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ENHANCED BIOSAFETY BSL3+ FACILITY DESIGN & PERFORMANCE QUALIFICATON

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14

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ENHANCED BIOSAFETY BSL3+ FACILITY DESIGN & PERFORMANCE QUALIFICATION

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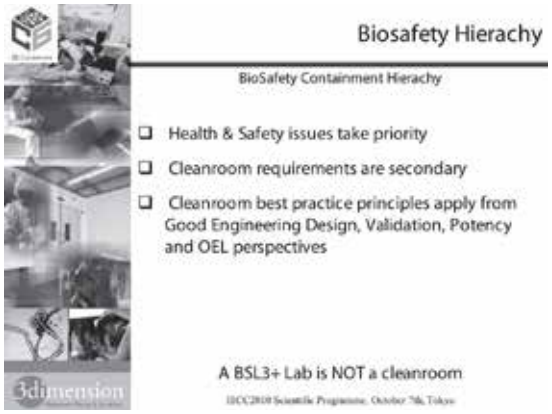
Abstract
This paper deals with biosafety change drivers, biosafety risk assessments, high containment biosafety design, secondary containment barrier design, commissioning & qualification as well as performance & verification testing of enhanced BSL3+ biosafety laboratories which are over and above the minimum requirements of the WHO BSL3 international biosafety standards.
While this paper is not intended to be a complete treatment of biosafety design particular attention is paid to biosafety facility design and construction issues including conflicts between personnel protection (biosafety) vs product protection (cleanroom), the importance of Risk Assessment in choosing the appropriate biosafety level and control measures, the critical linkage between design and a schedule of performance verification tests, common flaws and failures arising during commisioning & qualification and the importance of air leakage measurement in the verification of the Secondary Containment Barrier.

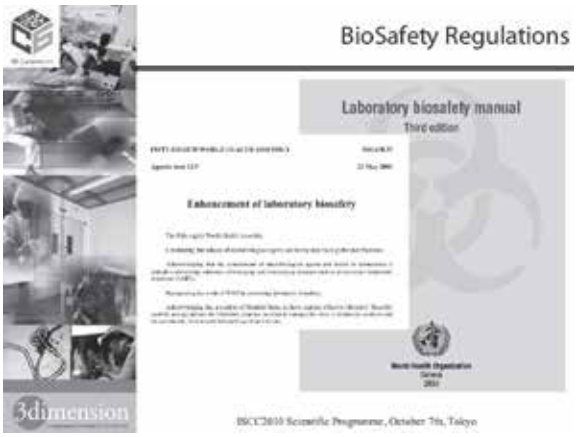
Introduction
The biosafety world has changed dramatically in the past ten years and is continuing to change. New microorganisms have appeared and old diseases have re-emerged. Biosecurity is now a significant risk factor. Infectious diseases today ignore geographic and political boundaries and constitute a global threat that puts every nation and every person at risk. In this age of expanding travel and international trade, infectious microbes are transported across borders every day, carried by infected people, animals, insects and goods. This has caused a growing concern for the authorities in the region and around the world as these outbreaks are often difficult to control and the spread across borders within the region and around the world can be so rapid that countries affected are unable to respond adequately. In order to respond to outbreaks effectively early isolation and identification of the causative agents becomes a requirement of paramount importance in the design and implementation of an effective disease control program. Countries lacking adequate biosafety laboratory capacity for preparedness and responsiveness to emerging diseases and biosecurity risks represent a real threat to global health and security. Laboratory containment capacity and biosafety are thus part of the important technical capabilities required by countries for effective public health safety and security.

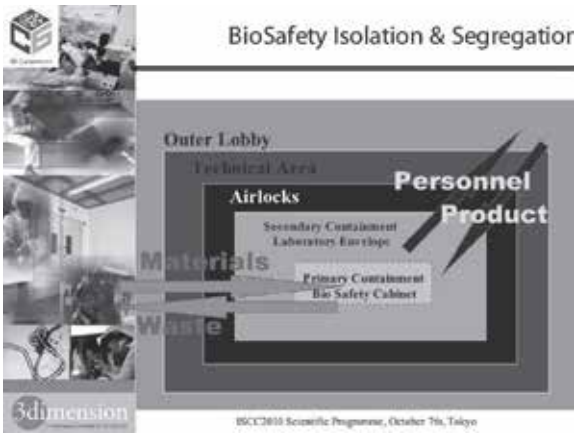
Personnel Protection (Biosafety) vs Product Protection (Cleanroom) Principles
The term biosafety is used to describe safe methods for handling infectious materials in the laboratory. The purpose of biosafety is to reduce or eliminate exposure of laboratory personnel, associated persons, and the outside environment to potentially infectious agents. A biosafety lab is not a cleanroom and Health and Safety is the dominant concern. Personnel who work in a laboratory handling infectious substances are at risk of exposure to the agents they handle and laboratory acquired infections (LAIs) are not uncommon.



