Policy & Procedure Manual

Of the

Institutional Biosafety Committee

Thomas Jefferson University

Version 1: July 28, 1995
Version 2: October 31, 2003
Version 3: June 2, 2006
Version 4: January 11, 2007
Version 5: April 1, 2008
Version 6: April 25, 2008
Version 7: August 18, 2008
Version 8: June 1, 2013

Table of Contents

Policy & Procedure Manual for the Institutional Biosafety Committee of Thomas Jefferson University

Mission Statement

The mission of the Institutional Biosafety Committee (IBC) at Thomas Jefferson University is to ensure that research involving recombinant DNA (rDNA), synthetic nucleotides, infectious agents (pathogens), biological toxins, nanotechnology, or select agents is classified at the appropriate biosafety level and done in accordance with all appropriate guidelines, regulations and good safety practices.

Requirements for an Institutional Biosafety Committee

Under the NIH *Guidelines for Research Involving Recombinant or Synthetic DNA Molecules (NIH Guidelines)*, each institution conducting or sponsoring recombinant or synthetic nucleic acid research covered by these Guidelines is responsible for ensuring that the research is carried out in full conformity with the provisions of the Guidelines. The institution must establish and implement policies that provide for the safe conduct of recombinant or synthetic nucleic acid research and ensure compliance with the Guidelines. The institution must also establish an Institutional Biosafety Committee (IBC) whose responsibilities need not be restricted to recombinant or synthetic nucleic acids. If the institution is engaged in recombinant or synthetic nucleic acid research requiring biosafety level-3 (BL-3) or higher containment or is engaged in large-scale (greater than 10 liters of culture media) research, it must appoint a Biological Safety Officer (BSO) who shall be a member of the IBC.

Under the Occupational Safety and Health Agency (OSHA) Bloodborne Pathogens Standard (29 CFR 1910.1030), the University is obliged to ensure that employees whose work requires them to come in contact with human blood or other potentially infectious material shall be adequately protected against occupational exposure.

The IBC is also responsible for working with the Institutional Animal Care and Use Committee (IACUC) to ensure that animal experiments in which biohazardous agents are used are conducted in a manner commensurate with Federal guidelines and/or regulations.

The IBC is also responsible for interacting with the University Health Services to ensure that investigators conducting research involving biohazardous agents are offered immunization against the agent being studied, in so far as, a vaccine is available.

The Authority of the Institutional Biosafety Committee

The authority of the IBC is derived predominantly from:

- *NIH Guidelines for Research Involving Recombinant and Synthetic DNA Molecules,* as amended effective March 5, 2013 (77 FR 54584). The *NIH Guidelines* specify practices for constructing and handling recombinant

molecules, synthetic DNA, as well as cells, organisms, and viruses containing either recombinant or synthetic DNA.

- Occupational Safety and Health Agency (OSHA) Bloodborne Pathogens Standard 29 CFR 1910.1030, which regulates exposure to human blood, tissues, body fluids, cells and cell lines.

- CDC/NIH *Biosafety in Microbiological and Biomedical Research Laboratories* (U.S. Department of Health and Human Services/Public Health Service Publication (5th Edition, 2009, HHS Publication # (CDC) 21-1112.)

The IBC also makes decisions based on:

- Thomas Jefferson University IBC Standard Operating Procedures for Biosafety Level 3 facilities
- Thomas Jefferson University IBC Standard Operating Procedures for Biosafety Level 2/3 facilities
- Thomas Jefferson University IBC Standard Operating Procedures for Vaccinia research
- Thomas Jefferson University Bloodborne Pathogens Control Plan for Research Laboratories
- Thomas Jefferson University Guide to Laboratory Safety

Responsibilities of the Institutional Biosafety Committee

- Review rDNA, synthetic nucleic acid, nanotechnology, infectious agent (pathogen), biological toxin, or select agent research conducted at or sponsored by Thomas Jefferson University
- Notify the Principal Investigator of the results of the IBC review and approval process
- Set containment levels
- Periodically review research conducted at the institution to ensure compliance with the NIH Guidelines
- Adopt emergency plans covering accidental spills and personnel contamination
- Report, along with the Principal Investigator, any significant problems or violations of the NIH Guidelines and any significant research related accidents or illnesses to the Department of Environmental Health and Safety as well as the appropriate institutional official AND the Office of Biotechnology Activities (OBA) at the NIH within 30 days. (see Appendix A)

Appointments to the Institutional Biosafety Committee

The President of Thomas Jefferson University appoints the members of the IBC each year in accordance with the NIH Guidelines. A current list of members and their affiliations is maintained in the Department of Environmental Health and Safety and can be found on their website (http://www.jefferson.edu/ohr/ibc).
The NIH Office of Biotechnology Activities is notified of the Committee membership not less than once a year. Most IBC members serve three years, with exceptions possible.

