Facility design for containment

Gordon Farquharson, July 2016
Agenda

• Understanding the hazards.
• Containment principles.
• Primary and secondary containment.
• Facility features:
  • Layout & Air locks.
  • Pressurisation.
  • Leakage.
  • HVAC configuration & Air filtration.
Understanding the hazards
• Toxic effect likely to be dose related.
• Ability to metabolise varies.
• Can be very difficult to render safe. May have to rely on cleaning.
• Broad occupational health and cross-contamination rules apply.
• Industry defines OELs & OEBs, and develops hazard risk mitigation measures.
• GMPs express cross-contamination ADE principles.

• Approach to risk management:
  • Risk assessment.
  • Define mitigation measures.
  • PPE a last resort.
  • Prove performance of equipment & systems.
  • Document rationale.
  • Explain and GMP/SHE conflicts.
• Harmful effect sometimes dose related.
• One bacteria could proliferate and kill/injure you.
• Severity of harm organism related.
• Can be inactivated by sterilisation or alternative bio-decontamination.
• There are bio-safety rules and guidance classifying levels of risk (BSL 1-4), and associated risk mitigation measures.

• Approach to risk management:
  • Risk assessment.
  • Define mitigation measures.
  • PPE a last resort. May not be acceptable in some markets.
  • Prove performance of equipment & systems.
  • Document rationale.
  • Explain and GMP/SHE conflicts.
- Harmful effect dose related.
- Ability to metabolise varies.
- Can be very difficult to render safe. May have to rely on cleaning.
- Can penetrate barriers.
- Often long half-life.
- Broad occupational health and cross-contamination rules apply.
- Industry defines safe limits & develops hazard risk mitigation measures.

- **Approach to risk management:**
  - Risk assessment.
  - Define mitigation measures.
  - PPE a last resort. Prove performance of equipment & systems.
  - Document rationale.
  - Explain and GMP/SHE conflicts.
Containment principles
Principles of handling hazardous materials – an escalating approach.

• Use an alternative less hazardous material.
• Dilute the hazardous agent.
• Work in a less hazardous material phase – liquid vs gas or solid/powder.
• Handle materials in closed systems.
• Place open systems in primary containment enclosures with secondary containment and PPE as appropriate.
• Place open process in containment room with reliance on PPE for operator protection.
Principles

Closed process

Open process in isolator

Open process
Operator PPE
Open aseptic process in an isolator

- Which way would you go?
  - -ve or +ve pressure isolator
  - Leakage integrity of isolator
  - Cleanliness Grade of the surrounding room
- Depends on the RISK of an adverse event:
  - Operator exposure vs Sterility assurance.

Grade C/D Room +ve

Grade A Isolator
+ve or -ve
Facility features

*Layout, Air locks & Pressurisation*
Airlocks in a containment scenario

Sink

Process room
++ve

A/L
+ve

Sink
A/L
-ve

Bubble

Process room
- -ve

A/L
-ve

Bubble
A/L
+ve

Cascade

Process room
- -ve

A/L
-ve

Safe corridor 0

© PharmOut 2016
Facility features

*Room leakage*
Leakage routemap

Choose Containment Standard

Select Leak tightness – Level

Choose test method
Available standards & guidance

Generally (exception Health Canada) national containment guidelines for human & animal pathogens, and genetically manipulated organisms are silent about room or device air-tightness (specific values).

• Means we have to use a risk based approach supported by the available guidance and standards.

Most significant/important guidance & standards are:

• EN 12469:2000 – Microbiological safety cabinets.
• AS/NZS 2243.3-2002 Safety in laboratories - Microbiological aspects and containment facilities.
• Canadian Guidance lbg_2004_e (Matrix 6 – Room Integrity).
• ASTM : E 779 – 03, Standard Test Method for Determining Air Leakage Rate by Fan Pressurization
Enclosure Leakage

Most common test methods

- Pressure decay (low leakage small enclosures, gloves)
- Pressure hold or leakage rate (high leakage & large enclosures)
- Oxygen diffusion testing methods can be used (low leakage small enclosures, gloves)
- Soap bubbles, aerosols, and ammonia can be used to trace leaks.

For test methods:

- EN/ISO14644-7 “Separative Enclosures”
- EN 12469 for microbiological safety cabinets.
- NSF 49 for microbiological safety cabinets.
- Lots of good information from the nuclear industry:
  - e.g. ISO 10648-2 “Containment Enclosures- Classification according to leak tightness and associated checking methods”.

