Facility Qualification

Eoin Hanley

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References

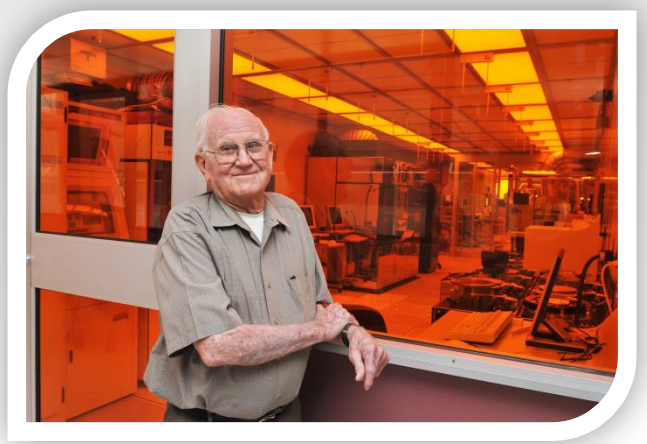
PHARMACEUTICAL INSPECTION CONVENTION

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)

ISO 14644-1:1999

Table 1 — Selected airborne particulate cleanliness classes for cleanrooms and clean zones

ISO classification number (*N*)	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)					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

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

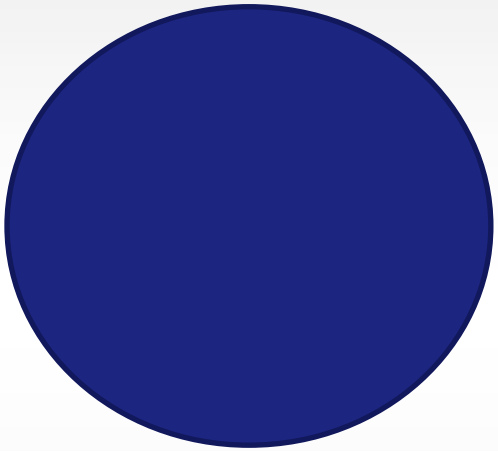
Room grades

Grade	Maximum permitted number of particles/m³ equal to or greater than the tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,520	20	3,520	20
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	not defined	not defined