Membership on the Institutional Biosafety Committee
The Thomas Jefferson University IBC membership is selected from the faculty on the basis of their experience and expertise in rDNA/synthetic nucleic acid technology and/or pathogenic organisms, biological toxins, select agents, biological safety and physical containment and the capability to assess the safety of experiments utilizing these various agents and any risk to public health and to the environment.

At least one member is from the Department of Medicine, Division of Infectious Diseases, and one member represents the Department of Environmental Health and Safety.

At least two of the members are not affiliated with the Institution and represent the interests of the surrounding community with respect to health and protection of the environment.

The Biological Safety Officer (BSO) is a member and Vice Chair.

Per the *NIH Guidelines*, the committee consists of a minimum of five people; two of which must be outside members not affiliated with the institution. The expertise of the remaining three individuals is based on the research being performed. For example, if the institution conducts either plant or animal research, then an expert in each of these fields is required to be on the committee. If the institution is required to have a BSO, then this individual also must sit on the committee. Thomas Jefferson University's IBC consists of between 15 and 18 members.

The Secretary of the IBC is an Administrative Assistant in the Department of Environmental Health and Safety.

Biological Safety Officer (BSO)
As recommended by the *NIH Guidelines*, a BSO must be appointed by any institution conducting research requiring biosafety level 3 (BL-3) or higher containment conditions and practices or engaging in large-scale research. The duties of the BSO as defined by the *NIH Guidelines* include, but need not be limited to:

1) Laboratory inspections to insure that proper biosafety levels are assigned and adhered to;
2) Report to the IBC and the institution any violations of NIH or Institutional Guidelines and any research-related accidents or illnesses;
3) Develop emergency plans for accidental spills and personnel contamination;
4) Investigate lab accidents involving exposures to recombinant and synthetic DNA as well as any infectious materials, biological toxins, or select agents
5) Provide technical advice to investigators and the IBC on research safety procedures;
6) Provide advice on laboratory security
7) Provide tutorial sessions for individuals planning to take the BL-3 examination;
8) Implement systems to gather data and produce reports related to items 1 to 7 above;

9) Reviewing animal protocols for the IACUC for biosafety issues;
10) Reviewing protocols submitted to the Institutional Review Board involving gene transfer for biosafety issues;
11) Serving as a resource and guidance source for investigators who are designing their biosafety plans;
12) Making recommendations to University Administration on biosafety issues; and
13) Reviewing allegations of failure to comply and propose sanctions, if required, to the University Administration.

Conflicts of Interests (COI) for IBC Members

In order to avoid real or perceived conflicts of interest in the conduct of IBC business, any IBC member must recuse themselves from the protocol review and approval process of any research protocol in cases where the IBC member has a significant financial interest in the sponsor of the research, or is involved in the design, conduct, or reporting of the research, or has any other interest that may reasonably be considered to interfere with an objective review of the research. (See the University's COI Policy which can be found by logging into Pulse and choosing University Policies under the Links section located on the left hand side of the page. Policies are listed in alphabetical order.)

Meetings of the IBC

The IBC meets on the second Friday of each month to review protocols and to conduct other items of business.

The IBC maintains minutes of its meetings. Minutes that have been approved by the IBC are available to the public for review, upon written request to the IBC. Prior to the release of any requested minutes, the IBC with assistance from the Office of University Counsel will redact the minutes to ensure that confidential and private information is not released. Confidential and private information shall include, but not be limited to, individually identifiable health information as defined in the Health Insurance Portability and Accountability Act of 1996 and any regulations and official guidelines promulgated there under directory information, proprietary information, intellectual property information, trade secrets, and attorney-client privileged information.

