



HARVARD UNIVERSITY  
Standing Committee on Microbiological Safety

# Policies & Procedures

Office of Research Subject Protection  
Harvard Medical School  
Gordon Hall, 411  
Phone (617) 432-4899 Fax (617) 432-6262  
[coms@hms.harvard.edu](mailto:coms@hms.harvard.edu)

Version 12.2  
Revised 30 January 2009

# Table of Contents

I. Fundamental Policy Statement.....	1	B. Clinical Studies.....	10
II. What Follows.....	1	1. Human Gene Transfer Studies.....	10
III. A Bit of History.....	1	2. Human Xenotransplants and Xenografts.....	10
IV. Responsibilities.....	2	3. Infectious Agents and Human Subjects.....	10
A. COMS.....	2	C. “Select” Agents.....	10
1. Functions and Organization.....	2	1. Security Specifics.....	10
2. Harvard, NIH, Boston, and Cambridge		V. Protocol Approval Procedure.....	11
Requirements.....	3	A. Introduction.....	11
a) NIH Requirements.....	3	B. Document Flow.....	11
b) Boston Requirements.....	3	1. Biosafety Officer’s Memo.....	12
B. Biological Safety Officers' Responsibilities.....	4	2. Reviewers.....	12
C. Principal Investigator, Laboratory Director, or		C. Procedures Common to All Applications.....	12
Supervisor Responsibilities.....	4	1. Biosafety Officer Evaluation.....	13
1. Laboratory Studies.....	5	2. Committee Approval.....	13
2. Clinical Studies.....	5	3. Investigator Presentations.....	13
D. Duties of the Biological Safety Office.....	5	4. Communicating with COMS.....	13
E. COMS Policies and Procedures.....	5	5. Protocol Termination.....	13
1. COMS Membership.....	5	D. Additional Considerations For Clinical Studies	
2. COMS Schedule and Mailings.....	6	1. NIH Regulations for Human DNA Transfer	
a) COMS Schedule.....	6	Studies.....	14
b) Contents of a Typical Mailing.....	6	2. Supplementary Material for Clinical Studies	
c) “Drop Dead Date”.....	6	.....	14
d) Mailing Schedule.....	7	3. Procedures for all Clinical Studies.....	14
3. Quorum.....	7	4. Multiple Clinical Sites.....	14
4. Conflicts Of Interest.....	7	5. Cooperative Arrangement with Dana-Farber	
5. Voting Biosafety Officers.....	7	Cancer Institute.....	14
6. Polices related to Clinical Trials.....	7	6. Human Research Protocol Renewals.....	14
a) The Principal Investigator for a Clinical		E. Amendments to Approved Research Protocols	
Trial is Solely Responsibility for its		.....	15
Conduct.....	7	VII. Biosafety Level Nomenclature.....	15
b) Clinical Holds:.....	7	VIII. Appendix A. Harvard University Policy With	
c) Referrals to Human Gene Transfer and		Respect to Hazardous Biological Agents.....	16
Xenotransplantation Trials at External		IX. Appendix B. “Select Agent” Listing.....	18
Institution.....	7	Exclusions:.....	20
d) Tissue Processing Laboratories for Human		X. Appendix C. Policies and Guidelines Adopted by	
Trials.....	8	COMS.....	21
e) COMS Interpretation of the OSHA		A. Retroviral Vector Guidelines.....	22
Bloodborne Pathogen.....	8	B. Guidelines for Microbiologic Safety in Clinical	
f) Annual Clinical Renewals.....	8	Trials Involving Xenotransplantation.....	23
g) Laboratory Studies Closely Associated		C. Certification Requirements for BL3	
with Clinical Studies.....	8	Laboratories.....	25
7. Policies Related to Laboratory Studies.....	8	D. Policy for Validating Attenuated Strains of BL3	
a) Updates, Amendments and New		Organisms.....	26
Registrations.....	8	XI. Appendix D. Acronyms.....	27
b) Annual Laboratory Renewals.....	9	XII. Appendix E. Biocontainment Recommendations	
c) Core Labs.....	9	.....	28
d) Protocols Involving Oligonucleotides.....	9	XIII. Appendix F. Vector Biocontainment DRAFT	31
e) Serum Storage.....	9	XIV. Appendix G. Biosafety and Risk Levels.....	32
8. Other COMS policies.....	9	XV. Index.....	36
V. Types of Protocols.....	10		
A. Laboratory Studies.....	10		
1. Recombinant DNA Materials.....	10		
2. Infectious Materials.....	10		



## I. FUNDAMENTAL POLICY STATEMENT

It is the policy of the Harvard Committee on Microbiological Safety that the Principal Investigator, Laboratory Director, or Supervisor is responsible for the safe handling of hazardous biological and recombinant DNA materials in their facility.

## II. WHAT FOLLOWS

This document describes the current policies of Harvard's Institutional Biosafety Committee (COMS<sup>1</sup>) and how it regulates research involving biohazardous agents. It is intended to help investigators, Committee members and Biosafety Officers comply with federal, state and local regulations.

## III. A BIT OF HISTORY

Responding to public concern about the effects of recombinant DNA technology the National Institutes of Health established a Recombinant DNA Advisory Committee in late 1974. The Committee, known by the acronym "RAC," was given authority to govern recombinant DNA research at all NIH funded institutions. In 1976 RAC published a set of research guidelines establishing local Institutional Biosafety Committees (IBC) with the authority to enforce the guidelines on a case by case basis. IBC's are composed of community representatives and members of the institutional staff.

Perhaps the most useful and lasting feature of the guidelines is a systematic nomenclature for biological hazard (called Risk Group) and corresponding containment and procedures (Biosafety Level). Risks and Biosafety Levels are graded from 1 to 4. Level 1 is the least hazard and level 4 refers to the greatest hazard. This nomenclature has been adopted in one form or another throughout the world. When evaluating a proposed experiment the IBC must decide the levels appropriate for the experiment. Additional information about Biosafety Levels can be found in Appendix G (page 32).

In 1975 the Harvard Medical School faculty established committees on recombinant DNA and microbiological hazards. In 1977 and 1978 the President and Fellows of Harvard University established a standing faculty committee, then called the Harvard Committee on the Regulation of Hazardous Biological Agents. This committee's mandate was (and remains) to oversee the use of all hazardous biologicals through out the University, not only recombinant DNA (for the text of this mandate see Appendix A starting on page 16). COMS is a direct descendent of this committee.

At about this time the Cities of Boston and Cambridge adopted the NIH recombinant DNA guidelines as city regulations, *i.e.* as law, and formed oversight committees to follow recombinant DNA research in their cities. Separate Harvard Biosafety Committees for Boston and Cambridge were established with the Cambridge committee retaining the CRHBA acronym and the Boston committee called the Committee on Microbiological Safety (COMS). In 1996 the several faculties involved voted to combine the two Biosafety committees into one centered at the Medical School under the COMS acronym.

Over the years various government bodies have increased IBC responsibilities. In addition to recombinant DNA research COMS also monitors xenotransplantation, bloodborne pathogens, and biological toxins. In accord with its original mandate the Committee also monitors all studies involving replicating microorganisms. More recently COMS has been given the responsibility of overseeing the use of certain "select" agents thought by the federal government to be of potential terrorist use (see listing on page 18). As of this writing, June 2008, it appears that COMS may be required to evaluate all biological research studies for their potential value to terrorist organizations.

---

<sup>1</sup> Acronyms are translated in Appendix D, Page 28.



Since 1977 COMS has registered over 4,400 research protocols. Active protocols come from >1,000 investigators.

## IV. RESPONSIBILITIES

### A. COMS

#### 1. Functions and Organization

The Committee establishes and enforces policies on the proper use of hazardous biological and recombinant DNA materials. Policy objectives are to protect staff, research subjects and the environment from biological hazards. The Committee reports to the Dean for Faculty and Research Integrity at the Harvard Medical School. COMS's administrative tasks are processed by staff at the Biosafety Office.

The Committee is responsible for the review and approval of research projects involving potentially hazardous biological agents. Protocols are reviewed by members of the Committee and by drawing upon the skills and knowledge of Harvard faculty.

COMS serves as the Institutional Biosafety Committee for Harvard University and thirteen affiliated medical institutions (May 2008). Each institution has its own Biosafety Officer and takes full responsibility for enforcing COMS requirements. For instance, if there are major Biosafety problems at the Brigham and Women's Hospital they are referred to Research Administration at the Brigham. Harvard Medical School is not involved.

The Committee is responsible for the review and commissioning of Biosafety Level 3 laboratories and animal facilities as well as Good Manufacturing Practices (GMP) facilities generating genetic and xenotransplant materials for use in humans. In the extremely unlikely event a laboratory persists in following procedures violating COMS requirements the Committee will recommend the imposition of sanctions by Deans or Heads of the affiliated institution's administration. BL4 recombinant DNA studies are forbidden in Boston and Cambridge.

Institution	Biosafety Officer	Telephone Number
Beth Israel Deaconess Medical Center	Susanne Simon	617-667-5148
Brigham and Women's Hospital	Ted Myatt	781-247-4300
Brigham and Women's Hospital	Casey Lucas	617-525-7341
Children's Hospital, Boston	Curtis Liddle	617-919-2288
Harvard Faculty of Art & Sciences	Sid Paula	617-495-2345
Harvard Institutes of Medicine	Maureen Oliver	617-432-2762
Harvard Medical Area	Kathy Gilbert	617-432-1671
Harvard Medical Area	Sarah Eberly	617-432-4727
Immune Disease Institute (CLS)	John Norris	617-278-6605
Joslin Diabetes Center	Maureen Oliver	617-732-2583
Massachusetts Eye and Ear Infirmary	Kathy Joseph	617-636-0964
Massachusetts General Hospital, McLean Hospital	Anne Sallee	617-724-4579
Massachusetts General Hospital, McLean Hospital	Kelly Williams	617-643-3024
New England Primate Research Center (HMS)	Kathy Gilbert	617-432-1671
New Research Building (Harvard)	Maureen Oliver	617-432-2762
Partners Research Building	Maureen Oliver	617-768-8212
Shriner's Hospital	Anne Sallee	617-724-4579
Schepens Eye Research Institute	Kathleen Gallagher	617-912-0244



## 2. Harvard, NIH, Boston, and Cambridge Requirements

COMS is responsible for satisfying requirements from several entities. Harvard's policies are based on a single document (see page 16) covering potentially pathogenic or oncogenic biological agents and recombinant DNA. The NIH requirements for research involving recombinant DNA are outlined in the form of a set of guidelines. Boston subscribes to the NIH Guidelines. Boston also has several regulations covering infectious agents. Cambridge also subscribes to the NIH guidelines.

### a) NIH Requirements

COMS acts on the behalf of Harvard and most of Harvard's affiliated research institutions.<sup>2</sup> It is responsible for reviewing recombinant DNA research to ensure compliance with the NIH Guidelines. To this end COMS independently assesses the proper level of laboratory facilities, necessary containment and procedure levels, and training for the research staff.

COMS is responsible for annual inspections of BL2 and BL3 registered laboratories. Purely BL1 laboratories should be inspected semi annually. Biosafety Officers carry out this responsibility. Any significant problems involving recombinant DNA research discovered during these inspections must be reported immediately to COMS and within 30 days to the NIH Office for Biotechnology Affairs.

NIH guidelines require COMS to provide copies of its minutes to any member of the public. In addition the guidelines encourage COMS to have its meetings open to the public. It is COMS policy to redact minutes to omit names of committee members and investigators.

The NIH guidelines place many other responsibilities on the Biosafety Committee. These include the development of emergency plans, recommending proper levels of containment and procedures, and notifying the NIH of accidental exposure to potentially hazardous organisms generated using recombinant DNA methods.

COMS 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.

The complete NIH recombinant DNA guidelines are at:  
<http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>

A simplified discussion of the guidelines can be found at  
[http://www.hms.harvard.edu/orsp/coms/Government/2002\\_NIH-Guidelines\\_Explained.pdf](http://www.hms.harvard.edu/orsp/coms/Government/2002_NIH-Guidelines_Explained.pdf)

### b) Boston Requirements

*Boston Summary.* Boston has four overlapping regulations dealing with laboratory safety; three from the Public Health Commission and one from the City Council. The texts and associated forms can be found at the Registration Tab of the COMS web site. The site can be Googled at "Harvard Biosafety" ("I'm Feeling Lucky").

The four regulations cover 1) laboratories working with recombinant DNA, 2) laboratories working with high hazard organisms, 3) reporting possible laboratory acquired diseases and 4) and a general ordinance that requires research laboratories to register with the Boston Fire Department.

