Facility Qualification

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References

PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME
Cleanroom

“A room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimise the introduction, generation and retention of particles inside the room, and in which other relevant parameters e.g. temperature, humidity and pressure, are controlled as necessary”

ISO 14644-1:1999

Willis Whitfield
Inventor of the modern cleanroom
(1919 – 2012)
### Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

<table>
<thead>
<tr>
<th>ISO classification number (N)</th>
<th>Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with equation (1) in 3.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0,1 µm</td>
</tr>
<tr>
<td>ISO Class 1</td>
<td>10</td>
</tr>
<tr>
<td>ISO Class 2</td>
<td>100</td>
</tr>
<tr>
<td>ISO Class 3</td>
<td>1 000</td>
</tr>
<tr>
<td>ISO Class 4</td>
<td>10 000</td>
</tr>
<tr>
<td>ISO Class 5</td>
<td>100 000</td>
</tr>
<tr>
<td>ISO Class 6</td>
<td>1 000 000</td>
</tr>
<tr>
<td>ISO Class 7</td>
<td></td>
</tr>
<tr>
<td>ISO Class 8</td>
<td></td>
</tr>
<tr>
<td>ISO Class 9</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE** Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level.
# Room grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>At rest</th>
<th>In operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5μm</td>
<td>5.0μm</td>
</tr>
<tr>
<td>A</td>
<td>3,520</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>3,520</td>
<td>29</td>
</tr>
<tr>
<td>C</td>
<td>352,000</td>
<td>2,900</td>
</tr>
<tr>
<td>D</td>
<td>3,520,000</td>
<td>29,000</td>
</tr>
</tbody>
</table>

ISO 14644-1/GMP Annex 1
Airborne Particles

Relative Particle size

- Thickness of Human Hair: ~100µm
- Visible Particle: ~50µm
- 0.5µm Particle
Planning for Facility Qualification

**Design Qualification**
- Requirements
- Concept Design
- Design Drawings & Specs
- Design Approval

**Installation Qualification**
- Construction Approval
- Facility Build
- Commission

**Operational Qualification**
- Functional Approval
- Facility Completed (As-Built)
- Process Equipment installed
- Facility At-Rest

**Performance Qualification**
- Operational Approval
- Fully Operational Facility
- Trained personnel present
- Process in Operation
Design, Construction & Start-up

• Requirements defined & agreed (URS)
• Criticality and Risks assessed
• Project Plan in place
• Quality Plan in place
• Formal Approved Design
Design, Construction & Start-up

- Construction according to Approved Design
- Change Control
- Cleaning Plan
- Commissioning Plan
- Acceptance Testing
Stages of Validation Testing

- DQ / Design Review
- IQ of the facility and HVAC system
- OQ of the environment-no personnel present
- PQ of the environment-personnel present
- All covered in a Validation Master Plan
Design Qualification (DQ) / Design Review

Annex 15 of PIC/S Guide to GMP for Medicinal Products:

“The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.”
Design Qualification (DQ) / Design Review

- Contamination control concept
- Personnel/materials flow
- Materials of construction
- Air supply/return
- Environmental monitoring
- Operations in separate/segregated areas
- Differential pressures, air change rates
Design Qualification (DQ) / Design Review

- Gowning
- Health, safety and environmental
- Facility layout, equipment
- Aesthetics, lighting, noise
- Temperature & humidity controls
- Documentation
- Calibration & Maintenance
Installation Qualification (IQ)

Annex 15 of PIC/S Guide to GMP for Medicinal Products:

“The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturers recommendations.”
Installation Qualification (IQ)-HVAC

Ensure that critical HVAC components are correctly installed:

- Terminal and AHU-mounted HEPA filters
  - Grade, details, leak tested

- Mechanical design mark-ups and updates carried out and ensure all components installed as shown

- Building Management System (BMS) configuration
Installation Qualification (IQ)-Facility

- Verify Materials of Construction
  - Walls, floors, ceilings, doors, etc
- Verify fixtures and fittings are correctly installed
- Correct installation of door interlocks & alarms
- Facility lights, sprinklers, fire detection
- Mechanical design/Drawing checks
- Calibration & Maintenance requirements
- Completion of HEPA filter integrity (leak) testing
  - Other work that could impact filter integrity must be first completed
### Operational Qualification (OQ) - Prerequisites

- **Facility IQ complete**
- **HVAC commissioning complete**
- **No OQ-impacting actions/work outstanding**
- **Sufficiently cleaned to commence environmental testing**
- **Operational and support SOP’s at least drafted**
- **HVAC OQ complete (if applicable)**
Operational Qualification (OQ)

Annex 15 of PIC/S Guide to GMP for Medicinal Products:

“The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.”
## Operational Qualification (OQ) Testing

<table>
<thead>
<tr>
<th>OQ Test</th>
<th>Typical Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airborne Particle Count</td>
<td>1-2 Days</td>
</tr>
<tr>
<td>Air Flow Velocity (unidirectional)</td>
<td>1 Day</td>
</tr>
<tr>
<td>Air Flow Rate (non-unidirectional)</td>
<td>1-2 Days</td>
</tr>
<tr>
<td>Room Air Change Rates</td>
<td>0.5 Day</td>
</tr>
<tr>
<td>Air Pressure Difference Test</td>
<td>Each day for 3 days*</td>
</tr>
<tr>
<td>Installed filter leak Test</td>
<td>1-2 Days</td>
</tr>
<tr>
<td>Airflow Direction/ Visualisation</td>
<td>1-2 Days</td>
</tr>
<tr>
<td>Temperature &amp; Humidity</td>
<td>Each day for 3 days*</td>
</tr>
<tr>
<td>Recovery Test</td>
<td>1-2 Days</td>
</tr>
<tr>
<td>Microbiological Levels</td>
<td>Each day for 3 days*</td>
</tr>
<tr>
<td>Lighting levels</td>
<td>0.5 Day</td>
</tr>
</tbody>
</table>