Deadline for Receipt of Studies

The deadline for the receipt of protocols by the IBC is the Friday two weeks before the meeting date. An electronic submission is due by this date. Submissions received after this date will be held over to the next meeting. A copy of the meeting dates and their deadlines is posted on the IBC website (http://www.jefferson.edu/ohr/ibc).

Who may submit a Protocol for IBC Review

Only full time paid faculty members (instructor level and above) may submit protocols for review by Thomas Jefferson University's IBC.

Registration

All full time paid faculty members are required to submit a registration form (IBC-1), available at (www.jefferson.edu/ohr/ibc) at the time of their hiring and in accordance

with their inspection interval thereafter (see **Inspection** section below). This form provides basic information about the researcher and the work being performed in his or her lab.

Who needs Institutional Biosafety Committee (IBC) approval for research?
Principal Investigators (P.I.s) who plan to carry out research that will involve any of the following materials must complete the appropriate IBC forms located at (www.jefferson.edu/ohr/ibc) describing all aspects of the research, and submit it to the Office of Human Research for review and approval by the IBC:

- Recombinant and/or synthetic nucleic acids not exempt by the NIH Guidelines (this includes transgenic plants and animals)
- Infectious Agents
- Human blood, body fluids, or unfixed tissue
    - Includes material that has been treated recombinantly, whether or not returned to the patient
    - Excludes material removed from the patient, treated mechanically or chemically, then returned to the patient
- Tissues, organs or cell cultures of human origin
    - Includes material that has been treated recombinantly, whether or not returned to the patient
    - Excludes material removed from the patient, treated mechanically or chemically, then returned to the patient
- Human Gene Transfer
- Old World primates – they may be carrying Herpesvirus simiae (Cercopithecine herpesbirus [CHV-1], B-virus)
- Sheep – they can carry Coxiella burnetii causing Q-fever.
- Select agents
- Toxins (Biological) – the use of toxins and hazardous chemicals requires submission of a Thomas Jefferson University IBC-14 internal form to the Biosafety Officer (toxins) or Environmental Health Officer (hazardous chemicals).
- Nanotechnology

Standard Procedure for Submission of Studies to the IBC
To assist investigators in ensuring the completeness of the registration forms, thereby reducing the need for returning incomplete submissions, each form is required to be pre-reviewed by a member of the IBC. The investigator should choose a member of the IBC with the appropriate area of expertise from the list of IBC members, which is posted on the IBC web site, http://www.jefferson.edu/ohr/ibc. The pre-reviewer's name is to be listed on the form where indicated. A form will **NOT** be brought before the entire committee until it has been pre-reviewed. Consequently, please submit your form to your pre-reviewer in a timely manner to allow for the pre-review and corrections to be made PRIOR to the submission deadline.

Each form submission must contain a succinct but complete abstract of the study, written in lay terms (written in terms that an individual with an 8th grade education can

understand) with all acronyms defined. The typical generalized abstract for a grant submission is not acceptable

An electronic copy, sent by email to the IBC Secretary, must be submitted by 5:00pm on the Friday two weeks prior to the IBC meeting date. A signed hard copy may also be delivered to EHS' office at 130 South Ninth Street, Suite 1620 by the same deadline. **PLEASE NOTE**, while review by the IBC is possible without a signed copy on file, a final approval letter will NOT be provided until the signed copy **is** received by the office.

