



STATE OF MARYLAND
DHMH

Maryland Department of Health and Mental Hygiene
201 W. Preston Street • Baltimore, Maryland 21201

Martin O'Malley, Governor – Anthony G. Brown, Lt. Governor – Joshua M. Sharfstein, M.D., Secretary

December 2, 2013

The Honorable Thomas M. Middleton, Chair
Senate Finance Committee
Miller Senate Office Building
11 Bladen Street
Annapolis, Maryland 21401-1991

The Honorable Peter A. Hammen, Chair
Health and Government Operations Committee
House Office Building
6 Bladen Street
Annapolis, Maryland 21401-1991

Re: Report on the Health and Safety Issues Associated with High Containment Laboratories in the State of Maryland

Dear Chair Middleton and Chair Hammen:

Senate bill 758, Containment Laboratories – Oversight, was introduced during the 2012 Legislative Session. The bill proposed to establish a Containment Laboratory Oversight Division that would operate as the exclusive State entity to regulate, license and provide oversight for private and academic biosafety level-3 and biosafety level-4 high containment laboratories. According to the bill, the Division was required to oversee the design standards, regulations, inspections and licensure of these facilities. This would subsequently ensure the health and safety of laboratory personnel and the public from potentially harmful biological agents.

However, the bill duplicated several existing federal and State regulations. The bill also did not include assessments of risk to identify the hazardous characteristics of infectious agents, the nature of the work being performed with them, the likelihood of exposures or releases and the probability of severe outcomes balanced against the important scientific advancements discovered by conducting research and the positive impact the operation of high containment laboratories have on Maryland's bioscience economy. Consequently, the Department of Health and Mental Hygiene was asked to convene a Workgroup to study the health and safety issues associated with operating high containment laboratories in the State of Maryland. The Workgroup was to convene for a period of one year and report its findings and recommendations to the Senate Finance and House Health and Government Operations committees.

Membership in the Workgroup consisted of learned professionals from the Maryland biosafety and biocontainment community. Affiliations include the Frederick County/City of Frederick Containment Laboratory Community Advisory Committee, Maryland State agencies, academia and the bioscience industry. The Workgroup focused on analyzing the current system of regulations and guidelines, and members proposed several recommendations for review. The recommendations provide a framework for regulatory structures, design techniques, communication strategies and registration/permitting processes. The Workgroup also assessed the potential impact that these recommendations would have on businesses and scientific organizations that operate or intend to operate high containment laboratories in Maryland. The Department does not currently take a position on the recommendations provided by the Workgroup.

The Honorable Thomas M. Middleton, Chair
The Honorable Peter A. Hammen, Chair
Page 2

The Workgroup has forwarded the Biocontainment Report and the accompanying recommendations to the Department for review. The public-at-large had an opportunity to review the report and express their comprehensive views, concerns and solutions during a thirty day comment period that ended on November 30, 2013. We will provide you with the unedited public comments and a summary review of their remarks.

Thank you for reviewing this report. We hope you find it comprehensive and informative. If you have any questions or need additional information, please feel free to contact Ms. Marie Grant, Director of the Office of Governmental Affairs, at (410) 767-6481.

Sincerely,



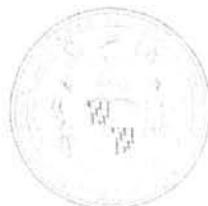
Robert A. Myers, Ph.D.
Director, Laboratories Administration

Enclosures

cc: Laura Herrera, M.D., M.P.H.
Marie Grant
Jennifer Barnhart
Patrick Dooley

THOMAS M. MIDDLETON
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THE SENATE OF MARYLAND
FINANCE COMMITTEE

May 1, 2012

Received

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Department of Health
and Mental Hygiene

The Honorable Joshua M. Sharfstein, Secretary
Department of Health and Mental Hygiene
201 W. Preston Street
Baltimore, Maryland 21201

Dear Secretary Sharfstein:

During the 2012 session, the Senate Finance Committee considered Senate Bill 758, Department of Health and Mental Hygiene – Containment Laboratories – Oversight. The bill would have established a Containment Laboratory Oversight Division in the department. The division was intended to be the only State entity that oversees and regulates containment labs in Maryland to protect the health and safety of the workers, the public, and the environment from harmful biological agents. During the bill hearing all parties who testified, including the sponsor, agreed that, rather than passing a detailed regulatory bill, the issue should be studied during the interim to develop effective and coherent policies that would govern specified containment laboratories.

The department's testimony included amendments that would have required the department to convene a workgroup, including all relevant stakeholders, to study the "health and safety risks of containment laboratories in the State and to identify any existing gaps in regulatory oversight of these laboratories." In lieu of a legislative mandate, I would encourage the department to convene the workgroup as envisioned in your suggested amendments to Senate Bill 758. We look forward to hearing the final findings and recommendations of the workgroup sometime before June 2013. In addition, it is possible that Senate Bill 758 may be re-introduced during the 2013 session. Therefore, I would appreciate an update of the workgroup's activities before December 15, 2012. Thank you for your attention to this important matter.

Very truly yours,

A handwritten signature in cursive script that reads "Thomas McLain Middleton".

Thomas McLain Middleton

TMM/DAS/ncs

cc: Senator Ronald N. Young
Members, Senate Finance Committee

Maryland Department of Health and Mental Hygiene

**Report on the Health and Safety Issues
Associated with
High Containment Laboratories
in the State of Maryland**

October 2013

*Robert A. Myers, Chair
Workgroup for Biocontainment Laboratories Oversight*

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EXECUTIVE SUMMARY

During the 2012 Legislative session, Senate Bill 758 was proposed to establish a Containment Laboratory Oversight Division that would function as the sole State governmental entity to regulate, license and provide oversight for private and academic biosafety level-3 (BSL-3) and biosafety level-4 (BSL-4) containment laboratories throughout the State of Maryland. The bill primarily did not move forward based on its' duplication of several existing federal and State regulations. Accordingly, the Department of Health and Mental Hygiene (DHMH) was asked to convene a workgroup to study the health and safety issues associated with high containment laboratories and identify existing gaps in regulatory oversight of biocontainment laboratories in the State of Maryland. The Committee requested that the workgroup report its findings to the Senate Finance and House Health and Government Operations Committees (Appendix A).

DHMH responded accordingly and convened a workgroup that lasted for the duration of one year. A balanced composition of membership was selected to form the Workgroup. Membership affiliations include the Frederick County/City of Frederick Maryland Containment Laboratory Community Advisory Committee, academia, bioscience industry, Maryland Biotechnology Center/Department of Business and Economic Development, Maryland Department of Agriculture, Office of Health Care Quality, Maryland Occupational Safety and Health Administration, and the Laboratories Administration DHMH. A complete listing of membership is attached in Appendix B. The Workgroup was charged to: (1) analyze community concerns regarding the health and safety issues associated with private and academic containment laboratories operating in the State of Maryland; (2) review and identify potential gaps in biocontainment laboratory oversight framework; and (3) develop and evaluate options. The scope of work for the Workgroup options is limited to Biosafety Level 3 laboratories which are operating in Maryland and are not located on federal property. The Workgroup convened a total of five productive meetings between October 2012 and April 2013. A public comment period will be made available after the Secretary of DHMH approves the report. Public comments are therefore not incorporated into this report.

The Workgroup reviewed a complex of biocontainment and biosafety oversight measures that currently exist in the United States and Maryland. They found facility and design construction standards for biocontainment laboratories are the least prescriptive and recognized that under and un-regulated facilities could potentially pose risks to public health, agriculture or the environment. In order to accurately assess the potential risks that could result from any lack of regulatory oversight of these facilities, the Workgroup established the need to identify and enumerate non-federal high containment (BSL-3 or BSL-4) laboratories that are located in Maryland, verify their operational scope and determine how they are currently regulated or accredited. The workgroup conducted a survey to identify these high containment laboratories. The voluntary survey results were not informative. Absent data on the

number of high containment facilities operating within the State, the Workgroup analyzed the scientific literature regarding perceived versus theoretical risk associated with operating biocontainment facilities. Based on published scientific evidence, the Workgroup concluded that the risk of Laboratory Acquired Infections (LAIs) and/or accidental release incidents are relatively low. Although design standards are the least prescriptive, BSL-3 laboratories design standards are based on the risk assessment of the agent being handled.

Rather than adopt specific recommendations, the Workgroup put forward options for regulation and presented an evaluation of the potential impact of each option. Options for regulation described in the Workgroup's report included the implementation of: (1) A permitting process to identify biocontainment laboratories operating in Maryland; (2) A State level registration process and regulatory protocols that are based on industry best practices; (3) A construction permitting/licensing process to determine if biosafety laboratory activities are present in certain commercial and/or residential areas; (4) Risk communication strategies to encourage acceptance, trust and understanding between operators of biocontainment laboratories, State regulators and the Community; and (5) A voluntary accreditation program for high containment laboratories that are not subject to regulation by the Select Agent Program. The Workgroup evaluated each option with an objective framework to optimize oversight of research and related activities in biocontainment laboratories through a coordinated approach that does not thwart scientific research but is balanced against paramount assurances of public safety. Both adequate high containment laboratory safety regulations and the research and development that occur at these facilities are equally critical to protect public health, agriculture and the environment of Maryland. Finally, the Workgroup assessed the potential impact of the proposed regulatory approaches from stakeholders such as the community, academic and teaching laboratories, bioscience industry and State agencies and analyzed the potential effect these options would have on the organizations and businesses that operate high containment laboratories in Maryland. The Workgroup did not favor one specific option and did not adopt a specific recommendation for regulation.

I. GENERAL BACKGROUND

Importance and risks of operating laboratories that can safely handle infectious microorganisms and hazardous biological materials

Disease causing microorganisms have threatened human health, agriculture and the environment for millennia. In recent years population growth, improved mobility, a global economy, war and intrusion into new ecological settings have increased the threat of emerging (e.g., Avian influenza, SARS corona virus, West Nile Virus) and reemerging infectious agents (e.g., multi-drug resistant *Mycobacterium tuberculosis*, foot-and-mouth disease virus) to cause devastating epidemics.¹ Pathogenic microorganisms are rapidly evolving, adapting to new hosts and overcoming human counter-measures such as vaccines, antibiotics and anti-viral drugs. In addition to the hazards of naturally acquired infections some of these pathogens (e.g., *Bacillus anthracis* [causative agent of anthrax in humans and animals]) can also be used malevolently by terrorists to threaten the nation and the world as weapons of mass destruction.

Therefore it is necessary to continue to conduct advanced scientific research with infectious microorganisms in laboratories that are designed, constructed and operated to safely handle these agents. This research contributes significantly to the understanding of human, plant, and animal pathogens and the diseases they cause; the development of new diagnostics, treatments, and preventive measures for protecting human, plant, and animal health; the development of a more robust and nutritious food supply; and the development of medical countermeasures for biodefense.² Additionally, these research initiatives are undertaken to gain a better understanding of their infectivity, modes of transmission, host range, mechanisms of pathogenesis and virulence and underpin the nation's ability to develop new and improved diagnostics, treatments, and preventive measures to successfully combat naturally emerging and re-emerging infectious diseases. In Maryland, universities, private research foundations, federal and State governmental agencies, federal government contractors and private biotechnology companies operate laboratories that are used to conduct research with infectious microorganisms and hazardous biological materials. These facilities are part of Maryland's thriving life sciences industry which is an important component of the region's economy.³

However, working with infectious microorganisms and hazardous biological materials in the laboratory always involves some level of risk. Accidental exposures to laboratory workers can result in laboratory acquired infections (LAI) which could potentially be subsequently transmitted to others in the community. Accidental or intentional releases of infectious microorganisms into the surroundings areas outside of the containment of the laboratory could potentially have a negative impact on public health, agriculture and the environment.

Definitions of Key Terms Used in this Report

In the United States the Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) co-authored the Biosafety in Microbiological and Biomedical Laboratories (BMBL). These publications have become the accepted code of practice for biosafety.⁴ Key technical terms in this report will rely primarily on definitions established by the BMBL.

Biosafety: the discipline addressing the safe handling and containment of infectious microorganisms and hazardous biological materials in the laboratory. The two basic principles of biosafety are containment and risk assessment.⁵

Biological agents: includes bacteria, viruses, parasites, fungi, other organisms and their associated toxins that are capable of causing substantial harm to human, animal or plant health.⁶

Select Agents: are biological agents or biological toxins that have the potential to be used in acts of bio-terror and pose a severe threat either to public health and safety or to agricultural plants and animals. The Department of Health and Human Services (HHS), Centers for Disease Control and Prevention (CDC) and the United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS) have been tasked to establish a list of biological agents that have this potential for malevolent use and regulate the laboratories that possess them. See Appendix C or the CDC/APHIS National Select Agent Registry website for further details: <http://www.selectagents.gov/Select%20Agents%20and%20Toxins.html>.⁷

Containment or Biocontainment: The term “containment or biocontainment” is used to describe the microbiological practices, safety equipment, and facility safeguards that protect laboratory workers, the environment, and the public from exposure to infectious microorganisms and toxins that are handled and stored in the laboratory. Proper training and strict adherence to standard microbiological practices is the most important element of containment. **Primary containment barriers** refer to biological safety cabinets (BSC's), enclosed centrifuge containers, personal protective equipment (gloves, gowns, respirators) and other safety devices that are designed to provide containment of infectious droplets or aerosols generated by microbiological procedures. **Secondary containment barriers** refer to the design and construction of the facility, including but not limited to specialized ventilation systems, controlled access zones, decontamination systems and other features that contribute to the laboratory workers safety and provide a barrier to prevent the accidental release of infectious agents into the environment surrounding the facility.⁸

Risk Assessment: The fundamentals of risk assessment are the process that enables the appropriate selection of microbiological practices, safety equipment, and facility safeguards that can prevent LAIs or release of the agent into the environment with possible exposures to the general public.⁹ Risk assessment falls into two broad categories, **agent hazards** and **laboratory procedure hazards**. The risk assessment of the biological agent and laboratory procedures to be performed determines the level of biocontainment needed to safely manipulate the pathogens in the laboratory.