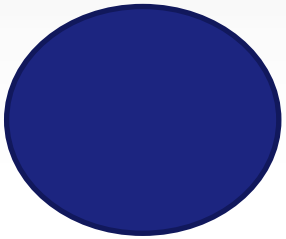
ISO 14644-1/GMP Annex 1

Airborne Particles

Relative Particle size



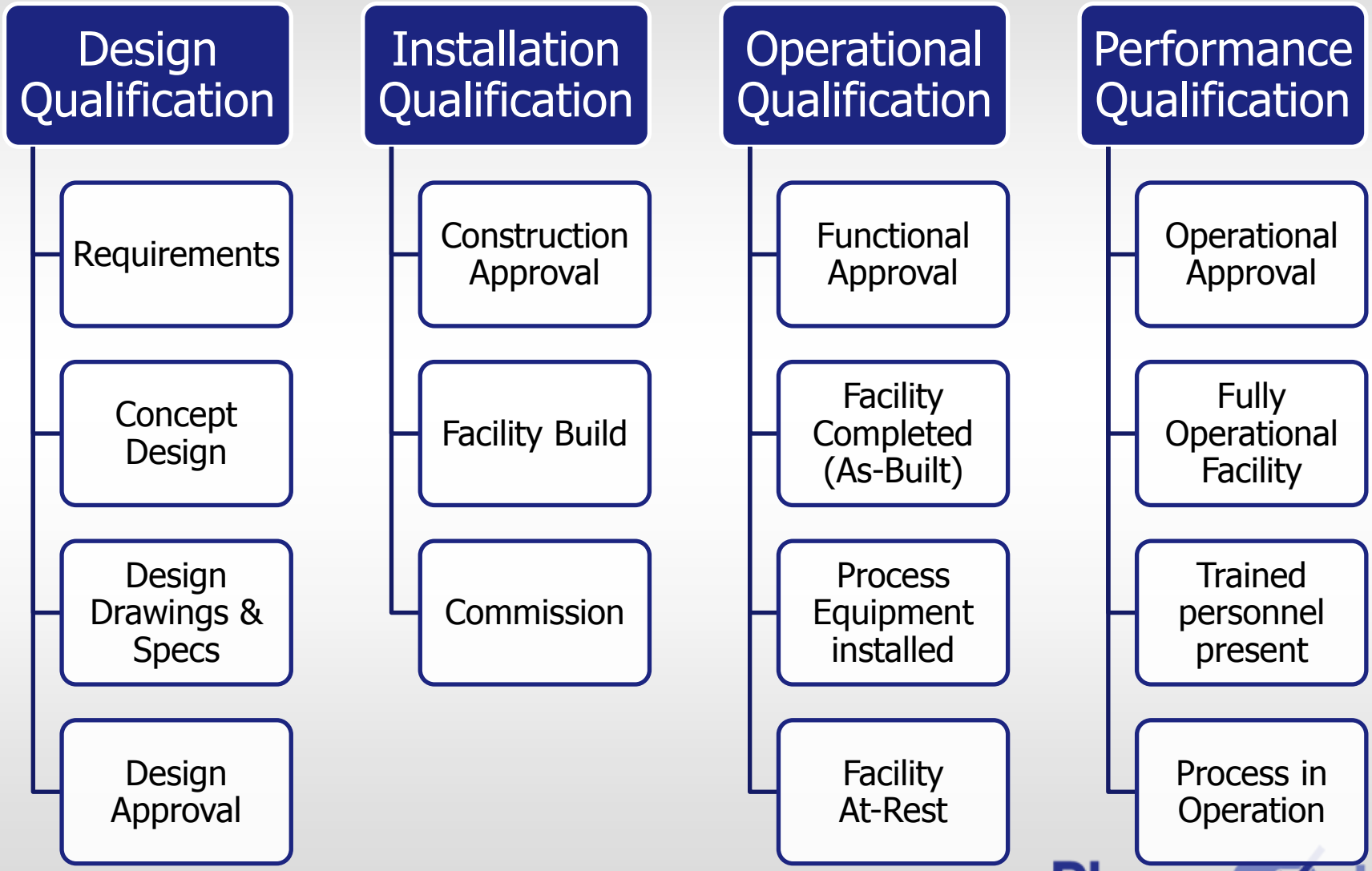
Thickness of Human Hair ~100µm



Visible Particle ~50µm

0.5µm Particle

Planning for Facility Qualification



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Design, Construction & Start-up

