Boston Public Health Commission

Biological Laboratory Safety Permit Application

SECTION 2: BSL-4 BIOSAFETY MANUAL

Boston University

National Emerging Infectious Diseases Laboratories

September 2014

This Biosafety Manual defines the biological safety policies and procedures and sets minimum standards and guidelines for the Biological Safety Level 4 (BSL-4) research and operational activities at the National Emerging Infectious Diseases Laboratories (NEIDL) at Boston University. These policies and procedures are designed to safeguard personnel and the environment from biologically hazardous materials and to comply with federal, state, and local regulatory requirements. Principal Investigators, laboratory workers, support staff, and visitors must adhere to the policies and procedures set forth in this manual.

For information about specific biological safety programs for operations not covered in this Biosafety Manual, contact the Institutional Biosafety Committee or the Biosafety Officer.

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Andrew Henderson	Kathryn Mellouk
Chair, Institutional Biosafety Committee	Associate Vice President, Research Compliance

Boston Public Health Commission

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CHAPTER 1

INTRODUCTION

1.0 PURPOSE

This Biological Safety Manual (BSM) defines the safety requirements for the handling, use, storage, transport, and disposal of biological materials in the National Emerging Infectious Diseases Laboratories (NEIDL) Biological Safety Level 4 (BSL-4) laboratories. The policies, procedures, and safety requirements described in this BSM are designed to provide safeguards for personnel and the environment from biologically hazardous materials without unduly limiting the academic research mission of the institution. This manual is used in conjunction with other plans, manuals, and standard operating procedures (SOPs) and policies listed in Appendix G and creates the framework to comply with federal, state, and local regulatory requirements.

The information specified in the BSM are based on standards and guidelines including Centers for Disease Control and Prevention's (CDC's) *Biosafety in Microbiological and Biomedical Laboratories (BMBL*), 5th edition; the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*; Boston Public Health Commission *Biological Laboratory Regulations*, U.S. Departments of Health and Human Services (DHHS) and Agriculture (USDA) *Select Agents and Biological Toxins* published final rules (42 CFR Part 73 and 9 CFR Part 121); other applicable regulations; and accepted safety best practices.

Implementation of this BSM is mandatory.

This BSM was prepared as a collaborative project of Boston University's (BU's) Environmental Health & Safety (EHS) department, scientific and support staff of the NEIDL BSL-4 containment facility, and the Institutional Biosafety Committee (IBC) and is consistent with the Boston University Institutional Biosafety Manual.

2.0 SCOPE

2.1 Applicability

This BSM applies to all biological research activities involving pathogens requiring BSL-4 containment, practices, and procedures. The procedures and safety requirements detailed in this BSM and its appendices apply to all research and operations in the BSL-4 laboratories. Changes to this BSM shall not be made without written approval of the Associate Vice President for Research Compliance and the Chair of the IBC or their designee. This BSM will be reviewed annually and

revised as necessary. Prior to working in the BSL-4 facility, all BSL-4 personnel must certify in writing that they have read and fully understand this BSM and will comply with its requirements.

2.2 Risk Assessment

The research conducted in the NEIDL BSL-4 facility involves work with Risk Group 4 (RG4) Agents or clinical specimens containing or suspected to contain these agents. The RG4 Agents are those deemed likely to cause serious or lethal disease for which preventive or therapeutic interventions are usually not available. The NEIDL BSL-4 and Animal Biosafety Level-4 (ABSL-4) laboratories are designed to meet all criteria listed in the *BMBL* 5th edition for containment and safe working with RG4 pathogens.

2.3 Biological Safety Program Goals

Biological Safety Program goals referenced in this BSM are to protect laboratory workers, staff, the public, and the environment from potentially hazardous biological agents. The Boston University IBC mandates the use of biological safety precautions that effectively reduce or eliminate the risk of exposure to hazardous biological agents used in research. In the development of this BSM, the IBC ensures that all policies and procedures are in accordance with both the regulatory frameworks governing the use of biological materials and the best practices adopted nationally.

The Biological Safety Program is working to apply the framework established under the Laboratory Biorisk Management Standard (CWA 15793:2011) as prepared by the European Committee for Standardization (CEN) Workshop 31, and adopted by CEN. This standard establishes application of a management systems approach in identifying and understanding the management of interrelated processes for a given objective to improve the organization's effectiveness and efficiency. The management systems approach enables an organization to effectively identify, monitor, and control the laboratory biosafety and biosecurity aspects of its activities. The successful implementation of the management system, with the involvement of all stakeholders, establishes a culture of safety that is paramount in the safety operation of the facility.

As noted in CWA 15793:2011, application of the management systems approach leads to the following actions:

- Defining the system by identifying or developing the processes that affect a given objective;
- Structuring the system to achieve the objective in the most effective manner;
- Understanding the interdependencies among the processes of the system;
- Continually improving the system through measurement and evaluation;
- Establishing resource constraints prior to action.

The international community has adopted the systems approach outlined above for the management of biological laboratories. An effective management systems approach builds on the concept of continual improvement through a cycle of planning, implementing, reviewing, and improving the processes and actions that an organization undertakes to meet its goals. This is known as the Plan-Do-Check-Act (PDCA) Principle:

Plan:	*Planning, including identification of hazard and risk and establishing goals*
Do:	*Implementing, including training and operational issues*
Check:	*Checking, including monitoring and corrective action*
Act:	*Reviewing, including process innovation, and acting to make needed changes to the management system*

In order to improve biorisk management, the organization must focus on the causes of nonconformities and undesirable events. Systematic identification and correction of system deficiencies leads to improved performance and control of biorisk.

The key factors in establishing and implementing a successful biorisk management system include:

- Commitment by top management:
  - Provide adequate resources, prioritization, and communication of biosafety and biosecurity policy;
  - Integrate biorisk management throughout the organization;
  - Identify opportunities for improvement and prevention, determine root causes and prevent recurrence.
- Focus on continual improvement:
  - Make continual improvement an objective for every individual in the organization;
  - Use periodic assessment against established risk criteria to identify areas for potential improvement;
  - Continually improve the effectiveness and efficiency of processes;
  - Promote prevention activities;
  - Provide personnel in the organization with appropriate education and training, including the methods and tools of continual improvement;
  - Establish measures and goals for improvement;
  - Recognize improvement.

3.0 GENERAL STATEMENT OF RESEARCH

Research at the NEIDL will involve the study of viral infectious diseases caused by pathogens that can only be worked with at BSL-4 maximum containment. Examples include filoviruses (e.g., Ebola and Marburg viruses), arenaviruses (e.g., Lassa, Junin, and Argentinian Hemorrhagic Fever viruses), henipah viruses (Nipah and Hendra viruses), and bunyaviruses (e.g., Crimean Congo Hemorrhagic Fever virus). The ultimate goal will be to develop vaccines and therapeutics that are effective countermeasures against these pathogens using both in vitro and in vivo systems. The use of sophisticated research equipment and processes including advanced imaging modalities, microscopy, and real-time specimen processing within a maximum containment space will augment established scientific approaches to combatting new and emerging infectious diseases. The NEIDL is uniquely designed and equipped to carry out aerobiology and tick vector studies, also within the safety of appropriate levels of biocontainment.

4.0 ROLES AND RESPONSIBILITIES

The following are responsible for the overall implementation and maintenance of the Biosafety Program in the NEIDL BSL-4 facility.

4.1 Associate Vice President for Research Compliance

The Associate Vice President for Research Compliance (AVP-RC) is the highest administrative official responsible for ensuring research compliance at BU. This individual:

- Provides oversight for the control of hazards in the research laboratories and for ensuring that comprehensive, enterprise-wide programs are in place for the safe handling of all hazardous materials.
- Is responsible for all non-financial research compliance at BU and Boston Medical Center (BMC). Has direct functional responsibility for the IBC, Biosafety Program, Environmental Health & Safety (EHS), Research Occupational Health Program (ROHP), Laboratory Safety Committees (LSC), laboratory animal use and care programs (both Institutional Animal Care and Use Committees [IACUC] and the animal care programs and other research-related oversight committees.
- Acts as the Responsible Official (RO) for the City of Boston's Public Health Commission Laboratory Regulation. This role is distinct from the RO of the Select Agent Program (SAP).
- Ensures communication between IBC, Institutional Review Board (IRB), IACUC, sponsored research offices, and regulatory agencies (e.g., City of Boston, CDC).
- Appoints various committee members in consultation with the provosts and deans at the University and BMC leadership.
- Accepts the final commissioning and decommissioning report of Biological Safety Level 4 (BSL-4) laboratory facilities on behalf of the Institution.

4.2 Director of National Emerging Infectious Diseases Laboratories

The Director of NEIDL has the ultimate responsibility for the oversight of scientific studies at the NEIDL and:

- Assumes overall responsibility for approval of research plans at the NEIDL.
- Works closely with the NEIDL administration to create and implement science policies and programs that foster and promote a culture of safety.
- Works with the NEIDL administration to build an organization that will successfully attain NEIDL's scientific mission and commitment to a culture of safety.
- Establishes and administers management that fosters close communication and collaboration among scientific and support staff to promote safety.

4.3 Responsible Official and Alternate Responsible Official for the CDC/Animal and Plant Health Inspection Service (APHIS) Select Agent Program

The Responsible Official (RO) for the Select Agent Program (SAP) has the authority and responsibility to act on behalf of Boston University to ensure compliance with the requirements of the Select Agent Final Rule. In the absence of the RO or in the event that it is required, BU has designated Alternate Responsible Officials (AROs) authorized to act on behalf of the RO and the institution with respect to SAP responsibilities.

- Maintains oversight of the SAP for Boston University.
- Is knowledgeable about current select agent regulations.
- Certifies the accuracy and truthfulness of information submitted to CDC/APHIS.
- Ensures that inspections are conducted and deficiencies are corrected.
- Ensures that inventories of select agents are routinely verified and CDC/APHIS is immediately notified of discrepancies, according to requirements.
- Ensures that all staff and personnel enrolled in the SAP are trained and maintain necessary clearances as required by the federal regulatory agencies and Boston University.
- Manages personnel and staff with responsibilities and delegated duties in the SAP.
- Ensures compliance with all of the Tier 1 requirements, including personnel reliability, security, training, biosafety, emergency response, and inventory control.
- Provides oversight of coordination by outside agencies such as police, fire, and EMS with BU programs.

4.4 Medical Director, Research Occupational Health Program

The Medical Director of the Research Occupational Health Program is the principal internal consultant to the Director of NEIDL, Core Directors, Principal Investigators, the Animal Science Center (ASC), RO, and EHS regarding medical monitoring, exposure, and medical care for personnel who are authorized to access BSL-4 laboratories. He or she:

- Acts as the Occupational Health Officer.
- Provides clinical expertise regarding potential occupational infection and medical issues.
- Serves as the subject matter expert, and consults with other health care providers and regulatory health agencies, on matters related to occupational infection and other occupation-related health issues.
- Acts as a liaison between BU, BMC, local, state, and federal health and regulatory agencies.
- Develops, maintains, and implements the medical surveillance and monitoring program for personnel approved to work in or access the BSL-4 facility.
- Conducts health evaluations and health- and behavior-related questionnaires as part of the medical surveillance program. Conducts pre-employment and post-employment health evaluations.
- Responds to and is immediately available to evaluate workers exposed to hazardous materials or who report ill as a result of work-related incidents.
- Provides training to workers approved to access BSL-4 laboratories on agent-specific hazards, signs, symptoms, treatment, and other medical information that may be relevant to the type of work performed by personnel.
- Reviews the agent(s) used by workers for recommended immunizations with investigational, Food and Drug Administration–approved, or foreign-derived vaccines, and provides recommendations for immunizations. Works with the CDC and other agencies to acquire vaccines and immunize personnel based on risk.
- Develops and maintains the Worker Absence Reporting Program. Monitors worker absences in accordance with Boston Public Health Commission (BPHC) Laboratory Disease Reporting requirements. The Research Occupational Health Program, under the direction of the Occupational Health Officer, monitors absences and provides notification as appropriate.

4.5 Director of NEIDL ABSL-4 Animal Core

The Director of the NEIDL ABSL-4 Animal Core has responsibility for the safe care and handling of ABSL-4 research animals, and:

- Determines the appropriate veterinary care for animals used in the facility, under the oversight of the Institutional Attending Veterinarian.
- Participates in the development and implementation of standard operating procedures and helps revise them as necessary to address work-related hazards.
- Oversees the mentoring of new Animal Core personnel and helps ensure that they are properly trained on procedures and processes.

4.6 Chief Safety Officer

The Chief Safety Officer (CSO) has full responsibility for ensuring that all aspects of NEIDL safety programs are being implemented and followed. The CSO is the Director of Research Safety for Boston University.

- Working with the Director of NEIDL and AVP-RC, the CSO has authority to suspend unsafe operations that have immediate impact on the health and safety of the community, workers, and the environment.
- Works closely with the research, administrative, and operations cores to develop safety matrices for their areas and provide regular reports of these activities to the safety committees and Director of NEIDL.
- Provides reports of incidents, accidents, near misses, and any observed safety concerns to the safety committees.

4.7 Biosafety Officer

The Biosafety Officer (BSO) is responsible for providing guidance on the safe handling, storage, and transport of biological agents and works with the Associate Director of Research Safety, NEIDL (ADRS-NEIDL) to manage the Biosafety Program at the NEIDL. The Biosafety Officer is the Associate Director, Research Safety (AD) for Boston University. He or she:

- Provides technical advice to the IBC and researchers on laboratory containment, biosecurity, and safety procedures.
- Assists with the development of emergency plans for handling spills and personnel contamination.
- Develops and works with the ADRS-NEIDL to implement biosafety programs, training programs, policies, and laboratory safety practices.
- Assists the ADRS-NEIDL to follow up on exposures, incidents, spills, and other related laboratory emergencies.
- Reviews new research with the ADRS-NEIDL and conducts risk assessments.
- Assists the ADRS-NEIDL with developing training programs, as approved by the IBC.

- Regularly reports on the status of the Biosafety Program to the IBC.

4.8 Associate Director for Research Safety-NEIDL (Maximum Containment)

The Associate Director for Research Safety-NEIDL (ADRS-NEIDL) has overall responsibility and oversight of safety in the BSL-4 and ABSL-4 containment facility and, as such:

- Conducts risk assessments and ensures that safety processes are incorporated into laboratory operations and are constantly being followed by all personnel in the BSL-4 and ABSL-4 laboratories.
- Coordinates and leads the daily safety meetings to review critical daily operations and activities and ensure that the issues identified are addressed in a timely manner.
- Conducts routine BSL-4 and ABSL-4 inspections to verify compliance with policies and procedures and ensure that physical containment systems, support equipment, waste disposal, and other operating features are in accordance with design intent, operational procedures, and applicable requirements.
- Works with the CSO, RO, and Core Directors to suspend unsafe work and practices and to address the issue before any resumption of work can begin.
- Coordinates annual facility recertification with Facilities Management.
- Provides oversight and training for all BSL-4 personnel. Ensures that personnel maintain the required training level. Keeps training records maintained and up to date.
- Coordinates personnel access to the BSL-4 facility with Public Safety, the RO, and ROHP to ensure that all personnel have obtained appropriate clearances prior to BSL-4 access.
- Provides oversight of the agent inventory and security program. Conducts periodic verifications and checks to ensure for accuracy of the inventories. Ensures immediate reporting of discrepancies to the RO.
- Assists the laboratory facilities with preparation for inspections and acts as liaison with regulatory agencies (e.g., BPHC, CDC/APHIS Select Agent Program, OSHA, MA-DPH, USDA/APHIS, Boston Fire Department, etc.) during their visits, reviews, inspections, and other safety-related responses for BSL-4 activities.
- Develops safety matrices for various safety activities within the NEIDL BSL-4 facility and provides regular reports of these activities to the RO and CSO.
- Works with the BSO in the investigation and reporting of all accidents and near misses to the CSO and RO with recommended action plans to address and prevent recurrence of the incident. Provides oversight for the implementation of any corrective actions or

programmatic changes recommended by any Independent Accident Review Committees appointed to review accidents.

- Responsible for oversight of all safety trainings, emergency drills, and safety awareness campaigns.
- Provides oversight of responses to emergencies and coordinates activities with research, operations, and Emergency Response Planning. Acts as a liaison and technical resource during emergencies, works with Emergency Response Planning, and implements emergency drills and exercises with BU and non-BU personnel.

4.9 Core Directors

The Core Directors have overall responsibility for the maintenance and proper operations of their core. Each core provides support and services for operations and research at the NEIDL, and each Core Director:

- Has overall responsibility for directing the safe operations within his or her core.
- Is responsible for, and acts as the primary responder to, emergencies that occur within the core. Works with the ADRS-NEIDL and provides risk assessment and recommended risk management information to emergency responders.
- Ensures that personnel are properly trained on their tasks and are competent to use equipment and trained on emergency response procedures.
- Reports any issues within the core, such as equipment malfunction, facility deficiencies, etc.
- Assesses staffing needs and requirements for the core.
- Develops, maintains, and implements SOPs.
- Maintains records necessary for the safe and compliant operation of the core.

4.10 Principal Investigators

Principal Investigators (PIs) are responsible for the health and safety of all personnel in their laboratories and for compliance with all applicable regulations and criteria established in this BSM. Each PI:

- Develops laboratory-specific standard operating procedures that cover the hazards and activities (both routine activities and unusual events) relevant to his or her laboratory. Makes correction as necessary to ensure that the procedures comply with the safety requirements and this BSM.
- Ensures that specific laboratory hazards are effectively communicated to laboratory personnel; that personnel have received appropriate training and are competent to

perform procedures in the laboratory; and that appropriate controls are in place to minimize risk associated with the agent and laboratory procedures.

- Works with EHS to ensure that all laboratory personnel receive and complete required training and that records are maintained and up to date.
- Notifies the IBC and obtains prior approval before initiating new research work.
- Ensures that all personnel working in the lab have appropriate clearances prior to the start of their work in the laboratory.
- Notifies BU/BMC Control Center and EHS of emergencies, including all spills or incidents involving biological agents.
- Ensures that biological agents are disposed of in accordance with regulations and BU policies and procedures as outlined in this BSM.
- Works with the ADRS-NEIDL to suspend the access privileges of any BSL-4 employee who fails to follow procedures and comply with safety standards.

4.11 Laboratory Workers

Laboratory workers are an important element in developing and maintaining a safe laboratory environment. Laboratory workers are responsible for their own health and safety, as well as that of their coworkers. An incident caused by one laboratory worker can have a widespread effect on others. Each lab worker:

- Complies at all times with established, policies, procedures, practices and training required to access and work in the BSL-4 environment.
- Follows procedures during spills and emergencies. Reports spills, accidents, and incidents immediately to the BU/BUMC Control Center.
- Reports any unsafe conditions and practices immediately to the PI and EHS.
- Conforms to the standards of safety practices as part of the work performance evaluation appraisal and culture of safety in the laboratory.

4.12 Quality Assurance Officer

The Quality Assurance Officer conducts a high-level review of the operations and systems conducted in BSL-4 laboratories. The review provides a top-level assessment of the operations and building system controls to ensure that every aspect of the operations meets or exceeds the intended design or outcome.

- The QA officer provides an independent review function.
- Develops an integrated QA/QC program to review systems and operation processes at the BSL-4 facility. Conducts independent assessments of these systems and processes.

