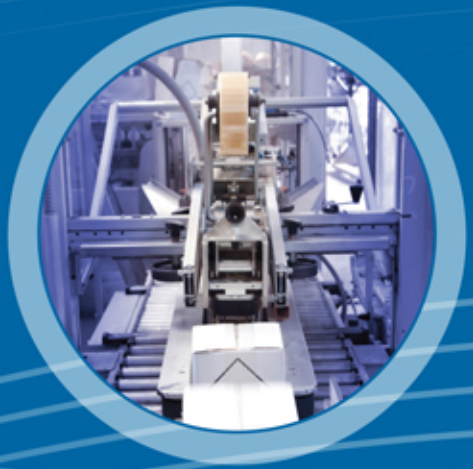
PDA
Parenteral Drug Association

Connecting People, Science and Regulation

Clarification Proposal Annex 1,

Cleanroom and Clean Air Devices



LIGHTHOUSE
WORLDWIDE SOLUTIONS
Technology That Counts

Hasim Solmaz Lighthouse Worldwide Solutions

Agenda

- GMP Annex 1 **Definitions**
- Cleanroom and Clean Air Device **Classification**
- Cleanroom and Clean Air Device **Monitoring**
- **One** Experiment

GMP ANNEX 1

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Principle (1st paragraph)

«...this type of manufacture (Sterile manufacturing) must strictly follow carefully established and validated methods of preparation and procedure»

- Note : *(2. Paragraph)*

This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. Reference should be made to other documents such as the **EN/ISO Standards.**

Cleanroom and Clean Air Device **Classification**

Cleanroom and Clean Air Device **Classification**

GMP Annex 1 Clause #4 «Clean rooms and clean air devices should be classified in accordance with EN ISO 14644-1.

Classification should be clearly differentiated from operational process **environmental monitoring.»**

ISO 14644-1:1999

Maximum concentration limits (particles M^3 of air) for particles equal to and larger than the considered sizes shown below:						
ISO Classification Number(N)	0.1µm	0.2µm	0.3µm	0.5µm	1.0µm	5.0µm
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1,000	237	102	35	8	
ISO 4	10,000	2,370	1,020	352	83	
ISO 5	100,000	23,700	10,200	3,520	832	29
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7				352,000	83,200	2,930
ISO 8				3,520,000	832,000	29,300
ISO 9				35,200,000	8,320,000	293,000

GMP Annex 1: 2008

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At Rest		In Operation	
Grade	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/DIS 14644-1.2 (will be voted 18 Nov, 2014)

Maximum concentration limits (particles M^3 of air) for particles equal to and larger than the considered sizes shown below: (a)						
ISO Classification Number(N)	0.1µm	0.2µm	0.3µm	0.5µm	1.0µm	5.0µm
ISO 1	b 10	d ~~2~~	d	d	d	e
ISO 2	100	24	10	d ~~4~~	d	e
ISO 3	1,000	237	102	35	d ~~8~~	e
ISO 4	10,000	2,370	1,020	352	83	e
ISO 5	100,000	23,700	10,200	3,520	832	d,e,f ~~29~~
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7	c	c	c	352,000	83,200	2,930
ISO 8	c	c	c	3,520,000	832,000	29,300
ISO 9	c	c	c	35,200,000	8,320,000	293,000

Classification table in Draft ISO 14644-1

Reviewing GMP Annex 1: 2003

	Maximum permitted number of particles per m³ equal to or greater than the tabulated size			
	At Rest		In Operation	
Grade	0.5µm	5.0µm	0.5µm	5.0µm
A	3 5**00**	**1***	3 5**00**	**1***
B	3 5**00**	**1***	35**0 000**	2 **000**
C	35**0 000**	2 000	3 5**00 000**	2**0 000**
D	3 5**00 000**	20 000	Not Defined	Not Defined

According to European Medicines Agency;
(EMA, Proposals for amendment, 21 September 2005)

*The maximum permitted number of particles at ≥5.0µm is established at 1/m³ but **for reasons related to false counts associated with electronic noise, stray light, etc. a limit of 20/m3 could be considered.**

Reviewing GMP Annex 1: 2003

- New developments in technology and with a new calibration standard ISO 21501-4:2007, better resolution, counting efficiency, less noise and false count rate is possible.

- Also, as per **GMP Annex 1, Clause #13**,

*«The occasional indication of ≥5.0 µm particle counts may be false counts due to **electronic noise, stray light, coincidence, etc.** However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated.»*

PDA , Proposal for Amendment

According to PDA comments letter to (April 24, 2006);

«we have revised the table **to be more aligned with EN ISO 14644-1,** which is internationally accepted standard for non-viable particle classification»

New GMP Annex 1: 20XX

Classification Standpoint

	Maximum permitted number of particles per m³ equal to or greater than the tabulated size			
	At Rest		In Operation	
Grade	0.5µm	5.0µm	0.5µm	5.0µm
A	3 520	**Not Defined/0**	3 520	**Not Defined/0**
B	3 520	**Not Defined/0**	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not Defined	Not Defined

Classification : Only 0.5µm can be used as per ISO 14644-1.

