-modified Risk Groups 2, 3, 4, or restricted organisms, see Sections V-A, V-G, and V-L, *Footnotes and References of Sections I-IV*. It is important that the investigator demonstrate that the fraction of the viral genome being utilized does not lead to productive infection. A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V-G, *Footnotes and References of Sections I-IV*).

Section III-D-4-b.
For experiments involving recombinant DNA, or DNA or RNA derived therefrom, involving whole animals, including transgenic animals, and not covered by Sections III-D-1, *Experiments Using Human or Animal Pathogens (Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems*, or III-D-4-a, *Experiments Involving Whole Animals*, the appropriate containment shall be determined by the Institutional Biosafety Committee.

Section III-D-4-c. Exceptions under Section III-D-4, *Experiments Involving Whole Animals*

Section III-D-4-c-(1).
Experiments involving the generation of transgenic rodents that require BL1 containment are described under Section III-E-3, *Experiments Involving Transgenic Rodents*.

Section III-D-4-c-(2). The purchase or transfer of transgenic rodents is exempt from the *NIH Guidelines* under Section III-F, *Exempt Experiments* (see Appendix C-VI, *The Purchase or Transfer of Transgenic Rodents*).

Section III-D-5. Experiments Involving Whole Plants

Experiments to genetically engineer plants by recombinant DNA methods, to use such plants for other experimental purposes (e.g., response to stress), to propagate such plants, or to use plants together with microorganisms or insects containing recombinant DNA, may be conducted under the containment conditions described in Sections III-D-5-a through III-D-5-e. If experiments involving whole plants are not described in Section III-D-5 and do not fall under Sections III-A, III-B, III-D or III-F, they are included in Section III-E.

NOTE - For recombinant DNA experiments falling under Sections III-D-5-a through III-D-5-d, physical containment requirements may be reduced to the next lower level by appropriate biological containment practices, such as conducting experiments on a virus with an obligate insect vector in the absence of that vector or using a genetically attenuated strain.

Section III-D-5-a.
BL3-P (Plants) or BL2-P + biological containment is recommended for experiments involving most exotic (see Section V-M, *Footnotes and References of Sections I-IV*) infectious agents with recognized potential for serious detrimental impact on managed or natural ecosystems when recombinant DNA techniques are associated with whole plants.

Section III-D-5-b.
BL3-P or BL2-P + biological containment is recommended for experiments involving plants containing cloned genomes of readily transmissible exotic (see Section V-M, *Footnotes and References of Sections I-IV*) infectious agents with recognized potential for serious detrimental effects on managed or natural ecosystems in which there exists the possibility of reconstituting the complete and functional genome of the infectious agent by genomic complementation *in planta.*

Section III-D-5-c.
BL4-P containment is recommended for experiments with a small number of readily transmissible exotic (see Section V-M, *Footnotes and References of Sections I-IV*) infectious agents, such as the soybean rust fungus (*Phakospora pachyrhizi*) and maize streak or other viruses in the presence of their specific arthropod vectors, that have the potential of being serious pathogens of major U.S. crops.

Section III-D-5-d.
BL3-P containment is recommended for experiments involving sequences encoding potent vertebrate toxins introduced

into plants or associated organisms.
Recombinant DNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD_{50} of <100 nanograms per kilogram body weight fall under Section III-B-1, *Experiments Involving the Cloning of Toxin Molecules with LD_{50} of Less than 100 Nanograms Per Kilogram Body Weight*, and require NIH/OBA and Institutional Biosafety Committee approval before initiation.

Section III-D-5-e.
BL3-P or BL2-P + biological containment is recommended for experiments with microbial pathogens of insects or small animals associated with plants if the recombinant DNA-modified organism has a recognized potential for serious detrimental impact on managed or natural ecosystems.

Section III-D-6. Experiments Involving More than 10 Liters of Culture

The appropriate containment will be decided by the Institutional Biosafety Committee. Where appropriate, Appendix K, *Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules*, shall be used. Appendix K describes containment conditions Good Large Scale Practice through BL3-Large Scale.

Section III-E.
Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation

Experiments not included in Sections III-A, III-B, III-C, III-D, III-F, and their subsections are considered in Section III-E. All such experiments may be conducted at BL1 containment. For experiments in this category, a registration document (see Section III-D, *Experiments that Require Institutional Biosafety Committee Approval Before Initiation*) shall be dated and signed by the investigator and filed with the local Institutional Biosafety Committee at the time the experiment is initiated.
The Institutional Biosafety Committee reviews and approves all such proposals, but Institutional Biosafety Committee review and approval prior to initiation of the experiment is not required (see Section IV-A, *Policy*). For example, experiments in which all components derived from non-pathogenic prokaryotes and non-pathogenic lower eukaryotes fall under Section III-E and may be conducted at BL1 containment.

Section III-E-1.
Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus

Recombinant DNA molecules containing no more than two-thirds of the genome of any eukaryotic virus (all viruses from a single Family being considered identical [see Section V-J, *Footnotes and References of Sections I-IV*]) may be propagated and maintained in cells in tissue culture using BL1 containment. For such experiments, it must be demonstrated that the cells lack helper virus for the specific Families of defective viruses being used. If helper virus is present, procedures specified under Section III-D-3, *Experiments Involving the Use of Infectious Animal or Plant DNA or RNA Viruses or Defective Animal or Plant DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems*, should be used.
The DNA may contain fragments of the genome of viruses from more than one Family but each fragment shall be less than two-thirds of a genome.

Section III-E-2. Experiments Involving Whole Plants

This section covers experiments involving recombinant DNA-modified whole plants, and/or experiments involving recombinant DNA-modified organisms associated with whole plants, except those that fall under Section III-A, III-B, III-D, or III-F.
It should be emphasized that knowledge of the organisms and judgment based on accepted scientific practices should be used in all cases in selecting the appropriate level of containment. For example, if the genetic modification has the objective of increasing pathogenicity or converting a non-pathogenic organism into a pathogen, then a higher level of containment may be appropriate depending on the organism, its mode of dissemination, and its target organisms. By contrast, a lower level of containment may be appropriate for small animals associated with many types of recombinant DNA-modified plants.

Section III-E-2-a.
BL1-P is recommended for all experiments with recombinant DNA-containing plants and plant-associated microorganisms not covered in Section III-E-2-b or other sections of the *NIH Guidelines*. Examples of such experiments are those involving recombinant DNA-modified plants that are not noxious weeds or that cannot interbreed with noxious weeds in the immediate geographic area, and experiments involving whole plants and recombinant DNA-modified non-exotic (see Section V-M, *Footnotes and References of Sections I-IV*) microorganisms that have no

recognized potential for rapid and widespread dissemination or for serious detrimental impact on managed or natural ecosystems (e.g., *Rhizobium* spp. and *Agrobacterium* spp.).

Section III-E-2-b. BL2-P or BL1-P + biological containment is recommended for the following experiments:

Section III-E-2-b-(1).
Plants modified by recombinant DNA that are noxious weeds or can interbreed with noxious weeds in the immediate geographic area.

Section III-E-2-b-(2).
Plants in which the introduced DNA represents the complete genome of a non-exotic infectious agent (see Section V-M, *Footnotes and References of Sections I-IV*).

Section III-E-2-b-(3).
Plants associated with recombinant DNA-modified non-exotic microorganisms that have a recognized potential for serious detrimental impact on managed or natural ecosystems (see Section V-M, *Footnotes and References of Sections I-IV*).

Section III-E-2-b-(4).
Plants associated with recombinant DNA-modified exotic microorganisms that have no recognized potential for serious detrimental impact on managed or natural ecosystems (see Section V-M, *Footnotes and References of Sections I-IV*).

Section III-E-2-b-(5).
Experiments with recombinant DNA-modified arthropods or small animals associated with plants, or with arthropods or small animals with recombinant DNA-modified microorganisms associated with them if the recombinant DNA-modified microorganisms have no recognized potential for serious detrimental impact on managed or natural ecosystems (see Section V-M, *Footnotes and References of Sections I-IV*).

Section III-E-3. Experiments Involving Transgenic Rodents

This section covers experiments involving the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic rodents). Only experiments that require BL1 containment are covered under this section; experiments that require BL2, BL3, or BL4 containment are covered under Section III-D-4, *Experiments Involving Whole Animals*.

Section III-F. Exempt Experiments

The following recombinant DNA molecules are exempt from the *NIH Guidelines* and registration with the Institutional Biosafety Committee is not required:

Section III-F-1. Those that are not in organisms or viruses.

Section III-F-2.
Those that consist entirely of DNA segments from a single nonchromosomal or viral DNA source, though one or more of the segments may be a synthetic equivalent.

Section III-F-3.
Those that consist entirely of DNA from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means.

Section III-F-4.
Those that consist entirely of DNA from an eukaryotic host including its chloroplasts, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species).

Section III-F-5.
Those that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent. A list of such exchangers will be prepared and periodically revised by the NIH Director with advice of the RAC after appropriate notice and opportunity for public comment (see Section IV-C-1-b-(1)-(c), *Major Actions*). See Appendices A-I through A-VI, *Exemptions Under Section III-F-5--Sublists of Natural Exchangers*, for a list of natural exchangers that are exempt from the *NIH Guidelines*.

Section III-F-6. Those that do not present a significant risk to health or the environment (see Section IV-C-1-b-(1)-(c), *Major Actions*), as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment. See Appendix C, *Exemptions under Section III-F-6* for other classes of experiments which are exempt from the *NIH Guidelines*.

SECTION IV. ROLES AND RESPONSIBILITIES

Section IV-A. Policy

The safe conduct of experiments involving recombinant DNA depends on the individual conducting such activities. The *NIH Guidelines* cannot anticipate every possible situation. Motivation and good judgment are the key essentials to protection of health and the environment. The *NIH Guidelines* are intended to assist the institution, Institutional Biosafety Committee, Biological Safety Officer, and the Principal Investigator in determining safeguards that should be implemented. The *NIH Guidelines*
will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, *it is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines as well as to their specifics.* Each institution (and the Institutional Biosafety Committee acting on its behalf) is responsible for ensuring that all recombinant DNA research conducted at or sponsored by that institution is conducted in compliance with the *NIH Guidelines*.
General recognition of institutional authority and responsibility properly establishes accountability for safe conduct of the research at the local level.
The following roles and responsibilities constitute an administrative framework in which safety is an essential and integral part of research involving recombinant DNA molecules. Further clarifications and interpretations of roles and responsibilities will be issued by NIH as necessary.

Section IV-B. Responsibilities of the Institution

Section IV-B-1. General Information

Each institution conducting or sponsoring recombinant DNA research which is covered by the *NIH Guidelines* is responsible for ensuring that the research is conducted in full conformity with the provisions of the *NIH Guidelines*. In order to fulfill this responsibility, the institution shall:

Section IV-B-1-a.
Establish and implement policies that provide for the safe conduct of recombinant DNA research and that ensure compliance with the *NIH Guidelines*. As part of its general responsibilities for implementing the *NIH Guidelines*, the institution may establish additional procedures, as deemed necessary, to govern the institution and its components in the discharge of its responsibilities under the *NIH Guidelines*. Such procedures may include: (i) statements formulated by the institution for the general implementation of the *NIH Guidelines*, and (ii) any additional precautionary steps the institution deems appropriate.

Section IV-B-1-b.
Establish an Institutional Biosafety Committee that meets the requirements set forth in Section IV-B-2-a and carries out the functions detailed in Section IV-B-2-b.

Section IV-B-1-c.
Appoint a Biological Safety Officer (who is also a member of the Institutional Biosafety Committee) if the institution: (i) conducts recombinant DNA research at Biosafety Level (BL) 3 or BL4, or (ii) engages in large-scale (greater than 10 liters) research. The Biological Safety Officer carries out the duties specified in Section IV-B-3.

Section IV-B-1-d.
Appoint at least one individual with expertise in plant, plant pathogen, or plant pest containment principles (who is a member of the Institutional Biosafety Committee) if the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix P, *Physical and Biological Containment for Recombinant DNA Research Involving Plants*.

Section IV-B-1-e.

Appoint at least one individual with expertise in animal containment principles (who is a member of the Institutional Biosafety Committee) if the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix Q, *Physical and Biological Containment for Recombinant DNA Research Involving Animals*.

Section IV-B-1-f.
Ensure that when the institution participates in or sponsors recombinant DNA research involving human subjects: (i) the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary), (ii) all aspects of Appendix M
have been appropriately addressed by the Principal Investigator; and (iii) no research participant shall be enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*), Institutional Biosafety Committee approval has been obtained,

Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained.
Institutional Biosafety Committee approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant DNA material into target cells for human application).

Section IV-B-1-g. Assist and ensure compliance with the *NIH Guidelines* by Principal Investigators conducting research at the institution as specified in Section IV-B-7.

Section IV-B-1-h.
Ensure appropriate training for the Institutional Biosafety Committee Chair and members, Biological Safety Officer and other containment experts (when applicable), Principal Investigators, and laboratory staff regarding laboratory safety and implementation of the *NIH Guidelines*.
The Institutional Biosafety Committee Chair is responsible for ensuring that Institutional Biosafety Committee members are appropriately trained.
The Principal Investigator is responsible for ensuring that laboratory staff are appropriately trained. The institution is responsible for ensuring that the Principal Investigator has sufficient training; however, this responsibility may be delegated to the Institutional Biosafety Committee.

