Laws, Regulations and Policies – Hazardous Substances, Recombinant NA and BSAT Guidelines

4 August 2013

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- Rules and Regulations
- Approval Process

Regulations and Guidance

- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
- Biosafety in Microbiological and Biomedical Laboratories (BMBL)
- Biological Select Agent and Toxin Regulations:
  - DHHS
  - USDA
- NIH Guide for the Care and Use of Laboratory Animals
- USDA Animal Welfare Regulations
- Good Laboratory Practice Regulations
- Other Federal, State, and Local Laws and Requirements
- NIH Design Guidelines
- USDA Design Guidelines

- "NIH Guidelines"
  - Not to be confused with the "Guide"
- BMBL

NIH Guidelines

- NIH Guidelines for Research Involving Recombinant DNA Molecules (*NIH Guidelines*)
- http://oba.od.nih.gov/rdna/nih_guidelines_oba.html
- New Amendments effective March 5, 2013
- Renamed: ***NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)***

History

- Dr. Berg, Stanford University, created an organism with the genetic elements from three separate organism
- Voluntary Moratorium on Genetic Engineering Research
- February 1975 – "Asilomar" Conference,
- NIH Established the Recombinant Molecule Program Advisory Committee (RAC)
- 1976 – First *NIH Guidelines*
- April 2002 – Latest *Guidelines* (revised in 2011)
  - Visit the OBA Web site at: http://oba.od.nih.gov/rdna/rdna.html

Original NIH Guidelines

- The NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) detail procedures and practices for the containment and safe conduct of various forms of recombinant DNA research, including research involving genetically modified plants and animals, and human gene transfer.

7

Current NIH Guidelines

- The amended *NIH Guidelines* apply to research with recombinant or synthetically derived nucleic acids, including those that are chemically or otherwise modified analogs of nucleotides (e.g., morpholinos), or both.

8

Purpose

- The purpose of the *NIH Guidelines* is to specify the practices for constructing and handling:
- (i) recombinant nucleic acid molecules,
- (ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, and
- (iii) cells, organisms, and viruses containing such molecules.

9

Definition

- In the context of the *NIH Guidelines*, recombinant and synthetic nucleic acids are defined as:
- (i) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids;
- (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids, or
- (iii) molecules that result from the replication of those described in (i) or (ii) above.

10

Who must comply with the *NIH Guidelines?*

- All institutions that receive NIH funding for recombinant or synthetic nucleic acid research must comply with the *NIH Guidelines.*
- Researchers at institutions that are subject to the NIH Guidelines must comply with the requirements even if their individual projects are not funded by NIH.

11

Voluntary Compliance

- Basic Policy – Voluntary Compliance
- Individuals, corporations, and institutions not otherwise covered by the *NIH Guidelines* are encouraged to follow the standards and procedures.
- For purposes of complying with the *NIH Guidelines*, an individual intending to carry out research involving recombinant or synthetic nucleic acid is encouraged to affiliate with an institution that has an Institutional Biosafety Committee approved under the *NIH Guidelines*.
- Special concerns of commercial organizations, such as protection of proprietary data.

12

Covered Experiments

- NIH Guidelines have six categories of experiments:
- Those that require Institutional Biosafety Committee (IBC) approval, RAC review, and NIH Director approval before initiation
- Those that require NIH/OBA and Institutional Biosafety Committee approval before initiation
- Those that require Institutional Biosafety Committee and Institutional Review Board approvals and RAC review before research participant enrollment
- Those that require Institutional Biosafety Committee approval before initiation
- Those that require Institutional Biosafety Committee notification simultaneous with initiation
- Those that are exempt from the *NIH Guidelines*

13

Require IBC Approval, RAC Review, and NIH Director Approval Before Initiation

- Major Actions under the *NIH Guidelines*
- Experiments considered as *Major Actions* under the *NIH Guidelines* cannot be initiated without submission of relevant information on the proposed experiment to the Office of Biotechnology Activities, National Institutes of Health
  - The publication of the proposal in the *Federal Register* for 15 days of comment
  - Review by RAC
  - Specific approval by NIH.
- The containment conditions or stipulation requirements for such experiments will be recommended by RAC and set by NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation.
- Specific experiments already approved are included in: *Major Actions Taken under the NIH Guidelines*

14

Require IBC Approval, RAC Review, and NIH Director Approval Before Initiation

- Example: The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally, if such acquisition could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by RAC.