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

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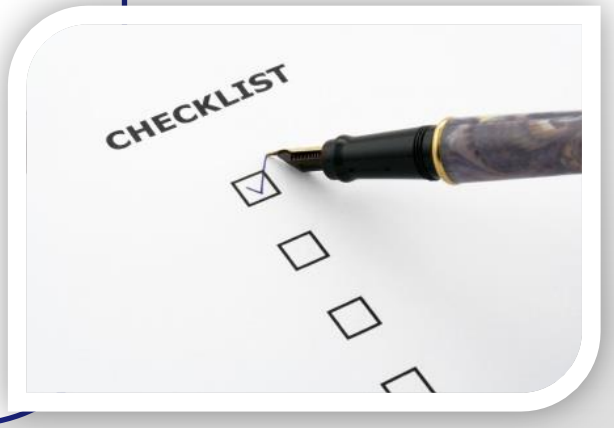
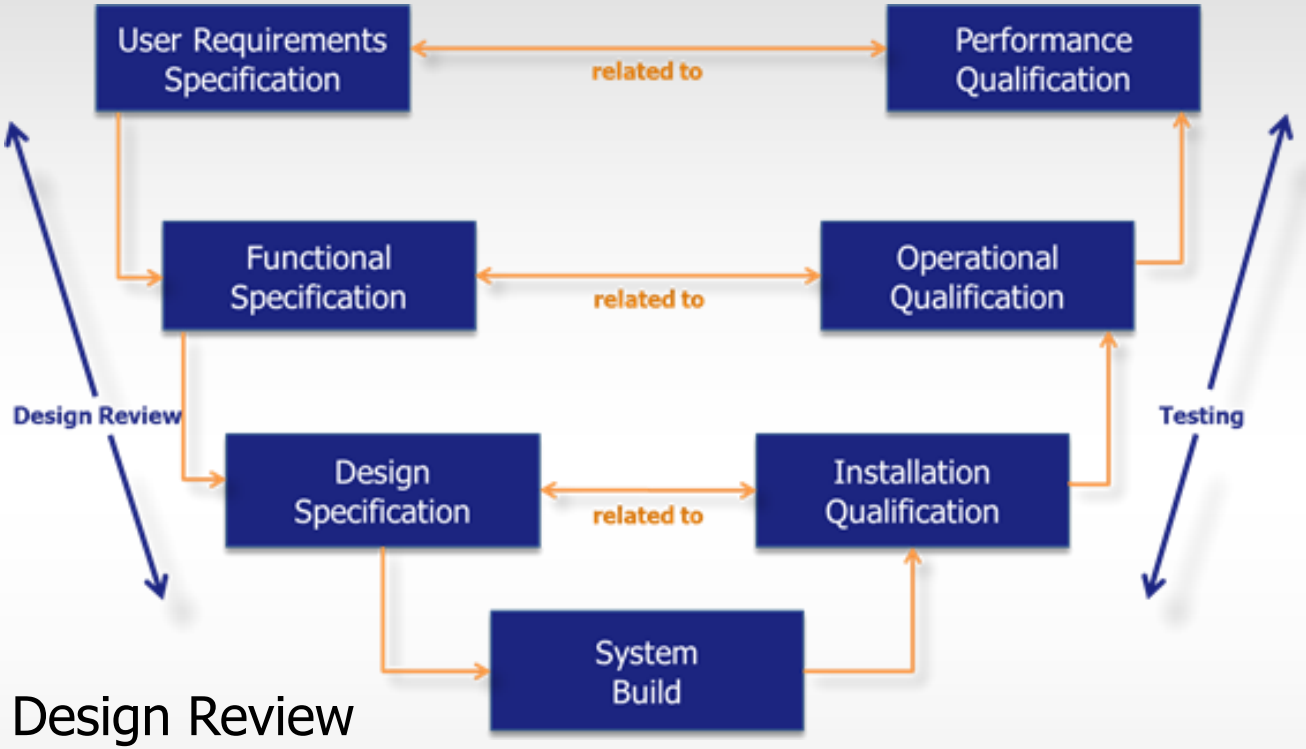
Design, Construction & Start-up

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



Stages of Validation Testing

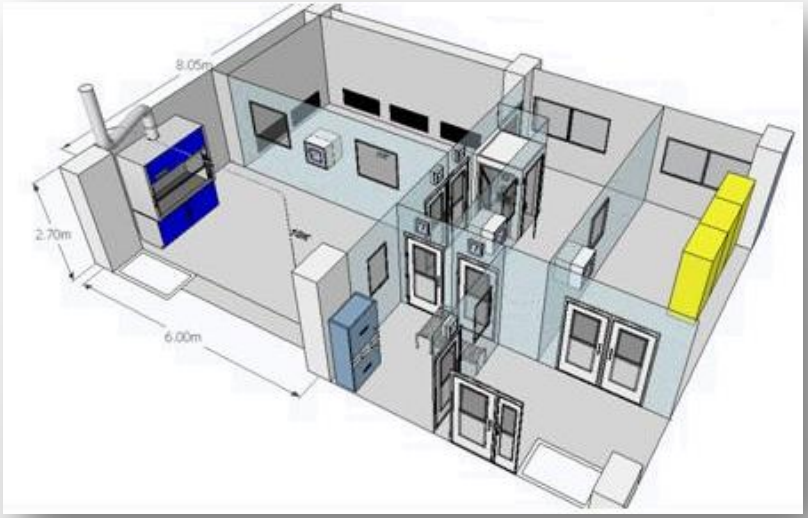


- DQ / Design Review
- IQ of the facility and HVAC system
- OQ of the environment-no personnel present
- PQ of the environment-personnel present
- All covered in a Validation Master Plan