Section IV-B-1-i.
Determine the necessity for health surveillance of personnel involved in connection with individual recombinant DNA projects; and if appropriate, conduct a health surveillance program for such projects. The institution shall establish and maintain a health surveillance program for personnel engaged in large-scale research or production activities involving viable organisms containing recombinant DNA molecules which require BL3 containment at the laboratory scale. The institution shall establish and maintain a health surveillance program for personnel engaged in animal research involving viable recombinant DNA-containing microorganisms that require BL3 or greater containment in the laboratory. The *Laboratory Safety Monograph*
discusses various components of such a program (e.g., records of agents handled, active investigation of relevant illnesses, and the maintenance of serial serum samples for monitoring serologic changes that may result from the employees' work experience).
Certain medical conditions may place a laboratory worker at increased risk in any endeavor where infectious agents are handled. Examples cited in the *Laboratory Safety Monograph* include gastrointestinal disorders and treatment with steroids, immunosuppressive drugs, or antibiotics. Workers with such disorders or treatment should be evaluated to determine whether they should be engaged in research with potentially hazardous organisms during their treatment or illness. Copies of the *Laboratory Safety Monograph*
are available from the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

Section IV-B-1-j. Report any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses to NIH/OBA within thirty days, unless the institution determines that a report has already been filed by the Principal Investigator or Institutional Biosafety Committee. Reports shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

Section IV-B-2. Institutional Biosafety Committee (IBC)

The institution shall establish an Institutional Biosafety Committee whose responsibilities need not be restricted to

recombinant DNA. The Institutional Biosafety Committee shall meet the following requirements:

Section IV-B-2-a. Membership and Procedures

Section IV-B-2-a-(1).
The Institutional Biosafety Committee must be comprised of no fewer than five members so selected that they collectively have experience and expertise in recombinant DNA technology and the capability to assess the safety of recombinant DNA research and to identify any potential risk to public health or the environment. At least two members shall not be affiliated with the institution (apart from their membership on the Institutional Biosafety Committee) and who represent the interest of the surrounding community with respect to health and protection of the environment (e.g., officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical, occupational health, or environmental concerns in the community). The Institutional Biosafety Committee shall include at least one individual with expertise in plant, plant pathogen, or plant pest containment principles when experiments utilizing Appendix P, *Physical and Biological Containment for Recombinant DNA Research Involving Plants*, require prior approval by the Institutional Biosafety Committee. The Institutional Biosafety Committee shall include at least one scientist with expertise in animal containment principles when experiments utilizing Appendix Q, *Physical and Biological Containment for Recombinant DNA Research Involving Animals*, require Institutional Biosafety Committee prior approval. When the institution conducts recombinant DNA research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee (see Section IV-B-3, *Biological Safety Officer*). When the institution participates in or sponsors recombinant DNA research involving human research participants, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary); (ii) all aspects of Appendix M have been appropriately addressed by the Principal Investigator; (iii) no research participant shall be enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*); and (iv) final IBC approval is granted only after the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*).
Institutional Biosafety Committee approval must be obtained from the institution at which recombinant DNA material will be administered to human research participants (rather than the site involved in manufacturing gene transfer products).

Note: Individuals, corporations, and institutions not otherwise covered by the *NIH Guidelines*, are encouraged to adhere to the standards and procedures set forth in Sections I through IV (see Section IV-D, *Voluntary Compliance*. The policy and procedures for establishing an Institutional Biosafety Committee under *Voluntary Compliance*, are specified in Section IV-D-2, *Institutional Biosafety Committee Approval*).

Section IV-B-2-a-(2).
In order to ensure the competence necessary to review and approve recombinant DNA activities, it is recommended that the Institutional Biosafety Committee:
(i) include persons with expertise in recombinant DNA technology, biological safety, and physical containment; (ii) include or have available as consultants persons knowledgeable in institutional commitments and policies, applicable law, standards of professional conduct and practice, community attitudes, and the environment, and (iii) include at least one member representing the laboratory technical staff.

Section IV-B-2-a-(3). The institution shall file an annual report with NIH/OBA which includes: (i) a roster of all Institutional Biosafety Committee members clearly indicating the Chair, contact person, Biological Safety Officer (if applicable), plant expert (if applicable), animal expert (if applicable), human gene therapy expertise or *ad hoc* consultant(if applicable); and (ii) biographical sketches of all Institutional Biosafety Committee members (including community members).

Section IV-B-2-a-(4).
No member of an Institutional Biosafety Committee may be involved (except to provide information requested by the Institutional Biosafety Committee) in the review or approval of a project in which he/she has been or expects to be engaged or has a direct financial interest.

Section IV-B-2-a-(5). The institution, that is ultimately responsible for the effectiveness of the Institutional Biosafety Committee, may establish procedures that the Institutional Biosafety Committee shall follow in its initial and continuing review and approval of applications, proposals, and activities.

Section IV-B-2-a-(6).
When possible and consistent with protection of privacy and proprietary interests, the institution is encouraged to open its Institutional Biosafety Committee meetings to the public.

Section IV-B-2-a-(7).
Upon request, the institution shall make available to the public all Institutional Biosafety Committee meeting minutes and any documents submitted to or received from funding agencies which the latter are required to make available to the public.
If public comments are made on Institutional Biosafety Committee actions, the institution shall forward both the public comments and the Institutional Biosafety Committee's response to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

Section IV-B-2-b. Functions

On behalf of the institution, the Institutional Biosafety Committee is responsible for:

Section IV-B-2-b-(1).
Reviewing recombinant DNA research conducted at or sponsored by the institution for compliance with the *NIH Guidelines* as specified in Section III, *Experiments Covered by the NIH Guidelines*, and approving those research projects that are found to conform with the *NIH Guidelines*. This review shall include: (i) independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research; (ii) assessment of the facilities, procedures, practices, and training and expertise of personnel involved in recombinant DNA research; (iii) ensuring that all aspects of Appendix M
have been appropriately addressed by the Principal Investigator; (iv) ensuring that no research participant is enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*), Institutional Biosafety Committee approval (from the clinical trial site) has been obtained, Institutional Review Board approval has been obtained, and all applicable regulatory authorizations have been obtained; (v) for human gene transfer protocols selected for public RAC review and discussion, consideration of the issues raised and recommendations made as a result of this review and consideration of the Principal Investigator's response to the RAC recommendations; (vi) ensuring that final IBC approval is granted only after the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*); and (vii) ensuring compliance with all surveillance, data reporting, and adverse event reporting requirements set forth in the *NIH Guidelines*.

Section IV-B-2-b-(2). Notifying the Principal Investigator of the results of the Institutional Biosafety Committee's review and approval.

Section IV-B-2-b-(3). Lowering containment levels for certain experiments as specified in Section III-D-2-a, *Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems*.

Section IV-B-2-b-(4). Setting containment levels as specified in Sections III-D-4-b, *Experiments Involving Whole Animals*, and III-D-5, *Experiments Involving Whole Plants*.

Section IV-B-2-b-(5).
Periodically reviewing recombinant DNA research conducted at the institution to ensure compliance with the *NIH Guidelines*.

Section IV-B-2-b-(6).
Adopting emergency plans covering accidental spills and personnel contamination resulting from recombinant DNA research.

Note: The *Laboratory Safety Monograph*
describes basic elements for developing specific procedures dealing with major spills of potentially hazardous materials in the laboratory, including information and references about decontamination and emergency plans. The NIH and the Centers for Disease Control and Prevention are available to provide consultation and direct assistance, if necessary, as posted in the *Laboratory Safety Monograph*.
The institution shall cooperate with the state and local public health departments by reporting any significant research-related illness or accident that may be hazardous to the public health.

Section IV-B-2-b-(7). Reporting any significant problems with or violations of the *NIH Guidelines* and any significant research-related accidents or illnesses to the appropriate institutional official and NIH/OBA within 30 days, unless the Institutional Biosafety Committee determines that a report has already been filed by the Principal Investigator. Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

Section IV-B-2-b-(8).
The Institutional Biosafety Committee may not authorize initiation of experiments which are not explicitly covered by the *NIH Guidelines* until NIH (with the advice of the RAC when required) establishes the containment requirement.

Section IV-B-2-b-(9).
Performing such other functions as may be delegated to the Institutional Biosafety Committee under Section IV-B-2, *Institutional Biosafety Committee*.

Section IV-B-3. Biological Safety Officer (BSO)

Section IV-B-3-a.
The institution shall appoint a Biological Safety Officer if it engages in large-scale research or production activities involving viable organisms containing recombinant DNA molecules.

Section IV-B-3-b.
The institution shall appoint a Biological Safety Officer if it engages in recombinant DNA research at BL3 or BL4. The Biological Safety Officer shall be a member of the Institutional Biosafety Committee.

Section IV-B-3-c. The Biological Safety Officer's duties include, but are not be limited to:

Section IV-B-3-c-(1). Periodic inspections to ensure that laboratory standards are rigorously followed;

Section IV-B-3-c-(2).
Reporting to the Institutional Biosafety Committee and the institution any significant problems, violations of the *NIH Guidelines*, and any significant research-related accidents or illnesses of which the Biological Safety Officer becomes aware unless the Biological Safety Officer determines that a report has already been filed by the Principal Investigator;

Section IV-B-3-c-(3).
Developing emergency plans for handling accidental spills and personnel contamination and investigating laboratory accidents involving recombinant DNA research;

Section IV-B-3-c-(4). Providing advice on laboratory security;

Section IV-B-3-c-(5).
Providing technical advice to Principal Investigators and the Institutional Biosafety Committee on research safety procedures.

Note: See the *Laboratory Safety Monograph* for additional information on the duties of the Biological Safety Officer.

Section IV-B-4. Plant, Plant Pathogen, or Plant Pest Containment Expert

When the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix P, *Physical and Biological Containment for Recombinant DNA Research Involving Plants*, the institution shall appoint at least one individual with expertise in plant, plant pathogen, or plant pest containment principles (who is a member of the Institutional Biosafety Committee).

Section IV-B-5. Animal Containment Expert

When the institution conducts recombinant DNA research that requires Institutional Biosafety Committee approval in accordance with Appendix Q, *Physical and Biological Containment for Recombinant DNA Research Involving Animals*, the institution shall appoint at least one individual with expertise in animal containment principles (who is a member of the Institutional Biosafety Committee).

Section IV-B-6. Human Gene Therapy Expertise

When the institution participates in or sponsors recombinant DNA research involving human subjects, the institution must ensure that: (i) the Institutional Biosafety Committee has adequate expertise and training (using *ad hoc* consultants as deemed necessary) and (ii) all aspects of Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)* , have been appropriately addressed by the Principal Investigator prior to submission to NIH/OBA.

Section IV-B-7. Principal Investigator (PI)

On behalf of the institution, the Principal Investigator is responsible for full compliance with the *NIH Guidelines* in the conduct of recombinant DNA research.
A Principal Investigator engaged in human gene transfer research may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written notification to the NIH OBA of the delegation and of the name(s), address, telephone, and fax numbers of the contact. The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

Section IV-B-7-a. General Responsibilities

As part of this general responsibility, the Principal Investigator shall:

Section IV-B-7-a-(1).
Initiate or modify no recombinant DNA research which requires Institutional Biosafety Committee approval prior to initiation (see Sections III-A, III-B, III-C, III-D, and III-E, *Experiments Covered by the NIH Guidelines*) until that research or the proposed modification thereof has been approved by the Institutional Biosafety Committee and has met all other requirements of the *NIH Guidelines*;

Section IV-B-7-a-(2). Determine whether experiments are covered by Section III-E, *Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation*, and ensure that the appropriate procedures are followed;

Section IV-B-7-a-(3). Report any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/OBA, and other appropriate authorities (if applicable) within 30 days.
Reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax);

Section IV-B-7-a-(4). Report any new information bearing on the *NIH Guidelines* to the Institutional Biosafety Committee and to NIH/OBA (reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax);

Section IV-B-7-a-(5). Be adequately trained in good microbiological techniques;

Section IV-B-7-a-(6).
Adhere to Institutional Biosafety Committee approved emergency plans for handling accidental spills and personnel contamination; and

Section IV-B-7-a-(7). Comply with shipping requirements for recombinant DNA molecules (see Appendix H, *Shipment*, for shipping requirements and the *Laboratory Safety Monograph* for technical recommendations).

Section IV-B-7-b. Information to Be Submitted by the Principal Investigator to NIH OBA

The Principal Investigator shall:

Section IV-B-7-b-(1). Submit information to NIH/OBA for certification of new host-vector systems;

Section IV-B-7-b-(2).
Petition NIH/OBA, with notice to the Institutional Biosafety Committee, for proposed exemptions to the *NIH Guidelines*;

Section IV-B-7-b-(3).
Petition NIH/OBA, with concurrence of the Institutional Biosafety Committee, for approval to conduct experiments specified in Sections III-A-1, *Major Actions Under the NIH Guidelines*, and III-B, *Experiments that Require NIH/OBA and Institutional Biosafety Committee Approval Before Initiation*;

Section IV-B-7-b-(4).
Petition NIH/OBA for determination of containment for experiments requiring case-by-case review; and

Section IV-B-7-b-(5). Petition NIH/OBA for determination of containment for experiments not covered by the *NIH Guidelines*.

Section IV-B-7-b-(6). Ensure that all aspects of Appendix M have been appropriately addressed prior to submission of a human gene transfer experiment to NIH OBA, and provide a letter signed by the Principal Investigator(s) on institutional letterhead acknowledging that the documentation being submitted to NIH OBA complies with the requirements set forth in Appendix M. No research participant shall be enrolled (see definition of enrollment in Section I-E-7) in a human gene transfer experiment until the RAC review process has been completed (see Appendix M-I-B, *RAC Review Requirements*);
IBC approval (from the clinical trial site) has been obtained; Institutional Review Board (IRB) approval has been obtained; and all applicable regulatory authorization(s) have been obtained.

For a clinical trial site that is added after the RAC review process, no research participant shall be enrolled (see definition of enrollment in Section I-E-7) at the clinical trial site until the following documentation has been submitted to NIH OBA:
(1) IBC approval (from the clinical trial site); (2) IRB approval; (3) IRB-approved informed consent document; (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

Section IV-B-7-c.
Submissions by the Principal Investigator to the Institutional Biosafety Committee

The Principal Investigator shall:

Section IV-B-7-c-(1).
Make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*;

Section IV-B-7-c-(2).
Select appropriate microbiological practices and laboratory techniques to be used for the research;

Section IV-B-7-c-(3).
Submit the initial research protocol and any subsequent changes (e.g., changes in the source of DNA or host-vector system), if covered under Sections III-A, III-B, III-C, III-D, or III-E (*Experiments Covered by the NIH Guidelines*), to the Institutional Biosafety Committee for review and approval or disapproval; and

Section IV-B-7-c-(4).
Remain in communication with the Institutional Biosafety Committee throughout the conduct of the project.