15

Require NIH/OBA and IBC Approval Before Initiation

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

16

Require NIH/OBA and IBC Approval Before Initiation

- Example: Deliberate formation of recombinant or synthetic nucleic acid molecules containing genes for the biosynthesis of toxin molecules lethal for vertebrates at an LD^{50} of less than 100 nanograms per kilogram body weight (e.g., microbial toxins such as the botulinum toxins, tetanus toxin, diphtheria toxin, and *Shigella dysenteriae* neurotoxin).

17

Require IBC and IRB Approvals, RAC Review Before Enrollment

- Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants
- No research participant shall be enrolled until the RAC review process has been completed

18

Require IBC and IRB Approvals, RAC Review Before Enrollment

Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or
2. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of the following criteria:
   - a. Contain more than 100 nucleotides; or
   - b. Possess biological properties that enable integration into the genome (e.g., *cis* elements involved in integration); or
   - c. Have the potential to replicate in a cell; or
   - d. Can be translated or transcribed.

Require Institutional Biosafety Committee Approval Before Initiation

- Prior to the initiation of an experiment that falls into this category, the Principal Investigator must submit a registration document to the Institutional Biosafety Committee which contains the following information:
  - the source(s) of DNA;
  - the nature of the inserted DNA sequences;
  - the host(s) and vector(s) to be used;
  - if an attempt will be made to obtain expression of a foreign gene, and if so, indicate the protein that will be produced; and
  - the containment conditions that will be implemented as specified in the *NIH Guidelines*.
- The Institutional Biosafety Committee will review and approve all experiments in this category prior to their initiation.
- Requests to decrease the level of containment specified for experiments in this category will be considered by NIH.

- **Section III-D-3. Experiments Involving the Use of Infectious DNA or RNA Viruses or Defective DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems**
- **Caution:** Special care should be used in the evaluation of containment levels for experiments which are likely to either enhance the pathogenicity (e.g., insertion of a host oncogene) or to extend the host range (e.g., introduction of novel control elements) of viral vectors under conditions that permit a productive infection. In

Require Institutional Biosafety Committee Approval Before Initiation

- **Section III-D-4. Experiments Involving Whole Animals**
- This section covers experiments involving whole animals in which the animal's genome has been altered by stable introduction of recombinant or synthetic nucleic acid molecules, or nucleic acids derived therefrom, into the germ-line (transgenic animals) and experiments involving viable recombinant or synthetic nucleic acid molecule-modified microorganisms tested on whole animals.
- For the latter, other than viruses which are only vertically transmitted, the experiments may *not* be conducted at BL1-N containment. A minimum containment of BL2 or BL2-N is required.

Require IBC Notice Simultaneous with Initiation

- Experiments not included in other sections/ subsections.
- All such experiments may be conducted at BL1 containment.
- Registration document shall be dated and signed by the investigator and filed with the local Institutional Biosafety Committee at the time the experiment is initiated.
- The Institutional Biosafety Committee reviews and approves all such proposals, but Institutional Biosafety Committee review and approval prior to initiation of the experiment is not required.

Require IBC Notice Simultaneous with Initiation

- This section covers experiments involving the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant or synthetic nucleic acid molecules, or nucleic acids derived therefrom, into the germ-line (transgenic rodents). Only experiments that require BL1 containment are covered under this section; experiments that require BL2, BL3, or BL4 containment are covered under Section III-D-4, *Experiments Involving Whole Animals*.
- Experiments involving the breeding of certain BL1 transgenic rodents are exempt under Section III-F, *Exempt Experiments* (See Appendix C-VII, *Generation of BL1 Transgenic Rodents via Breeding*).

Exempt Experiments

- The following recombinant or synthetic nucleic acid molecules are exempt from the *NIH Guidelines* and registration with the Institutional Biosafety Committee is not required; however, other federal and state standards of biosafety may still apply to such research

25

- The breeding of two different transgenic rodents or the breeding of a transgenic rodent and a non-transgenic rodent with the intent of creating a new strain of transgenic rodent that can be housed at BL1 containment will be exempt from the *NIH Guidelines* if:

(1) Both parental rodents can be housed under BL1 containment; and

(2) neither parental transgenic rodent contains the following genetic modifications: (i) incorporation of more than one-half of the genome of an exogenous eukaryotic virus from a single family of viruses; or (ii) incorporation of a transgene that is under the control of a gammaretroviral long terminal repeat (LTR); and

(3) the transgenic rodent that results from this breeding is not expected to contain more than one-half of an exogenous viral genome from a single family of viruses.

