Contamination Control Network

EN/ISO Cleanroom Standards BS EN ISO 14644-1&2:2015

Classification & Monitoring

A Refresher & Update webinar slidepack

12th May 2021

Contamination Control Network

EN/ISO Cleanroom Standards

BS EN ISO 14644-1&2:2015

Classification & Monitoring

A Refresher & Update

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May 2021

President CCN; Chair UK BSI LBI/030; Chair CEN TC243; UK HoD ISO TC209

Learning Objectives

Learn how contamination control standards specify requirements for Critical Environmental Control Parameters

- Essential features of BS EN ISO-14644-1:2015 – Classification of air cleanliness
- For Life-Sciences , the link with GMP Annex 1, Manufacture of Sterile Medicinal Products
- Link to BS EN ISO 14644-2:2015 – Monitoring (to provide performance evidence)

ISO Cleanroom Standards

ISO 14644-1:2015 Classification of air cleanliness:

Note this edition was published on the 15th December 2015.
Classification of air cleanliness by particle number concentration in cleanrooms and associated controlled environments.

- Defines the concentration of all (total) airborne particles (does not differentiate bio- contamination)
- Limited to a designated range of considered threshold particle sizes from ≥0.1 to ≥5.0 micron particles for specification of particle concentration limits. Using a particle counter.
- Generic standard, not application specific.

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Something about airborne Particle Counters

- Light scattering device
  - **L**ight **S**cattering **A**irborne **P**article **C**ounte
  - **LSAPC**
  - Counts number & Size BY Number and In flashes
- ISO 21501- 4 specifies performance ar of LSAPCs

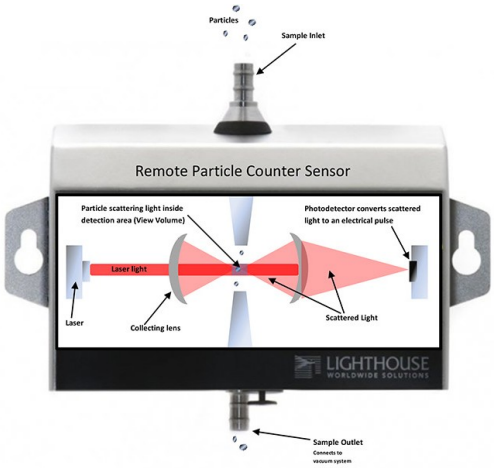

Image courtesy of LIGHTHOUSE WORLDWIDE SOLUTIONS

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BS EN ISO 14644-1:2015 Cleanroom Standard

Defines classification by

- ISO Class
- Occupancy State
- Designated particle sizes (minimum one size; if more, then dia D2 ≥ 1.5 x dia D1.

3 Occupancy States

- As Built
- At Rest
- Operational

Specifies

- Number of sampling locations for classification
- The sample size required at each location
- How to evaluate the data to determine the class

Use correct cleanliness designation

- Designation
  - ISO class number (1-9)
  - Occupancy State
  - Designated Particle size(s)
  - Example - ISO Class 4; at rest; 0.2 □m, 0.5 □m
- USE correct reference to the standard
  - ISO 14644 □ no meaning
  - ISO 14644-1 would always mean the latest version.
  - ISO 14644-1:2015 is a specific edition.
  - BS EN ISO 14644-1:2015 is the British version.

ISO 14644-1:2015 – Classification by Table 1

Table 1 — ISO Classes of air cleanliness by particle concentration

ISO Class number (*N*)	Maximum allowable concentrations (particles/m³) for particles equal to and greater than the considered sizes, shown below[a]					
	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1 µm	5 µm
1	*10*[b]	d	d	d	d	e
2	100	*24*[b]	*10*[b]	d	d	e
3	1 000	237	102	*35*[b]	d	e
4	10 000	2 370	1 020	352	*83*[b]	e
5	100 000	23 700	10 200	3 520	832	d, e, f
6	1 000 000	237 000	102 000	35 200	8 320	293
7	c	c	c	352 000	83 200	2 930
8	c	c	c	3 520 000	832 000	29 300
9g	c	c	c	35 200 000	8 320 000	293 000

- *c. Too many particles these sizes- coincidence error!*
- *d.Too few particles these sizes*
- *e. Low concentration & losses in sampling.*
- *f. Particles ≥ 5.0 µm not included in ISO Class 5. See clause C7.*

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Notes to Classification Table 1

a All concentrations in the table are cumulative, e.g. for ISO Class 5, the 10 200 particles shown at 0,3 µm include all particles equal to and greater than this size.

b These concentrations will lead to large air sample volumes for classification. Sequential sampling procedure may be applied; see Annex D.

c Concentration limits are not applicable in this region of the table due to very high particle concentration.

d Sampling and statistical limitations for particles in low concentrations make classification inappropriate.

e Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.

f In order to specify this particle size in association with ISO Class 5, the macroparticle descriptor M may be adapted and used in conjunction with at least one other particle size. (See C.7.)

g This class is only applicable for the in-operation state.