GMP Annex 1, Clause #5 «For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected»

New GMP Annex 1: 20XX

Classification Standpoint

	Maximum permitted number of particles per m³ equal to or greater than the tabulated size			
	At Rest		In Operation	
Grade	0.5µm	5.0µm	0.5µm	5.0µm
A	3 520	**Not Defined/0**	3 520	**Not Defined/0**
B	3 520	**Not Defined/0**	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not Defined	Not Defined

Classification : 5.0µm should be zero according to ISO/DIS 14644-1.2 Table 1 notes;

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

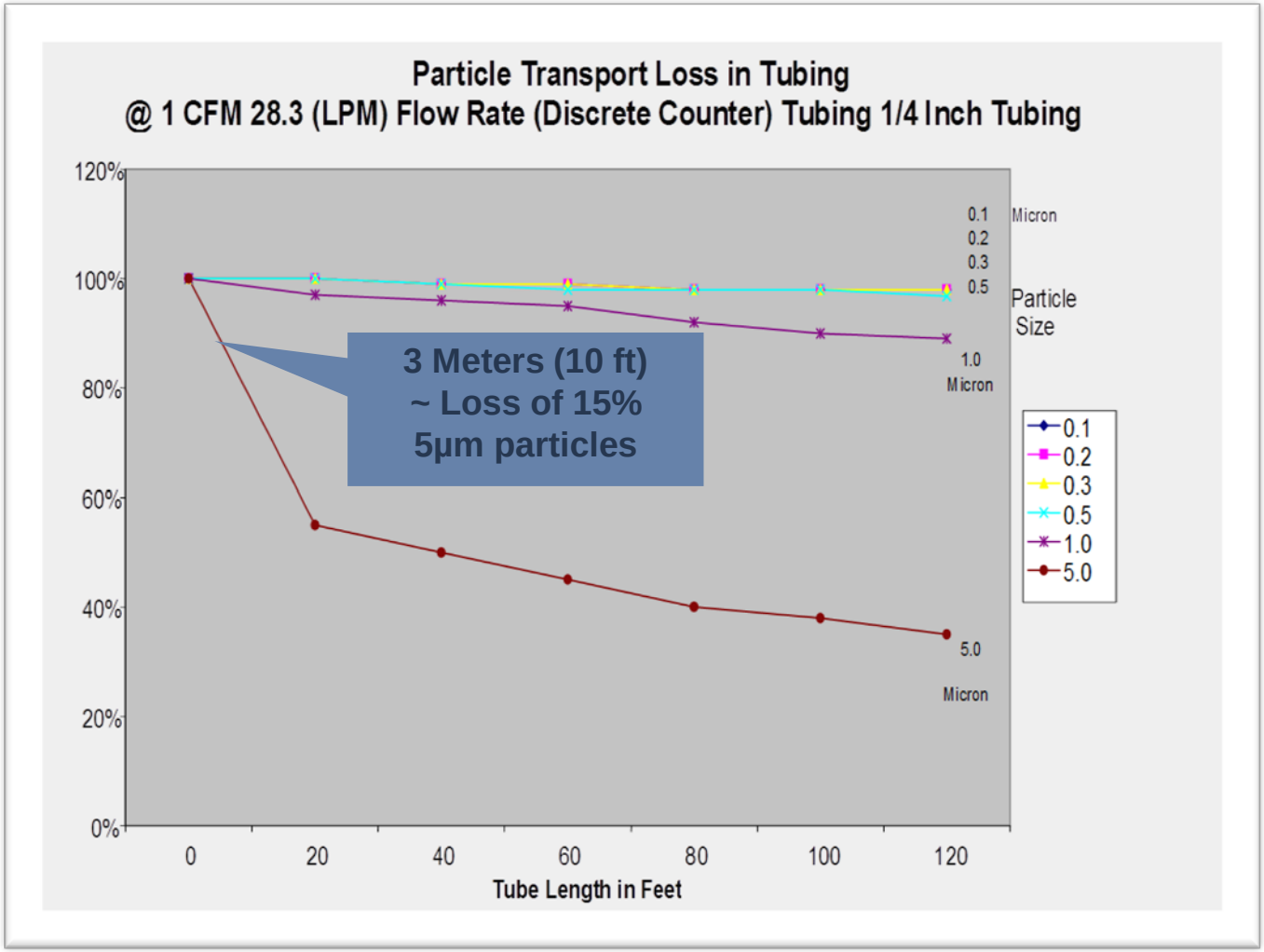
e) ... Greater than 1 micron particles make classification at this particle size inappropriate due to potential particle losses in sampling system

Cleanroom and Clean Air Device **Classification**

- **GMP Annex 1, Clause #6,**

«Portable particle counters with a short length of sample tubing should be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0µm in remote sampling systems with long lengths of tubing.»

- Lenght of tube sould defined based on experiment data.



Portable particle counters with less than 3 meters should be used...