26

Roles and Responsibilities

- The safe conduct of experiments involving recombinant or synthetic nucleic acid molecules depends on the individual conducting such activities.
- It is the responsibility of the institution and those associated with it to adhere to the intent of the NIH Guidelines as well as to their specifics.

27

Responsibilities of the Institution

- Establish and implement policies that provide for the safe conduct of recombinant or synthetic nucleic acid research and that ensure compliance with the *NIH Guidelines*.
- Establish an **Institutional Biosafety Committee** with adequate expertise and training (using *ad hoc* consultants as deemed necessary for human use
- Institutional Review Board approval
- Assist and ensure compliance with the *NIH Guidelines* by Principal Investigators
- Ensure appropriate training
- Health surveillance
- Report any significant problems or violations

28

What is an Institutional Biosafety Committee?

- The institution shall establish an Institutional Biosafety Committee whose responsibilities need not be restricted to recombinant or synthetic nucleic acid molecule research.
- Institutional Biosafety Committees (IBCs) provide local review and oversight of nearly all forms of research utilizing recombinant or synthetic nucleic acid. They ensure that research conducted at or sponsored by the institution is in compliance with the *NIH Guidelines.*
- A requirement of the NIH Guidelines is that an IBC must review and approve all research subject to the NIH Guidelines.

29

Functions

- Reviewing recombinant or synthetic nucleic acid research conducted at or sponsored by the institution for compliance with the *NIH Guidelines*
- Set containment levels
- Periodically reviewing recombinant or synthetic nucleic acid research conducted at the institution to ensure compliance with the *NIH Guidelines*.
- Adopting emergency plans covering accidental spills and personnel contamination resulting from recombinant DNA research.
- Reporting any significant problems with or violations of the *NIH Guidelines*
- Note: The Institutional Biosafety Committee may not authorize initiation of experiments which are not explicitly covered by the *NIH Guidelines*

30

Membership

- The Institutional Biosafety Committee must be comprised of no fewer than five members
- Experience and expertise in recombinant or synthetic nucleic acid technology and the capability to assess the safety of recombinant or synthetic nucleic acid research and to identify any potential risk to public health or the environment.
- At least two members shall not be affiliated with the institution and who represent the interest of the surrounding community with respect to health and protection of the environment
- Depending on study:
  - Plant
  - Animal
  - Human
  - Biosafety

31

Membership

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

32

Biological Safety Officer (BSO)

- When the institution conducts recombinant or synthetic nucleic acid molecule research at BL3, BL4, or Large Scale (greater than 10 liters), a Biological Safety Officer is mandatory and shall be a member of the Institutional Biosafety Committee

33

Biological Safety Officer's Duties

- Periodic inspections to ensure that laboratory standards are rigorously followed;
- Reporting to the Institutional Biosafety Committee and the institution any significant problems, violations of the *NIH Guidelines*, and any significant research-related accidents or illnesses of which the Biological Safety Officer becomes aware unless the Biological Safety Officer determines that a report has already been filed by the Principal Investigator;
- Developing emergency plans for handling accidental spills and personnel contamination and investigating laboratory accidents involving recombinant DNA research;
- Providing advice on laboratory security;
- Providing technical advice to Principal Investigators and the Institutional Biosafety Committee on research safety procedures.

34

Plant, Plant Pathogen, or Plant Pest Containment Expert

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

35

Animal Containment Expert

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

36

Human Gene Therapy Expertise

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

37

Principal Investigator Responsibilities

- Principal Investigators (PIs) are responsible for full compliance with the NIH Guidelines during the conduct of the research.

