PhEn-602

Notes #5

J. Manfredi

Clean Rooms and Controlled Environments

ISO vs FS209E: key differences

ISO limits are based strictly on a cubic meter

- **FS 209E has limits for both ft^3 and m^3**
- **Three new classes were introduced – ISO Class 1 and Class 2, (both of which are cleaner than FS 209E class 1), & ISO Class 9.**
- **ISO added the 1.0 micron particle size**

Clean Rooms and Controlled Environments

ISO vs FS209E: key differences

- **ISO generally requires fewer sampling locations than FS 209E**
- **With ISO, number of sample locations is based on clean room area, whereas with FS 209E it is based on Class, size of clean room, and whether or not unidirectional flow is present**
- **ISO has a minimum 1 minute sample time, FS 209E does not.**

Clean Rooms and Controlled Environments

- European Union classifications – (this list excludes viable particulate limits)

	At-Rest		In-Operation	
	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)
	0.5μm	5μm	0.5μm	5μm
Grade D	3,500,000 (100,000)	20,000 (570)	No spec.	No spec.
Grade C	350,000 (10,000)	2000 (57)	3,500,000 (100,000)	20,000 (570)
Grade B	3,500 (100)	None	350,000 (10,000)	2000 (57)
Grade A	3,500* (100)	None	3500 (100)	None

Clean Rooms and Controlled Environments

FDA vs. EU Requirements

- **Grade A approximates Class 100 in U.S., but *requires* unidirectional flow.**
- **Grade B in the "at rest" condition has the same particle limit as Grade A "at rest", but does not require unidirectional flow.**
- **Grade C is similar to Class 100,000 "in operation".**
- **Grade B in operation approximates Class 10,000 "in operation".**

Clean Rooms and Controlled Environments

FDA Aseptic Guidelines:

Uses both the FS 209E classifications and

ISO classifications for aseptic manufacturing.

- Non-viable particle levels must meet the FS 209E classes and ISO classes.
- Mentions the as-built and dynamic state of the cleanroom with more emphasis on the dynamic (“In-operation”) condition.
- Contains limits for viable particles

Clean Rooms and Controlled Environments

FDA vs. EU Requirements

- **EU has requirements for "At-Rest" and "In-Operation"**
- **FDA Aseptic guidelines are based on "In-Operation" condition only.**
- **EU focuses on two particle sizes – 0.5μm and 5μm**
- **FDA Aseptic guidelines: 0.5μm only**
- **EU has limits for the 5 micron particle, FDA Aseptic Guidelines do not.**

Clean Rooms and Controlled Environments

Useful cleanroom websites that cover some of the material discussed:

- www.s2c2.co.uk/docs/cccs.pdf
- www.particle.com
- www.clean-room.com
- www.fda.gov/cder/guidance/5882fnl.htm
  - Website for FDA Aseptic guidelines
- www.peakpureair.com/particlesize.htm

Clean Rooms and Controlled Environments

Testing the Cleanroom for Particle Class FS 209E

- Number of sampling locations is a function of area *and* classification
- Different sampling location formula for unidirectional and non-unidirectional flow clean rooms

Clean Rooms and Controlled Environments

FS 209E: For non-unidirectional flow clean rooms, the lesser of:

SI (metric) units:

$N_L = Ax64/(10^M)^{0.5}$

- Where M=SI description of class
- A= floor area of clean zone in m^2

English units:

$N_L = \mathbf{A/(N_c)^{0.5}}$

- A= floor area of clean zone in ft^2
- Where N_c is English class

Clean Rooms and Controlled Environments

ISO – number of sampling locations

- Particulate Testing - Number of sampling locations

$$N_L = \sqrt{A}$$

- N_L = minimum number of sampling locations
- A= area of clean room in square meters

Clean Rooms and Controlled Environments

- Particle testing

Particle Size (Microns)	Cumulative # (Per Ft.^{3})	Differential # (Per Ft.^{3})
0.3	200	70
0.5	130	30
1.0	100	80
5.0	20	20

Clean Rooms and Controlled Environments

Particle Size (Microns)	Cumulative # (Per Ft.^{3})	Differential # (Per Ft.^{3})
0.3	175	70
0.5	105	95
1.0	10	8
5.0	2	2

- Does the above data show that the room meets Class 100 conditions at 0.5 micron? NO
- Does the above room pass for ISO Class 5 at 1.0 micron? YES

Clean Rooms and Controlled Environments

ISO vs FS209E:

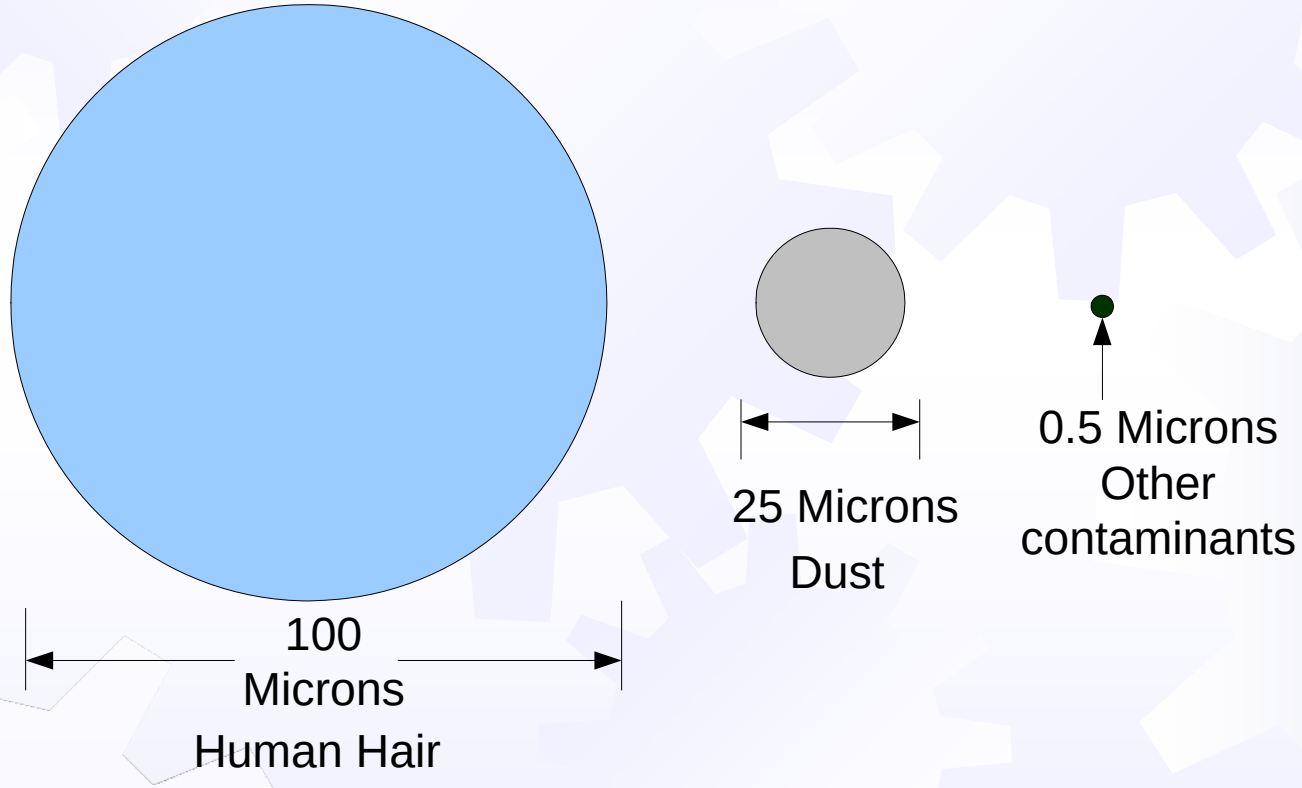
ISO 14644-1	FED Std 209E	
ISO Class	English	Metric
1		
2		
3	1	M1.5
4	10	M2.5
5	100	M3.5
6	1,000	M4.5
7	10,000	M5.5
8	100,000	M6.5
9		

Clean Rooms and Controlled Environments

ISO vs FS209E:

ISO 14644-1	FED Std 209E	
ISO Class	English	Metric
1		
2		
3	1	M1.5
4	10	M2.5
5	100	M3.5
6	1,000	M4.5
7	10,000	M5.5
8	100,000	M6.5
9		

Clean Rooms and Controlled Environments



Clean Rooms and Controlled Environments

Particle counting

- The particle count limits are for the particular size and larger
- The particle counter can distinguish between different particle sizes
- The counter typically prints out data that provides actual counts at the specific particle size (differential) and the cumulative count

Continuous Particle Monitoring Systems

- **Particle counting: continuous sampling – two types**
  - **Sequential monitoring system (manifold system)**
  - **Simultaneous monitoring system**

Clean Rooms and Controlled Environments

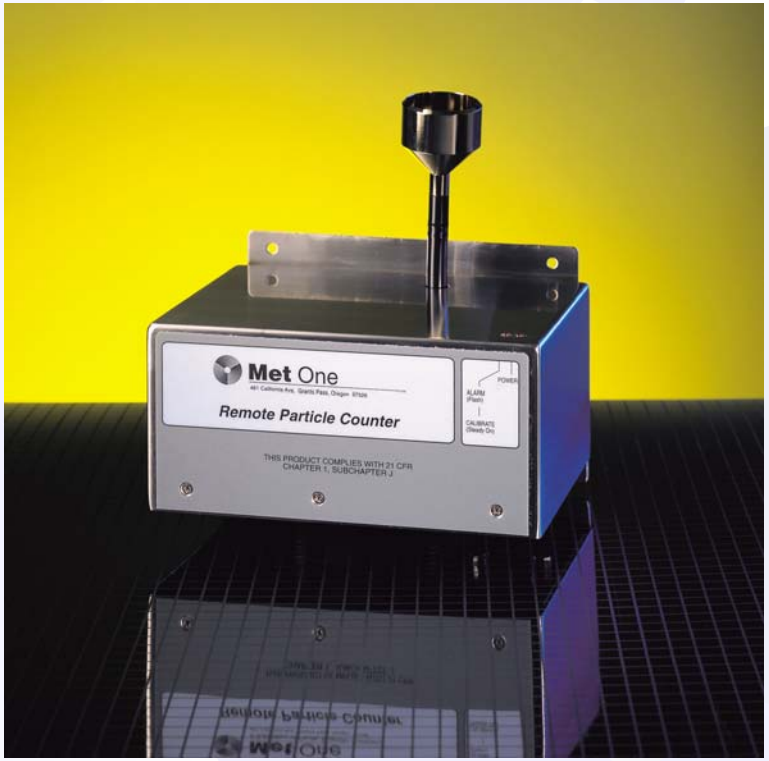
Typical Particle Counter

Controlled Environments-Cleanroom Standards

Continuous Particle Monitoring

Sequential (manifold)