Aerosolised pathogens present a serious risk in terms of inhalation, ingestion and contact with mucous membranes. Their infection routes are well developed and therefore safe working protocols aligned with correct equipment selection and PPE are critical in controlling LAIs. These factors have driven the increase in high containment facilities and the need to contain the increased risks involved.

Biosafety is provided by a combination of operational practices, containment equipment and facility design. The most important aspects of biosafety are the practices and procedures used by trained laboratory personnel. The World Health Organization's *Laboratory Biosafety Manual* states that "no biosafety cabinet or other facility or procedure alone guarantees safety unless the users operate safe techniques based on informed understanding." It is the responsibility of everyone involved including managers, laboratory staff, maintenance personnel, vendors, etc. to act, operate and behave in a safe and compliant manner.

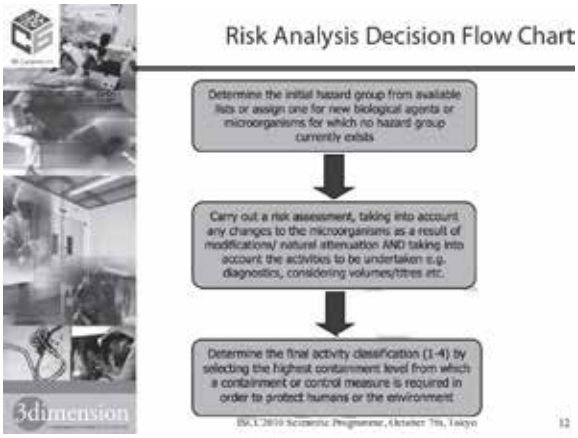




Risk Assessment

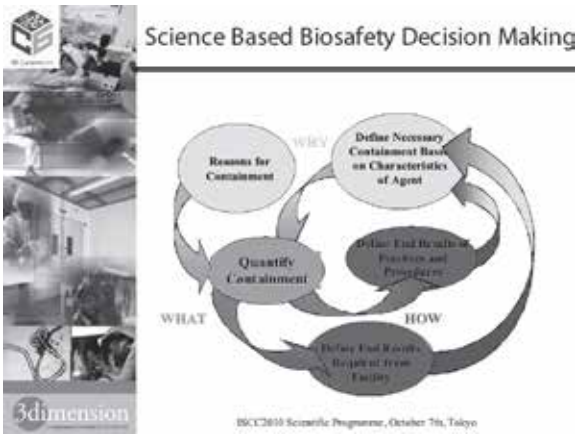
Risk assessment is the first critical step in the selection of an appropriate containment level for the microbiological work to be carried out. A detailed local risk assessment should be conducted to determine whether work requires biosafety containment level 1, 2, 3 or 4 facilities and operational practices.
In addition to the inherent characteristics of the biological agent, the following factors associated with the laboratory operation should also be carefully analysed:

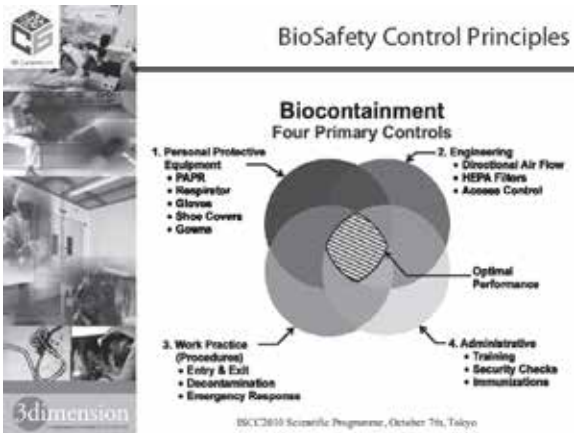
- potential for aerosol generation
- quantity
- concentration
- agent stability in the environment (inherent biological decay rate)
- manipulation including amplification
- type of work proposed (e.g., *in vitro*, *in vivo*, aerosol challenge studies)
- use of recombinant organisms