Cleanroom and Clean Air Device **Classification**

- **GMP Annex 1, Clause #7,**

*«"In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on **testing** to demonstrate **continued compliance** with the assigned cleanliness classifications.»*

- ISO/DIS 14644-2.2 ; **Monitoring** to provide evidence of cleanroom performance related to air cleanliness by particle concentration

(ISO 14644-2:2000 ; Specs for **testing and monitoring** to prove continued compliance with ISO 14644-1)

Cleanroom and Clean Air Device **Monitoring**

Cleanroom and Clean Air Device **Monitoring**

GMP Annex 1, Clause#8

*«monitoring locations based on a **formal risk analysis study** and the results obtained during the classification of rooms and/or clean air devices»*

Needs to refer **ICH Q9 Quality Risk Management** which is adopted and published by EMA on Feb, 2011 (INS/GMP/79766/2011).

New GMP Annex 1: 20XX

Monitoring Standpoint

	Maximum permitted number of particles per m³ equal to or greater than the tabulated size			
	At Rest		In Operation	
Grade	0.5µm	5.0µm	0.5µm	5.0µm
A	3 520	**0**	3 520	**0**
B	3 520	**0**	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not Defined	Not Defined

Monitoring : Grade A 5.0µm particles should not exist during operation except;

- *«...generation of particles or droplets from the product itself .» (Annex 1, #9)*
- *«The occasional indication of ≥5.0 µm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and should be investigated » (Annex 1, Clause #13).*

Cleanroom and Clean Air Device **Monitoring**

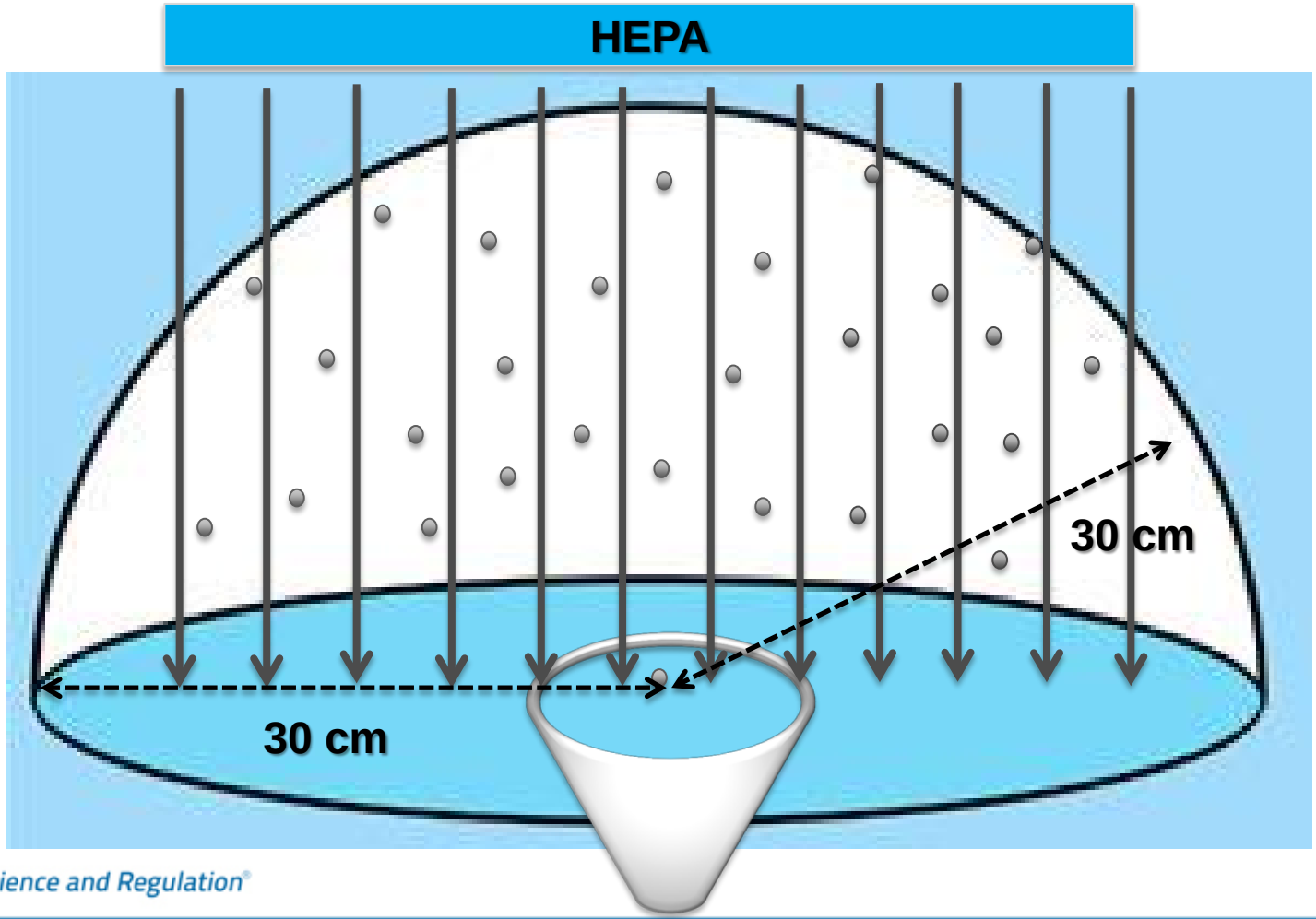
Monitoring locations definitions should be more informative.