Simultaneous – remote particle counters



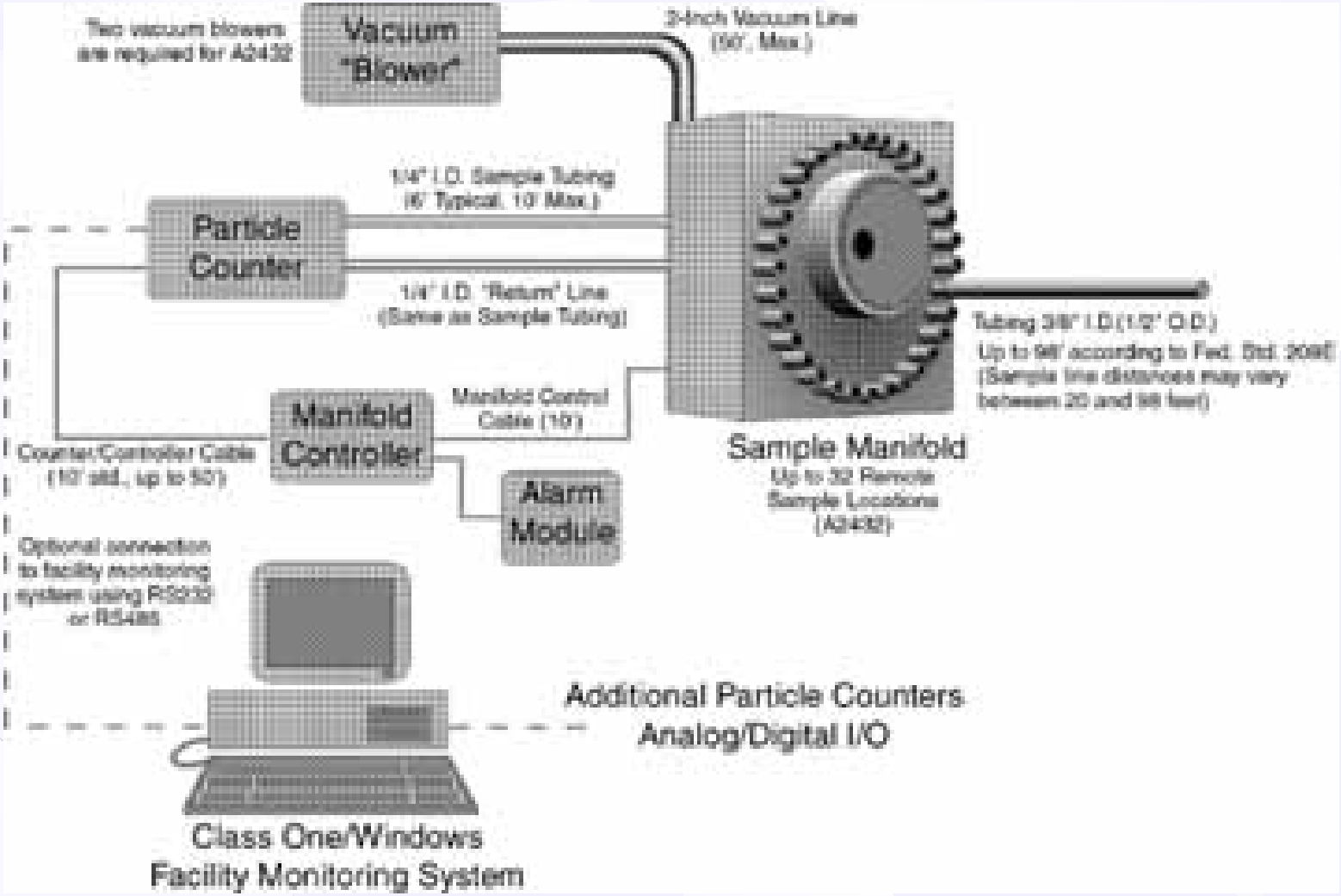
Continuous Particle Monitoring Systems

- **Particle counting: continuous sampling**
  - **Sequential monitoring system:**
    - **Single particle counter sequences through sample locations**
    - **Disadvantage: particle loss from long sampling tube lengths**
    - **Rotate thru sensors, can miss a potential high-reading**
  - **Simultaneous monitoring system**
    - **Multiple particle counters**
    - **Every location has a particle counter**
    - **More expensive than sequential**

Clean Rooms and Controlled Environments Other important notes

- Particle counting: continuous sampling
  - Sequential monitoring system (centralized manifold system):
    - Sample ports connected to central vacuum source
    - Air taken from each port in rotational fashion
    - Central vacuum pump and particle counter
  - Simultaneous monitoring system
    - Particle sensors connected via cabling to a central computer
- Both allow auto notification if particle levels exceed alert and action levels

Sequential Particulate Monitoring



The Scale of Things – Nanometers and More

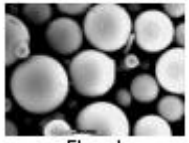
Things Natural

Dust mite

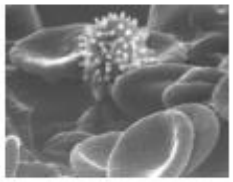
200 µm

Ant
~ 5 mm

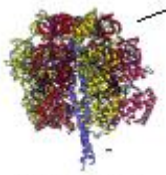
Human hair
~ 60-120 µm wide



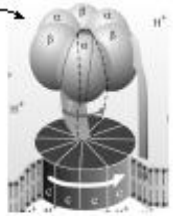
Fly ash
~ 10-20 µm



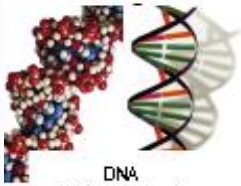
Red blood cells with white cell
~ 2-5 µm



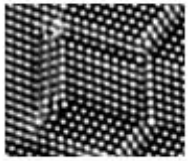
~10 nm diameter



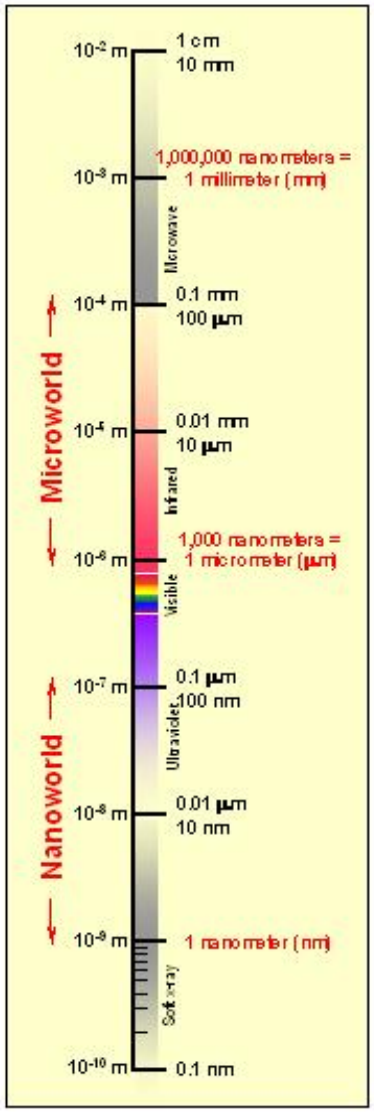
ATPsynthase



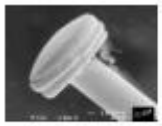
DNA
~2-12 nm diameter



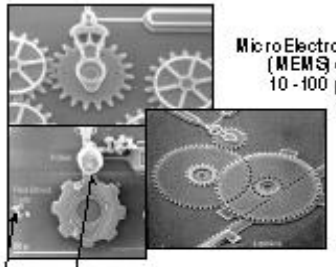
Atoms of silicon
spacing ~tenths of nm



Things Manmade

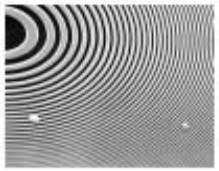


Head of a pin
1-2 mm

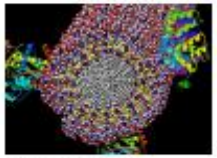


Micro Electro Mechanical (MEMS) devices
10 - 100 µm wide

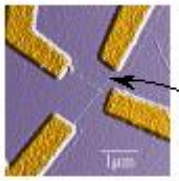
Pollen grain
Red blood cells



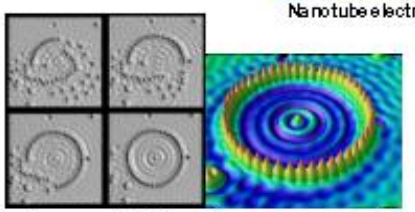
Zone plate x-ray "lens"
Outer ring spacing ~35 nm



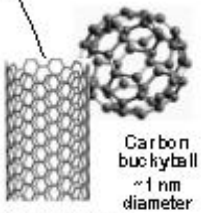
Self-assembled,
Nature-inspired structure
Many 10s of nm



Nanotube electrode



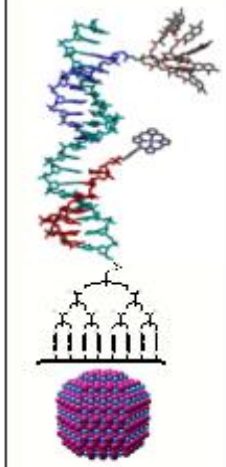
Quantum corral of 48 iron atoms on copper surface
positioned one ata time with an STM tip
Corral diameter 14nm