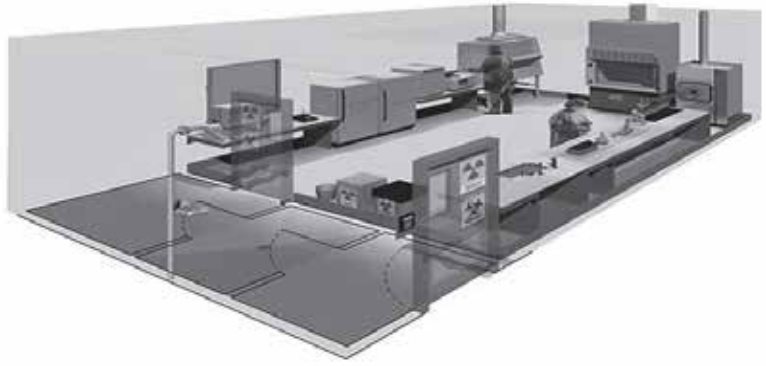
The World Health Organisation gives four classifications of organisms according to risk group and these are used to categorise the relative hazards of infective organisms. The factors used to determine which risk group an organism falls into is based upon the particular characteristics of the organism, such as:
- pathogenicity
- infectious dose
- mode of transmission
- host range
- availability of effective preventive measures
- availability of effective treatment.

High Containment Biosafety Design Principles
It is the specific responsibility of the design and construction team with clear direction from the Biosafety User Group to design and build high containment biosafety labs in such a way as to take into account all the risks, expected operation and the likely lifecycle of the facility including quirks, faults, unexpected events and challenges. In this regard decisions should be science based with good engineering biosafety control principles and practice.





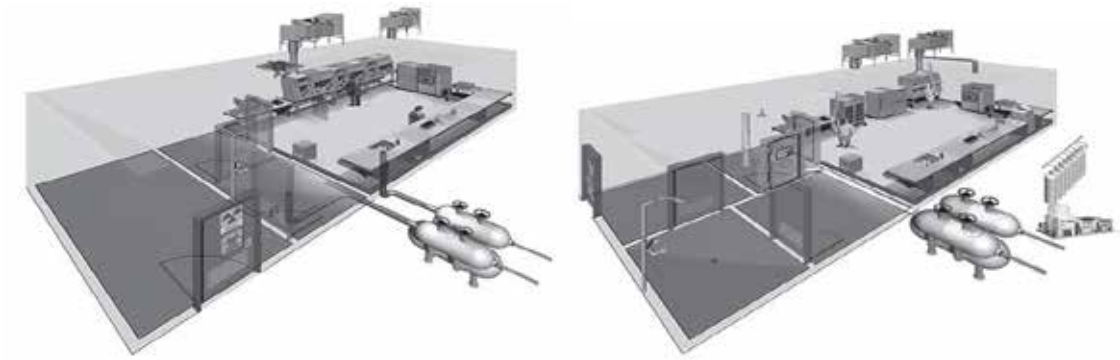
At Hazard Group 3 and 4 these pathogens produce very serious human diseases, are life threatening and often untreatable. They are considered to be readily transmitted from one individual to another, or from animal to human or human to animal, through direct or indirect means of infectious route. The concept of the Primary Containment barrier of using BioSafety Cabinets (BSCs) with appropriate equipment and processes contained within, such as centrifuges with sealed rotors or safety cups is well developed. Significant emphasis is now placed on appropriate personal protective equipment (PPE) including a minimum of lab coats, head and shoe protection, gloves and protective eyewear. In an increasing number of cases different levels of personalised respiratory headsets or complete isolating breathing suits are being used which allows the use of chemical showers as a decontaminating exit process.



Biosafety Level, BSL3

The concept of the Secondary Containment barrier, outside of BSL4 is less well developed. This secondary containment barrier is the external boundary of the laboratory envelope. This is the rigid impermeable barrier that protects the external environment. This secondary containment barrier is designed to contain any aerosolised pathogens not contained in the BSCs and prevent any breach and leakage of bio-contamination to the external environment. This is the design space where the concept of an enhanced BSL3 or BSL3+ facility arises. Based on the risks associated with unknown pathogens, bio-security, cross contamination and manipulation/ amplification processes increased containment and protection concepts are utilised. These include the use of Effluent Decontamination Systems (EDS), double ended autoclaves, decontamination systems such as chemical showers and enhanced personal protection.