Example 1; FDA Aseptic Processing Guideline ;

«... per-cubic-meter particle count of no more than **3520** in a size range **of 0.5 µm and larger** when counted at representative locations normally **not more than 1 foot *(30cm)* away** from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5)»

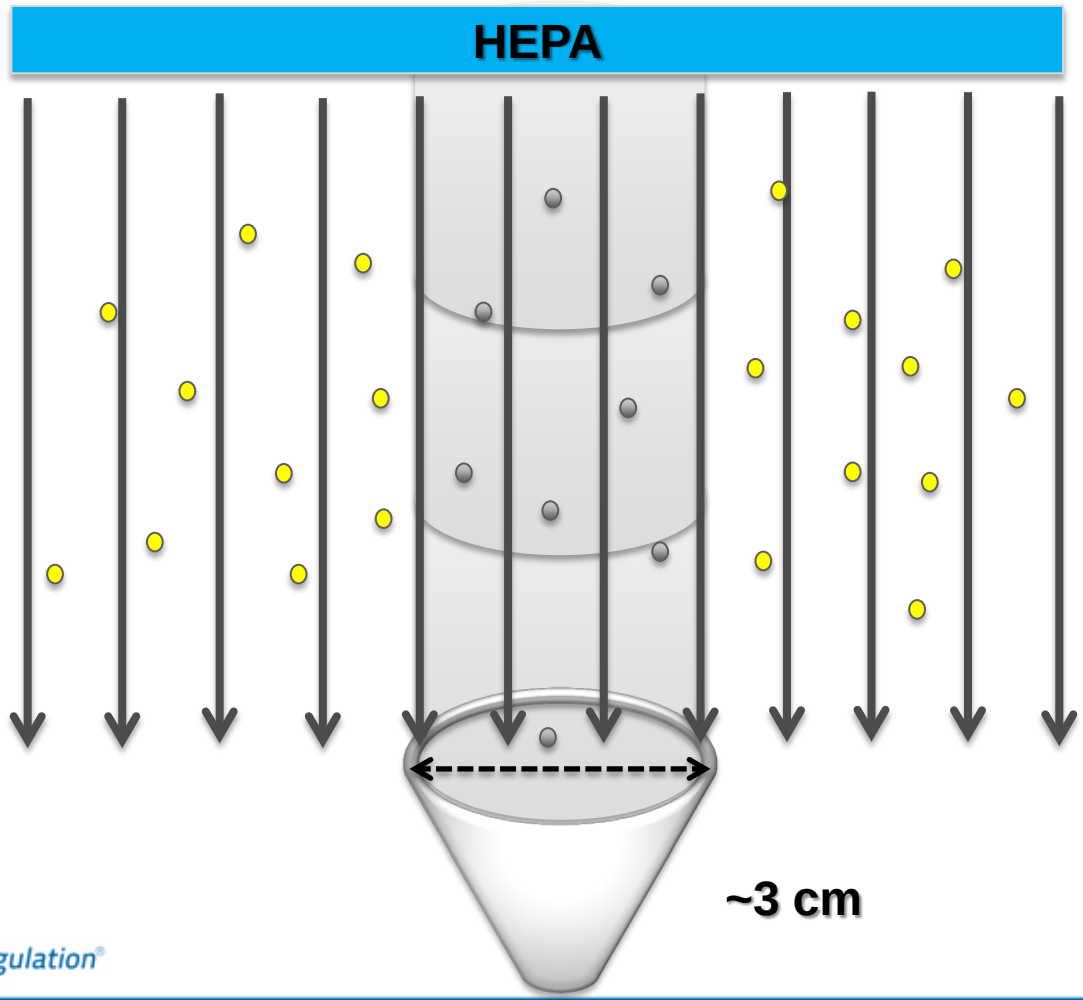
Particle Distribution Experiment

If particles are in laminar air flow, they should follow the pattern and fall vertically