Design Qualification (DQ) / Design Review

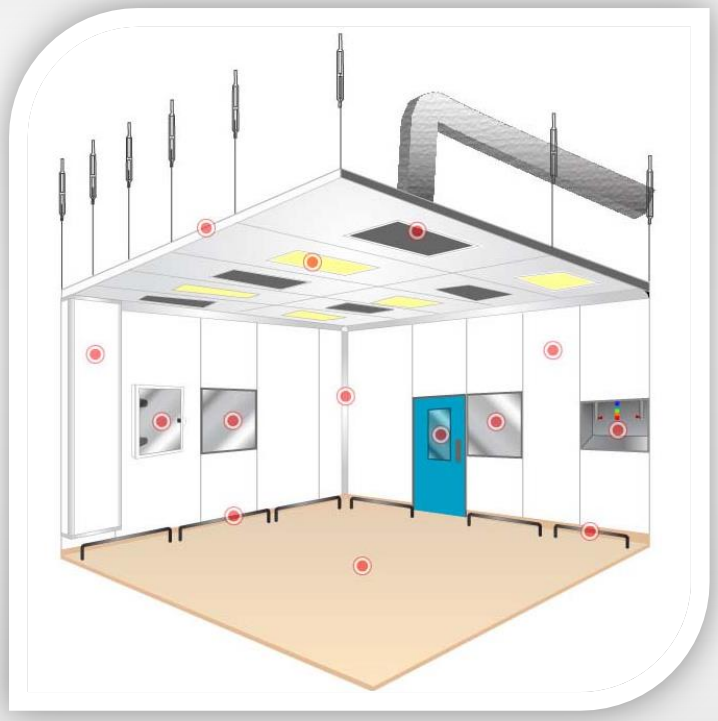
Annex 15 of PIC/S Guide to GMP for Medicinal Products:

"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)

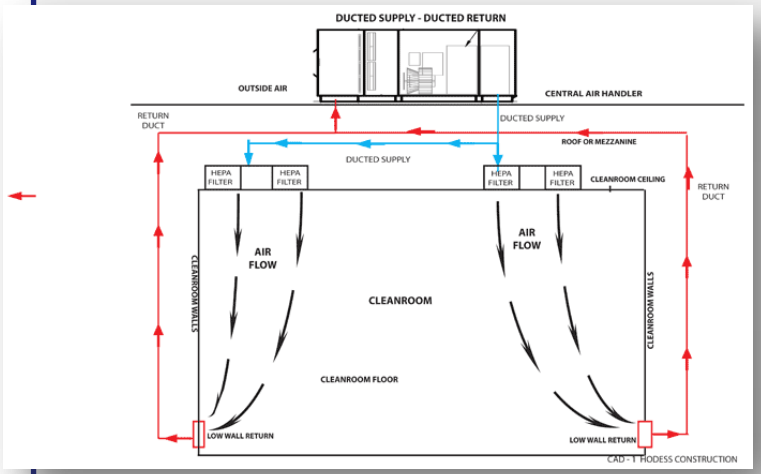
Annex 15 of PIC/S Guide to GMP for Medicinal Products :