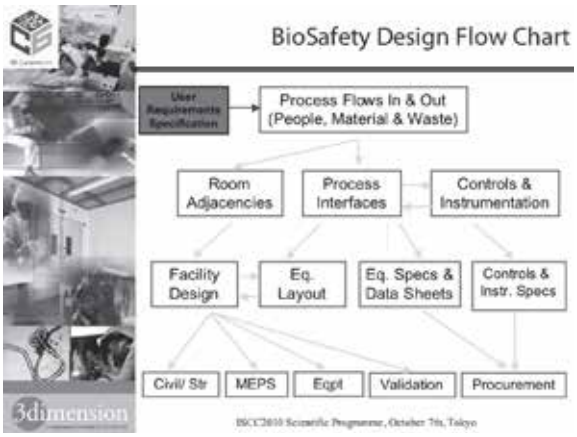
Biosafety Level, BSL4 Concepts – Isolation vs Isolation Personnel Suits

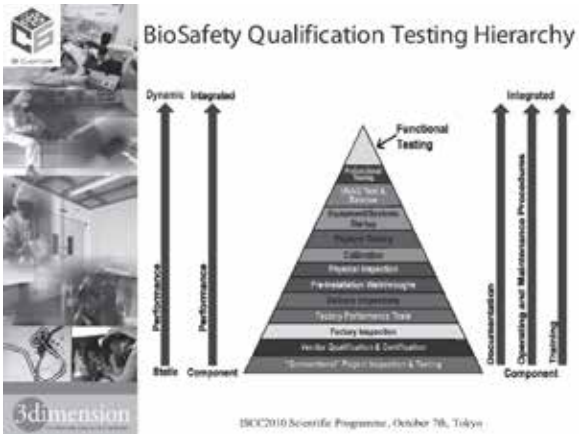


By way of comparison, at Biosafety Level BSL4 the emphasis is on maximum containment of the infectious agent(s) by complete sealing of the facility perimeter, use of balloon seal doors and dunk transfer tanks with confirmation by pressure decay testing; isolation of staff from the pathogen by his or her containment in a positive pressure suit or containment of the pathogen in a Class III Isolation BSC and decontamination of staff on exiting plus exhaust air and all other effluents produced in the facility. Based on risk assessments BSL3+ lab facilities use some of these techniques.

Commissioning & Qualification to meet Performance Verification Tests

Enhanced biosafety design starts with a Risk Assessment and then translates this into a schedule of individual Performance Verification tests. The detailed design then commences from the User Requirements Specification (URS) through functional design focused on meeting the listed performance verification tests. Developing a comprehensive Commissioning and Qualification Plan that integrates the requirements of the User Groups, Designer and Constructor ensures there are no gaps in communication and the WHO 2004 Biosafety guidelines are met with the greatest certainty of performance of 3rd party independent certification.





Common flaws and failures in the commissioning and qualification of BSL3+ labs come from a lack of attention to detail in either the design, system or component specification or construction execution.
Examples include:
- Reversal of airflow during failure conditions:
Maintaining containment through directional airflow is extremely important in the operation of high containment facilities. Inadequate stress/robustness testing of control systems both at design and commissioning stages means that the biosafety lab may go positive under certain conditions and this constitutes a critical failure scenario.
- Verification of Decontamination Modes:
Unless critical vendors, design components, decontamination modes and programme sequences, and User Group prootocols and procedures are co-ordinated adequately and well in advance the gaseous decontamination of the facility is a problem. Corrective action takes time and retesting.
- Prototype systems and inadequately developed solutions:
Unproven systems and solutions -- ranging from penetration design details, effluent decontamination systems, tissue digesters and autoclaves to new airflow controls strategies, architectural layouts, and engineering designs -- are consistently the cause of significant cost and schedule impacts due to fine tuning, adjusting, and potentially redesigning components that do not meet the performance requirements. While innovative solutions should definitely be considered and applied proper testing with mock ups must be carried out in advance to verify the design.
- Differential negative pressure cascades:
Proper configuration and control of the biosafety lab suite pressure differentials is always a challenge. Depending on air balancing approaches and controls strategies, the process of getting a final air balance with a stable system that is capable of alarming at cascading differential pressure gradients from high to low areas of containment can be very time consuming and repetitive until consistently achieved.

