



Facilities, Critical Services and Qualification

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Module Topics



Specifications and the V Model



Qualification of HVAC Systems



Qualification of Sterile Cleanrooms

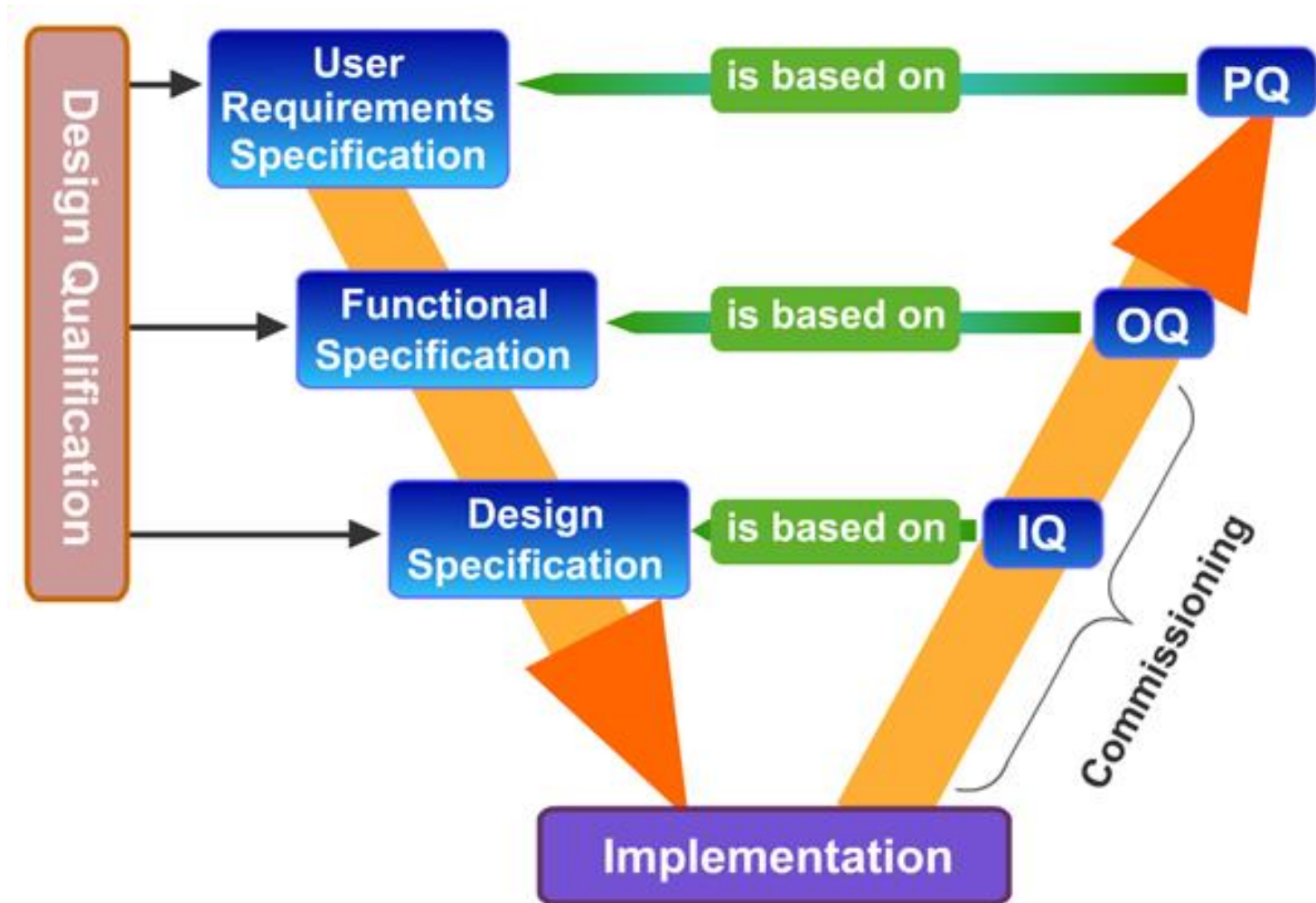


Cleanrooms and GMPs

Some Important References

- EU/PICs/TGA cGMP Annex 1 – Sterile Products
- PDA Technical Report #13 Fundamentals of an Environmental Monitoring Program
- USP <1116> Microbiological Evaluation of Cleanrooms
- FDA Guidance – Aseptic Processing
- ISO 14644 Series - Cleanrooms and associated controlled environments
- WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (Annex 5) – mainly for OSD Forms
- WHO good practices for pharmaceutical microbiology laboratories (Annex 2)
- PIC/S PI 009-1 Inspection of Utilities – Aide Memoire

V Model for Qualification



HVAC Systems Design and Qualification – Sterile Facilities

GMP Manufacturing Environment

PRODUCT PROTECTION

Contamination Control
(product and staff)

Protect from Product
Cross Contamination

Correct Temp. RH%

PERSONNEL PROTECTION

Prevent Contact with Dust

Prevent Contact with
Fumes

Operator Comfort
Conditions

ENVIRONMENTAL PROTECTION

Avoid Dust Discharge

Avoid Fume Discharge

Avoid Effluent Discharge

HVAC Standards

ISO 14644 - Cleanrooms and Associated Controlled Environments

ISO Document	Title
ISO-14644-1	Classification of Air Cleanliness
ISO-14644-2	Cleanrooms and associated controlled environments. Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
ISO-14644-3	Cleanrooms and associated controlled environments. Test methods
ISO-14644-4	Cleanrooms and associated controlled environments Design, Construction and Startup
ISO-14644-5	Cleanrooms and associated controlled environments. Operations
ISO-14644-6	Terms, Definitions & Units
ISO-14644-7	Cleanrooms and associated controlled environments. Separative devices (clean air hoods, gloveboxes, isolators and mini-environments)
ISO-14644-8	Cleanrooms and associated controlled environments. Classification of airborne molecular contamination
ISO-14698-1	Biocontamination: Control General Principles
ISO-14698-2	Biocontamination: Evaluation & Interpretation of Data
ISO-14698-3	Methodology for Measuring Efficiency of Cleaning Inert Surfaces

HVAC – what is its Purpose ?

- Should provide a suitable environment for the product and the workers in terms of temperature, humidity, and cleanliness.
- Cleanliness means suitable control over particulates, product residues, external contaminants and microbes.
- Removal of airborne contamination by directing to collection points and returns
- Should be easily monitored and maintained
- Suitable locations for filters on both supply and return (where needed)
- A HEPA filter provides 99.997% efficiency at 0.3µm, where a typical pharmaceutical particulate is much larger.

HVAC – Why is it important ?

- Supply clean “Pure” air to the production environment via terminal HEPA filters
- Regulate Room Temperature and Relative Humidity
- Capture airborne particles and direct them away from product and processes
- Exclude microbes and particles
- Create pressure differentials between work zones – exclusion and containment options.

