Standard ANSI Z9.14: Testing and performance verification methodologies for ventilation systems for Biological Safety Level 3 (BSL-3) and animal Biological Safety Level 3 (ABSL-3) facilities

Abstract. The American Industrial Hygiene Association (AIHA) and the American National Standards Institute (ANSI) are developing a national standard titled ''Testing and performance verification methodologies for ventilation systems for Biological Safety Level 3(BSL-3) and animal Biological Safety Level 3 (ABSL-3) laboratories'' known as ANSI/AIHA Z9.14. The ANSI Z9.14 standard will focus on performance verification of engineering controls related specifically to ventilation system features of BSL-3/ABSL-3 facilities. Currently the design of these facilities is largely guided by the criteria defined in successive versions of the Biosafety in Microbiological and Biomedical Laboratories (BMBL),[1] while facilities funded by the National Institutes of Health (NIH) follow BMBL as well as the NIH Design Requirements Manual (DRM).[2] Among professionals such as architects, engineers, contractors, commissioning agents and owners who are asked to specify or perform tests for performance of ventilation systems in high containment facilities, there is a consensus that there is no comprehensive methodology based on a risk assessment of each individual facility. An extensive literature review was conducted to determine if there are any regulations, standards or guidance available that provide a ''methodology'' to verify that the ventilation systems in such facilities are performing appropriately for the current or potential future use. This 'Gap and Needs Analysis' provides evidence that there is no single resource for a comprehensive testing methodology that can be used uniformly from one facility to another to verify that the ventilation systems in such facilities are performing appropriately. ANSI Z9.14 can provide one component of a more extensive graduated, risk-based approach to reaching containment goals appropriate to the risk of the agent and the laboratory activity.

By Farhad Memarzadeh, Lou DiBerardinis

OVERVIEW

Over 1356[3] BSL-3/ABSL-3 laboratories and animal facilities have been constructed in the United States. Their design has been largely guided by the criteria defined in successive versions of the Biosafety in Microbiological and Biomedical Laboratories (BMBL).[1] Facilities funded by the National Institutes of Health (NIH) follow the NIH Design Requirements Manual (DRM),[2] one of the only detailed design requirements and guidance manuals for biomedical research laboratories and animal research facilities in the United States. The select agent program (7 CFR 331; 9 CFR 121; 42 CFR 73)[4–6] uses checklists that have largely been derived from the BMBL 5th Edition.[1] Comparisons of laboratories demonstrate there is no consistent ventilation-based performance testing methods.

The design and the construction industry are guided by regulations, codes and guidelines that center on public, environment and asset safety

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and protection. It has become increasingly difficult to verify ventilation needs for BSL-3/ABSL-3 containment facilities. Architects, engineers, contractors, commissioning agents and owners, etc. (stakeholders) have attempted to define both design and test criteria for containment test methods while regulatory authorities have relied on risk assessments and performance based objectives that define preferred outcomes without establishing methods to achieve expectations. For example, several agencies and jurisdictions have adopted BMBL as the governing document for design, construction and verification of BSL-3 facilities. However, the language of BMBL is non-prescriptive and, as with other prevailing guidelines, it leaves too much room for interpretation in the application of the guidelines. A direct consequence of this is the enormous amount of time and expense incurred to satisfy the 'subjective' demands imposed during testing and verification.

The ventilation system of a high containment laboratory is central to its performance and operation and the ultimate key to ensure that the environment is safe for human occupants, research animals and the environment. In many cases, high containment facility stakeholders have expressed concern at various milestones in the design, construction or operation of their facility that there is a lack of uniformity in the ''methodology'' used from one facility to another to verify that the ventilation systems in such facilities are performing appropriately. Additionally, another factor to take into consideration in the development of ANSI Z9.14 is that if used as an Approved Testing Methodology, it could help assuage public perception of safety control oversight. A standard such as ANSI Z9.14 would be desirable to provide consistency in the industry and increase the confidence of the public that such a facility is operating properly.

An extensive literature review was conducted to determine what regulations, standards and guidance are currently available that provide a 'methodology' to verify that the ventilation systems in high containment facilities are performing appropriately for the current or potential future use. Among professionals who are asked to specify or perform tests for performance of ventilation systems in high containment facilities, there is a clear consensus that although some specific requirements and component testing procedures may be found in some documents (e.g., ANSI Z9.5,[7] NSF 49[8]), there is no single source for a comprehensive methodology that can be used to perform a risk assessment of each individual facility.

The ANSI Z9.14 standard will focus on performance verification of engineering controls related specifically to ventilation system features of BSL-3/ABSL-3 facilities. Such a standard would fill an identifiable gap as evidenced in this 'Gap and Needs Analysis'. The standard can provide one component of a more extensive graduated, risk-based approach to reaching containment goals appropriate to the risk of the agent and the laboratory activity.

The methodologies in ANSI Z9.14 will provide practical guidance to ensure that all reasonable facility ventilation system controls and prudent practices are in place to minimize, to the greatest extent possible, the risks associated with laboratory operations and the use of biohazardous materials as they are affected by the ventilation system. It will provide optional methods to validate that the facility can continue to perform at the safety level for which it was intended As well, the standard will serve as an umbrella methodology that ensures, validates and accounts for the completion of all other necessary and required processes or certifications. Thus, it is expected that verification of applicable ANSI/ASHRAE standards,[9,10] NSF Biosafety Cabinet certifications,[8,11] ANSI/ASHRAE Fume Hood certification requirements,[12] NFPA requirements,[13] etc. and any local code and standard requirements will be a part of this standard by reference. Ventilation Systems are affected by and have an effect on other systems and equipment in a laboratory and thus those systems and equipment may be included in the standard to some extent as an associated system. Because the standard will primarily focus on ventilation systems, it will not include the specifications of a comprehensive bio-risk management system which is covered already by the CWA 15793:2008.[14] However, the ANSI/AIHA Z9.14 will provide the technical specifications and background information needed to address the technical, engineering and associated systems for ventilation within a high containment laboratory. As such, it is fully compatible with the CWA 15793:2008 and other national and international health and safety management systems without duplicating or contradicting their requirements.