Carbon buckyball
~1 nm diameter

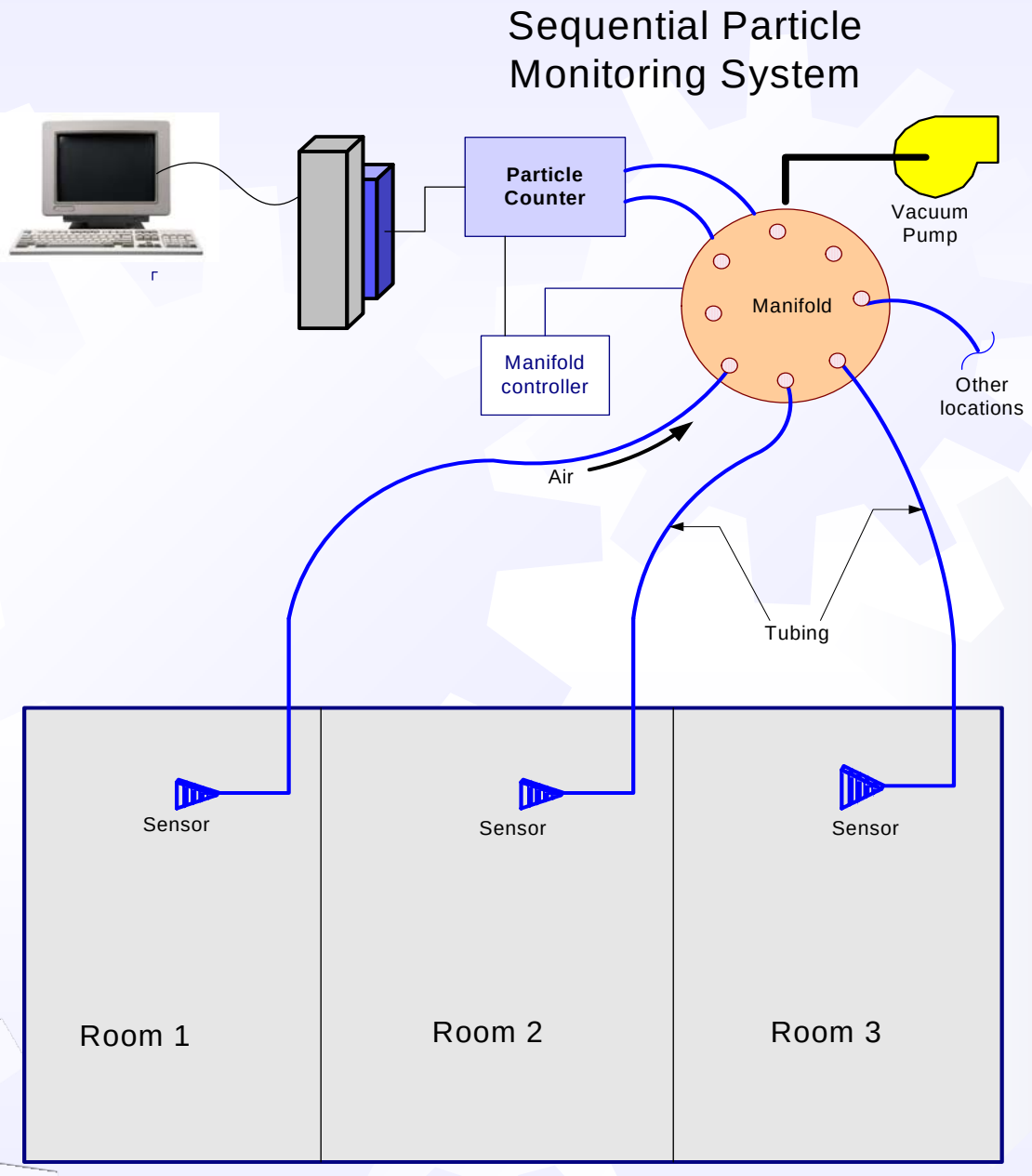
Carbon nanotube
~1.3 nm diameter

The Challenge

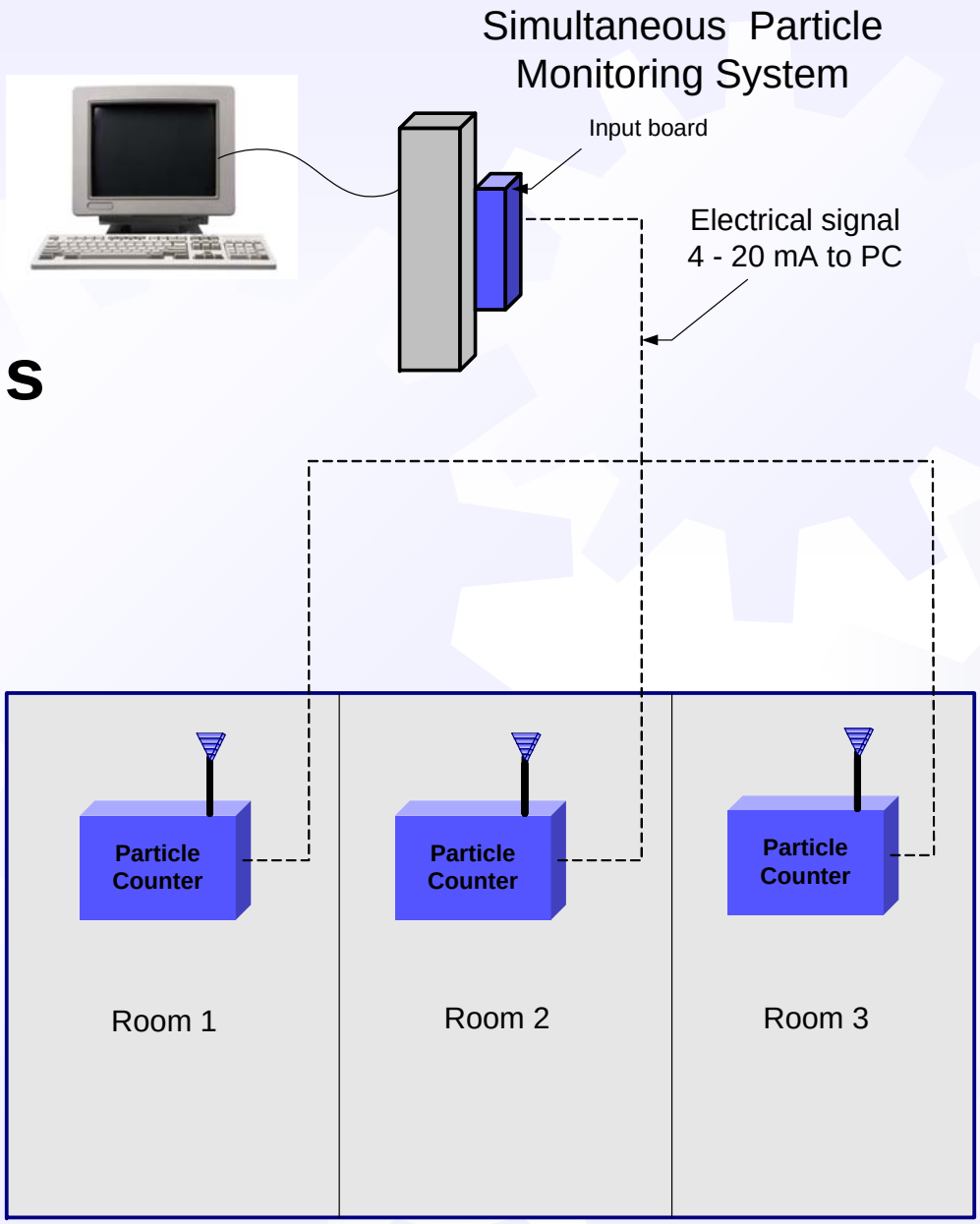


Fabricate and combine nanoscale building blocks to make useful devices, e.g., a photosynthetic reaction center with integral semiconductor storage.

Sequential Particle Monitoring System – an alternate look at it…..



Simultaneous Particle Counting



Clean Rooms and Controlled Environments

Common items - ISO Standard 14644-1 & 2 and FS 209E

- **No fewer than two sample locations**
- **Minimum sample volume and time is also dictated in each standard**
- **For the most part, ISO Class 3 through 8 are very similar to FS 209E Class 1 through 100,000.**
- **The particle limits are for the particle size stated *and larger***

Clean Rooms and Controlled Environments

FS 209E & ISO Standard 14644-1 & 2

- **Note that the number of sampling locations is the minimum required.**
- **It's often easier to sample a room at 10 or more locations, rather than going through the statistical analysis**

Clean Rooms and Controlled Environments

Important note regarding FDA Aseptic Guidelines:

- **FDA Aseptic guidelines do not allow averaging at a sampling site!**
- **Each discrete sample must be below the class limit.**
- **This is important, since you can pass ISO and FS 209E, and not meet FDA requirement.**
- **FDA aseptic guidelines still reference the FS 209E classes.**
- **FDA has no formal position regarding the ISO standards impact on pharmaceutical manufacturers**

Clean Rooms and Controlled Environments

European Union Guide to GMP (EU cGMP)

- **Formal title:*"The Rules Governing Medicinal Products in the European Union. Volume 4. Good Manufacturing Practices – Medicinal Products for Human and Veterinary Use"***
- **Establishes four grades: Grade A, B, C, D**
- **Grade A is cleanest, Grade D is least clean**
- **Each grade has limits for viable and non-viable particulates**
- **Refers to ISO standard for more details**

Clean Rooms and Controlled Environments

European Union Guide to GMP (EU cGMP)

- **"Grade A: The local zone for high-risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar flow work station. Laminar flow air systems should provide a homogeneous air speed"…**
- **"Grade B: For aseptic preparation and filling, this is the background environment for Grade A zone."**
- **"Grade C and D: Clean areas for carrying out less critical stages of the manufacture of sterile products."**

Clean Rooms and Controlled Environments

EU Classifications – (excludes viable particulate limits)