- From the NIH Guidelines, Major Actions: "Appendix D-15. Drs. R. Michael Blaese and W. French Anderson of the NIH, Bethesda, Maryland, can conduct experiments in which a gene coding for adenosine deaminase (ADA) will be inserted into T lymphocytes of patients with severe combined immunodeficiency disease, using a retroviral vector, LASN. Following insertion of the gene, these T lymphocytes will be reinfused into the patients. The patients will then be followed for evidence of clinical improvement in the disease state, and measurement of multiple parameters of immune function by laboratory testing."

38

General Responsibilities

- Initiate or modify no recombinant or synthetic nucleic acid research which requires Institutional Biosafety Committee approval prior to initiation until that research has been approved by the Institutional Biosafety Committee and has met all other requirements of the *NIH Guidelines*;
- Determine whether experiments are covered and ensure that the appropriate procedures are followed;
- Report any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses
- Report any new information bearing on the *NIH Guidelines* to the Institutional Biosafety Committee and to NIH/OBA
- Be adequately trained in good microbiological techniques;
- Adhere to Institutional Biosafety Committee approved emergency plans for handling accidental spills and personnel contamination
- Comply with shipping requirements for recombinant DNA molecules

39

Submissions by the Principal Investigator to the IBC

- The Principal Investigator shall:
- **Section IV-B-7-c-(1).** Make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*;
- **Section IV-B-7-c-(2).** Select appropriate microbiological practices and laboratory techniques to be used for the research;
- **Section IV-B-7-c-(3).** Submit the initial research protocol and any subsequent changes (e.g., changes in the source of DNA or host-vector system), if covered under Sections III-A, III-B, III-C, III-D, or III-E (*Experiments Covered by the NIH Guidelines*), to the Institutional Biosafety Committee for review and approval or disapproval; and
- **Section IV-B-7-c-(4).** Remain in communication with the Institutional Biosafety Committee throughout the conduct of the project.

40

Responsibilities of the PI During the Conduct of the Research

- The Principal Investigator shall:
- **Section IV-B-7-e-(1).** Supervise the safety performance of the laboratory staff to ensure that the required safety practices and techniques are employed;
- **Section IV-B-7-e-(2).** Investigate and report any significant problems pertaining to the operation and implementation of containment practices and procedures in writing to the Biological Safety Officer (where applicable), Greenhouse/Animal Facility Director (where applicable), Institutional Biosafety Committee, NIH/OBA, and other appropriate authorities (if applicable);
- **Section IV-B-7-e-(3).** Correct work errors and conditions that may result in the release of recombinant or synthetic nucleic acid molecule materials; and
- **Section IV-B-7-e-(4).** Ensure the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., purity and genotypic and phenotypic characteristics).
- **Section IV-B-7-e-(5).** Comply with reporting requirements for human gene transfer experiments conducted in compliance with the *NIH Guidelines* (see Appendix M-I-C, *Reporting Requirements*).

41

Safety Considerations

- Risk Assessment/Risk Groups
- Risk assessment is ultimately a subjective process.
- The investigator must make an initial risk assessment based on the Risk Group (RG) of an agent
- Containment

42

Risk Assessment

- The Vector
- The Expression Cassette
- Method of Delivery
- Health Status of the Therapy Recipient

- Comparative Medicine, Vol 53:2 Components of Gene Therapy Experimentation that Contribute to Relative Risk

43

Risk Groups

- Agents are classified into four Risk Groups (RGs) according to their relative pathogenicity for healthy adult humans by the following criteria:
- (1) Risk Group 1 (RG1) agents are not associated with disease in healthy adult humans.
- (2) Risk Group 2 (RG2) agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available.
- (3) Risk Group 3 (RG3) agents are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available.
- (4) Risk Group 4 (RG4) agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available.

44

Containment

- Effective biological safety programs rely upon mechanisms that can be divided into two categories:
- Standard laboratory practices; and
- Physical barriers.
- Third containment mechanism – Biological barriers.
  - Natural barriers exist that limit either:
  - (i) the infectivity of a vector or vehicle (plasmid or virus) for specific hosts, or
  - (ii) its dissemination and survival in the environment.
- Three means of containment are complementary.