- Conducts random reviews and spot checks of programs to ensure persons in different departments comply with programs outlined by the leadership based on their understanding of the regulations and BU policies.
- Reviews research, animal, and facility operations operating procedures to ensure that they meet the intended outcomes and comply with appropriate regulations, standards, and BU policies.
- Provides recommendations for mitigation of findings and issues.
- Actively participates in formulation of policies, guidelines, procedures, and the sharing of information.
- Acts as document control manager. His/her role regarding SOPs is to ensure that the appropriate subject matter experts perform the technical and safety review of the SOPs. He or she then ensures a final quality check and submits the SOP for final approval.
- Provides quarterly reports to the AVP-RC on findings, along with recommendations.
- Reports issues of immediate concern to AVP-RC and RO upon discovery of the issue.

4.13 Director of Facilities, NEIDL

The Director of Facilities, NEIDL has overall responsibility for the oversight and maintenance of the BSL-4 and ABSL-4 facilities and the building and containment systems that service the laboratories.

- Serves as a point of contact for the monitoring, maintenance, and repair related to facility and utilities, and responds to building systems alerts associated with the facility, containment, and utilities.
- Manages the facilities operations group to address day-to-day repair and preventive maintenance, and identifies operations and systems support needs.
- Reports any operational issues and alarms affecting the building systems and integrity of containment immediately to the Laboratory and Control Center.
- Is responsible for oversight and completion of annual recertification and testing of facilities, equipment, and building systems.
- Oversees the process and completion of facility decommissioning.

4.14 Institutional Biosafety Committee

The Institutional Biosafety Committee (IBC) is responsible for the overall oversight of the Biosafety Program at BU. The IBC is registered with the Office of Biotechnology Activities of the National Institutes of Health (NIH) and the City of Boston Public Health Commission (BPHC), and carries out these oversight functions pursuant to requirements set forth by the NIH, the CDC,

Occupational Safety and Health Administration (OSHA), the BPHC, the Massachusetts Department of Public Health (DPH), and Boston University. The full description of the IBC, its policies, procedures, research application registration forms, review procedures, and minutes of monthly meetings are available at http://www.bu.edu/orccommittees/ibc/. The IBC:

- Provides oversight of the Institutional Biosafety Program at BU and BMC, including the development and review of biosafety policies and procedures.
- Reviews and approves training programs and establishes qualifications for individuals working with biological materials.
- Coordinates the implementation of the biosafety program with other committees and departments to ensure consistency.
- Reviews and approves new research proposals involving biohazardous material in accordance with guidelines established by the BPHC, DPH, OSHA USDA, CDC, NIH, and BU, as well as maintains project approvals and reviews amendments.
- Sets required biological safety containment levels for research projects. Generally, the BSL recommended by the CDC and NIH will be used. The IBC also has the authority to increase laboratory containment levels if the protocol review identifies specific hazards associated with the proposed operations (e.g., the IBC can escalate an RG3 Agent to BSL-4 containment due to the specific protocol requirements).
- Approves design specifications and criteria for containment facilities developed by the BSO and conducts the final review and acceptance of BSL-4 laboratories.
- Works with the BSO and the ADRS-NEIDL on findings of inspection programs and investigates violations of biosafety procedures or policies and significant accidents or illnesses involving biological agents, and recommends corrective actions as appropriate.
- Communicates and reports laboratory occupational exposures to appropriate regulatory agencies.
- Reviews and approves required annual reports and reports of exposures sent to the BPHC and NIH's Office of Biotechnology Activities.
- Recommends disciplinary action for noncompliant researchers to the proper BU officials.

4.15 Institutional Animal Care and Use Committee

The Institutional Animal Care and Use Committee (IACUC) has oversight of the care and use of animals and ensures compliance with the USDA Animal Welfare Act and Regulations; Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals; the *Guide for the Care and Use of Laboratory Animals*, 8th edition; *AVMA Guidelines for the Euthanasia of Animals*

(2013 edition) from the American Veterinary Medical Association; and the accreditation standards of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

- Reviews and approves all animal-related research projects prior to their start.
- Conducts verification of compliance to applicable regulations and standards.
- Enforces all applicable regulations, standards, and BU policies.

4.16 Radiation Safety Committee

The Radiation Safety Committee has oversight responsibilities for the enforcement of regulations and policies governing the use of radioactive materials in research. The EHS Radiation Safety Division enforces these requirements and ensures that regulations, policies, and procedures are followed. The Radiation Safety Committee:

- Reviews and approves all research projects involving radiation prior to their start.
- Conducts audit verification of compliance to applicable regulations and standards.
- Enforces all applicable regulations, standards, and BU policies.
- Trains personnel.

4.17 External Scientific Advisory Committee

The primary role of the External Advisory Committee is to advise the Director of the NEIDL on long-term strategic planning for NEIDL research programs that address the changing landscape of research in infectious diseases both in the United States and abroad.

4.18 Internal Scientific Advisory Committee

The Internal Scientific Advisory Committee reviews the aims and goals of the research project to ensure that it meets the mission of the NEIDL.

4.19 Laboratory Safety Committee

The Laboratory Safety Committee (LSC) has oversight of all chemical safety practices, approves the Chemical Hygiene Plan, and reviews research involving highly hazardous chemicals, including their use in research animals. The LSC, in collaboration with EHS, recommends safe work practices, use of safety equipment, and appropriate personal protective equipment for working with highly hazardous chemicals.

4.20 Institutional Review Board

Research investigations involving human subjects are under the purview of the BUMC Institutional Review Board (IRB), which must approve all such research proposals prior to their commencement

as well as all modifications to approved protocols. The IRB recommends and implements policies and procedures for the protection of the rights and welfare of human subjects.

CHAPTER 2

ADMINISTRATIVE REQUIREMENTS

1.0 LABORATORY ACCESS

Access to BSL-4 and ABSL-4 laboratories is restricted to personnel who have a need to access the laboratories as part of their job function. BSL-4 laboratory workers and support personnel are only granted access after successfully meeting the requirements established in the *Personnel Suitability and Reliability Policy*, BSL-4 trainings, medical clearances, and the Select Agent Program Security Risk Assessment (SRA) clearance. Employees who are enrolled in the Select Agent Program and have received their SRA clearance are granted access to certain areas of the BSL-4 and ABSL-4 laboratories based upon their work or job responsibilities.

Access into the laboratory is controlled with the use of proximity card readers and biometric iris scanners. These security controls are programed so that an employee can only access spaces that have been previously approved, as requested by their supervisor and based on job function. Personnel must not share their proximity cards; to do so is subject to disciplinary action.

When an individual laboratory or support staff member no longer requires access to the BSL-4 laboratories, the supervisor immediately contacts the RO and Public Safety. Public Safety will revoke access privileges to the areas to which the employee no longer requires access by disabling proximity card and biometric iris scan access. The RO will report the termination of an employee from the Select Agent Program to CDC/APHIS.

Employees must immediately report a lost or misplaced proximity card to Public Safety at 4-4444 *and* the RO at 8-8838 (617-414-4444 and 617-638-8838 if calling from an outside line). Public Safety will then immediately inactivate the lost proximity card and issue a new one to the employee as a replacement.

Access records are reviewed monthly by the RO or ARO and Public Safety. Violation of access procedures can result in suspension or revocation of access to the BSL-4 facility.

1.1 Supervised Access

A new employee who has successfully completed BSL-4 baseline training with the EHS Training Core will be granted supervised access to the BSL-4 facility. The employee will be assigned to conduct specific work under the close supervision of a mentor as the final phase of the employee BSL-4 training program. A full description of the BSL-4 training program is available in Section 15: Training Plan.

1.2 Access without a Mentor

Upon completion of the mentorship, an employee's proficiency and ability to conduct assigned work and duties safely is assessed by the training mentor, BSL-4 trainer, and EHS. The assessment is submitted to the NEIDL Training Advisory Committee, which then provides final sign-off for independent access to the BSL-4 laboratory.

1.3 Visitor Access

Visitors who need access to the BSL-4 facility receive background checks from Public Safety and visitor-level clearances from ROHP. Visitors are screened for their previous use of the personal protective equipment and receive training prior to their access to the laboratories. All visitors are escorted at all times by the BSL-4 host.

2.0 PERSONNEL SUITABILITY AND RELIABILITY PROGRAM

As a requirement of CDC/APHIS for agents classified as Tier I and as a policy of the University and the NEIDL, before employees can access the BSL-4 laboratories, they are required to undergo a series of suitability checks. The purpose of the suitability check is not only to comply with established policies and procedures set forth by the University and the NEIDL, but also to ensure the appropriateness of employees for access to the NEIDL BSL-4 laboratories and select agents. Once employees have successfully completed the program, their suitability for continued access to the NEIDL and BSL-4 laboratories, is checked on an ongoing basis (i.e., reliability).

Criminal background checks are completed in accordance with BU Public Safety guidelines and all federal, state, and local laws and regulations.

- *Department of Justice Criminal Background Check and Fingerprinting*. Completed in accordance with CDC requirements as part of the application to request access to select agents.
- *Basic Background Check*. This includes, but is not limited to:
  - Social Security number
  - Academic credentials
  - Past employment
  - Licenses and credentials
  - Sexual Offender Registry Information (SORI) check
  - Credit history check
  - RMV/DMV driving record, if required.

Additional information is available in the *Personnel Suitability and Reliability Policy*.

3.0 RESEARCH OCCUPATION HEALTH PROGRAM

The NEIDL occupational health program for its BSL-4 employees is administered and managed by the Research Occupational Health Program (ROHP). The program provides medical evaluation by a certifying medical health officer; conducts behavioral health screenings, drug testing, and medical consultations; oversees health care management of exposed employees with hospital care; manages triage and response during exposures; and acts as liaison with regulatory health agencies.

All BSL-4 employees are informed about and are enrolled in the ROHP medical surveillance program. The key elements of the program include:

- Enrollment in the mandatory BSL-4 medical surveillance program.
- Pre-placement and initial health questionnaire and determination.
- Ongoing, annual, and event-driven medical evaluations and follow-up.
- Vaccinations, as applicable.
- Serum banking, as applicable.
- Illness reporting.
- Absence reporting.
- Agent Information Sheets (AIS). Agent-specific resource material designed for laboratory personnel with important information about the pathogenicity of the agent, signs and symptoms, transmissibility, and other important information.
- Agent-Specific Identification Cards. Agent-specific wallet cards provide agent name(s) and 24/7 emergency contact information for ROHP. (See Appendix F, Agent ID Card.)

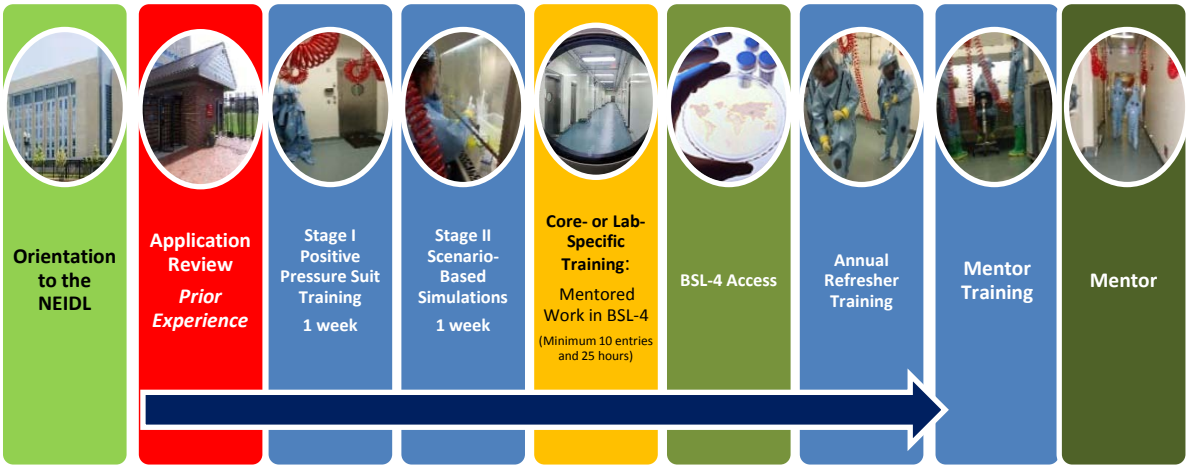
Additional information on the ROHP is available in Section 7: Disease Surveillance Plan.

4.0 BSL-4 TRAINING AND MANAGEMENT

The purpose of a comprehensive training program is to ensure that employees are aware of the hazards to which they might be exposed, are familiar with work safety procedures, and know how to protect themselves, their colleagues, and the environment from potential exposure. Additional site-specific training for BSL-4 facilities is an IBC mandate and requires additional training on laboratory SOPs.

Training is the joint responsibility of the employee, Core Director and Supervisor, Associate Director of Maximum Containment Training, and Associate Director of Research Safety-NEIDL. All personnel must complete required trainings in a consistent and timely manner. Core Directors and Supervisors ensure that all personnel attend and complete their required training.

Training for BSL-4 personnel is described in Section 15: Training Plan.



NEIDL-Specific Training Stages

New staff who will work in BSL-4/ABSL-4 laboratories and undergo BSL-4 training are initially assessed for their laboratory experience, abilities, and skills by the Associate Director of the BSL-4 Training Core, Associate Director of Research Safety NEIDL, and their Supervisor. The training is a regimented program and includes formalized didactic and practical trainings. The didactic training is conducted in a classroom setting, whereas suited, practical, and hands-on exercises are done in the BSL-4 Simulator Laboratory. The training is tailored toward an individual's previous biocontainment experience, his or her role within the BSL-4 facility, and other related trainings previously completed.

Stage I training is a baseline training and consists of a "Suit Suitability Assessment" within the BSL-4 simulator (this takes approximately one week). After completing baseline training, the trainee completes a mandatory facility tour with EHS and Facilities (to learn how various containment systems and processes work) and a review of appropriate guidelines and regulations. Stage II training focuses on specific areas of proficiency in activities that will be encountered by the investigator or staff member and uses a scenario-based set of simulations and problem solving (this also takes approximately one week). A performance assessment is conducted by the Associate Director of Research Safety-NEIDL, and if the outcome is satisfactory, an individual mentor is assigned. Additional training, including any core-specific training, is then commenced within the BSL-4 laboratory. This is supervised access only under the direct supervision of the assigned mentor(s). This requires a minimum of 10 entries and 25 hours of supervised core-specific work or more, depending on the experience and competence of the individual. The number of entries, hours worked, tasks performed, and competency are documented, along with any requirements for improvement. After core-specific training is complete, a final review is conducted consisting of 1) performance assessment and review of training documentation by the ADRS-NEIDL, individual mentor, and Supervisor, and 2) sign-off by the Training Advisory Committee.

After access without a mentor is granted, each BSL-4 worker must undergo annual refresher training or remedial training, if required. In addition, select individuals undergo mentor training in order to be able to escort and mentor new trainees. Mentors are volunteers with demonstrated experience and aptitude for serving as mentors.

The Associate Director of BSL-4 Training Core and Associate Director of Research Safety-NEIDL are responsible for implementation of the training. The facility also has routine emergency and evacuation drills and site-specific safety and security trainings. At least three drills are conducted at the NEIDL each year; they are documented using Homeland Security Exercise and Evaluation Program (HSEEP) procedures.

4.1 Mentorship Program (Training to be a Mentor)

Mentors must undergo selection and training. Mentor selection is based on BSL-4 experience and knowledge, and the ability to transfer knowledge to others. Mentors are selected by NEIDL leadership, the ADRS-NEIDL and the NEIDL Training Advisory Committee (NTAC). Training for candidate mentors consists of three components: an on-line course designed to provide reflection and insight into the individual's mentoring skills; a case study review of mentoring; and a guided discussion on mentoring do's and don'ts. The mentor works with the ADRS-NEIDL and NTAC to develop a training plan for the trainee who will undergo mentorship. Mentor training continues with ongoing meetings of the mentors to discuss areas of improvement and solutions to any training difficulties encountered.

4.2 Other Mandated Trainings

Trainees must complete the following:

- *General Laboratory Safety Training.* Personnel who work within the laboratory or provide research support must undergo this annual online training.
- *General NEIDL-Specific Annual Training*. This annual training includes emergency response, facilities and public safety events, and lessons learned as well as refresher training on personnel suitability and reliability requirements.
- *OSHA Bloodborne Pathogens*. Personnel who work with human blood and other bodily fluids complete the initial training and are refreshed in this training annually thereafter. The training covers hazards when working with human materials, sharps safety and precautions, and good laboratory practices and procedures.
- *Agent-Specific Training*. Agent-specific training is required for laboratory and animal workers who handle specific types of infectious agents. The training educates workers on the unique hazards they will encounter, specifically, pathogenicity, modes of transmission, signs and symptoms, treatment modalities, and procedures to follow if they become sick or exposed. The training is completed initially and refreshed annually.

- *Select Agent Training.* All viruses studied in BSL-4 laboratories are classified as select agents, and some are designated as Tier 1 Select Agents. Personnel authorized to use select agents in BSL-4 laboratories are required not only to receive training but also to pass and maintain the requirements of the Personnel Suitability and Reliability Program. The Select Agent Training is designed to meet the specific requirements of 42 CFR Part 73; 7 CFR Part 331; and 9 CFR Part 121 Select Agents and Toxins Final Rule. It must be completed initially prior to any work with select agents and refreshed annually.
- *Packaging and Shipping of Infectious Agents*. Personnel who package and ship infectious agents such as microorganisms, blood, and infected tissue samples are trained according to IATA and DOT regulations. Personnel are retrained every two years.
- *MRI Safety Training*. Personnel who work around the MRI are trained on MRI safety. The training is refreshed annually.
- *NEIDL Orientation.* All new employees are required to attend the NEIDL Orientation when they first report to work. This provides the employee with information on NEIDL, including security requirements, general building and facility information, building evacuation procedures, and basic information on laboratory facilities at the NEIDL. The orientation is only required to be completed once.

The following trainings must be completed when working with animals:

- Working with Nonhuman Primates
  - Training conducted by ABSL-4 Animal Core
- Working with Laboratory Animals
  - Training provided by ABSL-4 Animal Core

CHAPTER 3

SELECT AGENT PROGRAM

1.0 PROGRAM DESCRIPTION

The U.S. Department of Health and Human Services (DHHS) and the U.S. Department of Agriculture's (USDA's) Select Agent and Biological Toxin regulations, Titles 42 CFR 73, 7 CFR 331, and 9 CFR 121, require entities that possess, use, or transfer certain microbiological agents and biological toxins (known as "select agents") be registered and approved by DHHS or USDA. The regulation is enforced by the Centers for Disease Control and Prevention (CDC) and Animal and Plant Health Inspection Service (APHIS), an agency within the USDA, and administered through the National Select Agent Registry Program. Select agents and biological toxins are considered to be severe threats to public health, animal livestock, and agriculture and have the potential to be used as bioterrorism agents.

DHHS and USDA established a list of Select Agents and Toxins. Select Agents and Toxins are a subset of biological agents and toxins that the DHHS and USDA have determined to have the potential to pose a severe threat to public health and safety, to animal or plant health, or to animal or plant products.

A subset of Select Agents and Toxins has been designated as Tier 1 because these biological agents and toxins present "the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effect to the economy, critical infrastructure, or public confidence." Tier 1 Select Agent viruses will be studied at the NEIDL, and therefore the entire NEIDL BSL-4 facility must conform to Tier 1 requirements. The Select Agent and Tier 1 lists are reviewed and, if necessary, updated by the DHHS and USDA.

The BU Select Agent Program administers and manages the possession, use, and transfer of select agents in NEIDL BSL-4 containment. The program has oversight and coordinates the management of personnel clearances, trainings, agent inventory controls, security, facility access, emergency response, agent transfer, records, and all other aspects required to sustain the program.