All four regulations have the force of law. Violation may lead to severe penalties. In the first three regulations there is a requirement that accidental exposures to hazardous organisms must be immediately (within 24 hours) reported to the Boston Public Health Commission.

*Boston Recombinant DNA.* This long standing regulation relates to recombinant DNA studies. In essence the regulation adopts parts, but not all, of the NIH current recombinant DNA guidelines. All institutions

---

<sup>2</sup> The Dana Farber Cancer Institute has its own Biosafety Committee. The Broad Institute in Cambridge is a joint Harvard and MIT research institution. It is covered by the MIT Biosafety Committee.



working with recombinant DNA must apply for and receive a permit. Recombinant studies requiring Biosafety Level 4 facilities are not permitted in Boston.

The basic biosafety aspects of the NIH guidelines are adopted by this regulation. Major Actions are left to the NIH RAC. Boston requires investigators working with recombinant DNA fill out a one page form for each study. The form is forwarded to the Boston Public Health Commission once a year along with COMS meeting minutes and a listing of COMS members.

*Boston High Hazard Laboratories.* This regulation covers Biosafety Level 3 and Biosafety Level 4 laboratories and organisms appropriate to these levels. Institutions with Level 3 and/ or 4 facilities must apply and receive a three year permit from the Boston Public Health Commission. Laboratory containment and procedures must follow standard federal guidance documents. Unannounced annual inspections will examine staff for their understanding of appropriate procedures in the lab and knowledge of standard operating procedures. Staff training documentation will be examined. Standard Operating Procedures will be examined.

Experiments designated by the Federal Government as “Top Secret”, “Secret”, or “Confidential” are forbidden in Boston.

*Boston Reporting Illness.* A third, wide ranging, regulation is directed to early detection of “high hazard” biological agents. While much of the regulation involves clinics and hospitals one section is concerned with occupationally acquired illness in laboratories working with high hazard organisms and toxins. These agents are listed on the COMS web page under the Regulations Tab.

All research laboratories working with high hazard agents must register and then update the registration with the Boston Public Health Commission twice a year.

Employees working with high hazard agents who are absent for two consecutive days must be evaluated by an Occupational Health professional to determine whether the illness is laboratory acquired. If there is reason to believe the illness is due to a high hazard agent the Occupational Health Officer must immediately notify the Boston Public Health Commission.

*Boston Laboratory Registration.* The fourth Boston regulation helps the Fire Department prepare for emergencies involving hazardous agents in laboratories. To this end laboratory facilities must register and subsequently submit annual updates to the Department. While the Department’s greatest concern is with chemicals, Biosafety Level 3 and 4 laboratories and animal facilities must be clearly marked on architectural floor plans.

## ***B. BIOLOGICAL SAFETY OFFICERS' RESPONSIBILITIES***

Biological Safety Officers (BSO) employed by the University or its affiliates are primary intermediaries between investigators and COMS. During periodic inspections they help each laboratory to implement COMS’ and NIH policies and procedures.

BSOs evaluate research applications and make recommendations to COMS as to appropriate containment, procedures and protective garments. If the application is considered to have novel procedures or organisms it will be submitted to reviewer and then forwarded to the Committee for consideration.

Biosafety Officers are required to monitor IACUC, IRB applications and Material Transfer Agreements to alert COMS to new procedures or organisms.

## ***C. PRINCIPAL INVESTIGATOR, LABORATORY DIRECTOR, OR SUPERVISOR RESPONSIBILITIES***

All research projects involving potentially hazardous biological materials must be registered with COMS. There are some differences between the registration process for laboratory studies (including animal



studies) and for clinical studies. The processes are outlined below. For additional advice on the registration process investigators should consult the Biosafety Officer for their institution.

### *1. Laboratory Studies*

An investigator must have COMS approval before starting work involving hazardous biological agents, biological toxins, pathogens or recombinant DNA. The investigator is responsible for training the laboratory staff in the risks associated with the study, in safe procedures and the proper use of safety equipment. The investigator must immediately notify the Committee, through the local Biosafety Office, of accidents or adverse events concerning the use of hazardous biological agents or recombinant DNA.

### *2. Clinical Studies*

Investigators must obtain approval from the Committee before administering recombinant DNA or xenotransplant materials to human subjects. All communications between a study sponsor and COMS must go through the Principal Investigator. The sponsor may not communicate directly with COMS. For details on this policy see page 13.

Investigators must provide annual updates and reports to the Committee concerning the progress of clinical trials. Investigators are required to train clinical staff about the risks associated with the study, about safe procedures and the proper use safety equipment.

## **D. DUTIES OF THE BIOLOGICAL SAFETY OFFICE**

- Provides administrative support necessary for Committee activities.
- Prepares agendas, minutes and notes for COMS meetings.
- Organizes a monthly Biosafety Officers meeting to determine policy and discuss areas of mutual interest.
- Advises and supports Biosafety Officers. Acts as an intermediary between Biosafety Officers and COMS.
- Archives records of research projects, minutes of Committee and Advisory Committee meetings, and other documents related to Committee and Advisory Committee activities. Archives are in the HMS Countway Library.
- Other paper records, such as applications, supplementary materials, Biosafety Officer comments, and letters of approval are stored in the Harvard Depository, Southborough, Massachusetts.
- Assists Biosafety Officers in generating an annual report on activities to University Deans and to Hospital Administration.
- Acts as liaison with University and affiliated hospital Institutional Review Boards (IRBs), Institutional Animal Care and Use Committees (IACUCs), Infection Control Units, and Occupational Health Offices.
- Represents COMS at University Policy Committee meetings as needed.
- Maintains a secure electronic database covering all registered laboratories and projects.
- Monitors national state and local regulatory trends and communicate any changes to the Biosafety Officers and responsible institutional representatives.
- Generates annual reports to the NIH and City of Boston.

## **E. COMS POLICIES AND PROCEDURES**

### *1. COMS Membership*

The Committee is composed of community representatives, scientists, clinical investigators and administrators from Harvard University and its affiliate institutions. Four Biosafety Officers, selected by the Biosafety Officers as a group, are also voting members. Members are appointed for a renewable term of three years.



Non-voting members: By virtue of their administrative or regulatory positions the remaining Biosafety Officers, the Longwood Associate Director, Science Programs, the Director of Harvard University Environmental Health and Safety, the Harvard Director for Biological Safety, and the HMS Dean for Faculty and Research Integrity are non-voting Committee members.

Members are recruited from all Harvard schools doing biological research and from the affiliated institutions. New members are usually recommended by current members or research administrators. An effort is made to represent all the major hospitals, to have a mix of tenured and non-tenured faculty and to include roughly equal numbers of men and women.

## 2. COMS Schedule and Mailings

### a) COMS Schedule

COMS meetings are scheduled for the last Friday of each month. In November and December the meeting is scheduled for the Friday preceding Thanksgiving or Christmas. Meetings are open to the public and are announced at an open web site ([www.harvard.edu/orsp/coms/](http://www.harvard.edu/orsp/coms/))

### b) Contents of a Typical Mailing

#### (1) *Agenda*

The agenda is a listing of planned COMS meeting items, the minutes of the previous meeting and a listing of initially approved registrations since the previous meeting. The agenda is not available to the public.

#### (2) *Supplementary Material*

Confidential and sensitive material is to be contained in a supplementary material packet. The packet is not part of the agenda and is therefore not available to the public.

Material related to human gene transfer and xenotransplantation trials and some complex or novel laboratory studies is to be included in the Supplementary Material package. The complete package of material submitted in support of these studies can be very long – hundreds of pages. Much of this is pure boilerplate and need not be included in the package sent to all COMS members. A judicious selection is necessary. Introductory sections, drug preparation and shipment, HIPPA statements, and bookkeeping issues rarely relate to safety issues and should be culled. If uncertain, the COMS office will include rather than cull. Entire applications are supplied on a CD-ROM included in the mailing.

#### (3) *CD ROM – Supplementary Materials and Initial Approvals*

A substantial number of applications are initially approved by the COMS Office at the recommendation of the Biosafety Officers. These applications have “ample” precedent (see the definition on page 13) and are covered by Section III-E, Section III-F and Appendix C of the NIH Recombinant DNA Guidelines as well as a variety of applications not covered by the Guidelines.

It is COMS policy that none of these studies can without begin without initial approval. It is understood that formal approval will take place at the following COMS meeting.

To conserve paper the applications and the justification for each initial approval are burned onto a CD ROM which is included with the agenda. The CD-ROM is considered to be confidential.

### c) “Drop Dead Date”

All material relating to *laboratory studies* for the next COMS meeting must be in the COMS office by noon the Wednesday of the week before the meeting week – that is *9 days before the meeting*. This is the “Drop Dead Date.” Material to be sent to COMS members must be submitted to the printing office the afternoon of the Drop Dead Date with the understanding it will be returned to the COMS office by noon of the next day (Thursday).



All material relating to *clinical studies* must be submitted to the COMS office one month and 9 days before the meeting. Clinical studies involve human subjects in gene transfer research, infectious agent research or xenotransplantation research.

#### d) Mailing Schedule

The agenda and any supplementary material are to be received by each COMS member the Friday before the COMS meeting. This means material to be “FedExed” must go out Thursday afternoon. Hand delivered material should be distributed on Friday.

### 3. Quorum

A quorum is defined as 50 percent plus one of the voting membership and must include at least one community representative. Non-voting members are not counted when determining a quorum. Written proxies do not count toward a quorum.

### 4. Conflicts Of Interest

A conflict of interest is loosely defined as financial involvement with a commercial sponsor or personal relationship with the investigators or a sponsor. Members with a conflict must disclose the conflict to the Committee and the Committee will decide the proper course of action, by vote if necessary.

### 5. Voting Biosafety Officers

COMS voting membership will include four Biosafety officer selected by COMS office and confirmed by the Biosafety officers at their monthly meeting. Voting membership will rotate periodically. At least two voting Biosafety Officers should come be from institutions with Biosafety Level 3 facilities.

### 6. Policies related to Clinical Trials

#### a) The Principal Investigator for a Clinical Trial is Solely Responsibility for its Conduct

It is COMS policy that all materials, documents and other formal communications relating to a proposed human gene transfer or xenotransplantation study come from the Principal Investigator, *not the sponsor*. It is the responsibility of the Principal Investigator to be fully informed about issues that pertain to the safe conductance of his/her study.

Hence, all written responses to Committee queries must be submitted on the Principal Investigator's letter head and must be signed and dated by the Investigator. Signature stamps and signatures by others in the Investigator's name are not acceptable.

#### b) Clinical Holds:

Investigators must immediately notify COMS of an FDA required hold. The Harvard study will automatically have its COMS approval held, as well. A release of the hold by the FDA will not automatically constitute a release by COMS. Rather, the circumstances necessitating the original hold and the extenuating information resulting in its release will be provided to the COMS Chairman. If he/she agrees release of the hold is appropriate, the investigator will be notified that he or she may proceed. If the Chairs feel that the issues require committee discussion, the protocol will be scheduled for the earliest possible COMS meeting.

#### c) Referrals to Human Gene Transfer and Xenotransplantation Trials at External Institution

This policy refers to human gene transfer and human xenotransplantation studies in which investigators associated with Harvard recruit and follow participants but do not administered the test article.

Human gene transfer and human xenotransplantation studies in which investigators associated with Harvard affiliated institutions recruit and follow participants but do not administer the test article will be fully reviewed by COMS. This means the Harvard institution must submit: a copy of the remote site IBC and IRB approvals, a completed COMS application form covering the entire study, a completed NIH



recombinant DNA Guideline Appendix M (if required by the NIH), a completed FDA protocol, an FDA investigator s brochure, informed consent forms for both sites, NIH biosketches of investigators at the non-Harvard institution, and a description of the facilities involved. COMS will defer or reject the application, if deficient.

In a mirror situation, one in which the drug or tissue is administered in a Harvard Institution but recruitment and follow-up are done elsewhere, COMS will not require NIH biosketches of investigators at the non-Harvard institution or a description of the facilities involved.

#### d) Tissue Processing Laboratories for Human Trials

It is COMS policy that processing of eukaryotic cells or tissues modified with recombinant DNA and destined for human recipients must be carried out in a laboratory accredited, or, in special cases, is actively seeking accreditation, by an independent, outside, clinical organization appropriate to the manipulations.

#### e) COMS Interpretation of the OSHA Bloodborne Pathogen

All studies involving primate cells or certain primate body fluids, no matter what their history, must be regarded as potentially hazardous and, therefore, must be registered with COMS as infectious agents. All laboratories working with primate cells or certain body fluids must subscribe to the requirements of the OSHA Bloodborne Pathogen Standard. Examples of cell lines covered by this policy are HeLa cells (Human cervical carcinoma) and COS7 cells (African Green Monkey). Tissues covered include any unfixed soft tissue, various secretions and fluids including saliva and cerebrospinal fluid. Urine, hair, finger and toe nails and cleaned bones are not covered.