Biosafety professionals are increasingly demanding the use of risk assessments to determine the Heating, Ventilation and Air Conditioning (HVAC) system requirements for design and testing. For example, there is no basic BSL-3/ABSL-3 standard that defines the extent of ventilation redundancy. This basic premise for safe and continuous operations is essential to meet the new BMBL 5th Edition standard defined as, 'The laboratory shall be designed such that under failure conditions the airflow will not be reversed'.[1] There are other examples of common laboratory requirements that can have many solutions without consistent guidance for testing to achieve both prescriptive or performance objectives. Specific gaps exist suggesting that a new performance testing standard is required. These include:

1. There are minimal defined standards for BSL-3/ABSL-3 ventilation systems that are either performance based or prescriptive in the USA. Although the NIH Design Requirements Manual[2] and USDA ARS 242.1[15] are fairly prescriptive in establishing minimum standards for ventilation system performance, neither provides a methodology to test ventilation performance or performance verification methods for all BSL-3/ABSL-3 facilities.
2. There are many BSL-3/ABSL-3 facilities with similar functions and risks that do NOT follow the same testing methods for ventilation.

In other words, there is no testing standardization, uniformity or consistency.

3. There are many BSL-3/ABSL-3 laboratories that cannot meet the current ventilation recommendations of the BMBL 5th Edition for 'no air reversal'. Test methods to achieve this are absent.
4. Many users of older laboratories cannot meet current ventilation requirements of the BMBL 5th Edition when renovating or re-testing; they are requesting help as to how to perform tests.
5. NIH commissioning standards are specific to their own facilities and do not provide methodologies for BSL-3/ABSL-3 ventilation systems testing.
6. The possession, use, and transfer of select agents and toxins that have the potential to pose a severe threat to public health and safety, to animal or plant health, or to animal or plant products are regulated by select agent rules 7 C.F.R. Part 331,[4] 9 C.F.R. Part 121,[5] and 42 C.F.R. Part 73.[6] These regulations do not define test methodologies for BSL-3/ABSL-3 performance verification.
7. Animal and Plant Health Inspection Service (APHIS) standards [7 C.F.R. Part 331 (APHIS-plant); 9 C.F.R. Part 121 (APHIS animal)][4,5] which regulate laboratories working with select agents and toxins posing a risk to animal and plant health or animal and plant products do not define methods for verifying BSL-3/ABSL-3 ventilation performance.
8. Although ANSI standards are based in the United States, many countries are interested in the outcome of this proposed ANSI Z9.14 standard due to the relative void in the global biosafety industry.
9. Other countries are developing programs to verify evidence-based criteria for containment performance.

Many professionals in the industry, who design, build and operate high containment facilities recognized from their experience, that there is a lack of uniformity in the 'methodology' used from one facility to another to verify that the ventilation systems in such facilities are performing appropriately. This fact is evident from a variety of sources including the lack of literature on the topic when one does an Internet search; frustration of engineers tasked with testing facility ventilation systems, and discussions related to this topic at national meetings. The ventilation system of a high containment laboratory is central to its performance and operation and the ultimate key to ensure that the environment is safe for human occupants, research animals and the environment. It is important to emphasize again that a direct consequence of the lack of clear and prescriptive language in prevailing guidelines results in an enormous amount of additional time and expense to satisfy the 'subjective' demands imposed during testing and verification.

This 'Gap and Needs Analysis' indicates that although there are many guidance documents, there is no single document that provides a comprehensive methodology for testing and verifying that the ventilation systems in BSL-3/ABSL-3 facilities is performing appropriately.

The following is a list and brief description of the available guidance pertaining to high containment laboratories. This list is not exhaustive but aims to address some of the more common guidance documents available to the professional community. As well, some of the documents listed may have tangential bearing on guidance related to high containment facilities in that they should be considered in their application to facility design but do not address ventilation systems (e.g., Americans with Disabilities Act, some OSHA regulations, and other codes).

GAO 09-574 ''Report on High Containment Laboratories: National Strategy for Oversight Is Needed''[16] provides evidence that strongly supports the need for the ANSI/AIHA Z9.14 standard. The GAO report states, ''According to our expert panel, a clear and unambiguous set of standards stating the various capabilities that are required to maintain the integrity of all high-containment laboratories is necessary. These standards should be national – not subject to local interpretation – and address the possibility that one or more emergency or backup systems may fail. Most importantly, any set of scenarios aimed at maintaining containment integrity must be empirically evaluated to demonstrate its effectiveness.''

GAO report 09-574[16] further notes that ''since no single agency is in charge of the expansion, no one is determining the aggregate risks associated with this expansion. As a consequence, no federal agency can determine whether high-containment laboratory capacity may now meet or exceed the national need or is at a level that can be operated safely… while laboratory accidents are rare, they do occur, primarily due to human error or systems (management and technical operations) failure, including the failure of safety equipment and procedures…''Other GAO reports[17,18] provide further evidence that there needs to be a more coordinated effort in high containment laboratory oversight. The GAO reports, which are recommendations only, generally apply to surveillance and tracking of laboratories that work with biological agents in high containment laboratories (only those laboratories working with select agents are required to register with CDC/APHIS).[4–6]

Currently, there is no single federal agency providing consistent oversight and tracking of high containment laboratories, nor are there any standards applicable to all high containment laboratories. There is a limited system managed by the Centers for Disease Control and Prevention (CDC) and the Animal and Plant Health Inspection Service (APHIS) that applies to a subset of laboratories that work with select agents. CDC/APHIS[4–6] oversees regulation of select agent possession, transfer, and use. It focuses mainly on two areas: people who have access to select agents and facilities where select agents are used and stored. The USDA 242.01 ARS[15] Facilities Design Standards, Appendix 9.B provides a testing procedure that must be conducted at the factory and/or the field to verify the containment integrity of the critical components of

biological containment systems and to test he containment room or envelope to determine if the walls, floors, ceilings, penetrations, and other containment barrier features have adequate integrity to prevent leakage of air from the containment space. A testing protocol is available for gas tight ductwork and isolation valves.

The ANSI/AIHA Z9.14 standard will provide one tool to help understand the sources of risk related to ventilation systems in high containment laboratories. It may serve as a first step in meeting the GAO recommendations.