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Number of Sampling Locations – BS EN ISO 14644-1:2015

- Look up table (was new in 2015)
- Vertical plane for horizontal UDAF
- Horizontal plane for vertical UDAF

Note: UDAF = (unidirectional airflow)

Area of cleanroom (m^2) less than or equal to	Minimum number of sampling locations to be tested (N_L)
2	1
4	2
6	3
8	4
10	5
24	6
28	7
32	8
36	9
52	10
56	11
64	12
68	13
72	14
76	15
104	16
108	17
116	18
148	19
156	20
192	21
232	22
276	23
352	24
436	25
636	26
1 000	27
> 1 000	See Formula (A.1)

Table A.1 - Look-up table for MINIMUM number sampling locations.

Statistical basis is: 95% confidence that at least 90% of the zone will comply with the class limit.

Can choose more locations if you wish.

A.4.4 Sample Size Calculation – ISO 14644-1:2015

At each sampling location, sample a volume of air sufficient to detect a minimum of 20 particles if the particle concentration for the largest selected particle size were at the class limit for the designated ISO Class.

The single sample volume, V_s, per sampling location is determined by using Formula (A.2):

$$V_s = \left(\frac{20}{C_{n,m}}\right) \times 1\,000 \qquad \text{(A.2)}$$

where

Vs is the minimum single sample volume per location, expressed in litres (except see Annex D);

$C_{n,m}$ is the class limit (number of particles per cubic metre) for the largest considered particle size specified for the relevant class;

20 is the number of particles that could be counted if the particle concentration were at the class limit.

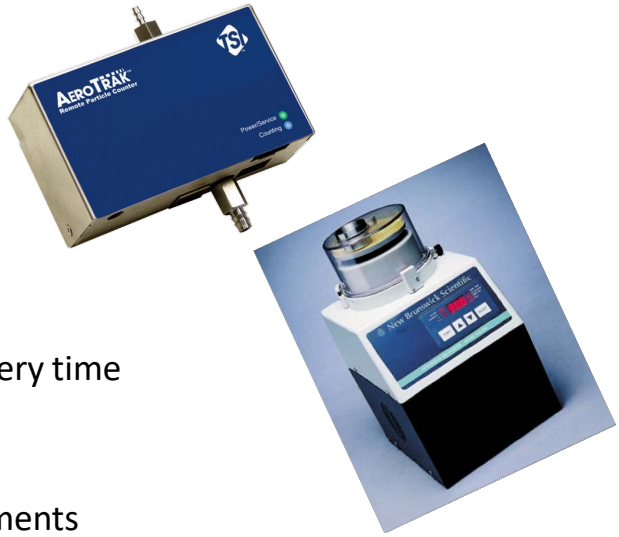
- Each location - Min 2 litre sample; Min 1 minute sample time.
- Sample volume at each location the same.
- Can apply 'Sequential sampling (Annex D) for very large sample sizes/times.

Class Evaluation – ISO 14644-1:2015

- All locations must comply with the class limits.
- Can average multiple counts at each location.
- The 95% UCL from the 1999 version has been removed. There are more sampling locations. For 100 m^2 , now 16 was 10.
- Special guidance for dealing with EU GMP Annex 1, Grade A and B ≥ 5.0 □ requirements. (What I call the 5 micron challenge!)

The environmental control requirements defined in GMPs

- Environmental cleanliness levels
  - Airborne particles
  - Microbiological contamination
    - Airborne
    - Surfaces
- Pressure differentials
- Air-change rates implied by recovery time (ventilation effectiveness)
- Uni-directional airflow velocities
- Air filtration (final filters) requirements



Annex 1- Table of area/zone Cleanliness (particles)

	At Rest		In Operation			
Grade	Max Particles ≥ stated sizes				Microbiological (also finger dabs and contact plates)	
	0.5µ	5.0µ	0.5µ	5.0µ	Air sample cfu/m³	90mm settle plate cfu/4hr
A	3 520	20	3 520	20	<1	<1
B	3 520	29	352 000	2 900	10	5
C	352 000	2 900	3 520 000	29 000	100	50
D	3 520 000	29 000	Not defined	Not defined	200	100

Not included in ISO Class 5 in BS EN ISO 14644-1:2015

Must use the Macro-particle descriptor

Dealing with the GMP Annex 1 20 & 29 limits

Remember…..ISO Standards are the Toolbox for Classification – to be used in conjunction with the levels defined in the GMP Guidance.