Agent hazards: The principal hazardous characteristics of an agent are (1) its capacity to infect and cause disease in a susceptible host, (2) its virulence as measured by the severity of disease, (3) the availability of preventative measures and (4) effective treatments. Using these criteria, the World Health Organization (WHO) and NIH assign classifications of infectious microorganisms to four risk groups on the basis of hazard to laboratory workers and the community.¹⁰

Laboratory Procedure Hazards: Five transmission routes for LAIs have been identified. These are (1) parenteral inoculations with syringe needles or other contaminated sharps, (2) spills and splashes onto skin and mucous membranes, (3) ingestion through mouth pipetting, (4) animal bites and scratches, and (5) inhalation exposures to infectious aerosols. The exact causes for most LAIs are unknown. However it is estimated that exposures to infectious or toxin-containing aerosols account for approximately 50% of the exposures leading to LAIs.¹¹ A risk assessment of both the infectious agent and how it will be manipulated in the laboratory determine possible transmission hazards and establish what procedures need to be implemented to safely work with these pathogens.

Biosafety Levels (BSL): Four ascending biosafety levels (BSL-1 to BSL-4) are defined in the BMBL. They refer to the level of containment needed to safely handle human pathogens. The levels are based on the specific infectious agent and the type of work conducted with the agent. The BMBL also assigns infectious agents with the levels for biosafety (see Table 2: Summary of Recommended Biosafety Levels for Infectious Agents in Appendix D).

Biosafety Level 2 (BSL-2): Laboratories that operate at biosafety level 2 practices, safety equipment, and facility design and construction are appropriate when work is done with any human-derived blood, body fluids, tissues, or primary human cell lines where the presence of an infectious agent may be unknown. Except in extraordinary circumstances, the initial processing of

clinical specimens and serological identification of isolates can be done safely at BSL-2. Additionally, even though organisms routinely manipulated at BSL-2 are not known to be transmissible by the aerosol route, appropriate measures must be taken to mitigate risk.¹²

Biosafety Level 3 (BSL-3): Laboratories that operate at biosafety level 3 are often referred to as “**high containment laboratories.**” Biosafety level 3 practices, safety equipment and facility design and construction are applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents. These agents have the potential for respiratory transmission which may cause serious and potentially lethal infection. However, preventive or therapeutic interventions are *often* available.¹³ Such agents include, but are not limited to, *Francisella tularensis*, *B. anthracis*, *Chlamydia psittaci*, West Nile virus, SARS coronavirus, several species of *Brucella* and Yellow Fever virus.

Biosafety level 4 (BSL-4): Laboratories that operate at biosafety level 4 are often referred to as “**maximum containment laboratories.**” Biosafety level 4 practices, safety equipment, and facility design and construction are applicable for work with dangerous and exotic agents that pose a high individual risk of life-threatening disease. These agents may be transmitted via the aerosol route for which there is no available vaccine or therapy.⁴ Such agents include Smallpox virus, Marburg or Congo-Crimean hemorrhagic fever viruses, Ebola virus, Lassa virus, and various other hemorrhagic diseases.

Animal Biosafety Levels (ABSL): The BMBL also defines containment levels for laboratories that work with naturally infected vertebrate animals (ABSL 1 to ABSL 4). The animal biosafety levels parallel the assigned biosafety levels used for research on human pathogens. The BMBL also provides recommendations for facility design, practices, procedures and safety equipment for animals that might require containment.⁴

Biosafety Level 3 Agricultural (BSL-3AG): The USDA has established a risk assessment for agricultural research. The risk assessment was designed to study the economic and trade implications associated with animal and plant morbidity and mortality resulting from contact with infectious agents released by containment research laboratories. BSL-3AG is unique to agriculture as this safety level is designed to protect animal and plant environments from high consequence pathogens.⁸

For the purposes of this report, laboratories that work with high consequence pathogens at BSL-3, ABSL-3 and BSL-3AG will be referred to as “high containment” laboratories. The Workgroup only focused on BSL-3 laboratories because all known existing BSL-4 labs are located on federal property in Maryland (i.e., Fort Detrick). It is not within the purview of this Workgroup to advise on the operations of federal facilities.

Concerns of the General Public

In the State of Maryland, the potential release of highly infectious microorganisms and biohazardous materials on the local population, livestock industry, businesses and infrastructure due to unregulated high containment (non-federally funded facilities) is of community concern and for many residents, may be remedied by prudent regulatory measures which will oversee and monitor biocontainment activities.

Specifically, the public concerns in regard to BSL-3 laboratories include (1) deliberate or accidental release of high consequence biological agents into the environment; (2) laboratory workers exposed to infectious agents and potentially transmitting infections to the public; (3) locations of high containment laboratories; and (4) questions regarding the adequacy of the framework, oversight and standards for biosafety.

These public concerns burgeoned when the United States Government Accountability Office (GAO) acknowledged that “no single federal agency was responsible for assessing overall laboratory needs.”¹⁷ The CDC regulates and provides oversight over those laboratories working with pathogens known as “select agents”. These are potential biowarfare or bioterror pathogens such as *Bacillus anthracis* and *Yersinia pestis* (causing anthrax or plague in man or animals, respectively). However, no government entity regulates or provides oversight of laboratories working with BSL-3 pathogens not on the “select agent” list. Such organisms may include: *Mycobacterium tuberculosis* (tuberculosis), Middle East Respiratory Syndrome corona virus (MERS), *Hantavirus*, *St. Louis Encephalitis Virus*, *Western Equine Encephalitis Virus* and others. Additionally, there is no federal or State regulatory standard requirement for non-select agent research. There is also no government entity tracking everyone who operates a BSL-3 laboratory or where these laboratories are located. Thus, private BSL-3 research laboratories not working with select agents may adopt safety standards voluntarily and are self-policing.

The Number of High Containment Laboratories Currently Operating In Maryland Is Difficult To Accurately Ascertain

The Workgroup agreed that the initial step in addressing the public's concerns about possible gaps in regulatory oversight of high containment laboratories and the risk these unregulated facilities could potentially pose

was to attempt to quantify the number of high containment (BSL-3) facilities operating in Maryland. The Workgroup attempted to gather this information through a survey (Appendix E). On two separate occasions surveys designed to identify non-federal high containment laboratories operating in Maryland were forwarded to approximately one-thousand (1,000) business entities within the State. Contact information for these business entities were provided by the Maryland Department of Business and Economic Development (DBED).

The first round of survey requests yielded approximately sixty (60) responses. However, the survey responses were not very informative because (a) they were not representative of the surveyed population due to low response rate and (b) most responses received indicated that they were not operating and not planning to operate BSL-3 facilities within the next 24 months. The second round of survey requests using a more recently validated contact list were slightly more informative as approximately ninety-six (96) responses were received. A further assessment of the responses received revealed that most laboratory facilities (approximately 90%) do not, nor do they plan in the next 24 months to operate a high containment laboratory. Two (2) responded that they currently do not operate but they do plan on operating a BSL-3 laboratory in the next 24 months. Of the ten responses that indicated that they do currently operate a high containment laboratory, most indicated that they have a Biosafety Plan in place. The respondents that indicated they operate high containment facilities also provided data to support that some level of regulatory oversight of their operations was already in place, such as the Maryland Biological Agents Registry (BAR) program, NIH or Clinical Laboratory Improvement Amendments (CLIA).

The inability to accurately enumerate and assess the operational scope of these high containment laboratories in Maryland obscures the ability to fully examine and assess any potential risks that could result from any lack of regulatory oversight of these facilities.

II. Summary and Review of Existing Regulations and Guidelines

The 2009 U.S. GAO Report (see <http://www.gao.gov/products/GAO-09-574>) and the 2007 Report of the Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight (see <http://www.phe.gov/Preparedness/legal/boards/biosafetytaskforce/Pages/default.aspx>) are excellent overviews of the regulatory environment in the United States. This section will rely primarily on these reports as references.

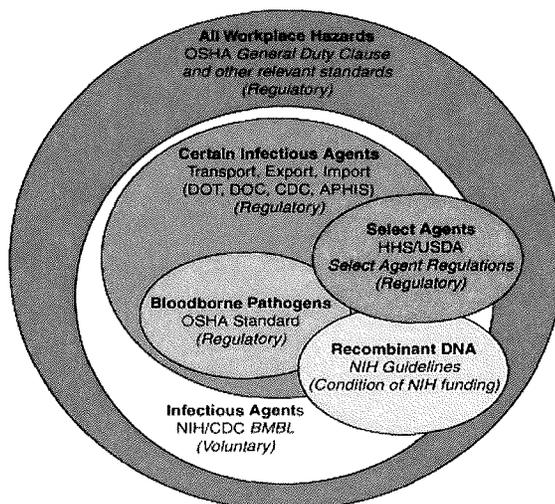
Current Framework for Biosafety and Biocontainment Oversight

Multiple, complementary and sometimes overlapping biosafety and biocontainment oversight requirements exist within the Federal government; among Federal, State, and municipal governments; and among various levels of government and individual research institutions. The redundancy in the biosafety and biocontainment framework helps ensure the protection of laboratory workers, public health, animal and plant health, the food supply, and the environment from exposure to hazardous biological agents and toxins used in laboratories. The individual elements of biosafety and biocontainment oversight vary, depending on the facilities and activities that require oversight, and the numerous government agencies and local institutions that play roles in particular oversight activities.¹⁸

How the Current System of Biosafety and Biocontainment Oversight Works: Federal Regulations and Enforcements Entities

Various Federal departments and agencies share responsibility for oversight of high and maximum containment research activities and facilities, depending on the nature of the research, as depicted in Figure 1. Certain Federal entities also are responsible for ensuring compliance with biosafety/biocontainment regulations, standards, and other requirements.

Figure 1: Biosafety/ Biocontainment Regulations, Standards, and Guidelines Pertinent to High and Maximum Containment Research



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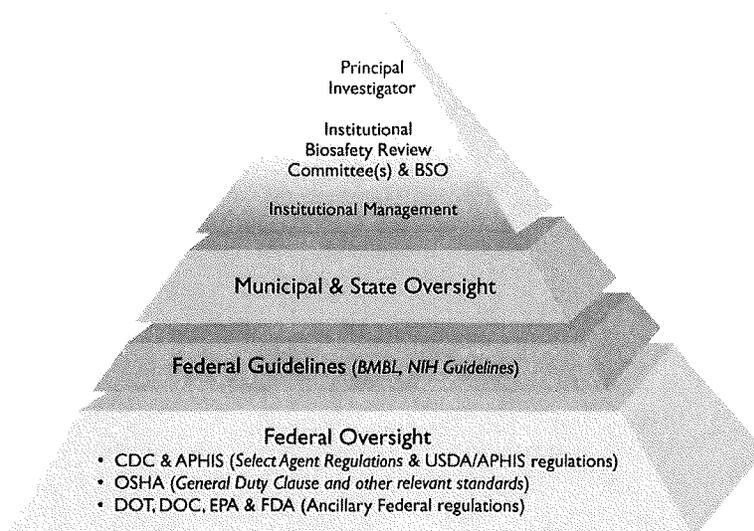
The federal entities that have primary regulatory oversight responsibility for high and maximum containment research facilities are the Department of Labor (DOL), Occupational Safety and Health Administration (OSHA), Health and Human Services Centers for Disease Control and Prevention (CDC), the United States Department of Agriculture Animal and Plant Health Inspection Service (APHIS) and Centers for Medicare & Medicaid Services Clinical Laboratory Improvement Amendments (CLIA). The biosafety/biocontainment regulations, requirement, and guidelines most relevant to research involving biohazards at high and maximum containment laboratories are the OSHA *General Duty Clause*, *Bloodborne Pathogens Standard*, and *Personal Protective Equipment Standards*; HHS and USDA *Select Agent Regulations*; USDA regulations that require permits for work with highly infectious microorganisms and bio-hazardous materials; CDC regulations that require a permit for the import of any infectious agent known or suspected to cause disease in humans. The Federal guidelines that pertain most directly to research activities in high containment laboratories are the *Biosafety in Microbiological and Biomedical Laboratories*, fifth edition, a guidance document developed by CDC and the NIH, and *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*, which require compliance by any entity funded by NIH for recombinant DNA (rDNA) research. Other Federal agencies also require compliance with the *NIH Guidelines* as a term and condition of their own funding. Compliance with *NIH Guidelines* is required by Federal Regulations, Title 7, Code of Federal Regulations (CFR) Part 340 *et seq.*²⁰

Some of these regulations and guidelines focus on protecting humans from exposure to biological hazards; others are designed to ensure the effective containment of high consequence agricultural agents that could endanger animal or plant health, or threaten the food supply; and some address both human and agricultural pathogens. OSHA regulations help ensure the safety of workers in all workplaces, including personnel in high and maximum

containment research laboratories. The *BMBL* is designed specifically to protect laboratory workers from exposure to infectious organisms and certain biological toxins that pose various levels of risk to human health. Through its permitting system, USDA/APHIS regulates the transport and use of agents that are hazardous to agriculture (certain livestock, poultry, and crop pathogens). APHIS also inspects facilities to ensure they provide adequate containment of regulated agriculture agents. The HHS and USDA *Select Agent Regulations* cover both human and agricultural pathogens and toxins, and provide for Federal oversight of laboratories that possess, use, or transfer any agent or toxin on a designated list of select agents that pose significant risks to public health or agriculture.²¹

The approach to biosafety and biocontainment oversight rests on a foundation of Federal regulations and guidelines, is provided at multiple levels, but is implemented locally, i.e., at individual research institutions, beginning with the Principal Investigators (PIs) who are responsible for the safety activities in their laboratories. This pyramid of oversight is illustrated in Figure 2.²²

Biosafety and Biocontainment Oversight



Federal Regulations

OSHA Regulations and Standards to Ensure Workplace Safety

OSHA is responsible for the general oversight of workplace safety in the U.S. OSHA regulations are based on the *Occupational Safety and Health Act of 1970 (OSH Act)*, 29 U.S.C 651 *et seq.* (for more information about OSHA regulations, see <http://www.osha.gov>). High and maximum containment research laboratories throughout the U.S.

are expected to provide safe and healthful working conditions and must comply with the OSH Act and applicable OSHA regulations.²³

OSHA General Duty Clause (29 U.S.C. 654(a)(1)) allows OSHA to enforce workplace safety and health in all occupational settings covered by the *OSH Act*, particularly work environments in which OSHA does not have regulations addressing a specific occupational hazard. This provision applies to all high and maximum containment research facilities that work with biological agents and toxins. If serious hazards are identified, the *General Duty Clause* requires that the employer implement feasible measures such as engineering and work practice controls and the use of personal protection equipment to abate the hazard. Feasible abatement measures may also include hazard assessment, exposure monitoring, medical surveillance and training.²⁴

Bloodborne Pathogens Standard (29 CFR, 1910, 1030). The OSHA *Bloodborne Pathogen Standard* mandates that employers protect workers from infection with human bloodborne pathogens in the workplace. The standard requires that information and training must be provided before the employee begins work where occupational exposure to bloodborne pathogens may be present, annually thereafter, and before the employee is offered hepatitis B vaccinations.²⁵

Personal Protective Equipment Standards (29 CFR 1910 subpart I). The OSHA Personal Protective Equipment Standards (PPE Standards) require that employers provide and pay for PPE and ensure that it is used wherever "hazards of processes or environment...[are] encountered in a manner capable of causing injury in the function of any part of the body through absorption, inhalation or physical contact" (29 CFR 1910.132(a)).²⁶

Additional Relevant Standards. Provisions in the following standards also help eliminate or minimize exposure to biological agents and toxins:²⁷

- Occupational Exposure to Hazardous Chemicals in Laboratories (Laboratory Standard) 29 CFR 1910.1450
- Hazardous Waste Operations and Emergency Responses 29 CFR 1910.120
- Sanitation 29 CFR 1910.141

- Medical Services and First Aid 29 CFR 1910.151
- Access to Employee Exposure and Medical Records 29 CFR 1910.1020
- Hazard Communication 29 CFR 1910.1200
- Retention of DOT Markings, Placards and Labels 29 CFR 1910.1201

Failure to comply with applicable OSHA regulations and standards may result in issuance of citations that carry monetary penalties for all serious workplace hazards.