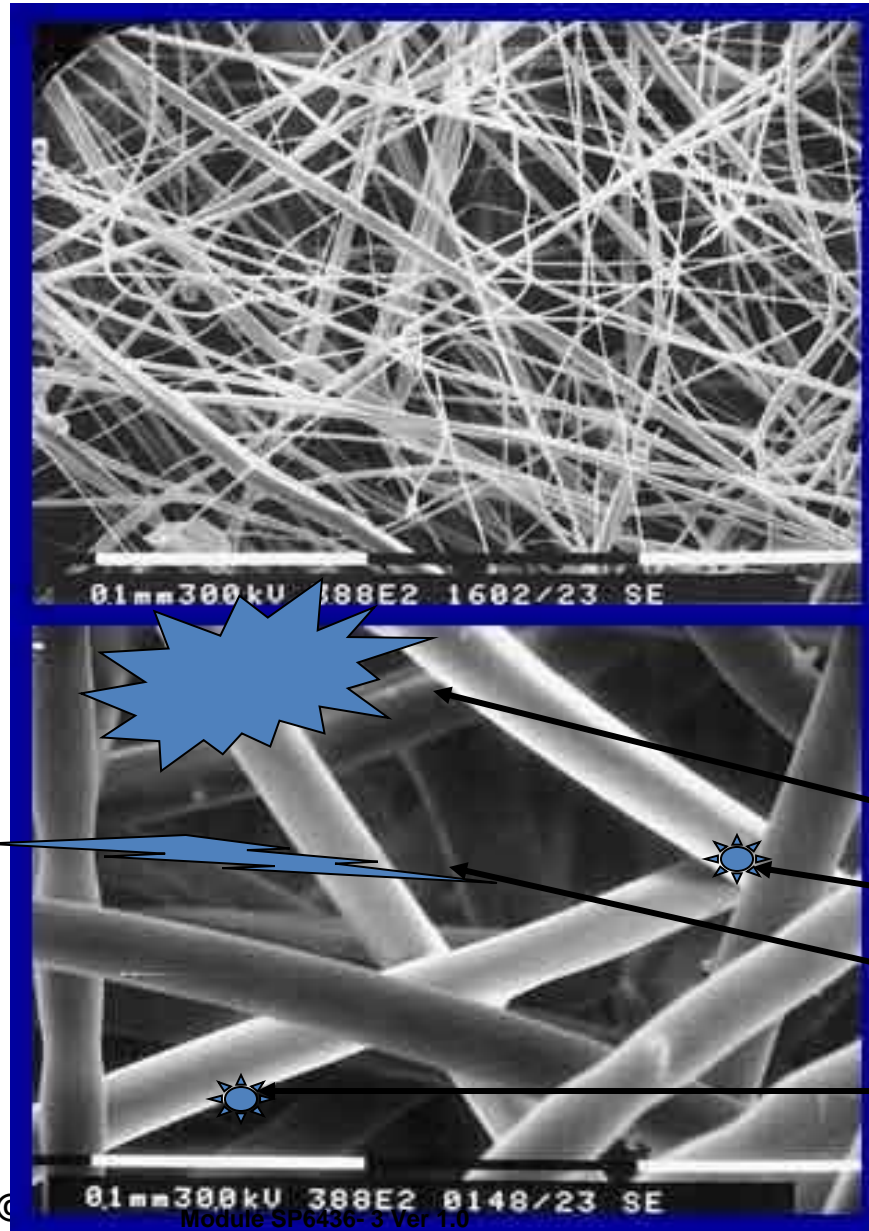
Air Handling Systems (AHUs) and Ductwork

- Separate systems for separate zones controlled by a BMS
- AHUs generally commissioned under GEP
- Must be correctly sized by engineering design and calculations – account for some leakage
- Once installed ductwork must be cleaned and inspected before installing the HEPAs – part of IQ record
- Once HEPAs in place conduct balancing of rooms to get velocity and relative pressures right – part of IQ record
- Must have a maintenance program

Air Handling Systems and HVAC Ductwork (what's in the ceiling)

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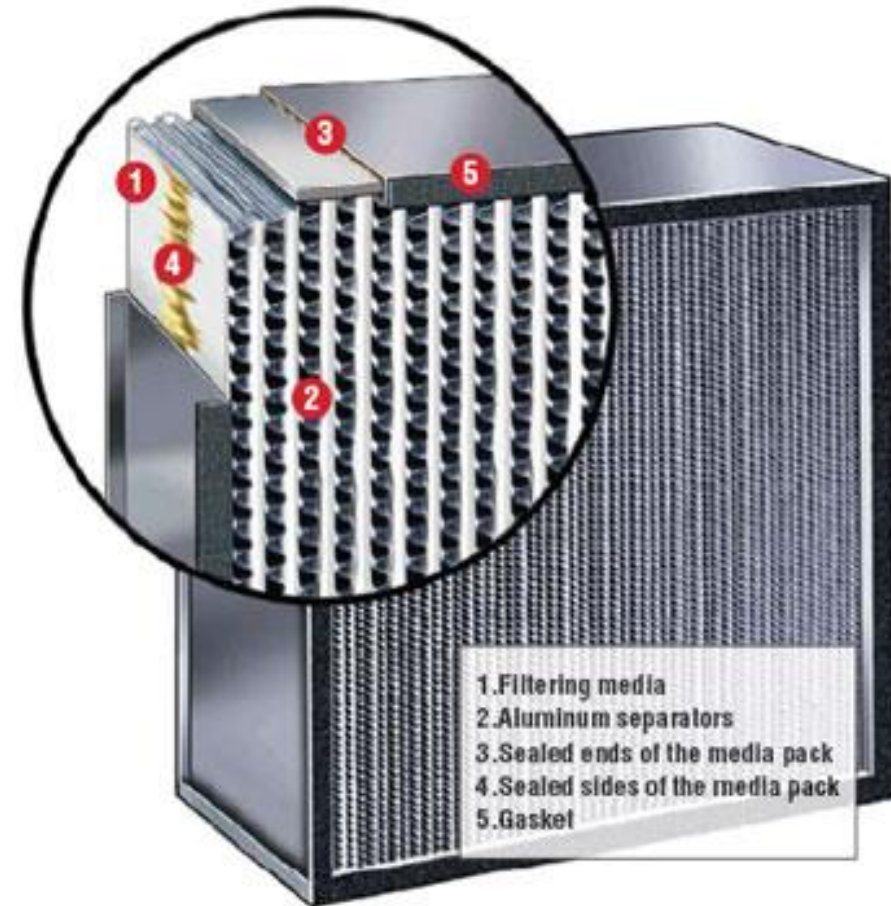


- Typical air filters are depth filters, particles are trapped in tortuous paths.
- Problems:
 - Bleed through
 - Arrestance is not absolute
 - Arrestance can be gravimetric or by size
- Trapped by
 - sieving,
 - impaction
 - bridging and
 - electrostatic forces

High Efficiency Particulate Air

A closer look at a HEPA filter

- Generally Terminal
- For containment purposes can have HEP on Returns
- Over time
- Use of Pre-filters extend the life of HEPA filters.
- Must be tested for leakage / integrity on install and periodically
- Should consider a replace plan



Leak Testing of HEPAs - Aerosols

ISO 14644-3: Cleanrooms and associated controlled environments; Test methods.