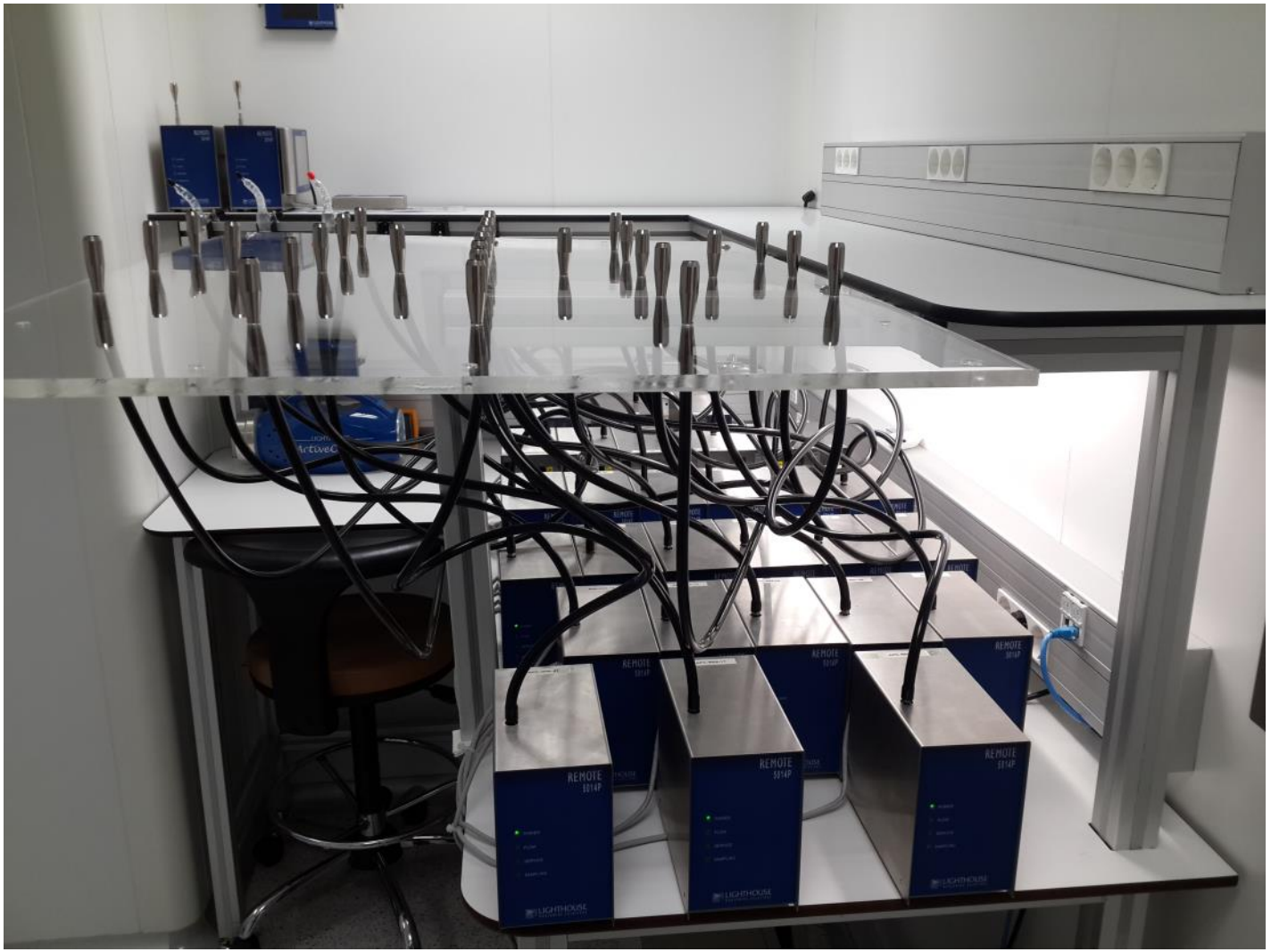


Particle Distribution Experiment

If particles are in laminar air flow, they should follow the pattern and fall vertically, so isoprobe should represend only an air column, not less than 30 cm (1 foot)