Section IV-B-7-d. Responsibilities of the Principal Investigator Prior to Initiating Research

The Principal Investigator shall:

Section IV-B-7-d-(1).
Make available to all laboratory staff the protocols that describe the potential biohazards and the precautions to be taken;

Section IV-B-7-d-(2). Instruct and train laboratory staff in: (i) the practices and techniques required to ensure safety, and (ii) the procedures for dealing with accidents; and

Section IV-B-7-d-(3).
Inform the laboratory staff of the reasons and provisions for any precautionary medical practices advised or requested (e.g., vaccinations or serum collection).

Section IV-B-7-e.
Responsibilities of the Principal Investigator During the Conduct of the Research

The Principal Investigator shall:

Section IV-B-7-e-(1).
Supervise the safety performance of the laboratory staff to ensure that the required safety practices and techniques are employed;

Section IV-B-7-e-(2).
Investigate and report any significant problems pertaining to the operation and implementation of containment practices and procedures in writing to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/OBA, and other appropriate authorities (if applicable) (reports to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax);

Section IV-B-7-e-(3).
Correct work errors and conditions that may result in the release of recombinant DNA materials; and

Section IV-B-7-e-(4).
Ensure the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., purity and genotypic and phenotypic characteristics).

Section IV-B-7-e-(5).
Comply with reporting requirements for human gene transfer experiments conducted in compliance with the *NIH Guidelines* (see Appendix M-I-C, *Reporting Requirements*).

Section IV-C. Responsibilities of the National Institutes of Health (NIH)

Section IV-C-1. NIH Director

The NIH Director is responsible for: (i) establishing the *NIH Guidelines*, (ii) overseeing their implementation, and (iii) their final interpretation. The NIH Director has responsibilities under the *NIH Guidelines* that involve OBA and RAC. OBA's responsibilities under the *NIH Guidelines* are administrative. Advice from RAC is primarily scientific, technical, and ethical.
In certain circumstances, there is specific opportunity for public comment with published response prior to final action.

Section IV-C-1-a. General Responsibilities

The NIH Director is responsible for:

Section IV-C-1-a-(1). Promulgating requirements as necessary to implement the *NIH Guidelines*;

Section IV-C-1-a-(2). Establishing and maintaining RAC to carry out the responsibilities set forth in Section IV-C-2, *Recombinant DNA Advisory Committee* (RAC membership is specified in its charter and in Section IV-C-2);

Section IV-C-1-a-(3). Establishing and maintaining NIH/OBA to carry out the responsibilities defined in Section IV-C-3, *Office of Biotechnology Activities*;

Section IV-C-1-a-(4).
Conducting and supporting training programs in laboratory safety for Institutional Biosafety Committee members, Biological Safety Officers and other institutional experts (if applicable), Principal Investigators, and laboratory staff.

Section IV-C-1-a-(5). Establishing and convening Gene Therapy Policy Conferences as described in Appendix L, *Gene Therapy Policy Conferences.*

Section IV-C-1-b. Specific Responsibilities

In carrying out the responsibilities set forth in this section, the NIH Director, or a designee shall weigh each proposed action through appropriate analysis and consultation to determine whether it complies with the *NIH Guidelines* and presents no significant risk to health or the environment.

Section IV-C-1-b-(1). Major Actions

To execute *Major Actions*, the NIH Director shall seek the advice of 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)-(a). Changing containment levels for types of experiments that are specified in the *NIH Guidelines* when a *Major Action* is involved;

Section IV-C-1-b-(1)-(b).
Assigning containment levels for types of experiments that are not explicitly considered in the *NIH Guidelines* when a *Major Action* is involved;

Section IV-C-1-b-(1)-(c).
Promulgating and amending a list of classes of recombinant DNA molecules to be exempt from the *NIH Guidelines* because they consist entirely of DNA segments from species that exchange DNA by known physiological processes or otherwise do not present a significant risk to health or the environment;

Section IV-C-1-b-(1)-(d). Permitting experiments specified by Section III-A, *Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation*;

Section IV-C-1-b-(1)-(e).
Certifying new host-vector systems with the exception of minor modifications of already certified systems (the standards and procedures for certification are described in Appendix I-II, *Certification of Host-Vector Systems*). Minor modifications constitute (e.g., those of minimal or no consequence to the properties relevant to containment); and

Section IV-C-1-b-(1)-(f). Adopting other changes in the *NIH Guidelines*.

Section IV-C-1-b-(2). Minor Actions

NIH/OBA shall carry out certain functions as delegated to it by the NIH Director (see Section IV-C-3, *Office of Biotechnology Activities*). *Minor Actions*
(as determined by NIH/OBA in consultation with the RAC Chair and one or more RAC members, as necessary) will be transmitted to RAC and Institutional Biosafety Committee Chairs:

Section IV-C-1-b-(2)-(a). Changing containment levels for experiments that are specified in Section III, *Experiments Covered by the NIH Guidelines* (except when a *Major Action* is involved);

Section IV-C-1-b-(2)-(b). Assigning containment levels for experiments not explicitly considered in the *NIH Guidelines*;

Section IV-C-1-b-(2)-(c). Revising the *Classification of Etiologic Agents* for the purpose of these *NIH Guidelines* (see Section V-A, *Footnotes and References of Sections I-IV*).

Section IV-C-1-b-(2)-(d). Interpreting the *NIH Guidelines* for experiments to which the *NIH Guidelines* do not specifically assign containment levels;

Section IV-C-1-b-(2)-(e). Setting containment under Sections III-D-1-d, *Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems*, and III-D-2-b, *Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems*;

Section IV-C-1-b-(2)-(f).
Approving minor modifications of already certified host-vector systems (the standards and procedures for such modifications are described in Appendix I-II, *Certification of Host-Vector Systems*);

Section IV-C-1-b-(2)-(g). Decertifying already certified host-vector systems;

Section IV-C-1-b-(2)-(h). Adding new entries to the list of molecules toxic for vertebrates (see Appendix F, *Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates*); and

Section IV-C-1-b-(2)-(i).
Determining appropriate containment conditions for experiments according to case precedents developed under Section IV-C-1-b-(2)-(c).

Section IV-C-2. Recombinant DNA Advisory Committee (RAC)

The RAC is responsible for carrying out the functions specified in the *NIH Guidelines*, as well as others specified in its charter or assigned by the Secretary of Health and Human Services or the NIH Director. The RAC membership and procedures, in addition to those set forth in the *NIH Guidelines*, are specified in the charter for the RAC which is filed as provided in the General Services Administration Federal Advisory Committee Management regulations, 41 CFR part 101-6, and is available on the OBA web site, http://www4.od.nih.gov/oba/rac/RACcharter2002.pdf. In the event of a conflict between the *NIH Guidelines* and the charter, the charter shall control.

The RAC will consist of not less than 15 voting members, including the Chair, appointed under the procedures of the NIH and the Department of Health and Human Services. The maximum number of voting members will be established in the charter of the RAC.
At least a majority of the voting members must be knowledgeable in relevant scientific fields, e.g., molecular genetics, molecular biology, recombinant DNA research, including clinical gene transfer research. At least 4 members of the RAC must be knowledgeable in fields such as public health, laboratory safety, occupational health, protection of human subjects of research, the environment, ethics, law, public attitudes or related fields. Representatives of the Federal agencies listed in the charter shall serve as non-voting members. Nominations for RAC members may be submitted to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax).

All meetings of the RAC shall be announced in the *Federal Register*, including tentative agenda items, 15 days before the meeting. Final agendas, if modified, shall be available at least 72 hours before the meeting. No item defined as a *Major Action* under Section IV-C-1-b-(1) may be added to an agenda following *Federal Register* publication.

RAC shall be responsible for:

Section IV-C-2-a. Advising the NIH Director on the following actions: (1) Adopting changes in the *NIH Guidelines*. (2) Assigning containment levels, changing containment levels, and approving experiments considered as *Major Actions* under the *NIH Guidelines*, i.e., the deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture.
(3) Promulgating and amending lists of classes of recombinant DNA molecules to be exempt from the *NIH Guidelines* because they consist entirely of DNA segments from species that exchange DNA by known physiological processes or otherwise do not present a significant risk to health or the environment. (4) Certifying new host-vector systems.

Section IV-C-2-b. Identifying novel human gene transfer experiments deserving of public discussion by the full RAC;

Section IV-C-2-c. Transmitting to the NIH Director specific comments/ recommendations about: (i) a specific human gene transfer experiment, or (ii) a category of human gene transfer experiments;

Section IV-C-2-d.
Publicly reviewing human gene transfer clinical trial data and relevant information evaluated and summarized by NIH/OBA in accordance with the annual data reporting requirements;

Section IV-C-2-e.
Identifying broad scientific, safety, social, and ethical issues relevant to gene therapy research as potential Gene Therapy Policy Conference topics;

Section IV-C-2-f.
Identifying novel social and ethical issues relevant to specific human applications of gene transfer and recommending appropriate modifications to the *Points to Consider*
that will provide guidance in the preparation of relevant Informed Consent documents; and

Section IV-C-2-g. Identifying novel scientific and safety issues relevant to specific human applications of gene transfer and recommending appropriate modifications to the *Points to Consider* that will provide guidance in the design and submission of human gene transfer clinical trials.

Section IV-C-3. Office of Biotechnology Activities (OBA)

OBA 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. OBA shall carry out such other functions as may be delegated to it by the NIH Director. OBA's responsibilities include (but are not limited to) the following:

Section IV-C-3-a.
Serving as the focal point for public access to summary information pertaining to human gene transfer experiments;

Section IV-C-3-b. Serving as the focal point for data management of human gene transfer experiments;

Section IV-C-3-c.
Administering the annual data reporting requirements (and subsequent review) for human gene transfer experiments (see Appendix M-I-C, *Reporting Requirements*);

Section IV-C-3-d.
Transmitting comments/recommendations arising from public RAC discussion of a novel human gene transfer experiment to the NIH Director.
RAC recommendations shall be forwarded to the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate.

Section IV-C-3-e.
Collaborating with Principal Investigators, Institutional Biosafety Committees, Institutional Review Boards, and other DHHS components (including FDA and the Office for Human Research Protections), to ensure human gene transfer experiment registration compliance in accordance with Appendix M-I, *Requirements for Protocol Submission, Review, and Reporting-Human Gene Transfer Experiments* of the *NIH Guidelines*.

Section IV-C-3-f. Administering Gene Therapy Policy Conferences as deemed appropriate by the NIH Director (see Appendix L, *Gene Therapy Policy Conferences*).

Section IV-C-3-g. 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_{50} 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, *Experiments Involving the Cloning of Toxin Molecules with LD_{50} of Less than 100 Nanograms Per Kilogram Body Weight*, Appendix F, *Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates*);

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

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

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

Section IV-C-3-i-(2).
Announcements of Gene Therapy Policy Conferences and tentative agendas at least 15 days in advance;

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

Section IV-C-3-j.
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, *Institutional Biosafety Committee (IBC)*, giving its approval to the Institutional Biosafety Committee membership.

Section IV-C-4. Other NIH Components

Other NIH components shall be responsible for certifying maximum containment (BL4) facilities, inspecting them periodically, and inspecting other recombinant DNA facilities as deemed necessary.

Section IV-D. Voluntary Compliance

Section IV-D-1. Basic Policy - Voluntary Compliance

Individuals, corporations, and institutions not otherwise covered by the *NIH Guidelines* are encouraged to follow the standards and procedures set forth in Sections I through IV. In order to simplify discussion, references hereafter to "institutions" are intended to encompass corporations and individuals who have no organizational affiliation. For purposes of complying with the *NIH Guidelines*, an individual intending to carry out research involving recombinant

DNA is encouraged to affiliate with an institution that has an Institutional Biosafety Committee approved under the *NIH Guidelines*.

Since commercial organizations have special concerns, such as protection of proprietary data, some modifications and explanations of the procedures are provided in Sections IV-D-2 through IV-D-5-b, *Voluntary Compliance*, in order to address these concerns.

Section IV-D-2. Institutional Biosafety Committee Approval - Voluntary Compliance

It should be emphasized that employment of an Institutional Biosafety Committee member solely for purposes of membership on the Institutional Biosafety Committee does not itself make the member an institutionally affiliated member.
Except for the unaffiliated members, a member of an Institutional Biosafety Committee for an institution not otherwise covered by the *NIH Guidelines*
may participate in the review and approval of a project in which the member has a direct financial interest so long as the member has not been, and does not expect to be, engaged in the project. Section IV-B-2-a-(4), *Institutional Biosafety Committee*, is modified to that extent for purposes of these institutions.

Section IV-D-3. Certification of Host-Vector Systems - Voluntary Compliance

A host-vector system may be proposed for certification by the NIH Director in accordance with the procedures set forth in Appendix I-II, *Certification of Host-Vector Systems*. In order to ensure protection for proprietary data, any public notice regarding a host-vector system which is designated by the institution as proprietary under Section IV-D, *Voluntary Compliance*, will be issued only after consultation with the institution as to the content of the notice.

Section IV-D-4. Requests for Exemptions and Approvals - Voluntary Compliance

Requests for exemptions or other approvals as required by the *NIH Guidelines* should be submitted based on the procedures set forth in Sections I through IV.
In order to ensure protection for proprietary data, any public notice regarding a request for an exemption or other approval which is designated by the institution as proprietary under Section IV-D-5-a, *Voluntary Compliance*, will be issued only after consultation with the institution as to the content of the notice.

Section IV-D-5. Protection of Proprietary Data - Voluntary Compliance

Section IV-D-5-a. General

In general, the Freedom of Information Act requires Federal agencies to make their records available to the public upon request.
However, this requirement does not apply to, among other things, “trade secrets and commercial or financial information that is obtained from a person and that is privileged or confidential.” Under 18 U.S.C. 1905, it is a criminal offense for an officer or employee of the U.S. or any Federal department or agency to publish, divulge, disclose, or make known “in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, (or) processes...of any person, firm, partnership, corporation, or association.” This provision applies to all employees of the Federal Government, including special Government employees. Members of RAC are “special Government employees.”

In submitting to NIH for purposes of voluntary compliance with the *NIH Guidelines*, an institution may designate those items of information which the institution believes constitute trade secrets, privileged, confidential, commercial, or financial information.
If NIH receives a request under the Freedom of Information Act for information so designated, NIH will promptly contact the institution to secure its views as to whether the information (or some portion) should be released. If NIH decides to release this information (or some portion) in response to a Freedom of Information request or otherwise, the institution will be advised and the actual release will be delayed in accordance with 45 Code of Federal Regulations, Section 5.65(d) and (e).