45

Responsibilities of the National Institutes of Health (NIH)

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

46

General Responsibilities – NIH Director

- Promulgating requirements as necessary to implement the *NIH Guidelines*;
- Establishing and maintaining RAC to carry out their responsibilities;
- Establishing and maintaining NIH/OBA to carry out their responsibilities
- Conducting and supporting training programs in laboratory safety for Institutional Biosafety Committee members, Biological Safety Officers and other institutional experts (if applicable), Principal Investigators, and laboratory staff.
- Establishing and convening Gene Therapy Policy Conferences

47

Specific Responsibilities

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

48

What is the NIH Office of Biotechnology Activities?

- The NIH Office of Biotechnology Activities (OBA) supports the Office of Science Policy and is within the Office of the Director of NIH.
- Promotes science, safety, and ethics in biotechnology through the advancement of knowledge, enhancement of public understanding, and development of sound public policies.
- A core responsibility of OBA is to foster awareness of, and adherence to, the standards and practices set forth in the *NIH Guidelines.*

49

Office of Biotechnology Activities (OBA)

- OBA shall serve as a focal point for information on recombinant or synthetic nucleic acid molecule activities and provide advice to all within and outside NIH including institutions, Biological Safety Officers, Principal Investigators, Federal agencies, state and local governments, and institutions in the private sector. OBA shall carry out such other functions as may be delegated to it by the NIH Director.

50

Recombinant DNA Advisory Committee (RAC)

- The RAC is responsible for carrying out the functions specified in the *NIH Guidelines*, as well as others specified in its charter or assigned by the Secretary of Health and Human Services or the NIH Director.
- The RAC membership and procedures, in addition to those set forth in the *NIH Guidelines*, are specified in the charter for the RAC which is filed as provided in the General Services Administration Federal Advisory Committee Management regulations, 41 CFR part 101-6, and is available on the OBA web site, http://oba.od.nih.gov/oba/rac/RACCharter2009.pdf.

51

RAC shall be responsible for:

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

52

RAC shall be responsible for:

- Identifying novel human gene transfer experiments deserving of public discussion by the full RAC;
- Transmitting to the NIH Director specific comments/ recommendations about: (i) a specific human gene transfer experiment, or (ii) a category of human gene transfer experiments;
- Publicly reviewing human gene transfer clinical trial data and relevant information evaluated and summarized by NIH/OBA in accordance with the annual data reporting requirements;
- Identifying broad scientific, safety, social, and ethical issues relevant to gene therapy research as potential Gene Therapy Policy Conference topics;
- Identifying novel social and ethical issues relevant to specific human applications of gene transfer; and
- Identifying novel scientific and safety issues relevant to specific human applications of gene transfer

53

RAC - Membership

- The RAC consists of not less than 15 voting members (Charter lists up to 21), including the Chair, appointed under the procedures of the NIH and the Department of Health and Human Services.
- At least a majority of the voting members must be knowledgeable in relevant scientific fields, e.g., molecular genetics, molecular biology, recombinant DNA research, including clinical gene transfer research.
- At least 4 members of the RAC must be knowledgeable in fields such as public health, laboratory safety, occupational health, protection of human subjects of research, the environment, ethics, law, public attitudes or related fields.
- Note: There are representatives of 22 Federal agencies listed in the charter as non-voting members.

54

RAC - Minutes

- All meetings of the RAC are announced in the *Federal Register*, including tentative agenda items, 15 days before the meeting.
- Final agendas, if modified, are available at least 72 hours before the meeting.
- Four Meetings scheduled annually
- No item defined as a *Major Action* may be added to an agenda following *Federal Register* publication.

55

Oversight of Human Gene Transfer Trials

- NIH conducts assessments of Serious Adverse Events (SAEs) of gene therapy trials that may be important for the health and safety of trial participants.
  - A "serious adverse event" is any event occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
- This is done in coordination with the FDA.

56

Example: Gene Insertion SAE

- On December 5, 2002 and February 10, 2003, the NIH Recombinant DNA Advisory Committee (RAC) reviewed the clinical and molecular data concerning two adverse events that occurred in a human gene transfer study being conducted in France to correct X-linked SCID.
- This study involves engraftment of an autologous bone marrow derived, CD34+ hematopoietic stem cell enriched, cell population transduced with a Moloney murine leukemia retrovirus derived replication incompetent vector encoding the common gamma chain (γc) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21.
- Two children in this study developed T-cell acute lymphoblastic leukemia (T-ALL) almost 3 years after their gene therapy treatment. The leukemias in both children appear to share the common causative mechanism of insertional mutagenesis at or near the *LMO-2* gene with aberrant production of *lmo-2* protein, which contributed to the abnormal growth of these leukemic cells.