	At-Rest		In-Operation	
	At-Rest Max # particles per cubic meter	At-Rest Max # particles per cubic meter	In-Operation Max # particles per cubic meter	In-Operation Max # particles per cubic meter
	0.5μm	**5μm**	**0.5μm**	**5μm**
Grade D	3,500,000	20,000	No spec.	No spec.
Grade C	350,000	2000	3,500,000	20,000
Grade B	3,500	None	350,000	2000
Grade A	3,500*	None	3500*	None

*EU Grade A requires unidirectional flow

Clean Rooms and Controlled Environments

EU Classifications – (excludes viable particulate limits)

(per cubic foot numbers in parenthesis)

	At-Rest		In-Operation	
	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)	Max # particles per cubic meter (per cubic ft.)
	0.5μm	**5μm**	**0.5μm**	**5μm**
Grade D	3,500,000 (100,000)	20,000 (570)	No spec.	No spec.
Grade C	350,000 (10,000)	2000 (57)	3,500,000 (100,000)	20,000 (570)
Grade B	3,500 (100)	None	350,000 (10,000)	2000 (57)
Grade A	3,500* (100)	None	3500 (100)	None

*EU Grade A requires unidirectional flow

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class – EU Requirements

Aseptic Preparation:

- Washing of components - Grade D environment
- Compounding - Grade C if later filtered.
- Filling: Grade A with Grade B background

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class

FDA/US Requirements – Aseptic processes

Typical Process Step	Background environment	Product/container closure exposure area
Dispensing	Class 100,000	Local protection – specific enclosures
Compounding	Class 100,000	Class 10,000
Filtration	Class 10,000	Class 100
Initial prep/washing components	Pharmaceutical - Class 100,000 "at rest"	Pharmaceutical - Class 100,000 "at rest"
Final rinse of components/containers	Class 100,000	Class 100,000

From ISPE Baseline Guide – Volume 3 – Sterile Manufacturing Facilities

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class

FDA/US Requirements – Terminally sterilized processes

Typical Process step	Background environment	Product/container /closure exposure area
Dispensing	Class 100,000	Class 100,000
Compounding	Class 100,000	Class 100,000
Filtration	Class 100,000	Class 100
Initial prep/washing components	Pharmaceutical -Class 100,000 “at rest”	Pharmaceutical - Class 100,000 “at rest”
Final rinse of components/containers	Pharmaceutical -Class 100,000 “at rest”	Class 100,000
From ISPE Baseline Guide – Volume 3 – Sterile Manufacturing Facilities		

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class

FDA/US Requirements – Aseptic processes

Typical Process step	Background environment	Product/container/ closure exposure area
Loading of components and containers for sterilization/depyrogenation	Class 100,000	Class 100,000
Sterilization of components/depyrogenation of containers - unloading	Class 10,000	Class 100 (or wrapped/sealed)
Filling and stoppering	Class 10,000	Class 100
Lyophilization Operation	N/A	Closed system
Lyophilization transfer	Class 10,000	Class 100

From ISPE Baseline Guide – Volume 3 – Sterile Manufacturing Facilities

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class – FDA/US Requirements – Terminal Sterilized processes

Typical Process step	Background environment	Product/container/ closure exposure area
Sterilization of components/depyrogenation of containers - loading	Pharmaceutical Class 100,000 at rest	Class 100,000 (or wrapped/sealed)
Sterilization of components/depyrogenation of containers - unloading	Class 100,000	Class 100 (or wrapped/sealed)
Filling and stoppering	Class 100,000	Class 100
Capping	Pharmaceutical	Local protection
Terminal sterilization	Pharmaceutical	N/A

From ISPE Baseline Guide – Volume 3 – Sterile Manufacturing Facilities

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class
FDA/US Requirements – Aseptic processes

Typical Process step	Background environment	Product/container/ closure exposure area
Capping and Crimping	Pharmaceutical -Class 100,000 “at rest”	Local protection – laminar flow or enclosure
Inspection	Pharmaceutical	N/A
Label and Package	Pharmaceutical	N/A
From ISPE Baseline Guide – Volume 3 – Sterile Manufacturing Facilities		

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class
FDA/US Requirements – Aseptic processes

Typical Process step	Background environment	Product/container/closure exposure area
Inspection	Pharmaceutical	N/A
Label and Package	Pharmaceutical	N/A
From ISPE Baseline Guide – Volume 3 – Sterile Manufacturing Facilities		

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class – EU Requirements

Aseptically produced products

Grade	Examples of operations
A	**Aseptic Preparation and filling**
C	**Preparation of solutions to be filled.**
D	**Handling of components after washing**

Clean Rooms and Controlled Environments

Manufacturing Operation and Clean Room Class – EU Requirements

Terminally sterilized products

Grade	Examples of operations
A	**Filling of products, when unusually at risk**
C	**Preparation of solutions, when unusually at risk. Filling of "less susceptible products".**
D	**Preparation of solutions and components for subsequent filling**

Clean Rooms and Controlled Environments

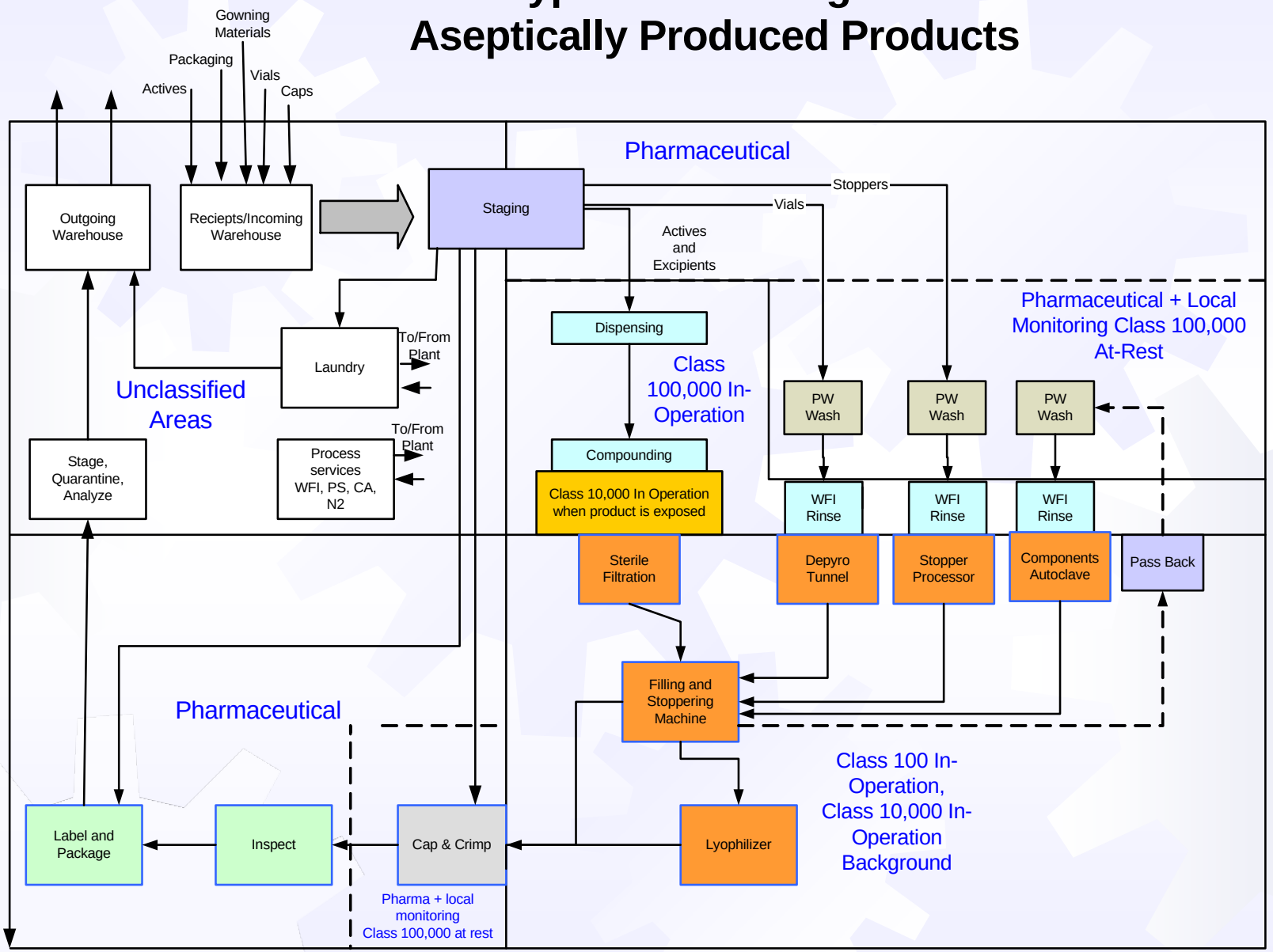
Manufacturing Operation and Clean Room Class – EU & FDA Requirements

With terminally sterilized products, you can scale back on the cleanliness of many of the clean rooms.

Summary of Grades and Classes vs. Process

Type of Processing	Process Step/Activity	Nearest equivalent ISO 14644-1 class "in operation"	US GMP expectation "in operation"	EU GMP Grade
Aseptic	Aseptic formulation and filling operations	5	100/M3.5	A
Aseptic	Background to the above activities	7	10,000/M5.5	B
Aseptic	Preparation of solutions to be filtered	8	100,000/M6.5	C
Aseptic	Component handling after washing when exposed to the environment	8	100,000/M6.5	C
Terminally sterilised	Filling of "unusually at risk" products	5	100/M3.5	A
Terminally sterilised	Filling of products, "unusually at risk" solution preparation	8	100,000/M6.5	C
Terminally sterilised	Preparation of products and solutions	unclassified/ controlled	Pharmaceutical	D

Typical Flow Diagram
Aseptically Produced Products



High Efficiency Air Filtration

- HEPA filters
  - Typically 99.97% efficient at 0.3 micron
  - Used for Clean Room Classes 100,000 thru 100
  - For Class 10 and better, use ULPA filters, Ultra Low Penetration Air filters
- ULPA Filters
  - Have an efficiency greater than 99.999% against 0.1 – 0.2 micron particles.