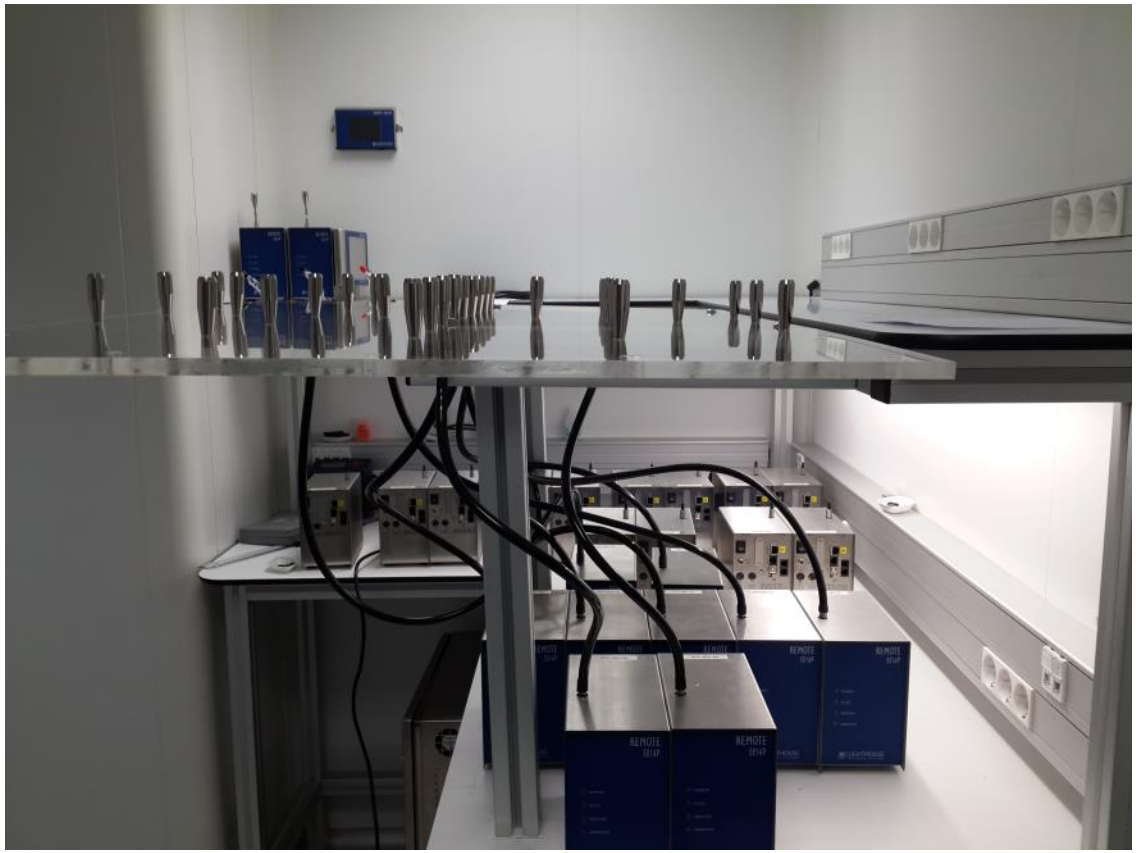


Particle Distribution Experiment

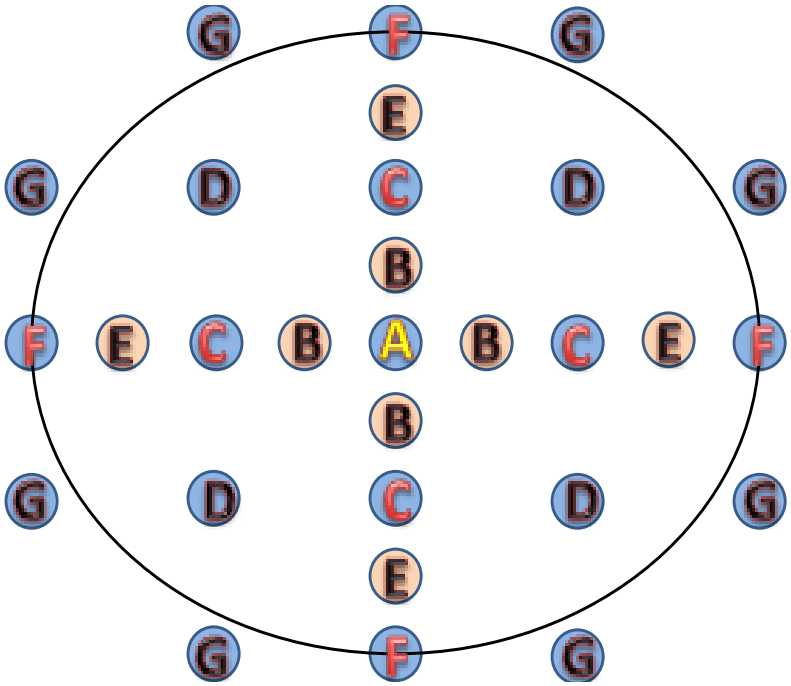


Particle Distribution Experiment

- 29 pcs. Online Particle counters,
- 0.5 and 5.0 micron channels



Particle Distribution Experiment



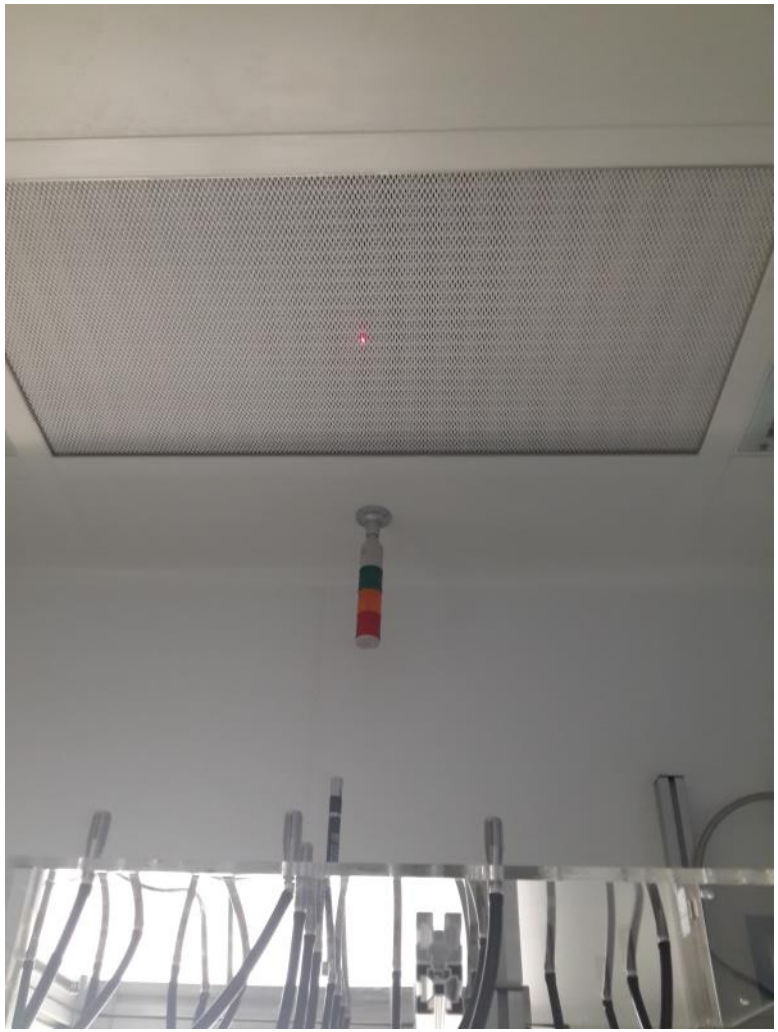
A	:	Center Point	No of Points : 1
A ↔ B	:	75 mm	No of Points : 4
A ↔ C	:	150 mm	No of Points : 4
A ↔ D	:	212 mm	No of Points : 4
A ↔ E	:	225 mm	No of Points : 4
A ↔ F	:	300 mm	No of Points : 4
A ↔ G	:	335 mm	No of Points : 8