CDC and APHIS Select Agent Regulations

The CDC and APHIS, under the *Select Agent Regulations*, regulates and requires registration of all entities that possess, use and transfer select agents and toxins that have the potential to pose a severe threat to health and safety, or animal and plant health and plant products.

An entity applying to possess, use or transfer a select agent must identify a single point of contact to represent that entity, the Responsible Official (RO), who must ensure compliance with the requirements of the Select Agent Regulations. The RO, and any other individuals within the entity who need access to select agents or toxins, must undergo a Security Risk Assessment (SRA) conducted by the Federal Bureau of Investigation (FBI), Criminal Justice and Information Services (CJIS), and the Department of Justice (DOJ).²⁸

All entities registered to possess, use or transfer select agents or toxins are required to develop and/or implement (1) a written security plan sufficient to safeguard the select agent or toxin from unauthorized access, theft, or loss; (2) a written biosafety plan to safeguard against the release of select agents or toxins; (3) a written incident-response plan that must include response procedures for any hazards associated with the select agent or toxin. Additionally, all entities that possess, use, or transfer select agents or toxins are required to provide safety and security training for all individuals who work with or visit areas containing select agents and toxins that addresses the needs of the individual, the type of work the person will do, and the risks posed by the select agents or toxins. Entities must also notify the Select Agent Program upon discovery of a theft, loss or release of a select agent or toxin.²⁹

Any entity possessing, using or transferring select agents or toxins is subject to inspection prior to issuance of a Certificate of Registration to verify that the facility has accurately represented the information it has submitted to the Select Agent Program, and has in place the procedures and processes necessary to ensure compliance with *Select Agent Regulations*.³⁰ The *Select Agent Regulations* also permit unannounced inspections (42 CFR 73.18, 7 CFR 331.18, and 9 CFR 121.18). CDC and APHIS also use specific checklists to guide their inspections. CDC and APHIS developed these checklists from the select agent regulations and the BMBL, and they are available at www.selectagents.gov.

Other Regulations Affecting High and Maximum Containment Research Facilities

HHS/CDC: *Import Permit Regulations (42 CFR 71.54)*. The CDC Etiologic Agent Import Permit Program (EAIPP) regulates the importation of etiological agents, hosts, and vectors of human disease (e.g., microorganisms and microbial toxins capable of causing disease in humans, bats, arthropods, snails and non-human primate trophies) into the U.S. When such materials are imported in the U.S., they must be accompanied by a permit issued by the CDC Director. The EAIPP works in conjunction with the CDC Division of Global Migration and Quarantine, which is charged with preventing the introduction, transmission, or spread of communicable diseases from foreign countries into the U.S., and the U.S. Customs and Border Protection agency ensures that all agents requiring an etiologic permit have been issued before importation into the U.S. Any person violating any provision of 42 CFR Part 71 shall be subject to a fine or to imprisonment.³¹

USDA/APHIS: *Plant Protection Act (7 U.S.C. 7701 et. seq.)*. Under the authority of the Plant Protection Act, the USDA Secretary may prohibit or restrict the importation, entry, exportation, or movement in interstate commerce of any plant, plant product, biological control organism, noxious weed, article (including baggage, mail, garbage, earth, stone, and quarry products) or means of conveyance if such actions are necessary to prevent the introduction into or the dissemination within the U.S. of a plant pest or noxious weed. Permits for "Organism and Soil"/ "Plants and Plant Products" are granted through the Plant Protection and Quarantine (PPQ) Service.³²

USDA/APHIS: *Animal Health Protection Act (AHPA) (7 U.S.C. 8301 et. seq.)* and related legislation. The AHPA authorizes the Secretary of Agriculture to prohibit or restrict the importation or movement in interstate commerce of any animal, article, or means of conveyance if the Secretary determines that the prohibition or restriction is necessary to prevent the introduction or dissemination of any pest or disease of livestock into or within the U.S. Permits under this act are granted through the Veterinary Services Centers.³³

Department of Transportation: Transportation of Etiological Agents: Infectious substances and materials (i.e. microorganisms or other agents which can cause disease in human or animals) known or suspected to contain them are regulated as Division 6.2 (infectious) hazardous materials by DOT, under the Pipeline and Hazardous Materials Safety Administration (PHMSA) Hazardous Materials Regulations (HMR; 49 CFR 171-180) (for more information about PHMSA, an agency of DOT, see <http://www.phmsa.dot.gov/home>). The packaging and shipment of an infectious substance must conform to all applicable HMR requirements when offered for transportation by aircraft, motor vehicle, railcar or vessel. DOT regulations also require (1) that the shipping entity have a security plan to prevent unauthorized access; (2) that the package be designed to withstand rough handling and other forces experienced in transportation; (3) that the package be appropriately labeled to enable transport workers and emergency response personnel to identify correctly the material and respond efficiently in an emergency situation; and lastly (4) shippers and carrier be trained about these regulations so they can properly prepare shipments, and recognize and respond to the risks posed by these materials. There are civil penalties for inadvertent, non-willful violations; and higher penalties for willful violations of the HMR that lead to death or serious injury (49 CFR 107.333 and 107.335).³⁴

EPA Regulations Governing Antimicrobial Pesticides. The Environmental Protection Agency (EPA) regulates the sale, distribution and use of antimicrobial pesticides under the authority of the *Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)* (7 U.S.C. 136 and 40 CFR 150-189). Antimicrobial pesticides (e.g. sanitizers, disinfectants, and sterilants), which are used to decontaminate laboratories for a wide range of pathogens, are registered (licensed) by EPA in accordance with the requirements of *FIFRA*. Safety and efficacy-related data, as well as correct product labeling, are submitted to EPA as part of an application for registration. Before registering an antimicrobial pesticide, EPA must accept the data and labeling and conclude that the product will not cause "unreasonable adverse effects" when used in accordance with label directions and commonly recognized practices. Product users are required to follow all safety precautions and use directions on the labeling. Not following the label may be considered "use inconsistent with the labeling," which is a potential violation of *FIFRA*.³⁵

CMS: Clinical Laboratory Improvement Amendments (CLIA). The Department of Health and Human Services, Centers for Medicare & Medicaid Services (CMS) (42 CFR 493 *et. seq.*) regulates all laboratory testing (except research) performed on humans in the U.S. through CLIA. The purpose of the CLIA program is to ensure quality laboratory testing. Regulatory requirements of CLIA include verification of performance specifications, calibration verification, risk management procedures, quality control procedures, proficiency

testing, and personnel competency. Laboratories accredited through CLIA are compliant with best practices of quality assurance. Criminal penalties for violating CLIA regulations include a year's imprisonment as well as civil monetary penalties of \$10,000 per day and exclusion from federal programs.³⁶

Federal Biosafety Guidelines and Requirements

Biosafety in Microbiological and Biomedical Laboratories (BMBL)

For decades, the BMBL has been the code of practice, authoritative reference, and de facto standard of operation for U.S. laboratory biosafety and biocontainment principles, practices and procedures. The *BMBL* is published jointly by CDC and NIH. Periodic updates to the BMBL are made to refine guidance based on new knowledge and experiences, address new risks to laboratory workers and public health. Adhering to the BMBL is a requirement for entities in receipt of funding from the Department of Defense (DOD) or HHS Public Health Service (PHS) agencies, including NIH, for certain classes of research grants and contracts. The *Select Agent Regulations* cite the BMBL but do not require adherence to it, although many Federal agencies require their own laboratory personnel to comply with the BMBL and recognize it as the minimal performance standard.¹⁰

The guidelines in the BMBL are designed to ensure the safety and security of working with biological agents, the protection of laboratory workers and the public, and the containment of biological hazards within the laboratory. The BMBL emphasizes individual, site, and procedure-specific risk assessment; the use of personal protective equipment, administrative and managerial controls; and facility safeguards to mitigate risk to laboratory incidents through supervisory and agency-level chains of communication. It includes agent summary statements that provide information about biosafety requirement for infectious agents depending on the type of work being performed. The guidance in the BMBL applies to biomedical research laboratories and research animal facilities, although the general principles of biosafety and biocontainment apply to many other kinds of scientific facilities.³⁸

NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

The NIH Guidelines specify scientifically based principles for the review and containment of organisms employed in rDNA research. They also articulate the responsibilities of institutions, investigators, Institutional Biosafety Committees (IBC), Biological Safety Officers (BSO), the NIH Recombinant DNA Advisory Committee, and the NIH Director in the oversight of rDNA research. Strict adherence to the NIH

Guidelines is a required condition of receiving NIH funding for rDNA research. An investigator or institution that disregards them is placing the institution at risk of special oversight or loss of NIH funding. And while the guidelines are only mandatory for those institutions receiving NIH funding, they have become generally accepted standards for safe working practices in the area of research and are followed voluntarily by many companies and other institutions not otherwise subject to NIH requirements.³⁹

- Institutional Biosafety Committees

NIH Guidelines requires the establishment of an IBC at all institutions that sponsor or conduct recombinant DNA research and are funded by NIH. The purpose of IBC's is to ensure the health and safety of all personnel working with biohazardous substances by (1) ensuring that potentially hazardous biological agents are adequately contained; (2) providing monitoring of potentially hazardous experiments; (3) communicating with the public regarding experimental plans that have the potential to be hazardous; and (4) interacting with researchers and healthcare providers regarding hazardous protocols and procedures.⁴⁰

- Biological Safety Officers

The duties of BSOs are formally defined under the NIH Guidelines. BSOs are responsible for the oversight of research with rDNA agents, and their presence is mandated for institutions conducting large-scale rDNA research or rDNA work in BSL-3 or BSL-4 laboratories.⁴¹

State and Municipal Oversight of Biosafety and Biocontainment Laboratories

In addition to the federal regulations and agencies that provide oversight of biocontainment laboratories, several States and municipalities have adopted additional regulatory structures for laboratories that operate within their jurisdictions.

Maryland Regulations (C.O.M.A.R. 10.10.11, Biological Agents Registry Program Authority: Health-General Article, §§17-601—17-605, Annotated Code of Maryland)

The State of Maryland established the Biological Agent Registration (BAR) Program, which is managed by the Office of Laboratory Emergency Preparedness and Response at the Maryland Department of Health and Mental Hygiene (OLEPR) because the APHIS/CDC Select Agent Program was unwilling or unable

(HHS has designated select agent information as "Sensitive But Unclassified (SBU)" information) to provide DHMH with information ("persons" or "entities" that possess, maintain, or transfer select agents within the State). The BAR Program is almost identical to the Federal Select Agent Program, with the addition of the local Emergency Management Director (EMD), local Health Officer, and the OLEPR being informed of entities that possess, maintain, transfer, or receive biological agents in the State. The EMD and OLEPR also receive copies of the entities Biological Agent Incident Response Plan and any information exchanged with the federal Select Agent Program. The purpose of the BAR Program is to help protect the people of Maryland against the potential threat of biological terrorism by establishing a program to register persons that possess, maintain, transfer, or receive biological agents in the State and utilize that information for planning and response.

Annual State registration is required for facilities working with select agents or high consequence livestock pathogens and toxins, including genetically modified organisms or genetic element encoding toxins, toxin subunits, or disease-associated factors from an organism listed as a select agent or overlap select agent. The BAR Program has the authority to conduct on-site inspections,⁴² but since the federal Select Agent Program already conducts inspections, the BAR Program accepts their results (Certificate of Registration). However, the BAR Program does review the entity's Biological Agent Incident Response Plan and verify that the entity has sent it to the local EMD.^{43, 44} Maryland State law reporting requirements include the identification of biological agents and their location (laboratory and storage), containment/biosafety level, verification of receipt or transfer of biological agents, responsible officials' contact information, and a biological incident response plan.

Other Existing Maryland Regulations DHMH Office of Health Care Quality (OHCQ)

DHMH OHCQ provides licensure oversight⁴⁵ and acts as an agent for CLIA.⁴⁶ These clinical laboratories test human specimens to provide medical treatment. In some cases these laboratories may be testing for the presence of organisms that are select agents. Also, a small number of research laboratories working with select agents may report out results for treatment of patients and may obtain a state license and a CLIA certificate which results in oversight by OHCQ. Oversight for state licensure and CLIA is focused on the quality of the laboratory testing and not on the safety and security of the community, which is the focus of this review on biocontainment laboratories. The OHCQ also regulates forensic laboratories for state licensure.⁴⁷ Regulations for forensic laboratories focus on chain of custody and the quality of the testing. Current laboratory surveyor staff employed by the OHCQ in the clinical and forensic laboratory programs lack training or education to oversee a biocontainment laboratory regulatory system. Despite the lack of

specific expertise in the area of biocontainment laboratory oversight, the OHCQ, has more than twenty years experience in regulating laboratories. OHCQ understands the various processes that must be implemented to establish regulatory oversight.