2.0 RESPONSIBLE OFFICIAL AND ALTERNATE RESPONSIBLE OFFICIAL

The Select Agent Program is administered by the Responsible Official (RO) for Select Agents. The BU Select Agent Program has designated Alternate Responsible Officials (AROs) to assist the RO in the administration of the Select Agent Program and assume the duties of the RO in his or her absence. The RO has the authority and responsibility to ensure that the requirements of the appropriate

regulations are met. The RO reports to the Associate Vice President for Research Compliance. The CDC approves the RO and AROs and clears their Security Risk Assessment (SRA).

Responsible Official (RO):

Ron Morales	617-638-8838 (office)

Alternate Responsible Officials (ARO):

John Tonkiss	617-638-7548 (office)
Joe Barbercheck	617-638-8842 (office)
Bob Whitfield	617-638-7244 (office)

Emergency Contact for the RO or AROs can be made through the Control Center at 617-638-6666.

3.0 SELECT AGENT REGISTRATION

The select agent research conducted in NEIDL BSL-4 laboratories is reviewed and approved by appropriate federal and local regulatory agencies, including the CDC and BPHC, as well as by the BU IBC, IACUC, and scientific advisory committees. The Select Agent Program is administered and managed by the RO with the assistance of the AROs.

3.1 BU NEIDL Entity Select Agent Registration

The National Select Agent Registry Program requires the registration of entities-including government agencies, research institutions, universities, and commercial entities-that possess, use, or transfer select agents. The NEIDL is an entity at BU registered to possess, use, and transfer select agents. The registration covers specific select agents; specific research activities; specific locations; and personnel who have been cleared by the Federal Bureau of Investigation's (FBI's) Criminal Justice Information Services Division (CJIS) and BU Public Safety's background checks. The registration is granted by the CDC/APHIS and is valid for three years. The NEIDL BSL-4 facilities are subject to inspection by the CDC as a condition of their certificate of registration and approval.

3.2 Research Project Approval

Principal Investigators (PIs) planning to use, possess, or transfer select agents may do so only after approval from internal committees, including the IBC and IACUC if involving live animal work, and regulatory agencies such as CDC/APHIS and BPHC.

The IBC and the IACUC review and approve proposed research work that might involve select agents prior to obtaining them at the NEIDL BSL-4 facility. Information on the IBC registration procedure is available at http://www.bu.edu/orccommittees/ibc/. Information on the IACUC registration procedure is available at http://www.bu.edu/orccommittees/iacuc/.

The PI must contact the RO to initiate the registration process for use of the select agent with CDC/APHIS. The APHIS/CDC Form 1, *"Application for Laboratory Registration for Possession, Use, and Transfer of Select Agents and Toxins,"* must be completed by the RO and submitted to CDC/APHIS to register the select agent prior to acquisition.

3.3 Select Agent Registration Amendment

The select agent registration is amended with CDC/APHIS by submitting the changes using the relevant page(s) of APHIS/CDC Form 1. The RO works directly with the CDC/APHIS Select Agent Officer assigned to BU and submits the completed relevant pages of the form for approval.

3.4 Termination of Registration

To terminate a registered agent, the PI must notify the IBC and the RO in writing. Once permission is granted, the RO/ARO will be present to supervise and witness the destruction or transfer of the select agent. Destruction of agents will be properly documented and reported to CDC/APHIS and BPHC. Transfer of agents to another select agent facility requires approval by CDC/APHIS.

4.0 SECURITY REQUIREMENTS

4.1 Security Plan

A written site-specific Security Plan has been developed for the NEIDL BSL-4 laboratories. The plan meets the Select Agent Regulation (42 CFR Part 73). The purpose of the plan is to establish policies and procedures to ensure the physical security and control of select agents. The plan describes the safeguards in place to prevent unauthorized access, theft, loss, or release of select agents. The safeguards are based on a SRA that includes ID verification entry controls, proximity cards, biometric iris scanners, controlled keys, and 24/7 security control by Public Safety Officers.

4.2 Individual Security Clearance

Research personnel with access to select agents must successfully complete an FBI Security Risk Assessment. Researchers must complete and sign the FD-961 Form that is supplied by the RO. Once complete, the form is reviewed and signed by the RO. The completed FD-961 Form must be brought to the Public Safety Suitability Officer by the researcher. Fingerprints are

obtained from the researcher and both the FD-961 Form and fingerprints are submitted to the FBI office by the Public Safety Suitability Officer. CDC will contact the RO when the SRA clearance is approved. Once approved, the SRA clearance is valid for three years. Researchers are also enrolled in the Personnel Suitability and Reliability Program administered by the NEIDL.

4.3 Inventory Control

All access to select agents in storage is tracked and recorded in an electronic inventory control. Authorized personnel keep track of and record the transactions in the inventory control. The information includes the strain(s) of agent(s); the amount added to the inventory, removed, or destroyed; the name of the persons conducting the transaction; and the date and time of the transaction. Any discrepancy in the inventory record must be reported immediately to Public Safety at 4-4444 and the RO at 8-8838. The RO/ARO and Public Safety will conduct an investigation. The incident will be immediately reported to the CDC and BPHC should it be determined that the sample is missing.

5.0 SELECT AGENT TRAINING

All employees enrolled in the Select Agent Program who have access to select agents are trained initially and then annually thereafter, as required in the Select Agent Final Rule. Employees are trained to ensure that all Select Agent Program participants have appropriate knowledge of their roles and responsibilities, the Select Agent Final Rule, agent-specific information, biosafety, security, incident response, and other pertinent information.

6.0 RECORDS MANAGEMENT

All records associated with the Select Agent Program are kept secured, maintained, updated, and archived for a period that is required by regulation or BU policy. The RO has oversight of all records and documents associated with the Select Agent Program. Records are kept in accordance with the requirements of the Select Agent Final Rule.

6.1 Select Agent Inventory Requirements and Records

The select agent inventory record is kept and maintained electronically via a secured inventory system. The data is maintained and updated by authorized and designated laboratory personnel who are enrolled in the Select Agent Program and have received clearance for accessing the inventory. The records are secured from electronic intrusions. The RO/ARO and the Quality Assurance Officer routinely check these records.

An accurate inventory record of all select agents, from receipt to destruction or disposal is maintained. The inventory includes specific information on individual containers and vials, as

well as a record of each use and ultimate disposal. The select agent inventory record is reviewed by the AD with the RO monthly or after new transactions. Any discrepancy between the inventory record and the actual inventory is reported immediately to the RO at 8-8830 and Public Safety at 4-4444.

The inventory records contain the following information:

- Name of agent(s)
- Quantity acquired, source, date
- Quantity, volume, mass destroyed or disposed, date
- Quantity used
- Transfers: quantity, date, individual
- Current quantity held
- Written explanation of any discrepancy
- Name of authorized personnel(s) who performed the transaction.

All experimental animals infected with select agents used for research are treated as select agents and accurately accounted for. The inventory includes:

- Species
- Number of animals
- Location
- Date placed in housing
- Agent(s) used to infect the animal(s)
- Date animal was sacrificed or died
- Final disposition

6.2 Transfer Records

Transaction records of transfers and receipts of select agents are kept secured with the oversight of the RO. The records are kept for five years from the time of the transactions.

6.3 Personnel Security Risk Assessment Records

Employee Security Risk Assessment (SRA) records are kept secured with the oversight of the RO. SRAs are valid for three years and must be renewed 30 to 60 days prior to their expiration.

6.4 Security Access Records

Public Safety maintains security access records for the BSL-4 facility. These include video surveillance, biometric iris scanner records, proximity card records, and visitor and guest records. These records are kept secured, and the records for access to the BSL-4 laboratories are reviewed monthly by the RO/ARO.

6.5 Training Records

Employees approved to work in the BSL-4 facility must successfully complete the required training programs before starting work as well as the annual refresher training required thereafter. The ADRS-NEIDL manages, coordinates, and conducts training for personnel. Personnel are automatically reminded to complete their refresher training before the required date. The records are kept secured with the oversight of the RO.

6.6 Occupational Health Records

The Research Occupational Health Program (ROHP) manages and implements the Occupational Health Program and medical surveillance of employees working in the BSL-4 facility. Employee medical records are maintained and updated by the ROHP, which alerts personnel for scheduled medical surveillance follow-up and maintenance, as required by the program

6.7 Facility Maintenance Records

Facility Core personnel manage and update maintenance records for the building automation system (BAS), recertification, routine testing, replacements, and repairs.

7.0 INSPECTIONS

The ADRS-NEIDL performs inspections and checks of the facility, containment systems, equipment, laboratory practices, and inventory control. These inspections are both scheduled and unannounced. Unannounced random checks are done to verify that personnel are following required practices and procedures in the laboratories and that the inventories are being accurately maintained. The ADRS-NEIDL also periodically reviews the working stock inventory records. Additional information is available on inspections in Section 10 Laboratory Inspection Plan.

8.0 INCIDENTS AND EMERGENCIES

The NEIDL Comprehensive Emergency Management Plan (CEMP) is a NEIDL-specific component of the Boston University Emergency Response Plan and is consistent with the University-wide plan in providing an overall organizational framework and processes for responding to emergencies. The plan operates under the Incident Command System (ICS) in response to emergencies that involve select

agents. The plan identifies and defines roles and responsibilities, the command structure, and emergency events, and implements strategies to mitigate emergencies. The RO or ARO acts as the initial Incident Commander (IC) and, using the CEMP, works with laboratory personnel and EHS Emergency Response Planning personnel, to evaluate the hazards and risks, and develops and implements plans for mitigation. The plan includes incident management and post-incident mitigation. Implementation of the ICS supersedes normal standard operational practices. All personnel working in BSL-4 containment must adhere to Section 8: Comprehensive Emergency Management Plan and follow specific Emergency Response Plans based on the type of emergency.

8.1 Unauthorized Persons

All employees must wear their ID tags when in the NEIDL. Public Safety Officers stop and question anyone not wearing his or her ID and persons suspected of not having authorization to enter the NEIDL. Employees who encounter persons who they believe are not authorized to be where they are encountered must report the infraction immediately to Public Safety at 4-4444. Public Safety will notify and report the incident to the RO at 8-8838.

8.2 Theft or Loss of Select Agent(s)

Any discrepancy in the inventory and theft or loss of select agent(s) must be reported immediately to Public Safety at 4-4444 and the RO at 8-8838. Public Safety will report the matter to the FBI. The RO will report it to CDC/APHIS immediately after the incident is verified. The RO will also notify the BPHC. The BPHC acts as the lead agency for the City of Boston and will coordinate communications with other city agencies, including the Boston Fire Department (BFD), Boston Police Department (BPD), and Emergency Medical Services (EMS), as necessary.

8.3 Failure to Receive a Select Agent Shipment

In the event that a shipment fails to arrive at the scheduled time, the RO will: 1) immediately notify the sender and 2) immediately report it to the CDC/APHIS using the appropriate form for documentation. The procedure for Reporting of Theft or Loss of Selects Agents will be followed as required by CDC/APHIS and the BU Emergency Response Plan.

8.4 Security Breach

All security breaches must be immediately reported to Public Safety at 4-4444 and the RO at 8-8838. Public Safety responds to all BSL-4 breaches within 15 minutes of the breach being discovered and reported as mandated by Tier 1 Select Agent requirements. The facility will be secured once the breach is discovered. Work with select agents will be stopped until Public Safety and the RO deems that the security breach has been averted or resolved. The security breach will be reported to the CDC and BPHC by the RO. The RO will work with Public Safety and conduct a post-incident evaluation, and recommend and implement corrective actions.

8.5 Inventory Discrepancy

The ADRS-NEIDL conducts an inventory of select agents held in long-term storage on a quarterly basis. Full inventories are also conducted after the physical relocation of select agent inventory, departure or arrival of a PI with select agent inventory collection, or in the event of a theft or loss of a select agent. All samples, including any animals that are intentionally or accidentally exposed to or infected with a select agent are accounted for against the previous inventory. Upon successful review of the inventory, the RO/ARO signs and dates the current inventory list for the records. In the event of a discrepancy, a full recount of the entire inventory will be conducted, and once the discrepancy is verified, it will be immediately reported to the CDC/APHIS, BPHC, and the FBI.

8.6 Fire, Smoke, Explosion, and Required Evacuation

Evacuation may be necessary in the event that a fire, smoke, or explosion occurs in a BSL-4 laboratory. When the incident requires an evacuation, all personnel follow the evacuation procedure.

8.7 Bomb Threat and Suspicious Package

Shipments delivered into the BSL-4 facility are initially screened before being delivered. Persons who receive a suspicious package or a bomb threat must report it immediately. In the event of a bomb threat or suspicious package, all personnel will follow the *Bomb Threat, Suspicious Device, Package, or Letter* Emergency Response Plan.

8.8 Power Outage

The BSL-4 facility is designed with N + 1 emergency back-up power generators to ensure continuous operation of life support systems, alarms, laboratory and animal containment exhaust ventilation, lighting and electric power to critical equipment. In the event of a power outage, all personnel will follow the *Loss of Electricity* Emergency Response Plan.

8.9 Chemical Spill

The NEIDL keeps only minimal types and volumes of chemicals, based on need for research and operations. In the event of a chemical spill in the BSL-4 facility, all personnel will follow the *Chemical Spill* Emergency Response Plan.

8.10 Biological Material Spill

Infectious materials in a BSL-4 laboratory are handled by researchers in a Biological Safety Cabinet (BSC). Samples are placed in non-breakable closed secondary containers when being transported to a different room. In the event of a biological material spill in the BSL-4 facility,

personnel will alert other laboratory members and follow the *Spill Procedures Involving Biohazardous Materials in BSL-4 Laboratories.*

8.11 Release of a Select Agent

Release of a select agent includes an accidental release of viable agent outside of containment; damage to the containment affecting the integrity of the biocontainment barrier (i.e., an earthquake or building collapse); aerosol generation coincident with High Efficiency Particulate Air (HEPA) filter exhaust system failure; and confirmed occupational exposure. Release of agents must be reported to the RO and Public Safety immediately. Release of an agent requires immediate notification of CDC/APHIS and BPHC. All personnel will follow the *Select Agent Security Breach* plan.

8.12 Medical Emergency and Exposure

All personnel working in a BSL-4 laboratory are certified to provide first aid, CPR, and AED assistance. Personnel who witness or are involved in a medical emergency in the BSL-4 facility must secure assistance from other laboratory staff and immediately implement the *Medical Incident* plan.

8.13 Severe Weather or Natural Disasters

BU may decide to close the Medical Campus in the event of a severe weather event or a natural disaster. If the campus is closed, access to the NEIDL and the BSL-4 facility will be restricted to essential personnel (e.g., laboratory scientists, and animal care and support personnel as well as operations and security). BU will implement the *Severe Weather, Earthquake, Flood,* or *Hurricane Response* plan, as appropriate, in the event of a natural disaster.

8.14 Workplace Violence

Workplace violence must be immediately reported to Public Safety at 4-4444 and the RO through the Control Center at 4-6666. All personnel will follow the *Workplace Violence Plan.*

9.0 SELECT AGENT TRANSPORT AND SHIPMENT

All select agents to be shipped and transferred outside of the BSL-4 facility receive final approval from the RO. The preparation and packaging of the sample follows the *External Shipping and Receiving of Biological Materials at Boston University* and Section16: Transportation Plan for taking samples out of the BSL-4 laboratory for shipment or transfer.

For removal of viable select agents from BSL-4 laboratories for the purpose of shipping to another BSL-4 facility registered for the specific agent, the PI or laboratory designee completes and submits the transfer request form to the ADRS-NEIDL for review and submits it to the RO. The RO

completes CDC/APHIS Form 2 and works to secure the necessary transfer permit approvals from CDC/APHIS and notifies BPHC. Once the transfer request has been approved, the PI or designee places the non-breakable and sealed sample vial in containers approved for passage through the dunk tank. The sealed and packaged samples are submerged in a pass-through dunk tank containing appropriate chemical disinfectant (e.g. Microchem Plus).. The sample package is retrieved by the ADRS-NEIDL from the other side of the dunk tank inside the airlock and final packaging for shipment is performed according to the International Air Transport Authority (IATA) regulations. NEIDL uses commercial shippers that are permitted to transport hazardous materials. Shipping and transport of the agents will follow Section 16: Transportation Plan. Samples destined for irradiation treatment will be placed in a secured leak-proof container and transported to the irradiator by the ADRS-NEIDL and a Public Safety Officer. Transfer of an agent will follow *Intra-entity Transfer of Non-select Agents and Select Agents and Toxins* SOP for transport of samples from the BSL-4 laboratory to the irradiator.

The RO maintains records of all transfers, including chain-of-custody documents. All transfers are indicated in the inventory record. Only individuals registered with the CDC Select Agent Program may handle, ship, or receive packages containing select agents. Shipping and transport of the agents will follow Section 16: Transportation Plan.

CHAPTER 4

BSL-4 CONTAINMENT AND SUPPORT SYSTEMS

1.0 INTRODUCTION

The NEIDL was designed to provide maximum protection of laboratory personnel working inside the containment facility and other personnel who work in the NEIDL and on the Boston University campus, in the surrounding community, and the environment. Personnel who work in the BSL-4 laboratories are trained on the facility, equipment, personal protective equipment, and processes related to their work.

2.0 GENERAL LABORATORY DESCRIPTION

The BSL-4 laboratories are located on the second floor of the NEIDL. The floor above them is dedicated to mechanical equipment and systems supporting the BSL-4 laboratories. These include, but are not limited to, control air compressors, HEPA filters and housings, bio-seal dampers, normal and emergency breathing air systems, and air compressors serving the chemical shower. The floor below the BSL-4 laboratories contains other support equipment, a gamma cell irradiator, and a liquid decontamination system for heat sterilization of liquid wastes coming from the BSL-4 laboratories.

The BSL-4 facility has been commissioned and tested to ensure that the facility and containment systems meet and operate according to the specified design standards prior to containment operations. The BSL-4 laboratories are recertified annually.

Safety systems inherent in the design of the facility include:

- Single-pass, non-recirculating directional air flow
- Redundant water supply lines
- Redundant power feeds
- Redundant air handling equipment
- Double HEPA filters on exhaust air
- HEPA filters on supply air
- Emergency generators capable of supporting the entire electrical load of the facility
- Multiple sterilization tanks for the decontamination of all liquid BSL-4 wastes
- Autoclaves for the decontamination of solid BSL-4 wastes
- Class II and III Biological Safety Cabinets
- Warning strobe lights and LCD monitor screens for reporting alarms

- Strict access control
- Positive pressure suits
- Airlock chambers
- Down-draft tables
- Building automation system and monitoring
- Automatic fire suppression
- Double-walled, stainless steel sewer waste lines
- Chemical decontamination showers
- Hands-free sinks

There are two types of BSL-4 laboratories in the NEIDL.

2.1 BSL-4 Cabinet Laboratory

The BSL-4 Cabinet Laboratory contains a dedicated Class III Biological Safety Cabinet (BSC). This BSC is fully contained and is used for working with Risk Group 4 infectious material.

Class III Biosafety Cabinet

The BSL-4 Cabinet Laboratory design includes:

- Outer change room
- Personal body shower
- Inner change room
- Class III BSC room

- A hands-free laboratory sink connected to the liquid effluent decontamination system (EDS)

The Class III BSC is equipped with:

- An air supply HEPA filter
- Two exhaust HEPA filters
- A supplementary blower (located before the two exhaust HEPA filters that serves to draw air through the supply filter into the cabinet)
- Decontamination ports
- Docking station pass-through to a HEPA-filtered, rapid transport cart in the adjoining suit laboratory
- Glove ports with Hypalon gloves for manipulations inside the BSC

After passage through two HEPA filters, at the level of the cabinet, the BSC exhaust exits the room via a hard-ducted, HVAC exhaust duct. Room exhaust air enters a bypass in the same duct distal to the two BSC exhaust HEPA filters, whereupon it passes through a HVAC exhaust housing containing two more HEPA filters in the mechanical space. Room air supply passes through a single HVAC HEPA filter.