#### f) Annual Clinical Renewals

Human trials involving gene transfer or xenotransplantation are approved for one year. Renewals involve a short report of the year's activities and results. Renewals are required during the follow-up phase. The PI can adjust the renewal timing to correspond with annual reports to other bodies – IRB, FDA, and so on. At the COMS meeting of 25 June 2004 it was decided to request the most recent Data Safety Monitoring Board report as a means of summarizing all results at multi-site clinical trials.

If an investigator ignores this requirement, particularly when there are numerous reminders from the local Biosafety Officer, the clinical study will be inactivated and the IRB, NIH and OPRR will be notified. The investigator will have to cease recruiting or enrolling study subjects and will be required to submit a new registration request.

#### g) Laboratory Studies Closely Associated with Clinical Studies

Research laboratory studies in support of a clinical study carried out in a hospital setting on materials taken from a clinical study can be registered with COMS or, if the Biosafety Officer deems it appropriate, responsibility can be placed with the hospital's infection control unit. In the latter case the Infection Control Unit will take full responsibility for technician safety and training.

### *7. Policies Related to Laboratory Studies*

#### a) Updates, Amendments and New Registrations.

**Updates** are changes without safety consequences. For instance, staff changes or addition of new strains of previously approved or closely related cell type are updates. Updates should be sent by the local Biosafety Officer to the COMS office.

**Amendments** are necessary when the change may have safety consequences but the basic thrust of the study stays the same. In general the change will not involve a change in containment. For example, addition of a new pathogen or vector to a study will usually require an amendment. Addition of a toxic gene will also require an amendment. Amendment requests will be approved by the COMS Chair. The



Biosafety Officer should send a small package with the PIs request, a memo to the Chair explaining the change, a recommendation for how to proceed and an approval letter for the Chair to sign.

**New Registrations** are required when there is a change in the basic thrust of a project – a new goal.

b) Annual Laboratory Renewals

Every January a letter is sent to each laboratory investigator. It contains the database contents of all the PI's active registrations and requests entries be corrected and updated. There is a check box for "no change."

If there is no response, a second letter is sent a month later. If there is no response to the second letter a third letter is sent another month later. This letter gives a deadline and threatens the registration's inactivation if there is no response by the deadline. In addition the local Biosafety Officer is notified. The Biosafety Officer makes a personal appeal to the PI. Finally, if there is no response by the deadline the registration is inactivated and the PI required to submit a completely new registration. The Sponsored Programs Administration is notified as is the local IACUC.

There are several reasons for this policy. First, COMS is using update in place of a new renewal for practical reasons. Second, the update system identifies PIs who have left or moved. Third, the letter reminds PIs of their active registrations. Finally, this is a way for COMS to keep up to date with what a PI is doing. [The update is mandated by Harvard University policies. See page 16.]

c) Core Labs

It is COMS policy to register a core lab (example, transgenic core) and have PI's refer to the Core registration number when using the core facilities.

Some core facilities actually provide space for investigators to do their work. How should we deal with this? Core notifies Biosafety Officer and updates their registration if the new PI working in the core brings in a new procedure or new organisms the Core amends their registration through the usual procedure.

d) Protocols Involving Oligonucleotides

The use of oligonucleotides is outside of the Committee's jurisdiction. However, in the future human oligonucleotide therapy protocols will be examined by the local Biosafety Officer and COMS coordinator to determine whether they pose safety issues best addressed by COMS. At present this means biologically active polynucleotides such as RNAi constructs will not require COMS approval unless they are generated through recombinant techniques or are administered using viral vectors.

e) Serum Storage

COMS does not have a policy on serum baseline sampling and storage. The NIH Recombinant DNA Guidelines and the CDC-NIH "*Biosafety in Microbiological and Biomedical Laboratories*" (BMBL) 5th Edition recommend serum sampling for studies at BL2, BL2-N, BL3, BL3-N, BL4 and BL4-N. Neither the World Health Organization Laboratory Biosafety Manual, 3rd edition or the Canadian Laboratory Biosafety Guidelines 3rd Edition recommend serum baseline sampling and storage. COMS leaves the decision as to serum sampling to the individual Harvard Schools and individual affiliated research institutions.

*8. Other COMS policies*

Several policies are too complicated to summarize here. They can be found in Appendix C (page 21): Transgenic Animal and Plant Policies on page 21; Retroviral Vector Policies on page 22, Xenotransplantation Guidelines on page 23; the commissioning of Biosafety level 3 laboratories (page 25).



## V. TYPES OF PROTOCOLS

### A. LABORATORY STUDIES

#### 1. Recombinant DNA Materials

Research involving recombinant DNA materials must comply with the NIH Guidelines for Research Involving Recombinant DNA Molecules. Copies are available on the web (<http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>) or from a local Biosafety Officer.

#### 2. Infectious Materials

All laboratory research involving the use of infectious agents, pathogenic or not, human or non-human primate blood, unfixed human or non-human primate tissues, and human and non-human primate cell lines.

### B. CLINICAL STUDIES

#### 1. Human Gene Transfer Studies

Research involving the deliberate transfer of recombinant DNA or RNA derived from recombinant DNA into human subjects. *NOTE: All human gene transfer studies must be submitted for evaluation to the NIH Office of Biotechnology Activities, Recombinant Advisory Committee (the "RAC"). COMS cannot approve a Human Gene Transfer study until the RAC has made a determination.*

#### 2. Human Xenotransplants and Xenografts

Research and investigational therapeutic approaches involving the transfer of organs, tissue, or cells of animal origin into human subjects. *Ex vivo* use of animal tissue or cells for treating human subjects in a manner that may result in infectious agents being passed to human subjects.

#### 3. Infectious Agents and Human Subjects

Research and investigational therapeutic approaches involving the treatment of human subjects with infectious agents, whether they are pathogenic or not.

### C. "SELECT" AGENTS

In the wake of the 9/11 catastrophe regulations dealing with so called Select Agents were established by Congress. Select Agents are thought to have potential terrorist application. A list of these agents is given on page 18. The list contains both viable agents such as bacteria and viruses, and biological toxins. Some attenuated variants of the viable agents are "excluded" from the regulations. Similarly small amounts of the toxins are "excluded", as well.

Possession or access to Select Agents is restricted to institutions and their employees who have registered with the Centers for Disease Control or the Department of Agriculture. Registration involves a security check by the FBI to ensure that persons with certain backgrounds do not work with these agents. COMS is responsible for administering this program.

#### 1. Security Specifics

It is expected that any institution housing a Select Agent will provide adequate security to prevent unauthorized access. The CDC and NIH have made several recommendations for enhancing the security of laboratories working with Select Agents (<http://www.cdc.gov/od/ohs/biosfty/bmb14/b4af.htm>).

The main recommendations are:

1. Recognize that laboratory security is related to but different than laboratory safety.  
Get help from security experts, train the staff, and review policies regularly



2. Control access to areas where biologic agents or toxins are used and stored.  
Keep doors locked, use key cards for routine entry, record all entries.
3. Know who is in the laboratory area.  
Make background checks before giving routine access, wear visible IDs, escort visitors.
4. Know what materials are being brought into the laboratory area.  
Open Select Agent shipments in a Biosafety Cabinet, verify contents.
5. Know what materials are being removed from the laboratory area.
6. Have an emergency plan.  
Prepare for accidents, fires, health emergencies. Coordinate with emergency responders.
7. Have a protocol for reporting incidents.  
Incidents: undocumented visitors, missing chemicals and Select Agents, threats.

## VI. PROTOCOL APPROVAL PROCEDURE

Registration procedures differ slightly between laboratory and clinical studies.

### A. INTRODUCTION

The use of standard application forms makes it easier for Biosafety Committee members to review projects and to make recommendations as to proper safety procedures. Investigators can get these forms from the local Biosafety Officer or on the web at our COMS site.<sup>3</sup> There are three principal application forms. One for laboratory and/or animal studies, one for Human Gene Transfer studies and one for Human Xenotransplantation studies. Supplementary material, listed on page 14, is required for human studies. In the future it may be possible to submit the forms electronically. Until then the investigator should fill out the appropriate form, sign the form and submit it and supplementary material to the local Biosafety Officer. Recombinant DNA studies in Boston must be registered with the city. The appropriate form is attached to the standard COMS application form and, when completed, is submitted to the City by the Biosafety Office.

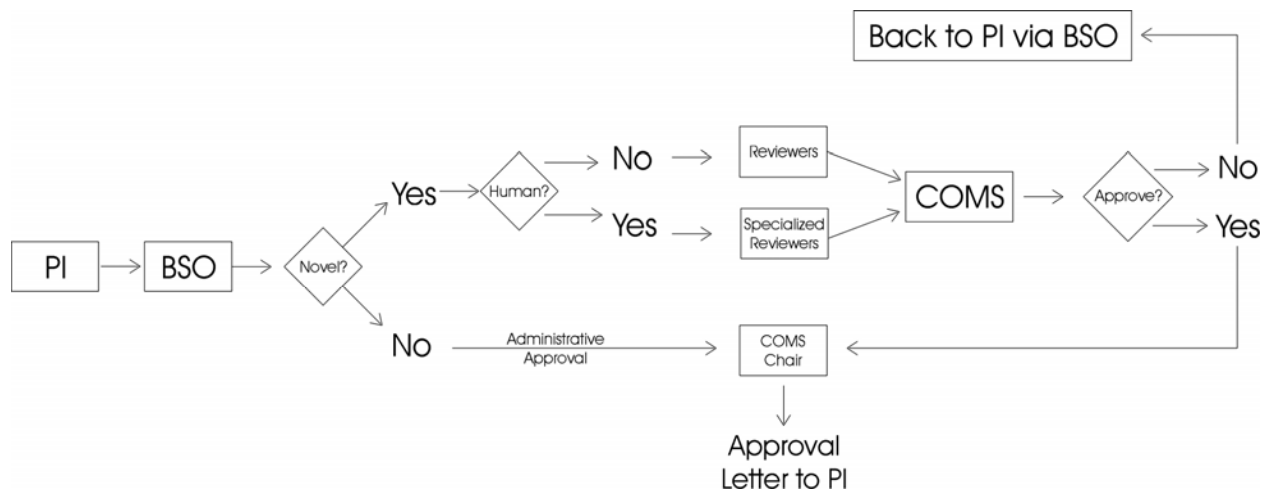
Investigators applying for laboratory study registrations need only fill in the laboratory and/or animal studies form (two pages). Occasionally, the Biosafety Officer will request additional information, particularly for studies using methods in which COMS has little experience.

### B. DOCUMENT FLOW

---

<sup>3</sup> <http://hms.harvard.edu/orsp/coms/forms.htm>. We occasionally revise application forms. Investigators should consult this web site to ensure they are using the most recent version.





Investigators submit completed applications to the local Biosafety Officer. The Biosafety Officer examines the application and decides how to proceed. If the study has ample precedents, the Biosafety Officer can advise the Committee Chair that initial approval is reasonable (“ample” precedent is defined on page 13).

### 1. Biosafety Officer’s Memo

A memo with the following items: **a)** summarizing the study, **b)** outlining the biosafety issues involved, **c)** listing at least three appropriate COMS precedents, **d)** recommending and justifying a biosafety level for the study, **e)** certification that the laboratory is adequate to the proposed biosafety level and the date of inspection, and **f)** for studies involving recombinant DNA, citation of the relevant section of the NIH recombinant DNA guidelines. The Biosafety Officer will send the memo, the investigator’s application, and a draft approval letter to the Biosafety Office for processing. Once the Biosafety Office evaluates the application the material is sent either directly to the COMS Chair for signature or submitted to one or two reviewers for presentation at the next COMS meeting.

### 2. Reviewers

If the proposal is novel, one or two reviewers are selected by Biosafety Office for their recommendations. Members of the faculty with expertise in the field are asked to examine the applications. The studies along with the reviews are then presented at the next COMS meeting and the Committee votes on whether to approve or not. The Committee often attaches stipulations to an approval. Human trials are approved for one year. Renewals involve a short report of the year’s activities and results. Renewals are required during the follow-up phase.

## C. PROCEDURES COMMON TO ALL APPLICATIONS

In most respects laboratory and clinical study reviews follow the same approval pathway. However, additional steps are necessary for clinical study approval. Aspects specific to clinical trials are given in a subsequent section. After an application is submitted, the Biosafety Officer will decide whether more information is necessary and, if so, will get in touch with the investigator. Once the application is complete the Biosafety Officer writes a memorandum to the COMS Chair summarizing the salient characteristics of the study, listing any COMS precedents and recommending whether the study should be initially approved, be submitted to reviewers and/or scheduled for full committee action. The Committee Chair reviews the protocol and determines which course of action will be followed.