Total 29 points, 21 points are less than 30 cm from center.

Particle Distribution Experiment

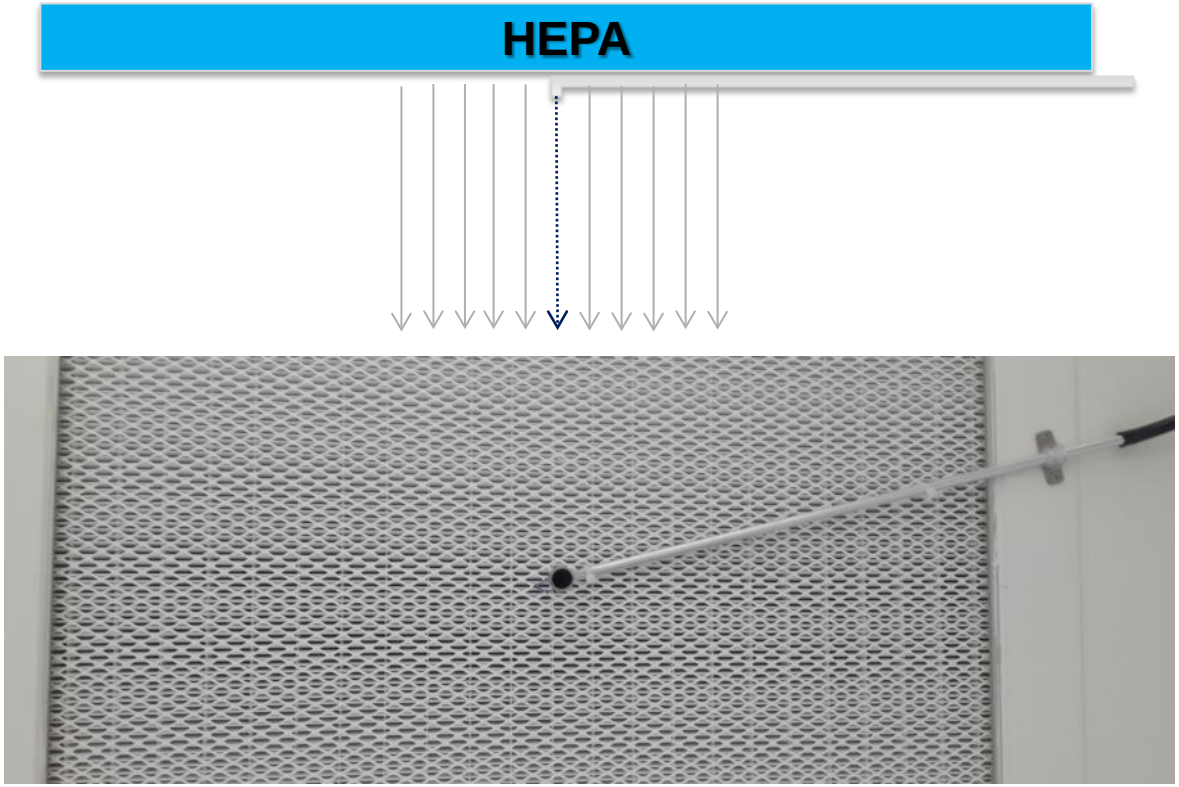
- ISO Class 5, Grade A Conditions
- Under HEPA
- 0.45 m/s laminar airflow
- 0.5 micronPolystyrene Latex(PSL) particles

Particle Distribution Experiment



Particle Distribution Experiment

- 0.5 micron Polystyrene Latex(PSL) particles introduced to laminar airflow, in same direction and same air velocity (0.45m/s)

