Cleanroom Design: Classification, Qualification, Air Visualization

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Scope

Qualifications

- General requirements
- Non viable
- Viable
- Smoke studies/Air visualisation
- Requalification

General Requirements

- Section 4 (different to section 9)
- Recovery study 15 to 20 mins (but how)
- Air change rates – 20 minimum!?
- Integrity test (AKA DOP) – at the right point in time, no point doing it while building works are still on going
  - If outsourced have method of works and witness if possible, don't introduce to extracts
  - Where has the equipment been
  - Might need to be part of your overall contamination control

Temperature humidity and lighting? No defined limits in the regs but needs some common sense

General Qualification Considerations

Non viable qualification (other)

- Pressure differentials (10 to 15 Pascals?)

Setpoints and the criticality of pressure differentials should be documented within the CCS. Pressure differentials identified as critical should be continuously monitored and recorded.

Where alarm delays are set, these should be assessed and justified within the CCS

- Air speed (where to measure and what are the limits)
  - Filter face or critical operational working height

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Non viable qualification

Annex 1 (some key points)

Reference for the qualification of the cleanrooms and clean air equipment can be found in the ISO 14644 series of standards.

- Qualify using justified particle size
- Formulaic grid approach from ISO 14644 for initial qualification (X points per square metre)
- Then need risk-based approach late-stage qualification (when the lines and process are in place)

Non viable -Two measurements (in operation and at rest)

i. The definition of “at rest” state is the condition whereby the installation of all the utilities is complete including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.

ii. The definition of “in operation” state is the condition where the installation of the cleanroom is complete, the HVAC system fully operational, equipment installed and functioning in the manufacturer’s defined operating mode with the maximum number of personnel present performing or simulating routine operational work.

	At Rest	In operation
Grade A	ISO 5	ISO 5
Grade B	ISO 5	ISO 7
Grade C	ISO 7	ISO 8
Grade D	ISO8	Not defined

Regulatory guidance:

Annex 1 (some key points)

- 5.0um not a requirement for qualification for Grade A (but may be considered)
- Grade D In operation - limits no defined but now need to be defined based on risk by the manufacturer

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Viable

Regulatory guidance:
EU GMP (viable)

Grade	Air sample CFU/m3	Settle plates (diameter 90mm) CFU/4 hours (a)	Contact plates (diameter 55 mm) CFU/plate
A	No Growth		
B	10	5	5
C	100	50	25
D	200	100	50

Viable

EU GMP (viable)

(a) Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

- ***Note 1:*** All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.
- ***Note 2:*** Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.
- ***Note 3:*** For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.
- ***Note 4:*** Sampling methods should not pose a risk of contamination to the manufacturing operations.

Viable qualification

EMPQ

- Risk Assessment *(where, when, how and who)
  - Frequency
  - Type of monitor
  - Locations
  - Incubation strategy (temperature and duration)
  - Media (don't forget neutralising agents)
    Note: Annex 15 requires recovery studies
- Disinfection efficacy
  - Which ones when
    - Do we need to rotate?
  - Application time (drying out)
  - Procedure for application

Viable qualification

EMPQ

- Different phases e.g.
  - As built (data gathering numbers and flora type)/ For information only?
  - After clean up started/Ad Hoc limits
  - In operation routine limits

  Looking for decreases that show clean up strategy is working
  EMPQ may then have two "operational phases" e.g. high-level of scrutiny for a period of time e.g. one month
  Then reducing down as you get confidence
  - Need to set alert limits based on initial "trends" (not just 50% of action)
  - Can reduce sample locations and frequency but need to be careful

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Smoke Studies

Key changes

– 4.30 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working position (e.g. where high-risk operations occur and where product and/or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.

Smoke Studies

Key changes

- 4.15 Airflow patterns within cleanrooms and zones should be visualised to demonstrate that there is no ingress from lower grade to higher grade areas and that air does not travel from less clean areas (such as the floor) or over operators or equipment that may transfer contamination to the higher-grade areas. Where unidirectional airflow is required, visualisation studies should be performed to determine compliance, (see paragraphs 4.4 & 4.19). When filled, closed products are transferred to an adjacent cleanroom of a lower grade via a small egress point, airflow visualization studies should demonstrate that air does not ingress from the lower grade cleanrooms to the grade B area. Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective actions, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (e.g. simulating operator interventions). Video recordings of the airflow patterns should be retained. The outcome of the air visualisation studies should be documented and considered when establishing the facility's environmental monitoring programme.

Smoke Studies

Key changes

- 4.31 The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table 2. Qualification should include both “at rest” and “in operation” states.

Smoke Studies

Points to consider

- Key part of the risk assessment (need to use it to support your EM placement)
- Used to review process so we need a clear statement in the report conclusions
- Can be used to support training
- Must be representative of the actual process
- Often used by regulators as a way to view you process
  - Need to be well documented, justification of what we are going to record (and not record).
  - May need different types of smoke generation
  - Two camera angles is often important

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Requalification

Annex 1 (some key points)

- (Note: For grade B, C and D the air velocity test should be performed according to a risk assessment documented as part of the CCS. However, it is required for filling zones supplied with unidirectional airflow (e.g. when filling terminally sterilised products or background to grade A and RABS). For grades with non-unidirectional airflow, a measurement of recovery testing should replace velocity testing).
- The maximum time interval for requalification of grade A & B areas, is 6 months.
- The maximum time interval for requalification of grade C & D areas, is 12 months.

Requalification

Annex 1 (some key points)

- Requalification should include

i. cleanroom classification (total particle concentration),
ii. integrity test of final filters,
iii. airflow volume measurement,
iv. verification of air pressure difference between rooms, and
v. air velocity test

- Not mentioned but should be considered, alarm functionality

Requalification

Routine viable

- Grade A and B continuously – especially set up
- C and D based on risk assessment
- Trends
  - Flora
  - Numbers
  - Every 1 month/ 3 months annual? Needs to be a rolling trend
- Will review as part of periodic CCS review (do deviations indicate we are not monitoring in the right place.
- Significant changes (even outside of the area)
- No products/Processes

Thank You

Any questions?