Activities Requiring IBC Approval

- All recombinant and synthetic nucleic acid research needs to be reviewed and approved by the full committee. (The IBC-1 is available on the IBC website for submission of BL-1 protocols. An approval letter will be issued and an inspection required as detailed below.)
- Research requiring work with biological toxins is reviewed by the Chair and Vice Chair of the IBC, or their designee. An IBC-14 form (available at www.jefferson.edu/ohr/ibc) is to be submitted detailing this work.
- All research requiring Biosafety Level 2 containment or above must be approved by the IBC either simultaneously with or prior to beginning work on the project. The appropriate IBC form(s) is to be submitted for this work.
- All nanotechnology experiments must be approved by the IBC prior to beginning work on the project. The appropriate IBC form(s) is to be submitted for this work.
- Any experiment that falls under the concerns listed in the Fink Report (a January 2003 report detailing experiments which could result in the development or production of agents that could be employed by terrorists) must be approved by the IBC **prior** to beginning work on the project. These concerns are:
    - Demonstrate how to render a vaccine ineffective
    - Confer resistance to therapeutically useful antibiotics or antiviral agents
    - Enhance the virulence of a pathogen or render a nonpathogen virulent
    - Increase transmissibility of a pathogen
    - Alter the host range of a pathogen
    - Enable the evasion of diagnostic/detection modalities
    - Enable the weaponization of a biological agent or toxin
- Any experiment involving the use of select agents (as listed in 42CFR73.3 and 73.4, include all biological agents and toxins that pose a potential threat to public health and safety) must be approved by the IBC **prior** to beginning work on the project. A list of select agents as well as the regulations governing them can be found at http://www.selectagents.gov. (**Note:** The use of select agents also **REQUIRES** registration with the Federal government. Please contact the BSO if you wish to begin work with select agents.)

Change of Existing Protocol

IBC approval must be obtained if changes are made in approved research that involves changes in the current safety or containment level. Such changes that would require IBC approval include, but are not limited to the following.

- New pathogens, new vector systems
- *In vitro work* being changed to work *in vivo*
- *In vivo* work being changed to *in vitro* procedures
- Work with new cell lines which change the biosafety level or whose use causes a significant change to the protocol
- Changes in constructs or systems that result in significantly higher titers
- Enhanced replication or infectivity
- Expression of toxic products
- Partial viral genomes increased to more than two-thirds of whole genome
- New or altered procedures that pose increased risk of aerosol or other types of exposure

If you are uncertain about whether a change in your research or protocol requires IBC approval, please contact either the Chair of the Committee or the Biosafety Officer.

Criteria For Granting IBC Approval

In order to approve protocols involving rDNA, synthetic nucleic acids, nanotechnology, pathogens, select agents, or biological toxins the Committee shall consider all of the following:

1) Activities: All research involving rDNA, synthetic nucleic acids, nanotechnology, infectious agents, bloodborne pathogens, biological toxins, or select agents must be carried out in accordance with NIH Guidelines, OSHA Bloodborne Pathogen Regulations and/or Select Agent Guidelines.

2) Training and Qualifications: All personnel involved in the proposed research must be appropriately trained according to the Guidelines or Regulations by the Laboratory Director before beginning the proposed research. Training must be documented. Individuals conducting research requiring BL-3 containment and practice must attend a tutorial session provided by the BSO and pass an institutional certifying examination administered by the BSO on behalf of the IBC. Investigators planning animal experiments requiring BL-3 containment must also satisfy the requirements of the Office of Animal Research (OAR) and the Institutional Animal Care and Use Committee (IACUC).

3) Facilities: Laboratories planning to conduct research requiring biosafety containment conditions and practice of BL-2 or higher must prepare Standard Operating Procedures and be inspected by the BSO or designee on behalf of the IBC, in order to be certified as meeting the requirements for the appropriate biosafety level.

4) Deviation from Requirements: Any requests for deviation from the biosafety level assigned or any of the requirements must be justified on a scientific basis and presented in writing for review by the IBC.

5) Protocol Reviews: All activities described in the section entitled “Activities Requiring IBC Approval” must be reviewed by the IBC, regardless of funding

source (intramural or extramural), in accordance with the *NIH Guidelines* and OSHA Regulations. This is done through the submission of completed IBC form(s), including any supplementary information such as a written description of the research in lay language, the personnel involved in the research, and the individuals' immune status regarding the agent involved, if applicable. The administrative office for the IBC is located in the Department of Environmental Health and Safety, 130 South Ninth Street, Suite 1620. A pre-review of the research protocol is carried out by a member of the IBC only to ensure completeness. A successful pre-review does NOT automatically mean approval from the IBC

Additional information is obtained about the use of radioactivity and/or animals in the experiments which may necessitate interaction of the IBC with the Institutional Animal Care and Use Committee and the Non-Human Use Radiation Subcommittee of the Radiation Safety Committee.