Section IV-D-5-b. Pre-submission Review

Any institution not otherwise covered by the *NIH Guidelines*, which is considering submission of data or information voluntarily to NIH, may request pre-submission review of the records involved to determine if NIH will make all or part

of the records available upon request under the Freedom of Information Act.

A request for pre-submission review should be submitted to NIH/OBA along with the records involved to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax). These records shall be clearly marked as being the property of the institution on loan to NIH solely for the purpose of making a determination under the Freedom on Information Act.
NIH/OBA will seek a determination from the responsible official under DHHS regulations (45 CFR Part 5) as to whether the records involved, (or some portion) will be made available to members of the public under the Freedom of Information Act.
Pending such a determination, the records will be kept separate from NIH/OBA files, will be considered records of the institution and not NIH/OBA, and will not be received as part of NIH/OBA files. No copies will be made of such records.

NIH/OBA will inform the institution of the NIH Freedom of Information Officer's determination and follow the institution's instructions as to whether some or all of the records involved are to be returned to the institution or to become a part of NIH/OBA files.
If the institution instructs NIH/OBA to return the records, no copies or summaries of the records will be made or retained by DHHS, NIH, or OBA.
The NIH Freedom of Information Officer's determination will represent that official's judgment at the time of the determination as to whether the records involved (or some portion) would be exempt from disclosure under the Freedom on Information Act if at the time of the determination the records were in NIH/OBA files and a request was received for such files under the Freedom of Information Act.

SECTION V. FOOTNOTES AND REFERENCES OF SECTIONS I THROUGH IV

Section V-A. The NIH Director, with advice of the RAC, may revise the classification for the purposes of the *NIH Guidelines* (see Section IV-C-1-b-(2)-(e), *Minor Actions*). The revised list of organisms in each risk group is reprinted in Appendix B, *Classification of Human Etiologic Agents on the Basis of Hazard*.

Section V-B. Section III, *Experiments Covered by the NIH Guidelines*, describes a number of places where judgments are to be made.
In all these cases, the Principal Investigator shall make the judgment on these matters as part of his/her responsibility to "make the initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*" (see Section IV-B-7-c-(1)). For cases falling under Sections III-A through III-E, *Experiments Covered by the NIH Guidelines*, this judgment is to be reviewed and approved by the Institutional Biosafety Committee as part of its responsibility to make an "independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research" (see Section IV-B-2-b-(1), *Institutional Biosafety Committee*). The Institutional Biosafety Committee may refer specific cases to NIH/OBA as part of NIH/OBA's functions to "provide advice to all within and outside NIH" (see Section IV-C-3,).
NIH/OBA may request advice from the RAC as part of the RAC's responsibility for "interpreting the *NIH Guidelines* for experiments to which the *NIH Guidelines* do not specifically assign containment levels" (see Section IV-C-1-b-(2)-(f), *Minor Actions*).

Section V-C. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention and the National Institutes of Health. *Biosafety in Microbiological and Biomedical Laboratories*, 4th Edition, 1999. Copies are available from:
Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402-9371 (stock # 017-040-00547-4), Phone (202) 512-1800.

Section V-D. *Classification of Etiologic Agents on the Basis of Hazard*, 4th Edition, July 1974, U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, Office of Biosafety, Atlanta, Georgia 30333.

Section V-E. Chin, James ed., *Control of Communicable Diseases Manual*, 17th Edition, 2000. ISBN: 087553-242-X, American Public Health Association, 800 I Street, N.W., Washington, D.C. Phone: (202) 777-2742.

Section V-F. *World Health Organization Laboratory Biosafety Manual*, 2nd edition. 1993. WHO Albany, NY. Copies are available from: WHO Publication Centre, USA, (Q Corp) 49 Sheridan Avenue, Albany, New York 12210; Phone:

(518) 436-9686 (Order # 1152213).

Section V-G.
A U.S. Department of Agriculture permit, required for import and interstate transport of plant and animal pathogens, may be obtained from the U.S. Department of Agriculture, ATTN: Animal and Plant Health Inspection Service (APHIS), Veterinary Services, National Center for Import-Export, Products Program, 4700 River Road, Unit 40, Riverdale, Maryland 20737. Phone: (301) 734-8499; Fax: (301) 734-8226.

Section V-H.
American Type Culture Collection Catalogues of plant viruses, animal viruses, cells, bacteria, fungi, etc. are available from American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209. Phone: (703) 365-2700.

Section V-I. U.S. Department of Labor, Occupational Safety and Health Administration, 29 CFR 1910.1030, *Bloodborne Pathogens*. See also*, Exposure to Bloodborne Pathogens,* OSHA 3127, 1996 (Revised).

Section V-J. As classified in the *Virus Taxonomy: The Classification and Nomenclature of Viruses. The Seventh Report of the International Committee on Taxonomy of Viruses*, Academic Press, 2000 (0123702003) San Diego, CA.

Section V-K. *i.e.*, the total of all genomes within a family shall not exceed two-thirds of the genome.

Section V-L.
Organisms including alastrim, smallpox (variola) and whitepox may not be studied in the United States except at specified facilities. 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).

Section V-M.
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-G, *Footnotes and References of Sections I-IV*).
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.

APPENDIX_A.htm

APPENDIX_B.htm

APPENDIX_C.htm

APPENDIX_D.htm

APPENDIX_E.htm

APPENDIX_F.htm

APPENDIX_G.htm

APPENDIX_H.htm

APPENDIX_I.htm

APPENDIX_J.htm

APPENDIX_K.htm

APPENDIX_L.htm

APPENDIX_M.htm

APPENDIX_P.htm

APPENDIX_Q.htm

B

Bacterial Agents	BSL
Actinetobacter calceticus	2
Actinobacillus sp.	2
Actinomyces sp.	2
Aeromaonas sp.	2
Arachnida propionica	2
Bacillus alvei	2
Bacillus anthracis*	2
Bacteroides sp.	2
Bartonella sp.	3
Bordetella sp.	2
Bordetella pertussis	2
Borrelia sp.	2
Brucella sp.*	2/3
Campylobacter fetus var. jejuni	2
Camplobacter sp.	2
Chlamydia psittaci	2
Chlamydia pneumoniae	2/3
Chlamydia trachomatis	3
Clostridium botulinum*	2/3
Clostridium tetani	2
Corynebacterium diphtheriae	2
Corynebacterium equi	2
Corynebacterium haemolyticum	2
Corynebacterium pseudotuberculosis	2
Corynebacterium pysogenes	2
Corynebacterium renale	2
Enterobacteriaceae all other	2
Erysipelothrix rhusiopathiae	2
Escherichia coli	2
Escherichia coli K12 derivative	1
Francisella tularensis*	2/3
Fusobacterium sp.	2
Haemophilus sp.	2
Klebsiella sp.	2
Legionella pneumophilia	2/3
Leptospira interrogans all servars	2
Listeria sp.	2
Moraxella sp.	2
Mycobacterium avium	2
Mycobacterium bovis	3

Mycobacterium leprae	2
Mycobacterium sp.	2
Mycobacterium tuberculosis	2/3
Mycoplasma sp.	2
Neisseria gonorrhoreae	2/3
Neisseria menegitidis	2/3
Nocardia sp.	2
Pasteurella sp.	2
Pseudomonas mallei	2/3
Neisseria gonorrhoeae	2/3
Pseudomonas testoserone	2
Rotococcus (Coryne.) equi	2
Salmonella sp.	2
Salmonella typhi	2/3
Shigella sp.	2
Staphylococcus sp.	2
Streptococcus sp.	2
Streptocacillus moniliformis	2
Streptomyces somaliensis	2
Treponema pallidum	2
Vibrio sp.	2
Yersinia pestis*	2/3

Fungal Agents	**BSL**
Blastomyces dermatitides	2
Coccidioides immitis*	2/3
Cryptococcus neoformans	2
Epidermophyton - pathogenic sp.	2
Histoplasma capsulatum	2/3
Microsporum - pathogenic sp.	2
Paracoccidioides brasilienisis	2
Sporothrix schenckii	2
Trichophyton - pathogenic sp.	2
Candida albicans	2
Miscellaneous Molds	2

Parasitic Agents	**BSL**
Anaplasma sp.	2
Ascaris sp.	2
Coccidia sp.	2
Cryptosporidia sp.	2
Echinococcus Granulosus	2

Ehrlichia sp.	2
Entamoeba sp.	2
Enterobius sp.	2
Fasciola sp.	2
Giardia sp.	2
Haemobartonella sp.	2
Hymenolepsis nana	2
Leishmania sp.	2
Leukocytozoon sp.	2
Naegleria sp.	2
Plasmodium sp.	2
Sarcocystis sp.	2
Schistosoma sp.	2
Strongyloides sp.	2
Taenia solium	2
Toxocara canis	2
Toxoplasma sp.	2
Trichinella spiralis	2
Trypanosoma sp.	2

Rickettsial Agents	**BSL**
Coxiella burnetii*	2/3
Rickettsia akari	2/3
Rickettsia australis	2/3
Rickettsia canada	2/3
Rickettsia conorii	2/3
Rickettsia prowazekii*	2/3
Rickettsia rickettsii*	2/3
Rickettsia siberica	2/3
Rickettsia tsutsugamushi	2/3
Rickettsia typhi (R. mooseri)	2/3
Rochalimaea quintana	2
Rochalimaea vinsonii	2
Spotted Fever Group - other	2/3

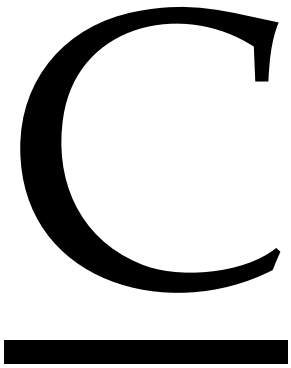
Viral Agents	**BSL**
Adenoviruses	2
Adenoviruses - animal - all	2
Aleutian Disease Virus	2
Arboviruses - certain	2
Arboviruses - certain	3
Arboviruses - certain	4

Arenaviruses - certain	3
Arenaviruses - certain	4
Avian Erthyroblastosis Virus	2
Avian Leucosis Virus	2
Avian Lymphomatosis Virus	2
Avian Myeloblasotosos Virus	2
Bovine Encephalomyelitis Virus	2
Bovine Leukemia Virus	2
Bovine Respiratory Syncytial Virus	2
Bovine Rhinotracheitis (IBR)	2
Cache Valley Virus	2
Canine Hepatitis Virus	2
Canine Distemper Virus	2
Caprine Arthritis	2
Coxsackie A & B Viruses	2
Cytomegaloviruses	2
Encephalomyelitis Virus*	2
Echovirus	2
Dengue Virus	2
Encephalomyocarditis Virus	2
Epidemic Diarrhea Infant Mice	2
Epstein-Barr Virus	2
Feline Leukemia Virus	2
Feline Sarcoma Virus	2
Filoviruses	2
Flanders Virus	2
Gibbon Ape Lymphosarcoma	2
Hart Park Virus	2
Hemorrhagic Fever Agents*	2
Hepatitis A Virus, Hepatitis E Virus	2
Hepatitis B Virus, Hepatitis C Virus, Hepatitis D Virus	2
Herpesvirus - other	2
Herpesvirus ateles	2
Herpesvirus saimir	2
Herpesvirus Simiae (B-virus)	3
Human Herpesviruses	2
Hog Cholera Virus	2
Human T-Cell Leukemia Virus I & II	2
Infectious Bronchitis Virus	2
Influenza Virus	2
Influenza Virus Virulent Avian	3

K (Rate) Virus	2
Lactic Dehydrogenase Elevating	2
Langat Virus	2
Laryngotracheitis Virus	2
Lassa Virus*	4
Low Risk Oncogenic Viruses	2
Lymphocytic Choriomeningitis Virus	2/3
Marburg Virus*	4
Measles Virus	2
Memingopneumonitis Virus	2
Mouse Encephalomyelitis Virus	2
Mouse Hepatitis Virus	2
Mouse Leukemia Virus	2
Mouse Pneumonia Virus	2
Mumps Virus	2
Myxomatosis Virus	2
Newcastle Disease Virus	2
Newcastle Disease Virus (VVND)	2
Non-Defective Adenovirus 2SV40 HYB	2
Papilloma Virus Shope	2
Parainfluenza Virus	2
Poliovirus - all types	2
Polyoma Virus	2
Poxvirus alastrim	2
Poxvirus monkey pox	3
Poxvirus - Smallpox*	
Poxvirus sp.	2
Pseudorabies Virus	2
Rabies Virus	2/3
Reovirus sp.	2
Respiratory Syncytial Virus	2
Retroviruses, including HIV & SIV	2/3
Rhinovirus sp.	2
Rous Sarcoma Virus	2
Rubella Virus	2
Simian Virus - other	2
Simian T-Cell Leukemia Virus	2
Sindbis Virus	2
Slow Viruses	2
Tensaw Virus	2
Tick-Borne Encephalitis Complex	4

Transmissible Spongiform Encephalopathies (Creutzfeldt-Jakob, kuru, and related agents	2
Turlock Virus	2
Vaccinia Virus	2
Venezuelan Equine Encephalitis*	3
Vesicular Stomatitis - lab adapted	2
Vesicular Somatitis Virus	3
Woolly Monkey Fibrosarcoma	3
Yaba Virus	2
Yellow Fever Virus 17D Strain*	2
Yellow Fever Virus Except 17D*	3

* - Select agents



SUBMIT BY MAIL OR E-MAIL

E-MAIL: esegal@stanford.edu
or
Mail original and ***16 copies*** to:
Environmental Health and Safety Department
c/o Biosafety Manager
480 Oak Road - Mail Code 8007
Stanford, CA 94305-8007
Telephone: (650) 725-1473

FOR OFFICIAL USE ONLY

APPLICATION ID: _____

DATE OF APPROVAL: _____

EXPIRES: _____

STANFORD UNIVERSITY
ADMINISTRATIVE PANEL ON BIOSAFETY
REQUEST FOR INSTITUTIONAL REVIEW/APPROVAL FOR RESEARCH INVOLVING BIOHAZARDOUS AGENTS, RECOMBINANT DNA, AND USDA-REGULATED MATERIALS

Principal Investigator: _____ Date: _____
Title: _____ Phone Number: _____
Department: _____ E-mail Address: _____
Mail Code: _____ FAX Number: _____

Title of Research Project: _____

Duration of Initial Grant: From: _____ To: _____
Biohazardous Agent(s) Used: _____

Biosafety Level (BSL) of Biological Agents: _____

SPONSORED PROJECT	FELLOWSHIP PROJECT
Source of funds:	Source of funds:
Grant number:	Fellowship title:
SPO Number:	
P.I. on grant:	Name of Fellow:

OTHER INSTITUTIONAL REVIEWS/APPROVALS SPECIFIC TO THIS PROJECT

Administrative Panel on Laboratory Animal Care

Use of animals: Yes ☐ No ☐ Approved: Yes ☐ Pending ☐ No ☐
Animal biosafety level: _____ Protocol number: _____

Administrative Panel on Use of Human Subjects
Use of Human Subjects: Yes ☐ No ☐ Approved: Yes ☐ Pending ☐ No ☐

Date of Approval:

Administrative Panel on Radiological Safety
Use of Radiological material: Yes ☐ No ☐ Approved: Yes ☐ Pending ☐ No ☐

CRA number:

PERSONNEL

The list of personnel should include all those who will physically handle the biohazardous agents or recombinant DNA molecules and are conceivably at risk from research procedures involving the use of these biological materials. Approval of the proposed experiment is given only for the identified personnel listed below. The Biosafety Officer must be notified if any new personnel are added. List additional personnel on a copy of this sheet as needed.