National US and Local Initiatives: Laws, Standards and Guidelines that address ventilation systems but DO NOT address a comprehensive performance testing methodology to ensure that these systems operate appropriately. Neither do they emphasize the special requirements of BSL-3/ABSL-3 facilities.

Agricultural Bioterrorism Protection Act of 2002[19] was signed into law as part of the Public Health Security and Bioterrorism Preparedness Response Act of 2002. This law requires that entities, such as private, State, and Federal research laboratories, universities, and vaccine companies that possess, use, or transfer agents or toxins deemed a threat to public health and safety or to animal or plant health or products register these agents with the appropriate Federal Department such as the Secretary of the U.S. Department of Agriculture (USDA). USDA's Animal and Plant Health Inspection Service (APHIS) has been designated by the Secretary as the agency responsible for implementing the provisions of the law for USDA. Entities that possess, use, or transfer toxins or agents deemed a threat to public health must register with the Secretary of the U.S. Department of Health and Human Services (HHS). The Centers for Disease Control and Prevention (CDC) has been designated by the HHS Secretary as the agency responsible for implementing the provisions of the law for HHS.

ANSI/ASHRAE Standard 62.1-2010: Ventilation for Acceptable Indoor Air Quality[9] sets minimum ventilation rates and other requirements for commercial and institutional buildings.

ANSI/ASHRAE Standard 62.1-2010: User's Manual[10] – The 62.1 User's Manual provides explanatory material, detailed information, figures and examples to guide users in designing, installing and operating buildings in accordance with ANSI/ASHRAE Standard 62.1-2010, Ventilation for Acceptable Indoor Air Quality, which sets minimum ventilation rates and other requirements for commercial and institutional buildings. Also highlighted is the application of useful tools used for compliance with Standard 62.1-2010, including a newly revised spreadsheet that assists in Ventilation Rate Procedure calculations.

ANSI/AIHA Z9.5-2003 – Laboratory Ventilation[7]: This standard sets forth the requirements for the design and operation of laboratory ventilation systems. The standard does not apply to explosives laboratories; radioisotope laboratories; laminar flow hoods (e.g., a clean bench for product protection, not employee protection) or biological safety cabinets except as it may relate to general laboratory ventilation. The purpose of this standard is to establish minimum requirements and best practices for laboratory ventilation systems to protect personnel from overexposure to harmful or potentially harmful airborne contaminants generated within the laboratory. It does not apply to comfort or energy considerations unless they have an effect on contaminant control ventilation. This standard sets forth ventilation requirements that will, combined with appropriate work practices, achieve acceptable concentrations of air contaminants; inform the designer of the requirements and conflicts among various criteria relative to laboratory ventilation; and inform the User of information needed by designers.

ANSI/ASHRAE 110-1995[12]: This is a standard that provides a method of Testing Performance of Laboratory Fume Hoods to check their operation.

Agricultural Research Service (USDA ARS): The USDA Agricultural Research Service (ARS) Manual[15] provides design policies and criteria to guide the design of USDA ARS construction projects. ARS buildings shall be designed and constructed to best meet the functional, safety, and environmental needs of the programs they house. General guidance is provided for the design of facilities which support research activities with biohazardous materials. Its objective is to provide, by incorporating special equipment and features in the design of the facility, the best possible physical containment of these agents. The entire physical containment system for such a facility supporting agricultural research is unique in that it must function to prevent the spread of infectious agents to the environment, to other animals or plants, and between research experiments, as well as to humans.

Testing Requirements (ARS Manual, Appendix 9.B) are prescribed with specifications for all testing to be performed and documented. At a minimum, the following equipment and systems shall be tested and validated.

A. Leak tightness of the supply and exhaust ductwork, at the pressures specified.
B. Factory-testing of HEPA filters, filter housings, isolation valves and other critical components.
C. Field-testing of HEPA filters and housings after installation.
D. Differential pressures and/or directional airflows between adjacent areas.
E. Field-testing of biological safety cabinets.
F. Pressure decay testing of containment spaces.

Appendix 9.B provides the requirements for testing and certification that must be conducted at the factory and/or in the field to verify the containment integrity of the critical components of biological containment systems. It covers testing of biological safety cabinets in accordance with the latest version of NSF Standard 49,[8] Class II (laminar flow) Biohazard Cabinetry, as well as testing and certification of HEPA filter assemblies with in place HEPA filter testing to verify that the filters do not contain pinhole leaks in the filter

media, the bond between the filter media and the filter frame and the filter frame gasket to filter housing. Filter testing is intended to be completed in a similar manner to industry standards for certification of HEPA filters in biological safety cabinets. The testing contractor may submit an alternate written testing procedure for approval by the Research Program Safety Officer (RPSO) prior to making filter certifications. If the alternate testing procedure is not approved, an Approved Testing Procedure is provided.

A testing protocol for a containment room is provided to test the containment room or envelope to determine if the walls, floors, ceilings, penetrations, and other containment barrier features have adequate integrity to prevent leakage of air from the containment space. Testing is typically completed by subjecting the containment area to negative or positive air pressure in excess of the anticipated operating conditions, and monitoring the containment air pressure over a test period. The goal of the pressure decay testing is to create a 2-in. W.C. (500 Pa) pressure differential in the containment zone with acceptance criterion of two consecutive pressure decay tests demonstrating a minimum of 1 in. W.C. (250 Pa) negative differential pressure remaining after 20 min, from an initial negative pressure differential of 2 in. W.C. (500 Pa). A testing protocol for gas tight ductwork and isolation valves is provided. USDA ARS is a prescriptive document and describes testing methodologies for biocontainment laboratories with a specific use. Although it addresses pressure decay testing, it does not address ventilation systems. Neither does it provide a comprehensive list of components to be tested as is proposed for ANSI Z9.14.

USDA also has a manual dealing with security concerns, ''USDA Departmental Manual No. 9610–001, USDA Security Policies and Procedures for Biosafety Level-3 Facilities.''[20] Although the manual addresses security concerns with the placement of intakes and exhaust stacks on buildings, this document does not address ventilation system performance.