### *1. Biosafety Officer Evaluation*

Research protocols involving recombinant DNA that fall under the requirements of the NIH recombinant DNA Guidelines are first evaluated by the local Biosafety Officer. The Biosafety Officer places the proposed study into one of several NIH mandated categories; some protocols are exempt from the Guidelines, others require full COMS discussion and formal vote and others fall in between. "In between" studies (covered by NIH Guideline Section III-E) receive interim approval from the COMS Chair on the recommendation of the Biosafety Officer. COMS gives final formal approval at its next meeting.

Studies not covered by the NIH Guidelines – for instance studies solely involving pathogenic organisms – can be initially approved on the recommendation of the Biosafety officer and the Director of Biological Safety. In these cases initial approval is contingent on ample COMS precedent.

#### *a. Definition of "Ample" Precedent*

Ample precedent requires three consistent, recent and relevant precedents. If there is ample precedent the Biosafety Officer may, at her discretion, generate a recommendation as to the appropriate containment and procedures and write an approval letter incorporating the recommendation for the Committee Chair to sign. The Chair may either accept the Biosafety Officer's recommendation or ask for further review. NOTE: COMS precedents are already established for a large number of agents. They are listed in Appendix E, page 28.

#### *b. Procedures Necessary to Reach "Ample" Precedent*

An initial study using a novel technique, vector, or gene must be reviewed by at least two members of the Committee and must have COMS' formal approval. Second and third applications involving this technique, vector or gene must be reviewed by at least one COMS member and then forwarded to COMS for formal approval.

### *2. Committee Approval*

Novel research protocols, without ample precedents, and studies that according to the NIH guidelines, require COMS approval will be reviewed by the full committee at scheduled meetings. In general a proposal is sent to two reviewers for comment and recommendations. The reviewers present their findings to the Committee. A decision is often made by consensus. Clinical studies involving gene transfer are always subjected to a formal vote.

### *3. Investigator Presentations*

When the Chair deems it advisable, investigators will be invited to Committee meetings to clarify their proposal and respond to members' questions. However, these presentations rarely advance the PI's case and are discouraged.

### *4. Communicating with COMS*

Investigators communicate with the Committee through their local Institutional Biosafety Officer. In rare circumstances it may be advisable to communicate through the COMS coordinator, Andy Braun, (617) 432-4899. All written communications with the Committee must be signed by the Principal Investigator.

### *5. Protocol Termination*

Approval may be canceled if the Principal Investigator is found to be routinely in violation of COMS policies and regulations. Recombinant DNA and infectious agent research not complying with NIH guidelines may cause NIH action affecting individual and institutional funding.



## D. ADDITIONAL CONSIDERATIONS FOR CLINICAL STUDIES

### 1. NIH Regulations for Human DNA Transfer Studies

NIH regulations requiring Institutional Biosafety Committees await action by the NIH Recombinant DNA Advisory Committee (RAC) before approving and human study involving DNA transfer. The RAC can simply pass the protocol to the FDA or it can decide to evaluate the proposal at its next quarterly meeting. This new procedure can delay study approval by as much as six months. However, if an investigator sends a Gene Transfer protocol to COMS at the same time as it is sent to the RAC, local approval can come immediately after the RAC acts.

### 2. Supplementary Material for Clinical Studies

In addition to the application form clinical investigators must submit copies of a) the Clinical Protocol, b) the Investigator's Brochure and c) informed consent forms. Gene Transfer study applications must also be accompanied by a completed Appendix M, "Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects" from the Recombinant DNA NIH Guidelines.<sup>4</sup> As these documents are a part of the standard FDA application no additional effort is required by the investigator.

### 3. Procedures for all Clinical Studies

In consultation with the local Biosafety Officer the COMS Chair decides on one of three courses of action.

1) For completely novel procedures the application material is sent to every COMS member. Two members are selected to review the material in depth and report to the committee at its next meeting. At the COMS meeting a decision is taken as to approval, approval with stipulations, deferral, or outright rejection.

2) For studies with ample precedent faster approval is likely. One COMS member is assigned to review the study. The recommendation can be for initial approval, further review or discussion by COMS at its next meeting. In all cases the COMS chair has the responsibility of accepting the recommendation or choosing another path.

3) Finally, studies deemed to have low risk and some (but not "ample") precedent will be sent to two COM members for their recommendations.

### 4. Multiple Clinical Sites

Many clinical studies involve multiple centers. When two (or more) centers fall under the COMS umbrella an application from a Principal Investigator at each institution is expected. However, identical protocols from different institutions can be considered together and approval for one will be approval for all.

### 5. Cooperative Arrangement with Dana-Farber Cancer Institute.

The Dana-Farber Cancer Institute (DFCI) is not covered by COMS. DFCI has its own Biosafety Committee - the Biohazard Control Committee (BCC). On occasion COMS and the BCC are asked to approve the same gene transfer protocol. Principal Investigators will have submitted applications to the IBC serving their institution that include an identical IRB protocol, Investigator's Brochure and Appendix M plus an institution specific application form. In such cases the two IBCs have agreed to accept each others decisions. The decision as to which IBC takes the lead will be made on a case to case basis.

### 6. Human Research Protocol Renewals

Clinical studies are approved for one year only. A renewal is necessary to proceed. Recently COMS has taken the position that a recent Data Safety Monitoring Board (DSMB) report can be substituted for a

---

<sup>4</sup> Office of Biotechnology Affairs: <http://www4.od.nih.gov/oba/guidelines.html>, OR <http://www4.od.nih.gov/oba/oct2000guide2.pdf>



standard renewal. In this connection the term “recent” means any time since the last renewal. Renewal for the subsequent year will be required one year after the date of the DSMB report.

A standard renewal form is available at the COMS web site for use when a timely DSMB report is not available. The form can be found at <http://www.hms.harvard.edu/orsp/coms/forms.htm>

#### **E. AMENDMENTS TO APPROVED RESEARCH PROTOCOLS**

Laboratory and Clinical protocol amendments are processed much in the same way as original submissions, without the necessity of submitting a formal application. A short letter or e-mail describing the additions and changes is usually all that is necessary. The local Biosafety Officer then evaluates the changes and decides whether the changes require a new application. If not, the Biosafety Officer generates a memorandum to the Committee Chair outlining the changes and recommending initial approval or full committee action.

### **VII. BIOSAFETY LEVEL NOMENCLATURE**

Laboratory and animal protocols are approved at a specific containment and procedure level<sup>5</sup>. The NIH Recombinant DNA Guidelines define a series of containment and procedure Biosafety Levels (BL) numbered from 1 (least restrictive) to 4 (most restrictive). Corresponding Biosafety Levels for animal studies are called BL1-N through BL4-N by the NIH.<sup>6</sup>

In addition to the defined NIH Biosafety Levels COMS has defined several variations on the BL1 through BL4 sequence. These are unique to COMS. It is possible the Committee will eventually dispense with these novel definitions. Until then the following levels are in use:

BL2 (B) and BL2-N (B) are convenience designations to indicate a study is to be carried out under BL2 conditions and procedures exclusively because it involves the use of human and/or non-human primate tissues or cells in culture. It is, therefore, under the OSHA Bloodborne Pathogen Standard.

BL2+ refers to studies in which physical containment follows BL2 guidelines while the procedures follow BL3 recommendations. This designation is applied to agents with serious pathological consequences but are not airborne pathogens. Studies with HIV are often carried out at BL2+.

ASL (Arthropod Safety Level) refers to conditions and procedures required for laboratories studying arthropods. [Arthropods are animals having an exoskeleton, a body divided into distinct parts, jointed legs and appendages and bilateral symmetry. The range from fruit flies to lobsters!] There are no “official” definitions of ASLs. However, a useful description can be found in the journal *Vector-Borne and Zoonotic Diseases*, **3 (2)**: issue of June 2003, particularly pp75-90. It can be reached at <http://www.liebertonline.com/vbz>

As a rule uninfected Arthropods can be housed under ASL1 conditions and procedures designed to prevent escape. Arthropods infected with human or animal pathogens are to be held under ASLs appropriate to the Biosafety Level required for the infectious organism. Finally genetically modified arthropods should be held at ACL2 or higher.

---

<sup>5</sup> Biosafety Levels are not used in clinical studies. Most Hospitals and clinics use terminology such as “Droplet Precautions” that do not have a counterpart in Biosafety nomenclature.

<sup>6</sup> Unfortunately, the Centers for Disease Control use a slightly different nomenclature. Laboratory levels are designated BSLx (for Bio Safety Level) and animal levels are designated ABSLx for Animal Bio Safety Levels.



## VIII. APPENDIX A. HARVARD UNIVERSITY POLICY WITH RESPECT TO HAZARDOUS BIOLOGICAL AGENTS



Policies and Procedures Governing the Use of Hazardous Biological Agents in Research or Instruction  
Under the Faculties of Arts and Sciences, Medicine and Public Health

Voted by the President and Fellows of Harvard College  
March 7, 1977 and December 11, 1978

1. Research involving hazardous or potentially hazardous biological agents shall be specially controlled.
2. Hazardous biological agents include:
  - a. Known pathogenic bacteria, viruses, and other infectious agents
  - b. Oncogenic viruses
  - c. Infected, or potentially infected, human and animal cells
  - d. Strains of bacterial, viruses, etc. whose pathogenicity is uncertain or whose use in the laboratory is not well established
  - e. High concentrations of infectious agents
  - f. Infectious nucleic acids
  - g. Hybrids of two or more agents or recombinant DNA molecules
3. Principal investigators shall be responsible for:
  - a. Estimating the potential biohazards associated with experiments performed in laboratories under their direction
  - b. Instituting the appropriate safeguards within these laboratories
  - c. Developing procedures for minimizing the effects of accidents
  - d. Training and ensuring the proficiency of relevant personnel in the application of these safeguards and procedures
  - e. Informing personnel both of the potential hazards and of the basis on which these hazards have been estimated
  - f. Maintaining these practices on a continuing basis.
4. Principal investigators shall secure the approval of the Committee on the Regulation of Hazardous Biological Agents before introducing a hazardous biological agent into their laboratories. The principal investigator shall be responsible for maintenance of records and incident reports related to all such agents in the laboratory.
5. Principal investigators shall consult with the Departmental Biohazards Safety Officer on questions regarding biohazards policy and shall seek the advice of the Committee on the Regulation of Hazardous Biological Agents on problems or questions that cannot be resolved by the Departmental Biohazards Safety Officer.



6. Principal investigators shall immediately notify the Committee on the Regulation of Hazardous Biological Agents of accidents or incidents in laboratories utilizing hazardous biological agents which raise doubts about the adequacy of the safeguards used.

7. These policies and procedures, so far as they are relevant, shall govern also instructional exercises which utilize hazardous biological agents.

## PROCEDURES

1. There shall be appointed a Standing Committee on the Regulation of Hazardous Biological Agents which shall be authorized to review and approve or disapprove, or state conditions for, the conduct of any research involving hazardous biological agents by an officer or other employee of the Faculty, or by a student.

2. Supervision and evaluation of the program of biohazard control shall be the responsibility of the Committee. It will formulate general safety related policy and will provide advice and direction regarding safety equipment, general procedures, training and information. The Committee will maintain permanent records of all potentially hazardous agents in use under the Faculty and of any significant laboratory accidents or illnesses. It will maintain appropriate health records and survey the Faculty, as needed, to keep such records up to date. It will conduct an annual survey of principal investigators whose research might include use of hazardous biological agents. The Committee will ensure the maintenance of a library of reference materials, books, articles and other background information relevance to biohazards safety. It will oversee the preparation and dissemination of educational materials needed by principal investigators and ensure proper liaison with the Fire and Police Departments and other service units which may require entry to areas in which hazardous agents are in use. To assure a minimum level of knowledge among all personnel using hazardous biological agents the Committee will sponsor preparation of a basic lecture and demonstration program which shall be presented to all new personnel before they begin work with such agents, and repeated annually for those already employed. Finally, the Committee shall ensure the conduct of frequent, on-site inspections of laboratories using hazardous Biological agents noting in its records the dates of such visits and the observations made.

3. The Division of Environmental Health and Safety of the University Health Services shall maintain an Office of Biohazards Health and Safety adequately staffed with individuals familiar with biohazards safety procedures to assist the Committee in carrying out its function.