State of Connecticut⁴⁸

The State of Connecticut per the Public Health Code (Regulation 19a-36-A25 to 19a-36-A35) requires all laboratories including laboratories that handle infectious agents to biannually register with State Department of Public Health and be subject to initial and periodic state biosafety inspections. Laboratories working with infectious agents in the State of Connecticut need to disclose the biosafety level the facility operates at, purpose of use, and information about the biosafety equipment and practices at the facility to be registered. The laboratories also must notify the Department of Public Health when laboratory directors are changed and when the facility moves to a new location.

City of Cambridge, MA (Cambridge Biosafety Regulation – promulgated October 16, 2009)⁴⁹

The Cambridge Biosafety Regulation identified the Cambridge Biosafety Committee (created and defined by Chapter 8.20.030 of the Cambridge Municipal Code) as having the duties and responsibilities of carrying-out the Regulation. Guidelines were established utilizing the NIH Guidelines and the BMBL, 5th Edition to establish policies, procedures and criteria for “persons” proposing to use biological agents (high-containment BSL-3 and maximum containment BSL-4 agents) in the City. Persons would be required to obtain a permit to use these biological agents and must renew it annually. There are also requirements of medical surveillance programs, protection against rodents and insects, requirements for reporting violations, and requirements for reporting exposures or accidental releases. There is a requirement for the establishment of an IBC to oversee the implementation of the regulation.

This regulation requires an application process to include health and safety plans and training, floor plans, site visits, and maintenance of records. There is also a requirement for a decommissioning process (decontamination) prior to the cessation of use for a permit to be terminated. The regulation also requires fees to be paid based on the size of the facility to be regulated and allows for financial penalties for violations of the regulations.

City of Boston, MA (Boston Public Health Commission (BPHC), Biological Laboratory Regulations, adopted September 19, 2006)⁵⁰

The biological laboratory regulations were adopted in 2006 and require anyone operating or planning to operate a Biosafety Level 3 or Level 4 biological research laboratory within the City of Boston to apply for and receive a permit to operate from the Boston Public Health Commission. The regulations require that the Boston Public Health Commission have complete knowledge of the research that is being performed at the facility and cannot declare their activities secret or classified. Laboratories that do not disclose their activities would have their permit revoked. After an extensive application process, the application is reviewed by the Boston Biosafety Committee and several City agencies including, police, fire, emergency medical service, and the inspection service. The facility is then inspected for initial compliance and at least annually after the permit is issued. Additionally, the permitted containment laboratory may be inspected at any time in response to an incident or a safety concern. In addition to inspections, each permitted lab must submit an annual report to the BPHC that includes copies of all minutes from the IBC meetings and a complete roster of the IBC's members, a report on any quality assurance and quality improvement efforts during the year, and updated information from the permit application. The institution must also notify the BPHC each time a new project or program in the lab is approved by the IBC at least thirty days before the project begins. Finally, the regulations require the immediate reporting of any laboratory incidents. Any of these may trigger an inspection or other investigative action. Fines can be imposed and revocation of the permit can occur for non-compliance.

Regulation of Biocontainment Laboratories in Other Countries

Finally, other nations have adopted or are in process of adopting regulations for biocontainment that are operating within their borders.

Canada:

In 2009, the Human Pathogens and Toxins Act (HPTA) was authorized as a frame work to regulate biocontainment laboratories in Canada.⁵¹ When fully enacted the HPTA will function as a National Registry and require licensing of all institutions that process and work with WHO Risk Group 2 through 4 agents. It requires that licensees be identified by name and location, provide a facility description and an inventory of all agents used. There are provisions in the HPTA for Criminal penalties for noncompliance.

Recently in June of 2013, the Public Health Agency of Canada (PHAC) and the Canadian Food Inspection Agency (CFIA) have also developed joint Canadian Biosafety Standards and Guidelines (CBSG).⁵² These

standards and guidelines were designed to help streamline various biosafety practices into a single set of standards and guidelines for laboratory researchers and workers in facilities possessing, handling, storing or using such pathogens and toxins that are regulated by both PHAC and the CFIA.

United Kingdom:

In the United Kingdom (U.K.), new high-containment laboratories that work with human, animal, or genetically modified (GM) pathogens need to notify the U.K. regulator (the Health and Safety Executive (HSE) and receive either consent (for GM human pathogens) or license (for animal pathogens) before they commence their activities. Like Canada the U.K. is planning to implement a single regulatory framework for human animal and genetically modified pathogens that will include a legal requirement for duty holders to consult the regulatory authority prior to construction.⁵³

Industry Standards in the U.S. Affecting Some High Containment and Maximum Containment Laboratories

Medical Laboratories—Requirements for Safety, ISO 15190, Geneva, International Organization for Standardization, 2003.

The ISO standard (referred to as ISO 15190) provides the framework for management of a safety program as well as specific requirements for working safely in laboratories, including facilities in which workers handle infectious agents, chemicals, or radionuclides. Information concerning management of the laboratory safety program includes laboratory design, staffing, audits, reporting, training, safe laboratory practices, fire precautions, emergency evacuations, management of spills, waste management, and transport of specimens.⁵⁴

Protection of Laboratory Workers from Occupationally Acquired Infections, Clinical and Laboratory Standards Institute (CLSI), M29-3A; Approved Guidelines, Third Edition.

The CLSI guidelines provide general safety protocols for clinical laboratories as well as functions and practices that can apply to other healthcare workplaces. These guidelines also outline research and animal facilities where exposures to infectious agents might occur. Specific guidelines are additionally provided for the safe handling of highly infectious agents that pose a risk for life threatening diseases (e.g., hepatitis B and C viruses, and HIV) and other infectious agents that can be transmitted by blood, aerosol, droplets, and

body fluids. Other areas addressed include waste management, special precautions regarding procedures and equipment, and managing laboratory accidents.⁵⁵

Final Thoughts

These previous two sections offer an overview of biosafety and biocontainment practices and oversight, describe the importance of research that requires high and maximum containment, and explain the extensive biosafety and biocontainment oversight framework, with emphasis on oversight mechanisms used by individual research institutions and the Federal Government. These entities, together with oversight entities at the State and municipal levels, form a multi-layered system of complementary and sometimes overlapping biosafety and biocontainment oversight measures.

III. Facility Design and Construction Standards for Biosafety Laboratories

Background

The purpose of biohazard containment is to physically contain infectious agents and toxins that present potential or actual risk to humans, animals, and/or plants either directly or indirectly. The design and construction of the bio-containment facilities accounts for secondary containment barriers that contribute to the laboratory workers safety and provide a barrier to prevent the accidental release of infectious agents into the environment surrounding the facility.

The recommended secondary barrier(s) will depend on the risk of transmission of specific agents. Secondary barriers in bio-containment laboratories may include separation of the laboratory work area from public access, availability of a decontamination facility (e.g., autoclave), and hand washing facilities. At BSL-3 laboratories, where the risk for aerosol exposures to infectious agents is high, multiple secondary barriers are needed to prevent the agents from escaping into the environment. Secondary barriers in BSL-3 laboratories include specialized ventilation systems to ensure directional airflow, air treatment systems to decontaminate or remove agents from exhaust air, controlled access zones, airlocks at laboratory entrances, or separate buildings or modules to isolate the laboratory.⁵⁶

In the U.S., the design for biocontainment laboratories are drawn heavily from the recommendations in the BMBL and the NIH Design Requirements Manual for Biomedical Laboratories and Animal Research Facilities (DRM) (<http://orf.od.nih.gov/PoliciesAndGuidelines/BiomedicalandAnimalResearchFacilitiesDesignPoliciesandGuidelines/Documents/Design%20Requirements%20Manual/NIH%20Design%20Requirements%20Manual%20ver%205-13.pdf>). The DRM prescribes minimum performance design standards for NIH owned and leased new buildings and renovated facilities and ensures that those facilities will be of the highest quality to support biomedical research.⁵⁷ Other federal entities also are required to follow the DRM when constructing new biocontainment facilities. Design engineers for laboratories may also refer to specific ventilation recommendations as found in the Laboratory Design Guide published by the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE).⁵⁸

Facility Considerations

The planning and designing of biocontainment facilities requires the implementation of best practices and a review of methods for decontamination and waste management. However, facility considerations that warrant

particular focus include (1) Directional Airflow; (2) HEPA exhaust; (3) Materials for Construction; (3) Finishes; and (4) Security.

Directional Air Flow

Directional airflow in biocontainment facilities provides protection to staff in the event that there has been a release of an infectious substance into the immediate environment (workspace or secondary containment area). Therefore, the appropriate design for a facility under construction or retrofitting must involve a careful review of the laboratories structural configuration and the protocols and procedures designed for the facility. Federal regulations regarding directional airflow vary. Although the BMBL does not reference the use of a particular ventilation system, the NIH and the USDA provide parameters for airflow differential (the amount of air that should consistently flow from areas of least hazard potential toward areas of greatest hazardous potential).^{59, 60}

High-Efficiency-Particulate-Air (HEPA) Exhaust

HEPA exhaust filters provide superior filtration of airborne particles traveling through air ducts. For BSL-3 laboratories, the BMBL recommends that the laboratory exhaust air should be HEPA filtered if it cannot be dispersed away from occupied areas and from building air intake locations.⁶¹

Materials for Construction

Materials must ensure compliance with specifications set by the engineers and architects charged with construction. Biocontainment laboratories should also be constructed with materials that will provide sufficient primary and secondary containment to support all applications that will be conducted in the lab.

Security

Currently, there are no federal requirements for the development of biosecurity programs (protection of microbial agents from loss, theft or intentional misuse). However, the BMBL provides principles and guidelines for laboratory security management. According to the BMBL, limiting access to facilities and research materials can be accomplished by developing sound risk management practices based on site specific assessments.⁶²

Finishes

The level and quality in which biocontainment laboratories are constructed are based on the design, high-end materials and equipment. The interior design for a facility should be developed as a complete and coordinated part of the building design, expressing both the functional and aesthetic needs of the user. Finish materials are what the user and visitor sees, touches and walks on and therefore produce an immediate impact. All interior components and their related construction details, finishes and products, shall be based on the anticipated use, engineering limitations, fire and other health and safety requirements, applicable codes and regulations, life cycle costs, housekeeping and maintenance costs, durability, aseptic characteristics, and the appropriateness of the particular material or combination of materials to the environment being created.⁶³

Good Manufacturing Practice (GMP)

Good Manufacturing Practice (GMP) regulations have been established by the Federal Food, Drug and Cosmetic Act under the authority of the U.S. Food and Drug Administration. GMP regulations require manufacturing processes to be clearly defined and controlled. Manufacturing processes must also be validated to ensure consistency and compliance with relevant specifications. Consequently, areas addressed by GMP regulations include recordkeeping, equipment verification, process validation and guidelines to minimize the introduction of airborne contaminants into the various laboratory areas.⁶⁴

Association for Assessment and Accreditation of Laboratory of Animal Care International /Vivarium

The Association for Assessment and Accreditation of Laboratory of Animal Care International (AAALAC) monitors the care and well-being of animals who are subjects in animal research.⁶⁵ AAALAC is a private non-profit organization dedicated to promoting the humane treatment of animals used in science. Through a voluntary accreditation and assessment program, institutions volunteer to participate in an effort to achieve optimal efficiency in animal care and use.⁶⁶ AAALAC also has an array of available resources to assist with the design and construction of animal facilities.

The housing of animals in vivariums is critical for maintaining healthy environments for all species in animal research programs. Vivariums are enclosed areas used for raising and maintaining animals and plants under observation.⁶⁷ A part of the ecosystem for both plants and animals are simulated and the environmental conditions are continuously controlled.⁶⁸

Required General Containment Guidelines for BSL-3 Laboratories

With specific reference to BSL-3 laboratories, the facilities must be entirely disconnected from places open to the public and from corridors used by laboratory personnel who do not work in the facility. All work must be conducted in primary containment equipment. Hand washing stations, that are foot, elbow, or automatically operated, are mandatory. All laboratory clothing must be decontaminated prior to being washed. Cages must be washed then rinsed at 180 degrees or autoclaved or thoroughly decontaminated before cleaning. Appropriate cautionary signs must be present. The biosafety area must be in a separate building or in an isolated zone within the building.⁶⁹

All BSL-3 areas require a Class II or Class III biological safety cabinet (BSC). The HEPA filtered exhaust air from Class II, Type A BSC's may be returned to the laboratory environment or discharged to the outside. Class II, Types B1 and B2, and Class III cabinets typically need external exhaust fans that can be directly attached to a building's exhaust system. All treated exhaust from these cabinets must be discharged outside.⁷⁰ The air balance of the rooms and BSCs must not interfere with the room supply and exhaust systems nor by the exhaust systems of these cabinets.⁷¹ The location of all cabinets must allow them to be easily maintained, decontaminated, and certified.⁷²

A method for decontaminating infectious waste is required. Bench tops must be impervious to water, resistant to acids, alkalis, organic solvents and moderate heat. Interior surfaces of walls, floors, and ceilings must be monolithic, resistant to liquids and chemicals, with all penetrations sealed.⁷³ All drains in the floors must contain traps filled with chemical disinfectant. All windows should be closed and sealed. Facility doors must be self-closing.⁷⁴ Ducted exhaust ventilation is also required. Airflow can only go into the containment area with a visual monitoring device. In order to manage ventilation systems, electronic direct digital controls should be used as well as a Building Automation System.⁷⁵

All finishes and penetrations must be sealed and doors must be sealable to allow gaseous biological decontamination in the BSL-3 area.⁷⁶

If part of the biocontainment barrier is formed by the ceiling itself, easily cleanable or easily disposable standard ceilings materials may be used.⁷⁷ Light fixtures should be recessed and sealed to limit dirt deposits and ceiling diffusers should be sealed to control air leaks.⁷⁸

All containment greenhouses must be glazed with double-paned laminated glass. The BSL-3 facility design must include any provisions for dealing with scheduled maintenance or equipment repair problems and should minimize the entrance of non-research personnel into containment spaces for maintenance services.⁷⁹ Compressor monitors or gas supplies that can be isolated should be made accessible from outside the containment space. In that outside containment area, compressed gas cylinders supplying carbon dioxide should be stored, while manifold piping should be used to provide the gases inside the area.⁸⁰ Within the containment space, small individual vacuum pumps with in-line HEPA filters should be used.⁸¹

IV GAPS IN REGULATORY OVERSIGHT

Are there unregulated BSL-3 Laboratories Operating in Maryland?