57

OBA Initiatives

- Scientific Symposia and Policy Conferences
- Genetic Modification Clinical Research Information System (GeMCRIS)
- Gene Transfer Safety Assessment Board (GTSAB)
- National Science Advisory Board for Biosecurity (NSABB)
- Dual Use Research
- Clinical Research Policy Analysis and Coordination (CRpac)

58

Recent Publications

- United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern

59

Recent Activities

- Gain-of-Function Research on Highly Pathogenic Avian Influenza H5N1 Viruses

60

BMBL

- Biosafety in Microbiological and Biomedical Laboratories (BMBL), 5th edition http://www.cdc.gov/biosafety/publications/bmbl5/index.htm

61

History

- In 1974, the NIH published *National Cancer Institute Safety Standards for Research Involving Oncogenic Viruses.* These guidelines established three levels of containment based on an assessment of the hypothetical risk of cancer in humans from exposure to animal oncogenic viruses or a suspected human oncogenic virus isolate from man.
- In 1976 NIH first published the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).* The *NIH Guidelines* described in detail the microbiological practices, equipment, and facility safeguards that correspond to four ascending levels of physical containment and established criteria for assigning experiments to a containment level based on an assessment of potential hazards of this emerging technology.
- In 1984, the CDC and NIH, a broad collaborative initiative involving scientists, laboratory directors, occupational physicians, epidemiologists, public health officials and health and safety professionals developed the first edition of BMBL.

62

Risk Assessment

- Risk Group: Risk groups are the result of a classification of microbiological agents based on their association with, and resulting severity of, disease in humans.
- Risk Groups 1, 2, 3, 4

- Biosafety Level: Biosafety level represent those conditions under which the agent ordinarily can be safely handled.
- Related to the facility, procedures, etc.
  - Biosafety Level 1, 2, 3, 4 for laboratories
  - Animal Biosafety Levels 1, 2, 3, 4 for animal areas
  - USDA also has BSL/ABSL-3 enhanced or BSL-3 Ag

63

Risk Groups

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

64

Biosafety Levels

- Principles of Biosafety

- Laboratory and Animal Biosafety Levels

- Agent (Classification based on Risk Group)
- Practices (Personnel Controls)
- Primary Containment (Engineering Controls)
- Facilities/Secondary Containment (Engineering Controls)

65

Examples

- *Bacillus anthracis*
  - Sterne strain: Risk group 2, BSL/ABSL 2
  - Ames strain: Risk group 3, BSL/ABSL 3

- Influenza Virus (H1N1)
  - 120 different strains/mutants in BEI Resources
  - Risk Group 2
  - 2009 H1N1 virus
    - BSL-2 for Diagnostic/Lab Work
    - BSL-3 for viral isolation
    - ABSL-3 for animal studies

66

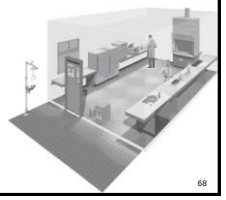
Biosafety Level 1 – Moldy Bread

- Agent: Not known to consistently cause disease in healthy humans (risk group 1)
- Practices: Standard Microbiological Practices
- Primary Barriers and Safety Equipment: None required
- Facilities: Laboratory bench and sink
- Example: *Bacillus subtilis*

67

Secondary Containment

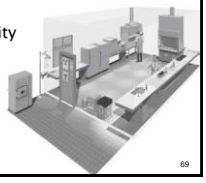
- BSL1: In general, a BSL-1 facility represents a basic level of containment that relies on standard microbiological practices with no special or secondary barriers recommended, other than a sink for hand washing, and self closing and lockable doors.