* *Testing can be carried out in parallel*
Performance Qualification (PQ) - Prerequisites

- Facility OQ complete
- No critical deviations open
- No PQ-impacting actions/work outstanding
- Training of staff has been completed
- Operational and support SOPs made effective
- EMS has been validated (if applicable)
Performance Qualification (PQ)

Annex 15 of PIC/S Guide to GMP for Medicinal Products:

“The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method, and product specification.”
PQ Testing

PQ “manned” testing normally associated with sterile/aseptic operations

PQ carried out to show that the procedures and Facility/HVAC can maintain conditions to the required levels during manned production

Testing locations should be similar (if not the same) as OQ
PQ Testing

- In operation non-viable particle monitoring
- In operation viable particle monitoring
  - Surface monitoring
  - Active air sampling
  - Settle plates
  - Operators: swabs & touch places

- Testing should be over and above that used for routine monitoring
- 3 days intensive monitoring-cover all shifts
Maintaining the validated state

• Huge effort to design, build, install & qualify facility

• Large investment and important to maintain the validated state

• Need to monitor the following:
  – Ongoing Calibration
  – Planned Preventative Maintenance
  – Performance of the Facility
  – Ongoing Training
Maintaining the validated state

- Change Control
- Maintenance & Calibration
- Managing Non-Conformances
- Training
- Periodic Reviews
- Routine Monitoring
Routine Monitoring

May be variability in the facility as a result of:

- HVAC performance
- Behaviour of personnel
- Controlled changes
- Adverse events
Routine Monitoring

- Continuous Particle Monitoring
- Air and Facility Microbial Monitoring
- Differential pressure, Temperature, Humidity
- Personnel Monitoring & ongoing training
- Suitable frequency
- Detailed Sampling Plan and SOPs
- Alert/Action limits
- Target Critical Areas (greatest risk)
  - Exposed product
  - Personnel activity
  - Specific operations
Proposed Changes to ISO 14644-1:1999

- Removal of 5.0µm particle spec limits for ISO 5.
- Remains current in PIC/S and EU GMP codes.

Table 1: The basic classification table proposed in ISO (DIS) 14644-1:2010. Concentration limits in brackets indicate requirements from ISO 14644-1:1999 that have been removed in the new version.

<table>
<thead>
<tr>
<th>ISO Classification Number (N)</th>
<th>0.1 µm</th>
<th>0.2 µm</th>
<th>0.3 µm</th>
<th>0.5 µm</th>
<th>1.0 µm</th>
<th>5.0 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO Class 1</td>
<td>10</td>
<td>(2)</td>
<td>10</td>
<td>(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISO Class 2</td>
<td>100</td>
<td>24</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISO Class 3</td>
<td>1 000</td>
<td>237</td>
<td>102</td>
<td>35</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>ISO Class 4</td>
<td>10 000</td>
<td>2 370</td>
<td>1 020</td>
<td>352</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>ISO Class 5</td>
<td>100 000</td>
<td>23 700</td>
<td>10 200</td>
<td>3 520</td>
<td>832</td>
<td>(29)</td>
</tr>
<tr>
<td>ISO Class 6</td>
<td>1 000 000</td>
<td>237 000</td>
<td>102 000</td>
<td>35 200</td>
<td>8 320</td>
<td>298</td>
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<tr>
<td>ISO Class 7</td>
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<td></td>
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<td>352 000</td>
<td>83 200</td>
<td>2 930</td>
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<td>3 520 000</td>
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<td></td>
<td></td>
<td>35 200 000</td>
<td>8 320 000</td>
<td>293 000</td>
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</tbody>
</table>

Of particular note for the pharmaceutical and related industries is the removal of 5.0µm particle specification limits for ISO 5 areas. While this is a significant shift and one which may have future ramifications for these industries, manufacturers need to be aware that the current PIC/S and EU GMP codes still require assessment of this particle size for both classification and monitoring events.
Proposed Changes to ISO 14644-1:1999

- New table for # of sample locations
- Remove the need to evaluate the 95% UCL for low sample location numbers (2-9)
- Measurements be taken at random from within each sub-division
- Can include locations identified as high risk

Table 2: Number of sample locations required with respect to cleanroom area.

<table>
<thead>
<tr>
<th>Area (m²) Less than or equal to</th>
<th>Min number of sample locations</th>
<th>Area (m²) Less than or equal to</th>
<th>Min number of sample locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>72</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>76</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
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<td>8</td>
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<td>64</td>
<td>12</td>
<td>436</td>
<td>25</td>
</tr>
<tr>
<td>68</td>
<td>13</td>
<td>500</td>
<td>26</td>
</tr>
</tbody>
</table>
Proposed Changes to ISO 14644-2:2000

• Now identifies that there is a difference between routine strategic testing and real-time (RT) monitoring

• Formal classification testing must be undertaken annually, as a minimum except:
  – where real-time air cleanliness monitoring and room pressure differential demonstrate ongoing control AND
  – where industry regulation allows longer period (that is, not within the pharmaceutical or related industries)

• New Annexes (RT monitoring system, monitoring air volume or air velocity in air treatment systems)
Activity - Environmental conditions

- Define the environmental conditions for the rooms in the facility diagram
- Work in groups
- Complete the worksheet
- Contribute to group discussion

30 mins
Activity – Test certificate review

- Review following test certificates:
  - Filter leakage test
  - Airborne particle count

- Identify any errors in the certificates
- Discuss with your group
- Contribute to overall group discussion
Thank you for your time. Questions?

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Senior Consultant

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