In spite of the myriad of overlapping federal, state and local regulations and guidance documents no single regulatory agency has specific responsibility for biosafety in all of the high containment laboratories that operate in Maryland. In the biocontainment laboratory survey respondents indicated they operate high containment facilities provided data to support that some regulatory structures were in place, such as CDC/AHPIS Select Agent program, the NIH guidelines or CLIA.

However, it could be possible that a private research foundation laboratory or private biotechnology company operating a BSL-3 Laboratory would not fall under the oversight of regulatory entities listed above. This situation could happen if (1) the laboratory does not receive NIH funding or other sources of federal funding; and (2) it works with BSL-3 level pathogens or toxins that are not on the Select Agents list. What risks would these operations pose to the communities in which they are located via LAIs or accidental releases into the surrounding environment? What would happen after several years of operation these laboratories decide to close their facilities? Which regulatory entity assures that their facilities are properly decontaminated before they are released to a new tenant?

Again the inability to accurately enumerate and assess the operational scope of high containment laboratories operating in Maryland makes it difficult to fully and accurately evaluate any potential risks that could result from any lack of regulatory oversight of these facilities.

Inadequate oversight design

There are inadequate guidelines defining the construction for BSL-3 and BSL-4 laboratories (including ABSL Facilities). While ASHRAE Guidelines, the NIH Construction Guidelines (NIH Design Requirements Manual for Biomedical Laboratories and Animal Research Facilities (DRM or "NIH Design Guidelines)), the BMBL, and the AAALAC Guide do provide guidance, these do not account for the fact that local permitting authorities often do not have the expertise or experience to (1) translate these guidelines to compliance standards, or (2) have adequate experience or even a basis to reject any component of the design.

Educating companies/end-users on the appropriate collaborative approach for the construction/retrofitting of biocontainment laboratories can be challenging. Companies/end-users need to have a clear understanding of what is needed to create up-to-date and certifiable containment environments. Design and construction decisions,

details on space allocation, equipment, materials, potential risk(s) and project costs are a few of the areas that must be defined before outcome expectations can be successfully achieved.

Alternatively, educating local permit offices to sufficiently communicate the requirements for obtaining applicable permits can also present challenges. Permitting requirements at times vary between federal, state and local agencies. Therefore, local permitting offices need to be able to effectively convey (1) the application process for permits; (2) parameters of the permit review process; (3) information regarding inspections; (4) methods used by inspectors to confirm compliance; and (4) ramifications for non-compliance.

Decontamination Safeguards When Laboratory Facilities are Vacated or Repurposed

There are existing regulations pertaining to the decontamination of vacated laboratory facilities for toxic chemicals and radiation hazards. The Workgroup is currently not aware of any regulations that pertain to the decontamination of high containment laboratories working with non-select agents in Maryland.

Chemical Hazards

The Maryland Department of the Environment (MDE) has promulgated regulations that restate the federal Resource Conservation and Recovery Act (RCRA) concerning chemical decontamination procedures upon closure and post-closure of a hazardous waste facility⁸² (for more information on the RCRA please see <http://www.epa.gov/osw/laws-regs/rcrahistory.htm>). Owners and operators of hazardous waste facilities in Maryland are required to submit a written closure plan with their permit application. That closure plan must include:

1. A description of how each hazardous waste management unit at the facility will be closed.
2. An estimate of the maximum inventory of hazardous wastes ever on-site over the active life of the facility and detailed description of the methods to be used during partial closures and final closure, including, but not limited to, methods for removing, transporting, treating, storing, or disposing of all hazardous wastes, and identification of the type or types of the off-site hazardous waste management units to be used, if applicable.
3. A detailed description of the steps needed to remove or decontaminate all hazardous waste residues and contaminated containment system components, equipment, structures, and soils during partial and final

closure, including, but not limited to, procedures for cleaning equipment and removing contaminated soils, methods for sampling and testing surrounding soils, and criteria for determining the extent of decontamination required to satisfy the closure performance standard.

4. A detailed description of other activities necessary during the closure period to ensure that all partial closures and final closure satisfy the closure performance standards.
5. A schedule for closure of each hazardous waste management unit.

The owner or operator of a facility must also notify the Secretary of MDE in writing if and when it intends to follow through with its closure plans.

Radiation Hazards

At the federal level, the Multi-Agency Radiation Survey and Site Investigation Manual (MARSSIM) <http://www.ornl.gov/ptp/PTP%20Library/library/NRC/NUREG/1575.htm> has detailed regulations regarding the decontamination and decommissioning of facilities that have handled radioactive materials.

Biological Hazards

The Maryland BAR Program, as part of its permitting process, requires all high containment laboratories working with select agents to submit a written decontamination plan as part of their permitting process.⁸³ Although individual laboratories have developed internal decontamination and decommissioning procedures for biohazards based on BMBL guidance, no specific State or federal regulations regarding decontamination and decommissioning procedures for high containment laboratories working with non-select agents were identified by the Workgroup.

V. Risk Assessment

Introduction

Biosafety practices and procedures are designed to reduce the exposure of laboratory personnel, the public, agriculture, and the environment to potentially infectious agents and other biological hazards. The key principles of biosafety are risk assessment and containment. The communication of these risks, by not only the BSO and PI, is an important aspect for not only the laboratory workers but also community members. Regardless of containment principles, practices, facilities and guidelines, laboratory infections do occur, suggesting that biosafety procedures or rules are not always effective or complied with – this may be due to training issues (lack of adequate training) of personnel competency.

But, zero risk can only be achieved by shutting down the operation(s), with a concomitant loss of basic research and development aimed towards enhancing the life of people, animals and the environment through development of vaccines and therapeutic modalities. However, risks have been encountered and documented encompassing accidental environmental releases and LAIs (the environmental release of genetically-modified organisms or recombinant organisms will not be considered in this discussion as they are controlled and regulated.)

Pathogens that are handled in BSL-3 containment facilities are those that have the potential to cause serious or lethal disease, and for which preventive measures and effective treatment may be available.⁸⁴ In general, risk to public health could potentially exist if a pathogen is accidentally released during transport, during normal laboratory operations, or after laboratory operations have ceased if the facility is not properly decontaminated and decommissioned. Accidental releases of pathogens could also occur in the event of a natural or man-made disaster. The magnitude of a public health risk from an accidental release of a pathogen depends on several factors including but not limited to the number of people that could become infected, the severity of disease outcomes, and the availability of effective preventive measures and treatment.⁸⁵ There is also a subset of microorganisms that are routinely handled in BSL-2 facilities using BSL-2 work practices, but which under certain circumstances require the use of BSL-3 practices, containment equipment, and facilities where large quantities or high concentrations of cultures are being manipulated, or where there is a high potential for aerosol production.⁸⁶ *Bacillus anthracis*, the etiologic agent of anthrax, is an example of a bacterial pathogen routinely handled at designated BSL-2 facilities, but which requires the use of BSL-3 practices, containment equipment, and facilities where large quantities or high concentrations of cultures are being manipulated, or where there is a high potential for aerosol production.⁸⁷

Non-select agents that are handled under BSL-3 conditions or in BSL-3 laboratories include but are not limited to *Bordetella pertussis*, *Chlamydia psittaci*, *Legionella pneumophila*, *Mycobacterium tuberculosis* complex, *Neisseria meningitides*, *Rickettsia* species, *Salmonella typhi*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, hepatitis B, C, and D viruses, HIV, human herpes viruses, *lymphocytic choriomeningitis* virus, rabies virus, and hantavirus.⁸⁸ Most of these agents are normally handled in BSL-2 facilities. Depending on a risk assessment, these agents are sometimes handled in a BSL-2 facility with BSL-3 work practices, and occasionally in a BSL-3 facility for production level activities. While all of these microorganisms have the potential to be aerosolized and become an inhalation hazard in the laboratory environment, few, if any, pose a significant risk to the surrounding community via an exposed laboratory worker. *Legionella pneumophila*, *Chlamydia psittaci*, *Rickettsia* spp., *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Lymphocytic choriomeningitis* virus, rabies virus, and Hantavirus pose little or no risk of human to human transmission.⁸⁹ For transmission of HIV and hepatitis viruses to occur among humans, there must be close, intimate contact with an infected person, including transmission of blood or other potentially infectious material.⁹⁰ There are vaccines available for hepatitis B, *Salmonella typhi*, *Varicella zoster* virus, *Bordetella pertussis*, and *Neisseria meningitides*.⁹¹ *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides immitis* fungal agents all exist in nature.⁹² Antimicrobial treatments are generally effective at treating human infections of many of these non-select agents.⁹³

Perceived Risks

The general public's concerns about potential accidents at biocontainment laboratories are not completely unmerited because accidents happen, procedures fail or are not followed, equipment breaks, competent people make mistakes. The CDC, scientific journals and the media have reported containment laboratory accidents in the past several years. The community is concerned that there is currently no mechanism for any government entity to know about or respond to the safety performance of unregulated private laboratories. The community's particular concerns are outlined below.

- **Laboratory Acquired Infections (LAIs).** A worker unknowingly exposed to a contagious pathogen, goes home, moves about the community and is not diagnosed for weeks. A community laboratory may find itself also unknowingly performing a culture from the sick worker, on an organism that should only be handled in a high containment setting. Procedures suggest that this could never happen. But it has. There are documented instances of worker illnesses, and some deaths, from laboratory-acquired infections. Fortunately, these infections have not spread to the broader community. But many more labs have opened in recent years, with many more workers.^{94, 95}

- **Insider threat.** This occurred with the 2001 Anthrax letters, with resulting deaths, serious illnesses, trauma and economic consequences for many. The GAO and others consider the "insider threat" to be the single greatest risk associated with the growth of high containment labs in the last ten years. Although, the concepts of biosafety and biosecurity are interrelated complimentary concepts for the purpose of this Workgroup we will be focusing on biosafety issues only. Moreover, biosecurity procedures and protocols that are implemented to thwart insider threats and other criminal activities that could lead to the misappropriation or malevolent misuse of infectious agents from biocontainment laboratories are within the realm of law enforcement which is beyond the stated biosafety purview of the Workgroup.
- **Facility Accident or Major System Failures.** A major seismic event, fire, or tornado could result in failure of the building structure, potentially resulting in a release pathway. Even without major structural damage, the failure of systems relied on for safety, such as the failure of the ventilation system to properly filter or maintain negative pressure control, or the failure of the autoclave system to destroy all pathogens prior to disposal, could result in the release of live pathogens outside of the facility boundary.
- **Transportation risks.** Pathogens are routinely transported between laboratories across our nation's highways. There is always a risk of a transportation related accident, with some potential related risk of an infection to the public. There is also a risk of inadvertently transporting a different, more virulent pathogen than intended or authorized. In 2004 a private BSL-3 Lab in Frederick accidentally mailed live Anthrax to Children's Hospital of Oakland (CA).⁹⁶
- **Risks posed by novel pathogens.** The potential risks cited above can be exacerbated for novel pathogens created by laboratory methods such as rDNA or synthetic biology. Effective treatment may not be available for treating diseases caused by such pathogens.

Documented Risks

The following are examples of LAIs and environmental releases that have occurred in the past:

An accidental release of foot and mouth disease virus (FMD) occurred in the United Kingdom in 2007 at the Institute of Animal Health Laboratory in Pirbright (southwest of London). This was not the first documented release at this facility. FMD is a highly contagious and easily transmissible animal disease that affects cattle, sheep, goats, pigs, and other cloven-hoofed animals and nearly 100 percent of exposed animals become infected. The accidental

release resulted in eight separate outbreaks of FMD on surrounding farms that summer. A likely source of the release was a leaking drain pipe at Pirbright that carried waste from contained areas to an effluent treatment plant. The virus then spread to local farms by contaminated mud splashing onto vehicles that, having unrestricted access to the contaminated area, easily drove on and off the site. The investigations found a failure to properly maintain the site's infrastructure. FMD has no health implications for humans but it can have significant agricultural consequences.⁹⁷

The last cases of smallpox in the world occurred in an outbreak of two cases (one of which was fatal) in Birmingham, United Kingdom in 1978. A medical photographer, Janet Parker, contracted the disease at the University of Birmingham Medical School and died on September 11, 1978. She worked in a darkroom above a laboratory where research on live smallpox viruses was being conducted. The virus(es) most likely spread through a service duct that connected the two floors. A similar exposure occurred in 1966.⁹⁸ It is important to mention that these two viruses, FMD virus and Smallpox virus, are only researched in the U.S. at authorized facilities - FMD virus at the Plum Island Animal Disease Center, near the northeast coast of Long Island in New York state, (operated by the Department of Homeland Security Directorate for Science and Technology) and Smallpox virus at the Centers for Disease Control and Prevention in Atlanta, Georgia. We are not aware of additional documented accidental environmental releases of microorganisms at this time.