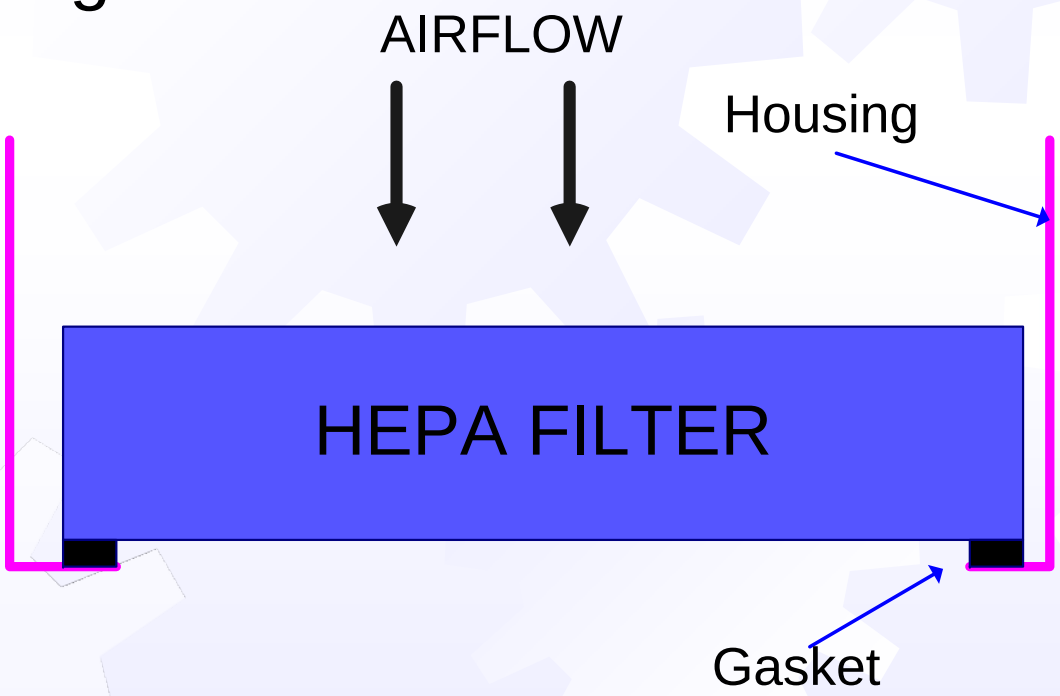
High Efficiency Air Filtration

- ULPA Filters
  - Typically used in the micro-electronics industry.
  - Some Pharmaceutical firms are using ULPA's in their Class 10,000 (Grade B) and Class 100 (Grade A) clean rooms
  - Care is required due to the increased pressure drop with ULPA's vs. HEPA's. This can impact overall airflow if filters switched in an existing system – system resistance changes (increases).

High Efficiency Air Filtration

Methods of sealing HEPA and ULPA filters

- Gasketed method – typically neoprene rubber gasket



High Efficiency Air Filtration

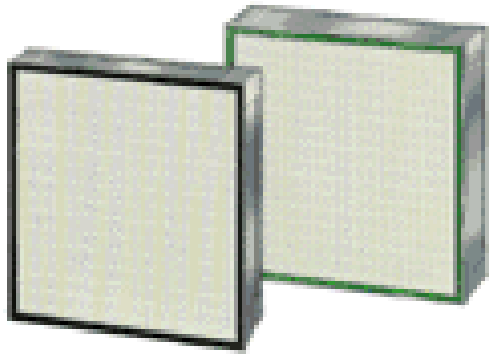
Methods of sealing HEPA and ULPA filters

- Fluid Seal method

High Efficiency Air Filtration

Areas where leakage can occur:

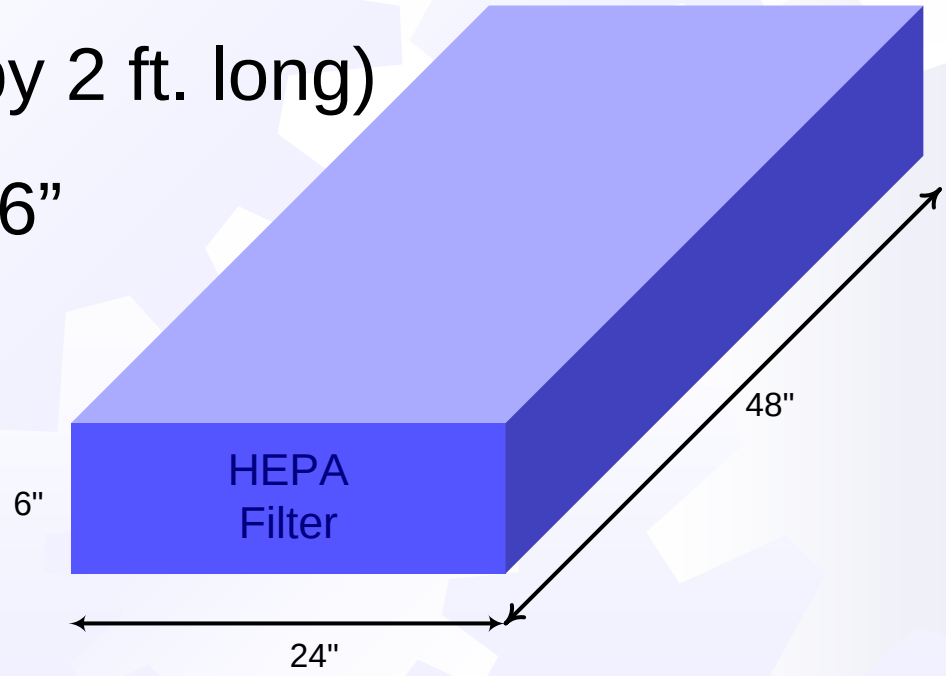
- Housing to filter seal
  - Very important potential leak source
- Filter paper
- Filter paper to case cement area
- Frame joints
- Gasket



High Efficiency Air Filtration

Typical sizes of HEPA filters

- 2 x 4 (2 ft. wide by 4 ft. long)
- 2 x 2 (2 ft. wide by 2 ft. long)
- Typical height is 6”



High Efficiency Air Filtration

Other points about HEPA Filtration:

- When replacing, should be fitted so that replacement can be made from the Aseptic room side – thus keeping integrity of room
- Efficiencies of 99.97% at 0.3 micron and 99.99% at 0.3 micron often used.

Clean Rooms and Controlled Environments Summary of Tests for Cleanroom Certification

Quantity of air: sufficient quantity to ensure removal of contaminants

- For turbulent or non-unidirectional flow clean room, the volume of air and air change rate is important

Clean Rooms and Controlled Environments
Summary of Tests for Cleanroom Certification

Seven primary tests:

1. Airflow Volume
2. Air Change Rate Calculations
3. Air Velocity Testing:

   (For a unidirectional flow clean room, it is velocity that is critical)

   Airflow direction between clean rooms: air should travel from cleaner room to less-clean room
4. Room to Room DP Testing
5. Filter Installation Leak Testing:

   To ensure no contaminants from the air system enter the clean room
6. Airflow pattern test (smoke test):

   Airflow direction within the clean room: air should flow from clean portion of room to dirty portion and then be extracted
7. Particle count testing

Frequency of HEPA filter leak testing

- Depends on use of area. For for critical (Class 100 and sub-critical (Class 10,000) areas: twice per year per FDA Aseptic guidelines.
- Class 100,000 areas – typically every 6 months or every year – depends on manufacturer. PDA recommends annually.
- Many pharmaceutical manufacturers shutdown their facilities every six months for the certification
- Conduct major maintenance activities during the same time

Clean Rooms and Controlled Environments
Summary of Tests for Cleanroom Certification

Additional tests that may be performed:

- Temperature and relative humidity testing
- Lighting
- Sound levels
- Vibration levels

Clean Rooms and Controlled Environments
Clean Room Design Principles

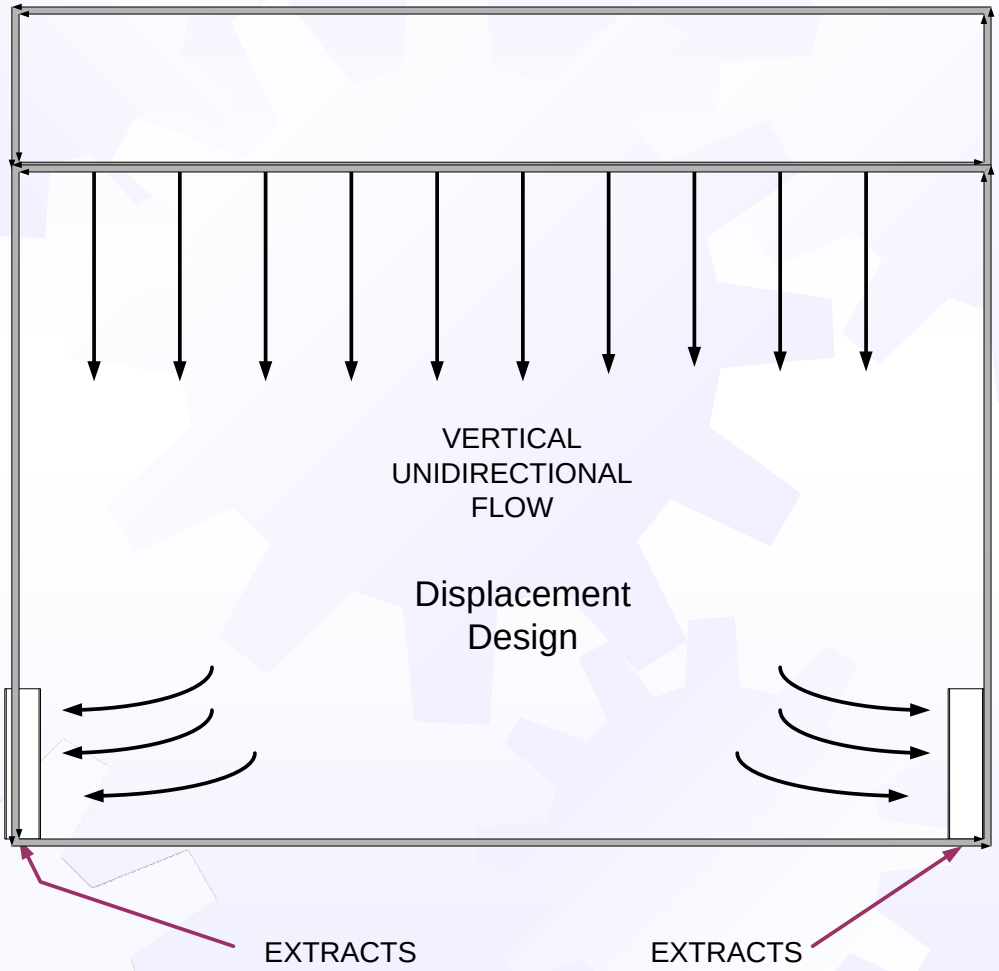
- *Displacement Design*
- *Dilution Design*