- Suitable aerosols include:
 - Poly-alpha-olefin (PAO)
 - Dioctylphthalate (DOP) – being phased out due to safety concerns
- Particles are specific sizes to provide an even challenge to the filter
- Must know the incoming challenge to ensure the test is suitable - Particles will lodge on upstream filter
- Scan downstream with calibrated particle counter
- Must make sure particles don't promote microbial growth

Contamination Control Aspects

Product Protection

- Classification of environment ... Grade D minimum ?
- Laminar flow cabinets/ Isolators
- Positive pressure differentials (+ 15 Pa)
- Operator gowning and techniques
- First Air over open product

External Environment Protection

- Positive pressure differentials (+15 Pa) for exclusion
- Negative pressure differentials (-15 Pa) for containment
- HEPA on returns
- Air flow directions
- High pressure external building skin

Personnel Protection

- Operator gowning and techniques
- Biohazard Safety Cabinets
- Full protection suits
- Isolators

Manufacturing Rooms

Design Considerations – Product Protection

- hazardous nature of the Materials being processed
- process being carried out (**open or closed system**)
- **product containment** or **environment exclusion** needed
- material and personnel flow
- gowning procedures
- equipment movement between zones
- occupancy - # personnel
- cleaning standard operating procedures (SOPs).

Manufacturing Rooms

Key Design Considerations - Facility

- 100% fresh air or % re-circulation
- air filtration systems (HEPA or not)
- need for materials and personnel locks (MALs and PALs)
- relative room pressures (cascades) & air change/ flushing rate
- location of air terminals and directional airflow
- outside air conditions (temp. and RH%)
- temperature and relative humidity controls needed for products
- surface finishes and cleanability

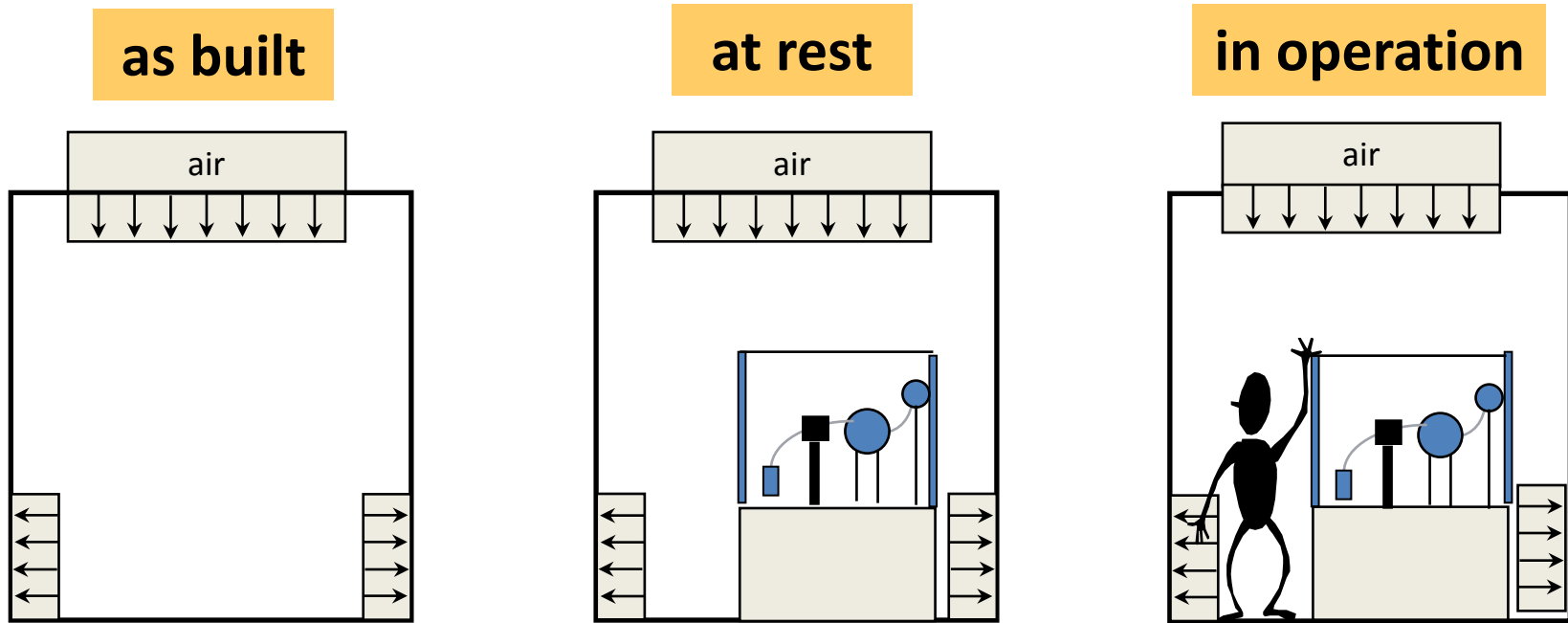
“Once Through” vs Re-circulating HVAC Systems

- **Once through systems** do not recirculate the air through the HVAC – air is fresher however are more expensive to run.
- **Recirculation systems** are cheaper to run – generally about 5% - 20% “make up” air
- HVAC can convey aerosols to other areas
- The ductwork and AHUs may become contaminated and are a risk to maintenance personnel and the environment.
- These issues may be overcome by providing redundant HEPA filtration on returns.