Biosafety in Microbiological and Biomedical Laboratories (BMBL)[1] is a guidance document that provides minimum performance based recommendations and best practices to be applied to all levels of biosafety laboratories. It is typically voluntary but widely adopted as policy. The BMBL describes the combinations of standard and special microbiological practices, safety equipment, and facilities constituting Biosafety Levels 1–4, which are recommended for work with a variety of infectious agents in various laboratory settings. The advisory recommendations are intended to provide a voluntary guide or code of practices as well as goals for upgrading operations. They are also offered as a guide and reference in the construction of new laboratory facilities and in the renovation of existing facilities.

Department of the Army (DOA) Pamphlet 385-69, 6 May 2009[21] prescribes the technical safety requirements for the use, handling, transportation, transfer, storage, and disposal of infectious agents and toxins (IAT) rated at Biosafety Level 2 (BSL-2) and above used in microbiological activities in clinical laboratories, biomedical and biological research settings, microbiology teaching laboratories, and veterinary reference laboratories. The DOA pamphlet requires the mandatory use of the latest edition of the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention (CDC) and National Institutes of Health's Biosafety in Microbiological and Biomedical Laboratories (BMBL) and applies specifically to all U.S. Army activities and facilities in which IAT are used, produced, stored, handled, transported, transferred or disposed. This document refers to the NIH BSL-3 Certification requirements as a reference document for certification.

Guide for the Care and Use of Laboratory Animals, 8th Edition[22] provides a framework for the judgments required in the management of animal facilities. This updated and expanded resource of proven value is important to stakeholders involved in animal research and care responsibilities and for animal welfare advocates.

NIH Design Requirements Manual (DRM)[2] is one of the only detailed design requirements and guidance manual for biomedical research laboratories and animal research facilities in the U.S. Compliance to the DRM, which promulgates minimum performance design standards for NIH owned and leased new buildings and renovated facilities, ensures that those facilities will be of the highest quality to support Biomedical research. The DRM is prescriptive and specific to NIH facilities.

Note: the following list of documents that provide guidance to certify or accredit systems of a BSL-3/ABSL-3 facility to ensure that they are systematically reviewed for all safety features and processes associated with the laboratory (engineering controls, personal protective equipment, building and system integrity, standard operating procedures (SOPs) and administrative controls such as documentation and record retention systems). These documented processes assure that all reasonable facility controls and prudent practices are in place to minimize, to the greatest extent possible, the risks associated with laboratory operations and the use of biohazardous materials. These may be either performance based or prescriptive. They may or may not specifically cover ventilation systems but they DO NOT provide methodologies to test a ventilation system, which is the intent of ANSI Z9.14.

- In the US, the National Institutes of Health has developed Biosafety Level 3 Laboratory Certification Requirements and Checklist[23] as part of its Design Requirements Manual 2008.[2] BSL-3/ABSL-3 facility certification is required for all NIH funded BSL-3/ABSL-3 laboratories and animal facilities and is highly recommended when NIH has grantee oversight responsibilities. The NIH certification document contains a comprehensive checklist of administrative and engineering controls required for certification of BSL-3/ABSL-3 laboratories. Many of the checklist items are based on NIH's experience with the numerous NIH-funded laboratories currently being designed and constructed. An

emphasis is placed on validation of appropriate standard operating procedures, protocols, training and maintenance of documentation for all regulatory compliance concerns, inspections and internal certifications (equipment, training, HVAC, etc.).

- American Biological Safety Association (ABSA)[3,24] currently manages programs for certification and registration of biosafety professionals as described below.

- ABSA is developing an accreditation program for the independent accreditation of high containment laboratories in the U.S. Such an oversight process would assure lab workers and the community that a biocontainment facility has in place the necessary practices, procedures, personnel, and equipment to protect people, animals, plants, and the environment and minimize the potential of lab-acquired infections and lab accidents. Accreditation, conducted by an independent third party, is an objective assessment of the technical competence and quality system of an organization or laboratory as it relates to biohazard management, including personnel training and experience. Accreditation using relevant national and international standards is an effective way of ensuring competence in a comprehensive and uniform manner in laboratories working with biohazards. Typically, accreditation is voluntary. Key components assessed by an effective accreditation program would include: (1) the biosafety expertise and training of personnel managing and conducting the research; (2) the adequacy and function of the biosafety management structure supporting the research activities; and (3) the adequacy and function of biocontainment measures, including facilities, equipment, practices, and record-keeping systems, in place at the facility that is evaluated. ABSA has extensive experience in evaluating all three of these components. In addition, ABSA has established alliances with other groups that would provide support of this effort. The accreditation process uses the CEN Workshop Agreement (CWA) as a guide for evaluating an organization's management system.[14]

- There are numerous state and university laboratory certification documents. These are based primarily on the requirements specified in the BMBL. They are checklists, not methodologies, for ventilation performance verification. Examples of these documents include:
  i. Connecticut Dept. of Public Health, Division of Health Systems Regulation, Laboratory Biosafety Inspection Checklist Rev. 6/10/2005[25]
  ii. Oklahoma State University Laboratory Biosafety Inspection Report[26]
- Some other regulations and standards of note are listed here. There are likely other codes and regulations whose content have some bearing on the design of high containment facilities. This list is not exhaustive.
  - Americans with Disabilities Act Accessibility Guidelines (ADA)[27] which contain scoping and technical requirements for accessibility to sites, facilities, buildings, and elements by individuals with disabilities. The requirements are to be applied during the design, construction, additions to, and alteration of sites, facilities, buildings, and elements to the extent required by regulations issued by Federal agencies under the Americans with Disabilities Act of 1990 (ADA).
  - The Facilities Standards for the Public Buildings Service (P-100)[28] Standard for Historical Structures Establishes design standards and criteria for new buildings, major and minor alterations, and work in historic structures for the Public Buildings Service (PBS) of the General Services Administration (GSA). This document contains policy and technical criteria to be used in the programming, design, and documentation of GSA buildings.
  - NSF/ANSI Standard 49[8,11] Class II (laminar flow) biosafety cabinetry applies only to Class II biological safety cabinets, as designed to minimize the hazards inherent in working with agents assigned to Biosafety Levels 1, 2, or 3. The standard defines the tests for which a cabinet must comply to become NSF Certified The standard includes basic requirements for design, construction, and performance that are intended to provide personnel, product, and environmental protection, reliable operation, durability, cleanability, noise level and illumination control, vibration control, and electrical safety. In addition, the standard includes detailed test procedures and recommendations for installation, field certification tests, and decontamination procedures.
  - NFPA Standards[13] including:
    - NFPA 30 Flammable and Combustible Liquids Code
    - NFPA 45 Standard on Fire Protection for Laboratories Using Chemicals
    - NFPA 55 Standard for the Storage, Use, and Handling of Compressed Gases and Cryogenic Fluids in Portable and Stationary Containers, Cylinders, and Tanks
    - NFPA 70 National Electrical Code
    - NFPA 101 Life Safety
  - Occupational Safety and Health Administration (OSHA) Regulations.
    - 29 CFR 1910.1450 Occupational exposure to hazardous chemicals in laboratories.[29]
    - 1910.1030 Bloodborne pathogens.[30]