When operating, the BSC is always under negative pressure. Air is passively supplied to the cabinet as it is drawn through the cabinet supply filter (rather than being blown into the BSC). The duct pressure and cabinet pressure are monitored with an alarm through the building automation system (BAS). If the room exhaust fails, the supplementary blower is designed to shut down and the cabinet becomes neutral.

2.2 BSL-4 Suit Laboratory

In the BSL-4 Suit Laboratory, the Risk Group 4 Agents are manipulated in Class II Biological Safety Cabinets and the worker wears a fully encapsulating, positive pressure protective suit to prevent accidental exposure to those pathogens on which he or she is working.

BSL-4 Suit Laboratory

The BSL-4 Suit Laboratory spaces are:

- Outer change rooms
- Personal body showers
- Inner change rooms
- Restrooms
- Suit rooms
- Chemical showers
- BSL-4 laboratories
- ABSL-4 animal vivaria
- Animal procedure rooms
- Animal necropsy rooms
- Imaging rooms
- Insectaria
- Support storage rooms
- Fumigation airlocks
- Pass-through disinfectant dunk tanks
- Pass-through laboratory autoclaves
- Pass-through bulk autoclaves

3.0 DIRECTIONAL AIR FLOW SYSTEM

Directional airflow based on room air pressure relationships is a critical safety feature of the BSL-4 facility. In the BSL-4 Suit Laboratory, the air pressure becomes increasingly negative with the progression from the outer change room, to the personal body shower, to the inner change room, to the suit room, to the chemical shower, and finally into the BSL-4 laboratory.

In the BSL-4 Cabinet Laboratory spaces, the room air pressure becomes progressively more negative from the outer change room, to the personal body shower, to the inner change room, and finally in the Cabinet Laboratory itself.

This controlled directional airflow ensures that the negative air pressure within the BSL-4 laboratory is greater than in the support and surrounding areas, preventing the escape of potential aerosols from the BSL-4 laboratory. The directional airflow gradient is maintained by dedicated exhaust and supply air fans and controls that are HEPA filtered. Any failure of these mechanical systems to maintain the gradients will result in a system-programmed shutdown and closure of the bubble-tight dampers on the supply and exhaust air systems, and activation of the alarms.

4.0 BREATHING AIR SYSTEM

An important life safety feature of the BSL-4 Suit Laboratory is the breathing air system. The primary breathing air system has compressors that supplies grade D breathing air to the suits via numerous flexible air hoses that are strategically located in the work areas and paths of travel in these work areas. During normal operations, breathing air is provided by mechanical compressors that are lead and lag. The air goes through a quality control tower (one per compressor) that controls moisture and monitors for carbon monoxide (CO) and is then stored in high-pressure storage receiving tanks. Each of the receiving tanks is fitted with static pressure gauges to indicate the availability of breathing air at all times. The air from the receiving tanks is reduced in pressure before feeding the lines that supply the suits. The final air pressure fed into the suits is in the 35-45 psi range. The system is supported by a back-up breathing air system, consisting of three high-pressure storage cylinders. These cylinders are kept fully charged by means of a separate compressor.

BSL-4 breathing air hose drops

- The static pressure of the primary and backup breathing air systems are checked and recorded daily by EHS or by designated, trained alternates as part of the daily systems check. A copy of the checklist may be found on Appendix C.
- The system is monitored continuously by the Building Automation System (BAS). In the event of a breathing air system failure, the BAS is alerted and the visual alarm mounted on the walls in all the laboratories are triggered. Personnel are trained and instructed to evacuate the laboratory according to the *Breathing Air Failure Response Plan.*
- The manifold pressure (pressure going to the suits) is regulated at 35–45 psi for the IL Dover suits.
- In the event of a power loss, emergency generator activation is instantaneous. An Uninterrupted Power Supply (UPS) keeps the compressors running in the unlikely event that the emergency generators fail to activate.

5.0 CHEMICAL SHOWER

The BSL-4 Suit Laboratory has six chemical showers that are used by laboratory personnel for suit decontamination prior to exiting the laboratory. The chemical shower uses high-pressure spray nozzles to completely cover the suits with 5% Microchem Plus disinfectant, which decontaminates the suits. This is then followed by a water rinse.

Chemical shower and spray nozzles

- The shower sequence is a total of 7 minutes: 3 minutes Microchem Plus and 4 minutes water rinse.
- Each time the air pressure resistant (APR) door to BSL-4 containment is accessed, the shower sequence is automatically activated upon closure of that door.
- The chemical from the showers is supplied through gravity feed from two storage tanks filled with 5% Microchem Plus by the automated mixing tank system.
- The conductance of the chemical (which has a linear relation to the concentration) is checked during the daily checks by EHS. A copy of the daily checklist is available in Appendix C.

Chemical deluge shower back-up inside chemical shower

- In the event of a chemical shower failure, the chemical deluge shower located in each of the chemical showers must be manually activated for decontamination of suits prior to exit.

6.0 COMMUNICATION SYSTEMS

Communication between personnel inside BSL-4 areas and outside BSL-4 areas is essential to the performance of their work and, most importantly, to safety. In general, communication in BSL-4 areas is accomplished in several ways.

6.1 Personal Communication Device (Vocera™)

Vocera™ is a mobile personal communication device that allows personnel in BSL-4 laboratories to communicate with coworkers in the same the room or in another BSL-4 area, to individuals or cores within the NEIDL but outside the BSL-4 area, or to the Control Center. All personnel are trained to use, and are encouraged to wear, the personal communication device before going into the containment area. The device is worn underneath the suit. Personnel are trained, and follow procedures, on standard use of the device as well as any restrictions on use when a person is conducting hazardous procedures to avoid distraction (for safety reasons).

Vocera™ personal communication device

6.2 Telecommunication Device

The BSL-4 areas are equipped with telephones with volume-controlled, audible ringers, and full dial-out capability. These telephones are primarily used as backup to communicate with and report emergencies to the Control Center.

6.3 In/Out Status Board

All personnel in the BSL-4 laboratories are required and trained to use the In/Out Status Board. All personnel who are authorized to access BSL-4 areas must log in under their name and review the Daily Systems Checklist report from EHS that is posted on the board before entering the containment laboratory. All personnel are required to log their entry in the electronic BSL-4 laboratory schedule. Once in the suit storage room, all personnel enter their suit maintenance observations into the electronic suit maintenance log.

7.0 GAMMA IRRADIATOR

The gamma irradiator is used primarily for inactivation of pathogens so that they may be handled at a lower containment level or shipped to collaborating laboratories. Strict controls are in place to request, authorize, and remove infectious materials from BSL-4 areas. The material will be transported by EHS personnel to the irradiator (on the first floor), under a Public Safety Officer escort, maintaining a clear and documented chain of custody at all times (refer to Transfer of Biohazardous Materials from the BSL-4 Laboratory to the Gamma Irradiator). Once the material has been placed in the gamma irradiator, personnel from EHS (Radiation Safety) inactivate the samples by operating the irradiator. The delivery of the required dose of radiation and the effectiveness of pathogen inactivation is initially validated and verified thereafter.

8.0 EFFLUENT DECONTAMINATION SYSTEM

Liquid effluent from BSL-4 areas is treated with Microchem Plus disinfectant before exiting the laboratory through a dedicated stainless steel drain system, which is piped to the Effluent Decontamination System (EDS). This closed system is designed to provide secondary decontamination of all liquid waste generated by the BSL-4 and ABSL-4 sinks, floor drains, and chemical showers as well as the condensate from the autoclave chambers.

The closed EDS consists of three cook tanks, each holding a capacity of 1,500 gallons of liquid effluent. While one tank is sterilizing its contents (cook mode), the second tank is filling (fill mode), and the third tank is in reserve (standby mode). The sterilization of each tank is a lengthy process, and the system has the capacity to sterilize only one tank at a time. In the event that the EDS cannot accommodate additional effluent, EHS and Facility personnel are alerted to stop or limit their generation of liquid effluent via the visual alarm system.

BSL-4 Effluent Decontamination System

9.0 TISSUE DIGESTER

A 600-pound-capacity steam jacketed tissue digestion unit provides a means of carcass disposal for the BSL-4 laboratories. The tissue digester uses potassium hydroxide (KOH) as the active chemical in the alkaline hydrolysis process. Effluent resulting from the digestion process is cooled, then pH adjusted by CO2 injection prior to release to the sanitary sewer.

10.0 FIRE SUPPRESSION SYSTEMS

There are two fire suppression systems servicing the BSL-4 and ABSL-4 laboratories: a manual pre-action system and a high-pressure mist system. Detection of fire within the maximum containment spaces occurs through a combination of smoke detection (in the central corridor and duct work) and dedicated heat detectors and thermal fuses on the sprinkler heads. The systems report back to the fire command station and to two remote stations.

10.1 Mist System

The mist system is the primary fire suppression system. It automatically activates when the thermal fuse ruptures at a particular head, which requires heat in excess of 155°F. The system is a high-pressure system that aerosolizes water and reduces the availability of oxygen, thus suffocating the fire. As this works on the basis of water aerosols, it requires less water than traditional sprinkler systems, thereby reducing damage and water and waste to be cleaned up.

10.2 Pre-Action Sprinkler System

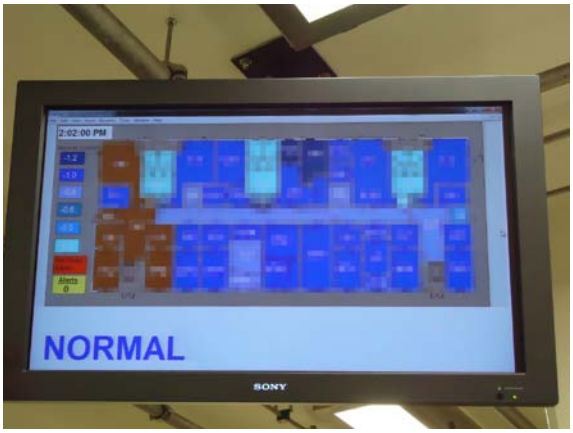
The manual pre-action system is a backup to the mist system. Although the system does have thermal fuses on each of the sprinkler heads, water will not flow from the system even if the fuses melt (at 155°F). Rather, being a manual backup to the mist system, this system is activated by Fire Department personnel in the event that Boston Fire Department determines the mist system is not effectively suppressing a fire.

BSL-4 fire suppression system:
Mist system on left and pre-action sprinkler on right

11.0 EMERGENCY NOTIFICATION, ALERTS, ALARMS, AND RESPONSE BUTTON SYSTEMS

11.1 LCD Notification Panels

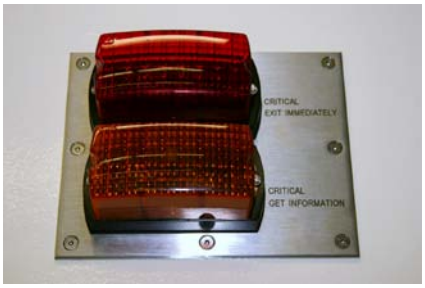
Each BSL-4 laboratory is equipped with numerous LCD notification panels. These LCD panels are designed so that lab staff can receive information when alarms are activated. The panels indicate the nature of the problem, the affected area, and any action required by staff. All staff are trained and instructed to check the LCD panels for information upon activation of the visual alarm strobe. The LCD panels also provide information on room pressures in the laboratory and surrounding area.



LCD Notification Panel

11.2 Visual Strobe Alarm System

Each BSL-4 laboratory is equipped with a visual alarm system. The system alerts personnel of emergencies inside the BSL-4 laboratory or failures of containment systems supporting it. The visual strobe alarm consists of wall-mounted YELLOW and RED strobe lights.



BSL-4 visual alarm strobe

11.2.1 Yellow Strobe Light

The yellow strobe light alarm illuminates when a general alert occurs that does not require an immediate evacuation. All personnel are instructed and trained to check the LCD panels for information. Some examples include:

- APR Door Open
- -80° Freezer Alarm
- Medical Assistance Required

11.2.2 Red Strobe Light

The red strobe light alarm illuminates when situations that pose immediate threat to life and health of the workers occur. Some examples include:

- Breathing Air System Alarm
- Fire Alarm
- Air Pressure Gradient Alarm

The alarm signals are activated in pre-programmed conditions. Depending on the nature of the alarm, the alarm signal may trigger for the entire BSL-4 area or be specific to a room.

11.3 Laboratory Alert Button

The laboratory alert button is used to provide initial notification to the Control Center of a problem requiring immediate response. Laboratory personnel use the laboratory alert button to report a fire, medical emergency, or any situation that requires immediate help from outside of the room to respond to the issue.

This alert is particularly useful in situations where a worker must provide immediate assistance to a coworker or respond without delay to a hazardous incident. The Control Center will consult the closed circuit TV (CCTV) feed, evaluate the situation, assist in coordinating the response, and place appropriate information on the overhead monitors.

Laboratory alert button

11.4 Emergency Door Overrides

Emergency override buttons are located on select doors in BSL-4 areas. The override buttons are protected with a cover that must be raised in order to activate the override in the event of door release failure. For APR doors, upon pressing and holding the release button, the door gasket is deflated and the magnetic lock is released, allowing personnel to pass through the door. In the case of compression-gasketed doors, the magnetic lock is released upon engaging the emergency release button, allowing the handle to be operated to open the door. Operation of the override button generates an alarm at the building automation system and a response.

Emergency override button

11.5 Fire Alarm System

Fire alarms are mounted on the walls in BSL-4 laboratories. These fire alarms “strobe” if the standpipe, manual red pull stations, or mist and pre-action sprinkler systems are activated. The fire alarm strobes alert personnel to secure infectious materials, prepare to leave the lab following normal exit procedures, and check the LCD notification panels for further instructions.

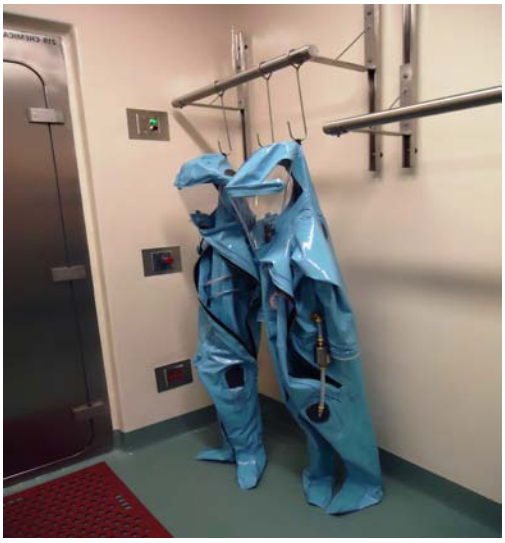
Fire alarm horn and strobe light

12.0 PERSONAL PROTECTIVE EQUIPMENT

Personal protective equipment is used by personnel when entering a BSL-4 laboratory for protection against exposure to the pathogenic organisms handled and stored there.

12.1 Fully Encapsulated Positive Pressure Suit

The fully encapsulated positive pressure suit is worn by all personnel who access and work in the BSL-4 and ABSL-4 Suit Laboratory. The suit acts as a barrier to prevent direct exposure to the Risk Group 4 pathogens that are used in the laboratory.



ILC Dover Chemturion™ Suit

The BSL-4 Suit Laboratory currently uses the Chemturion™, ILC Dover fully encapsulated positive pressure suits, but may use other suits based on safety and usability. The body, head, arms, and legs of the suit are constructed of chlorinated polyethylene. This material has an excellent chemical resistance profile. Of 504 chemicals tested against the suit material, only 5% demonstrate a negative compatibility rating. EHS reviews all chemicals for incompatibilities prior to their use in the BSL-4 Suit Laboratory.

The suit visor is made of optical grade, 40 mil. thick, press-polished vinyl (polyvinyl chloride). Care is taken not to abrade or scratch the visor, especially when donning, doffing, and storing the suit. Although the suit material is not easily punctured, it is not puncture resistant, and users are made aware of this during training. All of the seams in the suit are welded and heat sealed. The user is responsible for checking the suit prior to each wearing, and this includes examination of all seams.

Positive air pressure is maintained for the internal ventilation system by air supplied to the suit through the air-inlet manifold assembly with HEPA filtration. Attached to this is an external hose. Airflow provides clean air for breathing and maintains a positive pressure within the suit to prevent intake of potentially contaminated air from the laboratory.

12.1.1 Breathing Air Supply

Air is supplied to the suit by means of air drops (umbilical hoses that hang from overhead breathing air pipes). These are equipped with fittings (female) that connect with fittings (male) attached to a tube emanating from the suit. Once these connections are made, a valve operates to allow air to flow into the suit, thereby maintaining it at a positive pressure relative to the laboratory environment.

Breathing air hose female fitting

Breathing air hose male fitting

12.1.2 Breathing Air Suit Distribution

Suit HEPA filter

Air distribution hose

Hood spray

Umbilical-fed air passes through the suit HEPA filter, which is connected to the suit via a NIOSH-approved pass through. Air is distributed to arms and legs for cooling, and to the hood spray bar (~60%) for CO2 wash, breathing, cooling, and defogging. Air flows from 5 to 9 cubic feet per minute during use.

12.1.3 Breathing Air Exhaust

Air is exhausted from the suit through four exhaust vents. The vents incorporate one-way exhaust valves that are designed to release air from the suit when the wearer bends over, bends at the knees, or when pressure in the suit exceeds threshold.



(All above) Multiple breathing air exhaust vents

12.1.4 Suit Closure

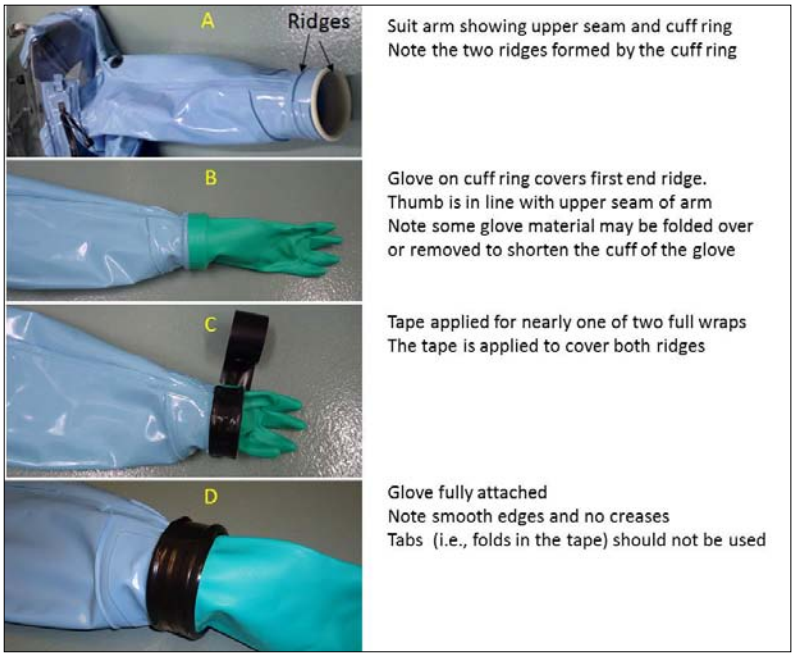
The suit is designed with a pressure sealing closure designed to close over the zipper teeth, providing an air-tight seal. It is located on the front of the suit.