NAME*	TITLE	DEPARTMENT	E-MAIL	TELEPHONE

* List name as appears in Stanford WhoIs

LOCATIONS OF EXPERIMENTS, STORAGE OF AGENTS, AND AUTOCLAVE

Approval of the proposed experiments is given only for the locations listed below.

	BUILDING	ROOM NUMBER	BS LEVEL	SHARED ROOM
LOCATIONS EXPERIMENTS CONDUCTED				Yes ☐ No ☐
				Yes ☐ No ☐
				Yes ☐ No ☐
				Yes ☐ No ☐
LOCATIONS AGENTS STORED				Yes ☐ No ☐
				Yes ☐ No ☐
				Yes ☐ No ☐
NEAREST AUTOCLAVE				Yes ☐ No ☐

* Indicate if room is used by more than one Protocol Director.

PHYSICAL CONTAINMENT EQUIPMENT

BUILDING	ROOM	Biosafety Cabinet MANUFACTURER	MODEL	SERIAL #	DATE OF CERTIFICATION

Do NOT use a non-vented biosafety cabinet if you plan to use volatile radioactive isotopes in work involving viable biohazardous agents at Biosafety Level 2 or above. Consult the Biosafety Manual or contact Environmental Health and Safety at 725-1473 for recommended practices.

DESCRIPTION OF THE EXPERIMENT

Provide a short ***summary*** of the project ***in lay language*** **and a** ***technical description*** of the project, explaining the goal(s) and methods to be used. List experimental procedures and assays that will be used to enhance biosafety; describe procedures that may create biohazards (i.e., aerosol generation from centrifugation, FACS analysis, exposure to sharps, etc). If animal work is included, state experimental procedures to be used. Provide information concerning potential biohazard shedding during the animal model and any model specific hazards. Continue on a separate sheet if necessary.

1. Does proposed research involve rDNA? ☐ Yes ☐ No
If no, proceed to question #2.

If vector is plasmid based, describe plasmid and insert, or nature of synthetic nucleic acid, using maps if available. Provide source of plasmid material (e.g., made in lab A, purchased from Company X, gift from Dr. Y)

If vector is viral in origin, complete following:

☐ Adenovirus ☐ Adeno Associated Virus ☐ Alphavirus (e.g., SFV, SIN)

☐ Herpesvirus ☐ Poxvirus (e.g., Vaccinia) ☐ Other _____

☐ Retrovirus

Murine Strain _____

Lenti Vector Backbone (e.g. HIV, SIV, etc) _____

☐ Helper Plasmids _____

Provide strain, vector backbone: _____

Wild type deletions:

Replication status: _____

Envelope packaging system(s): _____

Include source of vector (e.g., made in lab A, purchased from Company X, gift from Dr. Y).

Describe host cells into which rDNA will be introduced. Include source of host cells.

Provide information concerning nature of insert (specific gene(s), class of gene, source of insert, gene function, etc.).

2. Does proposed research involve infectious agents? ☐ Yes ☐ No
If yes, answer below questions.
Information on many infectious agents can be found at: http://www.phac-aspc.gc.ca/msds-ftss/index.html

Name of agent(s) and Biosafety level. Include source of agent.

Provide antibiotic/antiviral drug resistance profile for specific strain of agent(s) to be used in project.

Concentration and volumes of agents generated. Will volumes in excess of 10 liters be generated?

List target cells/animals to be used. If animals used, describe biosafety precautions to be taken. Include housing conditions and methods of animal transport, if appropriate.

Indicate if you will be following Stanford University's recommended procedures for the following (if not, provide information on substitute procedures to be used):

Biohazardous agents will be stored in secondary containment ☐ Yes ☐ No

All equipment used with biohazards agents will be with Biohazard labels ☐ Yes ☐ No

All biohazards agents will be placed in secondary containment prior to transport within Stanford University. Containers will be labeled with Biohazard stickers. ☐ Yes ☐ No

Decontamination will be performed using 0.5% sodium hypochlorite (1:10 dilution of bleach). If bleach is not appropriate (e.g., corrosive to equipment) provide name of disinfectant(s), concentration to be used and contact time. ☐ Yes ☐ No

3. Describe precautions to be taken when handling materials.
PPE: Check all that apply

☐ Mask ☐ Gloves ☐ Lab coat ☐ Shoe covers ☐ Disposable Gown ☐ Safety Sharps

☐ Head cover ☐ Respirator (provide type ___________) ☐ Other – describe ______________________

4. Describe risk of infection, clinical symptoms, and any recommended medical surveillance and preventive laboratory practices to be used.

5. Indicate training status of all listed personnel for:

a. *Bloodborne Pathogen (BBP) web based training (required yearly) (http://somsafety.stanford.edu/)
b. *Completion of BBP Exposure Control Plan) (http://www.stanford.edu/dept/EHS/prod/researchlab/bio/practical.html#bloodborne)
c. Shipping of Dangerous Goods web based training (required every two years) (http://www.stanford.edu/dept/EHS/prod/researchlab/bio/practical.html#danger_goods)

* required if personnel will have exposure to human blood or other potentially infectious material.

NAME	BLOODBORNE PATHOGENS	EXPOSURE CONTROL PLAN	SHIPPING OF DANGEROUS GOODS
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐
	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐	Yes ☐ No ☐ N/A ☐

STANFORD UNIVERSITY
ADMINISTRATIVE PANEL ON BIOSAFETY

PROTOCOL DIRECTOR'S STATEMENT OF AGREEMENT FOR RESEARCH INVOLVING RECOMBINANT DNA, BIOHAZARDOUS AGENTS, OR USDA-REGULATED AGENTS

Protocol Director: _____ Telephone Number: _____ .

Address: _____

I attest that the information contained in the attached application is accurate and complete. I agree to comply with the requirements pertaining to shipment and transfer of biohazardous agents, recombinant DNA, and USDA-regulated agents. I am familiar with and agree to abide by the provisions of the current NIH Guidelines and other specific granting agency instructions pertaining to the proposed project.

I further attest that all research personnel are familiar with and understand the potential biohazards, proposed precautions, and appropriate emergency procedures, and that the practices and techniques required to ensure safety will be followed. I agree to accept responsibility for training of all laboratory workers involved in the project. I will ensure that all listed personnel have received or will receive the required appropriate training in safe laboratory practices and the procedures for this protocol ***prior*** to any work beginning on this project.

I will submit a request to the Biosafety office for approval of any significant modifications to this study, facilities or procedures. I will also submit Annual Updates for this study.

Written reports will be submitted to the Panel on Biosafety through the Department of Environmental Health and Safety concerning:

1. Any accident that results in inoculation, ingestion, and inhalation of biohazardous agents or recombinant DNA or any incident causing serious exposure of personnel or danger of environmental contamination:

2. Any problems pertaining to operation and implementation of biological and physical containment safety procedures or equipment or facility failure: and,

3. Any new information bearing on the Guidelines such as technical information relating to hazards and safety procedures or innovations.

I will not carry out the work described in the attached application until it has been approved by the Administrative Panel on Biosafety or, when necessary, until it has been approved by that Panel and all sponsoring agency requirements have been met.

If submitting electronically, check box and provide date. If submitting hard copy, sign and date where indicated.

☐ By checking this box, I verify that I am the Principal Investigator responsible for the research protocol being submitted to the Administrative Panel on Biosafety for review.

Protocol Director: _____ Date: _____
(Signature - no per signature)

D

Submit to:
Medical Human Subjects Panel (10 copies)
Attn: Amy Bertelsen
Administrative Panels Office
1215 Welch Road, Mod. A
Stanford University
Stanford CA 94305-5401
Campus Mail Code: 5401
AND
Administrative Panel on Biosafety (16 copies)
Attn: Ellyn Segal
EH & S, 480 Oak Road
Stanford University
Stanford CA 94305-8007
Campus Mail Code: 8007
DO NOT FAX OR E-MAIL

PROTOCOL FOR HUMAN SUBJECTS INVESTIGATION USING BIOLOGICAL AGENTS OR RECOMBINANT DNA VECTORS

STANFORD UNIVERSITY

For additional copies of this form, visit
http://humansubjects.stanford.edu/medical/GeneTxApp.rtf
or http://www.stanford.edu/dept/EHS/bio/

Protocol #
Approval Dates:
APB

HSP

For Office Use Only

For submission deadlines, visit http://researchcompliance.stanford.edu/meetings.html

PLEASE TYPE OR PRINT

Principal Investigator		Degree: MD/PhD	Title	
Dept/Div	Mail Code	Phone	Fax	E-mail

Other Investigators/personnel: (Include all individuals who will physically handle the vector leading up to and including delivery to patients as well as those who provide post-treatment patient care – use an additional sheet, if needed)

Name Degree: Title Department/Division Phone # E-mail

1

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Protocol Title:

Check all Applicable:	**Yes**	**No**	
Subject Populations:	☐	☐	Training Grant? Attach list of projects.
☐ Minors (Under 18)	☐	☐	Program Project Grant? Attach list of projects.
☐ Pregnant Women	☐	☐	Cooperating Institution(s)? Attach approval(s) Name(s): _____
☐ Fetuses	☐	☐	Radioisotopes/Radiation-producing Machines?
☐ Abortuses	☐	☐	Biohazardous Agents? Agent:
☐ Mentally Retarded	☐	☐	Human Blood or Body Fluids?.
☐ Mentally Disabled	☐	☐	Will medical equipment used for human patients/subjects also be used on
☐ None of the Above	☐	☐	animals?
	☐	☐	Investigational Drug? Name: _____ IND#: _____
	☐	☐	Investigational Device?
			☐ Non-significant Risk *or* ☐ Significant Risk, IDE#: _____
	☐	☐	Proprietary information contained in protocol?
	☐	☐	Do investigators have financial interests/obligations to sponsor? See Sec #1 below regarding Conflict of Interest.

FUNDING (include pending)

GRANTS/CONTRACTS: SPO # _____ Grant # _____ Funded by: _____

(include pending) (if available) (if available)
(if more than one, attach list)
Principal Investigator: _____
Title: _____

ATTACH ONE COPY OF EACH APPLICABLE **FEDERAL GRANT APPLICATION**, INCLUDING COMPETING RENEWALS.

☐ Yes ☐ No For PHS projects, are contents of this protocol the same as described in PHS proposal application?

FELLOWSHIPS (if more than one, attach list)

Fellow: _____ Funded by: _____

Fellowship Title: _____

If not either of the above, check one:

☐ None
☐ Dept Funding (add fund/acct below)
Fund Name: _____
Acct. No.
☐ Gift Funding; Company Name:
☐ Other Funding (e.g., VA, PAIRE); Describe:

Dept. Chair Signature **Date**

(to be signed only if department, gift, other or none is checked above)

Other Institutional Reviews/Approvals

Administrative Panel on Radiological Safety

☐ Yes ☐ No Radioisotopes will be used in conjunction with biohazardous agents or recombinant DNA molecules in this clinical trial?

If yes,
☐ Yes ☐ No Has approval been received for this usage? CRA number: Date:

Locations of the Clinical Trial

On Campus	**Location**	**Building**	**Room**
Off Campus	**City**	**State**	**Hospital/University**

Biosafety Information

Source of Vectors Used (e.g., sponsor's name)	
Proprietary Name of Recombinant DNA Molecule (if applicable, eg., VacEaze)	
Biohazardous Agent(s) Used (e.g. adenovirus)	
Biosafety Level of Biohazardous Agent(s) (per CDC)	

Preparation and Storage of Vectors

☐ Yes ☐ No Will vectors used in the clinical trials be stored at Stanford? Where (building and room #) will vectors be stored?

☐ Yes ☐ No Will the vectors be prepared and loaded in syringes/other delivery devices for delivery on campus or elsewhere? If Yes, complete the following table on containment:

Physical Containment Equipment for Vector Preparation (complete only if biosafety cabinet is necessary for preparation)

Building	Room	Biosafety Cabinet Manufacturer	Model	Serial Number	Date of Certification

Protocol Submittal Requirements

1. **Reporting Conflict of Interest (CoI) -** If materials being studied in the protocol will be supplied by commercial entities with which investigators consult or have financial interest, please identify this arrangement and answer the following questions:
   a) ☐ Yes ☐ No Do any investigator(s) or co-investigator(s) have a consulting agreement (as defined in the Faculty Research Policy Handbook and any applicable School Policy) with the sponsoring company?
   b) ☐ Yes ☐ No Do any investigator(s) or co-investigator(s) have stock, stock options or any other financial interest in the sponsoring company?
   c) ☐ Yes ☐ No Are any investigator(s) or co-investigator(s) a member of an advisory board with a sponsoring company?
   d) ☐ Yes ☐ No Is the study primarily driven by commercial interests as opposed to academic or patient care concerns?
   e) ☐ Yes ☐ No Are graduate students, residents or other trainees involved? If yes, how will their interests be protected? (Use a separate page to explain further where appropriate)

   If you answer yes to any of the questions above, institutional CoI reporting requirements may be applicable. Please refer to "Faculty Policy on Conflict of Commitment and Interest" web site at: http://www.stanford.edu/dept/DoR/rph/4-1.html and "Guide to Ad Hoc Conflict of Interest Disclosures" web site at: http://www.stanford.edu/dept/DoR/adhoc.html.