NATIONAL INITIATIVES OUTSIDE THE US

- Canada has developed ''Containment Standards for Laboratories, Animal Facilities and Post Mortem Rooms Handling Prison Disease Agents.''[31,32] This is a detailed document with a check list defining

recommendations versus requirements for each type of facility. The Containment standards for Veterinary Facilities Services[32] include a certification program for high containment laboratories. Chapter 7 discusses the need for pre-certification preparation that includes having available a complete set of 'as built' and 'as modified' drawings and all test results. This section indicates that operational protocols must be established before work with pathogens at the specified containment level can begin. A training component is emphasized. These guidelines incorporate the various components of the laboratory that require independent certification (e.g., biosafety cabinet, fume hood, air handling system, controls etc.) as a part of the overall certification. Canada is in the process of amalgamating its containment standards to include performance test methods and will cover both human and animal containment criteria.

- The Canada Food Inspection Agency (CFIA) Containment Standards for Veterinary Facilities Canada-Public Health Agency of Canada (PHAC)[33] provides a detailed list of the tests that should be performed and the criteria that must be met in order to achieve certification. While these are procedures specifically used in Canada, they can be applied to almost any containment lab in the world. Items that must be examined for structural integrity are the interior windows, the ductwork, piping, electrical conduits, and finishes on the walls and floors. Inward directional airflow must be checked by using a smoke pencil to verify the flow through every door of the facility. An Internet search of the Canadian documents did not produce a performance testing methodology for ventilation systems.
- UPDATE Australian Government Department of Health and Ageing. Australian Guidelines and Forms for Certification of Physical Containment Facilities. 2006[34] is a prescriptive standard that provides guidance on the certification of a Physical Containment Level 3 (PC3) laboratory. It states that ''A PC3 (BSL-3/ABSL-3) laboratory should be constructed so that it achieves upon commissioning an air leakage rate, at a differential pressure of 200 Pa, of no more than 120 L/min. At all times after commissioning an air leakage rate of no more than 1200 L/min should be maintained.'' The same criteria are applied to PC4 (BSL4) facilities. The standard requires verification every 3 years. Test equipment is available to provide this type of reliable and repeatable air leakage test and decay testing that allows for testing and verification of the quality of the secondary containment barrier on an ongoing basis. Australia has developed ''Guidelines for Certification of Facilities/Physical Containment Requirements,'' but they specifically address facilities where genetically manipulated organisms are used. Many of the principals in this guideline are applicable and transferrable for further development to a BSL-3/ABSL-3 certification process. For example, these guidelines discuss how to implement a transition period prior to certification taking effect; address confidentiality concerns for non-federally funded industries; and implement changes to the certification, compliance, monitoring and consequences of non-compliance to the certification.
- Singapore Ministry of Health (MOH) has a Laboratory Certification Checklist[35] based on the WHO Laboratory Biosafety Manual 3rd Edition The MOH has included certification criteria specific to their document and note these in the checklist with an (M). The Singapore requirements define, to a limited extent, the requirements for a certifier's registration.
- In the United Kingdom, the Department for Environment, Food and Rural Affairs (DEFRA) provides Certification and Accreditation of Operational Standards of Institutes/Universities/Laboratories/ Commercial Organizations Exporting Products to the UK/Receiving Products.[36] Regulatory staff is involved at the design stage and at various points during the construction process for new high-containment laboratories that work with human, animal, or genetically modified pathogens. This early involvement has been helpful in ensuring that new facilities meet the standards set out in the legislation and supporting guidance (related to the management, design, and operation of high containment laboratories). This involvement has also enabled the regulatory agency to address the application of new technologies in high-containment laboratories (e.g., alkaline hydrolysis for waste destruction as an alternative to incineration). In April 2010, the UK plans 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 and for the regulatory authority to be a statutory consultee as part of the planning authorization. It appears that the UK has a rather complex system of certification and it is not clear from an Internet search exactly what their requirements are for certification of laboratories. The following excerpt describes what appears to be a self imposed and monitored accreditation/certification system. Several consulting containment commissioning companies from North America have been requested to write and implement HVAC testing procedures for higher containment projects as there are no established ventilation test methods available.

INTERNATIONAL INITIATIVES

Several initiatives are currently under way as part of an international approach to certification. None of these initiatives have performance testing methodologies for ventilation systems.