"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



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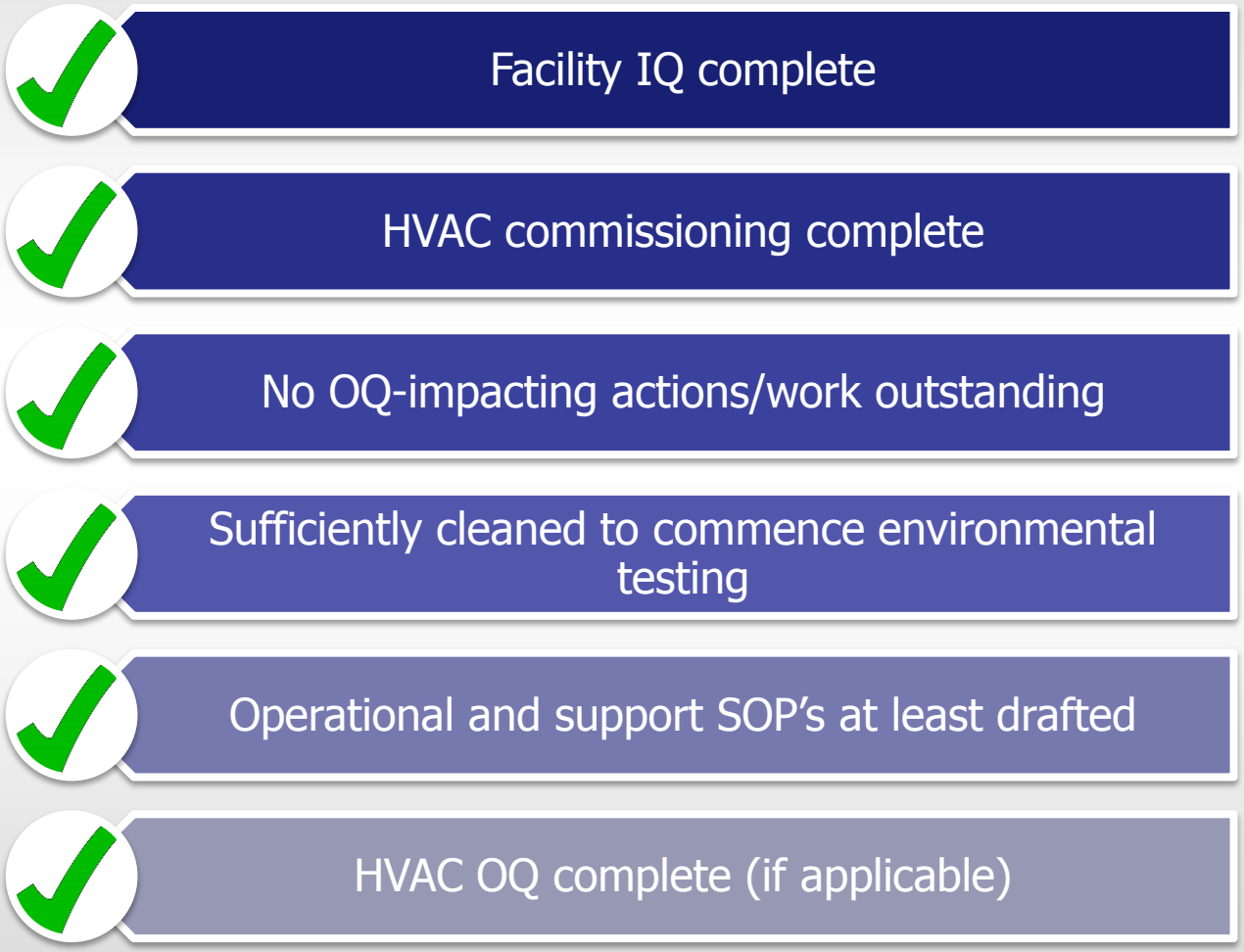
Installation Qualification (IQ)-Facility

- 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



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Operational Qualification (OQ)