© PharmOut 2016
Choosing a level of leakage(1)

This needs to be a risk based decision. Take into account:

- The level/class of biological agent.
- The concentration of the biological agent inside the containment boundary.
- The concentration of bio-inactivation chemical (usually formaldehyde, chlorine dioxide or hydrogen peroxide) inside the containment boundary.
- The potential for escape through the containment envelope (usually HVAC failure modes will present the worst case situation), and the relationship with the resilience of the associated HVAC system.
- Also critical if a classified cleanroom is held at negative pressure.
Choosing a level of leakage (2)

The clearest standard to use is AS/NZS 2243.3-2002

- Appendix G applies. This considers the following:
  - The risk of biological agent escape (pathogen hazard)
  - Acceptable loss of bio-decontamination gas commensurate with obtaining the necessary kill
  - The acceptable leakage of the bio-decontamination gas through the fabric
- It defines a leakage coefficient $\beta$ ($m^3/Pa.\sec$)
- Gives examples of $\beta$ for isolators, Australian CSIRO, US Dept of Agriculture, and Health Canada
- Gives suggested leakage levels:
  - CL3 & 4 using Class III MBSCs, $\beta = 10^{-4} \rightarrow 10^{-5}$ at 200 Pa.
  - CL 3 or 4 using room as primary containment, $\beta = 10^{-6}$ at 200 Pa.
Choosing a level of leakage (3)

Look at the application of these leakage levels using AS/NZS 2243.3-2002:

- Consider a CL3 room using Class III MBSCs
- $\beta = 10^{-4} \rightarrow 10^{-5}$ at 200 Pa from the standard
- This gives a leakage range of $20 \rightarrow 2$ litres/sec at 200 Pa for any size room
- It is also necessary to test the safety & efficacy of the bio-decontamination process for the completed facility

Other common leakage specifications – there are many used by different organisations.

- $\sim 0.1 \text{ m}^3/\text{m}^2.\text{hr}$ – based on surface area of containment
Pressure Standards

The Australian / New Zealand standard concerning leak tightness of containment facilities AS/NZS 2243.3-2002
Pressure Standards

ASTM Test Method standard
ASTM : E 779 – 03
Specification of fabric & finishes

Options for construction
- In-situ (stick built)
- Pre-fabricated & pre-finished systems (cleanroom)
- Evaluation of options

Specification of components & details
- Services penetrations
- Windows
- Doors

Build and approve mock-up unless prior experience exists
Specify the Containment solution
Materials, components
Services entry details

Services distributed in “safe” service chase. Entries inspectable both sides.

Walk-in service chase between clean containment labs
Services entry details
Ducts & pipes enter via service plates on ceiling membrane. Entries inspectable both sides.
Services entry details
Industrial transits used to provide flexible entry of cables and pipes. Inspectable both sides.
Door control mechanism (access & interlock), surface mounted in sealed assembly to avoid wall penetrations.
Construction & Installation QA

(Including Leak Testing)
QA Construction & Installation

Clean construction protocol

- Control materials
- Inspect build quality progressively

Leak testing – select appropriate method

- Pressure hold – leak rate test. (most suitable for CL3 and CL4 cabinet line rooms.
- Pressure decay (most suitable for Class III MBSCs and CL4 rooms).
- Photometer & aerosol method (method suitable for seeking leak pathways).
- Ultrasound (method suitable for seeking leak pathways).
- Tracer gas (method suitable for seeking leak pathways).

Undertake leak testing progressively

- At the conclusion of the construction of the basic shell.
- When service penetrations have been cut and service entries installed.
- When final finishes have been applied.
Pressure Hold Test Apparatus

Testing in accordance with ASTM : E 779 – 03.

Very similar to a ductwork leak-rate test. Measures the air volume required to compensate for leakage and maintain constant pressure. Typical test pressure 50-200 Pa.
Pressure Hold Test

Apparatus

Test being applied to CL3 and 4 containment facilities.

Notice the blank door used for this test, with pressure tapping connected to the test apparatus.

This test was used to prove compliance with a leakage rate specified in accordance with AS/NZS 2243.3-2002. The test was carried out in accordance with the principles specified in ASTM : E 779 – 03

Image courtesy of Bovis Lend Lease
And finally
Ongoing Operations
Periodic Room Leak Testing
Routine room leakage test

Not mandated in regulations (typical for MBSCs).
Becoming more common – safety risk management.

Typical frequencies

- 6 monthly
- Annually
- For cause – e.g. After major maintenance or works.