Documenting Room Specifications

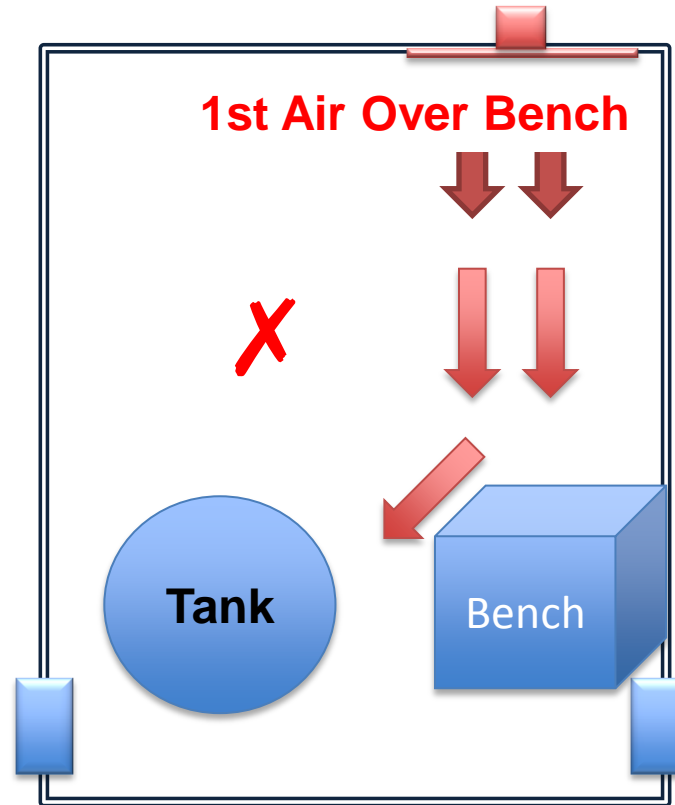
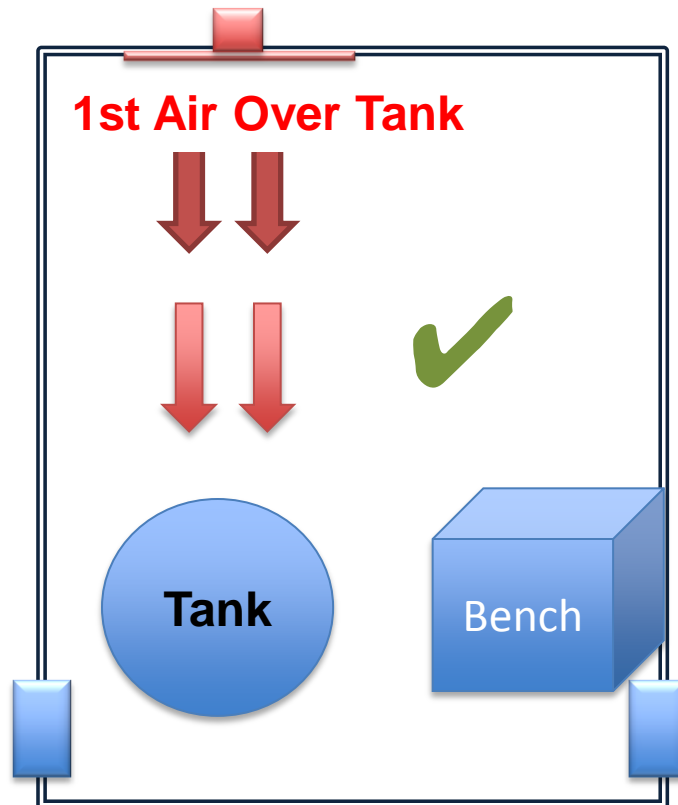
Room Name	Area / m ²	As Built Class	In Op. Class	Target Pressure (Pa)	Air change per Hr	Temp (°C)	(% RH) Max.	Room Air Filtrat'n	100% fresh or Recircul
De-Gown room	3.60	D	I	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc
Hand wash room	3.30	D	II	30 Pa (25 - 35)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc
Weigh room	2.40	D	II	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	100%
Mixing room	5.32	D	III	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	100%
Filling room	4.50	D	III	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	100%
Bottle Wash Room	4.95	D	III	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc
Wash Room	3.36	D	II	15 Pa (10 - 20)	Min. > 12 Target > 24	<25	60%	One HEPA	20% Recirc

WHO Definition of Cleanroom Conditions



- ▶ The "**at-rest**" state is the condition where the installation is installed and operating but with no operating personnel present.
- ▶ The "**in operation**" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working

Principle of “First Air”



WHO Cleanroom Qualification OQ, PQ

Test	Uni-directional airflow /LAF	Turbulent Mixed Air
Differential pressure on filters	2	2
Room differential pressure	N/A	2, 3
Airflow velocity / uniformity	2, 3	Optional
Airflow volume / rate	2	2
Parallelism/Laminarity	2	N/A
Air flow pattern	2	3
Recovery time	N/A	2
Room class (airborne particle)	2	2, 3
Temperature, humidity	N/A	2, 3

IQ tests are not mentioned on this slide

1 := As built (ideally used to perform IQ)

2 = At rest (ideally used to perform OQ)

3 = Operational (ideally used to perform PQ)

PIC/S Annex 1 “Cleanroom” Standards

Grade	Maximum permitted number of particles/m ³ 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

	Recommended limits for microbial contamination ^(a)			
Grade	Air sample cfu/m ³	Settle plates (diam. 90 mm), cfu/4 hours ^(b)	Contact plates (diam. 55 mm), cfu/plate	Glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Minimum schedule of tests to demonstrate (continuing) compliance

Test parameter	Reason	Max. time interval	Test procedure
Filter leakage tests	Verify filter integrity)	24 months	<ul style="list-style-type: none"> Filter penetration test (HEPA only)
Containment leakage	Verify absence of cross contam' n	24 months	<ul style="list-style-type: none"> airflow direction smoke tests room air pressures.
Recovery	Verify cleanup time	24 months	<ul style="list-style-type: none"> < 15 min clean up time to remove contaminant
Airflow visualization	Verify required airflow patterns	24 months	<ul style="list-style-type: none"> clean to dirty areas cross-contamination uniformly from laminar flow units.

(recommended in ISO14644)

Cleanroom Re-Certification

(Required Testing (ISO 14644-2))

Schedule of Tests to Demonstrate Continuing Compliance

Test Parameter	Class	Maximum Time Interval	Test Procedure ISO14644-2
Particle Count Test	\leq ISO 5	6 Months	Annex A
Particle Count Test	$>$ ISO 5	12 Months	Annex A
Air Pressure Difference	All Classes	12 Months	Annex B5
Air Pressure Difference	All Classes	12 Months	Annex B5

Re-Qualification of Cleanrooms Due to Change

- Modifications to, or relocation of, equipment should only follow satisfactory review and authorisation of the documented change proposal through the change control procedure.
- Part of the review procedure should include consideration of re-qualification of the equipment. Minor changes should be handled through the documentation system of the preventative maintenance programme.

PIC/S Recommendations on Validation –July 2004

- Whenever cleanrooms are “opened up” for major maintenance they must be re-certified and EM program restored. (Governed by SOPs)