- International Veterinary Biosafety Workgroup (IVBWG)[37] is a specialist international forum for dealing with biosafety issues in high containment (BSL 3 and above) large

animal facilities. It contributes to the development of generic biosafety guidance and participates in the International Biosafety Working Group. It publishes the Veterinary Containment Facilities: Design and Construction handbook.[38]

- The World Health Organization (WHO) Laboratory Biosafety Manual[39,40] 3rd Edition, Chapter 4 addresses the laboratory design and facilities at the BSL-3 level. Like the BMBL, the WHO Laboratory Biosafety Manual does not address a performance testing methodology for ventilation systems. Chapter 8 addresses Laboratory Certification and provides a brief checklist to use as a tool in the certification process. Most institutions that have either a BSL-3/ABSL-3 Certification or Inspection process use the WHO Biosafety Manuals checklist and the BMBL as the basis for their requirements. The WHO manual states that adequately trained safety and health or biosafety professionals may conduct laboratory certification activities. Institutions may employ personnel having the appropriate skill-set required for conducting audits, surveys or inspections (these terms are used interchangeably) associated with the certification process. However, institutions may consider engaging or be required to engage a third party to provide these services. Biomedical research and clinical laboratory facilities may develop audit, survey or inspection tools to help ensure consistency in the certification process. These tools should be flexible enough to allow for the physical and procedural differences between laboratories necessitated by the type of work being conducted, while at the same time providing a consistent approach within the institution. Care must be taken to ensure that these tools are used only by appropriately trained personnel, and that they are not used as a substitute for a sound professional biosafety assessment. Findings of the audit, survey or inspection should be discussed with laboratory personnel and management. Within the laboratory, an individual should be identified and made responsible for ensuring that corrective actions are taken for all deficiencies identified during the audit process. Certification of the laboratory should not be completed, and the laboratory should not be declared functional, until deficiencies have been adequately addressed.
- The Global Action Plan for Laboratory Containment of Wild Polioviruses[41] was issued by WHO in December 1999 and updated in a second edition. It was based on broad input from biosafety experts, epidemiologists, laboratory scientists, ministries of health and vaccine manufacturers. It incorporates lessons learned from biomedical laboratory surveys and inventories in more than 100 countries in five of the six WHO regions. It expands previous recommendations to include vaccine-derived polioviruses (VDPVs). It defines biosafety requirements in terms of risks. It describes two phases of activities leading to containment: the laboratory survey and inventory phase and the global certification phase. Finally, it examines the implications of post certification immunization policies on poliovirus biosafety requirements. The present document provides the background, rationale and strategy for ensuring that laboratory facilities and biosafety practices are consistent with the risk of inadvertent transmission of poliovirus to the community. The purpose of laboratory containment of wild polioviruses is to minimize the risk of reintroducing wild polioviruses from the laboratory to the community. This document is very specific to containment and eradication of polio virus.
- Another initiative is being conducted by the Global Health Security Action Group (GHSAG),[42] a subgroup of the G7, to form an international network of high-containment laboratories which could work together and respond to an outbreak of diseases on an international scale. The GHSAC wants to achieve standardized international certification procedures that would facilitate easier operations on a global level with the import/export of agents, exchange of diagnostic procedures, and staff exchange.
- The CEN (European Committee for Standardization) Workshop Agreement (CWA)15793[14] Laboratory biorisk management standard 2008 is a performance based certification process that is regarded as best practice. A biosafety safety management system is an organized and documented approach to managing biosafety issues within an organization. The aim of such a system is to help employees and other stakeholders effectively and efficiently accomplish the organization's goals and objectives relative to the safe, secure, and legal use of biological materials in research. Additionally, a management system must include appropriate monitoring and review to ensure effective functioning of the program and to identify and implement corrective measures in a timely manner.

- Its intent is to facilitate international exchange and collaboration; promote training and learning; increase awareness and adoption of management system approaches within the sector; provide organizations with a means for internal audit and third party certification of their facilities and management systems as a demonstration to stakeholders including regulators, funding organizations and assuring the community that there are adequate measures in place to responsibly manage risk associated with biosafety and biosecurity and provide stakeholders with a standard to be used as a benchmark in setting requirements for facilities in the areas of biosafety and biosecurity.
- The objective of the CEN Workshop was to develop and promote the adoption of recognized standards for management of biological risks. Although it is appreciated that this is a wide ranging field, commonly shared biorisk principles and practices do apply. Among the objectives proposed it will allow laboratories to:

- Establish a biosafety and biosecurity management system to minimize

risk to employees, the community and the environment that may be exposed to biological materials as a consequence of its activities.

- Implement, maintain and continually improve biosafety and biosecurity management.
- Assure itself of conformance with its stated biosafety and biosecurity policy.
- Demonstrate such conformance to others.
- Make a self-determination and declaration of conformance.
- Seek internationally recognized third party certification of its biosafety and biosecurity management system.

It is important to emphasize again that none of the above standards and documents specifically describe a methodology to test and verify ventilation systems in biocontainment facilities where the ventilation system is the key to safe operations. A standard such as Z9.14 would also go a long way in reducing public sector anxiety over safety concerns.

Use of the final Z9.14 standard will be voluntary. Some organizations, such as universities and federal and state government may choose to adopt the final standard either as guidance or as a requirement for their facility. Since there currently is no 'Testing and Performance Verification' entity in the U.S., actual final verification of the BSL-3/ABSL-3 facility will be the ultimate responsibility of the 'owner' although it is encouraged that an independent third party conduct or participate in the process. The standard will be designed to provide clear, unambiguous minimum recommendations about what should be measured to ensure that the facility's ventilation systems are performing as needed based on the risk assessment of its current use. Once laboratories have been commissioned and begin operating, continuing maintenance and testing/validation programs are needed to ensure that operating standards and regulatory compliance are maintained. Along with expansion of BSL-3/ABSL-3 facilities nationwide, there needs to be a commensurate development of both operational procedures to address known deficiencies and, as far as practicable, a proactive evaluation of future risks.