68

Biosafety Level 2 – Cold Sore

- Agent: Associated with human disease. Routes of transmission include percutaneous injury, ingestion, and mucous membrane exposure.
- Practices: Standard Microbiological Practices; plus limited access, biohazard warning signs, sharps precautions, and a laboratory biosafety manual
- Primary Barriers and Safety Equipment: Physical Containment (Class I or II BSCs) and Personnel Protective Equipment (lab coats and masks)
- Facilities: Autoclave available in the facility
- Example: Hepatitis B or HIV



69

Biosafety Level 2

- Biosafety Level 2 builds upon BSL-1.
  - BSL-2 is suitable for work involving agents that pose moderate hazards to personnel and the environment. It differs from BSL-1 in that:
  - 1) laboratory personnel have specific training in handling pathogenic agents and are supervised by scientists competent in handling infectious agents and associated procedures;
  - 2) access to the laboratory is restricted when work is being conducted; and
  - 3) all procedures in which infectious aerosols or splashes may be created are conducted in BSCs or other physical containment equipment.
  - 4) Autoclave, or other appropriate type of biohazardous waste treatment, to process infectious wastes

70

Biosafety Level 3

- Agent: Indigenous or exotic agents with potential for **aerosol transmission**, disease may have serious or lethal consequences
- Practices: Standard Microbiological Practices, controlled access, decontamination of all waste, decontamination of laboratory clothing, and baseline serum(?)
- Primary Barriers and Safety Equipment: Physical Containment (Class I or II BSCs) and Personnel Protective Equipment (protective clothing, gloves, respiratory protection)
- Facilities: BSL2 plus: physical separation for access corridors, self-closing, double door access, exhaust air not recirculated, negative airflow into lab.
- Examples: *Bacillus anthracis* and *Mycobacterium tuberculosis*

71

Example

- Potential for Aerosol Transmission:
  - *Bacillus anthracis*, Ames Strain
    - Cutaneous Form: 95% of cases, >1% mortality
    - Oropharyngeal/Gastrointestinal Form: Up to 50% mortality
    - Inhalational Form: Up to 100% mortality

72

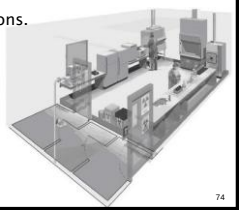
Biosafety Level 3

- At BSL-3, more emphasis is placed on primary and secondary barriers to protect personnel in contiguous areas, the community, and the environment from exposure to potentially infectious aerosols.
- For example, all laboratory manipulations should be performed in a BSC or other enclosed equipment, such as a gas-tight aerosol generation chamber. Secondary barriers for this level include controlled access to the laboratory and ventilation requirements that minimize the release of infectious aerosols from the laboratory.
- Biosafety Level 3 is applicable to clinical, diagnostic, teaching, research, or production facilities where work is performed with indigenous or exotic agents that may cause serious or potentially lethal disease through inhalation route exposure.

73

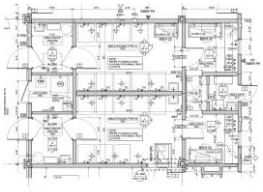
Secondary Containment

- BSL3: The unique features which distinguish the BSL-3 facility from the BSL-1 and BSL-2 facilities are the provisions for:
  - access control,
  - safety equipment,
  - specialized ventilation system,
  - and sealed finishes and penetrations.



74

Access Control: Physical separation



Controlled access with an anteroom, two self closing interlocked doors in series and a personnel shower.

75

BSL-3 Ag: Secondary Containment

- BSL3 Ag: A BSL-3Ag requires a special type of facility, where the facility barriers, usually considered secondary barriers, now act as primary barriers.
- Also called BSL-3+ and BSL-3 enhanced

Dedicated Laboratory
Dedicated Shower
Dedicated Autoclave
Anteroom with Controlled Access

76

Biosafety Level 4

- Agent: Dangerous/exotic agents which pose high risk of life threatening disease, Aerosol-transmitted laboratory infections have occurred; or related agents with unknown risk of transmission
- Practices: BSL3 plus, clothing change before entering, shower on exit, and all material decontaminated on exit from facility
- Primary Barriers and Safety Equipment: All procedures conducted in a Class III hood or with a full-body, positive pressure suit and a Class I or II BSC.
- Facilities: BSL3 plus, separate building or isolated zone, dedicated supply and exhaust, vacuum, and decon systems.
- Examples: Marburg or Congo-Crimean hemorrhagic fever

77

Biosafety Level 4

- There are two models for BSL-4 laboratories:
- (1) A Cabinet Laboratory where all handling of agents must be performed in a Class III BSC.
- (2) A Suit Laboratory where personnel must wear a positive pressure protective suit.