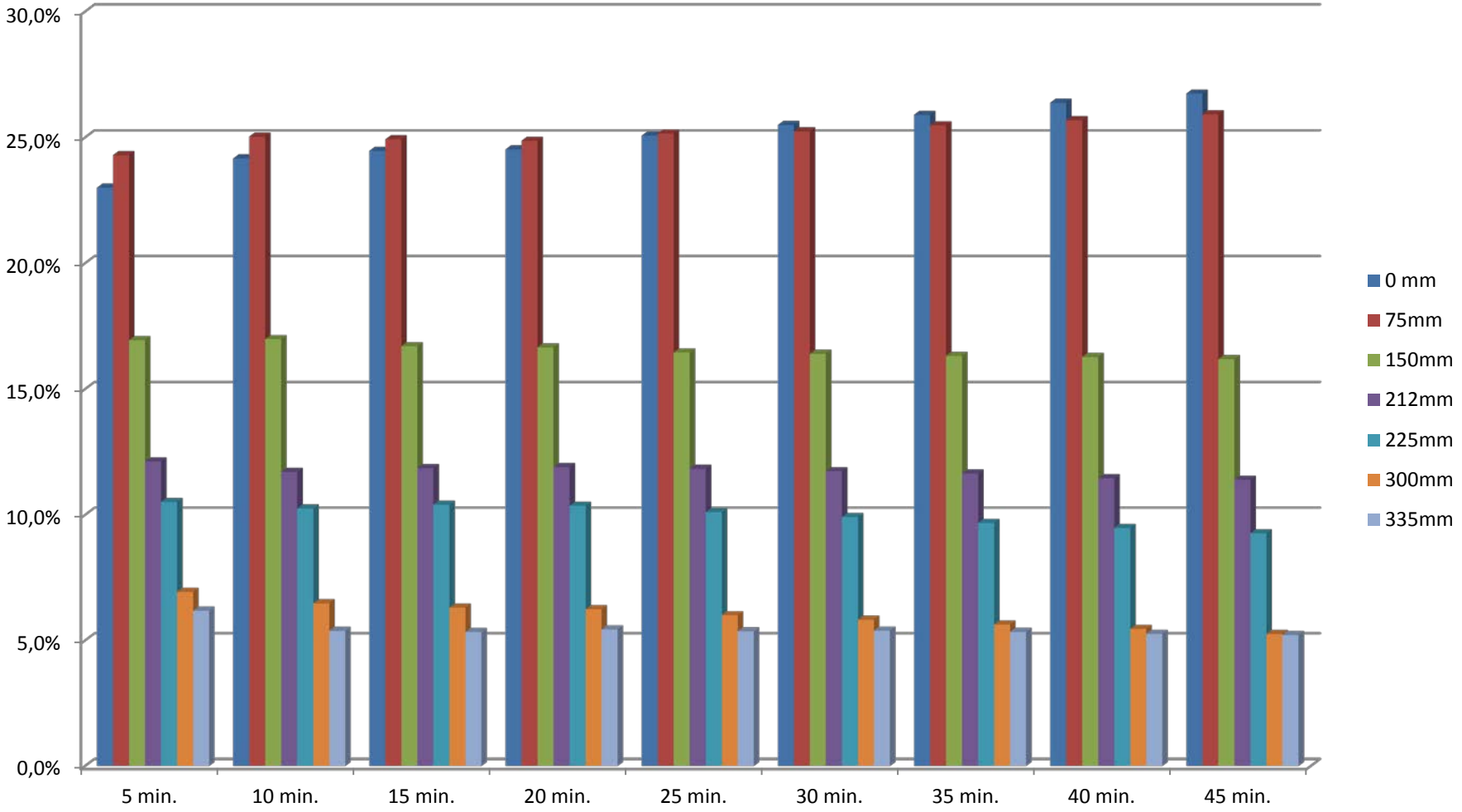


Particle Distribution Experiment

- Results

	DISTRIBUTION PERCENTAGE (%) vs. SAMPLING DURATION								
	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.
0 mm	23.0%	24%	24.5%	24.5%	25.1%	25.5%	25.9%	26.4%	26.7%
75mm	24.3%	25.0%	24.9%	24.9%	25.2%	25.2%	25.5%	25.7%	25.9%
150mm	16.9%	17.0%	16.7%	16.7%	16.5%	16.4%	16.3%	16.3%	16.2%
212mm	12.1%	11.7%	11.9%	11.9%	11.8%	11.7%	11.6%	11.5%	11.4%
225mm	10.5%	10.3%	10.4%	10.4%	10.1%	9.9%	9.7%	9.5%	9.3%
300mm	6.9%	6.5%	6.3%	6.2%	6.0%	5.8%	5.6%	5.5%	5.3%
335mm	6.2%	5.4%	5.3%	5.4%	5.4%	5.4%	5.3%	5.3%	5.2%

Particle Distribution Experiment



Particle Distribution Experiment

- Results,
  - ~95% of all particles distributes within 30 cm
  - Particles are not following the laminar pattern
  - Reason? : Other Forces;
    - Brownian motion: small particles suspended in gas or liquids come into contact with gas molecules.
    - Thermal variation (thermophoresis)
    - Electrostatic charges

Cleanroom and Clean Air Device **Monitoring**

GMP Annex 1, Clause #11,

«...the length of tubing and the radii of any bends in the tubing must be considered...»

Example 2; ***ASTM F50-07*** *Standard Practice for Continuous Sizing and Counting of Airborne Particles*

«...a maximum transit tube length of 3 m can be used. If a flexible transit tube is to be used, then no radius of curvature below 15 cm shall be used.»

Thank you!

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