Clean Rooms and Controlled Environments
Clean Room Design Principles

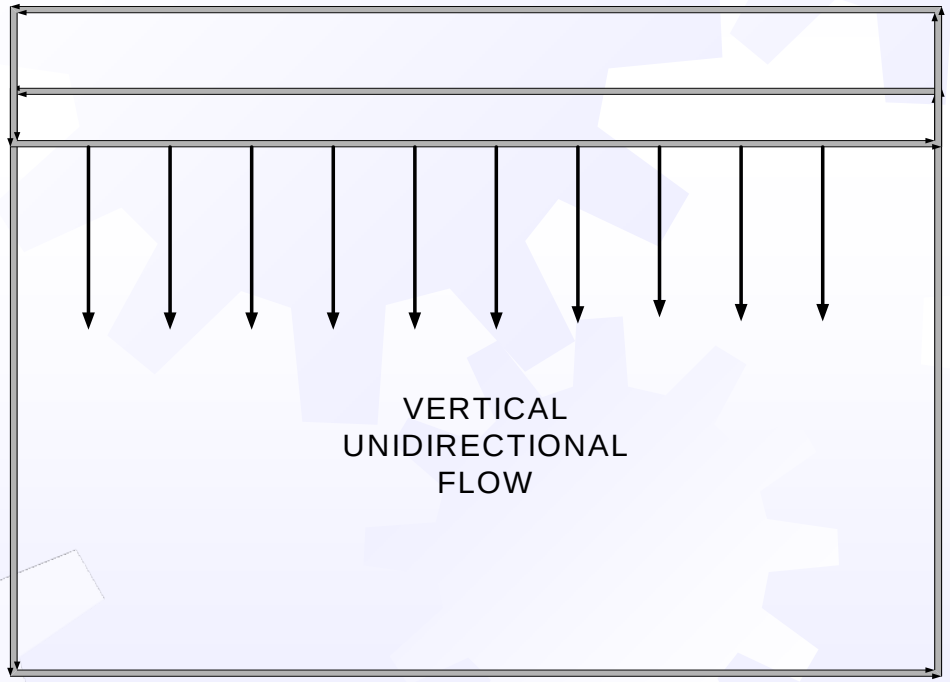
Displacement Design:

- Dirty air is displaced by clean air, travelling at a relatively high velocity
- Typical of unidirectional flow clean rooms (Class 100 rooms, EU Grade A rooms).

Displacement Design



- Displacement design: Unidirectional Flow: Also called *Laminar Flow* – airflow having generally parallel streamlines, operating in a single direction, and with uniform velocity over its cross section.



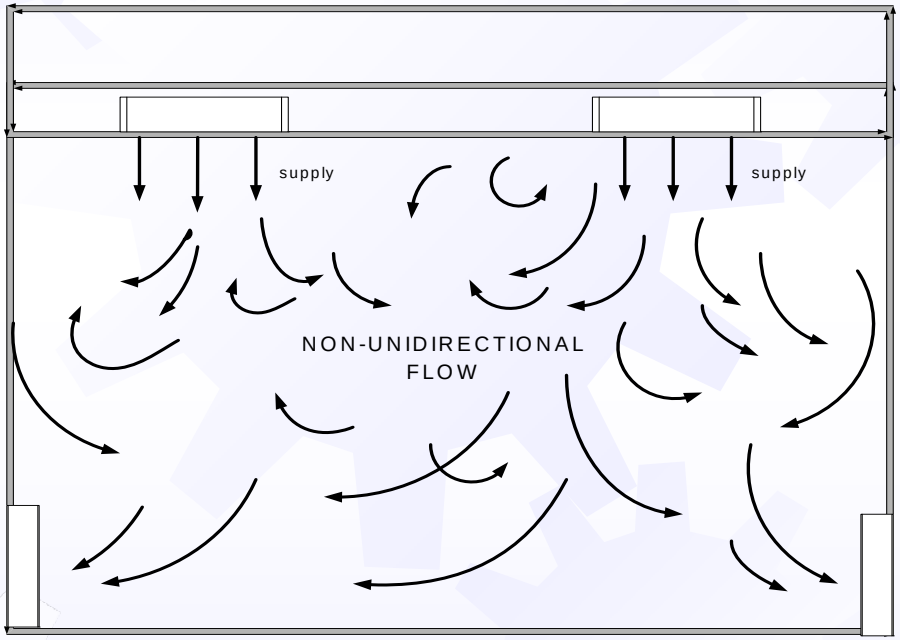
HVAC Design Principles

Dilution Design:

- "Dirty" air is mixed continuously with "clean" air.
- Turbulent air mixing – reduces the particulate load in the room.
- Typical of Class 10,000 and Class 100,000 rooms
- Dilution rooms are called mixed flow rooms
- Often have local regions in the room with displacement features

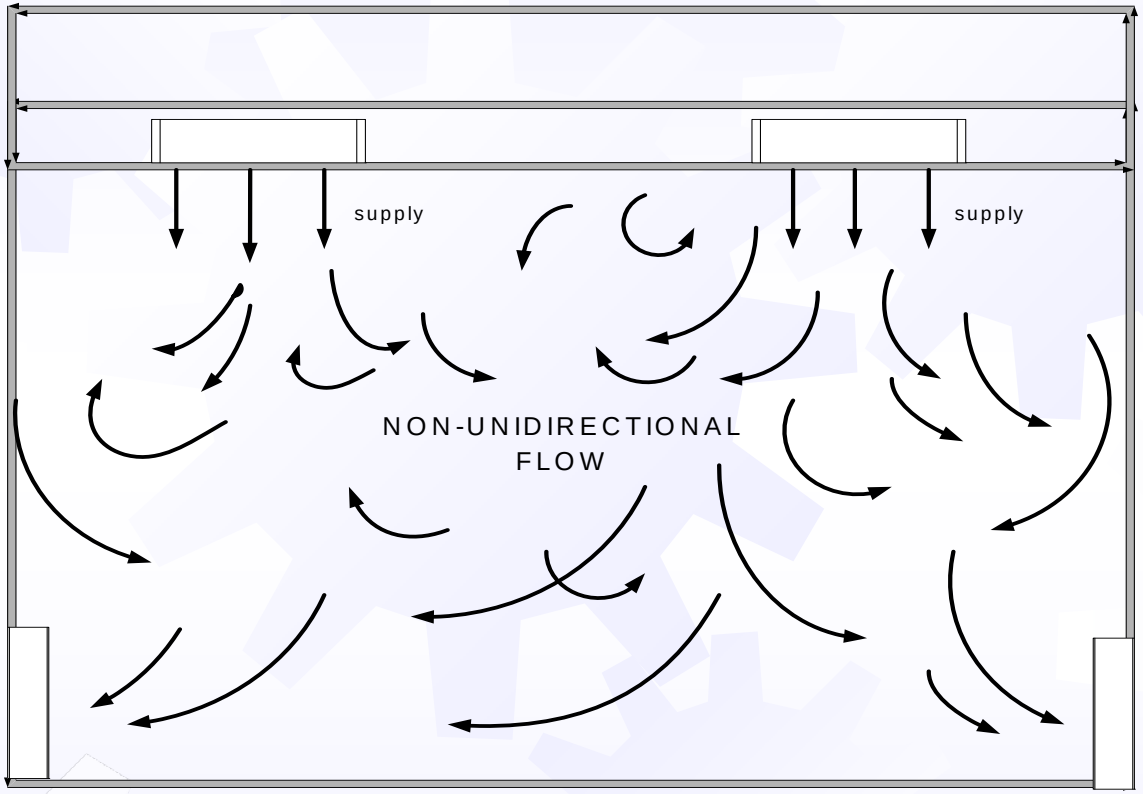
- Dilution Design: Non-unidirectional Flow:

  Also called “mixed-flow” or “turbulent flow” - airflow which is not unidirectional.