IBC Decision on the Protocol
The possible decisions that are determined by the IBC for the status of the protocol(s) reviewed are as follows:

- Approved
- Provisionally approved, pending receipt of additional information/modification (work may or may not begin, depending on the section of the Guidelines it falls under, see Appendix B.)
- Disapproved
- Provisionally approved upon investigator's official start date at Jefferson (This is a special category for P.I.s who are transferring to the institution but have not officially started here at the time approval is given. This allows investigators to get the regulatory approvals required to transfer their grants in a timely manner.)

The actions of the Committee shall be entered into the IBC database including an assigned protocol number, status of the protocol, biosafety level assigned, requirement for immunization, status of laboratory inspection and other pertinent data, as necessary.

An email will be sent by the IBC to the Principal Investigator notifying the investigator of the actions of the IBC and of any additional information required by the IBC. Once these requirements have been met, an official letter will be sent to the Principal Investigator indicating the approved Biosafety Level, a control number, and a brief description of the work. (The IBC control number is to be used on the electronic Proposal Transmittal Form (ePTF) when submitting grant applications.)

Circumstances Under Which Institutional Biosafety Committee Approval is NOT Required
If you are an investigator who has been issued an IBC Control Number indicating approval by the IBC to conduct work of a specific nature using rDNA, synthetic nucleic

acids, nanotechnology, pathogens, select agents, or biological toxins, you do not need to submit new documentation to the IBC if:

- a new grant is submitted to an outside agency for work previously approved
- a new line of research is to be conducted that consists of work similar to the work previously approved by the IBC

If new research involves a cloning or delivery vector or a pathogenic agent that the investigator has not used before, even if the new work falls under the same risk group and biosafety level designation already approved, then a request in the form of a letter to the IBC describing the proposed amendments to the work is required. The letter must include sufficient detail to permit a safety assessment by the IBC.

Inspections

After the study has been approved by the IBC, the laboratory in which the research will take place must be inspected by the Institutional Biosafety Officer or designee and approved as meeting the requirements for the type of research before the study can begin.

If the biosafety level assigned to the project is BL-2 or higher, the BSO will schedule a laboratory inspection based on the NIH/CDC *Biosafety in Microbiological and Biomedical Laboratories* and, in the case of research falling under the Bloodborne Pathogens Standard, a Bloodborne Pathogens Control Plan. The inspection shall be carried out by the BSO or designee.

If the inspection is satisfactory, the BSO or designee will send a formal letter specifying the biosafety level and the period of the approval. The approval period will vary with the biosafety level (see chart below). If the laboratory does not conform to the requirements of the inspection checklist and/or the Bloodborne Pathogens Control Plan or other regulations and so fails the inspection, the Principal Investigator shall initiate the required changes. The BSO will be notified when these changes are complete so that the facilities may be re-inspected. This shall be done as soon as possible, but no later than thirty days after the initial inspection.

- Inspection Approval Periods
    - BL3 facilities—every 6 months
    - Select Agent Labs—yearly
    - BL2/3 facilities—yearly
    - BL2—every two (2) years
    - BL1—every five (5) years

When the laboratory has been approved for the work, the P.I. will receive a letter of approval from the BSO, on behalf of the IBC, and will be issued an inspection number. Each P.I., whose laboratory and research have been approved, will receive both an IBC control number (This is the number to be used on the internal electronic Proposal Transmittal Form (ePTF) when submitting grant applications.) **and** an inspection number.

Research Requiring Biosafety Level-3 Containment
Investigators conducting research involving certain Risk Group 2 agents that undergo aerosolization and/or present public health issues, and Risk Group 3 agents, must carry out the research in a Biosafety Level 3 (BL-3) containment facility. In order to have access to a BL-3 facility the investigator must have specific training/experience with aseptic technique, tissue culture, and in working with infectious agents or rDNA/synthetic nucleic acids either in vivo or in vitro under BL-2 containment conditions.

All individuals whose research requires them to work under BL-3 containment conditions must take a tutorial from the BSO, to prepare to work safely in a BL-3 facility. Personnel are also required to pass a written certifying examination to document their knowledge of the facilities and procedures required for conducting research at the BL-3 level of containment.
Experimental protocols and procedures requiring the use of BL-3 facility must be approved **in advance** by the IBC.

Entrance to the facility by non-research personnel requires the approval of the Manager of the facility, who shall accompany all such individuals.