Although the profession of microbiology addresses the prevention, treatment and cure of infectious diseases, it can in certain circumstances also be a potentially dangerous discipline for the individuals performing the research.⁹⁹ During the past 150 years, there were many cases of researchers who have died because of their professional activity (e.g., nursing, field work, self-inoculation, and laboratory procedures such as mouth pipetting and use of a syringe or needle) or have come close to death from infection by agents that were the subject of their research.¹⁰⁰ This was a time when the concept of safety, cleanliness and contagion, the transmission of disease from person to person, was in its infancy. Incidents have occurred in microbiological laboratories, clinical laboratories, animal facilities, research and development venues and production (vaccine) installations. It is often difficult to discern whether the incident was a result of a laboratory mishap or was community-acquired. Historical accounts of incidents occurring since the 1850s have been documented.^{101, 102, 103, 104, 105, 106, 107}

Laboratory-acquired infections occurring at research facilities in Maryland have been documented. Rusnak and colleagues conducted a review of 234 persons evaluated for potential laboratory exposures to potential agents of bioterrorism at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick in Frederick from 1989 to 2002. There were only five confirmed laboratory-acquired infections during this period, with the majority of individuals (78%) in this review having received licensed or investigational new drug vaccines before

their exposure.¹⁰⁸ In 2000, a laboratory worker was infected with *Burkholderia mallei*, the causative agent of glanders. The individual did not recall any laboratory mishaps. However, he admitted that on occasion he had handled laboratory equipment containing live *Burkholderia* strains without wearing protective gloves.¹⁰⁹ Six cases of glanders were reported as a laboratory-acquired infection during World War II at Camp Detrick (now Fort Detrick). Some of these cases were attributed to inhalation of infectious aerosols generated by spillages of liquid culture media containing the bacterium. Other cases were reported to have no obvious cause other than the routine handling of the organism (Howe and Miller, 1947).¹¹⁰ Laboratory-acquired infections are not expected to occur frequently in the current lower-risk biodefense research setting because of improvements in biosafety equipment and changes in biosafety policies. The data support the idea that research with these agents should be restricted to laboratories with experience in handling highly hazardous agents and where appropriate safety training and precautions can be implemented.¹¹¹

In late 2003 at a federal research facility near Washington, D.C, an individual was accidentally exposed to *Escherichia coli* O157:H7 through an experiment performed by a technician from another group. Individuals were evaluating the efficacy of various chemical sanitizers on *E. coli* O157:H7-contaminated apple slices. The individual survived this infection in spite of developing hemolytic uremic syndrome with multiple organ failure. The technician working with *E. coli* O157:H7 was new and had received very little relevant training. His supervisor, a food technologist, had no specific training in infectious diseases or microbiology. The research leader of the facility was trained as a plant physiologist.¹¹²

In August 2007, a laboratory worker at a government facility in Maryland unintentionally inoculated a finger with approximately 5 microliters of a solution containing vaccinia virus (VACV), after injection of a research animal. The inoculum contained up to 10,000 plaque forming units (particles) of the virus, which was a recombinant strain of WR VACV. The laboratory worker immersed the wound in a disinfectant containing hypochlorite for a few minutes but did not wash the exposed area immediately. The worker had received a primary VACV vaccination in 2001, but immunization was unsuccessful (i.e., no lesion developed at the site of the vaccination). On the day of the incident, the laboratory worker went to the occupational health clinic and was revaccinated with VACV. Vaccinia immunoglobulin was not administered. When the worker was reevaluated on days 3, 4, and 5 post-vaccination, no evidence of VACV infection was observed at the site of inoculation, and a characteristic lesion developed at the site of vaccination, evidence of successful vaccination.¹¹³

In November 2009, a laboratory worker at a Federal Facility in Maryland developed pneumonia. A *Francisella Tulercisellus* infection was subsequently diagnosed by serology and PCR testing. The worker was given antibiotics and completely recovered. It was determined the worker was occupationally exposed to *Francisella*

Tulercisellus while working within a BSL-3 laboratory and a later internal investigation indicated that a breakdown of biosafety procedures occurred when the worker removed contaminated waste from under the biosafety cabinet (BSC) and placed it in a waste container outside the BSC. Additionally, the worker was unvaccinated and was wearing only a mask rather a powered air purifying respirator which might have prevented the respiratory infection.¹¹⁴

There has been a decrease in incidents and laboratory-acquired infections over the years. This finding undoubtedly reflects an improved awareness of the hazards of working with infectious agents or bio-hazardous materials and placement of a greater emphasis on laboratory safety, through the use of personal protective equipment and robust training. Legislation and guidelines that were introduced over the years have reduced but not eliminated the risk of occupational exposure to infectious or toxin-containing agents. In addition, there have been improvements in laboratory design, such as the use of laminar-flow biological safety cabinets, which provide unidirectional airflow that entraps any aerosolized particles in the airstreams and subsequently into air filters.¹¹⁵ LAIs and environmental releases occurring at private and academic laboratories that do not work with select agents is unknown. This information is not systematically tracked by any entity. Exposures and mishaps at select agent laboratories are tracked by the CDC and APHIS. The CDC issued a summary report on high containment laboratory accidents and exposures at select agent laboratories in January 2013.

The Prevalence of Laboratory Acquired Infections (LAIs) in Maryland

Illnesses resulting from exposure to biological agents that are handled in biocontainment laboratories in Maryland are required to be reported to DHMH epidemiologists by health care providers and medical laboratory directors by statute, Maryland Health-General Code Ann. §18-202, and by regulation, COMAR 10.06.01.03 and 10.06.01.04. For some illnesses and conditions these regulations also obligate the medical laboratories testing diagnostic specimens from the infected patients to submit pathogen isolates and/or clinical materials containing infectious agents to the DHMH Public Health Laboratory for further testing and possible genetic characterization (see COMAR 10.06.01.03 for listing).

However, the prevalence of LAIs in Maryland cannot be readily or systemically determined from these reports because "occupational exposure" is not entered as a separate field into the standardized CDC National Electronic Disease Surveillance System (NEDSS) form that is used to record these illnesses at DHMH. When information regarding occupational exposure is provided in NEDSS it resides in the comments section of the report forms which are not easily searchable. However a small number of sporadic cases of LAIs have been documented in Maryland and, in recent years, were identified through the interview process during case investigations by DHMH epidemiologists or by utilizing molecular testing methods performed at the DHMH Public Health Laboratory that can

link isolates of genetically related pathogens recovered from the infected patient to isolates of the biological agents the individual was exposed to in their laboratory work place. Most of these LAIs involved BSL-2 level pathogens such as enteric bacteria (e.g., Salmonella, Shigella), bloodborne pathogens (e.g. HIV) or vaccinia virus (see above).

Additionally, businesses including laboratories with more than 10 employees in the State are required to annually report occupationally related injuries and illnesses using a OSHA 300 Form to Maryland Occupation Safety and Health (MOSH) in the Department of Labor Licensing and Regulation. Inquiries regarding the historical prevalence of LAIs in Maryland were made by the Workgroup to the MOSH Office of Research and Statistics. The MOSH Office of Research and Statistics indicated that information reported on the OSHA 300 form is not comprehensive or detailed enough to be utilized to reliably track and determine the prevalence of LAIs in Maryland and that their office has no existing statistical compellations of LAIs in the State. According to MOSH, the information reported on the OSHA 300 form is biased toward workplace injuries or chronic work related illness (e.g. repetitive motion conditions) and are not sensitive enough to comprehensively track LAIs because the employee must report the illness to their employer, miss several days of work and then file a workman's compensation claim. Also laboratories with small staffs (<10 employees) would not be compelled to file a report.

Final Findings

The Workgroup was very focused on the perceived versus theoretical risk associated with operating high containment laboratories. Based on the evidence, the Workgroup found that based on the number of incidents over the total person hours when working in high containment laboratories, the risk of LAIs and/or accidental release incidents are relatively low (see Appendix F). However, absent data on the magnitude of under and unregulated BSL-3 facilities, the Workgroup cannot conclusively extrapolate the potential for a singular high consequence release.

VII. OPTIONS

The following are options proposed by the Workgroup over the past year to mitigate potential risks posed by high containment laboratories operating in Maryland. It is to be noted that these options were collaboratively developed. These options do not necessarily represent the opinions of everyone on the Workgroup, but take all of the opinions into consideration. The options focused on regulatory structures, design processes, communication strategies and voluntary self-accreditation.

1) **Permitting Process to Identify and Characterize Biocontainment Laboratories Operating in Maryland**

A possible option was made for a simple, inexpensive mandatory permitting or registration process to be enacted to identify biocontainment laboratories operating in Maryland. The permit applications (renewed yearly or every 2 years) would gather information regarding the location, size and containment level (BSL or ABSL) the facility operates at and what non-select agent pathogens or biohazardous materials the facility is working with or plans to work with. The application would also determine if the biocontainment laboratories are already regulated (e.g. CDC/APHIS Select Agent Program, HHS-CLIA, and NIH Guidelines) or if they are accredited by a recognized entity (e.g., ABSA – see <http://www.absa.org/aiahclap.html>).

This information would give regulators an improved understanding of the number of unregulated or under-regulated biocontainment laboratories that are operating in Maryland and provide a more reliable estimate of the potential risks these facilities could pose to the communities where they are located. The permit application information would allow the State to focus its regulatory efforts on the unregulated biocontainment laboratories that are identified. Unregulated high containment laboratories could be compelled to seek accreditation or be subject to routine State inspections. Fines could also be imposed if facilities fail to obtain permits and adverse events occur at the unregistered facility that harm public health, agriculture or the environment.

2) **Required Registration of Biocontainment Laboratories and Reporting of LAIs**

A possible option was made for a State-level mechanism(s) to devise protocols (regulations) based on current best practices (i.e., BMBL, 5th edition and NIH Guidelines) and to consider a registration process of all laboratories - whether they are clinical or research laboratories. Such a process is currently in place with the HHS and/or by the USDA for those laboratories working with select agents (those agents having the potential to pose a severe threat to public health and safety). Registration should briefly include the type of work being conducted at the laboratory and the agents being worked with. Similar to the federal select agent

program, registration would be required every three years. During registration process the facility would be required to provide copies of their (1) Security Plans; (2) Incident Response Plans; (3) Safety Plans; (4) Communication Plans (Notifications); (5) Training Plans; and (6) Maintenance Records of their operating biocontainment laboratories. Registration should also encompass a requirement to report any LAI within 48 hours of occurrence to local health personnel. The impact on the registering laboratory would be minimal - registering and reporting of an LAI can be done electronically and with minimal administrative burden. For the State of Maryland, the negative impact of a registration and reporting mechanism is financial - there would be a need for a State-level office to administer the registration process, maintain a real-time database, and monitor each LAI. There would be a need for sufficient qualified personnel to review all submitted documents and to physically inspect the facilities. If a facility is already regulated (e.g., CDC/APHIS Select Agent Program, HHS-CLIA, NIH Guidelines) or if they are accredited by a recognized entity (e.g., ABSA), receipt and acceptance of inspection reports from the regulatory agencies would be acceptable. This will provide the State with the minimum oversight needed to monitor the activities of these labs. This will also enable the State to inform the public that there are systems in place to oversee the operation of these facilities. Summary data should be available for perusal by anyone, and should be published and provided annually to community political officials and through local newspapers. Additionally, implement measures which would allow the permitting/licensing entity to fine the laboratory for non-compliance, or in extreme cases revoke permit/licensure of the laboratory, will encourage strict adherence to BMBL and NIH Guidelines. The positive impact of a registration process would be real-time notification of laboratories operating within Maryland and a mechanism to ensure the public that the laboratories are operating safely.

3) Establishing a Construction Permitting/licensing Process for Biocontainment Laboratories and Coordination between Regulatory Entities

A possible option was made to implement a construction permitting/licensing process for biocontainment facilities. A permitting process would include a prescriptive design process that would focus on HVAC (heating, ventilation and air conditioning) and engineering controls as a public safety assurance. It may also be worthwhile to request access to a database which contains information on Certificates of Occupancy (building permits). This may be a useful tool in determining whether there is ongoing biosafety laboratory activity in certain commercial and/or residential areas throughout Maryland. Additionally, implementing measures which would allow the permitting/licensing entity to fine the laboratory for non-compliance, or in extreme cases revoke permit/licensure of the laboratory, may also encourage strict adherence to BMBL and NIH guidelines. The Workgroup recognized that improved coordination between federal, state and local regulatory authorities (i.e. NIH/CDC, DHMH/MDE and County/City agencies) would provide more effective

oversight regarding the total number of biocontainment laboratories operating in the State of Maryland. More efficient coordination would also allow these agencies to better determine whether biocontainment laboratories are operating in accordance with their design and construction guidelines. Even oversight of the processes for commissioning, decommissioning and decontamination can be more efficiently managed.

4) Develop Risk Communication Strategies between the Operators of Biocontainment Laboratories, State Regulators and the Community

Risk communication is important as it will involve an exchange of information between the State, biocontainment facilities and the public regarding the assessment of risk and how unknown risks can be more appropriately addressed. Risk communication is the process of informing people about potential hazards to their person, property, or community.¹¹⁶ Biosafety professionals or facility spokespersons must promote their safety program both to individuals internal to the facility (i.e., management and line workers) and those external to the facility (i.e., investors and stakeholders, regulatory agencies, the media and the public). When communicating with the public, one must be prepared, address only one focal point, and be honest, open and credible. One must treat everyone like an adult as they may not have the technical skills of someone with years of experience. Speak clearly and with compassion. A general rule for crisis communication with the public and press when making a statement, is to consider the 3, 9 and 27 rule: no more than three messages or major thoughts, no longer than 9 seconds (more than that media can cut and paste as they please), and no longer than 27 words. This will enable the message to be simple, clear and to the point.