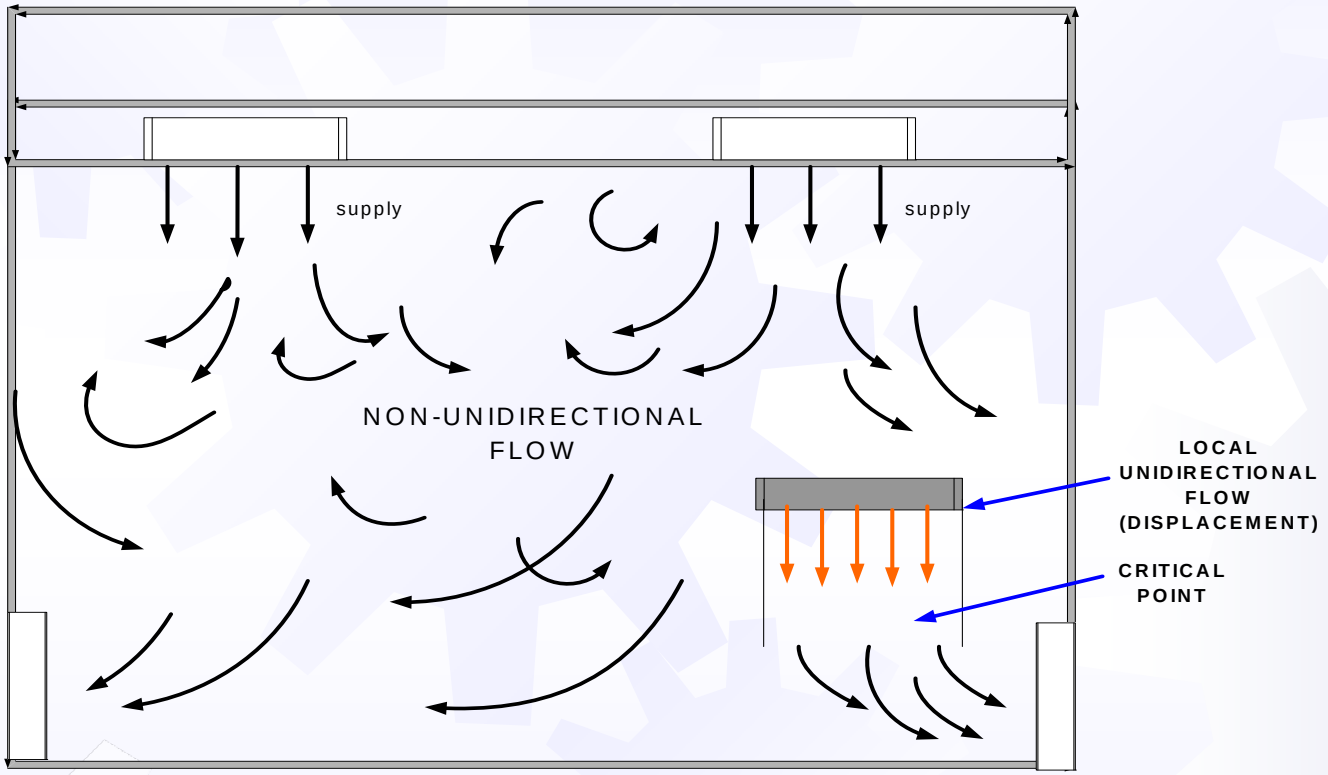
Example of a Dilution Design room

Dilution Design Room



Example of a Dilution Design room

Dilution with Local Unidirectional Zone



Example of a Dilution Design room

HVAC Design Principles

Dilution Design:

- Local regions with unidirectional flow assist with the dilution effect (they add to the overall room air change rate).

HVAC Design Principles

Unidirectional Flow (Displacement) Cleanrooms vs. Non-unidirectional Flow (Dilution) Cleanrooms

- Can generally achieve Class 10,000 with dilution design. In some cases even Class 1,000 is achievable.
- Higher cleanliness classes (i.e. cleaner than Class 1,000) requires unidirectional flow.
- Unidirectional Flow Cleanrooms have higher flow rates and as a result are more expensive to build
- Many more HEPA filters used with higher material costs

HVAC Design Principles

Vertical unidirectional flow clean rooms

- Return can be through floor. The ideal case ensures uniform unidirectional flow throughout width of room. This provides very effective sweeping of contaminants

OR

- Return through low mount extracts – either room mounted grills or return air walls – very common but less effective than raised floor

HVAC Design Principles

With vertical unidirectional flow clean rooms:

- Desirable to minimize the width of the room. Maximum width is generally 6 meters (20 ft).
- Difficult to achieve good unidirectional flow in center of room

Clean Rooms: Airflows and Air Change Rates

- CFM per HEPA Filter: Q_f

  $Q_f = V_{avg} A_f$

  Average Face Velocity x Filter Area

- Room Total Flow = #HEPA Filters x CFM per HEPA

  $Q_r = N_f Q_f$

Clean Rooms: Airflows and Air Change Rates

Alternate Formula:

- Room Total Flow = Sum of flow through each HEPA filter in room (CFM per HEPA)

$$Q_r = \sum Q_{fi}$$

Clean Rooms: Airflows and Air Change Rates

- Air Change Rate: *Air changes per minute*

  ACR = Total room flow / room volume

  ACR = Q_r **/** V_r

  Room Volume V_r = H x W x L

- Requirements are based on *air changes per hour*

  ACPH = ACR x 60 or $(Q_r/V_r) \times 60$

Clean Rooms: Airflows and Air Change Rates

- $Q_f = V_{avg} \times A_f$
- $Q_r = n_f Q_f$ or $\sum Q_{f\,i}$
- $ACR = Q_r / V_r$
- $ACPH = ACR \times 60$ or $(Q_r/V_r) \times 60$

Units:

A_f in square feet (Ft^2)
V_{avg} in Ft/Min
V_r in cubic feet (Ft^3)
Q_r and Q_f in cubic feet per minute (CFM)
ACR in air changes per minute
ACPH in air changes per hour

Clean Rooms: Airflows and Air Change Rates

- Minimum airchange rate for Class 100,000 clean rooms: **20 ACPH**
- What dictates this?

  1987 FDA Aseptic Manufacturing Guidelines

  2004 FDA Aseptic Manufacturing Guidelines
- There is no clear criteria for minimum air change rates for Class 1,000, 10,000 or Class 100
- There are targets however, from IEST.

Clean Rooms: Airflows and Air Change Rates

IEST recommended air change rates

RP-CC-012.1:

- Targeted airchange rates:
  - **Class 100,000 5 – 48[1] ACPH ISO Class 8**
  - **Class 10,000 60-90 ACPH ISO Class 7**
  - **Class 1,000 150-240 ACPH ISO Class 6**
  - **Class 100 240 – 480[2] ACPH ISO Class 5**

Important Notes:

1. Minimum air change rate for Class 100,000 rooms is 20 ACPH per 2004 FDA Aseptic Guidelines.
2. Air change rates for Class 100 rooms typically exceed 480 ACPH.

Clean Rooms: Airflows and Air Change Rates

- Airflow Velocity Specifications
  - No spec for Class 100,000, 10,000 or 1,000
  - Target for Class 100 Rooms:

    90 Ft/min +/- 20%

    Where does this requirement come from?
  - **1987 FDA Aseptic Manufacturing Guidelines**

Clean Rooms: Airflows and Air Change Rates

- ***Air change rate should be based on satisfying the maximum particle load, based on the specific operation performed.***
- Varies depending on:
  1. ***Operation: Amount of particles generated in the space***
  2. ***Heat gain within the space***
  3. ***Required recovery time***

Any of the above can determine the minimum air change rate.

Calculating air volume to offset heat gain is a standard HVAC system design issue.

Clean Rooms: Air Change Rates per FDA

2004 FDA Aseptic Guidelines, section 4, part c:

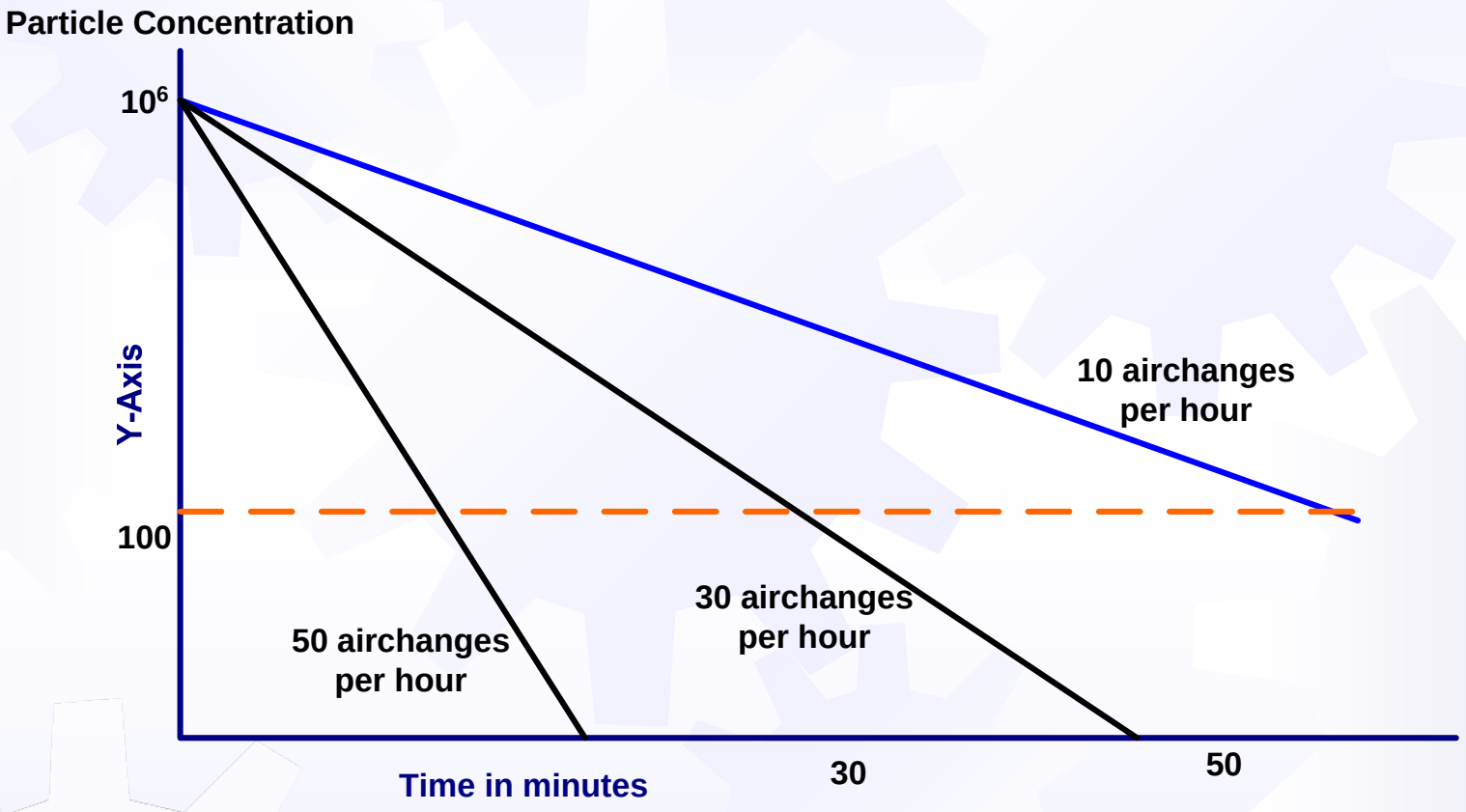
"Air change rate is another important cleanroom design parameter. For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas".