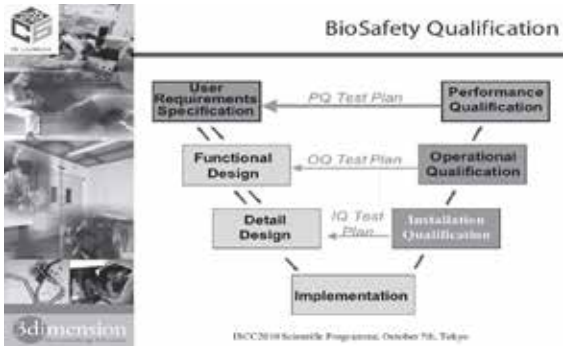
Secondary Containment Barrier & Decontamination
Biosafety Lab sealability for decontamination is a key requirement of the WHO 2004 Biosafety guidelines. Traditionally vapourised formaldehyde was used to decontaminate a biosafety lab. However formaldehyde is recognised as a personal safety hazard as it has been proven to be carcinogenic. There are now viable alternatives to gaseous formaldehyde fumigation, including vapourised hydrogen peroxide and also chlorine dioxide. These agents have lower exposure levels and semi automated processes have been developed to remotely control the decontamination process and mitigate personnel safety risks. There is increasing evidence that these have broad spectrum, rapid antimicrobial decontamination efficacy against a wide range of microorganisms. However the activity of any gaseous decontamination process will vary depending upon the type of surface being decontaminated. Porous materials in particular demonstrate poor penetration of these alternative agents in comparison with other materials and may require longer cycle times.

Secondary Containment Barrier & BSL3+ Lab Envelope Sealability
Single point responsibility should be given to one biosafety specialist to accept and deliver on the performance responsibility for the secondary containment barrier, i.e. the biosafety lab envelope which acts as a specific pathogen free (SPF) barrier. This ensures a "womb to tomb" approach of a biosafety specialist with knowledge of the process, the equipment and the systems involved. Walls and ceilings plus associated accessories of windows and doors are standard design and selection details. However the critical and weakest link in the secondary containment barrier is the design and management of penetrations, which should be kept to a minimum. A detailed penetration strategy should be developed with a schedule of standardised and tested details. Containment leakage is directly proportional to the physical joint/ connection circumferential length or distance of all the penetrations. The integrity of the joint, the robustness of the seal connection and the ability to withstand building movements over the facility lifetime are the critical factors. A consistent, repeatable and quantitative test method is required to demonstrate compliance on an ongoing basis.

Secondary Containment Barrier & Air Leakage Testing
Traditionally the driver for sealability was driven by the health and safety risk to the external environment associated with a leakage of the decontamination fumigant, normally vapourised formaldehyde and not necessarily the risk of an infectious agent. However in recent years risk assessment and analysis have

driven additional measures to an enhanced BSL3 or BSL3+ biosafety level. As part of the need to protect the external environment there was a need for a repeatable measurement of the secondary containment barrier. The WHO 3rd Edition 2004 biosafety manual recommends that countries adopt national codes of practice based on their guidance. Some countries specify smoke plume testing and/ or room smoke penetration tests to demonstrate sealability but this is very much a qualitative and subjective test which is difficult to repeat on a consistent basis. Other countries have adopted specific leak testing requirements which are the same as BSL4 to demonstrate compliance.
ISO 13829: 2000 deals with the thermal performance of buildings and includes a test for the determination of air permeability or air tightness of buildings. This focuses on an acceptable leakage loss rate in terms of the surface area of the perimeter so it is expressed in m3 per second per m2 and uses a modified fan pressurisation method from an earlier ISO standard ISO 9972:1996.
However what is becoming more popular is the combined Australian and New Zealand Standard giving guidance on the certification of a Physical Containment Level 3 laboratory, and was published in 2006. This states that "A PC3 (BSL3) laboratory should be constructed so that it achieves upon commissioning an air leakage rate, at a differential pressure of 200Pa, of no more than 120L/min. At all times after commissioning an air leakage rate of no more than 1200L/min should be maintained." The same criteria is applied to PC4 (BSL4) facilities. The standard requires verification every 3 years which seems too long.
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. From a secondary containment perspective such a leakage test is the ultimate proof of containment.


Air Leakage Test Rig photo courtesy of Clean Air Technologies



Conclusions

Changes in the global biosafety environment and resulting risk assessments have driven the need for an increasing number of high containment biosafety facilities. Most of these will be of the enhanced BSL3 or BSL3+ biosafety lab requirement which is beyond the minimum requirements for BSL3 in the WHO Laboratory Biosafety guidance, 3rd Edition, 2004.
More recent national standard requirements along with the availability and a clearly demonstrable performance of new technologies, processes and test equipment mean that a greater certainty of performance and containment at both the primary and secondary containment barrier can be achieved. The final decision to adopt these technologies, processes and test methods will depend on the nature of the biosafety threat and the associated risk assessment over the lifetime of the biosafety facility.

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