Suit zipper open position

Suit zipper close position

12.2 Suit Glove

The sleeves of the suit terminate in a beaded wrist ring. External gloves (suit gloves) are attached to the suit for barrier and protection of the hands. The gloves are attached to the suit by stretching the cuffs over the wrist ring and applying water tight tape approximately two times around to secure to the suit. These gloves are inspected for rips, tears, and general condition (e.g., material characteristics, elasticity, etc.) upon each entry and must be replaced at least once every seven entries or 14 days from last replacement, whichever is sooner.



Attaching suit gloves

12.3 Overboots

Suit feet are integral to the suit as they are heat welded to the legs. The suit feet are smooth and have no grip. Over time, these feet will abrade on the rough epoxy floor and become compromised. Overboots are worn in the BSL-4 Suit Laboratory to protect both the user's feet and the suit. Overboots are donned after entry through the chemical shower. The overboots are removed prior to exit to the chemical shower and are stored on stainless steel shelves within containment. Like suits, NEIDL BSL-4 may use other boots based on safety and usability.

Suit feet

Rubber overboots

CHAPTER 5

GENERAL LABORATORY PRACTICES

1.0 TWO-PERSON GUIDELINES

NEIDL maximum containment BSL-4 laboratories are designed to provide a safe and secure facility in which to conduct research studies on Risk Group 4 Agents. These agents cause severe infectious diseases in humans and are a concern for potential use as bioterrorism threats. To comply with applicable regulations, including the requirements of the Select Agent Final Rule, all personnel who work in a BSL-4 laboratory and have access to select agents must be cleared and receive Security Risk Assessment (SRA) by the CDC/APHIS.

Because of the potential for an occurrence of a medical emergency while in the maximum containment laboratory, all personnel cleared by the Select Agent Program Security Risk Assessment who are allowed to work in a BSL-4 laboratory must follow the two-person guideline when entering the BSL-4 area. Additional information on the two-person guideline is available in the *Personnel Suitability and Reliability Policy.*

2.0 GENERAL RULES FOR ENTRY AND ACCESS

Access to the maximum containment BSL-4 facility is restricted and controlled as described in Section 12: Security Plan. Access is granted only to individuals who have a work-related need to be in the laboratory. The access requirement process includes security and background checks described in the *Personnel Suitability and Reliability Policy*, medical clearance, and trainings as described in this manual. Personnel are granted access to specific areas in the NEIDL based on their work responsibilities. It is a violation to allow unauthorized personnel to enter the BSL-4 facility.

2.1 Hours of Operation

The BSL-4 facility is maintained under operational status 24 hours a day. Normal hours (i.e., hours for which optimal coverage is provided from support staff) are Monday through Friday, 6:00 a.m. to 8:00 p.m. The facility is monitored 24/7 (24 hours a day, 7 days a week)-including holidays-by NEIDL personnel.

2.2 Access During Off-Hours

As a Tier I requirement, access to the BSL-4 facility during off-hours, Saturdays, Sundays, and on holidays must be first approved by the RO/ARO. Requests must be sent in writing and approved by the RO/ARO. Request for recurring access, such as checks necessitated for animal care and welfare by the BU Animal Science Center (ASC) and science staffs as well as other research activities

during these times must be submitted in writing and approved by the RO/ARO. All personnel must follow the two-person guideline when entering the BSL-4 laboratory during off-hours.

2.3 Health-Related Processes

All personnel using full-body encapsulated suits have an annual medical/physical check to reduce the likelihood of an accident being caused by ill health. The Research Occupational Health Program (ROHP) monitors, maintains, and conducts medical follow-up checks annually. Any personnel without valid medical clearance from ROHP will be denied access to the BSL-4 laboratories.

2.3.1 First Aid and CPR

All personnel working in full-body encapsulated suits are trained to Level 1 First Aid (basic first aid) and CPR as a minimum requirement. These personnel are also trained to follow emergency response procedures in the event that a laboratory member collapses and become unconscious (refer to *Medical Incident* ERP).

2.3.2 Feeling Unwell

Any personnel feeling unwell on a particular day must not enter and work in a BSL-4 laboratory. Unwell personnel must report to, and be seen by ROHP and can “opt out” as described in the Personnel Suitability and Reliability Policy. The Core Director or the individual’s Supervisor must be informed of the matter.

2.3.3 Absence Reporting

The Supervisor must report an employee’s unplanned absence of more than two days to ROHP.

2.3.4 Return to Work

Any personnel returning to work in the BSL-4 from an extended period of absence such as maternity leave, medical surgery, and other similar circumstances will need a medical clearance from ROHP before returning to work in a BSL-4 area. Returning personnel must complete refresher BSL-4 training and sufficient hours of accompanied work with the Core Director or Supervisor in a BSL-4 laboratory to satisfy competence requirements for those returning personnel.

2.3.5 Agent ID Card

Each person working in the BSL-4 facility is issued (and must carry with them at all times), special wallet-sized cards that indicate their affiliation and work in the BU laboratory. During training, BSL-4 personnel are instructed to present the card to the attending physician in the event that the person seeks medical care for an exposure, or symptoms consistent with an infection with a BSL-4 agent or other high-risk pathogen. The card provides the initial

caregiver with information about the specific agents used by the individual, as well as contact phone information for the BU ROHP to obtain additional guidance (refer to Appendix F, Agent ID Card).

2.4 Daily External Systems Check

Each working day, prior to entry of laboratory personnel, an EHS staff member or an authorized designee performs an external check of BSL-4 life systems, critical containment systems, and equipment to ensure that they are operating normally. The system and equipment checks include ensuring the proper function of the air handling system, liquid waste system, breathing air system, autoclaves, tissue digester, chemical shower system, and the concentration (conductance) of the dunk tank disinfectant. The daily check report is posted on the In/Out board. All personnel are required to review the report prior to their entry at the beginning of the day.

2.5 Visitor Access (Non-SRA Approved Personnel)

Visitors who require access to the BSL-4 laboratories (e.g., regulatory inspectors) must secure approval for entry through their BU/NEIDL sponsor. The sponsor will submit the request along with the necessary information about the visitor to the Public Safety Suitability Officer. Upon approval of access, each visitor undergoes mandatory orientation and safety training. Once completed, the visitor is allowed entry to the specific space(s) requested and continuously escorted within sight by an SRA-approved individual. All visitor entries and exits are monitored and documented.

Warning placards are posted at each entry point from the buffer corridor to the BSL-4 containment spaces.

3.0 NORMAL ENTRY

There are three possible points of entry for normal entry into the BSL-4. The following summarizes entry through any one of those three entry points.

3.1 Locker room

There is access control at the entrance to each locker room. Access to these areas is provided only to authorized personnel. Access control is also in effect at the exit from the locker room to permit entry back to the outer (non-containment) corridor.

3.2 Chemical Showers

Access to the BSL-4 space is through APR doors located at the entrance to the chemical showers in the suit storage room. This access is strictly controlled by biometric devices. Personnel who have been SRA cleared and approved to access areas protected by biometric devices are enrolled into the

system. Upon biometric verification of the identity of the individual, and upon authentication, access to the space is permitted.

3.3 Request to Enter Button (APR Door)

Upon biometric authentication, the personnel will:

- Push the white illuminated button marked “press to open.”
- The gasket in the air pressure resistant door deflates and the amber light illuminates.
- Once the gasket is fully deflated, the green light illuminates and personnel may pull the door and open it.

APR door buttons

The APR doors that penetrate the outer wall of the BSL-4 facility and other doors within the laboratories are equipped with magnetic locks and sealed with inflatable silicone gaskets to be airtight when closed and pneumatically operated. Each door is equipped with a panel of three round lights located on the doorframe-red, amber, green (see pictures above). When the door is sealed (normal condition) the red light is illuminated. When the opening mechanism is activated by pressing the white button at the base of the panel, the light turns to amber as the gasket is being deflated, and then turns to green when the magnetic lock is disengaged and the door can be opened. When the door is shut, the red light will illuminate once the magnetic lock is engaged. Many of the APR doors are magnetically interlocked such that one cannot be opened without another being closed.

4.0 PERSONNEL ENTRY

Personnel working with BSL-4 agents are required to be trained, approved, and experienced in work with BSL-4 agents. The Core Director or the staff's Supervisor ensures that all laboratory personnel under their supervision always maintain their trainings and competencies required to perform their tasks safely.

4.1 Suit Laboratory

The BSL-4 Suit Laboratory has three possible entry points, and each is equipped with access control devices. Further, each entry point has separate gender access to the lockers and inner change areas where all street clothes are removed and personnel change into scrubs. The personnel then go through the personal shower, to the inner change area, and enter the suit room. They put on the positive pressure protective suits before entering into containment, leaving all possessions (including their proximity card) in lockers in the outer change room. Each entry/exit point is installed with two chemical disinfectant showers for decontamination before exiting the BSL-4 facility. Personnel follow procedures for inspecting and donning the positive pressure suit and subsequent entry into the maximum containment through the chemical shower (refer to S*tandard Entry Procedure for the BSL-4 Laboratory*).

4.2 Cabinet Laboratory

There is one entry point to access the BSL-4 Cabinet Laboratory. Entrance to the outer change room from the buffer corridor requires verification of identity using a biometric device. Once in the outer change room, street clothing is removed. The individual dons scrubs and pushes the APR door button for entry into the body shower. Once in the body shower, the individual enters the inner change room where additional personal protective equipment (disposable gloves, dedicated Crocs shoes) is put on before entering the BSL-4 Cabinet Laboratory (refer to *Standard Entry Procedure for the BSL-4 Cabinet Laboratory*).

5.0 PERSONNEL EXIT

Personnel normally exiting from the containment laboratory must follow procedures.

5.1 Suit Laboratory

When exiting the BSL-4 Suit Laboratory, personnel must first ensure that all interior doors (to the BSL-4 laboratory and the central hallway) are closed. The personnel then enter the chemical shower and close the door. The chemical shower begins its cycle upon closure of the inner shower door. The shower occupant must ensure that all areas of the positive pressure suit receive adequate contact with the chemical disinfectant and water rinse (refer to *Standard Exit Procedure for the BSL-4 Suit Laboratory*).

5.2 Chemical Shower Failure

In the event of a chemical shower failure, a back-up deluge chemical shower is available and must be used. The deluge chemical shower contains 5% Microchem Plus. The shower is operated by manually pulling the overhead handle and allowing 60 seconds of chemical shower on the suit. The handle must be pushed back manually to shut off the shower.

5.3 Outer Chemical Shower Door Failure

In the event that the outer door to the chemical shower fails to open, it is possible to press and hold the red emergency door override button. This button may be pressed only if the suit has been decontaminated.

5.4 Cabinet Laboratory

Personnel preparing to exit the Cabinet Laboratory must remove their gloves and discard them in the biowaste container. Personnel go first to the inner change room and remove the scrubs and Crocs, and proceed to the personal body shower and exit to the outer change room (refer to *Standard Exit Procedure for the BSL-4 Cabinet Laboratory*).

6.0 MOVEMENT WITHIN THE CONTAINMENT FACILITY

6.1 Movement of Personnel

Personnel working in BSL-4 containment can only access specific areas that they have been cleared for and granted access to in order to accomplish their work. The Core Directors are responsible for identifying areas that their staff need to access and submit the request to Public Safety.

6.2 Movement of Infectious Materials in the Laboratory

In general, infectious materials are moved between laboratory suites in covered non-breakable secondary containers to minimize the potential for spills of biohazardous materials.

7.0 INTRODUCTION OF SUPPLIES, MATERIALS, AND ANIMALS

In general, materials should not be taken into the containment facility unless they need to remain inside and be used. If certain materials are intended to be removed from the containment space at a later date, EHS must first be informed prior to their entry so that appropriate decontamination procedures can be organized. Equipment, tools, materials, research animals, and animal care supplies will need to be moved into the BSL-4 maximum containment facility during operations (refer to *Entry of Equipment and Supplies into BSL-4 and ABSL-4 Space*).

There are procedures to employ, depending on the nature and type of the materials, in a Suit Laboratory and a Cabinet Laboratory.

7.1 Suit Laboratory

There are several approved ways to bring materials and supplies used for research work into the BSL-4 Suit Laboratory.

7.1.1 Entry through Fumigation Airlock

The BSL-4 Suit Laboratory has two fumigation airlocks. Each airlock has two APR doors that are on automatic interlocked systems. The outside door is a compression-gasketed door and opens to the buffer corridor. The airlock is always decontaminated by gas/vapor decontamination and validated whenever the inner containment door to the BSL-4 Suit Laboratory is opened, keeping it always clean and ready for use. Only authorized personnel have access to the clean-side door. The fumigation airlock is used as a pass-box for the transfer of large pieces of equipment and bulk quantities of supplies into the maximum containment space. EHS oversees and supervises this process because airlocks serve as emergency egress. Thus, only one of the two airlocks is used for this process at one time.

7.1.2 Entry through Pass-Through Autoclave

Autoclaves may be used as a pass-box to transfer supplies and equipment into the maximum containment space. After completion of a normal cycle, the autoclave is allowed to cool and supplies and equipment are loaded into the autoclave from the “clean side” for transfer into the space. Entry via this method is coordinated with appropriate Research Cores, PIs, and animal care personnel. The autoclave doors do not open outside of the containment space unless the autoclave has successfully completed a cycle.

7.1.3 Entry through Chemical Shower

The chemical shower is used for limited entry of small items that can be hand-carried by personnel in a fully encapsulating suit. Examples of these materials include small amounts of non-hazardous reagents and tools.

7.1.4 Entry through Chemical Dunk Tank

The dunk tanks may be used as a pass-box for the transfer of small pieces of equipment and limited quantities of supplies into the maximum containment space. EHS must supervise this process because the dunk tanks are located in the airlocks, which serve as emergency egress. Thus, only one of the two airlocks can be used for this process at one time, and only authorized personnel have routine access to that space.

7.1.5 Entry through an ABSL-4 Room from Buffer Corridor

Animals and equipment related to animal research (cages, racks, etc.) that EHS has validated and approved for transfer into an ABSL-4 room or suite are introduced directly into an

ABSL-4 room or suite from the outer buffer corridor, once the room or suite has undergone gas/vapor decontamination.

7.2 Cabinet Laboratory

Work in the Cabinet Laboratory is performed inside the Class III Biosafety Cabinet that is specially designed and constructed for aerobiology and animal research work. The Class III BSC is sealed and has no opening from the Cabinet Laboratory. Introduction of materials, supplies, and animals used for research studies are done through the pass-through portable HEPA filtered BSC that is docked to the Class III BSC through the Suit Laboratory.

8.0 REMOVAL OF MATERIALS, TOOLS, AND EQUIPMENT

All materials from the BSL-4 facility must be decontaminated before they are removed from the BSL-4 space, irrespective of their perceived intrinsic hazard potential (refer to *Exit of Equipment and Tools from BSL-4 Space*).

8.1 Suit Laboratory

The following methods are employed when removing materials, tools, and equipment from the BSL-4 space.

8.1.1 Removal through Fumigation Airlock

Only items unable to be autoclaved due to their size or physical properties can be removed through the fumigation airlock (e.g., large or bulky equipment in need of repair). It is important to decontaminate the item with chemical disinfectant initially before it is moved to the fumigation airlock for final gas/vapor decontamination. The surfaces and accessible interior components of the item are chemically decontaminated inside the BSL-4 maximum containment space prior to placement in the fumigation airlock. EHS coordinates or executes all removal activities. Personnel inside the BSL-4 Suit Laboratory will open the inner door and place the item in the fumigation airlock. EHS performs gas/vapor decontamination of the fumigation airlock and its contents, and verifies the efficacy of the decontamination activity prior to releasing the materials outside of the containment barrier.

8.1.2 Removal through Pass-Through Autoclave

Items that can be autoclaved safely, for either reuse or disposal, may be subjected to sterilization in the autoclave prior to removal from the BSL-4 space.

8.1.3 Removal through Chemical Shower

The chemical shower is used to bring out small, impervious items that can be decontaminated by the chemical disinfectant used in the shower. EHS must conduct a risk assessment to determine the actual and potential hazards associated with the specific materials to be removed. If the risk assessment identifies an inadequate level of control, the user cannot use this route of exit.

Waterproof items may be passed through the dunk tank containing disinfectant, and later retrieved from the clean side of the dunk tank in the fumigation airlock and surface dried prior to removal from the BSL-4 maximum containment facility.

8.2 Cabinet Laboratory

All equipment, tools, and supplies (including waste) are removed from the Class III biosafety cabinet via the docked rapid transfer cart in the BSL-4/ABSL-4 Suit Laboratory. Disposable PPE used in the actual cabinet side (e.g., inner gloves) are disinfected, double bagged, and brought into the BSL-4 Suit Laboratory for autoclaving.

9.0 REMOVAL OF BIOLOGICAL MATERIALS

Biological materials will eventually need to be removed from the BSL-4 laboratory and sent to a collaborating BSL-4 facility, another laboratory, or treated in the irradiator facility. Such materials include virus-containing fluids, diagnostic specimens, sera, tissue culture cells, and other samples (refer to the SOPs for *BSL-4 Dunk Tank Operation: BSL-4 Dunk Tank Operation: Removal of Viable Material; Transfer of Biohazardous Materials from the BSL-4 Laboratory to the Gamma Irradiator*; and *Removal of Non-Viable Material from BSL-4 Containment Space*).

9.1 Viable Biological Materials

An application form to request removal of viable biological materials from a BSL-4 laboratory must be submitted to EHS. The completed request is reviewed by EHS to determine the nature of the material, whether it is being shipped off-site (to another BSL-4 facility registered for the specific agent), or transferred to the gamma irradiator for treatment. EHS then submits the removal request to the RO for review and approval.

9.2 Live Microorganism

Removal of live microorganisms from a BSL-4 laboratory will follow BSL4 Dunk Tank Operation: Removal of Viable Material., and (where appropriate) Transfer of biohazardous materials from the BSL4 laboratory to the gamma irradiator. The PI or designated research staff is responsible for preparing the sample sealing it into approved containers, and passing it through the dunk tank (filled with 5% Microchem plus disinfectant). EHS retrieves the sample from the clean side of the dunk tank inside the fumigation airlock. The sample is then either for packaged for shipment following IATA standard; or placed inside a leak-proof, shatter-proof container and transported to

the irradiator facility for treatment. A Public Safety Officer provides security escort during transfer of the material to the irradiator.

When sending live microorganisms to a collaborating BSL-4 laboratory, the RO works with CDC/APHIS and the recipient BSL-4 laboratory to complete and submit CDC/APHIC Form 2 for approval. The RO also notifies BPHC prior to transfer of the material.

9.3 Non-Viable Biological Material

The IBC must approve all methods to be used to inactivate viable biological materials in the BSL-4 facility. Provided that the inactivation method is followed exactly as specified and is documented at the time of inactivation (e.g., in a live agent inactivation log), the material may be removed according to the SOP *Removal of Non-Viable Material from BSL-4 Containment Space*. This may be done either through the chemical disinfectant dunk tank (preferred) or via the chemical shower. This removal must be entered into the removal of non-viable material log.

Any shipment of inactivated material to another facility or investigator must be accompanied by a letter stating the exact treatment the samples have received for inactivation, and the letter must be signed by an authorized individual from Boston University. Where requested, or advised by the IBC, proof of non-viability may be required.