The IBC has available a "Standard Operating Procedures for Biosafety Level-3 Facilities" on their website for individuals planning to take the tutorial and the certifying examination.

Review of Human Gene Transfer Protocols
Human gene transfer protocols are subject to dual review by the IBC and the Institutional Review Board (IRB). A joint IBC/IRB Subcommittee will review both human subject and biosafety issues. The IBC members, chosen for their expertise in the area of the protocol, will review the protocol in accordance with the *NIH Guidelines* for review of Gene Transfer protocols. (Please refer to Appendix M in the *NIH Guidelines* (http://oba.od.nih.gov/rdna/nih_guidelines_oba.html] for these guidelines.) The subcommittee shall make recommendations to the full IBC and IRB for final approval.

PIs' Responsibilities Under Appendix M of the *NIH Guidelines*
Appendix M of the *NIH Guidelines*, referenced above, outline specific responsibilities for the PI in the conductance of gene transfer trials. For your convenience, a summary is listed in Appendix C of this document.

Reporting Adverse Events in Human Gene Transfer Trials
All research involving human subjects requires reporting of adverse events and unanticipated problems involving risks to subjects and others.

In gene transfer studies, additional reporting responsibilities apply. The Principal Investigator is required to report all serious adverse events to the appropriate offices/agencies as listed below and in DHSP Policy GA 111

(http://www.jefferson.edu/human_research/irb, then choose "Policy and Procedures Handbook" from the left hand menu) regardless of whether they are thought to be related to the gene transfer intervention.

Section E-1-7, Appendix M-VII-C-1-3, of the *NIH Guidelines* requires that Principal Investigators (or their designated sponsors) conducting gene transfer clinical trials to immediately** report serious adverse events to the following:

- Institutional Review Board (IRB)
- Institutional Biosafety Committee (IBC)
- Office of Human Research Protections (if applicable)
- NIH/OBA (Office of Biotechnology Activities) and the Food and Drug Administration (FDA)

followed by the submission of a written report filed with each group.

** "Immediate" written reporting of serious adverse events is to occur as soon as possible, but no later than 15 days after the event has occurred.

Serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential as defined under the Freedom of Information Act, 5 USC 552. Serious adverse event reports should be stripped of individually identifiable patient information.

Adverse events that meet the reporting criteria for unanticipated problems posing risks to subjects or others will be reported as defined and outlined in DHSP Policy GA 120 (http://www.jefferson.edu/human_research/irb, then choose "Policy and Procedures Handbook" from the left hand menu). The report form is the OHR-20 and can be accessed on the OHR website http://www.jefferson.edu/ohr/irb Once on the IRB website, choose "IRB forms and submission materials."

On-site adverse event reporting is done using the electronic reporting system (eSAEy) at the following web address: http://osa.tju.edu/ae

Reports of serious adverse events for gene transfer studies must follow the format provided in the **Adverse Event Reporting Form available on the NIH/ORDA's web site at** http://oba.od.nih.gov/oba/rac/adverse_event_template.pdf.

Policy for Volunteers in Research Laboratories

Institutional regulations require that volunteers (unpaid workers not processed through Human Resources) such as visiting faculty, summer students, foreign visitors, etc., who work in research laboratories be registered. The policy for registering volunteers working in research laboratories can be found by signing onto Pulse and choosing University Policies under the Links section located on the left hand side of the page.

APPENDIX A
REPORTING REQUIREMENTS

The *NIH Guidelines* outline the PI's and institution's reporting responsibilities in several sections as outlined below. Below each description of the section from the *NIH Guidelines* is an example(s) of the type of incident that should be reported to either the appropriate internal officials or to the NIH/OBA.

- One section pertains to the PI's responsibilities during the conduct of recombinant DNA research. Section IV-B-7-e-(2) states "Investigate and report any significant problems pertaining to the operation and implementation of containment practices and procedures in writing to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/OBA, and other appropriate authorities (if applicable)."
  - The PI will report **ANY** release of recombinant material from the lab to the Biological Safety Officer and the Animal Facility Director (if appropriate), whether it is the result of malfunctioning equipment or technical error.