For expansion or modification of a facility, it is helpful if the community and those of surrounding townships have a long history of acceptance of the risks associated with cutting-edge scientific research. The foundation of acceptance is entrenched in awareness about the procedures established to mitigate these research risks. Community acceptance of research activities must continue to be nurtured through communication, education and partnership. One way this community acceptance can be achieved is through formation of a community liaison committee to include members of the communities, political representatives, and facility staff. The committee should meet periodically throughout the year as well as before and throughout any proposed expansion or modification(s) of the facility. Annually, an open house and tour should be provided to the committee members to motivate interest and excitement about the technologies and science being developed at the facility. The scientific community will have the opportunity to speak proudly of their research activities to educate and gain public support and acceptance of their work. These opportunities inspire our youth to become conversant in and enthusiastic about the benefits of basic

science. An added benefit to an annual briefing would be to offer training and observance of emergency exercises to community fire, police and first responders. An important resource of the facility is its personnel. They are the most critical element of the safety and security programs at the facility and serve as ambassadors. Of utmost importance is to show that personnel are well trained, competent and comfortable in their work, and understand that their safety and security are of vital importance. A policy regarding the reporting of incidents and/or concerns must be in place, and the reporting of such events must be treated seriously. The focus is corrective rather than punitive - that is, what can we learn from these incidents and how can we prevent them in the future? These numbers must be shared with the community to provide evidence of compliance with national best practices guidelines and local and national regulations. Such a thought process and safety climate tends to cultivate and sustain a working relationship among community members and research and support staff through continuous interaction among investigators, technicians, engineers and safety officers. The outcome is that research activities involving pathogenic microorganisms and toxins reveal knowledge and lead to products that improve the economy, environment and well-being of people worldwide.¹¹⁷

5) **Voluntary Accreditation of Biocontainment Laboratories**

In response to federal government reports and public concerns about insufficient oversight of high-containment BSL-3 laboratories, the American Biological Safety Association (ABSA) developed a voluntary accreditation program for BSL-3 Laboratories that are not subject to regulation by the Select Agent Program (for more information on the ABSA, please see <http://www.absa.org/>). ABSA based its accreditation criteria on recognized guidelines including the BMBL and the NIH Guidelines to assess the technical aspects of an institution's biosafety programs and practices.¹¹⁸

This biosafety accreditation program is modeled from other successful U.S. Accreditation programs such as The College of American Pathologists (CAP) and the Accreditation of Laboratory Animal Care International (AAALAC). Maryland Forensic (Crime) Laboratories can also be regulated by accreditation by an organization recognized by DHMH OHCQ in lieu of inspections by the State.^{119, 120}

Considerations of these Options

Decisions related to the role of Maryland in the oversight of biocontainment laboratories must balance multiple factors. These factors include the following:

- The industry may view a burdensome regulatory process as a barrier to doing business in Maryland and may elect to relocate or move to another state where the industry is not regulated. The regulatory structure should balance the safety of the public with the ability of these laboratories to be successful in Maryland.
- The public wants to know that these laboratories operate in a safe and secure manner and that there is a mechanism to know where these laboratories are located and hold them accountable for safety while in operation and after vacating a laboratory site.
- The security of the laboratories' information. Unlike other laboratories regulated by the State, security must be a consideration for biocontainment laboratories.
- The impact on the Maryland State Government and the regulatory agencies' budgets. Since both OHCC and the Laboratories Administration do not have staff with expertise in the area of biocontainment laboratories, a plan to provide staffing and additional resources for development of a regulatory program would be required by the agency. Depending on the scope of the regulatory oversight the budget may need to include administrative staff, an engineer, pathologists, industrial hygienists and laboratory scientist surveyors as well as scientific and environmental equipment to evaluate systems. The fiscal note for a regulatory program could be significant.
- High containment laboratories are self-policing. Implementation of voluntary self-accreditation in lieu of inspections may be a feasible option.

It should be noted that it is difficult to develop sensible fiscal notes and impact statements for the oversight of biocontainment laboratories when there is no good estimate of the number of laboratories that may need to be regulated.

VIII. IMPACT

Introduction

The following outlines the perceived impact(s) of the proposed options to address gaps that are specific to the stakeholders.

Impacts on Academic Research Laboratories

Academic research laboratories already have institutional requirements of approval. Moreover, many of these facilities receive federal dollars to conduct their research activities. This mandates them to follow federal regulations accordingly (refer to Section II for overview of Federal regulations). The impact of providing additional regulatory oversight to these facilities may be redundant and/or over-regulation. This could result in deterring and/or stifling the research activities performed at high containment laboratories.

Impacts on Industry: Biotechnology, pharmaceutical and other commercial non-clinical laboratories

High containment laboratories are often found in companies where Small Business Innovation Research (SBIRs), Small Business Technology Transfer (STTRs) or other federally funded research is being carried out. Under such circumstances, federal safety standards must be met to continue to be eligible for funding. In addition, individuals handling infectious organisms or samples from infected patients are motivated by self-interest to adhere to safe practices in the laboratory. As a general rule, however, when industries are confronted with additional regulations, they will assess the impact (cost/personnel) of compliance with the regulations. Depending on the degree of regulation and the cost of compliance, companies may review their decision to remain in a location.

Existing businesses which may not have the infrastructure to support increased regulation may decide to move. New businesses which complete a state by state competitive analysis regarding "the cost of doing business," may simply eliminate that state from their choices. Therefore, the regulatory climate will clearly be one of the business factors that are assessed in any company's decision to remain. Essentially, increasing regulation in any area of business practice has the potential to have a negative impact on the local economy for that business sector.

Approaches and Impact of Regulatory Oversight

Several approaches could be considered when determining if Maryland should oversee biocontainment laboratories. The following identifies just some of the approaches Maryland could take in how it regulates these laboratories and the impact it will have if such an approach is selected.

Approach 1

No oversight of biocontainment laboratories. The current status would not change. BSL- 4 Laboratories in Maryland, but which are located on federal property, would continue to operate under the current federal oversight programs. There would be no impact to state agencies or to the industry. The public's desire for oversight would not be met.

Approach 2

Require state registration or licensure of the laboratories through DHMH or another state agency. This would provide an accounting of the location of all BSL-3 laboratories not working with select agents. This would also provide an accounting of the infectious agents and biohazardous materials that are used or stored at these facilities.

Mandated bonding of the laboratory could provide a source of funds for clean up after closure, relocation or an accident, if needed to minimize exposure of the public to select agents. The laboratory would be required to notify the Department if it relocates, moves or closes. Statute and regulations would focus on the licensing registration process, limiting risk through a requirement for a bond and sanctions for failure to comply.

This approach would require the establishment of a regulatory unit within the State to administer the licensing/registration program that includes administrative and qualified support staff and the establishment of database and other support systems. Statutory language and regulations would focus on the licensing/ registration process, limiting risk through a requirement for a bond and sanctions for failure to comply. While there will be fiscal requirements to support this program, the cost would be the least costly of the various regulatory approaches.

As the workgroup has been unable to identify the exact number of laboratories that may be considered under this mandate, Approach 2 may be a good intermediate step to pursue in an effort to determine the scope of this industry and potentially what risks these biocontainment laboratories pose to the communities in which they are located. Registration or licensure with minimal requirements could serve as a means to identify the number of laboratories, their locations, the select agents used without a negative impact on this growing industry in the state of Maryland.

The public's concerns regarding biocontainment laboratories were largely focused on the lack of information regarding the numbers and the locations of these laboratories and the potential impact of a natural disaster or weather related incident on the laboratories and the surrounding communities. The public is clearly concerned that

local and state government does not know addresses for these laboratories and the infectious agents and biohazardous materials being handled. Approach 2 provides many of the requirements desired by the public. However, the registration procedure as described here would definitely have a major impact on the registering laboratory because reporting LAIs is only one of the many requirements. This is basically the same as the federal select agent program and presents a major burden on facilities.

Approach 3

In addition to Approach 2, the state could require the licensed or registered laboratories to report adverse events such as employee public exposures, injuries, accidents, spills, etc. to the Department. The Department would have authority to review the event either administratively or through an inspection. This approach would allow the State to have oversight of possible serious adverse events without developing an ongoing full inspection program. The oversight would be incident or complaint driven.

In addition, to the staffing required for Approach 2, the State would be required to establish a survey program capable of reviewing the incidents. Records reviewed by the workgroup did not identify patterns of significant adverse events related to biocontainment laboratories. Under Approach 3, some investigations of incidents could be reviewed by specially trained laboratory surveyors who have worked in biocontainment laboratories but other incidents may require technical consultation from experts in engineering, pathology, epidemiology and industrial hygiene. The numbers of laboratories and variability of incidents may not justify the employment of full-time State employees for these investigations. The state agency should consider contractual arrangements for provision of this expertise. The cost of hiring consultants could result in a significant fiscal impact on the state regulatory agency.

Reporting and activities required in the oversight of incidents will increase the financial and regulatory burden on the laboratories. However, this approach is a reasonable compromise to meeting the desires of the public for accountability yet will not be overly burdensome to the laboratory.

Approach 4

In addition to Approach 2 and 3 above, the laboratories would be subject to inspection and review by the Department for quality and safety. This approach would establish a regulatory process for the biocontainment laboratories including periodic inspections for licensure in addition to the incident reporting function identified in Approach 3. If the regulatory framework for clinical laboratories was used as a model for regulatory oversight, a biannual survey with follow up surveys and submission of corrective action for deficient practices would be employed to ascertain compliance with the regulations. As there may be construction and air handling concerns, a plans review

and pre-operational survey may be required to verify compliance with structural and engineering standards applicable to the safe handling of select agents.

As there are no units within DHMH with the required expertise, the Department would be required to establish a new program with staff knowledgeable in engineering, pathology, and industrial hygiene. Fiscal notes prepared for Senate Bill 758 DHMH-Containment Laboratories Oversight during the 2012 General Assembly session by the Laboratory Administration and OHCQ addressed the staffing and other budgetary considerations believed to be needed to regulate and inspect biocontainment laboratories that included inspections, plans reviews and pre-operational surveys. This approach is labor intensive and will be an expensive regulatory process due to the required expertise of the staff. The state would be likely to encounter some difficulties in recruiting and retaining individuals with the level of education and experience required to administer this regulatory program as the salaries may not be competitive with the private sector. Failure to employ a survey team with the needed level of expertise would result in a superficial survey process. This approach will be the most difficult and expensive for State regulatory agencies to absorb.

Approach 4 provides the public with the confidence that the State will be regularly investigating and holding the laboratories accountable to safe practices.

Approach 4 will also be the most cumbersome and burdensome to the industry and academia. The exact impact on the industry cannot be determined, but physical plant, documentation and staffing requirements imposed through regulations can result in additional costs to the laboratories. Therefore it could be considered a barrier to the establishment of new laboratories as well as a financial barrier for those laboratories currently located in Maryland.

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Acronyms

ABSA	American Biological Safety Association
ADA	Americans with Disabilities
AAALAC	Association for Assessment and Accreditation of Laboratory of Animal Care International
ABSL	Animal Biosafety Level
APHIS	Agriculture Animal and Plant Health Inspection Services
ASHRAE	American Society of Heating, Refrigerating and Air-Condition Engineers
BAR	Maryland Biological Agents Registry Program
BMBL	Biosafety in Microbiological and Biomedical Laboratories
BSAT	Biological Select Agent or Toxin
BSL	Biosafety Level
BSO	Biological Safety Officer
CDC	Centers for Disease Control and Prevention
CJIS	Criminal Justice and Information Services
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical and Laboratory Standards Institute
CMS	Centers for Medicare and Medicaid Services
DBED	Maryland Department of Business Economic Development
DHMH	Maryland Department of Health and Mental Hygiene
DOC	Department of Commerce
DOD	Department of Defense
DOJ	Department of Justice
DOL	Department of Labor
DOT	Department of Transportation
DRM	NIH Design Requirements Manual for Biomedical Laboratories and Animal Research Facilities
DSAT	Division of Select Agent and Toxins
EAIPP	Etiologic Agent Import Permit Program
EMD	Emergency Management Director
EPA	Environmental Protection Agency
FBI	Federal Bureau of Investigations
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FMD	Foot and Mouth Disease

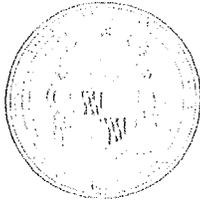
GAO	Government Accountability Office
HEPA	High-Efficiency-Particulate-Air
HHS	Department of Health and Human Services
HHS PHS	Public Health Services
HMR	Hazardous Materials Regulations
HPTA	Canada Human Pathogens and Toxins Act
IBC	Institutional Biosafety Committee
ISO	International Organization for Standardization
LAI	Laboratory Acquired Infection
MDE	Maryland Department of the Environment
MOSH	Maryland Occupational Safety and Health (MOSH)
NEDSS	National Electronic Disease Surveillance System
NFPA	National Fire Protection Association
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIH Guidelines	NIH Guidelines for Research Involving Recombinant DNA Molecules
OHCQ	Maryland Department of Health and Mental Hygiene-Office of Health Care Quality
OLEPR	Laboratories Administration's Office of Laboratory Emergency Preparedness and Response
OSHA	Occupational Safety and Health Administration
PHMSA	Pipeline and Hazardous Materials Safety Administration
PI	Principle Investigator
PPE	Personal Protective Equipment Standards
rDNA	Recombinant DNA
RO	Responsible Official
RPSO	Research Programs Safety Officer
SAP	Select Agent Program
SRA	Security Risk Assessment
USDA	United States Department of Agriculture
WHO	World Health Organization

Appendices

Appendix A

THOMAS M. MIDDLETON
CHAIR

JOHN C. ASHLE
VICE CHAIR



ROB GARAGIOLA
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CATHERINE E. PUGH

THE SENATE OF MARYLAND
FINANCE COMMITTEE
May 1, 2012

Received

MAY - 2 2012

Department of Health
and Mental Hygiene

The Honorable Joshua M. Sharfstein, Secretary
Department of Health and Mental Hygiene
201 W. Preston Street
Baltimore, Maryland 21201

Dear Secretary Sharfstein:

During the 2012 session, the Senate Finance Committee considered Senate Bill 758, Department of Health and Mental Hygiene – Containment Laboratories – Oversight. The bill would have established a Containment Laboratory Oversight Division in the department. The division was intended to be the only State entity that oversees and regulates containment labs in Maryland to protect the health and safety of the workers, the public, and the environment from harmful biological agents. During the bill hearing all parties who testified, including the sponsor, agreed that, rather than passing a detailed regulatory bill, the issue should be studied during the interim to develop effective and coherent policies that would govern specified containment laboratories.

The department's testimony included amendments that would have required the department to convene a workgroup, including all relevant stakeholders, to study the "health and safety risks of containment laboratories in the State and to identify any existing gaps in regulatory oversight of these laboratories." In lieu of a legislative mandate, I would encourage the department to convene the workgroup as envisioned in your suggested amendments to Senate Bill 758. We look forward to hearing the final findings and recommendations of the workgroup sometime before June 2013. In addition, it is possible that Senate Bill 758 may be re-introduced during the 2013 session. Therefore, I would appreciate an update of the workgroup's activities before December 15, 2012. Thank you for your attention to this important matter.