2. **Study Methodology Issues**
   a) Subject Participation in More Than One Protocol: Please explain whether subjects may be eligible to participate in more than one protocol and how the investigators will be cognizant of other protocols in which patients are enrolled.

   b) Probable Duration: Include an estimate of the probable duration of the entire study, as well as an estimate of the total time each subject is to be involved.

   Study Duration:
   Subject:

   c) Explain the alternative therapies available to patient(s) after the conclusion of the study?

   d) Tissue Sampling or Banking for Research.
   ☐ Yes ☐ No Are you taking samples of tissues, cells, blood or body fluids.
   ☐ Yes ☐ No Will they be stored for research?
   If yes to either question, explain below and include the appropriate language in the consent form.

   e) Vector Dose to be administered. What are the concentrations of virus that shall will be administered to the patients? Indicate volume, dose and number of doses that will be administered to the patients?

f) Among the recruited human subjects, are there any pre-existing patient conditions that may somehow amplify the risks of using this vector?

3. **Other Relevant Information–** Include any other information the Panels must possess in order to fulfill their responsibilities. Following are examples of items to be included, but any and all information relevant to the proposal should be included with the submittal.
   - ☐ **PROTOCOLS FROM COMPANIES** (e.g., drug companies)
   - ☐ **PROTOCOLS FROM COOPERATIVE GROUPS** (e.g., GOG, POG, ECOG, etc.)
   - ☐ The company's relevant **INVESTIGATOR'S BROCHURE**
   - ☐ Each applicable **NEW AND COMPETING RENEWAL FEDERAL GRANT PROPOSAL**.
   - ☐ Any **QUESTIONNAIRES, RECORDS, SURVEY FORMS**, ETC. to be used in the study
   - ☐ A Completed Company furnished **APPENDIX M of the NIH Recombinant DNA Guidelines**
   - ☐ **Other**

4. **Consent Forms** – A Sample Consent Form is available at: http://humansubjects.stanford.edu/medical/consent.html The Experimental Subject's Bill of Rights must be included in the consent form when performing a medical treatment. The Consent Form must be clearly written in lay language, provide full disclosure and risk information and be submitted with the protocol for review by the Panels. The Consent Form may be based on information from a sponsor furnished Consent Form but it must include Stanford specific information, such as the institutional statement regarding adenovirus usage, and other requirements provided on the sample Consent Form.

   Forms for Minors (Through 17 years of age)
   If gene therapy will be administered to a minor who is seven years of age or older**, consent must be obtained from the minor as well as both parents or guardians**.

5. **OBLIGATIONS OF PRINCIPAL INVESTIGATORS DURING PROJECT PERIOD -** Any change in the research protocol that alters the procedures or risks must be submitted to the Panel for review prior to the implementation of such change. Any complications in subjects or evidence of increase in the original estimate of risk should be reported at once to the Panel before continuing with the project. Inasmuch as the Medical Panel includes faculty, staff, legal counsel, public members, and students, protocols should be written in language that can be understood by all members of the Panel. The investigators must inform the participants of any significant new knowledge obtained during the course of the research. All continuing projects and activities must be reviewed and re-approved at least annually by the Medical Panel. Panel approval of any gene therapy project is for a maximum period of one year with quarterly reporting. It is the responsibility of the investigator to re-submit the project to the Panel for annual review prior to the end of that year. (A "RENEWAL" form [notice to renew protocol] is sent to the principal investigator 6 weeks prior to the expiration date of the protocol.) Please refer to the special guidelines for renewal projects. All data including all signed consent form documents must be retained for a minimum of three years past the completion of the research. Your funding agency, your department, or other entities may impose additional requirements. (Policy on Retention of and Access to Research Data, Research Policy Handbook, http://www.stanford.edu/dept/DoR/rph/2-10.html**.**

Note that all serious adverse events involving enrolled study patients, occurring here and at other institutions, must be reported to both the Human Subjects and Biosafety Panels regardless of whether or not the events are thought to be related to the gene transfer intervention.

Principal Investigator Signature **Date**

6. **RESPONSIBILITY OF THE ADMINISTRATIVE PANEL ON HUMAN SUBJECTS IN MEDICAL RESEARCH -** Pursuant to HHS Regulations, it is the responsibility of the institutional review panel:
   a) to determine if subjects are placed at risk, and if risk is involved, whether the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;
   b) to adequately protect the rights and welfare of any such subjects;
   c) to obtain legally effective informed consent by adequate and appropriate methods in accordance with HHS Regulations; and

d) to review the conduct of the activity at timely intervals during the course of the project.

7. **RESPONSIBILITY OF THE ADMINISTRATIVE PANEL ON BIOSAFETY REGARDING MOLECULAR THERAPIES AND VACCINES -** Pursuant to HHS Regulations, it is the responsibility of the institutional biosafety panel:
   a) to evaluate the potential of risk of the vector/biohazard agent to the patient, family members or the environment and determine controls as appropriate.
   b) to evaluate the efficacy and the possible or potential benefits of the therapy versus the concomitant biohazard risk of the vector with regard to the available alternative therapy to the patient
   c) to evaluate adverse events in previous clinical trials or animal studies to predict the potential for similar events in future trials
   d) to determine the appropriate level of monitoring for potential microbial shedding that may result from recombination, contamination, complementation, mutation or other untoward events.

Appendix M Information

The information that is required for the Appendix M submittal to the NIH is also required for the Stanford APB and Human Subjects Panel review and evaluation. If your sponsor has provided you with a Sponsor's Appendix M, you should review that material carefully and add to the information, as needed for the APB and IRB review panels. This Appendix M information must be filled out in its entirety-do not refer to paragraphs in the Sponsor Clinical Protocol, Investigational Brochure or other documents. The Appendix M that you will prepare as described in this section will be the one that will be forwarded to the NIH OBA/RAC.

Appendix M-I. Submission Requirements -- Human Gene Transfer Experiments

Investigators must submit the following material (see exemption in Appendix M-VIII-A, Footnotes of Appendix M) to the Office of Biotechnology Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, Phone 301-496-9838, FAX 301-496-9839. Investigators may submit this material electronically and can obtain specific instructions from the OBA home page http://www.nih.gov/od/oba regarding electronic submission requirements. For all submissions, whether printed or electronic, OBA will confirm receipt within three working days after receiving the submission. Investigators should contact OBA if they do not receive this confirmation. Proposals in printed form and/or in an electronic version shall be submitted to NIH/OBA in the following order: (1) scientific abstract; (2) non-technical abstract; (3) Responses to Appendix M-II through M-V, Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues (the pertinent responses can be provided in the protocol or as an appendix to the protocol); (4) clinical protocol as approved by the local Institutional Biosafety Committee and Institutional Review Board; (5) Informed Consent document as approved by the Institutional Review Board (see Appendix M-III, Informed Consent); (6) appendices (including tables, figures, and manuscripts); (7) curricula vitae--no more than two pages for each key professional person in biographical sketch format; and (8) all submissions must include Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) approvals and their deliberations pertaining to your protocol. IBC approval must be obtained from each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is ex vivo transduction of recombinant DNA material into target cells for human application). Because these written IBC and IRB approvals require appropriate signatures, investigators cannot submit them electronically. Investigators should submit these signed approvals either by mail or by facsimile transmission.

Investigational New Drug (IND) applications shall be submitted to the FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format. Submissions to the FDA should be sent to 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.

Note: NIH/OBA will accept submission material at any time. However, if a protocol is submitted less than eight weeks before a scheduled RAC meeting and subsequently is recommended for public discussion by the full RAC, the public discussion of that protocol will be deferred until the next scheduled RAC meeting. This eight-week period is needed to ensure adequate time for review by the committee members.

Appendix M-II. Description of the Proposal

Responses to this appendix should be provided in the form of written answers. 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, Research Design, Anticipated Risks and Benefits, 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 extra-chromosomal or integrated? Is the added DNA un-rearranged?

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--Human Gene Transfer Proposals).

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 (45CFR 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 Experiments

In order to maintain public access to information regarding human gene transfer protocols, NIH/OBA will maintain the documentation described in Appendices M-I through M-V (including protocols that are not reviewed by RAC). RAC prefers that information provided in response to Appendix M, Points to Consider contain no proprietary data or trade secrets, enabling all aspects of the discussion to be open to the public.

Appendix M-VI-A. RAC Members' Written Comments

Following receipt by NIH/OBA, summary information on each human gene transfer protocol will be forwarded to RAC members. Each RAC member shall notify NIH/OBA within 15 working days regarding the necessity for full RAC discussion. Full RAC review of an individual human gene transfer experiment can be initiated by the NIH Director or recommended to the NIH Director by: (i) three or more RAC members, or (ii) other Federal agencies. An individual human gene transfer experiment that is recommended for full RAC review should represent novel characteristics deserving of public discussion. If the Director, NIH, determines that an experiment will undergo full RAC discussion, NIH/OBA will immediately notify the Principal Investigator. RAC members may forward individual requests for additional information relevant to a specific protocol through NIH/OBA to the Principal Investigator. In making a determination whether an experiment is novel, and thus deserving of full RAC discussion, reviewers shall examine the scientific rationale, scientific context (relative to other proposals reviewed by RAC), whether the preliminary in vitro and in vivo safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. RAC recommendations on a specific human gene transfer experiment shall be forwarded to the NIH Director, the Principal Investigator, the sponsoring institution, and other DHHS components, as appropriate.

Appendix M-VII. Reporting Requirements -- Human Gene Transfer Protocols

Appendix M-VII-A. Investigational New Drug Application Reporting

Upon receipt of notification of permission to proceed with an Investigational New Drug application for a human gene transfer protocol, the Principal Investigator(s) shall submit a written report that includes the following information: (1) how the investigator(s) responded to RAC's recommendations on the protocol (if applicable), and (2) any modifications to the protocol as required by FDA.

Appendix M-VII-B. Annual Data Reporting and Gene Therapy Database

Investigators shall comply with annual data reporting requirements. Annual Data Report forms will be forwarded by NIH/OBA to investigators. Data submitted in these reports will be evaluated by RAC and NIH/OBA, and reviewed at a future RAC meeting. Information obtained through annual data reporting will be included in a human gene transfer database that will be administered by NIH/OBA. The purpose of this human gene transfer database is to:(1) maintain an institutional memory, (2) provide administrative details of protocol registration, (3) provide annual status reports of protocols, (4) facilitate risk assessment of individual applications of human gene transfer, and (5) enhance public awareness of relevant scientific, safety, social, and ethical issues.

Appendix M-VII-C. Adverse Event Reporting

Investigators who have received approval from FDA to initiate a human gene transfer protocol must report any serious adverse event immediately to the local Institutional Review Board, Institutional Biosafety Committee, Office for Protection from Research Risks (if applicable), NIH/OBA, and FDA, followed by the submission of a written report filed with each group. Reports submitted to NIH/OBA shall be sent to the Office of Biotechnology Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892-7010, (301) 496-9838.

Appendix VIII. Footnotes of Appendix M

Appendix VIII-A. Human studies in which 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 exempt from Appendix M-I, Submission Requirements, and Appendix M-VII, Reporting Requirements-Human Gene Transfer Experiments.

E

Stanford University
Administrative Panel on Biosafety
Annual Update of Previously Approved Research Application Involving
BIOHAZARDOUS AGENTS OR RECOMBINANT DNA

Principal Investigator_____ Date_____

Title_____ Phone_____

Department_____ e-mail_____

Mail Code_____ Fax_____

Title of Research Project_____

_____

Biosafety Identification Number_____ Biosafety Level_____

Duration of Approval_____

Biohazardous Agents_____

Recombinant DNA_____

Please check appropriate boxes:

- ☐ no changes
- ☐ add/delete rDNA molecules
- ☐ add/delete biological agents
- ☐ add/delete procedure using biohazardous agent
- ☐ add/delete Principal Investigator/Laboratory Personnel
- ☐ add/delete laboratory rooms
- ☐ add/delete use of human blood or human clinical specimens
- ☐ add/delete use of human subjects with rDNA and/or biohazardous agents
- ☐ add/delete use of animals with rDNA and/or biohazardous agents
- ☐ project is complete

Explanation of Changes:_____

_____

_____

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_____

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_____

_____

_____

Please e-mail/fax/or send completed form to: Ellyn Segal, Ph.D.
480 Oak Rd.
MC:8007

fax: 725.3468
email: esegal@stanford.edu

F

STANFORD UNIVERSITY ADMINISTRATIVE PANELS OFFICE
Cross reference form for use of Biohazardous agents/rDNA

Date:
To:
From:

Subject: Use of Recombinant DNA or Biohazardous Agents

Re:

Please answer the following questions regarding this project:

• Are biohazardous agents used? YES NO • If yes, provide name and class of agent(s): _____ 1 2 3 _____ 1 2 3 _____ 1 2 3	• Is recombinant DNA used? YES NO • If yes, provide category: EXEMPT NON-EXEMPT
See reverse for description of classification of biohazardous agents.	See reverse for description of recombinant DNA Exempt categories.

If the above listed project involves Class 1 agents and/or exempt recombinant DNA exclusively, stop here. Sign and return this notice to the address below (this project does not require APB approval or cross reference to an existing APB approval). Otherwise, continue completing this notice.

Are research procedures using biohazardous agents and/or exempt recombinant DNA **IDENTICAL** to a project application which has been approved or renewed by the APB in the last 12 months? YES NO

If NO: If the above listed project involves the use of Class 2 or Class 3 agents and/or non-exempt recombinant DNA molecules, you must complete the Administrative Panel on Biosafety Application (forms available in your Department Office of by calling the Biosafety Officer at 725-1473) or request a Renewal Form from the Biosafety Officer (available only if the APB approval of your existing project Application is less than 3 years old). Do not continue. Return this notice to the Biosafety Officer with the completed APB Application or Renewal Form.