C.7 Adaptation of the macroparticle descriptor to accommodate consideration of ≥ 5 µm particle size for ISO Class 5 cleanrooms

In order to express an airborne concentration of 29 particles/m³ in the particle size range ≥ 5 µm based on the use of an LSAPC, the designation would be "ISO *M* (29; ≥ 5 µm); LSAPC" and for 20 particle/m³ the designation would be "ISO *M* (20; ≥ 5 µm); LSAPC" (see Table 1, Note f).

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Sample Size Calculation - ISO 14644-1:2015 for Annex 1

The single sample volume, V_S, per sampling location is determined by using Formula (C.1):

$$V_s = \left(\frac{20}{C_{n,m}} \right) \times 1000 \qquad \text{(C.1)}$$

where

V_s is the minimum single sample volume per location, expressed in litres (except see D.4.2);

$C_{n,m}$ is the class limit (number of particles per cubic metre) for the largest considered particle size specified for the relevant class;

20 is the number of particles that could be counted if the particle concentration were at the class limit.

Where information on the stability of macroparticle concentration is required, make three or more measurements at selected locations at time intervals agreed between customer and supplier.

- Always based on the largest considered particle size.
- For Grade A (at rest, operational) 20 parts/m³, V_s = 1000 litre
- For Grade B (at rest) 29 parts/m³, V_s = 693 litre

- For Grade B (operational), 1 min sample
- For Grade C&D, 1 min sample

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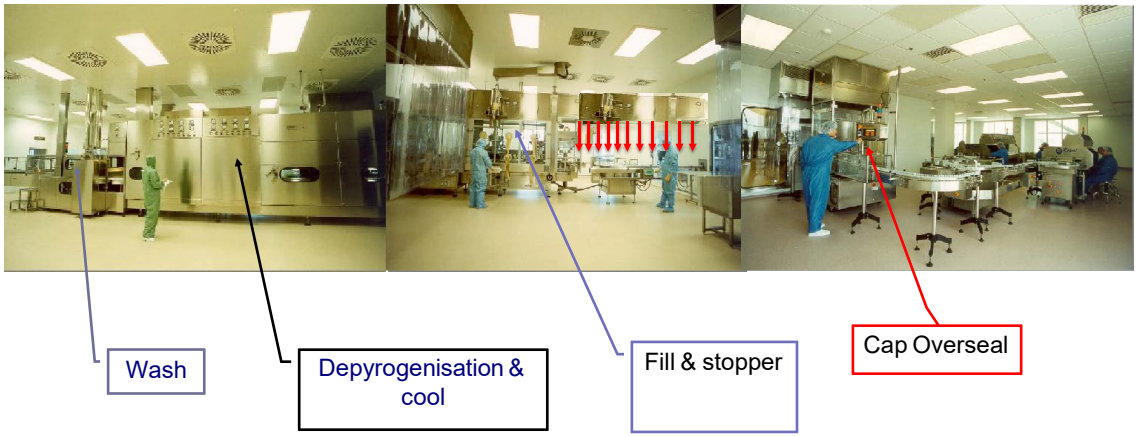
Example - Industrial integrated vial line Working out the number of sampling locations