PIC/S Guide to Inspection of Utilities HVAC Systems

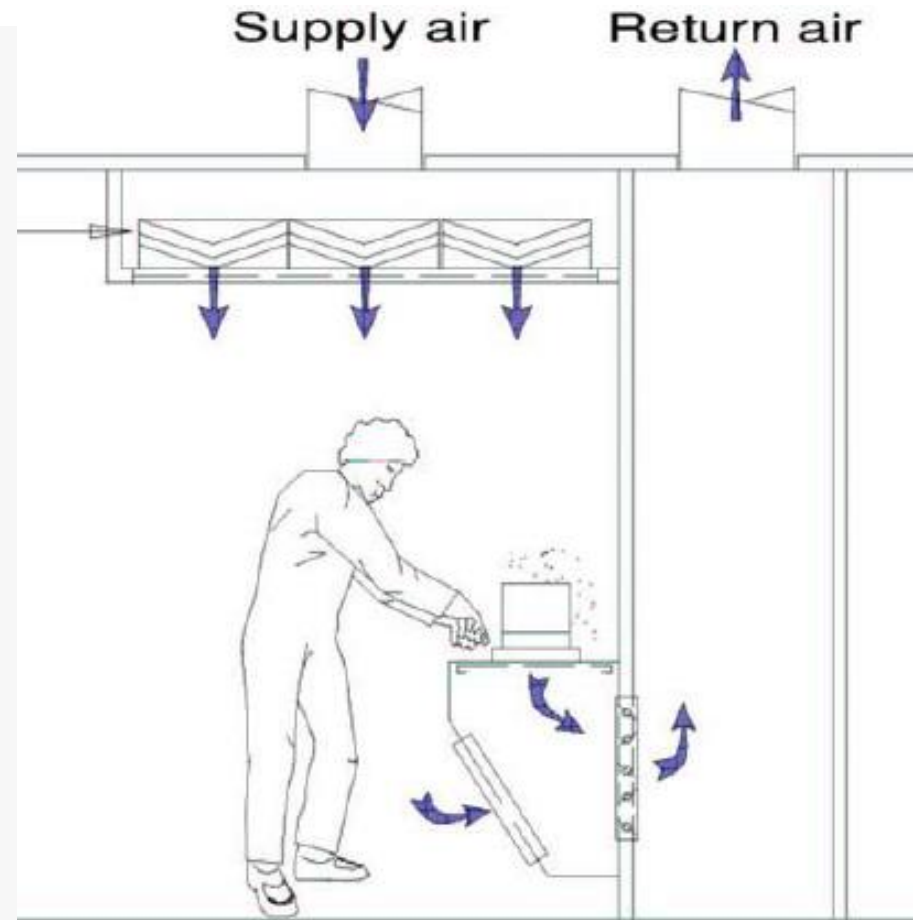
- Qualification Protocols/ Reports: DQ, IQ, OQ and PQ
- Average speed and uniformity of airflow
- Pressure differentials
- Air changes per hour
- Integrity and tightness of terminal installed final filters
- Number of particles (at rest and in operation)
- Room Recovery tests
- Air temperature and RH%
- Smoke tests – air visualization
- Requalification (parameters for requalification)
- Change control

PIC/S Guide to Inspection of Utilities (Critical Questions from Inspectors)

- Review of HVAC system drawings
- Is the BMS qualified ?
- How have you implemented recommendations and correct deviations mentioned in qualification reports?
- Who is responsible for evaluating if requalification is necessary?
- What are the requirements for regular requalification?
- Show me your deviations and change control reports for HVAC?
- How do you challenge your alarm systems?
- Place and procedure for sampling?
- Where and how do you weigh and refill starting materials?

Air Flow Directions

- The direction of air flow must be such that exposed product sees “First Air”
- Supply and exhaust registers should be sited with consideration to equipment location
- Supply and exhaust registers must be located so as to allow “sweeping” of the room.

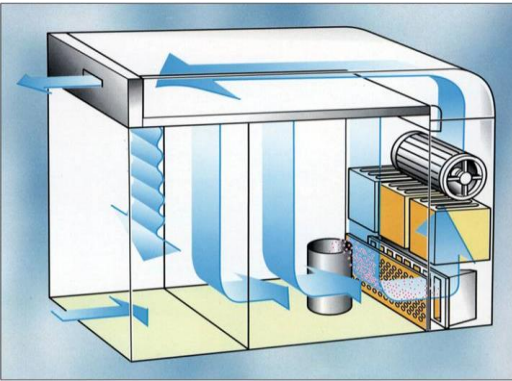


Sampling and Weighing Booths

- Unidirectional airflow (UDAF) should be used for weighing booths or sampling booths to provide both **operator and product protection** and should also have a slight air in-flow from the room to enhance containment. Either cross or down flow is acceptable.
- Dust containment at the weigh booth should be demonstrated by smoke airflow pattern tests, or other appropriate tests.
- UDAF can also be used to provide protection of other dusty processes.
- UDAF space airflow velocity of 0.36 to 0.54 m/s. However, in a weigh booth or sampling booth a lower velocity** can be used as a Grade A condition is not required.

**It is often necessary to reduce velocities to a lower level in order not to influence balance readings.

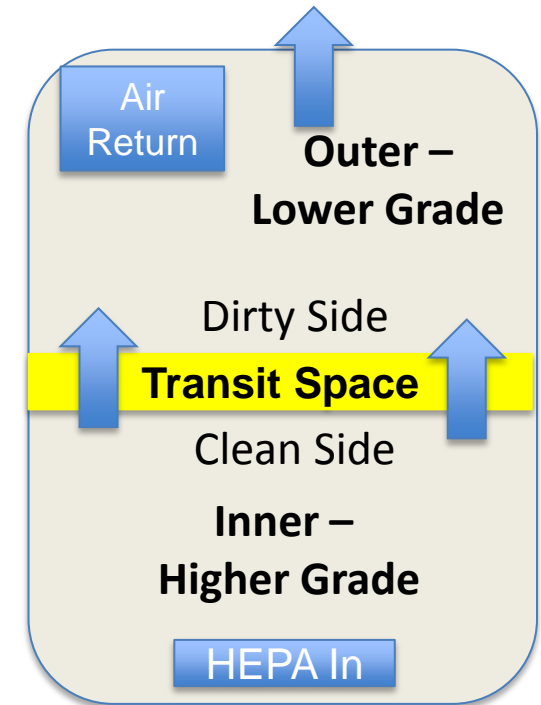
Sampling and Weighing Booths



Material and Personnel Airlocks

- **are NOT GMP storage areas**
- to prevent mechanical transfer of product from the processing room to the GMP corridor
- to separate gowning standards between rooms
- to provide a means to maintain pressure cascades
- to prevent contamination of the facility and product by external contaminants