10.0 REMOVAL OF CHEMICALS FROM THE BSL-4 FACILITY

The use of chemicals in the BSL-4 facility is limited to those that are specifically needed in order to conduct research experiments or perform work. On occasion, leftover or residual amounts of these chemicals need to be removed from a BSL-4 laboratory (refer to the SOP *Chemical Handling and Disposal in BSL-4 Suites*). A request for removal of chemicals from the BSL-4 facility is submitted to EHS.

EHS reviews and examines the nature of the chemical and size of the container. EHS first thoroughly wipes down the container with a chemical disinfectant and then submerges it into the chemical dunk tank. EHS retrieves the container from the clean side of the dunk tank in the fumigation airlock, for disposal.

Larger chemical containers for removal are thoroughly wiped down and the contents decontaminated with chemical disinfectant by EHS and taken through the chemical shower for external decontamination. The container is then removed from the BSL-4 facility upon completion of the chemical shower process.

11.0 TRANSPORT OF INFECTIOUS MATERIALS WITHIN THE BSL-4

When samples of infectious materials are transported between different rooms or suites within the BSL-4 facility, all samples must be placed in a secondary non-breakable, leak-proof container. The primary sample container must be wiped down with chemical disinfectant in the BSC before being placed in the

secondary container for transport. The secondary container must be wiped down with chemical disinfectant after each use before being stored away.

12.0 STORAGE OF SAMPLE MATERIALS

Agents and samples are stored according to the requirements given in APHIS and CDC's *Guidance on the Inventory of Select Agents and Toxins*. Master and sub-master samples are stored separately from working stock samples in designated and secured storage freezers, which are accessed only by authorized personnel. Working stock samples are stored by the PI in their secured, designated storage within their laboratory.

Sample containers are properly labeled and are made of material that can withstand freezing and thawing. Inventories of master and sub-master samples are maintained and updated. The ADRS-NEIDL is responsible for conducting sample inventories to check and verify security control. The AD conducts inventory of select agents held in long-term storage on a quarterly basis. Full inventories are also conducted after the physical relocation of select agent inventory collection, the departure or arrival of a PI with select agent inventory collection, or in the event of a theft or loss of a select agent.

PIs keep track of their working stock samples all the way from generation through their use and final disposal. The ADRS-NEIDL conducts reviews of the laboratory's working stock sample records.

All inventory control review and audit reports are reviewed by the RO.

CHAPTER 6

EQUIPMENT SAFETY TECHNIQUES

1.0 BIOLOGICAL SAFETY CABINETS

The biological safety cabinet (BSC) provides the laboratory worker and the environment a high level of protection from exposure to potentially infectious aerosols from materials being manipulated in the BSL-4 laboratory (refer to the SOP *Use of the Class II Biological Safety Cabinet*). In addition, the BSC also protects the integrity of the material being used from environmental contamination.

There are three types of BSC that are used in the BSL-4 laboratories.

1.1 Class II, Type A2 BSC

Class II, Type A2 BSC is the standard equipment used to contain all work with infectious agents in a BSL-4 laboratory. The BSC is non-ducted and the filtered exhaust air is recirculated back into the laboratory space. Typical work that is performed in this BSC includes cell tissue culture and viral manipulations. Other procedures, including sonication of samples that potentially produce infectious aerosols, is also conducted in the BSC.

1.2 Class II, Type B1 BSC

Class II, Type B1 BSCs are located in the necropsy rooms of the BSL-4 facility. This BSC is hard-ducted to the room's exhaust ventilation system; air from the BSC passes through a HEPA filter before entering the duct. The room exhaust ventilation itself is equipped with two HEPA filters, in series. As approximately 60% of the air descending onto the work surface passes directly into the rear grille and out of the cabinet (through a HEPA filter and negative pressure plenum), it can be used to control fumes from hazardous chemicals located at the rear of the cabinet. Typical work that is performed in the Class II, Type B1 BSC includes gross sectioning of animal tissues and suspension and fixation of tissues in formalin solution.

Class II, Type B1 BSC

Guidelines for Class II BSCs:

- The BSCs are tested and recertified during the annual laboratory recertification.
- BSCs should be left on after use. If the BSC is discovered to be off, turn on the BSC and allow it to purge for 5 minutes before setup and use.
- Check the air pressure gauge before conducting any work to ensure that the BSC air flow requirement is operating normally.
- Clean and disinfect the work surface.
- As a general principle, always work from the clean area to the dirty area in the BSC.
- Do not block the intake grills (for appropriate Class II BSCs).
- Do not place too many items in the BSC as it may impede its performance.
- Avoid making any rapid motions when working in the BSC.
- If a spill occurs while working, stop the procedure and clean up the spill immediately.
- Report major spills inside the BSC (i.e., volumes greater than 50 ml or any spill that enters into one of the grills) to EHS.
- Wipe and disinfect any item with 5% Microchem Plus when it is to be removed from the BSC.
- When work is complete, all materials that are to be removed from the BSC must be wiped down with a 5% Microchem Plus disinfectant solution prior to removal and all

interior surfaces, including the sides and back and front panels of the BSC, are be wiped with a 5% Microchem Plus disinfectant.

- To prevent sticky residue from the Microchem Plus, the BSC must be sprayed and wiped with 70% ethanol to clean it off.
- After clean-up is completed, turn off the light and leave the BSC running.

1.3 Class III BSC

The Class III BSC is used to contain all work inside the BSL-4 Cabinet Laboratory. This BSC provides the highest level of protection to personnel and the environment, as well as the integrity of the materials used during experiments. There are three pairs of arm-length, heavy-duty Hypalon gloves that are attached in a gas-tight manner on each side of the BSC. The gloves are used by personnel to manipulate and conduct research work with infectious agents and research animals. Personnel inspect each of the gloves before they are used, and the gloves are routinely replaced when signs of wear are apparent, or biannually.

Class III BSC

Entrance of materials, equipment, and animals into the BSC is through the pass-through docking port connected to the other side of the Suit Laboratory. A transportable HEPA-filtered and battery-operated rapid transfer cart (RTC) is used to gather the materials for research work and is docked securely to the Class III BSC. The docking door is opened from within the Class III BSC and all the materials are transferred from the RTC into the Class III BSC. The docking door must be closed and secured before the Class III BSC can be used. All of the materials, animals, and wastes from the experiment are removed through the same pass-through into the RTC and transported into the Suit Laboratory.

EHS coordinates with the research personnel and performs a gas/vapor decontamination of the BSC after the study has concluded and verifies the efficacy of the decontamination using biological indicators prior to releasing the equipment back into service.

Guidelines for Class III BSC operation:

- BSCs should be left on after use. If the BSC is discovered to be off, turn on the BSC and allow the air to purge for 5 minutes.
- Transfer clean materials for use in studies into the Class III BSC (i.e., reagents, animals, instruments, equipment, infectious agents, and infectious wastes) through the docking connection between the Class III BSC and battery-operated transportable BSC.
- Inspect the BSC gloves for damage, holes, and wear and tear before placing any materials inside the BSC. Do not use damaged gloves; replace them immediately.
- Check and recheck equipment set in the BSC to ensure proper function. Do not proceed with any procedures until all critical aspects of the equipment and process have been verified for safe operation.
- Clean up and disinfect all spills inside the BSC and report them to EHS before resuming work.
- At a minimum, waste is bagged, surface decontaminated, and transferred through the docking port into the transfer cart at the end of the day, and the BSC is surface-decontaminated (by wiping all surfaces with disinfectant). Equipment remains in the BSC until the conclusion of the study.
- At the conclusion of a study, any equipment and materials to be removed from the BSC are decontaminated before transferring them to the transport cart.
- Clean up and decontaminate the BSC with appropriate disinfectant (e.g. 5% Microchem Plus).
- To avoid the buildup of sticky residue from the Microchem Plus, the BSC may be wiped down with 70% ethanol.
- Leave the BSC running but turn off the light.
- The BSC is always gas/vapor decontaminated (and the efficacy of decontamination proven using biological indicators) at the end of a study

2.0 CENTRIFUGE OPERATION

Hazards associated with centrifugation include mechanical failure, breakage and spills, and the potential for creation of aerosols. To minimize the risk of mechanical failure, centrifuges are operated and maintained according to the manufacturer's instructions. Users are trained to safely operate the centrifuge and follow specific operating procedures to ensure safety for the type of centrifuge they are using (refer to *Use of Low Speed Centrifuges with Biohazardous Agents in BSL-3 and BSL-4 Laboratories*; *Use of Ultra Centrifuges with Biohazardous Agents in BSL-3 and BSL-4 Laboratories;* and *Use of Microcentrifuges with Biohazardous Agents* SOPs).

3.0 AUTOCLAVE OPERATION

Pass-through autoclaves are used to sterilize biological wastes from the BSL-4 laboratories. The autoclaves are operated following established and validated procedures (refer to the *Autoclave Use and Verification Procedures in BSL-4 Laboratories* SOP).

Pass-through autoclave

Guidelines to be followed for the operation of the autoclave:

- All autoclaves in the BSL-4 laboratories are fitted with interlocking double doors. Once the inner door (lab side) is closed, the sterilization cycle must be completed before the outer door in the buffer corridor can be opened.
- All autoclave runs are initiated by personnel on the *inside* of the BSL-4 laboratory.
- Simple autoclave operating instructions are posted next to each autoclave.

- Personnel log each autoclave run, including a record of the biological indicator and chemical (temperature) indicator results. EHS keeps these records and retains them for a period of no less than three years.

4.0 SHARPS HANDLING

Injuries from sharp objects present a great hazard in BSL-4 laboratories and use of sharps is strictly reviewed and assessed by EHS. During instances where there is no safe substitute or replacement for the sharps, EHS works with the Core Director to develop an SOP to prevent or minimize hazards associated with the sharps usage. The laboratory personnel are trained on the SOP. Upon a satisfactory evaluation by EHS and the Core Director that the personnel are proficient in using the sharps safely, they will be approved to conduct the work. EHS reviews the SOP with the Core Director annually to ensure that nothing in the process has changed.

Guidelines to be followed when using sharps:

- EHS reviews and approves the use of sharps only if there is no other safe substitute. Personnel only use sharps that have been approved by EHS.
- If the use of sharps cannot be avoided, disposable sharps (needles, scalpels, etc.) must be used unless there is no feasible substitute.
- All used disposable sharps are placed in containers designed for safe sharp disposal (puncture-resistant, leak-proof, autoclavable, and labeled with the word, “BIOHAZARD”).
- Syringes must have Luer-Lok attachments or be retractable.
- Needles must not be recapped, and scalpel blade covers are never replaced.
- Personnel are trained to always think before cutting, ensuring hands and fingers are not in the line of the cutting stroke.
- Only blunt-tipped scissors and forceps are used.

5.0 GLASS HANDLING

Items made of glass are not used in the BSL-4 unless approved by EHS. Before any glass material is used in the BSL-4, EHS works with the user to determine if there is a safe substitute or replacement that may be used. In the event that there is no other safe alternative, a risk assessment is performed based on the hazardous material and the procedure involved. Glass material is allowed to be used only after a thorough evaluation has been performed, an SOP is developed for safe use, and the user is trained and proficient in the safe use of the material.

Guidelines for handling any approved items made of glass:

- EHS reviews and approve the use of glassware only if there is no other, safer substitute. Glassware that has not been approved cannot be used.
- All approved material made of glass must be handled carefully.
- Personnel must hold glass containers securely on the side and never around the rim or neck of the container.
- When possible, personnel must wrap glass bottles with tape for added protection from impact and shattering.
- Hot glassware may not be put on a cold or wet surface, and cold glassware may not be put on a hot surface, as a sudden changed in temperature may break it.
- Glassware that is cracked or chipped must be discarded in a sharps container.

6.0 HAZARDOUS FLAMMABLE CHEMICALS

The use of chemicals in a BSL-4 area is limited to only those that are needed to conduct specific experiments or work. Some of the chemicals to be used may be hazardous, thus EHS reviews and approves all requests to bring chemicals into a BSL-4 laboratory and is responsible for the disposal of all chemicals from the BSL-4 laboratory.

Guidelines for use of chemicals that are flammable:

- All hazardous/flammable materials are to be limited to necessary working quantities.
- EHS will provide guidance for specific storage containers and rules for safe transport, handling, and labeling of these materials.
- Section 3: Chemical Hygiene Plan has detailed information on this topic.

7.0 SONICATORS AND HOMOGENIZERS

Sonicators and homogenizers are used to disrupt cells. The instruments generate a high-frequency sound (induces cavitation in liquids) and mechanical agitation to disrupt cells. Sonication or homogenizing of biological materials also has the potential to create aerosols. Although workers are protected from potential airborne exposures because of their full-body encapsulated suits, care must be taken to prevent or minimize the release of potentially infectious aerosols:

Guidelines to follow when sonicating or homogenizing:

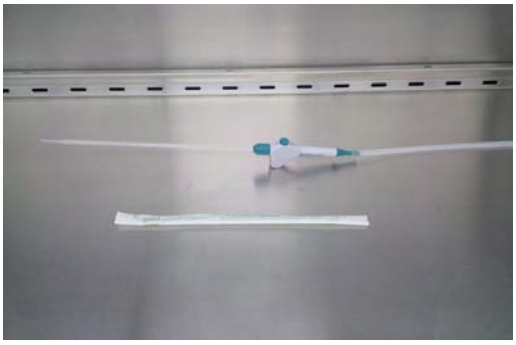
- Sonicate or homogenize infectious materials inside the BSC.
- Use closed-capped containers to hold samples for sonication.

- Do not leave the sonicator or homogenizer unattended while in operation.
- Use homogenizers that have sealed chamber assemblies.
- Clean and disinfect the sonicator or homogenizer after each use with an appropriate disinfectant.
- When cleaning homogenizer parts after use, place homogenizer probes in appropriate disinfectant with all blade ends positioned on the same side of the pan.

8.0 VACUSAFE™ VACUUM ASPIRATOR

Vacuum systems are used in the laboratory for aspiration of liquids and their subsequent disposal. The BSL-4 laboratories use the Vacusafe™ vacuum aspiration system primarily for the aspiration and removal of liquid media from cell cultures and supernatant fluids after centrifugation. The vacuum system is protected from contamination by hydrophobic HEPA filters, and the collection bottle is made of shatter-proof material and is autoclavable. It is equipped with a level sensor that will detect when the bottle is full, preventing overflow of liquid and foaming. All personnel are trained on proper assembly and operation of the Vacusafe™ (refer to *Vacusafe™ Use in BSL-4* SOP).

Vacusafe™ Vacuum System



Vacusafe™ Aspirator (Vacuboy)

Guidelines for operation of the Vacusafe™:

- When installing a fresh collection bottle, fill the container with the required amount of concentrated Microchem Plus disinfectant to ensure the correct final concentration once the container is full.

- Replace the hydrophobic HEPA filters as necessary and annually at a minimum.
- Discard the contents of the collection bottle into the sink when full (after a mandatory 24-hour hold period to ensure sufficient contact time).
- After emptying, disinfect the collection bottle with 5% Microchem Plus. Autoclave empty collection bottles before removing from the BSL-4 laboratories.

CHAPTER 7

CLEANING, DISINFECTION, AND STERILIZATION

1.0 GENERAL LABORATORY HYGIENE

The BSL-4 laboratory is designed so that it can be easily cleaned and decontaminated. The workbenches, sinks, and other equipment are mostly constructed of stainless steel and other materials possessing smooth, impervious surfaces for ease of cleanup and decontamination. For example, the walls, ceilings, and floors of the containment laboratory are coated with epoxy material, specifically for ease of cleaning and decontamination.

1.1 Surface Decontamination

Laboratory work surfaces, workbenches, equipment, chairs, and tools are routinely cleaned and disinfected (refer to *Cleaning and Sanitizing BSL 4 Laboratories & Equipment*) to ensure that the cleanliness of the laboratory is maintained and, more importantly, that these surfaces are routinely decontaminated to prevent the spread of potential contamination.

Cleanable stainless steel workbench and sink

Good housekeeping practices are an important component of laboratory safety and are followed by everyone who works in a BSL-4 laboratory. Workbenches are kept clutter-free and wiped down with Microchem Plus chemical disinfectant at the end of the day when they are used and immediately after a spill of potentially infectious materials. The aisles are maintained free of trip hazards. Floors are kept clean and mopped with Microchem Plus.

1.2 Space Decontamination

Space decontamination will be performed whenever the BSL-4 or ABSL-4 suites and rooms need to be certified as "clean" (i.e., free from viable pathogens). Decontamination activities will be coordinated and performed by EHS and may include vaporized hydrogen peroxide (VHP), chlorine dioxide, or formaldehyde.

Space decontamination using these methods occurs when:

- Maintenance and/or repairs inside the BSL-4 are required.
- After clean-up of a large spill of biohazardous material.
- A change in organisms under study that requires decontamination and recertification.
- The BSL-4 area is being prepared for periodic recertification.

1.3 Waste Handling and Disposal

1.3.1 Liquid Waste

Liquid waste from the BSL-4 is treated overnight with concentrated Microchem Plus chemical disinfectant (making up a final concentration of at least 5% Microchem Plus). The waste is disposed of into the laboratory sink or floor drain and goes directly to the effluent decontamination system tanks (EDS) via the double-walled pipes constructed of heavy gauge stainless steel. The double-walled pipes are monitored by a detection system that activates an alarm in the event of a leak in the primary pipe.

The effluent is collected in one of three 1,500-gallon EDS (steam sterilization) tanks. The waste in the tank is heated to 121°C for 60 minutes. After the sterilization process is completed, the treated effluent is cooled down and discharged to a pH neutralization tank and then to the sanitary sewer. The system runs automatically, but the processed waste will not be discharged in the event that the programmed parameters are not met. The efficacy of the EDS system is verified using biological indicators that are placed in the dry/wet well filled with thermal transfer oil. Verifications are performed quarterly for each tank. The load size, temperature, and time parameters are recorded for every single batch run.

1.3.2 Solid Waste

Solid BSL-4 laboratory wastes consist of those that have had direct contact with an agent (e.g., culture plates, specimen tubes, pipettes, pipette tips, and flasks) and those that have not been in contact with an agent (e.g., pipette wrappers, paper towels, etc.). Solid wastes that have been in contact with the agent are first decontaminated by immersion in Microchem Plus disinfectant, separated from the liquid using waste strainers, and autoclaved using validated cycles. Solid wastes with no contact with the agent are collected into approved

autoclavable biohazard bags and autoclaved using validated cycles (refer to *Autoclave Use and Verification Procedures in BSL-4 Laboratories* SOP).

Chemical and biological indicators are included in all BSL-4 laboratory waste autoclave runs. The autoclaves have pass-through doors that are interlocked. After autoclaving, the wastes are removed from the clean side of the autoclave and placed in biohazard boxes, where they are stored and discarded once the biological indicators test results are completed. All treated biohazard waste boxes are removed and disposed of by a licensed waste contractor.

1.3.3 Sharps Waste

Disposable sharps that are approved for use in the BSL-4 facility, such as disposable syringes, must be never be recapped. Procedures that require recapping will be reviewed by EHS and approved by the IBC to ensure that safe engineering methods and procedures are employed and followed. Sharps must be discarded into sharps containers immediately after their use.

1.3.4 Chemical Waste

The use of chemicals in BSL-4 areas is limited to only those that are needed to complete experiments and accomplish required tasks. Disposal of a chemical must comply with Section 17: Waste Disposal Plan. (Refer to SOP *Chemical Handling and Disposal in BSL-4 Suites.*)

1.4 Tools, Equipment, Scrubs, and Towels

Other reusable items will need to be properly cleaned and treated.