REFERENCES

1. Department of Health and Human Services (DHHS). The Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH): Biosafety in Microbiological and Biomedical Laboratories (BMBL). 5th ed. NIH, CDC, DHHS; Washington, DC, 2009, http://orf.od.nih.gov/PoliciesAndGuidelines/BiomedicalandAnimalResearchFacilitiesDesignPoliciesandGuidelines/DesignRequirementsManualPDF.htm [Accessed July 23, 2011].
2. National Institutes of Health (NIH). Design Requirements Manual; NIH, Division of Technical Resources; Bethesda, MD, 2008, http://orf.od.nih.gov/PoliciesAndGuidelines/BiomedicalandAnimalResearchFacilitiesDesignPoliciesandGuidelines/DesignRequirementsManualPDF.htm [Accessed July 23, 2011].
3. American Biological Safety Association (ABSA). Accreditation of High Containment Laboratories; ABSA; Mundelein, IL, 2008, http://www.absa.org/pdf/080418AccreditationofHCLabsPosition.pdf [Accessed June 27, 2011].
4. CFR 7 part 331 TITLE 7 – Agriculture Subtitle B – Regulations of the Department of Agriculture Chapter III – Animal and Plant Health Inspection Service, Department of Agriculture Part 331 – Possession, Use and Transfer of Select Agents and Toxins.
5. CFR 9 TITLE 9 – Animals and Animal Products Chapter I – Animal and Plant Health Inspection Service, Department of Agriculture Part 121 – Possession, Use and Transfer of Select Agents and Toxins.
6. CFR TITLE 42-Public Health C Chapter I – Public Health Service, Department of Health and Human Services Subchapter F – Quarantine, Inspection, Licensing Part 73 – Select Agents and Toxins.
7. American National Standard for Laboratory Ventilation ANSI/AIHA Z9.5; ''The American National Standard for Laboratory Ventilation" Method of Testing Performance of Laboratory Fume Hoods. American Society of Heating, Refrigerating and Air-Conditioning Engineers, 2003.
8. NSF International Standard, American National Standard for Biosafety Cabinetry – Biosafety Cabinetry: Design, Construction, Performance, and Field Certification. http://standards.nsf.org/apps/group_public/download.php/3604/NSF_49-08e-rep-watermarked.pdf [Accessed July 27, 2011].
9. American National Standard ANSI/ASHRAE Standard 62.1-2010. Ventilation for Acceptable Indoor Air Quality; American Society of Heating, Refrigerating and Air-Conditioning Engineers, 2010 pp. 1–54.
10. American National Standard ANSI/ASHRAE Standard 62.1-2010. Users Manual; American Society of Heating, Refrigerating and Air-Conditioning Engineers, 2010 pp. 1–178.
11. NSF Certification Policies for Biosafety Cabinetry. http://www.nsf.org/business/biosafety_cabinetry/policies.asp?program=BiosafetyCab [Accessed July 27, 2011].
12. American National Standard (ANSI). ANSI/ASHRAE 10-1995. Method of Testing Performance of Laboratory Fume Hoods. Purchase at: http://webstore.ansi.org/RecordDetail.aspx?sku=ANSI%2FASHRAE+110-1995 [Accessed July 27, 2011].
13. National Fire Protection Association (NFPA). Purchase all standards at: http://www.nfpa.org/categoryList.asp?categoryID=24&URL=Codes%20&%20Standards&cookie_test=1 [Accessed July 27, 2011].
14. European Committee for Standardization (CEN): CEN Workshop Agreement (CWA)15793 – Laboratory Biorisk Management Standard. European Committee for Standardization. Brussels: CEN, 2008. ftp://ftp.cenorm.be/PUBLIC/CWAs/wokrshop31/CWA15793.pdf [Accessed July 23, 2011].
15. USDA ARS Facilities Design Standards Number: 242.1-ARS. United States Department of Agriculture. Research, Education, and Economics, July 2002. http://www.afm.ars.usda.gov/ppweb/pdf/242-01m.pdf [Accessed June 6, 2011].
16. Government Accountability Office (U.S.GAO 09-574). GAO Report on High Containment Laboratories: National Strategy for Oversight Is Needed; GAO; Washington, DC, 2009, http://www.gao.gov/new.items/d09574.pdf [Accessed July 23, 2011].
17. Government Accountability Office (U.S.GAO-10-850). Biological Laboratories Design and Implementation Considerations for Safety Reporting Systems; GAO; Washington, DC, 2010, http://www.legistorm.com/showFile/