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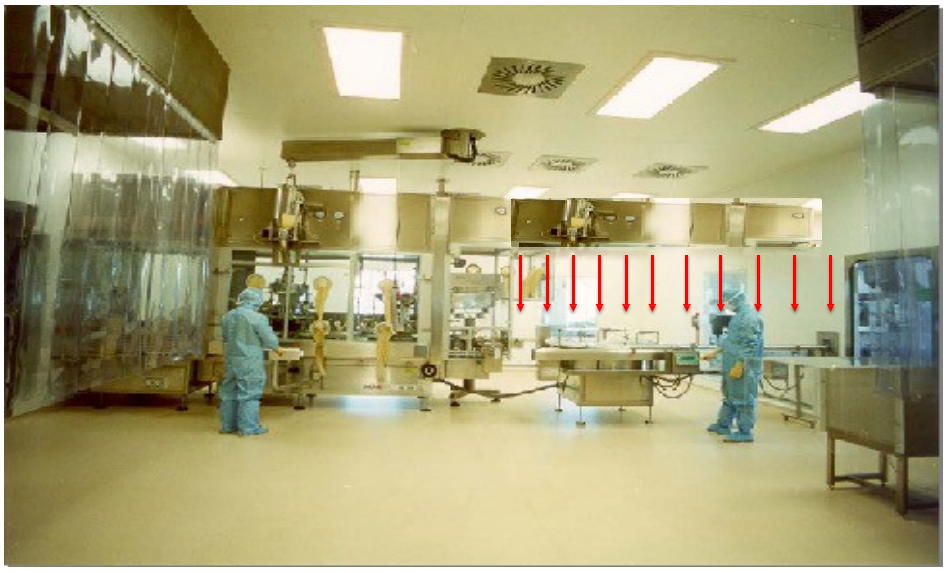
Number of sample locations – real world



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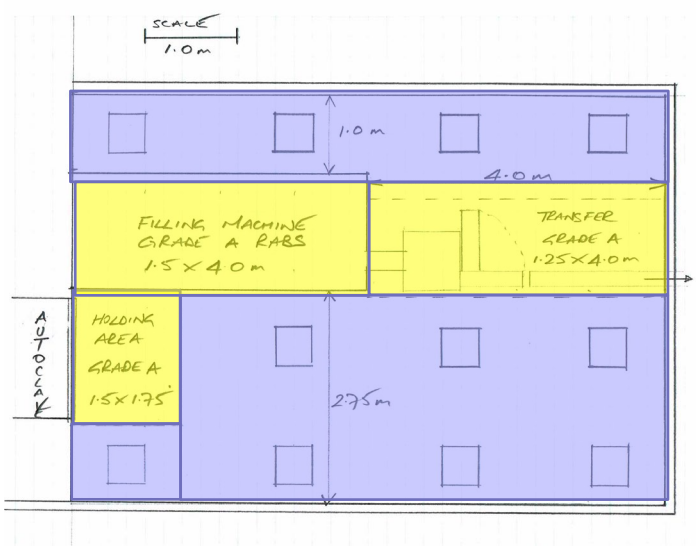
Number of sample locations – real



- Divide the cleanroom into logical zones:
  - By ISO Class
  - By areas or regions
  - Don't locate directly beneath a un-diffused HEPA supply in non-UDAF rooms

Grade B areas
8 x 1 = 8 m^2 → 4 locations
(8 x 2.75) – (1.5 x 1.75) = 19.37 m^2
→ 6 say 7 locations

Grade A areas
1.5 x 4 = 6 m^2 → 3 locations
1.25 x 4 = 5 m^2 → 3 locations
1.5 x 1.75 = 2.63 m^2 → 2 locations

"Operational" monitoring BS EN ISO 14644-2:2015

Clean room and clean air devices should be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

- Provides risk based guidance for developing and implementing a monitoring system.
- Provides some minimum requirements. GMPs are more specific and include levels/values.
- Guidance on 'Real Time' monitoring & 'Periodic tests'.

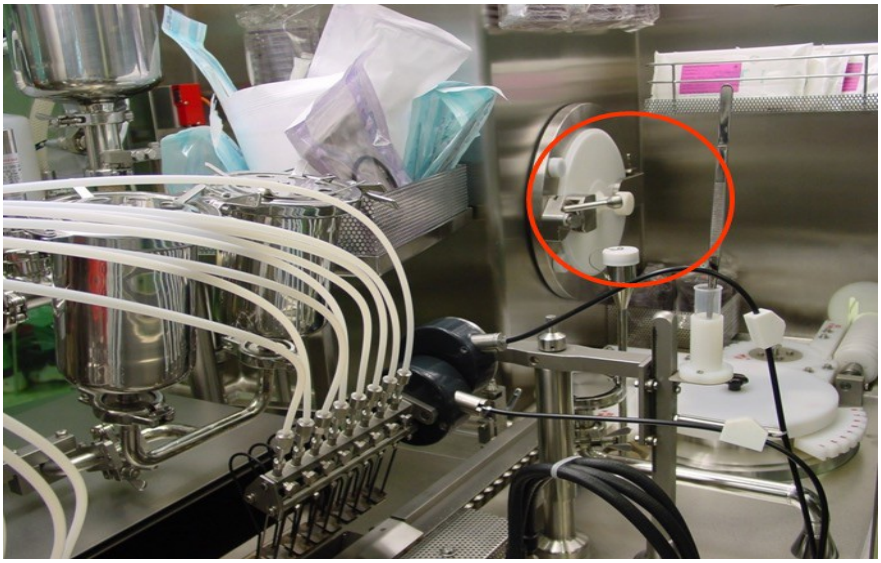
Parameters to be monitored (NA- UK national annex)