1.4.1 Work Tools

It is sometimes necessary to bring tools and equipment into the containment laboratory to conduct necessary repairs. Small tools and similar items that are able to withstand autoclaving are autoclaved before they are removed from the containment facility. Items that could be damaged by autoclaving are removed via the dunk tank or chemical shower. Items that would be damaged by the Microchem chemical disinfectant used in the dunk tank or the chemical shower, or that are too large to remove by either of those methods, must be decontaminated in the fumigation airlock using a gas or vapor decontamination method.

The following are considerations when bringing in tools in the containment facility:

- Tools made of metal can withstand high temperatures and can be autoclaved prior to removal from the containment. Place the tools in an autoclavable container and allow them to cool down before removing from the autoclave.
- If present, plastic and rubber parts can become damaged.
- Tools with electronic components may or may not be able to withstand chemical disinfection. Check with the manufacturer.

- Choose tools made of materials that have smooth surfaces for ease of decontamination.
- Do not use tools with sharp construction.

1.4.2 Equipment

Equipment within the containment space is decontaminated before it is removed through the fumigation airlock. EHS decontaminates the equipment using VHP, formaldehyde, or chlorine dioxide. The decontamination process is verified with biological indicators, and once the results are confirmed, the equipment is removed from the fumigation airlock.

1.4.3 Scrubs

Used scrubs, socks, and suit room towels (for drying suits) are autoclaved prior to being laundered.

2.0 ROUTINE CLEANING, MAINTENANCE, AND REPAIRS

Laboratory staff and animal care personnel are responsible for performing routine cleaning and housekeeping within the BSL-4/ABSL-4 spaces (refer to *Cleaning and Sanitizing BSL 4 Laboratories & Equipment* SOP). Custodial staff do not enter the containment facility. Highly accessed surfaces (door handles, floors, work surfaces, etc.) and those that have frequent contact with microbiological materials and infected animals are disinfected more frequently.

Generally, repair and maintenance staff do not enter into containment spaces unless the space has been decontaminated and the efficacy of the decontamination verified. In certain cases, urgent repairs may be necessary. Facilities personnel who are trained to work in BSL-4 spaces conduct the necessary repair work. Only personnel trained to enter and operate within the BSL-4 facility are permitted to perform such work, and they do so under the direct supervision of EHS.

Equipment or systems servicing the BSL-4 facility (e.g., waste plumbing, exhaust air HEPA filters and housings, autoclaves, EDS, etc.), which have the potential to be contaminated, are first decontaminated before they are serviced. Before a work order request on a system is performed by Facilities, it is first reviewed and assessed by EHS. Contaminated or potentially contaminated systems are decontaminated and the efficacy of the decontamination verified before any repair or service is performed.

3.0 SELECTION OF DISINFECTANT

The selection of disinfectants to be used in BSL-4 spaces is a joint responsibility of EHS and the BSL-4 laboratory users. Choosing the appropriate disinfectant includes, but is not limited to, the following factors:

- Agent to be inactivated
- Nature of the item to be disinfected
- Presence of organic materials

- Contact time required
- Temperature (typically room temperature) during inactivation
- Compatibility of the disinfectant with personal protective equipment
- Compatibility of the disinfectant with the effluent decontamination system

Depending on the microorganism that needs to be inactivated, there are different classes of chemical disinfectants that may be considered. Included among these are phenols (Lysol), quaternary ammonium compounds (Microchem, Roccal, etc.), and alcohols. In the BSL-4 laboratories, Microchem Plus is primarily used as a chemical disinfectant for inactivation of filoviruses, including Ebola and Marburg. Use of chlorine is discouraged as it may cause damage to the effluent decontamination tanks used to sterilize BSL-4 waste effluents.

Risk assessments associated with new biological agents prior to their introduction into a BSL-4 laboratory include determination of appropriate chemical disinfectants and their efficacy against the specific pathogens. The disinfectant selected is specified in all relevant SOPs.

4.0 PEST CONTROL

NEIDL implements and maintains an Integrated Pest Management (IPM) program that is focused on managing the NEIDL environment for the prevention of pest problems. EHS manages the program, which is implemented and maintained by a licensed contractor.

The IPM program and pest prevention is accomplished through:

- Building-wide and system-wide comprehensive surveys
- Procedures for reporting pest control issues and immediate response
- Review and monitoring of sanitation, hygiene, and housekeeping practices
- Ongoing assessment and monitoring of the building's structural integrity for prevention of vermin entry
- Implementation of policies to control unwanted introduction of pests in the building
- Use of monitors, traps, and least-toxic pest control methods
- Education of building occupants

The licensed contractor does not enter into containment but supplies pest monitoring devices and supplies. It is the responsibility of the BSL-4 users to check the traps and report the results to EHS.

The implementation of the IPM program ensures hygienic and good housekeeping operations in the NEIDL and the laboratories.

CHAPTER 8

ABSL-4 CONTAINMENT

Animal Biosafety Level 4 (ABSL-4) is required for work with animals infected with RG4 Agents and may be appropriate for some RG3 Agents following appropriate risk assessment.

Personnel involved in the care and use of research animals in the ABSL-4 have the greatest number of risks to mitigate while conducting routine work practices, procedures used in routine animal care and husbandry, and handling of animals or materials (e.g., biohazardous substances).

Small and large animals are used for research studies in the ABSL-4 laboratory. Common species include rodents and non-human primates (macaques). Animal studies proposed in the ABSL-4 laboratory are extensively reviewed by the Institutional Animal Care and Use Committee (IACUC) and the Institutional Biosafety Committee (IBC).

1.0 TRAINING

All personnel involved in the care and use of animals receive thorough and comprehensive trainings. In addition to the baseline phases of the BSL-4 laboratory training and practical exercises provided to all personnel who work in the BSL-4 laboratory, additional core-specific training is provided to individuals who will work in the ABSL-4 laboratory. Animal Core–specific training takes a staged approach similar to baseline training. Staff undergo an initial phase of didactic sessions covering principles of animal use in containment and specific biosafety controls. This phase also includes a review of all documents, including SOPs, pertinent regulations and policies, and emergency response plans. Specific equipment training, including caging, autoclaves, and cage washers, are covered. Information technology hardware and software used by the Animal Core is also covered.

Once approved, the individual progresses to a mentored stage of laboratory entries with one-on-one direct supervision and a set of learning objectives. A structured progression through direct and indirect supervision takes an individual to an accompanied access stage where he or she begins regular duties but is always supported by the presence of an experienced staff member. Each phase involves an assessment of proficiency and requires a review by the Animal Core Director before progression.

Not all Animal Core staff will carry out technical procedures or handle animals or sharps. Those who do will be fully proficient at lower biosafety levels and will undergo further didactic training as well as SOP review, observation, and direct supervision prior to taking on these duties.

Animal Core personnel provide the training and mentoring at lower containment levels and ABSL-4 specific training is guided by the ABSL-4 Animal Core Director and experienced Animal Core staff who have been designated as mentors.

Annual refresher training is required and given to all personnel handling research animals in the ABSL-4 laboratory. It is required that ABSL-4 personnel maintain proficiency and experience in performing animal handling procedures.

2.0 RULES AND POLICIES

The ABSL-4 rooms in the containment facility are operated in accordance with the "Animal Welfare Regulations" (as implemented under the authority of the USDA and APHIS), the Public Health Service Policy on Humane Care and Use of Laboratory Animals (i.e., PHS policy), and other applicable federal, state, and local laws, regulations, and policies. The housing, care, and handling of animals also conform to standards specified in the National Academies of Sciences' "Guide for the Care and Use of Laboratory Animals." Boston University animal facilities are AAALAC accredited. All protocols involving the use of animals are approved prior to the initiation of the experiment by the University's Institutional Animal Care and Use Committee (IACUC).

3.0 ANIMAL ROOMS

The animal suites in the ABSL-4 laboratory are designed and built with procedure rooms and animal holding rooms with cages. The APR doors to animal rooms are kept closed at all times except for entry and exit. The temperature inside the animal rooms is maintained within 3°F of the desired set point. An alarm registers at the Control Center when the temperature exceeds or falls below the set limits. The humidity of the animal rooms is maintained within 3% of the desired set point. An alarm registers at the Control Center when the humidity exceeds or falls below the set limits. Only authorized personnel are permitted to handle experimental animals. Authorization is based on training and proficiency. All procedures are performed carefully to minimize the contamination of the laboratory area and potential damage to the full body positive pressured suit and gloves. Two persons are required when working in the ABSL-4 laboratory.

4.0 GENERAL HANDLING AND HUSBANDRY OF EXPERIMENTAL ANIMALS

4.1 Animal Identification

Animals are identified when they are allocated to an approved research project. The animals may be identified by a range of methods, including physical marks, tattoos, individual tags, or a label or marking attached to the cage. Animal records are maintained and readily available at all times.

4.2 Animal Caging

Rodents are housed in a ventilated and filtered caging system. Non-human primates (macaques) are housed in individual stainless steel cages. Each cage is individually identified and includes the name of any infectious agent.

Flexible film isolators are used in the ABSL-4 laboratory based on the risk assessment and the *BMBL*, 5th edition. The risk assessment includes the type of animal, agent used for animal infection, and procedures performed.

4.3 Animal Care

Animal Core personnel perform daily management of animal care and husbandry, including feeding, management and hygiene of the animal rooms, cages, equipment, removal of wastes, and room disinfection. Staff also conduct daily checks and animal inventory (including number and species, location, appropriate disposition) and update of records. Any discrepancy in the inventory is immediately reported to the RO and Public Safety.

Animal handling is performed so that personnel are always maintaining the highest level of safety. Rodents and cage handling is done in the BSC or downdraft ventilated table. Non-human primate (NHP) cages have squeeze-back caging systems to safely and physically control the NHPs. NHPs are chemically restrained before removal from the cage. Except while animals are actively being removed from their cages, NHP cages remain locked at all times. Chemical and/or mechanical restraints are used wherever appropriate when handling infected animals.

5.0 ANIMAL TRANSPORT

Research animals are transported to different areas in the ABSL-4 laboratory, including the MRI Scanning Room, Class III Biosafety Cabinet, and the animal procedure room.

5.1 General Animal Transport

Animals are transported to the procedure room for examinations and other procedures necessary to conduct animal care. The animals are initially sedated so that they can be safely handled, and placed in a rubberized container lined with a workbench absorbent protector. The container is transported directly to the animal procedure room. The animal is placed back into the container once the procedure is completed and transported to the holding cage.

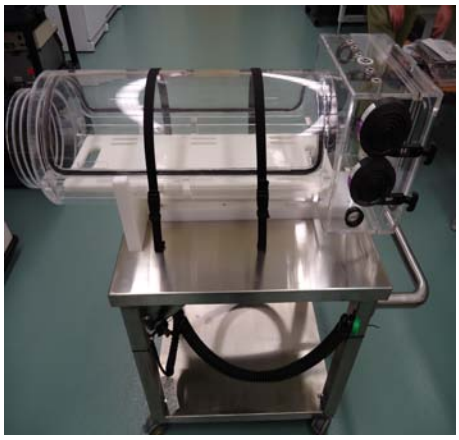
Animals that undergo necropsy are transported to the animal necropsy rooms with the same container. The container is cleaned and disinfected with 5% Microchem Plus after each use.

5.2 Animal Transport for Imaging

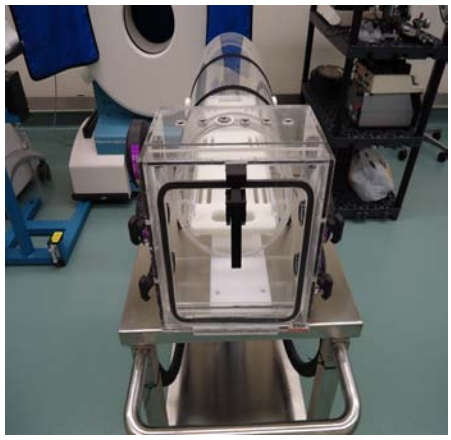
Animals are transported to the MRI facility in the ABSL-4 laboratory for imaging studies. The animals are first sedated then placed inside the transportable animal chamber. The chamber will be of size and design appropriate for the species.

An example of the current prototype is provided in the photographs below. It is constructed of a clear and non-breakable material that is self-contained with a HEPA filter. The chamber fits inside

the MRI tube, and the animal remains inside the chamber during the entire scanning process. The chambers are disinfected with 5% Microchem Plus after each use.



Transportable animal chamber (side)



Transportable animal chamber (front)

5.3 Transport to the Class III Biosafety Cabinet

Animals are transported to the Class III BSC for infection and exposure studies. If appropriate, animals will be chemically and/or physically restrained and moved inside the transportable self-contained enclosure. The enclosure is equipped with a HEPA filter. The portable enclosure is docked with the Class III BSC located on the other side of the suit containment laboratory. Once completely docked, the hatch is opened from the inside the Class III BSC and the animal is retrieved and placed inside the Class III BSC. The hatch is sealed closed prior to start of any experiment.

Once the experiment is completed, the hatch is opened and the animal is placed back into the transportable enclosure. The animal is then transferred back into its cage in the animal holding room. The transportable enclosure is decontaminated after each use.

Transportable enclosure (front)

Transportable enclosure (side)

6.0 ANIMAL INOCULATIONS AND EXPOSURES

The use of sharp instruments in the ABSL-4 laboratory is restricted and kept to a minimum. Safe needle devices such as needle locking safety syringes are used. Alternative syringe designs are considered on at least an annual basis. Any new syringe product is required to be evaluated for safety by EHS before use. All animals are chemically and/or physically restrained (e.g., anesthetized) prior to inoculation of an infectious agent, which is performed in the BSC whenever possible, to reduce risk of accidental injury to human handlers. Syringes and hypodermic needles are immediately discarded after use into an appropriate sharps container for safe disposal. Recapping of needles in the ASBL-4 laboratory is strictly prohibited.

7.0 ANIMAL NECROPSY

Animal necropsies are performed on the downdraft table or in the Class II, B1 BSC to minimize air contamination. The use of sharps is restricted and kept to a minimum.

Staff carrying out necropsies are fully trained and proficient. Necropsies require a coordinated effort; all staff participating in the necropsy procedure know their exact roles, including full understanding of space utilization and movement patterns.

Necropsy procedures involving larger species on downdraft tables utilize a range of practices to minimize contamination:

- Regular surface decontamination of suit and gloves by operators with assistance by support staff, as required;

- Use of thick absorbent materials when cutting blood vessels or body cavities such that fluids are immediately captured;
- Use of long-handled instruments at all times by operators;
- Regular placement of instruments into large beakers containing 5% Microchem Plus and exchange for clean ones.

Samples will be removed to the laboratory for processing promptly upon collection. All dead animals and carcass remains are placed in double autoclavable bags with the following information:

- Species
- Number of animals
- Infectious agents
- Investigator
- Date

After completion of a necropsy, reusable instruments are placed into a colander type basket and immersed into a container of 5% Microchem Plus for a minimum contact time of 10 minutes. They are then cleaned, rinsed, and dried. Instruments that can be autoclaved are placed in a pan after disinfection and autoclaved. Instruments are periodically placed in an appropriate preservative/lubricant per the manufacturer's recommendations. The necropsy table, as well as any other equipment or surfaces used, are appropriately cleaned and disinfected with 5% Microchem Plus.

Animal necropsy room with downdraft table and Class II, B1 BSC

Upon completion of an animal necropsy, the following are conducted:

- All instruments used must be properly disinfected and stored safely.
- All work surfaces, including floors, BSC, downdraft table, workbench, and work lights must be disinfected.
- All animal waste materials and carcasses must be placed in an autoclavable bag and autoclaved.
- All animal samples collected must be properly identified for inventory and removed for storage.

Spills that occur outside of the BSC or downdraft table must be handled as specified in the SOP *Spill Procedures Involving Biohazardous Materials: BSL-4 Laboratories*. This includes the prompt reporting of the incident to the Control Center.

8.0 INCIDENTS

8.1 Bites and Scratches

Personnel working with or near laboratory or research animals are trained and made aware of the risk of animal bites or scratches. Animal handlers practice proper animal handling techniques and wear appropriate PPE such that the likelihood of bites or scratches is very low. Regular drills will be carried out to train staff on the required steps. In addition, all animal handlers and caretaking staff are enrolled in the ROHP medical surveillance program and report all potential exposure incidents to the ROHP clinic.

8.2 Escaped Animals

All the animal rooms are kept closed at all times. Animal care staff ensure that the room is secured before handling animals. Any escaped animal will be located and secured back into the cage. Escaped animal kits are placed in every animal holding room; the kit contains signage to be placed on doors in the event of an escape. The door will not be opened until the animal is secured. The kits also contain animal capture aids and an information card. Escape of any animal is reported to the Animal Core Director as soon as practically possible. Animal escape events are also reported to EHS.

APPENDICES

APPENDIX A

Certificate of Supervised Access to BSL-4 Facility

Employee must read and sign:

Personnel who access and work in a BSL-4 laboratory must complete the required background and medical clearances and complete the BSL-4 training and NEIDL orientation. In addition, personnel are also required to pass the Security Risk Assessment (SRA) clearance by CDC/APHIS for Select Agents and Toxins.

You are being granted a provisional Supervised Access to specific areas in the BSL-4 facility to complete your mentoring training. At all times you may enter and exit the facility only with your Supervisor present. Your access to the facility will be terminated immediately should you fail to follow this requirement.

Employee Signature: _____ Date: _____

Supervisor Signature: _____ Date: _____

ADTC[1] Signature: _____ Date: _____

RO[2] Signature: _____ Date: _____

[1] Associate Director of Maximum Containment Training

[2] Responsible Official

APPENDIX B

Certificate of Post-Mentoring Access to the BSL-4 Facility

Employee must read and sign:

This certifies that I have completed the mentorship requirements for the BSL-4 facility. I have been briefed on my responsibilities and agree to follow and maintain procedures for safety in the laboratory. I understand that my failure to follow these requirements may suspend or terminate my access to BSL-4 areas.

