Cleanrooms & Containment Facilities: An Introduction

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Business Profile

Delivery of operationally critical facilities & systems based on a design build or design developed approach within key market sectors.

Pharmaceutical
Biotechnology
Healthcare
Nutraceuticals
Aerospace & Defence
Definitions

**Cleanroom:** A room or suite of rooms, purpose designed and constructed, with fabric and environmental control measures to limit the propagation, introduction and maintenance of airborne contamination.

**Containment Room:** A room or suite of rooms, purpose designed and constructed, with fabric and environmental measures to offer physical and bio-security control.
Classification Guidance

Containment Laboratories and Grade A - D

ACDP – Advisory Committee on Dangerous Pathogens
ISO Standard 14644 Pts 1 - 8
SAPO – Specified Animal Pathogens
GMP Guidelines (Orange Guide)
GMO (CU) – Genetically Modified Organisms
ISPE Baseline Guides
LPCB – Loss Prevention
ATCSA – Anti-Terrorism, Crime
Classification Ranking

- **Cleanrooms**
  - ISO 1
  - ISO 2
  - ISO 3
  - ISO 4
  - ISO 5 (Grade A)
  - ISO 6 (Grade B)
  - ISO 7 (Grade C)
  - ISO 8 (Grade D)
  - ISO 9

- **Containment Labs**
  - CL4
  - CL3
  - CL2
  - CL1
  - Bio-security Management

Legend:
- Highest
- Lowest
- Particle Management
- Particle + CFU Management
Sector Influence

Pharmaceutical
Biotech
Bio-sciences
Healthcare

Micro-electronics
Nanotechnology
Aerospace
Defence
Optics
Medical Device

BS EN ISO Guidelines

Regulatory influenced
- MHRA
- FDA
- VMD
- NICE
- HTA
- HFEA

C.GMP Guidelines
Sector Influence - Examples

Food & Drink – Sports Drinks
Particle Size Awareness

$1\mu m = 1$ millionth of a metre $= 0.000001m$

Particle Size - Cleanroom Scale $> 0.1\mu m$ to $> 5\mu m$

- Pin head Ø $= 1500 \mu m$
- Human hair Ø $= 40 - 300 \mu m$
- Cement dust $= 3 - 100 \mu m$
- Red blood cells $= 5 - 10 \mu m$
- Bacteria $= 0.3 - 60 \mu m$
- Viruses $= 0.005 – 0.3 \mu m$
Classification Referencing

Grade A:
The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed in a range of 0.36–0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated. A unidirectional air flow and lower velocities may be used in closed isolators and glove boxes.

Grade B:
For aseptic preparation and filling, this is the background environment for the grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products. The airborne particulate classification for these grades is given in the following table.

<table>
<thead>
<tr>
<th>Grade</th>
<th>at rest (b)</th>
<th>in operation (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>maximum permitted number of particles/m³ equal to or above (a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 μm (d)</td>
<td>5 μm</td>
</tr>
<tr>
<td>A</td>
<td>3 500</td>
<td>1(e)</td>
</tr>
<tr>
<td>B</td>
<td>3 500</td>
<td>1(e)</td>
</tr>
<tr>
<td>C</td>
<td>3 500 000</td>
<td>2 000</td>
</tr>
<tr>
<td>D</td>
<td>3 500 000</td>
<td>20 000</td>
</tr>
</tbody>
</table>

Recommended limits for microbial contamination (a)

<table>
<thead>
<tr>
<th>Grade</th>
<th>air sample cfu/m³</th>
<th>settle plates (diam. 90 mm), cfu/4 hours (b)</th>
<th>contact plates (diam. 55 mm), cfu/plate</th>
<th>glove print 5 fingers cfu/glove</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&lt; 1</td>
<td>&lt; 1 (d)</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>50</td>
<td>25</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>200</td>
<td>100</td>
<td>50</td>
<td>-</td>
</tr>
</tbody>
</table>

Notes:
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.