4. In each department where laboratory investigations involving hazardous biological agents are under-way, or in prospect, a member of the Faculty with knowledge of microbiology and interest in biohazards control shall be appointed Departmental Biohazard Safety Officer. This individual's primary responsibility is to serve as liaison between principal investigators, the Committee and the Office of Biohazards; he or she will advise investigators on prevailing policies and procedures and will advise the Committee about problems and difficulties relevant to biohazard control which may arise within the department.



## IX. APPENDIX B. "SELECT AGENT" LISTING

Updated 30 January 2009.

Except for exclusions listed in the last page of the Appendix, the viruses, bacteria, fungi, toxins, genetic elements, recombinant nucleic acids, and recombinant organisms specified in this list are HHS, USDA or HHS/USDA overlap select agents and toxins.

1. Abrin (HHS) [*See exclusion on last page*]
2. African horse sickness virus (USDA, Animal)
3. African swine fever virus (USDA, Animal)
4. Akabane virus (USDA, Animal)
5. Avian influenza virus (highly pathogenic) (USDA, Animal) [*See exclusions on last page*]
6. Bacillus anthracis (Overlap) [*See exclusions on last page*]
7. Bluetongue virus (exotic) (USDA, Animal)
8. Botulinum neurotoxin producing species of Clostridium (HHS)
9. Botulinum neurotoxins (HHS) [*See exclusion on last page*]
10. Bovine spongiform encephalopathy agent (USDA, Animal)
11. Brucella abortus (Overlap) [*See exclusions on last page*]
12. Brucella melitensis (Overlap)
13. Brucella suis (Overlap)
14. Burkholderia mallei (formerly Pseudomonas mallei) (Overlap)
15. Burkholderia pseudomallei (formerly Pseudomonas pseudomallei) (Overlap)
16. Camel pox virus (USDA, Animal)
17. Central European Tick-borne encephalitis virus (HHS)
18. Cercopithecine herpesvirus 1 (Herpes B virus) (HHS)
19. Classical swine fever virus (USDA, Animal)
20. Clostridium perfringens epsilon toxin (HHS) [*See exclusion on last page*]
21. Coccidioides immitis (HHS)
22. Coccidioides posadasii (HHS) [*See exclusion on last page*]
23. Conotoxins (HHS) [*See exclusions on last page*]
24. Cowdria ruminantium (Heartwater) (USDA, Animal)
25. Coxiella burnetii (HHS) [*See exclusion on last page*]
26. Crimean-Congo haemorrhagic fever virus (HHS)
27. Diacetoxyscirpenol (HHS) [*See exclusion on last page*]
28. Eastern Equine Encephalitis virus (HHS)
29. Ebola viruses (HHS)
30. Ehrlichia ruminantium (Heartwater)
31. Far Eastern Tick-borne encephalitis (HHS)
32. Flexal virus (HHS)
33. Foot-and-mouth disease virus (USDA, Animal)
34. Francisella tularensis (HHS) [*See exclusions on last page*]
35. Goat pox virus (USDA, Animal)
36. Guanarito, virus (HHS)
37. Hendra virus (Overlap)
38. Japanese encephalitis virus (USDA, Animal) [*See exclusion on last page*]
39. Junin virus (HHS) [*See exclusion on last page*]
40. Kyasanur Forest disease (HHS)
41. Lassa fever virus (HHS)
42. Lumpy skin disease virus (USDA, Animal)
43. Machupo virus (HHS)
44. Malignant catarrhal fever virus (exotic) (Alcelaphine herpesvirus type 1) (USDA, Animal)
45. Marburg virus (HHS)
46. Menangle virus (USDA, Animal)
47. Monkeypox virus (HHS)
48. Mycoplasma capricolum subspecies capripneumoniae (contagious caprine pleuropneumonia) (USDA, Animal)
49. Mycoplasma mycoides subspecies mycoides small colony (MmmSC) (contagious bovine pleuropneumonia) (USDA, Animal)
50. Nipah virus (Overlap)
51. Omsk Hemorrhagic Fever (HHS)
52. Peronosclerospora philippinensis (USDA, Plant)
53. Peste des petits ruminants virus (USDA, Animal)
54. Phoma glycinicola (formerly Pyrenochaeta glycines) (USDA, Plant)
55. Ralstonia solanacearum, race 3, biovar 2 (USDA, Plant)
56. Rathayibacter toxicus
57. Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (Reconstructed 1918 Influenza virus) (HHS)
58. Ricin (HHS) [*See exclusion on last page*]



- |  |   |
|--|---|
| <p>59. Rickettsia prowazekii (HHS)</p> <p>60. Rickettsia rickettsii (HHS)</p> <p>61. Rift Valley fever virus (Overlap) [<i>See exclusion on last page</i>]</p> <p>62. Rinderpest virus (USDA, Animal)</p> <p>63. Russian Spring and Summer encephalitis (HHS)</p> <p>64. Sabia virus (HHS)</p> <p>65. Saxitoxin (HHS) [<i>See exclusion on last page</i>]</p> <p>66. Sclerophthora rayssiae var. zea (USDA, Plant)</p> <p>67. Sheep pox virus (USDA, Animal)</p> <p>68. Shiga-like ribosome inactivating proteins (HHS) [<i>See exclusion on last page</i>]</p> <p>69. Shigatoxin (HHS) [<i>See exclusion on last page</i>]</p> <p>70. Staphylococcal enterotoxins (HHS) [<i>See exclusion on last page</i>]</p> <p>71. Swine vesicular disease virus (USDA, Animal)</p> | <p>72. Synchytrium endobioticum (USDA, Plant)</p> <p>73. T-2 toxin (HHS) [<i>See exclusion on last page</i>]</p> <p>74. Tetrodotoxin (HHS) [<i>See exclusion on last page</i>]</p> <p>75. Variola major virus (Smallpox virus) (HHS)</p> <p>76. Variola minor virus (Alastrim) (HHS)</p> <p>77. Venezuelan Equine Encephalitis virus (Overlap) [<i>See exclusions on last page</i>]</p> <p>78. Vesicular stomatitis virus (exotic): Indiana subtypes VSV-IN2, VSV-IN3 (USDA, Animal)</p> <p>79. Virulent Newcastle disease virus<sup>1</sup> USDA, Animal)</p> <p>80. Xanthomonas oryzae (USDA, Plant)</p> <p>81. Xylella fastidiosa (citrus variegated chlorosis strain) (USDA, Plant)</p> <p>82. Yersinia pestis (HHS) [<i>See exclusions on last page</i>]</p> |
|--|---|

**Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms:**

1. Nucleic acids that can produce infectious forms of any of the select agent viruses . . .
2. Recombinant nucleic acids that encode for the functional forms of any toxin . . . if the nucleic acids:
  - (i) Can be expressed *in vivo* or *in vitro*; or
  - (ii) Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.
3. Select agents and toxins . . . that have been genetically modified.

(The removed phrases, “. . .” refer to the Select Agent list)

-----  
<sup>1</sup>A virulent Newcastle disease virus (avian paramyxovirus serotype 1) has an intracerebral pathogenicity index in day-old chicks (*Gallus gallus*) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.



## EXCLUSIONS:

1. Any select 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.
3. Fixed tissues that bear or contain select agents or toxins.
4. Genetic elements or sub-units of agents or toxins, if the genetic elements or sub-units are not capable of causing disease.
5. The vaccine strain of Junin virus (Candid #1).
6. The vaccine strain of Rift Valley fever virus (MP-12).
7. Venezuelan Equine encephalitis virus vaccine strain TC-83.
8. Venezuelan equine encephalitis (VEE) virus vaccine candidate strain V3526.
9. Japanese encephalitis virus, SA14-14-2 strain.
10. *Coccidioides posadasii*  $\Delta$ chs5 strain.
11. *Coccidioides posadasii*  $\Delta$ cts2/ $\Delta$ ard1/ $\Delta$ cts3 strain.
12. *Coxiella burnetii* Phase II, Nine Mile Strain, plaque purified clone 4.
13. *Brucella abortus* strain RB51 (vaccine strain).
14. *Brucella abortus* Strain 19
15. *Yersinia pestis*:
  - strains which are Pgm<sup>-</sup> due to a deletion of a 102-kb region of the chromosome termed the *pgm* locus (i.e.,  $\Delta$ *pgm*). Examples are *Y. pestis* strain E.V. or various substrains such as EV 76.
  - strains (e.g., Tjiwidej S and CDC A1122) devoid of the 75 kb low-calcium response (Lcr) virulence plasmid.
16. *Bacillus anthracis*
  - strains devoid of both plasmids pX01 and pX02.
  - strains devoid of the plasmid pX02 (e.g., *Bacillus anthracis* Sterne, pX01+pX02-).
17. *Francisella tularensis*:
  - subspecies *novicida* (also referred to as *Francisella novicida*) strain, Utah 112 (ATCC 15482).
  - subspecies *holartica* LVS (live vaccine strain; includes NDBR 101 lots, TSI-GSD lots, and ATCC 29684).
  - ATCC 6223 (also known as strain B38).
18. Avian Influenza virus: Several recombinant reference vaccine strains of highly pathogenic subtypes have been excluded based on results from in-vitro and in-vivo studies indicating that these strains were not pathogenic in avian species. The data requirements necessary for exclusion consideration under 9 CFR 121.3 (g) can be downloaded from [http://www.aphis.usda.gov/programs/ag\\_selectagent/template-for-ai.pdf](http://www.aphis.usda.gov/programs/ag_selectagent/template-for-ai.pdf). Specific reference vaccine strains have not been listed here for proprietary reasons.
19. The following toxins (in the purified form or in combinations of pure and impure forms) if the aggregate amount under the control of a principal investigator does not, at any time, exceed the amount specified:
  - 100 mg of Abrin
  - 0.5 mg of Botulinum neurotoxins
  - 100 mg of *Clostridium perfringens* epsilon toxin
  - 100 mg of Conotoxins  
Conotoxins specifically **excluded** are: the class of sodium channel antagonist  $\mu$ -conotoxins, including GIIIA; the class of calcium channel antagonist  $\omega$ -conotoxins, including GVIA, GVII, MVIIA, MVIIIC, and their analogs or synthetic derivatives; the class of NMDA-antagonist conantokins, including con-G, con-R, con-T and their analogs or synthetic derivatives; and the putative neurotensin agonist, contulakin-G and its synthetic derivatives.
  - 1,000 mg of Diacetoxyscirpenol
  - 100 mg of Ricin
  - 100 mg of Saxitoxin
  - 100 mg of Shigatoxin
  - 100 mg of Shiga-like ribosome inactivating proteins
  - 5 mg of Staphylococcal enterotoxins
  - 100 mg of Tetrodotoxin
  - 1,000 mg of T-2 toxin



## X. APPENDIX C. POLICIES AND GUIDELINES ADOPTED BY COMS

Transgenic Animal Guidelines  
*Adopted by COMS 4 March 2005*

### Introduction

This policy is based on the assumption that the overwhelming majority of transgenic mice and other small mammals pose no risk to the investigators, staff and public. It is also assumed most mice and other small rodents pose no risk the wild gene pool because a) laboratory animals are poorly adapted to the wild and b) the risk to the external gene pool is no greater for most transgenic rodents than for standard laboratory strains.

### COMS policy:

“Normal animal husbandry and signage is acceptable for small transgenic mammals in central animal facilities. Door sweeps and animal traps are mandatory for rooms containing transgenic rodents. Satellite and temporary laboratory “use areas” will also have to conform to these practices.

“Lost transgenic animals must be reported to the investigator in common with the current standard practice for non-transgenic animals.

“It is possible some rare transgenic animal lines will pose hazards. In those cases specific procedures will be instituted. Examples of such animals are those expressing viable viral pathogens or those shedding toxins. It is unlikely these animals will come from commercial suppliers. Thus the animals will have to be identified before they are generated. To this end Biosafety Officers will identify potentially biohazardous transgenic constructs from a PI’s application. If the Biosafety Officer deems that potentially hazardous animals may be generated, the study will be referred to the entire committee for examination and approval. COMS will also rely on core facilities to similarly identify potentially dangerous constructs before they are generated.”



## A. RETROVIRAL VECTOR GUIDELINES

Adopted by COMS September 28, 2001

These guidelines are written to avoid specifics. They provide general guidance to Biosafety Officers, Investigators and COMS as to how one estimates hazard and the containment and procedures needed to render risks acceptable. Retroviral vectors are placed into 4 classes according to risk.

The Four classes:

1. CANNOT Infect Human Cells, lower risk	BL1, BL1-N
2. CANNOT Infect Human Cells, higher risk	at least BL1, BL1-N with tests for RCR
3. CAN Infect Human Cells, lower risk	BL2, BL2-Ni
4. CAN Infect Human Cells, higher risk	at least BL2, BL2-Ni with tests for RCR

General definition of Risk (additional factors may shift risk rating and stipulations, see the table below).