If YES: Please provide the Grant Number of the above listed project: _____

Has everyone working on this project attended the School of Medicine Safety Class or a similar training session provided by the PI or department: YES NO

Provide the Biosafety Identification Number of the existing approved project application (e.g. ABC-96-01-00):

_____

(This Identification Number is required in order to cross reference the above listed project to an existing APB approval. If necessary, call 725-1473 to obtain the Identification Number. Do not provide CRA, A-PLAC, etc. numbers.)

P.I. Signature: _____ Date: _____

Return this notice to Ellyn Segal (Biosafety Officer); ESF; MC 8007 (725-1473)

Classification of Biohazardous Agents

Class 1 agents are those of minimal potential hazard and are not known to cause disease in healthy humans. An example of this is *E-coli* K-12. Class 2 agents are those of moderate potential hazard to personnel and the environment. An example is *Salmonella Typhii*. Class 3 agents are those which may cause serious or potentially lethal disease as a result of exposure by the inhalation route. Class 3 agents include agents derived from outside the United States which require federal permit for importation unless they are specified in a higher classification. An example of a Class 3 agent is *Mycobacterium tuberculosis*. Class 4 and Class 5 agents are not permitted at Stanford University.

For your reference, a list of Class 2 and Class 3 agents may be found in the Stanford University Biosafety Manual and in the APB Application packet. For information, please contact the Biosafety Officer at 725-1473.

Exempt Recombinant DNA

Recombinant DNA molecules are either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (I) above.

Certain experiments involve the use of recombinant DNA molecules which are exempt from NIH Guidelines. Review/approval by the APB is not necessary for the following exempt categories:

Category	Description of DNA Molecules
III-F-1	Recombinant DNA molecules that are not in organisms or viruses.
III-F-2	Recombinant DNA molecules that consist entirely of DNA segments from a single non-chromosomal or viral DNA source though one or more of the segments may be a synthetic equivalent.
III-F-3	Recombinant DNA molecules that consist entirely of DNA from a prokaryotic host including the indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species) or when transferred to another host cell by well established physiological means.
III-F-4	Recombinant DNA molecules that consist entirely of DNA from a eukaryotic host including its chloroplasts, mitochondria, or plasmids (but excluding viruses) when propagated only in that host (or a closely related strain of the same species).
III-F-5	Recombinant DNA molecules that consist entirely of DNA segments from a different species that exchange DNA by known physiological processes though one or more of the segments may be a synthetic equivalent.
III-F-6	Recombinant DNA molecules which do not present a significant risk to health or the environment, as determined by the NIH.

For more information about recombinant DNA molecules, please call 725-1473

Note: If you are working with Class 2 or 3 biohazardous agents and/or non-exempt recombinant DNA molecules then you must have a current APB approval on file with the Biosafety Officer. This notice can not be used as a substitute for an APB Application if you do not have a formal APB approval on file. Please complete the APB Application and return it with this notice to the APB, c/o the Biosafety Officer, MC: 8007.

Return this notice to Ellyn Segal (Biosafety Officer), ESF, MC: 8007 (725-1473)

G

Stanford University Bloodborne Pathogens Exposure Control Plan 2005

PI/Supervisor_____Department_____
Room_____Phone_____email_____
Lab Safety Contact_____Phone_____

I. Introduction: The Stanford University Exposure Control Plan describes how to eliminate or minimize exposure of all Stanford University personnel to human/primate blood or human/primate blood products that might contain bloodborne pathogens. This plan is in compliance with the California OSHA Bloodborne Pathogens Standard (8 CCR • 5193) and provides tier III level training for personnel. **Each principle investigator (PI/supervisor) will complete an Exposure plan based on the nature of the work being carried out in their facilities. Once completed, the plan will remain on file in a central location within the laboratory/work place along with the Stanford University Biosafety Manual for all personnel to access**.

II. Universal Precautions [•5193(d)(1) and (b)]: Universal Precautions is an approach to infection control whereby all human/primate blood and other human/primate body fluids, tissues and cells are treated as if known to be infectious for HIV, HBV, HCV, and other Bloodborne pathogens (BBP's).

III. Exposure Determination [•5193(C)(2)]: **The PI/supervisor will indicate procedures and materials in the laboratory that have the possibility of exposing personnel to BBP's**. Note that this evaluation will not take into consideration the use of personal protective equipment (PPE). Many of the potential materials are listed here. **Indicate all that may apply below.**

A. Materials

► All moist body substances, including semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, pericardial fluid, peritoneal fluid, amniotic fluid, saliva in dental procedures, and other body fluid that is visibly contaminated with blood such as saliva or vomitus, and all body fluids in situations, such as emergency response, where it is difficult or impossible to differentiate between body fluids.

► Any unfixed human or primate tissue or organ (other than intact skin) from a human (living or dead).

► Any HIV, HBV, HCV-containing cell or tissue culture, organ cultures, and medium or other solutions, and blood, organs, or other tissues from experimental animals containing HIV, HBV, or HCV.

List all procedures and materials that may apply

_____

_____

_____

Fill out sections B, C, and D below for each worker who has the potential to be exposed to BBP's. Extra copies of these sections can be found at the end of the Exposure Plan (Appendix A) File all sheets with the Exposure Plan in a central location for documentation.

B. Job categories in which personnel may reasonably have contact with BBP's. Identify by name the worker for which this section is relevant.

Principle Investigator_____

Research/Sr. Research Scientist_____

LSRA/Technician_____

Post-Doctoral Fellow_____

Graduate Student_____

Undergraduate Student_____

Laboratory Worker_____

Other_____

C. Tasks and Procedures: Identify which procedures used in the work place that may create a risk of BBP exposure (check off all that might apply).

Phlebotomy or venipuncture of humans or primates
Injections into humans or animals using primate or human specimens
Other use of needles with human or primate specimens
Handling human or primate tissue, including preparation, dissection, cutting, or other
Pipetting, mixing, or vortexing human or primate blood, fluid, or tissue
Centrifuging human or primate blood, fluid, or tissue
Handling tubes or other container or human or primate blood, fluid, or tissue
Handling contaminated sharps or other contaminated waste
Cleaning spills of human or primate blood or other body fluids
Preparing or handling primary human or primate cell cultures
Others_____

_____

D. Training Provided: List the specific training provided by the P.I./Supervisor to the individual listed above.

_____

_____

_____

_____

Employees Signature

_____

P.I./Supervisors Signature

_____

Date

IV. Methods of Compliance [5193(d) (i)]:

A. Information and Training [5193(g)(2)]: General tier I level training concerning general laboratory safety is provided by the Stanford University School of Medicine (SOM) and Stanford EH&S. Tier II level training concerning BBP is provided by the SOM on a web based format, with mandatory annual updates. **Specific tier III training will be provided by the PI/supervisor and will include specific safety training for each person's duties, including specific equipment usage and procedures. Training shall be documented and the records maintained by the PI/supervisor (or department) for at least three years**.

B. Written Exposure Control Plan [5193(c)(1)]: Upon completion of this laboratory specific plan, the PI/supervisor will file it in a central location within the laboratory along with the Stanford University Biosafety Manual for all personnel to access. The plan will be reviewed and revised annually or whenever changes in procedure or personnel occur. Additional copies of the uncompleted plan are available at the Biosafety Office or on the web at the Stanford University Biosafety web site.

C. Engineering and Work Practice Controls [5993 (d)(2)]: Engineering and work practice controls must be used to eliminate or minimize exposure to individuals. The following engineering and work practice controls will be utilized:

1. Personal Protective Equipment [5193(d)(3)]:

Personal protective equipment (PPE) will be provided without cost to all individuals who are at risk of occupational exposure to bloodborne pathogens**.** All PPE must be inspected, cleaned, or replaced as needed at no cost to personnel. PPE will be chosen based on the anticipated exposure to blood or other potentially infectious materials. The protective equipment will be considered appropriate only if it does not permit blood or other potentially infectious materials to pass through or reach the individual's clothing, skin, eyes, mouth, or other mucous membranes under normal conditions of use and for the duration of time which the protective equipment will be used.

All PPEs must be selected with the goal of providing protection from a hazard. Selection of alternate choices of PPE should be considered if the user is at risk of physiological discomfort (such as contact dermatitis from latex gloves or asthma from wearing certain face masks). Proper training on the wearing and function of personal protective equipment is required PRIOR to using PPE. Consultation or advice on PPE is provided by Stanford University EH&S.

A) Eye protection

Protective eye wear must be worn in the laboratory when it is reasonably anticipated that blood or other potentially infected material may make contact with the mucous membranes of the eye. Face shields may be required if there is a potential for splashes, sprays, or aerosols.

B) Lab coats and uniforms

Laboratory coats, gowns, smocks, aprons, or uniforms must be worn while in the laboratory; long sleeves are required. Before leaving the laboratory for non-laboratory areas (e.g., cafeteria, library, administrative offices), this protective clothing must be removed and left in the laboratory. Sandals and open-toed shoes are not permitted.

C) Gloves

All personnel engaged in activities that may involve skin contact with potentially infectious fluids or tissues must wear gloves. Gloves are also required for laboratory workers with dermatitis or other lesions on the hands who may have direct or indirect contact with potentially infectious materials. Hand washing with soap and water must be a routine practice immediately after direct contact with potentially infectious materials and on completion of work, even when gloves are worn. Gloves should be removed before touching common equipment (phone, computer, appropriate laboratory equipment) to prevent contamination. Personnel must wear gloves, lab coat, and safety glasses whenever handling human or primate blood, fluids, or tissue. Gloves must be replaced frequently and immediately if they become contaminated or damaged in any way. In addition to above items, personnel must wear any additional PPE (apron, booties, face shield, etc.) that is needed to prevent blood or other potentially infectious material from contaminating their street cloths, skin, eyes, mouth, or other mucous membranes under normal conditions.

All PPEs shall be removed prior to leaving the work areas and placed in designated areas for disinfection or disposal. At no time will personnel be permitted to take home any PPE, including lab coats, for laundering or cleaning.

2) Hand washing

Personnel must wash their hands immediately upon removal of gloves and upon any contact with potential BBP materials.

3) Mouth pipetting

Mouth pipetting is prohibited.

4) No eating, drinking

Eating, drinking, smoking, applying cosmetics or lip balm, and handling contact lenses are not permitted in work areas. Food and drink are not to be placed or stored in areas (refrigerators, microwaves, etc.) where potential BBP are kept or may be present.

5) Needles, sharps, and broken glass

Used needles and other sharps are not to be sheared, bent, broken, recapped, or resheathed by hand. Used needles are not to be removed from disposable syringes. Disposable sharps must not be reused. **All sharps, contaminated or not**, **shall be disposed of in a puncture-resistant hard sided, labeled sharps container**.

The CAL-OSHA BBP Standard requires any laboratory using human or primate blood, blood products, cell lines, tissues or other potentially infectious materials to use **Needleless Systems/and or engineered sharps**. Needleless systems means a device that does not use needles (1) for the withdrawal of body fluids after initial venous or arterial access is established; (2) administration of medication or fluids; and (3) performance of any other procedure involving the potential for an exposure incident. Engineered sharps means either (1) a physical attribute built into a needle device such as barrier creation, blunting, encapsulation, withdrawal or (2) a physical mechanism which effectively reduces the risk of an exposure incident. **If the PI/supervisor decides that a non-compliant sharps is necessary for a certain procedure, the reason must be documented.**

Any broken glassware must not be directly handled with a gloved or bare hand. Use a mechanical tool (tongs, dustpan and broom) to collect the pieces into a hard-sided container labeled 'broken glass'. Contaminated broken glass must be placed in a puncture-resistant hard sided container and disposed of as biohazardous waste.

6) Minimization of aerosols

All procedures must be performed carefully to minimize the creation of aerosols. Biological safety cabinets (Class I or II) or other physical containment devices must be used whenever possible while performing operations capable of creating aerosols, including but not limited to:

- centrifugation
- blending
- homogenization
- opening pressurized containers.

If a biological safety cabinet cannot be used, the most effective means of minimizing exposure to aerosols is to contain them by using closed containers (centrifuge tubes, sealed centrifuge rotors, capped test tubes, etc.).

7) Disinfection of work area and spill cleanups

Blood and blood products shall be handled in an area that can be readily decontaminated. The work area must be disinfected before and after handling microorganisms. Non-laboratory personnel should not handle equipment that has been used with potential BBP's until it has been decontaminated. All spills must be cleaned up immediately and disinfected with a germicide by appropriate decontamination procedures determined by the laboratory supervisor. The laboratory supervisor or other laboratory personnel must immediately report laboratory accidents (major spills, injuries, illnesses) to EH&S.

8) Labeling

A biohazard warning sign incorporating the universal biohazard symbol shall be posted on the access door to the laboratory work area. All human tissue, body fluid, or other potentially infectious materials must be stored in a container labeled with a biohazard symbol. Refrigerators, freezers, incubators, or other pieces of equipment where potentially infectious materials are stored or handled must also be labeled with the biohazard symbol. All signs are available from EH&S.

9) Limited access

Access to a laboratory is limited or restricted by the laboratory supervisor when work is in progress. When work with blood or blood products is being performed, non-laboratory personnel (maintenance, administrative personnel) and non-Stanford personnel should be discouraged from entering. If they must enter a facility, the hazards of the work being performed must be fully explained. Maintenance and building services personnel may be unfamiliar with the potential hazards present in a laboratory and must be fully instructed and carefully supervised by the laboratory supervisor when working in areas where human blood and blood products are handled.

10) Transportation on Campus

Specimens of blood or other potentially infectious materials shall be placed in a primary container that prevents leakage (capped test tube, centrifuge tube, etc.) during collection, handling, and storage. If the specimens are transported through hallways, the primary containers must be placed in a secondary container (bucket, beaker, cooler, etc.) which would contain the contents if the primary container if it were to leak or break.