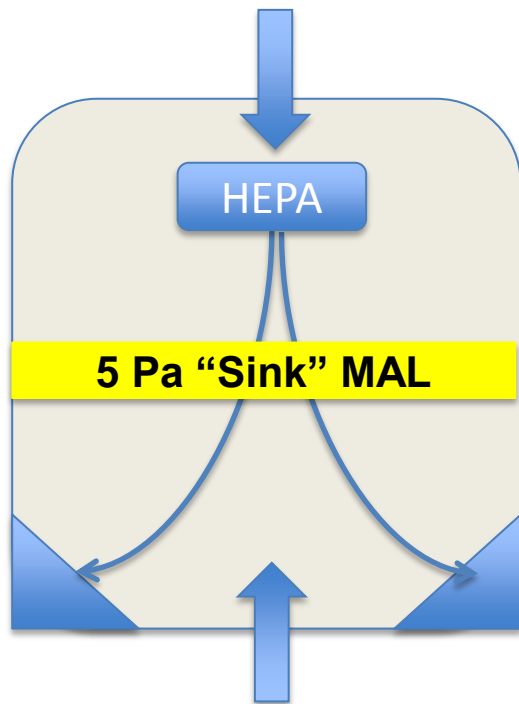
Exclusion MAL Design and Operation



Alternative MAL/PAL Designs

**Containment
with MAL as Sink**

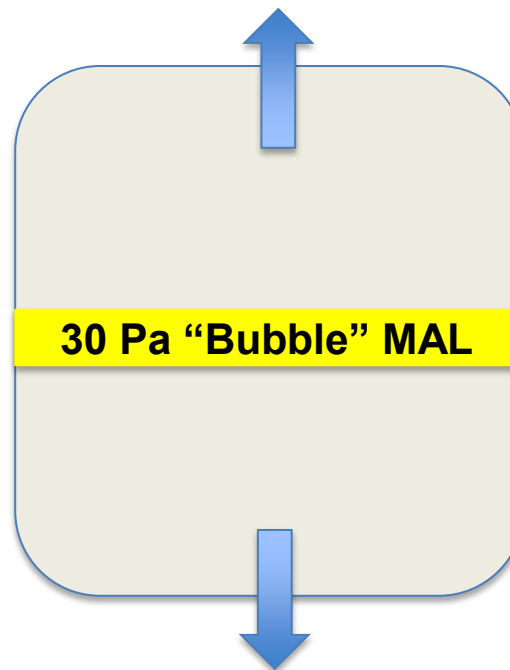
20Pa+ Outer



20Pa+ Process Room

**Containment
with MAL Overpressure**

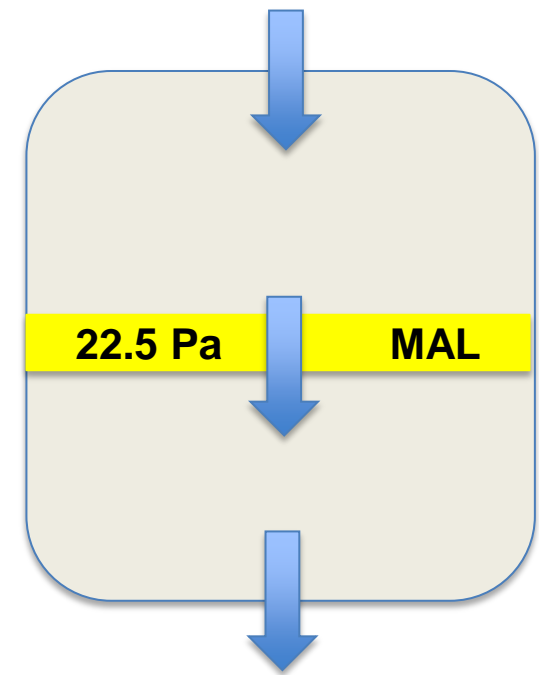
15Pa Corridor



15Pa Process Room

**Containment
MAL One Way Flow**

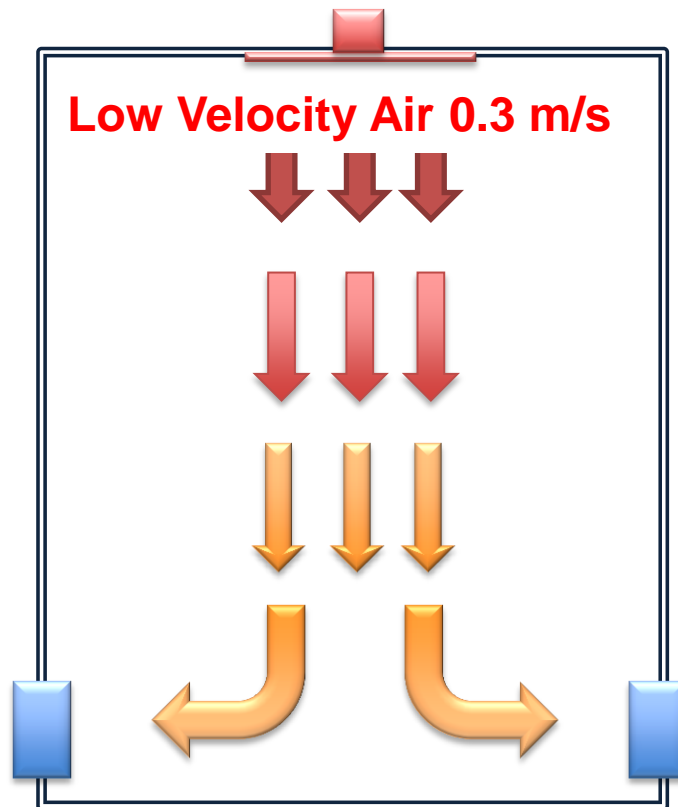
30Pa Corridor



15Pa Process Room

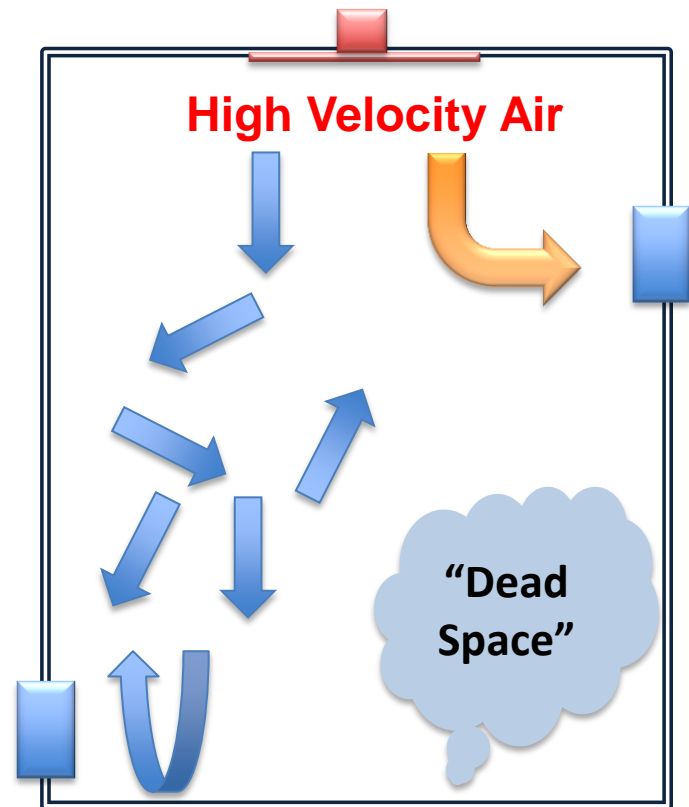
Particulate Generation and Removal Grade B Rooms

“Uni Directional”
Air Flow



Low Returns

Non Uni Directional
Air Flow



Low or High Returns

Calculating Optimal Air Change Rates

$$v = g / (x - s)$$

Where

- s is the supply air particulate concentration in particles per ft
- v is the supply air volume flow rate in terms of air-change rate per hour
- g is the internal generation rate in particles per ft³ per hour
- x is room or return air concentration in particles per ft³

For a typical Class 10,000 cleanroom space with a typical internal generation of approximately 5,000 per CFM, and supply air through 99.97% HEPA filters, what shall be the required air-change rate?