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

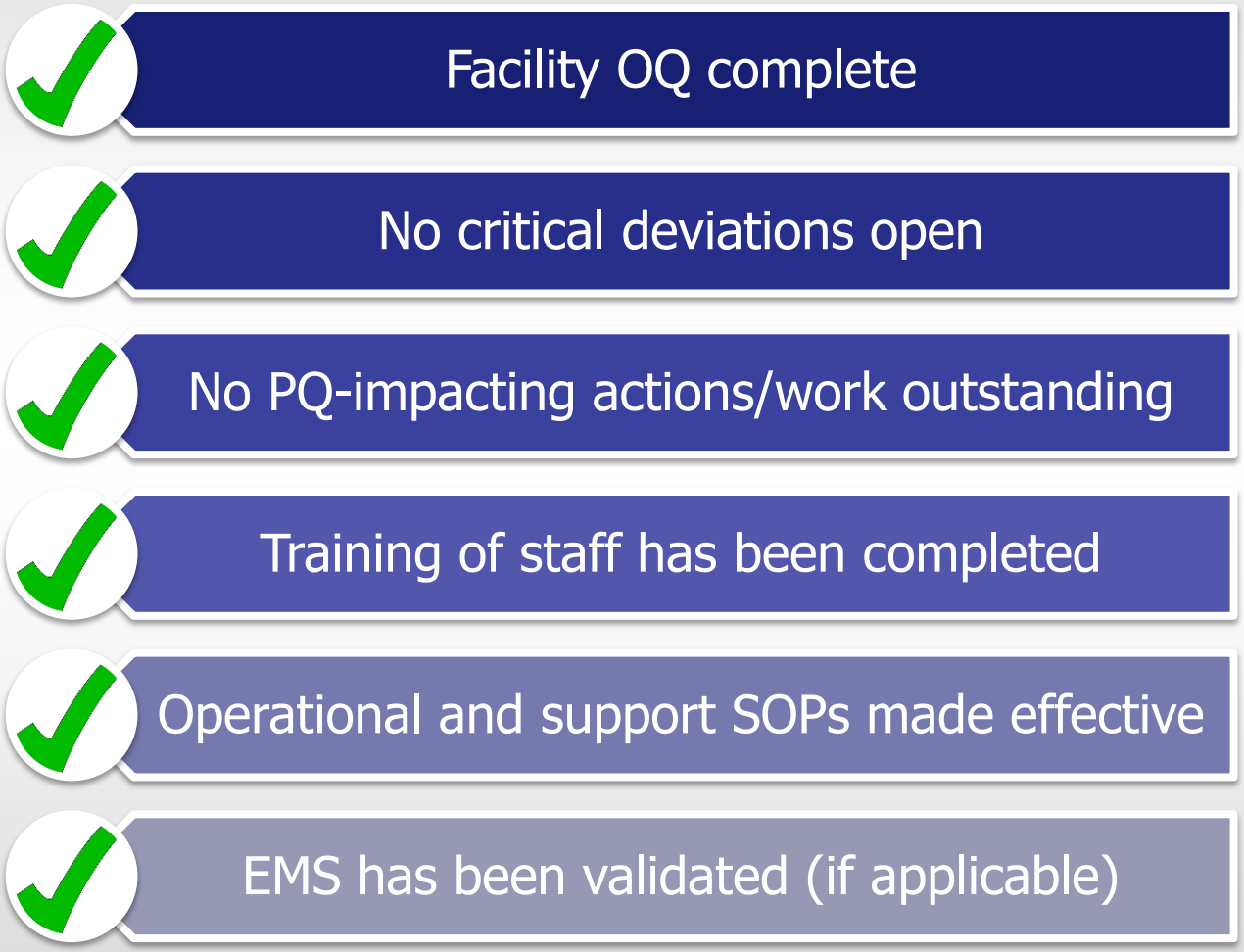
"The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges."

Operational Qualification (OQ) Testing

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

* *Testing can be carried out in parallel*

Performance Qualification (PQ)- Prerequisites



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."

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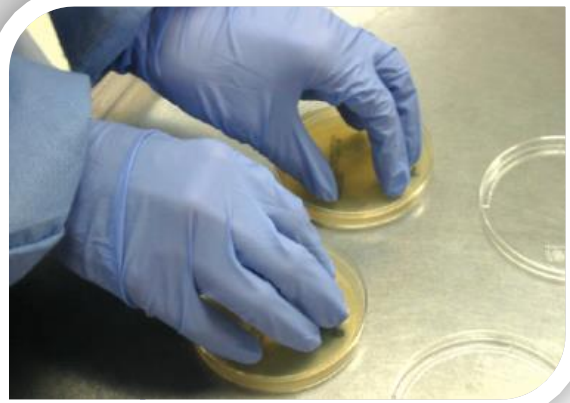
PQ Testing

- 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

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.

Table1: 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.

ISO Classification Number (N)	Maximum concentration limits (particles/m³)					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO Class 1	10	(2)				
ISO Class 2	100	24	10	(4)		
ISO Class 3	1 000	237	102	35	(8)	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	(29)
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	298
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000

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.