Air Change Rates: EU Guideline Expectations

"In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with terminal filters such as HEPA for grades A, B and C."

Re: Room recovery: "The particulate conditions given in the table for the "at rest" state should be achieved after a short cleanup period of 15-20 minutes (guidance value) after completion of operations"

Clean Rooms and Controlled Environments
Room Recovery Time vs. Air Change Rates



Graph illustrating increases in airchange rates reduces room recovery time

Unidirectional Flow Clean Rooms and air velocity

Air velocity in unidirectional clean rooms:

- Generally maintained between 60 fpm and 120 fpm
- For critical area: In the 1987 Aseptic Guide, FDA used to suggest 90 fpm +/- 20%.
- New FDA Aseptic Guide in 2004 changed this – they do not specify a target velocity or range.
- EU guidelines indicate 0.45 m/sec velocity, +/- 20% (guidance value). This equates to 0.36 – 0.54 m/s, or 70 fpm – 105 fpm.

Unidirectional Flow Clean Rooms and air velocity

- Parenteral Drug Association: Guidance on air velocity
- Topic A: Airflow Velocity How often tested?
- Problem Statement: **When do velocity measurements have to be taken?**
- Recommendation
  Airflow velocity measurements should be taken during operational and performance qualification studies. Frequency of routine monitoring should be at least annually. HEPA filters in critical areas should be tested semi-annually. More frequent measurements may be appropriate if other measures of clean room quality indicate a significant deviation.

Unidirectional Clean Rooms: Velocity Testing

- Airflow pattern studies should be repeated when any changes are made that might have an impact on the velocity measurements outside validated acceptance criteria (i.e., changes to air handling systems, aseptic processing equipment, HEPA filters). Evaluation of such impact should be made following applicable change management procedures. Airflow measurements can be area or line-specific.
- Rationale for Recommendation
  Airflow velocity is measured to ensure adequate airflow to protect exposed product, product contact packaging components, and product contact surfaces. It is also measured to ensure there have been no significant changes to the HVAC system. **Airflow criteria are established during qualification studies.**

Velocity Testing in Unidirectional Flow Clean Rooms

- During qualification, airflow pattern tests/smoke studies should be performed to establish the acceptable velocity range.
- Where do we take our velocity readings?
  - At filter face, 6” down? Or at Work level?

TABLE 1 - Air Classifications **CDER Aseptic Guidelines - 2004**

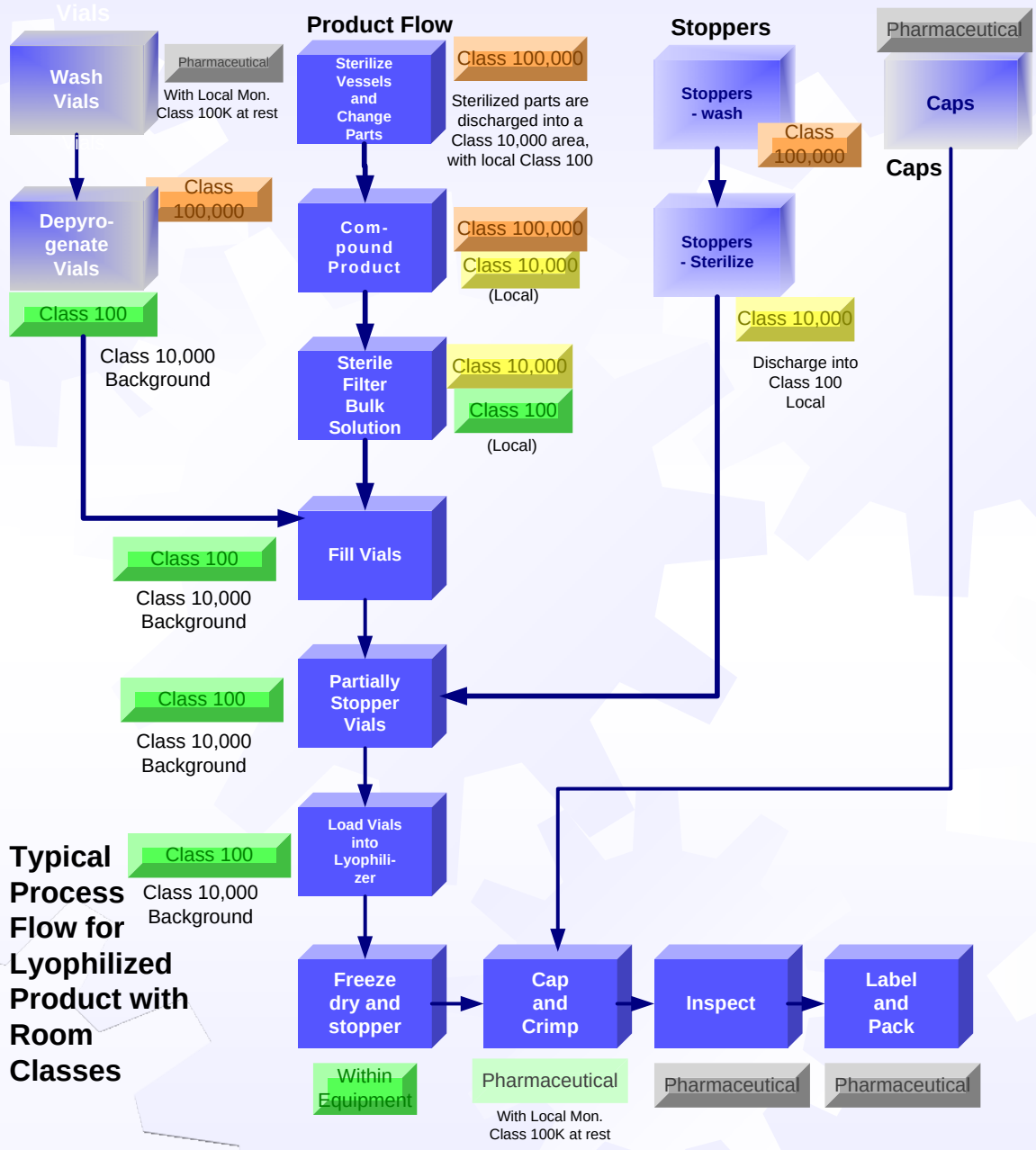
FDA Aseptic Guidelines Cleanroom Class

We will discuss Micro levels later in course

Clean Area Classification (0.5 micron particles/ft^3)	ISO Designation	G.T. or equal to 0.5 micron (particles/m^3)	Microbiological Active Air Action Levels (cfu/m^3)	Microbiological Settling Plates Action Levels (diam. 90mm, cfu/4 hours)
100	5	3,520	1	1
1,000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

Summary of Grades and Classes vs. Process

Type of Processing	Process Step/Activity	Nearest equivalent ISO 14644-1 class "in operation"	US GMP expectation "in operation"	EU GMP Grade
Aseptic	Aseptic formulation and filling operations	5	100/M3.5	A
Aseptic	Background to the above activities	7	10,000/M5.5	B
Aseptic	Preparation of solutions to be filtered	8	100,000/M6.5	C
Aseptic	Component handling after washing when exposed to the environment	8	100,000/M6.5	C
Terminally sterilised	Filling of "unusually at risk" products	5	100/M3.5	A
Terminally sterilised	Filling of products, "unusually at risk" solution preparation	8	100,000/M6.5	C
Terminally sterilised	Preparation of products and solutions	unclassified/ controlled	Pharmaceutical	D


Vials
Wash Vials
Pharmaceutical
With Local Mon.
Class 100K at rest
Depyro-genate Vials
Class 100,000
Class 100
Class 10,000
Background
Product Flow
Sterilize Vessels and Change Parts
Class 100,000
Sterilized parts are discharged into a Class 10,000 area, with local Class 100
Com-pound Product
Class 100,000
Class 10,000
(Local)
Sterile Filter Bulk Solution
Class 10,000
Class 100
(Local)
Stoppers
Stoppers - wash
Class 100,000
Stoppers - Sterilize
Class 10,000
Discharge into Class 100 Local
Pharmaceutical
Caps
Caps
Fill Vials
Class 100
Class 10,000
Background
Partially Stopper Vials
Class 100
Class 10,000
Background
Load Vials into Lyophili-zer
Class 100
Class 10,000
Background
Typical Process Flow for Lyophilized Product with Room Classes
Freeze dry and stopper
Within Equipment
Cap and Crimp
Pharmaceutical
With Local Mon.
Class 100K at rest
Inspect
Pharmaceutical
Label and Pack
Pharmaceutical

Example – Number of particles per location, per cubic meter.

	Particle size, in microns		
Location	**0.3**	**0.5**	**5.0**
1	**98**	**90**	**1**
2	**103**	**50**	**0**
3	**120**	**45**	**0**
4	**80**	**70**	**0**
5	**90**	**40**	**0**
6	**60**	**20**	**1**

Sample Problem

1. A firm is interested in determining whether the room meets ISO Class 3 requirements for the 0.3 micron particle size.
2. Is it necessary to perform statistical analysis to make this determination?
3. What is the 95% UCL?
4. Does the room meet ISO Class 3 conditions at 0.3 micron?
5. If the room dimensions were 5 m by 5 m, were the minimum number of sample locations per ISO met?
6. Does the room meet ISO Class 3 conditions for the 5 micron particle?
7. Does the room meet ISO Class 5 conditions for the 5 micron particle?
8. If the entire room was desired to be maintained at the required class for filling operations, and the readings were actually taken in the "in-operation" state, would the room meet EU requirements for filling operations for an aseptically produced product? (Assume unidirectional flow is provided).