Very truly yours,

Handwritten signature of Thomas McLain Middleton.
Thomas McLain Middleton

TMM/DAS/ncs

cc: Senator Ronald N. Young
Members, Senate Finance Committee

Appendix B

WORKGROUP FOR BIOCONTAINMENT LABORATORIES OVERSIGHT

Name	Title	Affiliation
Barnhart, MPH, Jennifer	Deputy Director, Laboratories Administration	Department of Health and Mental Hygiene
Britz, Ph.D., Judy	Director	Maryland Biotechnology Center
Callihan, Ph.D., Don	Staff Scientist and Biosafety Officer	BD Diagnostics System
Campbell, MS, Cristina	Compliance Hygienist	Maryland Department of Labor, Licensing and Regulation of Occupational Safety and Health
Costello, EMBA, Judith N.	Deputy Director	Maryland Biotechnology Center
Hawley, Ph.D., Robert	Private Bio-Safety Consultant	Independent Contractor
Hohenhaus, M.D., Guy	State Veterinarian	Maryland Department of Agriculture
Issac, DVM, Freeda E.	Director for Organisms, Vectors and Select Agents	USDA: Animal and Plant Health Inspection Service
Jaegar, Ph.D., James J.	Assistant Director	University of Maryland- Environmental Health and Safety
Kaye, BA, David	Vice Chair	The City of Frederick Maryland Containment Lab Community Advisory Committee
Loll, Kim	First Alternate Representative	The City of Frederick Maryland Containment Lab Community Advisory Committee
Morland, MSA, MS, Melissa A.	Assistant Director and Biosafety Officer	University of Maryland- Environmental Health and Safety
Myers, Ph.D., Robert A.	Director, Laboratories Administration Chair, Workgroup for Biocontainment Oversight	Department of Health and Mental Hygiene
Nguyen, BA, Cindy	Paralegal	Department of Health and Mental Hygiene
Pekosz, Ph.D., Andrew S.	Professor	Johns Hopkins University- Bloomberg School of Public Health
Peterson, CBSP, Janet S.	Assistant Director and Biosafety Officer	University of Maryland
Scurry, JD, Renee	Administrator	Department of Health and Mental Hygiene
Svrjcek, BA, James	Chief, Office of Laboratory Preparedness & Response	Department of Health and Mental Hygiene
Unal, MS, MBA, Onur	Manager, BioEntrepreneur Resources Program	Maryland Biotechnology Center
Webster, RS, Renee	Assistant Director for Hospitals, Laboratories, and Patient Safety	Office of Health Care Quality
Willis, BA, Elizabeth	Chair	The City of Frederick Maryland Containment Lab Community Advisory Committee

Appendix C

HHS AND USDA SELECT AGENTS AND TOXINS
7 CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73

HHS SELECT AGENTS AND TOXINS

Abrin
 Botulinum neurotoxins*
 Botulinum neurotoxin producing species of *Clostridium**
 Conotoxins (Short, paralytic alpha conotoxins
 containing the following amino acid
 sequence X₁CCX₂PACGX₃X₄X₅X₆CX₇)
Coxiella burnetii
 Crimean-Congo haemorrhagic fever virus
 Diacetoxyscirpenol
 Eastern Equine Encephalitis virus¹
 Ebola virus*
*Francisella tularensis**
 Lassa fever virus
 Lujjo virus
 Marburg virus*
 Monkeypox virus¹
 Reconstructed replication competent forms of the 1918
 pandemic influenza virus containing any portion of the
 coding regions of all eight gene segments
 (Reconstructed 1918 Influenza virus)
 Ricin
Rickettsia prowazekii
 SARS-associated coronavirus (SARS-CoV)
 Saxitoxin
South American Haemorrhagic Fever viruses:
 Chapare
 Guanarito
 Junin
 Machupo
 Sabia
 Staphylococcal enterotoxins A,B,C,D,E subtypes
 T-2 toxin
 Tetrodotoxin
Tick-borne encephalitis complex (flavi) viruses:
 Far Eastern subtype
 Siberian subtype
 Kyasanur Forest disease virus
 Omsk hemorrhagic fever virus
 Variola major virus (Smallpox virus)*
 Variola minor virus (Alastrim)*
*Yersinia pestis**

OVERLAP SELECT AGENTS AND TOXINS

*Bacillus anthracis**
Bacillus anthracis Pasteur strain
Brucella abortus
Brucella melitensis
Brucella suis
*Burkholderia mallei**
*Burkholderia pseudomallei**
 Hendra virus
 Nipah virus
 Rift Valley fever virus
 Venezuelan equine encephalitis virus¹

USDA SELECT AGENTS AND TOXINS

African horse sickness virus
 African swine fever virus
 Avian influenza virus¹
 Classical swine fever virus
 Foot-and-mouth disease virus*
 Goat pox virus
 Lumpy skin disease virus
*Mycoplasma capricolum*¹
*Mycoplasma mycoides*¹
 Newcastle disease virus^{1,2}
 Peste des petits ruminants virus
 Rinderpest virus*
 Sheep pox virus
 Swine vesicular disease virus

**USDA PLANT PROTECTION AND QUARANTINE
 (PPQ) SELECT AGENTS AND TOXINS**

Peronosclerospora philippinensis (*Peronosclerospora*
sacchari)
Phoma glycinicola (formerly *Pyrenochaeta glycinis*)
Ralstonia solanacearum
Rathayibacter toxicus
Sclerophthora rayssiae
Synchytrium endobioticum
Xanthomonas oryzae

*Denotes Tier 1 Agent

¹ Select agents that meet any of the following criteria are excluded from the requirements of this part: Any low pathogenic strains of avian influenza virus, South American genotype of eastern equine encephalitis virus, west African clade of Monkeypox viruses, any strain of Newcastle disease virus which does not meet the criteria for virulent Newcastle disease virus, all subspecies *Mycoplasma capricolum* except subspecies *capripneumoniae* (contagious caprine pleuropneumonia), all subspecies *Mycoplasma mycoides* except subspecies *mycoides* small colony (Mmm SC) (contagious bovine pleuropneumonia), any subtypes of Venezuelan equine encephalitis virus except for Subtypes IAB or IC, and Vesicular stomatitis virus (exotic); Indiana subtypes VSV-IN2, VSV-IN3, provided that the individual or entity can verify that the agent is within the exclusion category.

² A virulent Newcastle disease virus (avian paramyxovirus serotype 1) has an intracerebral pathogenicity index in day-old chicks (*Gallus gallus*) of 0.7 or greater or has an amino acid sequence at the fusion (F) protein cleavage site that is consistent with virulent strains of Newcastle disease virus. A failure to detect a cleavage site that is consistent with virulent strains does not confirm the absence of a virulent virus.

Appendix D

Table 2. Summary of Recommended Biosafety Levels for Infectious Agents

BSL	Agents	Practices	Primary Barriers and Safety Equipment	Facilities (Secondary Barriers)
1	Not known to consistently cause diseases in healthy adults	Standard microbiological practices	<ul style="list-style-type: none"> ■ No primary barriers required. ■ PPE: laboratory coats and gloves; eye, face protection, as needed 	Laboratory bench and sink required
2	<ul style="list-style-type: none"> ■ Agents associated with human disease ■ Routes of transmission include percutaneous injury, ingestion, mucous membrane exposure 	BSL-1 practice plus: <ul style="list-style-type: none"> ■ Limited access ■ Biohazard warning signs ■ "Sharps" precautions ■ Biosafety manual defining any needed waste decontamination or medical surveillance policies 	Primary barriers: <ul style="list-style-type: none"> ■ BSCs or other physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials ■ PPE: Laboratory coats, gloves, face and eye protection, as needed 	BSL-1 plus: <ul style="list-style-type: none"> ■ Autoclave available
3	Indigenous or exotic agents that may cause serious or potentially lethal disease through the inhalation route of exposure	BSL-2 practice plus: <ul style="list-style-type: none"> ■ Controlled access ■ Decontamination of all waste ■ Decontamination of laboratory clothing before laundering 	Primary barriers: <ul style="list-style-type: none"> ■ BSCs or other physical containment devices used for all open manipulations of agents ■ PPE: Protective laboratory clothing, gloves, face, eye and respiratory protection, as needed 	BSL-2 plus: <ul style="list-style-type: none"> ■ Physical separation from access corridors ■ Self-closing, double-door access ■ Exhausted air not recirculated ■ Negative airflow into laboratory ■ Entry through airlock or anteroom ■ Hand washing sink near laboratory exit
4	<ul style="list-style-type: none"> ■ Dangerous/exotic agents which post high individual risk of aerosol-transmitted laboratory infections that are frequently fatal, for which there are no vaccines or treatments ■ Agents with a close or identical antigenic relationship to an agent requiring BSL-4 until data are available to redesignate the level ■ Related agents with unknown risk of transmission 	BSL-3 practices plus: <ul style="list-style-type: none"> ■ Clothing change before entering ■ Shower on exit ■ All material decontaminated on exit from facility 	Primary barriers: <ul style="list-style-type: none"> ■ All procedures conducted in Class III BSCs or Class I or II BSCs in combination with full-body, air-supplied, positive pressure suit 	BSL-3 plus: <ul style="list-style-type: none"> ■ Separate building or isolated zone ■ Dedicated supply and exhaust, vacuum, and decontamination systems ■ Other requirements outlined in the text

Appendix E

Maryland Department of Health and Mental Hygiene
Voluntary Survey of High Containment Laboratory Activities



Please complete the following questionnaire in 30 days if your facility operates or plans to operate a high containment laboratory within 24 months (BSL-3/ABSL-3/BSL-3 Ag*). Type or print in black or blue ink. We thank you for your participation.

Completed questionnaires can be returned via e-mail, surface mail, or fax (**ONE method only**):

E-mail: cindy.nguyen@maryland.gov or sent by surface mail to:

Surface Mail: Attn: Cindy Nguyen, Biocontainment Laboratories Survey, Laboratories Administration, Department of Health and Mental Hygiene, 201 W. Preston Street, Baltimore, MD 21201

FAX: Attn: Cindy Nguyen, Biocontainment Laboratories Survey, 410-333-5403

***Definitions:**

Biosafety Level 3 (BSL-3) containment is applicable to clinical, diagnostic, teaching, research or production facilities in which work is done with indigenous or exotic agents that may cause serious or potentially lethal disease as a result of exposure by the inhalation route.¹

Animal Biosafety Lab 3 (ABSL-3) are used for laboratories that work with animals infected with indigenous or exotic agents.

Biosafety Lab -3 Agricultural (BSL-3 Ag) is used to describe laboratories where studies are conducted employing large agricultural animals.

¹ "Survey for Determining the Location, Capacity, and Status of Existing and Operating BSL-3 Laboratory Facilities within the United States," *Constella Health Sciences- Center for Health Research Laboratory Sciences Division* (2005 Jun 2). <http://dhmh.maryland.gov/laboratories/containment/Documents/NIAID%20BSL3%20Survey%202005.pdf>

SECTION 1 – FACILITY STATISTICAL INFORMATION

Answer the following questions by marking "X" in the appropriate box.

1. Are you a facility that contains a BSL-3/ABSL-3 laboratory? YES NO
2. If the answer to question No. 1 is "yes," then do you have a biosafety plan? YES NO
3. If the answer to question No. 1 is "no," then are you planning to build a BSL-3/ABSL-3 laboratory in the next twenty-four months? YES NO

If the response to both questions 1&3 is NO, there is no need to complete questions 4 - 12. Please complete Sections 2 and 3, and return the completed questionnaire by a method indicated above.

4. How many square feet of BSL-3/ABSL-3 space does your facility contain? _____ Not applicable
5. How many square feet of BSL-3/ABSL-3 space does your facility plan to build? _____ Not applicable
6. Are you registered in the Maryland Biological Agents Registry (BAR) program? YES NO
7. Do you receive National Institutes of Health (NIH) funding? YES NO
8. Do you receive Department of Defense (DOD) funding? YES NO
9. Are you a Clinical Laboratory Improvement Amendment (CLIA) regulated laboratory? YES NO
10. Do you receive United States Department of Agriculture (USDA) funding? YES NO
11. Do you work with select agents (as defined in 42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121)? YES NO
12. Do you work with other pathogenic organisms (non-select agent)? YES NO

List non-select agent worked with in your facility:

- | | |
|--|---|
| <input type="checkbox"/> <i>Bordetella pertussis</i> | <input type="checkbox"/> Hepatitis C Virus |
| <input type="checkbox"/> <i>Chlamydia psittaci</i> (avian origin) | <input type="checkbox"/> Hepatitis D Virus |
| <input type="checkbox"/> <i>C. trachomatis</i> LGV serovars | <input type="checkbox"/> Human Herpes Viruses |
| <input type="checkbox"/> <i>Chlamydia</i> spp. (non-LGV) | <input type="checkbox"/> Human and Simian Immunodeficiency Viruses |
| <input type="checkbox"/> <i>Legionella pneumophila</i> | <input type="checkbox"/> Lymphocytic Choriomeningitis Virus (LCV) |
| <input type="checkbox"/> <i>Mycobacterium tuberculosis</i> complex | <input type="checkbox"/> Rabies virus |
| <input type="checkbox"/> <i>Neisseria meningitidis</i> | <input type="checkbox"/> e Arbo- and hemorrhagic fever viruses (please specify) _____ |
| <input type="checkbox"/> <i>Rickettsia</i> species | <input type="checkbox"/> <i>Histoplasma capsulatum</i> |
| <input type="checkbox"/> <i>Salmonella typhi</i> | <input type="checkbox"/> Hantaviruses |
| <input type="checkbox"/> <i>Blastomyces dermatitidis</i> | <input type="checkbox"/> Hepatitis B Virus |
| <input type="checkbox"/> <i>Coccidioides immitis</i> | |

SECTION 2 – FACILITY INFORMATION

Record the correct information in the space provided for each item.

Facility Name:	
Street Name:	
Mailing Address:	
City:	
State:	
Zip Code:	
County:	

Main Phone Number:	
Main Fax Number	
SECTION 3 – SIGNATURES	
Form completed by (name/ title):	
Signature:	

Appendix F

Risk of Infection in the General Population vs. Risk of a Laboratory Acquired-Infection in Microbiologists of the Same Relative age

	Risk for general population /100 000	Risk for microbiologists /100 000
<i>Brucella species</i>	0.08	641
<i>Clostridium difficile</i>	8	0.2
<i>Coccidioides immitis</i>	12	13.7
<i>Neisseria meningitidis</i>	0.62	25.3
<i>Salmonella spp.</i>	17.9	1.5
<i>Shigella spp.</i>	6.6	6.6

Reference: Ellen Jo Baron and J. Michael Miller "Bacterial and fungal infections among diagnostic laboratory workers: evaluating the risks" *Diagnostic Microbiology and Infectious Disease* March 2008 60(3):241-6³