Employee Signature: _____ Date: _____

Mentor Signature: _____ Date: _____

Supervisor Signature: _____ Date: _____

ADTC[1] Signature: _____ Date: _____

RO[2] Signature: _____ Date: _____

[1] Associate Director of Maximum Containment Training

[2] Responsible Official

APPENDIX C

BSL-4 Daily Safety Checklist

First Floor		
Building Automation System, Effluent Decontamination System, and Tissue Digester		
Containment Status (Building Automation System [BAS]) Check Control Center printout of BAS alarms &/or EHS display	Alarm Status ☐ *Clear* ☐ *Alarm(s)*	
Indicate Alarms (and Issues Affecting Operational Status):		
Liquid Decontamination System *(Computer in control room)*	Alarm Status ☐ *Clear* ☐ *Warning (Yellow)* ☐ *Alarm (Red)*	
Liquid Decontamination System Room Visual Inspection *(Indicate Conditions and Comments)*		
Tissue Digester	Alarm Status ☐ *Clear* ☐ *Alarm*	
	Alarm Type:	
Tissue Digester Room Visual Inspection *(Indicate Conditions and Comments)*		
Second Floor (Buffer Corridor)		
Autoclaves and Dunk Tanks		
Lab Autoclave SV-120 *(Room 230A)*	Alarm Status ☐ *Clear* ☐ *Alarm*	Control Power Status ☐ *On* ☐ *Off*
Lab Autoclave SV-120 *(Room 228A)*	Alarm Status ☐ *Clear* ☐ *Alarm*	Control Power Status ☐ *On* ☐ *Off*
Lab Autoclave SV-120 *(Room 214D)*	Alarm Status ☐ *Clear* ☐ *Alarm*	Control Power Status ☐ *On* ☐ *Off*

Lab Autoclave SV-120 *(Room 212A)*	Alarm Status ☐ *Clear* ☐ *Alarm*	Control Power Status ☐ *On* ☐ *Off*
Dunk Tank A *(Room 246)*	Level Within Limits ☐ *Yes* ☐ *No*	Conductivity ≥3,500 µS ☐ *Yes* ☐ *No*
Rack Autoclave *(Room 244A)*	Alarm Status ☐ *Clear* ☐ *Alarm*	Control Power Status ☐ *On* ☐ *Off*
Rack Autoclave *(Room 234A)*	Alarm Status ☐ *Clear* ☐ *Alarm*	Control Power Status ☐ *On* ☐ *Off*
Dunk Tank B *(Room 232)*	Level Within Limits ☐ *Yes* ☐ *No*	Conductivity ≥3,500 µS ☐ *Yes* ☐ *No*
Laboratory Visual Inspection (Indicate Conditions and Comments)		

Third Floor		
Breathing Air System: Compressors, Storage Tanks, Backup Systems and Quality Control		
1. Chemical Shower Air Compressor Header Pressure	35-45 PSI	☐ *Yes* ☐ *No*
2. Backup Breathing Air, High Pressure (Storage tank pressure)	1,800–2,650 PSI	☐ *Yes* ☐ *No*
3. Breathing Air Header Pressure	95-125 PSI	☐ *Yes* ☐ *No*
4. Chemical Shower Air Compressor 1	Power Status	☐ *On* ☐ *Off*
5. Chemical Shower Air Compressor 2	Power Status	☐ *On* ☐ *Off*
6. Regulated Breathing Air Pressure (Gauges near tags: BA 374, BA 372)	25–35 PSI	☐ *Yes* ☐ *No*
7. Breathing Air Compressor (BAC-1)	Alarm Status	☐ *Clear* ☐ *Alert* ☐ *Alarm*
8. Breathing Air Compressor (BAC-2)	Alarm Status	☐ *Clear* ☐ *Alert* ☐ *Alarm*
9. Breathing Air Compressor (BAC-3)	Alarm Status	☐ *Clear* ☐ *Alert* ☐ *Alarm*
10. Breathing Air Quality Control Towers (BAC-1AQ1)	CO Alarm Status	☐ *Clear* ☐ *Alarm*
11. Breathing Air Quality Control Towers (BAC-2AQ2)	CO Alarm Status	☐ *Clear* ☐ *Alarm*
12. Breathing Air Quality Control Towers (BAC-3AQ3)	CO Alarm Status	☐ *Clear* ☐ *Alarm*

Seventh Floor			
Chemical Disinfectant Storage System			
Stock Chemical Levels	Barrel #1 ☐ ¼ ☐ ½ ☐ ¾ ☐ *Full*	Barrel #2 ☐ ¼ ☐ ½ ☐ ¾ ☐ *Full*	
Mixing Tanks	Conductivity (≥3,500 µS)	Mixing Tank #1 ☐ *Yes* ☐ *No*	Mixing Tank #2 ☐ *Yes* ☐ *No*
Chemical Storage Tank Levels	Tank # 1 ☐ ¼ ☐ ½ ☐ ¾ ☐ *Full*	Tank #2 ☐ ¼ ☐ ½ ☐ ¾ ☐ *Full*	

Clear To Enter: ☐ Yes ☐ No (Explain)

** Name & Signature:

Date:

Day: ☐ ☐ ☐ ☐ ☐ ☐ ☐

Sun Mon Tue Wed Thu Fri Sat

Time:

** Required for Entry

Signature Valid 24h

APPENDIX D

Laboratory and Equipment Decontamination Certificate

BOSTON UNIVERSITY

DECONTAMINATION CERTIFICATE

AUTHORIZATION TO ACCESS DECONTAMINATED ROOM(S) OR EQUIPMENT

Space Decon. Specify Room(s):		
Equipment Decon. Specify Equipment and Location:	Equipment	Location
Date of Decontamination Activity:		
Authorization to Access Decontaminated Room(s) or Equipment After Successful Decontamination Process:		
Authorized EHS Representative:		*Date Signed:*
Signature:		
THIS AUTHORIZATION MUST BE KEPT ON FILE FOR AT LEAST 3 YEARS FROM THE DATE OF ISSUANCE		

Title: Decontamination Certificate Document #: SAF-FRM-0175 Version: 1 Date Accessed: May 2, 2014

APPENDIX E

Regulations and Guidelines

The following is a summary of federal, state, and local agency regulations and guidelines that either regulate or provide guidelines covering the use of biological agents.

1.0 Centers for Disease Control and Prevention and the National Institutes of Health: *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), 5th Edition, 2009

The BMBL contains guidelines for BSL-4 facility containment, safe microbiological practices and procedures, and safety equipment. BMBL guidelines are recognized by regulatory and accrediting agencies and are considered a best source for the description of biosafety practices and procedures. The BMBL is the basis for this Biosafety Manual.

2.0 National Institutes of Health: *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines), November 2013.

NIH implemented guidelines for research involving recombinant and synthetic nucleic acid molecules. Boston University and other institutions with NIH-funded research are subject to the guidelines and must comply with the NIH requirements. The guidelines require that each institution establish an Institutional Biosafety Committee (IBC) with the authority to review and approve proposed recombinant or synthetic nucleic acid research and apply the NIH guidelines as the minimum standard. Furthermore, NEIDL complies with BPHC guidelines prohibiting or restricting recombinant DNA work that requires BSL-4 containment.

3.0 Occupational Safety and Health Administration (OSHA): Bloodborne Pathogens Standard, 29 CFR 1910.1030

The OSHA Bloodborne Pathogens Standard applies to all occupational exposure to blood and other potentially infectious materials. The regulation requires that engineering controls, safe work practices and procedures, training, medical occupational health programs, and recordkeeping be in place. Work in the NEIDL BSL-4 laboratories involves handling and analysis of blood and other bodily fluids that are known or suspected to contain Risk Group 4 pathogens, including filoviruses (e.g., Ebola and Marburg viruses), arenaviruses (e.g., Lassa, Junin, and Argentinian Hemorrhagic Fever viruses), henipah viruses (Nipah and Hendra viruses) and bunyaviruses (e.g., Crimean Congo Hemorrhagic Fever virus).

4.0 Boston Public Health Commission: Recombinant DNA Technology: Use Regulations (passed March 22, 1994), Disease Surveillance and Reporting Regulation (passed March 30, 2004, amended January 10, 2013), and Biological Laboratory Regulation (passed September 19, 2006)

The BPHC Biological Laboratory Regulation requires all institutions in the City of Boston that operate BSL-4 laboratories be permitted by BPHC. The Disease Surveillance and Reporting Regulation requires all institutions in the City of Boston that engage in research with select agents, Risk Group 4 Agents, and other agents listed by BPHC as high-risk agents, be registered and maintain disease surveillance and reporting programs in effect. The Recombinant DNA Technology: Use Regulations apply to all use of recombinant DNA molecules by institutions in the City of Boston and also require permitting by BPHC. These regulations require strict adherence to the CDC/NIH guidelines, as well as other regulations that the BPHC's Board of Health and Hospitals may apply.

5.0 Commonwealth of Massachusetts Department of Public Health: Minimum Requirements for the Management of Medical or Biological Waste, 105 CMR 480.000, 2010

The Commonwealth of Massachusetts regulates the storage and disposal of medical wastes from health care facilities and biological wastes from biomedical laboratories. The regulation includes treatment, storage, labeling, and recordkeeping requirements. Biological wastes from BSL-4 laboratories are treated and inactivated by validated autoclave sterilization prior to disposal by the biological waste contractor.

6.0 U.S. Departments of Health and Human Services and Agriculture: 42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121) Select Agents and Toxins Final Rule, October 5, 2012

Under United States law, the DHHS Centers for Disease Control and Prevention and USDA Animal and Plant Health Inspection Service jointly regulates the possession, use, and transfer of Select Agents and Toxins. These agents have the potential to pose a severe threat to public health and safety. The regulations include registration of the entity; appointment of a Responsible Official; biosafety, security, and emergency response plans; training; inventory control; and others. A subset of these Select Agents and Toxins have been designated as Tier 1 because these biological agents and toxins present the greatest risk of deliberate misuse with significant potential for mass casualties or devastating effect to the economy, critical infrastructure, or public confidence, and they pose a severe threat to public health and safety. Tier 1 requirements include a Personnel Suitability and Reliability Program, occupational health, training, security, and others. All Risk Group 4 Agents used in research studies in NEIDL BSL-4 laboratories are Tier 1 Select Agents.

7.0 U.S. Department of Transportation (DOT): Hazardous Materials Regulation 49 CFR 173.134–173.199

The law regulates the intrastate, interstate, and foreign shipment of hazardous materials. Requirements include packaging, shipping, and labeling and requirements for commercial carriers. The regulation requires appropriate training of carriers, permits, labeling, packaging, and other

requirements. BU complies with the DOT requirement, as described in Section 16: Transportation Plan.

8.0 International Air Transportation Association (IATA): Dangerous Goods Regulations

IATA regulates the shipment and transport of infectious substances. IATA regulations apply to shipment of infectious substances by air. Infectious substances are divided into two categories. Category A is an infectious substance capable of causing permanent disability or a life-threatening or fatal disease in otherwise healthy humans or animals. Category B is an infectious substance that does not meet the criteria for inclusion in Category A. The Risk Group 4 Agents including filoviruses (e.g., Ebola and Marburg viruses), arenaviruses (e.g., Lassa, Junin, and Argentinian Hemorrhagic Fever viruses), henipah viruses (Nipah and Hendra viruses), and bunyaviruses (e.g., Crimean Congo Hemorrhagic Fever virus) used for research studies in NEIDL BSL-4 laboratories are in Category A.

9.0 Centers for Disease Control and Prevention (CDC): 42 CFR Part 71, Foreign Quarantine; 42 CFR Part 71.54, Etiologic Agents, Hosts, and Vectors

The law governs the importation of hazardous materials (etiologic agents, vectors, and materials containing etiologic agents). Importation into the United States must be accompanied by a U.S. Public Health Service import permit. The NEIDL BSL-4 laboratories conduct research on viruses and human materials containing Risk Group 4 Agents, including filoviruses (e.g., Ebola and Marburg viruses), arenaviruses (e.g., Lassa, Junin, and Argentinian Hemorrhagic Fever viruses), henipah viruses (Nipah and Hendra viruses), and bunyaviruses (e.g., Crimean Congo Hemorrhagic Fever virus) and requires permits from CDC prior to their importation into the US.

10.0 Animal and Plant Health Inspection Service (APHIS) and Veterinary Services (VS)

The APHIS and VS regulate the import of animals and animal products into the US to ensure that exotic diseases are not introduced into the United States. Generally, an import permit is needed for materials derived from animals or exposed to animal-source materials. Materials that require a permit include animal tissues, blood, cells or cell lines of livestock or poultry origin, RNA/DNA extracts, hormones, enzymes, monoclonal antibodies for in vivo use in non-human species, certain polyclonal antibodies, antisera, bulk shipments of test kit reagents, and microorganisms. The NEIDL BSL-4 conducts research on materials from animals containing Risk Group 4 Agents, including filoviruses (e.g., Ebola and Marburg viruses), arenaviruses (e.g., Lassa, Junin, and Argentinian Hemorrhagic Fever viruses), henipah viruses (Nipah and Hendra viruses), and bunyaviruses (e.g., Crimean Congo Hemorrhagic Fever virus) and requires permits from APHIS and VS prior to their importation into the US.

11.0 U.S. Department of Commerce (DOC)

The DOC, through the Export Administration Regulations (EAR) governs the export of dual use items and their technology. These items have both commercial and military applications and include pathogens. The NEIDL BSL-4 conducts research with Risk Group 4 pathogens, including filoviruses (e.g., Ebola and Marburg viruses), arenaviruses (e.g., Lassa, Junin, and Argentinian

Hemorrhagic Fever viruses), henipah viruses (Nipah and Hendra viruses), and bunyaviruses (e.g., Crimean Congo Hemorrhagic Fever virus). Exportation of these pathogens is subject to export control requirements from DOC-EAR.

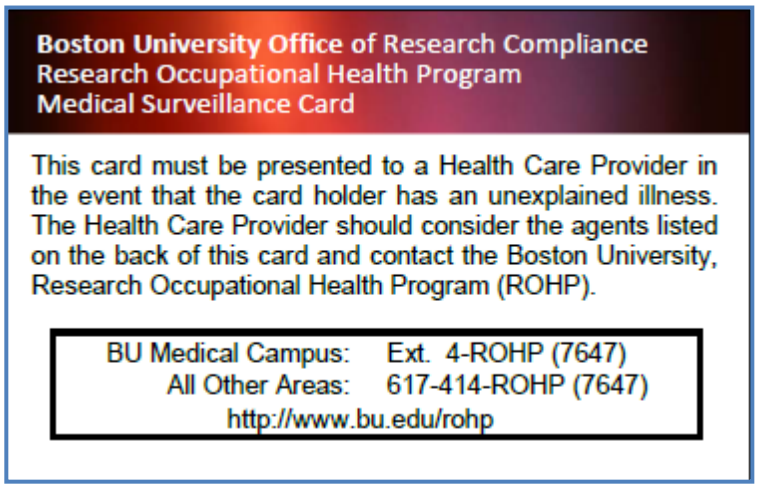
12.0 European Committee for Standardization's (CEN)

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom. CEN has developed a Laboratory Biorisk Management (CWA 15793:2011; prepared by CEN Workshop 31) that states "The organization shall establish, document, implement and maintain a biorisk management system in accordance with the requirements of this Laboratory biorisk management standard." This updated document is available at: ftp://ftp.cenorm.be/CEN/Sectors/TCandWorkshops/Workshops/CWA15793_September2011.pdf.

APPENDIX F

Agent ID Card

FRONT



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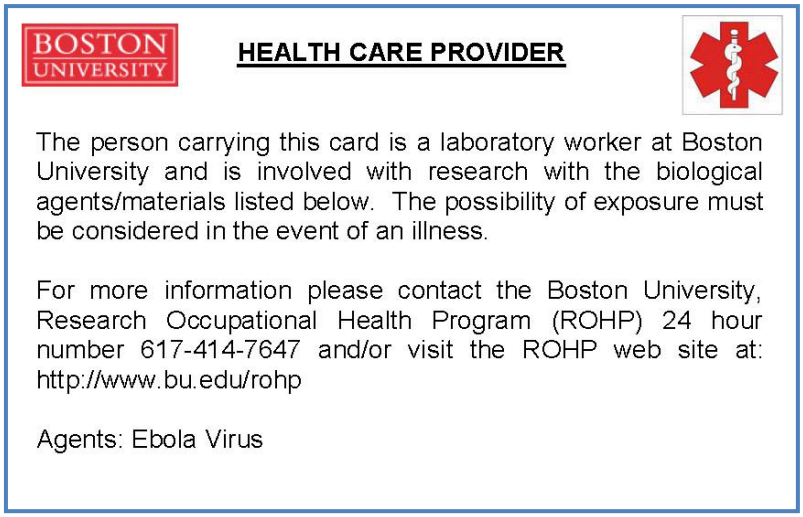

APPENDIX G

Applicable Policies, Plans, Manuals, and SOPs

1.0 Plans

Section 1: Introduction

Section 2: Biosafety Manual

Section 3: Chemical Hygiene Plan

Section 4: Commissioning Plan

Section 5: Decommissioning Plan

Section 6: Decontamination Plan

Section 7: Disease Surveillance Plan

Section 8: CEMP (Comprehensive Emergency Management Plan)

Section 9: Hazard Evaluation and Risk Management Plan

Section 10: Laboratory Inspection Program

Section 11: Management Commitments

Section 12: Security Plan

Section 13: Strain Verification

Section 14: Termination of Work with BSL-4 and ABSL-4 Agents

Section 15: Training Plan

Section 16: Transportation Plan

Section 17: Waste Disposal Plan

Section 19: Radiation Safety Plan

2.0 Standard Operating Procedures

Standard Entry Procedure for the BSL-4 Laboratory

BSL-4 Positive Pressure Protective Suit: Acceptance Testing

BSL-4 Positive Pressure Protective Suit: Pre-Entry Inspection and Testing

Operation of a Dual Sided Aerobiology Class III Biological Safety Cabinet in the BSL-4 Laboratory

Use of the Class II Biological Safety Cabinet

External Shipping and Receiving of Biological Materials at Boston University

Intra-Entity Transfer of Non-Select Agents and Select Agents and Toxins

Removal of Non-Viable Material from BSL-4 Containment Space

BSL-4 Dunk Tank Operation: Removal of Viable Material

Use of the Fumigation Airlock in an Emergency

Cleaning and Sanitizing BSL 4 Laboratories & Equipment

Decontamination of Dual Sided Aerobiology Class III Biosafety Cabinet with Vaporized Hydrogen Peroxide (VHP)

Spill Procedures Involving Biohazardous Materials BSL-4 Laboratories

Validation of Chemical Disinfectants for Biological Agents Contained at BSL-3 and BSL-4

Chemical Inactivation of Samples (Validation of Method)

Verification of the Effluent Decontamination System (EDS)

BSL-4/ABSL-4 Space Decontamination Using Vaporized Hydrogen Peroxide (VHP)

Formaldehyde Gas Decontamination of HVAC HEPA Filters and Housings

Autoclave Use and Verification Procedures in BSL-4 Laboratories

Standard Exit Procedure for the BSL-4 Suit Laboratory

Standard Entry Procedure for the BSL-4 Cabinet Laboratory

Standard Exit Procedure for the BSL-4 Cabinet Laboratory

Entry of Equipment and Supplies into BSL-4 and ABSL-4 Space

Exit of Equipment and Tools from BSL-4 Space

Periodic Inspection, Quality Check and Replacement of Class III Biological Safety Cabinet Gloves

Use of High Speed Centrifuges with Biohazardous Agents in BSL-3 and BSL-4 Laboratories

Use of Low Speed Centrifuges with Biohazardous Agents in BSL-3 and BSL-4 Laboratories

Use of Ultra Centrifuges with Biohazardous Agents in BSL-3 and BSL-4 Laboratories

Use of Micro Centrifuges with Biohazardous Agents

Operation of the TBJ, Inc. Model 30-70-DD Downdraft Table

BSL-4 Daily External Systems Safety Checklist

Biological Waste Handling and Disposal in BSL-4 Laboratories

Vacusafe Use in BSL-4

Transfer of Biohazardous Materials from the BSL-4 Laboratory to the Gamma Irradiator

Chemical Handling and Disposal in BSL-4 Suites

3.0 Emergency Response Plans

Medical Incident

Materials Transportation Management Policy

Animal Escape

Earthquake

Flood Plan

Hurricane Response Plan

Severe Weather Plan

Hazardous Materials

Chemical Spill

Radiation Spill

Suspicious Person

Loss Theft Agent Information

Code Green

Bomb Threat Suspicious Device, Package or Letter Response Plan

Hostage Situation

Select Agent Security Breach

Protests Plan

Cyber Attack Response Plan

Class III Biosafety Cabinet Failure Response Plan

Gas Leak Response Plan

Air Handling Failure

Elevator Failure

Transportation Incident

Breathing Air Failure Response Plan

EDS Tanks

Tissue Digester Emergency Response Plan

Irradiator Response Plan

Loss of Water

Loss of Gas

Loss of Electricity

Water Leak

4.0 Manuals

Boston University Biosafety Manual: http://www.bu.edu/orccommittees/ibc/policies/ibc-policies/

5.0 Policies

Personnel Suitability and Reliability Policy