Solution

The supply rate can be estimated using equation: $v = g / (x - s)$

Where

- $g = 5000 * 60$ ft³ per hour
- $x = 10,000$
- $s = 3$ for 99.97% efficient HEPA filters

$$v = 5000 * 60 / (10000 - 3) = \geq 30 / \text{hour}$$

Calculating Actual Air Change Rates

Must know:

- Volume of the room in cubic metres
- Surface area of the inlet HEPA in sq metres
- Velocity of filtered inlet air through the HEPA

Example

- Volume room = 60 cubic metres (4 x 5 x 3)
- HEPA area = 2.0 sq. metres
- Air Inlet Velocity = 0.3m/sec.

Calculation:

Inlet volume / hour = $1080 \times 2.0 = 2160$ cubic metres / hour

Air Change Rate = $2160 / 60 = 36$ changes per hour

Example of a GMP Processing Room



Microbiology Laboratories (WHO Annex 2 Clause 2.1.4)

- CFDA Guidance - Microbiology Laboratories
 - *“It should be noted that the requirements of the Chinese Pharmacopoeia with respect to premises of microbiology laboratories are mandatory and must be taken into account.”*
- There should be separate air supply to laboratories and production areas.
- Separate air-handling units and other provisions, including temperature and humidity controls where required
- Consider need for separate cleanrooms with access via airlocks, and appropriate entry and exit procedures including gowning.

PICs Annex 1 Cleanroom Activities

Grade	Examples of operations for terminally sterilised products (see para. 28-30)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see para. 31-35)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

Key GMP Requirements for Material/Components in Cleanrooms

- Only sterile/sterilised materials may enter Grade B from Grade C via PTCs;
- A layer of sterile wrapping should be removed whenever moving up a Grade; C → B → A
- Items removed from autoclave if stored best in Grade A space or have wrap removed from B → A;
- HAO vials must be stored under Grade A (since they cannot be wrapped) and transferred to fill line under Grade A
- Equipment wrap must be dry on exit from autoclave;
- Must validate any cleanroom hold time

Pass Through Cabinets (PTCs)

- Material pass-through-cabinets (PTC) or pass boxes (PB) can also be used for separating two different zones.
- PTCs fall into two categories, namely a dynamic PTC or a passive PTC.
- Dynamic PTCs have an air supply to or extraction from them, and can then be used as bubble, sink or cascade PTCs.
- Interlock doors with status and delay
- Validate transfer SOP



Key GMP Principles for Materials Movement through Pass Through Cabinets (PTCs)

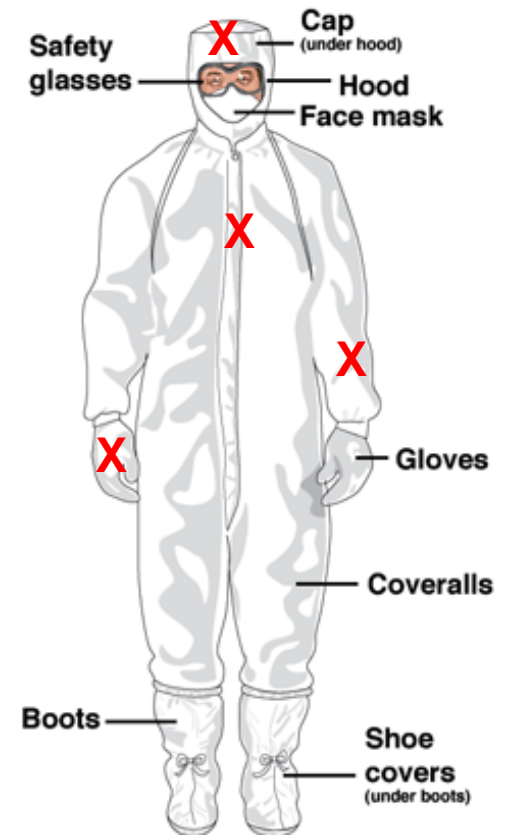
- PTC transfer process should be validated by air visualization studies under empty and loaded worst case
- Require air visualisation studies in “at rest” and “in operation” condition – verify no Grade C air can enter Grade B.
- Need to perform recovery studies at rest and loaded conditions;
- Need to verify interlocks, alarms and dwell time;
- Need an SOP for transfers – SOP should have a full list of items that can go through;
- Operators trained and EM monitored;

Personal Air Locks (PALs) and Gowning

- Gowning is a 3 grade transition
Grade - D → C → B with transition interfaces
- Doors should be interlocked and alarmed to preserve pressure
- Limit to number of personnel in any one space
- Exit ideally via separate route
- HEPA's should be located on inner side up high of PAL and returns on outer side down low
- For Material Air Locks (MALs) should be divided and inner an outer trolleys used. No cross over of persons;

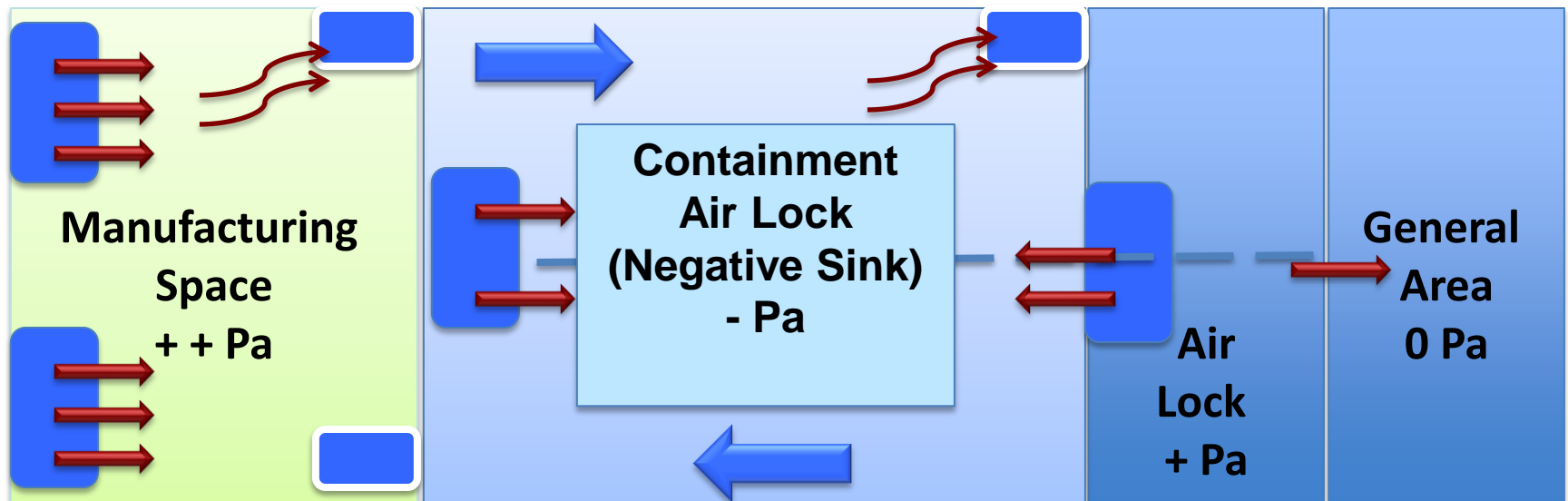
Operator gowning qualification for aseptic manufacture

- Gowning training and qualification
- Media trials (process simulations)- each operator at least annually.
- Assessment of aseptic training via constant bioburden testing of the environment
- Exit micro testing of gown bioburden and gloves



X – areas of greatest exposure to the product are monitored

Typical Containment Air Lock (with Sterile Facility Protection)



 **Air Flow**

 **Personnel Flow**

Aseptic Facility + = 15Pa

Expectation for GMP Doors

- No door tracks – frames are metallic, sealed and cleanable
- Doors should open to the high pressure side, so that room pressure assists in holding the door closed – use self closers.
- There should be a method to indicate if both doors to airlocks are open at the same time, or alternatively these should be interlocked.
- The determination of which doors should be interlocked should be the subject of a risk assessment study.
- Doors are considered high traffic areas so should be sanitised and monitored.