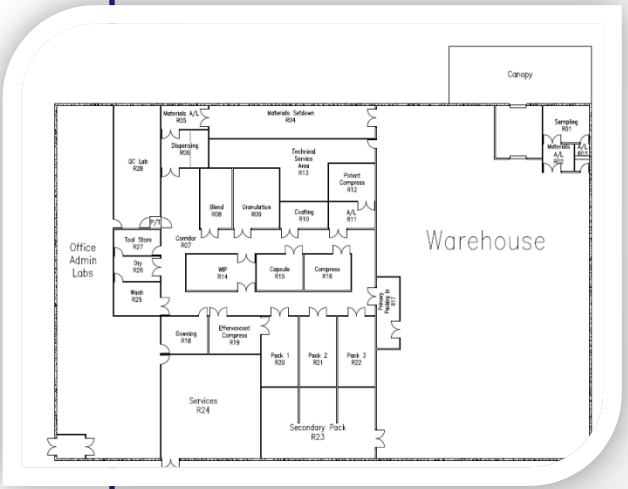
Area (m^2) Less than or equal to	Min number of sample locations	Area (m^2) Less than or equal to	Min number of sample locations
2	1	72	14
4	2	76	15
6	3	104	16
8	4	108	17
10	5	116	18
24	6	148	19
28	7	156	20
32	8	192	21
36	9	232	22
52	10	276	23
56	11	352	24
64	12	436	25
68	13	500	26

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

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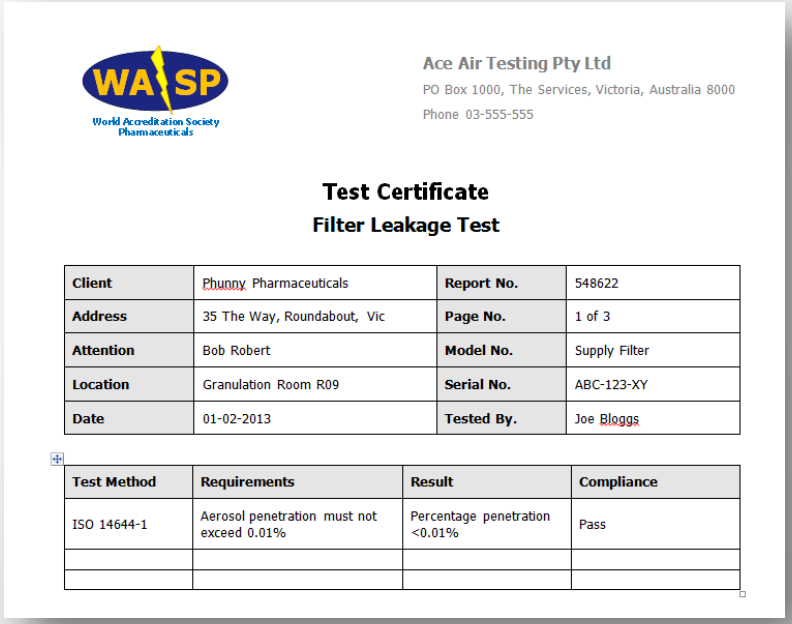
Activity – Test certificate review

- 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



WASP
World Accreditation Society Pharmaceuticals

Ace Air Testing Pty Ltd
PO Box 1000, The Services, Victoria, Australia 8000
Phone 03-555-555

Test Certificate
Filter Leakage Test

Client	Phunny Pharmaceuticals	**Report No.**	548622
Address	35 The Way, Roundabout, Vic	**Page No.**	1 of 3
Attention	Bob Robert	**Model No.**	Supply Filter
Location	Granulation Room R09	**Serial No.**	ABC-123-XY
Date	01-02-2013	**Tested By.**	Joe Bloggs

Test Method	Requirements	Result	Compliance
ISO 14644-1	Aerosol penetration must not exceed 0.01%	Percentage penetration <0.01%	Pass

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Thank you for your time. Questions?

Eoin Hanley

Eoin Hanley
Senior Consultant

Eoin.hanley@pharmout.net
www.pharmout.net