Infrastructure should be build in to do this conveniently

- Ability to isolate the HVAC system and any bio-safety cabinet connections.
- Provision of a port to apply test pressure to each separate enclosure to be tested.
- Availability of test points for pressure monitoring (and temperature in the case of the pressure decay test).
Facility features

*HVAC systems & Air filtration*
Potent Compounds - OSD, API

Use of HEPA filters

• Cross-contamination control in recirculation air handling systems.

• Prevention of discharge of potent compound dust to atmosphere – security or policing filters.

• HEPA filters of H13 or H14 specification are chosen because they can be leak tested:
  • Aerosol photometer method – scan or average leak test.
  • Particle counter method.
Let’s look at some of the position options

There are several possible locations:

- **Recirculation systems** –
  1. Final filter in air supply AHU.
  2. Terminal supply to room.
  3. In Return air duct to AHU.
  4. In Return at room boundary.

- **Once through systems**
  5. In Exhaust air duct to atmosphere.
  6. In Exhaust at room boundary + In Exhaust to atmosphere
1. Recirculation—HEPA at AHU Supply

Note: 1 CVD on every room return is required due to uneven loading of return air filters. Alternative is for ONE return air filter bank and a constant volume control on return fan. Note that DP gauges on rooms and filters, room temp and RH control, and supply fan control are not shown.
2. Recirculation–HEPA at Room Supply Terminal

Note: CVD on every room return is required due to uneven loading of return air filters. Alternative is for ONE return air filter bank and a constant volume control on return fan. Note that DP gauges on rooms and filters, room temp and RH control, and supply fan control are not shown.
3. Recirculation – In return duct to AHU

F7 - F7

Option H13

G4 - G4

Process Room 1

Process Room 2

© PharmOut 2016
4. Recirculation – In return at room boundary
5. Once Through – HEPA at room exhaust

Notes: 1. The example is appropriate for single product, multi-product campaign, or multi-product concurrent operation.
2. Optional dehumidifier not shown.
6. Once Through –
HEPA at room exhaust + System Exhaust

Notes:
1. The example is appropriate for single product, multi-product campaign, or multi-product concurrent operation.
2. Optional dehumidifier not shown.
Extract - Double Exhaust room filter (with bag-in/bag-out)
Bag-out systems

- Only provides protection to personnel during filter change.
- Essential in chemical and potent compound handling safety.
- Should not be used in bio-safety applications.
- Is a cumbersome manipulation to execute well.
- Consumes additional space in technical areas.
In-situ testing options
& developments
In-situ leak test methods

Most common

- Aerosol/Photometer method using Emery 3004 PAO.
- Most parties are happy with volumetric, global or average leak test; some require face scan leak test.

Some

- Use particle counter with enhanced aerosol.
- Most happy with volumetric or average leak test; some require face scan leak test.
- A few using automated face scan particle counter method.

A few

- Use biological challenge (bacillus Subtilis-Collison aerosol generator & cascade impactor sampler)
Particle counter face scanning

Automated face scan using particle counter system – MPPS, rapid and minimal access intervention required.

Manual Face-scan using an adapted bag-out section.

 Courtesy Camfil-Farr
Risk of missing a leak – single hole equivalent – PAO & Photometer

- 80 μg/litre Emery 3004 challenge
- 610 x 610 filter handling 0.5 m³/sec
- Assume all leakage through single hole (a simple approximation)
- This is why a scan test is better than an average volumetric test.
- This is why for higher hazard groups, 2 HEPAs in series are required.

<table>
<thead>
<tr>
<th>single hole</th>
<th>0.01%</th>
<th>0.003%</th>
<th>0.001%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mm dia</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>2 mm dia</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>3 mm dia</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>6 mm dia</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>10 mm dia</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Will different leak test accept criteria detect the leaks?

Global Leak Test
A Filtration Route map

• Be aware of the filter grades and how they are tested by the suppliers.
• Understand the configuration options.
• Define the stages of filtration required (Supply & Extract). Including pre-filters to prolong HEPA life.
• Select the in-situ leak test required (Face scan vs Average Volumetric).
• Configure filter network.
• Develop the leak testing procedure (on-line or off-line, depending on redundancy in the design).
• Review change-out procedure.
Thanks for your attention
Questions???
This presentation has been prepared and delivered by:-

Gordon J Farquharson
Principal
Critical Systems Ltd
Consulting in Safety & Quality Critical Systems
Guildford, Surrey, GU1 2SY, UK
tel +44 (0)1252 703 663
gjf@critical-systems.co.uk
www.critical-systems.co.uk