L2xzX3Njb3JlL2dhby9wZGYvMjAxMC85/ful40710.pdf [Accessed June 7, 2011].
18. Government Accountability Office (U.S.GAO-08-108T). GAO Report on High-Containment Biosafety Laboratories Preliminary Observations on the Oversight of the Proliferation of BSL-3 and BSL-4 Laboratories in the United States; Statement of Keith Rhodes, Center for Technology and Engineering, Applied Research and Methods, 2007 http://www.gao.gov/new.items/d08108t.pdf [Accessed July 27, 2011].
19. Agricultural Bioterrorism Protection Act of 2002. http://www.aphis.usda.gov/ programs/ag_selectagent/ag_bioterr_QA.shtml [Accessed July 27, 2011].
20. USDA Departmental Manual No. 9610-001. ''USDA Security Policies and Procedures for Biosafety Level-3 Facilities'' Agricultural Research Service, August 30, 2002. http://www.ocio.usda.gov/directives/doc/DM9610-001.pdf [Accessed July 27, 2011].
21. Department of the Army (DOA) Pamphlet 385-69. Safety Standards for Microbiological and Biomedical Laboratories, May 6, 2009. http://www.apd.army.mil/jw2/xmldemo/p385_69/main.asp [Accessed July 27, 2011].
22. Guide for the Care Use of Animals. Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC); National Academy Press; Washington, DC, 2010, http://www.nap.edu/openbook.php?record_id=5140 [Accessed July 23, 2011].
23. National Institutes of Health (NIH). Biosafety Level 3 Laboratory Certification Requirements (and Checklist); NIH; Bethesda, MD, 2006, http://dohs.ors.od.nih.gov/pdf/BSL-3/ABSL-3_certguide.pdf [Accessed on July 23, 2011].
24. American Biological Safety Association (ABSA). The ABSA Accreditation Task for oversight of high containment (BSL-3/ABSL-3) research labs-Response to Accreditation Comments; ABSA; Mundelein, IL, 2008, http://www.absa.org/pdf/AccreditationStandardsCommentsResponses.pdf [Accessed July 23, 2011].
25. Connecticut Department of Public Health (CDPH). Laboratory Biosafety Inspection Checklist; CDPH, Division of Health Systems Regulation; Hartford, CT, 2005, http://ors.uchc.edu/bio/resources/pdf/3.5.3_CTlabChklst05.pdf [Accessed July 23, 2011].
26. Oklahoma State University. Laboratory Biosafety Inspection Report, Oklahoma State University: Stillwater, OK. http://ehs.okstate.edu/hazmat/Biosafety_Inspection.PDF [Accessed July 23, 2011].
27. Americans With Disabilities Act Revised ADA Regulations Implementing Title II and Title III (Published in the Federal Register, September 15, 2010, and taking effect on March 15, 2011) (Updated November 15, 2010). http://www.ada.gov/index.html.
28. The Facilities Standards for the Public Buildings Service (P-100). http://www.gsa.gov/portal/content/104821.
29. Occupational Safety and Health Standards OSHA Toxic and Hazardous Substances1910.1450 Occupational exposure to hazardous chemicals in laboratories. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10106.
30. Occupational Safety and Health Standards OSHAToxic and Hazardous Substances1910.1030Bloodborne pathogens. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10051.
31. Canadian Food Inspection Agency (CFIA). Containment Standards for Laboratories, Animal Facilities and Post Mortem Rooms Handling Prion Disease Agents; CFIA; Canada, 2006, http://www.inspection.gc.ca/english/sci/bio/anima/prion/prionse.shtml [Accessed July 23, 2011].
32. Canadian Food Inspection Agency (CFIA). Containment Standards for Veterinary Facilities. http://www.inspection.gc.ca/english/sci/bio/anima/convet/convete.shtml [Accessed July 27, 2011].
33. Public Health Agency of Canada (PHAC). Health Canada Offers Certification Guidelines: Detailed Process Required for Containment Facilities; PHAC; Canada, 2005, http://www.phac-aspc.gc.ca/ols-bsl/pdf/tradeline_2005.pdf and http://www.absa.org/abj/abj/051003tradeline.pdf [Accessed July 23, 2010].
34. Australian Government Department of Health and Ageing. Australian Guidelines and Forms for Certification of Physical Containment Facilities; Australian Department of Health and Ageing; Canberra, 2001, www.health.gov.au/tga/genetech.htm [Accessed July 23, 2011].
35. Ministry of Health (MOH) Biosafety and Branch. Singapore Certification Requirements Checklist; MOH Biosafety Branch; Singapore, 2009, http://www.google.com/search?sourceid=chrome&ie=UTF-8&q=Ministry+of+Health+(MOH)+Biosafety+Branch.+Singapore+Certification+Requirements+Checklist [Accessed July 27, 2011].
36. Department for Environment, Food and Rural Affairs (DEFRA). United Kingdom Certification and Accreditation of Operational Standards of Institutes/Universities/Laboratories/ Commercial Organizations Exporting Products to the UK/Receiving Products in the UK; Department for Environment, Food and Rural Affairs; London, UK, April 2010, http://archive.defra.gov.uk/foodfarm/animaltrade/imports/pdf/lab-standards.pdf [Accessed July 27, 2011].
37. International Veterinary Biosafety Workgroup (IVBWG). http://www.unog.ch/80256EDD006B8954/(httpAssets)/46BE0B4ACED5F0E0C125747B004F447E/$file/biosafety+background+paper+-+advanced+copy.pdf [Accessed July 27, 2011].
38. Veterinary Containment Facilities: Design and Construction Handbook, International Federation of Biosafety Association. http://tecrisk.com/projekte/projekt1/Handbook_070323.pdf [Accessed July 27, 2011].
39. World Health Organization (WHO). Laboratory Biosafety Manual: Introduction to Biotechnology, ''Chap. 4: The containment laboratory – Biosafety Level 3'', in Biosafety Manual, 3rd ed. WHO; Geneva, 2004, http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf [Accessed June 7, 2011].
40. World Health Organization (WHO). Laboratory Biosafety Manual: Introduction to Biotechnology, ''Chap. 8: Guidelines for laboratory/facility certification'' in Biosafety Manual, 3rd ed. WHO; Geneva, 2004, http://www.who.int/csr/resources/publications/biosafety/en/Biosafety7.pdf [Accessed July 23, 2011].
41. WHO Global Action Plan for Laboratory Containment Wild Polio Virus. Department of Vaccines and Biologicals, WHO, 2004. http://www.polioeradication.org/content/publications/WHO-VB-03-729.pdf [Accessed July 23, 2011].
42. Global Health Security Initiative Group, GHSAG. http://www.ghsi.ca/english/background.asp [Accessed July 23, 2011].

OTHER RESOURCES FOR READERS

[43]Gottron, F.; Shea, D. A. American Biological Safety Association (ABSA):

Oversight of High-Containment Biological Laboratories: Issues for Congress, May 4, 2009; ABSA; Mundelein, IL, 2008, http://www.absa.org/leg/0905CRSHighContainmentLabs.pdf [Accessed on July 23, 2010].

[44]American Biological Safety Association (ABSA). Report of the Trans-Federal Task Force on Optimizing Biosafety and Biocontainment Oversight; ABSA; Mundelein, IL, 2009, http://www.absa.org/leg/090910transfedbiosafety.pdf [Accessed July 23, 2010].

[45]National Institutes of Health (NIH). Lab and Animal Facility Checklist; NIH, Office of Research Facilities; Bethesda, MD, 2008, [Available upon request].

[46]National Institutes of Health (NIH). BSL-3/ABSL-3 Design and/or Construction Checklist; NIH; Bethesda, MD, 2008, [Available upon request].

[47]Compendium of Regulatory Bodies, Regulations, Guidelines and Resources by Country, Topic and Subtopic. http://www.internationalbiosafety.org/english/pdf/Compendium_Update_Feb_10_2010.pdf.

[48]The Henry L. Stimson Center: ''Chap. 4: Considering US Proposals for Enhanced Biosafety, Biosecurity, and Research Oversight'' in Stimson Center Report No. 48. Stimson Center; Washington, DC, 2009, http://www.stimson.org/cbw/pdf/CTS-Chapter4.pdf [Accessed July 23, 2010].

[49]Memarzadeh, F. Health and safety risk assessment methodology to calculate reverse airflow tolerance in a Biosafety Level 3 (BSL-3/ABSL-3) or airborne infection isolation room (AII) environment. International Journal of Risk Assessment and Management, August 2010, .

[50]Department of Labor; OSHA; Occupational Safety and Health Act of 1970. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=2743&p_table=OSHACT.