EU GMP
Classification Referencing

Lab standards derived from pathogens handled

**CL4** Biological agents that can cause severe human disease with risk of spreading + usually no effective treatment available: Ebola virus, congo haemorrhagic fever

**CL3** Biological agents that can cause severe human disease with risk of spreading + usually effective treatment available: TB, bacillus anthracis, yellow fever

**CL2** Biological agents that could cause human disease but unlikely to spread + effective treatment available

**CL1** Biological agents unlikely to cause human disease
Starting Point

Validation

Process?

Regulatory Impact

Architecture

M&E Building Services
Environmental Performance

Facility Pressure Control (critical)

Particulate Control (critical)

Temperature Control (process or occupants?)

Humidity Control (process or occupants?)

Noise Control (process or occupants?)

Lighting Control (process or occupants?)
Pressure Control - Cleanroom

Positive Pressure Control - Typical

- 0pa Corridor
- 15pa Airlock
- 25 - 30pa Cleanroom Preparation
- 40 - 45pa Cleanroom Core
Pressure Control - Cleanroom

Negative Pressure Control – Process Dictates

0pa
Corridor

40 - 45pa
Airlock

25 - 30pa
Cleanroom Preparation

15pa
Cleanroom Core
Pressure Control CL3

Negative Pressure Control – Process Dictates

- 0pa Corridor
- -15pa Airlock
- -30pa CL3 Lab Prep
- -45pa CL3 Lab Core
HVAC - Cleanrooms

Room Contamination

Biggest space contaminator - operators

Process shedding

Room clean-up rates
HVAC – Operational Principle

ISO 7 – ISO Grades B, C, D
HVAC - Operational Principle
HVAC - Cleanrooms

High level air in

Low level air out

HLFU

Grade B background

UDAF return air

Vertical UDAF

Low level air return

High level air make-up
Air change rates

ISO 9 – 8: Turbulent flow, terminal HEPA filters not required

ISO 7 – 6: Turbulent flow, terminal HEPA filters required

ISO 5 – 1: UDAF, terminal HEPA filters required
Air change rates – Typical Norms

ISO 9 – 8: Turbulent flow, terminal HEPA filters not required 5 – 15 per hour

ISO 7 – 6: Turbulent flow, terminal HEPA filters required 20 - 50 per hour

ISO 5 – 1: UDAF, terminal HEPA filters required Not calculated
Supply Air Quality

ISO 9 – 8: Turbulent flow, terminal HEPA filters not required
- F5 + F9

ISO 7 – 6: Turbulent flow, terminal HEPA filters required
- G4 + F7 + H14

ISO 5 – 1: UDAF, terminal HEPA filters required
- F5 + F7 + H12 + H14/15
Negative pressure cascade critical

Air change rate not as important as with cleanrooms

Extract air must be HEPA filtered

- 30 pa

10 - 20 per hour

Not calculated
Cleanroom - Service Interface

High air change rates promotes large void needs
CL3 – Service Interface

Bio-security risks promotes minimal service interface
Commissioning & Validation

**Commissioning:** Testing, proving & documentation of facility system/s to demonstrate and satisfy the safe functionality in accordance with the design criteria.

**Validation:** Qualification practices, fully documented, to provide the necessary assurance, through pre-defined test/s to prove that the critical systems operate in accordance with the facility design criteria.
Through critical System Impact Assessment only those systems with direct affect on/to the product will be qualified. In essence this is a roadmap for the validation process, setting the criteria for:

- The URS defines the project requirements without being overly prescriptive.
- The DQ checks the design against the URS.
- The IQ checks the physical installation against the drawings.
- The static system component performance check.
- The operational qualification (OQ) review.
Commissioning & Validation

Validation Activities

- Room differential pressures
- Air & water pressures
- Air & water particulate pressures
- Air change rate
- Room clean-up rates
- Filter integrity checks
- Re-verification of particle rate checks
- UDAF air velocities (0.45m/s ± 20%)
- Temperature & humidity checks
- Noise level checks
- System pressure testing
- Air & water volumes
- Validation OQ Activities
- Control functionality
- Lighting checks
- Micro-biological challenge
- Air patterns from smoke visualisation
The facility should be air-tight

Switching off at night & running costs

Need to ramp the fans up when the doors open

All my HEPA’s have failed

It won’t hold pressure – get the mastic gun!!