Grade B and Grade A Space

- Must conduct air visualisation studies for Grade A space using a protocol;
- Entrainment and turbulence in at rest and simulated “in operation” condition;
- Identify critical surfaces and critical space in Grade A
- Simulate interventions and transfers B → A
- Use the information to conduct risk assessment on entries to Grade A and location of monitoring.
- Re-visualisation on any change and say every 3 years
- Grade A must have continuous particle monitoring
- Must have one probe adjacent to the filling station

GMPs and Grade A Space

- Capper must be separate remote station to fill line
- All aseptic connections must occur in grade A
- All aseptic connections must be validated.
- Glove printing of aseptic operators
 - After any aseptic connection;
 - Post set up of machine
 - Post any Grade A intervention
 - Limit is none detected on 5 fingers
- Must never work over the top of open components

Aseptic Operator Dos and Donts

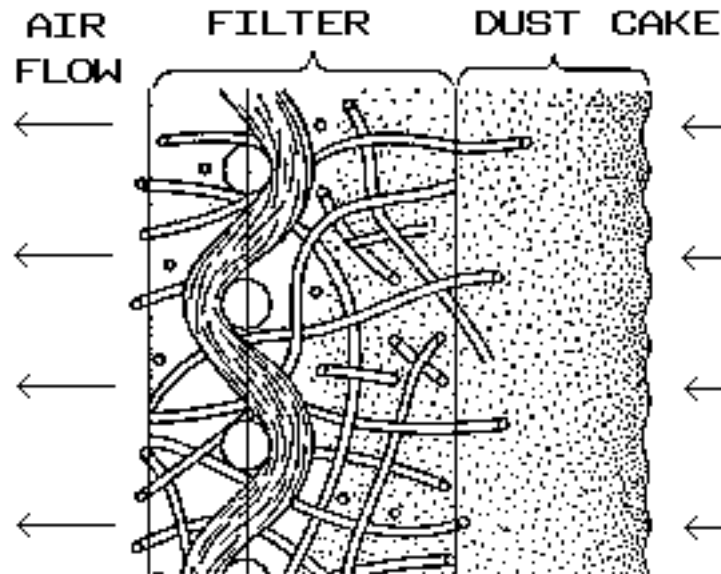
- ✓ Be aware of body position at all times
- ✓ Sanitise hands often
- ✓ Must sanitise pre entry to Grade A
- ✓ Move slowly
- ✓ Wear eye goggles
- ✓ Cut open bags
- ✓ Place forceps in sterile holders
- ✓ Stay out of Grade A as much as possible
- ✓ Verify pressures
- ✗ Tear open bags
- ✗ Touch face / skin
- ✗ Place forceps on machine
- ✗ Work over the top of critical surfaces
- ✗ Touch components with hands
- ✗ Sneeze!
- ✗ Stay in Grade A
- ✗ Ignore alarms

Cleanroom GMP Maintenance Programs

- Operating and maintenance (O&M) manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system. Pressure cascades, schematics and other specifications should appear.
- There should be a planned preventive maintenance programme, procedures and records for the HVAC system. Records should be kept.
- Maintenance should be inspected before back into service and should occur out of production hours.
- HEPA filters should be changed either by a specialist, and then followed by installed filter leakage testing.
 - Physically inspect HEPA surfaces for growth or damage
 - Qualify suppliers and testers
 - Review reports and any failures

Filter Collection Efficiency (Requirement for Maintenance)

At a certain age particles will break through the filter and emerge on the downstream side



The more the dust cake builds up the more efficient the filter but the more the resistance builds up and the less the air can pass through

- Filters can remove ONLY a portion of upstream contamination.
- No filter can reduce the amount of contamination introduced DOWNSTREAM of the filter.
- Some particles will break through most filters with time; enhanced by age, wear and vibration.

cGMP Citations - Air Control

- HEPA integrity testing is deficient in that LAF velocity measurements are not taken within 6" of the work surface.
- Lack of acceptance criteria defining leakage as % of the challenge agent.
- Smoke studies on laminar air flows fail to ensure airflow is laminar.
- Smoke studies of the HEPA's in front of the lyophilisers are not performed with the lyophiliser doors open.
- The pressure differentials between the class D gowning room and the non-classified entry way are not monitored to ensure that the classified areas obtain and maintain an acceptable level of positive pressure relative to the surrounding areas.

FDA 483s for HVAC and Air Handling

- The daily differential air pressure records are not reviewed by a second responsible individual for completeness and accuracy.
- There is no record to document the actual filter integrity readings that are obtained for the HEPA filter integrity testings to assure that the $<0.003\%$ penetration is achieved.
- Magnehelic gauges that are used to monitor that the laminar air flow cabinets are not calibrated.
- There have been no smoke studies performed for the aseptic filling area to assure that there is sufficient or suitable laminar air flow.

FDA 483s for HVAC and air handling

- The pressure differentials between the class x gowning room and the non-classified entry way, the class y areas and the surrounding support areas, are not monitored to ensure that the classified areas obtain and maintain an acceptable level of positive pressure relative to the surrounding areas.
- The strip charts that record the pressure differentials between the aseptic filling room and the surrounding areas are not completely reviewed.
- There is no written procedure that describes the course of events which are to be followed by the security guard during an alarm condition concerning the air pressure differentials or when there is a malfunction of the lyophilisers.

Sterile Facility Exclusion Design - Cleanrooms



Grades
A = 100
B = 10,000
C = 100,000
D = 100,000

Case Study

- Small group review of the cleanroom plan for the above layout.
 1. decide the product, materials and personnel flows
 2. Decide appropriate locations of inlets and returns for each cleanroom.
 3. Decide how you would get the following into the facility
 1. Vials
 2. Stoppers
 3. Caps
 4. Personnel
 5. Change parts
 6. Chemicals for formulation
 7. Movement of bulk product to the fill machine.



Steve Williams,
Director, CBE Pty Ltd
www.cbe-ap.com.au
 +61(0)417116476
 steve.williams@cbe-ap.com.au