Risk: Lower risk = at least three recombination events required to get an RCR, grown in murine cell, low toxicity transgene product.  
Higher risk = one of these characteristics: less than three recombination events required to get an RCR, grown in human cells, toxic transgene product.

BL2-Ni means administration at BL2 and shift to BL1 when it can be demonstrated that vector shedding is not possible (e.g., no vector RNA in blood, no detectable reverse transcriptase in blood. . . .)

### Factors that affect retroviral vector hazard

Relative to an ecotropic MoMLV vector from a transient murine cell packaging system based on a 3 plasmid system (gag-pol, env,  $\psi$  transgene) in which at least three recombination events are necessary to produce and RCR.

Characteristic	$\Delta$ Hazard	Why?
Ecotropic envelope protein	↔	Unlikely to infect human cells
Murine cell packaging system [Gal ( $\alpha$ 1-3) galactose epitope expressed]	↔	More chance of natural immunity inactivation
Three recombinations needed for RCR	↔	Much less likely to generate RCR
Transient packing system	↔	Less opportunity to recombine
Toxin gene expressed, Oncogene (defined loosely) expressed	↑↑	Gene product is potentially toxic
Single recombination event needed for RCR	↑↑	Likely to generate RCR
Protease, ribozyme expression	↑	Gene product is potentially toxic
Amphotropic envelope protein	↑	Can infect human cells
Two recombinations needed for RCR	↑	Less likely to generate RCR
Producer cell packaging system	↑	More opportunity to recombine
Human cell packaging system [No Gal ( $\alpha$ 1-3) galactose epitope expressed]	↑	Less chance of natural immunity inactivation
Lentivirus DNA flap	↑	Increases chance that DNA penetrates nuclear membrane
Self Inactivating system	↓	Reduces chance of RCR
Reduced homology among plasmids	↓	Reduces chance of RCR



## B. GUIDELINES FOR MICROBIOLOGIC SAFETY IN CLINICAL TRIALS INVOLVING XENOTRANSPLANTATION

Adopted by COMS on September 28, 2001

The goals of the Xenotransplantation Advisory Committee (XTAC) include the protection of subjects in clinical trials of xenotransplantation (XT), protection of the community at large, and the facilitation of such studies whenever possible. These goals are not contradictory. However, adherence to optimal safety practices will always take precedence when these goals come into conflict.

Xenotransplantation includes any study in which human tissues (including blood) come into contact (in vivo or ex vivo) with non-human fluids, cells, tissues, or organs. This includes cells or tissues intended for human uses that contact nonhuman cells in vitro (e.g., stem cells cultured with murine feeder cells). A central concern for any human study of XT is the possible introduction of novel infectious agents into the subjects and, subsequently, into their sexual and social contacts. This possibility has been reviewed extensively in the literature. For example, a number of potential pathogens have been described in swine including, but not limited to:

- ❑ Porcine endogenous retrovirus (PERV-A, B, and C): a family of C type retroviruses with some infectivity for human cell lines. No active infection of humans exposed to porcine tissues has been identified to date.
- ❑ Porcine cytomegalovirus (PCMV): a herpesvirus without known infectivity for human cells
- ❑ Porcine gammaherpesvirus: (PGHV) an agent associated with post-transplant lymphoma in immunosuppressed swine.
- ❑ Porcine circovirus: of unknown infectivity
- ❑ Many common pathogens of humans including mycobacteria, common bacteria (e.g., *S. suis* and *Salmonella spp.*), parasites (*Toxoplasma gondii*), fungi (*Aspergillus spp.*)

The risk of infection due to each of these organisms is unknown and unmeasurable for XT procedures. Thus, the FDA has developed guidelines and restrictions for the performance of such trials including sample archiving from donor animals and recipients, testing for a variety of infectious agents, and life-long-surveillance of recipients of xenogeneic tissues

(<http://www.cdc.gov/mmwr/PDF/rr/rr5015.pdf>).

It is the responsibility of each investigator to become familiar with relevant regulations and background materials and to assure that each protocol will adhere to these guidelines.

Specifically:

- ❑ The sponsor must ensure that appropriate counseling is provided to subjects and their close contacts (family and or sexual partners) to minimize the potential risk of transmission of infectious agents to social and sexual contacts (see pages 5, 17 and 18 of guidance document). Subjects must be required to agree to barrier protection during sexual contacts and to report unexplained illnesses after XT. Subjects must also educate close contacts and relatives regarding potential risks. Pregnancy and unprotected sexual contacts are central concerns regarding the possible transmission of pathogens to a fetus (potentially via germline transmission), to sexual contacts, and to society.
- ❑ Informational materials regarding potential hazards should be developed for staff and participants.



- ❑ Corporate sponsors are required to test donor animals and tissues for infectious agents (see pages 6-8, 16, 19-29 of guidance document) and to maintain archived blood and tissue samples. They must also report adverse events in clinical trials, and insure that appropriate and up-to-date microbiologic assays are in place for known and potential human pathogens. The sponsor of each study must maintain these records for 50 years. Surveillance samples are required from subjects, source animals, and health care workers (see pages 16, 27, 29, 33 of guidance document).
- ❑ Clinical centers performing XT trials should have the capability to culture and identify potential pathogens on site or through collaborators.
- ❑ Most clinical trials to date have tested blood cells or serum samples to ascertain the presence of potential infection during XT trials. Given that pathogens, including most viruses, have preferred tropism for specific tissues (e.g., brain, lymphocytes, liver), it is likely that such testing is not adequate to detect sub-clinical infection. Thus, it is reasonable to test multiple tissues during the course of each study (e.g., biopsies, blood samples, autopsy samples) using the most sensitive assays available. The development of new assays will necessitate the re-testing of stored samples. The absence of appropriate assays will necessitate the utilization of resources to develop such assays. Thus, for example, if a study involves xenotransplantation of porcine tissues into the brain, it is reasonable to test any brain tissue samples for PERV DNA and RNA. Other clinical compartments available for testing (i.e., blood) can be used for serial testing of cells and sera for PERV DNA and RNA. The risk for infection may be increased in some trials by the need for immune suppression to prevent graft rejection.

COMS considers the investigator responsible for all aspects of each XT trial. These responsibilities include, but are not limited to:

- ❑ Data regarding microbiologic risks are to be provided by corporate sponsors to the investigator. The investigator will provide such information to both COMS and the relevant IRB as part of, or as an amendment to, each XT proposal.
- ❑ The FDA requires that each XT trial includes appropriate infectious disease and epidemiological support to assure appropriate protection of subjects and their contacts throughout the trial and to assist in the evaluation of infectious syndromes if such occur.
- ❑ Annual reports of XT trials must be provided to COMS for review as a condition of trial continuation. As studies progress, it is reasonable to ask investigators to obtain and provide data obtained from earlier clinical trial subjects and from other participating centers. Corporate sponsors and/or investigators must assure that the maximum possible effort (up-to-date assay systems) has been made to identify any infection due to known or unknown infectious agents.
- ❑ The potential benefit to the patient and/or the scientific merit of the proposed trial must outweigh the perceived risks to the subject associated with XT procedures.
- ❑ Administrative review or approval of XT trials will not be available.
- ❑ Significant adverse events will be reported to the IRB and to COMS even if not considered related to the exposure to xenogeneic tissues. SAE's from other centers performing clinical trial must also be reported to COMS in a timely fashion. Any adverse event which may have implications for microbiologic safety must also be reported to COMS.
- ❑ Life-long monitoring of all subjects is required. Assurance of such monitoring is the responsibility of the investigator and trial sponsors. Subjects unable to comply with this or other aspects of the trial should not be included as trial subjects.
- ❑ Investigators should consider that review of complex XT trials is a time consuming process. The timely submission of materials will expedite the review process.



## C. CERTIFICATION REQUIREMENTS FOR BL3 LABORATORIES

### Commissioning

#### Proposal for the COMS Commissioning Committee

1. A committee of 4 or 5 members.
  - a. All the members do not have to be COMS members but should all have a connection with a Harvard affiliated institution.
2. The membership should be
  - a. A COMS public member.
  - b. A veterinarian for BL3-N facilities
  - c. Two COMS voting members without conflict for the site or people involved in the BL3 facility
  - d. A Biosafety Officer other than the one responsible for the inspected institution.
3. Before the inspection.
  - a. The Commissioning Committee will meet once, perhaps with a PI presentation, to plan the visit and to discuss the issues involved.
  - b. They will select a chair who will be responsible for leading meetings and preparing the final report.
  - c. The Commissioning Committee will be provided:
    - iii) As built engineering plans
    - iv) SOPs as requested, such as:
      - (1) Entry and exit procedures.
      - (2) Emergency plans.
      - (3) Training plans.
4. The inspection.
  - a. Commissioning Committee gathers at site. They will be provided with a meeting room to privately discuss the upcoming inspection, any last minute details, and to go over the planned visit.
  - b. The Commissioning Committee will gather in the same room after the inspection to formulate and questions that arose during the visit and to prepare for the final report. The Chair will outline the final report and give each member responsibility for writing a short report on one specific aspect of the inspection.
5. After the inspection.
  - a. The Commissioning Committee members will submit their short reports to the Chair via e-mail.
  - b. The Chair will put these sections into a final report and distribute the report to the Commissioning Committee for final comments.
  - c. The Chair will manage an e-mail vote on whether to approve the facility, to approve with stipulations, to reject, or to defer approval.
  - d. The final report will be sent to the COMS office for distribution before the next COMS meeting.
6. At COMS meeting
  - a. If a COMS member is associated with the BL3 facility this will be considered a conflict of interest and they will be asked to leave the room while the proposal is being discussed.
  - b. The Commissioning Committee Chair will present and summarize the final report. A recommendation as to approval will be made to COMS.
  - c. Individual Commissioning Committee members will present their point of view.
  - d. COMS will vote on whether to approve, approve with stipulations, reject or defer the BL3 facility.



## D. POLICY FOR VALIDATING ATTENUATED STRAINS OF BL3<sup>7</sup> ORGANISMS,

Adopted by COMS on 26 May 2006

Objective: To verify the identity of attenuated strains of BL3 organisms.

All attenuated strains of BL3 Select Agents obtained from outside sources must be shipped directly to the NERCE/BEID laboratory for validation.  
Call Gerald Beltz: 617-432-5520  
*This requirement does not apply to strains of **non**-select BL3 Agents. They can be tested in other labs.*

1. Possession and research involving attenuated BL3 organisms must be approved by COMS.
2. Validation.
  - a. Until attenuation is validated all experiments with attenuated BL3 organisms must take place at BL3 unless lesser containment is approved by COMS.
    - i. Harvard has no BL4 laboratories. Hence attenuated BL4 agents cannot be validated at Harvard.
    - ii. Validation procedures must be approved by COMS.
      - a) Approval by two reviewers with the necessary expertise will suffice.
    - iii. Validation must be carried out in an approved COMS registered laboratory equipped for and experienced with strain validation.
    - iv. Documentation of validation testing must be submitted to COMS or NERCE/ BEID for approval and permanent archiving.
  - b. After the initial validation, it is recommended the attenuated BL3 organism be grown and aliquoted in quantities sufficient for use until the project is completed. This will be the seed stock for future cultures.
    - i. Attenuated BL3 organisms must be stored in a secured, limited access facility.
    - ii. A detailed, legible, log of their use must be kept by the investigator.
3. Maintenance. Ensuring attenuated strains remain attenuated over long periods.
  - a. Vials of Seed Stock and Working Stock derived from Seed Stock should be sterilized and discarded after a single use.
    - i. Hence numerous aliquots should be generated by the receiving laboratory.
    - ii. Working Stock must be derived only from Seed Stock.
    - iii. When Seed Stock is nearly exhausted a sample of Master Stock can be obtained from NERCE/ BEID.
      - a). Revalidation is also acceptable if Master Stock is not available.
4. Transfer to another Laboratory.
  - a. Attenuated BL3 organisms or their derivatives may not be transferred to another laboratory without COMS approval.
  - b. Attenuated BL3 Select Agents or their derivatives may not be transferred to other laboratories.
    - i. Only NERCE / BEID is permitted to distribute attenuated Select Agents.
5. Failure to comply with these provisions may be the basis for disciplinary action.

---

<sup>7</sup> An attenuated BL3 organism is one that can be safely used at BL2 or (rarely) BL1 containment and procedures.