11) Shipping of samples

Specimens of blood or other potentially infectious materials that will be shipped to or from Stanford University must be clearly identified as human blood or blood products. The material shall be placed in a closed primary container and a leak proof secondary container prior to shipment. Personnel involved with shipping of biohazardous agents or potential BBPs **must have** documented training prior to shipping. Contact EH&S for more detailed guidelines and training on shipping samples or specimens.

12) Blood Collection

All human blood collection within Stanford University shall be performed in accordance with established phlebotomy procedures.

13) Biological Waste Disposal

Disposal of potentially hazardous biological materials shall be performed with appropriate consideration for the personnel involved in the handling of laboratory waste, as well as federal, state and local laws concerning the disposal of such materials. In accordance with the California Medical Waste Management Act, Health and Safety Code, Chapter 6.1, medical waste includes but is not limited to:

- Human or animal specimens or infectious cultures
- Sharps, including needles and syringes (clean or dirty)
- Cultures and stocks of infectious agents
- Wastes from the production of bacteria, viruses, or the use of spores, discarded live and attenuated vaccines, and culture dishes and devices used to transfer, inoculate, and mix cultures
- Animal parts, tissues, fluids, or carcasses suspected by the attending veterinarian of being contaminated with infectious agents contagious to humans
- Waste which contains recognizable blood, fluid blood products, containers or equipment containing blood, or blood from animals known to be infected with diseases which are communicable to humans

Specific procedures for the disposal of biological materials are available from EH&S and can also be found in the Biosafety Manual.

V. Reporting and Documenting Sharps Injuries: All sharps related injuries shall be reported immediately by completing a Stanford University Environmental Health and Safety Report (SU-17) and a Sharps Injury Log (within 14 days of the injury) (both forms are available on the Biosafety web site). The Sharps Injury Log is maintained for five years by EH&S. The log will be reviewed by the Biosafety Manager to identify trends and take corrective action.

VI. Medical Surveillance Program [5193(f)]: Stanford University Environmental Health and Safety (EH&S) will make provisions for all appropriate required medical services.

1. Hepatitis B Vaccination: A safe and effective vaccine is available for protection from Hepatitis B. The vaccine is well tolerated and has not been associated with serious side effects. While Stanford University strongly encourages employees to be vaccinated, accepting vaccination is not a condition of employment. Immunization requires three injections of vaccine over a six-month period. This vaccine is available at no cost to the employee. Post-vaccination serological testing to ensure that protective antibodies to hepatitis B have developed is also provided at no cost following completion of the vaccination series.

   The PI/supervisor will ensure that all personnel with potential for occupational exposure to BBP are offered the Hepatitis B (HBV) vaccination in a timely manner (within ten working days of contact with human or primate specimens). The HBV vaccination will be

offered to personnel as a prophylactic treatment or made available post-exposure. Hepatitis B immune globin is also offered as a prophylactic within 24 hours of an occupational exposure.

To schedule a vaccination or a medical consult concerning exposure risk: Stanford University students will be treated at Vaden Student Health Services (498-2336) and employees at the Occupational Health Center at EH&S. A healthcare professional can discuss the risks and benefits of the vaccination. If you decide to receive the vaccine there will be no charge to you. EH&S will notify your PI/supervisor that you have received appropriate medical services in a manner that does not breach medical confidentiality. If you decide not to be vaccinated but later change your mind you may still receive the vaccination at no cost. Each employee who declines the HBV vaccination series is required to sign a declination form to that effect (see Appendix B)

2. Post-Exposure Evaluation and Follow-up [5193(f)(3)(A)]: Any exposure (e.g. spill, needlestick, ingestion) resulting in direct, unprotected contact with human or primate blood, fluids, or tissue gives you the right to prompt medical evaluation and treatment with a qualified physician familiar with evaluations and treatment protocols as recommended by the Centers for Disease Control and Prevention. These services will be provided to you at no cost.

   What to do post-exposure:

   After any direct exposure to BBP, **immediately wash the affected area with soap and water.**

   In the event that a Stanford University employee or student is accidentally exposed to human blood or blood products, **students** should report to the **Vaden Student Health** (open M – Th, 8:30am – 8 pm, F 9 am – 9 pm, Sat, Sun 10 am – 5:30 pm) or to **Stanford Hospital Emergency Room if it is an emergency or after hours** and **employees** to the **Stanford Hospital Emergency Room for an emergency, after hours or on weekends)** where an established medical protocol will be followed. This protocol is designed to provide the individual with the most appropriate medical procedures, consultation and supportive therapy. The exposed employee or student will be provided with a written opinion that will include:

   - HBV vaccination status and recommendation
   - results of the post-exposure evaluation and follow-up
   - discussion of any medical conditions resulting from exposure to blood or other potentially infectious materials which requires further evaluation or treatment
   - all other findings or diagnoses shall remain confidential and will not be included in the written report.

   In some circumstances it may be appropriate (if possible) to acquire serology from both the exposed individual and the source sample. Consent must be obtained from the exposed individual and from the person(s) who contributed the source. Specific procedures to ensure individual confidentiality have been built into these procedures.

   An important component of hepatitis vaccination is post-vaccination serological testing. This is provided at no cost to employees at the appropriate time point following completion of the three-dose hepatitis vaccination series. This is done to ensure that protective antibodies to the hepatitis B surface antigen have developed. If there is an inadequate response, employees are encouraged to complete a second three-dose vaccine series followed by serological retesting. Employees who still do not have adequate antibody responses at this time are informed that they may be susceptible to HBV infection and are counseled on the precautions needed to prevent HBV infection

and the need for prophylactic administration of hepatitis B immune globulin within 24 hours of an occupational exposure.

Exposure to animal bites and scratches: it is important to report all bite wounds and scratches. Wounds must be cleansed immediately in your work area. Instructions for the proper cleaning of wounds will be given to you by your supervisor. **After you have cleansed the wound, go immediately to the Stanford Emergency Room where animal wound protocols are on file.**

Every individual handling material with potential BBP has the responsibility to report any exposure to the supervisor and the PI/supervisor. Documentation of the route of exposure and the circumstances under which the exposure occurred must be done. Any personnel who have experienced a potential BBP exposure due to injury with a sharps object (i.e. scalpel, broken glass, animal bite) must fill out an SU-17 and a Sharps Log Report. Medical information will not be discussed or revealed to supervisors, personnel representatives, or other health care professionals who do not need the information.

3. Recordkeeping [5193(h)]: The PI/supervisor must maintain all training record as discussed above for at least three years and provide recordkeeping for compliance with HepB vaccination. The medical provider maintains all medical records for thirty years.

Stanford University Hepatitis B Vaccination Declaration

A safe and effective vaccine is available for protection from Hepatitis B. While Stanford University strongly encourages employees to be vaccinated, accepting vaccination is not a condition of employment. This vaccine is available at no cost to the employee. Immunization requires three injections over a six-month period. Post-vaccination serological testing to ensure that protective antibodies to hepatitis B have developed is also provided at no cost following completion of the vaccination series. Hepatitis B vaccination is made available after the employee has received required training (Bloodborne Pathogens) and within 10 working days of initial assignment to employees who have occupational exposure [per 8CCR5193 (f) (2) (A)].

Please check the appropriate box:

☐ I have already received the Hepatitis B vaccine.

Approximate date of vaccine_____

I received the vaccine at_____

☐ I wish to receive the Hepatitis B vaccine.

☐ I do not wish to receive the Hepatitis B vaccine at this time.

If you wish to **decline** the Hepatitis B vaccine at this time, please read and sign the statement below.

I understand that due to my occupational exposure to blood or other potentially infectious materials I may be at risk of acquiring hepatitis B virus (HBV) infection. I have been given this opportunity to be vaccinated with hepatitis B vaccine at no charge to myself. However, I decline the hepatitis B vaccination at this time. I understand that by declining this vaccine, I continue to be at risk of acquiring hepatitis B, a serous disease. If in the future I continue to have occupational exposure to blood or other potentially infectious materials and I want to be vaccinated with hepatitis B vaccine, I can receive the vaccination series at no charge to me.

Name:_____ _____
(print) (signature)

Date:_____ Department:_____

Submit the completed form to your supervisor, who will either file the form (if vaccination is declined) or make arrangements with the medical provider for vaccination (if accepted). If you are art of the School of Medicine, contact David Silberman at 3.6336 for vaccination arrangements. If you are from another School, contact EH&S at 3.0448.

If you have any questions, please contact the Biosafety Manager at 725.1473.

Appendix A: use separate copy for each individual

A. Job categories in which personnel may reasonably have contact with BBP's. Identify by name the worker and the category for which this page is relevant (use a separate page for each person). Make extra copies of this page as needed.

Principle Investigator_____

Research/Sr.Research Scientist_____

LSRA_____

Post-Doctoral Fellow_____

Graduate Student_____

Undergraduate Student_____

Other_____

B. Tasks and Procedures : Identify which procedures used in the work place that may create a risk of BBP exposure (check off all that might apply).

Phlebotomy or venipuncture of humans or primates

Injections into humans or animals using primate or human specimens

Other use of needles with human or primate specimens

Handling human or primate tissue, including preparation, dissection, cutting, or other

Pipetting, mixing, or vortexing human or primate blood, fluid, or tissue

Centrifuging human or primate blood, fluid, or tissue

Handling tubes or other container or human or primate blood, fluid, or tissue

Handling contaminated sharps or other contaminated waste

Cleaning spills of human or primate blood or other body fluids

Preparing or handling primary human or primate cell cultures

Others_____

_____

C. Training Provided: List the specific training provided by the P.I./Supervisor to the individual listed above.

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Employees Signature

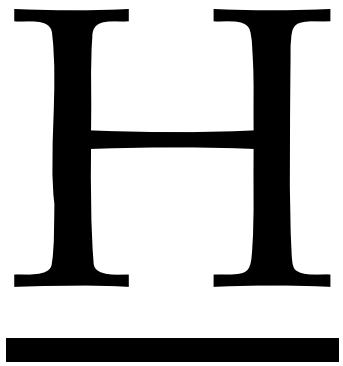
_____

P.I./Supervisors Signature

_____

Date

Note: extra copies of this section can be found at the end of the exposure control plan or at http://www.stanford.edu/dept/EHS/prod/researchlab/bio/docs/bloodborn_pat_exp_control.pdf
Please fill out a separate section for each appropriate laboratory member.



Stanford University Hepatitis B Vaccination Declaration

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Please check the appropriate box:

- ❑ I have already received the Hepatitis B vaccine.
  Approximate date of vaccine _____
  I received the vaccine at _____

- ❑ I wish to receive the Hepatitis B vaccine.

- ❑ I do not wish to receive the Hepatitis B vaccine at this time.

If you wish to **decline** the Hepatitis B vaccine at this time, please read and sign the statement below.

I understand that due to my occupational exposure to blood or other potentially infectious materials I may be at risk of acquiring hepatitis B virus (HBV) infection. I have been given this opportunity to be vaccinated with hepatitis B vaccine at no charge to myself. However, I decline the hepatitis B vaccination at this time. I understand that by declining this vaccine, I continue to be at risk of acquiring hepatitis B, a serous disease. If in the future I continue to have occupational exposure to blood or other potentially infectious materials and I want to be vaccinated with hepatitis B vaccine, I can receive the vaccination series at no charge to me.

Name: _____ _____
(print) (signature)

Date: _____ Department: _____

Submit the completed form to your supervisor, who will either file the form (if vaccination is declined) or make arrangements with the medical provider (853.2970) for vaccination (if accepted). If you are part of the School of Medicine, contact David Silberman at 3.6336 for vaccination arrangements.

If you have any questions, please contact the Biosafety Manager at 725.1473.

I

Select Agents

HHS Agents

- Crimean-Congo Haemorrhagic Fever Virus
- Ebola Viruses
- Lassa Fever Virus
- Marburg Virus
- Richettsia prowazeki
- Rickettsia rickettsii
- South American Haemorrhagic Fever Viruses
- Tick-Borne Enciphalitis Complex Viruses
- Variola Major Viruses (Smallpox Virus)
- Viruses Causing Hantavirus Pulmonary Syndrome
- Yellow Fever Virus
- Yersinia pestis
- Abrin
- Conotixins
- Diacetoxyscirpenol
- Ricin
- Saxitoxin
- Tetrodotoxin

USDA-HHS Overlap Agents

- Bacillus anthracis
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia (Pseudomonas) mallei
- Burkholderia (Pseudomonas) pseudomallei
- Clostridium botulinum
- Coccidioides immitis
- Coxiella burnettii
- Eastern Equine Encephalitis Virus
- Equine Morbillivirus (Hendra Virus)/Nipah Virus
- Francisella tularensis
- Rift Valley Fever Virus
- Venezuelan Equine Encephalitis Virus
- Aflatoxins
- Botulinum Toxins
- Clostridium perfringens epsilon Toxin
- Shigatoxin
- Staphlococcal enterotoxin
- T-2 Toxin

USDA High Consequence of Livestock Pathogens and Toxins

- African Horse Sickness Virus
- African Swine Fever
- Akabane Virus
- Avian Influenza Virus (Highly Pathogenic)
- Blue Tongue Virus (Exotic)
- Bovine Spongiform Encepalopathy Agent
- Camel Pox Virus
- Classical Swine Fever
- Cowdria ruminantium (Heartwater)
- Foot and Mouth Disease Virus
- Goat Pox Virus
- Japanese Encephalitis Virus
- Lumpy Skin Disease Virus
- Malignant Catarrhal Fever
- Menangle Virus
- Mycoplasma capricolum/M.F 38/M. mycoides capri (Contagious Caprine Pleuropneumonia Agent)
- Mycoplasma mycoides mycoides (Contagious Bovine Pleuropneumonia Agent)
- Newcastle Disease Virus (Exotic)
- Peste Des Petits Ruminants
- Rinderpest Virus
- Sheep Pox
- Swine Vesicular Disease Virus
- Vesicular Stomatitis Virus

J

Stanford University Contact Information

	Phone
Biosafety Manager	725.1473
Biological Waste (University)	725.7529
Biological Waste (Med School/Hosp)	723.6896
Health Physics	723.3201
Radioactive Waste	725.1408
Chemical Safety	725.1474
Chemical Waste Program	725.7520
EH&S main line	723.0448
EH&S emergency line	725.9999
Research Compliance Office	723.4697
School of Medicine Health & Safety	723.6336
Animal Care & Use	723.4550