- Another section applies to BL2 research. Appendix G-II-B-2-k states "Spills and accidents which result in overt exposure to organisms containing recombinant or synthetic nucleic acid molecules are immediately reported to the Institutional Biosafety Committee and NIH/OBA. Medical evaluation, surveillance, and treatment are provided as appropriate and written records are maintained."
  - The PI will report any overt exposure to the Biological Safety Officer and NIH/OBA
  - The PI will report any **potential** exposure to the Biological Safety Officer who will then report to any other appropriate entities.

- Another section applies to BL3 research. Appendix G-II-C-2-q states "Spills and accidents which result in overt or potential exposures to organisms containing recombinant or synthetic nucleic acid molecules are immediately reported to the Biological Safety Officer, Institutional Biosafety Committee, and NIH/OBA."
  - The PI will report any overt or potential exposure to the Biological Safety Officer (as Vice Chair of the IBC, she will notify the committee) and NIH/OBA.

- Lastly, Sections IV-B-1-j and IV-B-7-a-(4) require both the institution and PI to report any significant problems, violations of the *NIH* Guidelines, or any significant research related accidents and illnesses. The PI is required to report to the Biological Safety Officer (where applicable), Greenhouse/Animal Director (where applicable), IBC, NIH/OBA, and other appropriate authorities (if applicable) within 30 days. The institution is required to report these same issues to the NIH/OBA within 30 days.

- BL2 or higher research being performed on an open bench top rather than a biological safety cabinet.
- Failure to use proper safety equipment such as centrifuge cups to spin BL2/3 or higher samples.
- The use of rDNA at a lower level than approved by the IBC.
- Failure to register rDNA work with the IBC.

APPENDIX B
EXPERIMENTS COVERED BY THE *NIH GUIDELINES*

Please note that the categories listed below go from those that require the most oversight to those that require the least and are a summary of the Guidelines. Please refer to the *NIH Guidelines* to get the full explanation behind each category (http://oba.od.nih.gov/rdna/nih_guidelines_oba.html)

In addition, the differences between categories D and E are dependent on the associated risk of the experiment. For example, the vast majority of transgenic animal experiments will fall under category E. However, if the introduced material is of viral origin and can lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, then the experiment would be moved up to a category D.

A. Experiments that require IBC approval, RAC review, and NIH Director Approval before initiation
    1. Ex.—Deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such an acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture

B. Experiments that require NIH/OBA and IBC approval before initiation
    1. Ex.—Deliberate formation of recombinant DNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD_{50} of less than 100 nanograms per kilogram body weight

C. Experiments that require IBC and IRB approval and RAC review before research participant enrollment, i.e. gene transfer experiments
    1. Ex.—Deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA into human research participants
    2. Ex.--Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules into human research patients, that meet any one of the following criteria:
        i. Contain more than 100 nucleotides; or
        ii. Possess biological properties that enable integration into the genome; or
        iii. Have the potential to replicate in a cell; or
        iv. Can be translated or transcribed

D. Experiments that require IBC approval before initiation
    1. Ex.—Experiments using risk group 2, 3, or 4, or restricted agents as host-vector systems (refer to appendix B of the NIH Guidelines for representative organisms)

2. Ex.—Experiments in which DNA from risk group 2, 3, or 4, or restricted agents is cloned into nonpathogenic prokaryotic or lower eukaryotic host-vector systems
3. Ex.—Experiments involving the use of infectious DNA or RNA viruses or defective DNA or RNA viruses in the presence of helper virus in tissue culture systems
4. Ex.—Experiments involving whole animals
    i. Experiments creating transgenic rodents
    ii. Experiments involving viable recombinant or synthetic nucleic acid molecule-modified microorganisms tested on whole animals
5. Ex.—Experiments involving whole plants
    i. Experiments to genetically engineer plants by recombinant or synthetic nucleic acid molecule methods
    ii. Experiments that use the plants described above for other experimental purposes, such as stress response
    iii. Experiments that propagate such plants as described above
    iv. Experiments that use plants together with microorganisms or insects containing recombinant or synthetic nucleic acid molecules
6. Ex.—Experiments involving more than 10 liters of culture
7. Ex.—Experiments involving Influenza Viruses