78

Cabinet Laboratory

- All manipulations of infectious materials within the facility must be conducted in the Class III biological safety cabinet.
- The BSL-4 cabinet laboratory consists of either a separate building or a clearly demarcated and isolated zone within a building.
- Rooms in the facility must be arranged to ensure sequential passage through an inner (dirty) changing area, a personal shower and an outer (clean) change room prior to exiting
- An automatically activated emergency power source must be provided at a minimum for the laboratory exhaust system, life support systems, alarms, lighting, entry and exit controls, BSCs, and door gaskets. Monitoring and control systems for air supply, exhaust, life support, alarms, entry and exit, and security systems should be on an uninterrupted power supply (UPS).
- A double-door autoclave, dunk tank, fumigation chamber, or ventilated anteroom/airlock must be provided at the containment barrier for the passage of materials, supplies, or equipment.

79

Suit Laboratory

- All procedures must be conducted by personnel wearing a one-piece positive pressure suit ventilated with a life support system.
- All manipulations of infectious agents must be performed within a BSC or other primary barrier system.
- Entry into the BSL-4 laboratory must be through an airlock fitted with airtight doors.
- Personnel who enter this area must wear a positive pressure suit with HEPA filtered breathing air. The breathing air systems must have redundant compressors, failure alarms and emergency backup.
- A chemical shower must be provided to decontaminate the surface of the positive pressure suit before the worker leaves the laboratory.
- In the event of an emergency exit or failure of chemical shower system a method for decontaminating positive pressure suits, such as a gravity fed supply of chemical disinfectant, is needed.

80

Biosecurity

- New Section added in the 5th addition
- In the BMBL the term "biosecurity" refers to the protection of microbial agents from loss, theft, diversion or intentional misuse.
- The recommendations presented in this section are advisory. Excluding the Select Agent Regulations, there is no current federal requirement for the development of a biosecurity program.

81

Occupational Health

- Laboratory personnel and support staff must be provided appropriate occupational medical service including medical surveillance and available immunizations for agents handled or potentially present in the laboratory.
- A system must be established for reporting and documenting laboratory accidents, exposures, employee absenteeism and for the medical surveillance of potential laboratory-associated illnesses.
- An essential adjunct to such an occupational medical services system is the availability of a facility for the isolation and medical care of personnel with potential or known laboratory acquired infections.
- Required for high containment.

82

Laboratory Acquired Infections

Organism	Risk/100,000 microbiologists	Risk/100,000 general population
Brucella	641	0.08
Cocciodiodes	13.7	12
C. difficle	0.2	8
E. Coli O157:H7	8.3	0.96
N. meningitidis	25.3	0.62
Salmonella	1.5	17.9
Shigella	6.6	6.6

From: Baron and Miller, "Bacterial and Fungal Infections Among Diagnostic Laboratory Workers: Evaluating the Risks", Diagn Microbiol Infect Dis, 2008 Mar; 60(3):241-6

Pathogen Work at Texas A&M Suspended!

- In 2007, federal officials suspended all research on select agents at Texas A&M University (TAMU) in College Station after the school failed to report two cases of exposure to the CDC.
  - The first exposure at TAMU occurred in February 2006, when a lab worker cleaning a chamber containing brucella bacteria in a biosafety level-3 lab developed brucellosis; she recovered after treatment with antibiotics.
  - One month later, three other workers tested positive for antibodies to Coxiella burnetii, but didn't become sick.

84

Agent Summary Statements

- Background
- Occupational Infections
- Natural Infections
- Laboratory Safety
- Containment Recommendations
- Special Issues:
  - Select Agent
  - Transfer
  - Vaccines

Appendices

- Appendix A :Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets
- Appendix B: Decontamination and Disinfection
- Appendix C: Transportation of Infectious Substances
- Appendix D: Agriculture Pathogen Biosafety
- Appendix E: Arthropod Containment Guidelines
- Appendix I: Guidelines for Work with Toxins of Biological Origin

Approval Process

- For infectious disease protocols, who needs to approve them prior to doing the work?
  - Institutional Biosafety Committee
  - Animal Care and Use Committee (if applicable)
  - Select Agent Program – Responsible Official
  - Institute Director
- Concurrent or sequential processes?

Questions?

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