## XI. APPENDIX D. ACRONYMS

APHIS	Animal and Plant Health Inspection Service (Part of the US Agriculture Department)
BCC	DFCI Biohazard Control Committee
BIDMC	Beth Israel Deaconess Medical Center
BL1, BL2, BL3	Biosafety Level 1, Biosafety Level 2, Biosafety Level 3
BL1-N, BL2-N, BL3-N	Animal Biosafety Level 1, Animal Biosafety Level 2, Animal Biosafety Level 3
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSO	Biosafety Officer
BWH	Brigham & Women's Hospital
CBR	CBR Institute for Biomedical Research
CDC	Centers for Disease Control and Prevention
CHMC	Children' Hospital Medical Center
COMS	Committee on Microbiological Safety
DFCI	Dana-Farber Cancer Institute
FAS	Harvard Faculty of Arts and Sciences
GMP	Good Manufacturing Practice
HMS	Harvard Medical School
HSDM	Harvard School of Dental Medicine
HSPH	Harvard School of Public Health
IACUC	Institutional Animal Care and Use Committee
IBC	Institutional Biosafety Committee
IRB	Institutional Review Board
JDI, JDC	Joslin Diabetes Institute, Joslin Diabetes Center
McL	McLean Hospital
MEEI	Massachusetts Eye and Ear Infirmary
MGH	Massachusetts General Hospital
NIH	National Institutes of Health
PRB	Partners Research Building
RAC	Recombinant DNA Advisory Committee
SBI	Shriners Burns Institute
SERI	Schepen's Eye Research Institute



## XII. APPENDIX E. BIOCONTAINMENT RECOMMENDATIONS

Through the years COMS has made hundreds of decisions as to the proper procedures and containment for a great many biological agents. Although these precedents may be overruled by special circumstances or increased knowledge it is likely that future protocols using these agents will continue to be governed by precedent.

Thus investigators wishing to have an idea of the containment and procedures to be recommended by the Committee will find it useful to consult the following tables.

The term “toxic gene” in this table means biological toxins *and* oncogenes.

Viruses	Lab Containment	Animal Housing	Restrictions
Adeno Associated Virus	BL1	BL1-N	Packaged without helper virus and does not express toxic genes
Adenovirus	BL2	BL2-N	
Cytomegalovirus (CMV)	BL2	BL2-N	
Eastern Equine Encephalitis Virus	BL2	BL2-N	No newly hatched chicks or birds, No vectors <b>SELECT AGENT</b>
Epstein-Barr Virus	BL2	BL2-N	
Hepatitis B Virus (HBV)	BL2	BL2-N	BL3 for large scale studies
Hepatitis C Virus (HCV)	BL2	BL2-N	BL3 for large scale studies
Human Immunodeficiency Virus (HIV 1 & 2)	BL2	BL2-N	
Human T-Cell Leukemia Virus (HTLV)	BL2	BL3-N	Seems to be identical to Simian T-Cell Leukemia Virus
Herpesvirus saimiri (HVS)	BL2	BL2-N	
Recombinant HVS	BL2	BL2-N	
Herpes Simplex Virus (HSV) I, II	BL2	BL2-N	
HHV 8 (Human Herpes Virus 8, Kaposi related virus)	BL2	BL2-N	
Herpes Zoster, Varicella Zoster Virus (VZV, HHV3)	BL2	BL2-N	
Influenza A/PR/8/34 An attenuated strain.	BL2	BL2-N	
Lymphocryptovirus non-human, Cercopithecine herpesvirus 15, Rhesus EBV	BL2	BL2-N	
Lymphocytic Choriomeningtis Virus (LCMV)	BL2	BL2-N	
LCMV Armstrong strain	BL2	BL2-N	Armstrong strain is avirulent in hamsters and guinea pigs.
Murine Leukemia Virus	BL1	BL1-N	
Papilloma Virus	BL2	BL2-N	
Polyoma (Murine)	BL2	BL2-N	BL2 Practices during inoculation
Polio Virus	BL2	BL2-N	
Pseudorabies Virus	At least BL2	At least BL2-N	Highly toxic to farm animals, particularly pigs. Not a human pathogen. Strong state agriculture regulations.
Respiratory Syncytial Virus (RSV)	BL2	BL2-N	
Reovirus	BL2	BL1-N	BL2 Practices during inoculation



Viruses	Lab Containment	Animal Housing	Restrictions
Sindbis Virus VECTOR	BL2	BL2-N	
Recombinant SFV	BL2	BL2-N	
Simian Immunodeficiency Virus (SIV)	BL2	BL2-N (+ stipulations)	
Recombinant SIV	BL2	BL2-N	
Simian T-Cell Leukemia Virus (STLV)	BL2	BL1-N	Seems to be identical to Human T-Cell Leukemia Virus BL2 Practices during inoculation
Vaccinia Virus	BL2	BL2-N	<b>Staff must be made aware that a vaccine is available.</b>
Vesicular Stomatitis Virus (Lab strain)	BL2	BL2-N	BL3-N wild type or naturally infected livestock <b>SELECT AGENT IF EXOTIC</b>
Yellow Fever 17D strain	BL2	BL2-N	<b>EXCLUDED SELECT AGENT</b>

Bacteria	Lab Containment	Animal Housing	Restrictions
Bacillus anthracis	BL3	BL3-N	BL3 decided at COMS 10/6/06 <b>SELECT AGENT</b>
Bacillus anthracis (Sterne strain)	BL2	BL2-N	
Bacteroides fragilis	BL2	BL1-N	BL2 - practices during animal inoculation
Bacillus subtilis	BL2	BL2-N	
Borrelia burgdorferi	BL2	BL1-N no vector	BL2-N with vector
Chlamydia trachomatis	BL2	BL2-N	No intact pneumonic species
Enterococcus spp.	BL2	BL1-N	BL2-N antibiotic resistant strain
Escherichia coli K12, B	BL1	BL1-N	BL2 - practices during animal inoculation BL2/BL2-N-for pathogenic strains
Enteroinvasive E. coli Enteropathogenic E. coli	BL2	BL2-N	
Haemophilus influenza (group B)	BL2	BL2-N	
Legionella pneumophila	BL2	BL2-N	
Listeria monocytogenes	BL2	BL2-N	
Mycobacterium avium	BL2	BL2-N	
Mycobacterium bovis (BCG)	BL2	BL2-N	
Mycobacterium bovis	BL2	BL2-N	
Mycobacterium tuberculosis	BL3	BL3-N	
Pseudomonas aeruginosa	BL2	BL1-N	BL2 - practices during animal inoculation BL2-N antibiotic resistant strain
Salmonella typhimurium	BL2	BL2-N	
Shigella flexneri	BL2	BL2-N	
Staphylococcus aureus	BL2	BL1-N	BL2 - practices during animal inoculation BL2-N antibiotic resistant strain
Staphylococcus epidermidis	BL2	BL1-N	BL2 - practices during animal inoculation BL2-N antibiotic resistant strain
Streptococcus agalactiae	BL2	BL1-N	BL2 practices during animal inoculations BL2-N antibiotic resistant strain
Vibrio cholera	BL2	BL2-N	

Parasites	Lab Containment	Animal Housing	Restriction
Cryptosporidium parvum	BL2	BL2-N	
Leishmania spp.	BL2	BL1-N no vector	BL2-N with vector
Pneumocystis carinii	BL2	BL1-N	BL2 - practices during animal inoculation
Trichinella spirallis	BL2	BL1-N	BL2 - practices during animal inoculation BL2-N - initial 72 hours post exposure



<b>Fungi</b>	<b>Lab Containment</b>	<b>Animal Housing</b>	<b>Restriction</b>
Candida albicans	BL2	BL1-N	BL2 - practices during animal inoculation



# XIII. APPENDIX F. VECTOR BIOCONTAINMENT DRAFT

NOTE: Proper containment and procedures are affected by the nature of expressed transgenes. The recommendations below do not take the transgene into account.

In all cases COMS approval is required. In most cases initial approval based on precedent is required before a study begins. The study then is formally approved, by vote, at the next COMS meeting.

<b>Adenovirus Vector</b>	OBA Required Action	Citation(s)	COMS recommendation
Construction	IBC Approval before start	Section III-D-1-a, Appendix C-II	BL2
Possession	Not covered	I-B	BL2
Propagation (293 cells)	Not Covered	Section III-D-1-a (?)	BL2
Transduced Cells	Not Covered	I-B	BL2
Animal administration	Not Covered	I-B	BL2-Ni
<p>General Comments: Construction is NOT covered by the 2/3 rule.                      Adenovirus vectors with disabled E1, E3 and/or E4 regions cannot grow in normal cells. They can grow in specially engineered cells that express the missing gene products.                      Some packaging systems generate preparations contaminated with virulent adenovirus due to recombination between vector and homologous regions in the engineered host cell. The contaminant is not a helper virus.                      Adenovirus, Serotype 5, does not integrate into target eukaryotic cells. Thus transduction is transient.                      COMS' BL2 recommendation reflects the (low) possibility of virulent adenovirus contaminants.</p>			

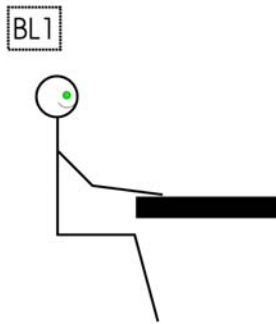
<b>Ecotropic Murine Retrovirus Vector</b>	OBA Required Action	Citation(s)	COMS recommendation
Construction	Exempt	Appendices B-V-1, C-I, C-II	BL1
Possession	Not covered	Section I-B, Appendix B-V-1	BL1
Propagation	Theoretically possible, but not practical at present.		
Transduced Cells	Not Covered	Section I-B	BL1
Animal administration	Not Covered	Section I-B	BL1-N
<p>General Comments: Construction is covered by the 2/3 rule.                      Retroviral SIN vectors cannot replicate. Retroviral vectors integrate into the target eukaryotic cell genome at random. The integrated DNA is not precisely homologous to the vector RNA.</p>			

<b>Amphotropic Murine Retrovirus Vector</b>	OBA Required Action	Citation(s)	COMS recommendation
Construction	Exempt	Appendices B-V-1, C-I, C-II	BL2
Possession	Not covered	Section I-B, Appendix B-V-1	BL2
Propagation	Theoretically possible, but not practical at present.		
Transduced Cells	Not Covered	Section I-B	BL2
Animal administration	Not Covered	Section I-B	BL2-Ni
<p>General Comments: Construction is covered by the 2/3 rule.                      Retroviral SIN vectors cannot replicate. Retroviral vectors integrate into the target eukaryotic cell genome at random. The integrated DNA is not precisely homologous to the vector RNA.</p>			

<b>Lentivirus (HIV-1) Retrovirus Vector</b>	OBA Required Action	Citation(s)	COMS recommendation
Construction	Exempt	Appendices B-V-1, C-I, C-II	BL2
Possession	Not covered	Section I-B,	BL2
Propagation	Theoretically possible, but not practical at present.		
Transduced Cells	Not Covered	Section I-B	BL2
Animal administration	Not Covered	Section I-B	BL2-Ni
<p>General Comments: Construction is covered by the 2/3 rule.                      Retroviral SIN vectors cannot replicate. Retroviral vectors integrate into the target eukaryotic cell genome at random. The integrated DNA is not precisely homologous to the vector RNA.</p>			

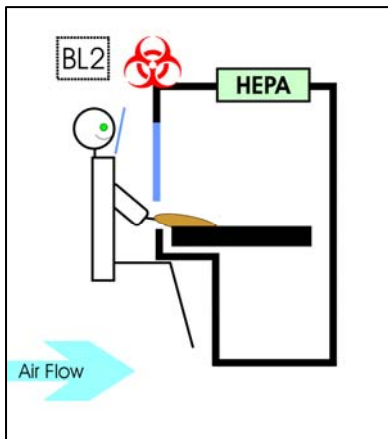


## XIV. APPENDIX G. BIOSAFETY AND RISK LEVELS<sup>8</sup>



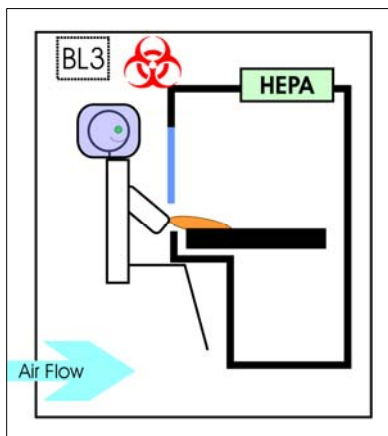
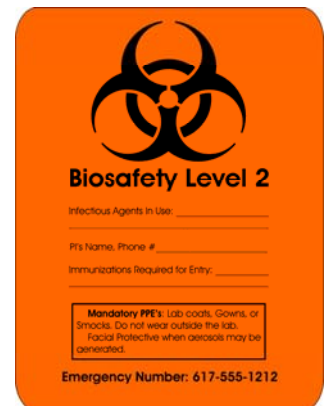
### Biosafety Level 1 Don't Eat It!