E. Experiments that require IBC notice simultaneous with initiation
    1. Ex.—Experiments involving the formation of recombinant or synthetic nucleic acid molecules containing no more than two-thirds of the genome of any eukaryotic virus
    2. Ex.—Experiments involving whole animals or plants that do not fall under the other categories
    3. Ex.—Experiments involving the use of infectious DNA or RNA viruses or defective DNA or RNA viruses in the presence of plasmids or specialized packaging cell lines
    4. Ex.—Experiments with recombinant or synthetic nucleic acid molecule-modified arthropods or small animals associated with plants, if the recombinant or synthetic nucleic acid molecule-modified microorganism has no recognized potential for serious detrimental impact on managed or natural ecosystems (otherwise it would be considered under category 4)
    5. Ex.—Experiments creating transgenic rodents

F. Exempt experiments
    1. Ex.—synthetic acid molecules that can neither replicate nor generate nucleic acids that can replicate in any living cell and are not designed to integrate into the DNA, and do not produce a toxin that is lethal for vertebrates at an LD50 of less than 100 nanograms per kilogram of body weight
    2. Ex.—recombinant and synthetic nucleic acid molecules not in organisms, cells, or viruses and that have not been modified or manipulated to render then capable of penetrating cellular membranes

3. Ex.—recombinant or synthetic nucleic acid molecules that consist solely of the exact recombinant or synthetic nucleic acid sequence from a single source that exists contemporaneously in nature
4. Ex.—recombinant or synthetic nucleic acid molecules that consist entirely of nucleic acids from a prokaryotic host including its indigenous plasmids or viruses when propagated only in that host (or a closely related strain of the same species), or when transferred to another host by well established physiological means
5. Ex.—recombinant or synthetic nucleic acid molecules that consist entirely of nucleic acids from an eukaryotic host including its chloroplasts, mitochondria, or plasmids (but EXCLUDING viruses) when propagated only in that host (or a closely related strain of the same species)
6. Ex.—recombinant or synthetic nucleic acid molecules that consist entirely of DNA segments from different species that exchange DNA by known physiological processes, though one or more of the segments may be a synthetic equivalent
7. Ex.—those genomic DNA molecules that have acquired a transposable element, provided the transposable element does not contain any recombinant and/or synthetic DNA
8. Ex.—recombinant or synthetic nucleic acid molecules that do not present a significant risk to health or environment as determined by the NIH Director, with the advice of the RAC, and following appropriate notice and opportunity for public comment

APPENDIX C
SUMMARY OF PI RESPONSIBILITIES IN APPENDIX M OF THE *NIH GUIDELINES*

The following is a summary of the PIs' responsibilities under Appendix M of the *NIH Guidelines.* Please refer to Appendix M for a complete detailing of these responsibilities.

Not enrolling research participants in the gene transfer experiment until 1) the RAC review process has been completed, 2) IBC approval (from the clinical trial site) has been obtained, 3) IRB approval has been obtained, 4) all applicable regulatory authorization(s) have been obtained.

No later than 20 working days after enrollment of the first research participant in a human gene transfer experiment, the PI shall submit the following documentation to the OBA: 1) a copy of the informed consent document approved by the IRB, 2) a copy of the protocol approved by the IBC and IRB, 3) a copy of the final IBC approval from the clinical trial site, 4) a copy of the final IRB approval, 5) a brief written report that includes the following information: a) how the investigator(s) responded to each of the RAC's recommendations on the protocol (if applicable) and b) any modifications to the protocol as required by the FDA, 6) applicable NIH grant numbers, 7) the FDA IND number, and 8) the date of the initiation of the trial

Within 60 days after the one-year anniversary of the date on which the IND application went into effect, and after each subsequent anniversary until the trial is completed, the PI (or delegate) shall submit the following 1) clinical trial information, 2) progress report and data analysis, and 3) a copy of the updated clinical protocol including a technical and non-technical abstract. (See Appendix M for specifics.)

PIs must submit a written report on 1) any serious adverse event that is both unexpected and associated with the use of the gene transfer product and 2) any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenecity, teratogenicity, or carcinogenicity.

PIs should adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and local institutional policies and procedures, as applicable.

PIs may delegate to another party, such as a corporate sponsor, the reporting requirements set forth in Appendix M, with written notification to the NIH OBA.

The PI *is* responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.