Table NA.1 — Recommended schedule for testing cleanrooms and clean zones

Test parameter/Performance attribute	Maximum time interval between tests
Airborne particle concentrations ≤ ISO Class 5	6 months
Airborne particle concentrations > ISO Class 5	12 months
Pressure differentials	Continuously monitored by frequent manual observation or by automated instrumentation
Installed filter leak test in unidirectional airflow and cleanliness classes ≤ ISO Class 5	6 months
Installed filter leak test in non-unidirectional airflow and cleanliness classes > ISO Class 5	12 months
Airflow velocities in unidirectional airflow	6 months
Airflow volume supply in non-unidirectional airflow	12 months
Containment leak (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Airflow visualization (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Recovery time in non-unidirectional airflow (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Particle deposition rates (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
Segregation tests (optional)	At commissioning, and thereafter every 4 years, or after any significant change to the airflow system or equipment content
a) Temperature b) Humidity c) Electrostatic and ion generator	As required, and in agreement with the cleanroom user

- When frequent or continuous monitoring systems are provided, intervals can be extended.
- Continuous automated systems are most common for room pressures and particle concentrations.
- A written monitoring rationale should be available.

Filling Machine 'Real Time' Particle Monitoring



Setting Alert and Action levels

- Part 2 has Informative Annex B "Considerations for setting alert and action levels".
  - Establish normal operating range – (likely to need time to refine).
  - Alerts give warning of a drift before Action levels are reached – (time to do something about it).
  - Ensure instrument calibration programme is established.
  - Ensure you have considered impact of equipment and facility operations.
  - May need to set delay time on alarms - (to tolerate normal short term transients).
  - Review data for trends.
  - Define a clear response plan for Alerts & Actions.

Summary & Conclusions

- ISO-14644-1&2:2015 – Classification of air cleanliness & Monitoring – are the core Cleanroom Standards. It's what differentiates a cleanroom from other controlled spaces.
  - Remember the Standards are generic
  - Use the correct nomenclature/terminology
  - Understand how to *apply* the standards correctly in the real world.
  - In the Life Science sector, ensure you understand the *link* between regulations (GMPs) and the standards. The standards are generic.
  - Ensure there is a clear plan for moving from Classification to Operational Monitoring.
  - Keep a look out for the revision to the standards.

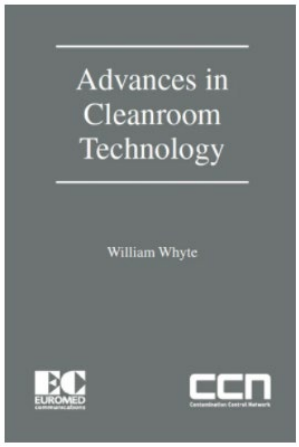
And finally – **Contacting the CCN**

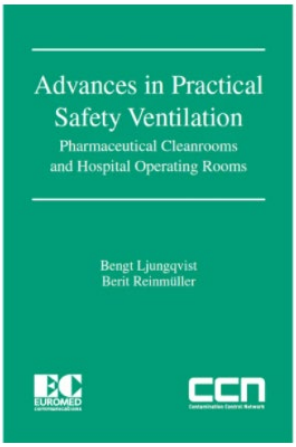
Want to join the Contamination Control Network or find out more ?

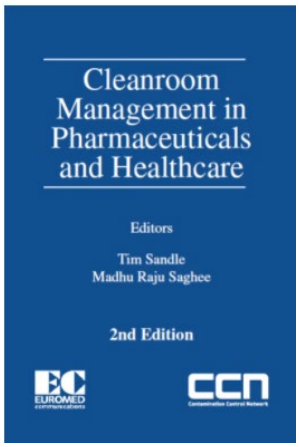
Go to
https://www.theccnetwork.org/

Thanks for your attention

Further reading on Cleanroom subject matter (click on cover for links)







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