Working at a bench,  
No gloves, No goggles, No lab coat,



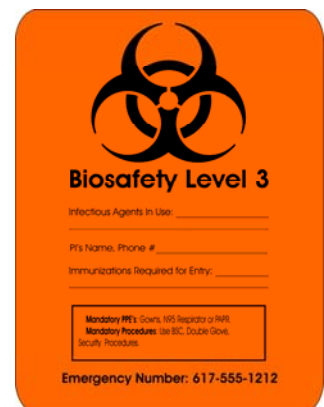
### Biosafety Level 2 Don't Touch It!

Working at Bench or in Biosafety Cabinet (if aerosols are possible).  
Gloves, Safety goggles or face shield, Lab coat, Closed door, Air flow into BL2 lab, Warning sign outside door, Biosafety Cabinet, Autoclave available.



### Biosafety Level 3 Don't Breathe It!

Work must be in Biosafety Cabinet.  
Biosafety level 2 PLUS Sealed Lab, Respirator (preferably PAPR), Changing room outside facility, Double door vestibule(s), Autoclave inside facility.



### Biosafety Level 4 Don't Do It!

Summary of Risk Groups on page 33.  
Summary of Biosafety Levels on page 34.  
Summary of Animal Biosafety Levels on page 35.

<sup>8</sup> With a tip of the hat to our mentor, Gwladys Caspar.

**CLASSIFICATION OF INFECTIOUS MICROORGANISMS BY RISK GROUP**

Note: Risk Groups correlate with but do not equate to biosafety levels.

RISK GROUP CLASSIFICATION	NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES 2002	WORLD HEALTH ORGANIZATION LABORATORY BIOSAFETY MANUAL 3 <sup>RD</sup> EDITION 2004
Risk Group 1	Agents that are not associated with disease in healthy adult humans.	(No or low individual and community risk) A microorganism that is unlikely to cause human or animal disease.
Risk Group 2	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are <i>often</i> available.	(Moderate individual risk; low community risk) A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.
Risk Group 3	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions <i>may be</i> available (high individual risk but low community risk).	(High individual risk; low community risk) A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.
Risk Group 4	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are <i>not usually</i> available (high individual risk and high community risk).	(High individual and community risk) A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available. <sup>3</sup>



**SUMMARY OF RECOMMENDED BIOSAFETY LEVELS FOR *INFECTIOUS* AGENTS**

Note: BSL (Biological Safety Level) in BMBL is equivalent to BL (Biosafety Level) in the NIH recombinant DNA Guidelines

BSL	AGENTS	PRACTICES	PRIMARY BARRIERS AND SAFETY EQUIPMENT	FACILITIES (SECONDARY BARRIERS)
1	Not known to consistently cause diseases in healthy adults	Standard Microbiological Practices	None required	Open bench and sink required
2	<ul style="list-style-type: none"> <li>Agents associated with human disease</li> <li>Routes of transmission include percutaneous injury, ingestion, mucous membrane exposure</li> </ul>	BSL-1 practice plus: <ul style="list-style-type: none"> <li>Limited access</li> <li>Biohazard warning signs</li> <li>“Sharps” precautions</li> <li>Biosafety manual defining any needed waste decontamination or medical surveillance policies</li> </ul>	Primary barriers: <ul style="list-style-type: none"> <li>Class I or II BSCs or other physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials</li> </ul> PPEs*: <ul style="list-style-type: none"> <li>Laboratory coats; gloves; face protection as needed</li> </ul>	BSL-1 plus: <ul style="list-style-type: none"> <li>Autoclave available</li> </ul>
3	<ul style="list-style-type: none"> <li>Indigenous or exotic agents with potential for aerosol transmission</li> <li>Disease may have serious or lethal consequences</li> </ul>	BSL-2 practice plus: <ul style="list-style-type: none"> <li>Controlled access</li> <li>Decontamination of all waste</li> <li>Decontamination of laboratory clothing before laundering</li> <li>Baseline serum</li> </ul>	Primary barriers: <ul style="list-style-type: none"> <li>Class I or II BSCs or other physical containment devices used for all open manipulation of agents</li> </ul> PPEs*: <ul style="list-style-type: none"> <li>Protective laboratory clothing; gloves; respiratory protection as needed</li> </ul>	BSL-2 plus: <ul style="list-style-type: none"> <li>Physical separation from access corridors</li> <li>Self-closing, double-door access</li> <li>Exhaust air not recirculated</li> <li>Negative airflow into laboratory</li> </ul>
4	<ul style="list-style-type: none"> <li>Dangerous/exotic agents which pose high risk of life-threatening disease</li> <li>Aerosol-transmitted laboratory infections have occurred; or related agents with unknown risk of transmission</li> </ul>	BSL-3 practices plus: <ul style="list-style-type: none"> <li>Clothing change before entering</li> <li>Shower on exit</li> <li>All material decontaminated on exit from facility</li> </ul>	Primary barriers: <ul style="list-style-type: none"> <li>All procedures conducted in Class III BSCs or Class I or II BSCs in combination with full-body, air-supplied, positive pressure personnel suit</li> </ul>	BSL-3 plus: <ul style="list-style-type: none"> <li>Separate building or isolated zone</li> <li>Dedicated supply and exhaust, vacuum, and decontamination systems</li> <li>Other requirements outlined in the text</li> </ul>

\* PPE – Personal Protective Equipment



**SUMMARY OF RECOMMENDED BIOSAFETY LEVELS FOR ACTIVITIES IN WHICH EXPERIMENTALLY OR NATURALLY INFECTED VERTBRATE ANIMALS ARE USED**

Note: ABSL (Animal Biological Safety Level) in BMBL is equivalent to BL-N in the NIH recombinant DNA Guidelines.

ABSL	AGENTS	PRACTICES	PRIMARY BARRIERS AND SAFETY EQUIPMENT	FACILITIES (SECONDARY BARRIERS)
1	Not known to consistently cause diseases in healthy adults	Standard animal care and management practices, including appropriate medical surveillance programs	As required for normal care of each species	Standard animal facility: <ul style="list-style-type: none"> <li>• No recirculation of exhaust air</li> <li>• Directional air flow recommended</li> <li>• Hand washing sink is available</li> </ul>
2	<ul style="list-style-type: none"> <li>• Associated with human disease</li> <li>• Hazard: percutaneous exposure, ingestion, mucous membrane exposure.</li> </ul>	ABSL-1 practice plus: <ul style="list-style-type: none"> <li>• Limited access</li> <li>• Biohazard warning signs</li> <li>• “Sharps” precautions</li> <li>• Biosafety manual</li> <li>• Decontamination of all infectious wastes and of animal cages prior to washing</li> </ul>	ABSL-1 equipment plus primary barriers: <ul style="list-style-type: none"> <li>• Containment equipment appropriate for animal species</li> <li>PPEs*: • Laboratory coats, gloves, face and respiratory protection as needed</li> </ul>	ABSL-1 plus: <ul style="list-style-type: none"> <li>• Autoclave available</li> <li>• Hand washing sink available</li> <li>• Mechanical cage washer recommended</li> </ul>
3	<ul style="list-style-type: none"> <li>• Indigenous or exotic agents with potential for aerosol transmission</li> <li>• Disease may have serious health effects</li> </ul>	ABSL-2 practice plus: <ul style="list-style-type: none"> <li>• Controlled access</li> <li>• Decontamination of clothing before laundering</li> <li>• Cages decontaminated before bedding removed</li> <li>• Disinfectant foot bath as needed</li> </ul>	ABSL-2 equipment plus: <ul style="list-style-type: none"> <li>• Containment equipment for housing animals and cage dumping activities</li> <li>• Class I, II or III BSCs available for manipulative procedures (inoculation, necropsy) that may create infectious aerosols.</li> <li>PPEs: • Appropriate respiratory protection</li> </ul>	ABSL-2 facility plus: <ul style="list-style-type: none"> <li>• Physical separation from access corridors</li> <li>• Self-closing, double-door access</li> <li>• Sealed penetrations</li> <li>• Sealed windows</li> <li>• Autoclave available in facility</li> </ul>
4	<ul style="list-style-type: none"> <li>• Dangerous/exotic agents that pose high risk of life threatening disease</li> <li>• Aerosol transmission, or related agents with unknown risk of transmission</li> </ul>	ABSL-3 practices plus: <ul style="list-style-type: none"> <li>• Entrance through change room where personal clothing is removed and laboratory clothing is put on; shower on exiting</li> <li>• All wastes are decontaminated before removal from the facility</li> </ul>	ABSL-3 equipment plus: <ul style="list-style-type: none"> <li>• Maximum containment equipment (i.e., Class III BSC or partial containment equipment in combination with full body, air-supplied positive-pressure personnel suit) used for all procedures and activities</li> </ul>	ABSL-3 facility plus: <ul style="list-style-type: none"> <li>• Separate building or isolated zone</li> <li>• Dedicated supply and exhaust, vacuum and decontamination systems</li> <li>• Other requirements outlined in the text</li> </ul>

\* PPE – Personal Protective Equipment



## XV. INDEX

A Bit of History .....	1	Fundamental Policy Statement .....	1
Additional Considerations For Clinical Studies .....	14	Guidelines for Microbiologic Safety in Clinical Trials Involving Xenotransplantation .....	23
Amendments to Approved Research Protocols .....	15	Harvard, NIH, Boston, and Cambridge Requirements .....	3
Annual Clinical Renewals .....	8	Human Gene Transfer Studies .....	10
Annual Laboratory Renewals .....	9	Human Research Protocol Renewals .....	14
Appendix A. Harvard University Policy With Respect to Hazardous Biological Agents.....	16	Human Xenotransplants and Xenografts .....	10
Appendix B. Select Agent Listing .....	18	Index .....	36
Appendix C. Policies and Guidelines Adopted by COMS.....	21	Infectious Agents and Human Subjects .....	10
Appendix D. Acronyms .....	27	Infectious Materials .....	10
Appendix E. Biocontainment Recommendations .....	28	Introduction .....	11, 21
Appendix F. Vector Biocontainment DRAFT .....	31	Investigator Presentations .....	13
Appendix G. Biosafety and Risk Levels.....	32	Laboratory Studies.....	5, 8, 10
Biological Safety Officers' Responsibilities .....	4	Laboratory Studies Closely Associated with Clinical Studies .....	8
Biosafety Level Nomenclature .....	15	Mailing Schedule .....	7
Biosafety Officer Evaluation .....	13	Multiple Clinical Sites .....	14
Biosafety Officer Memo .....	12	NIH Regulations for Human DNA Transfer Studies .....	14
Boston High Hazard Laboratories .....	4	NIH Requirements .....	3
Boston Laboratory Registration.....	4	Other COMS policies .....	9
Boston Recombinant DNA .....	3	Polices related to Clinical Trials.....	7
Boston Reporting Illness .....	4	Policies Related to Laboratory Studies.....	8
Boston Requirements.....	3	Principal Investigator, Laboratory Director, or Supervisor Responsibilities .....	4
Boston Summary .....	3	Procedures Common to All Applications .....	12
Certification Requirements for BL3 Laboratories .....	25	Procedures for all Clinical Studies.....	14
Clinical Holds .....	7	Protocol Approval Procedure .....	11
Clinical Studies.....	5, 8, 10, 14	Protocol Termination.....	13
Committee Approval .....	13	Protocols Involving Oligonucleotides .....	9
Communicating with COMS .....	13	Recombinant DNA Materials .....	10
COMS... 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 21, 22, 23, 24, 25, 26, 27, 28, 29, 31		Referrals to Human Gene Transfer and Xenotransplantation Trials at External Institution .....	7
COMS Interpretation of the OSHA Bloodborne Pathogen .....	8	Responsibilities.....	2, 4
COMS Membership.....	5	Retroviral Vector Guidelines.....	22
COMS Policies and Procedures.....	5	Reviewers .....	12
COMS Schedule .....	6	Security Specifics .....	10
COMS Schedule and Mailings .....	6	Serum Storage .....	9
Contents of a Typical Mailing .....	6	Supplementary Material for Clinical Studies.....	14
Cooperative Arrangement with Dana-Farber Cancer Institute. ....	14	Tissue Processing Laboratories for Human Trials.....	8
Core Labs.....	9	Types of Protocols .....	10
Document Flow .....	11	Updates, Amendments and New Registrations.....	8
Duties of the Biological Safety Office.....	5	What Follows.....	1
Functions and Organization.....	2		

