



Centre for Biopharmaceutical Excellence


## Cleanroom Management and Qualification

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## Module Topics

-  Specifications and the V Model
-  Qualification of HVAC Systems
-  Qualification of Sterile Cleanrooms
-  Cleanrooms and GMPs

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Introduction

## Some Important Reg. 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

## Who Writes the Cleanroom Standards?

- ISO
  - TC / 209 – Experts by country, formed into Working Groups
    - ISO 14644 – Cleanrooms and associated controlled environments
    - ISO 14698 – Biocontamination control
- Australian Standards
  - ME – 060 Controlled Atmospheres – Representatives of Australian and New Zealand Organisations
    - AS 1807 Suite of standards – Cleanroom Testing
    - AS 2252 Suite of standards – Cleanroom Devices
    - AS/NZS ISO 14644 Suite of standards
    - AS4273 – Pharmaceutical isolators

## TC / 209 - Standards

### **ISO 14644 – Cleanrooms and associated clean environments**

Part 1: Classification of air cleanliness

Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1

Part 3: Test methods

Part 4: Design, construction and start-up

Part 5: Operations

Part 7: Separative devices (clean air hoods, gloveboxes, isolators, and mini-environments)

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## TC / 209 - Standards cont.

### **ISO 14644 – Cleanrooms and associated clean environments cont.**

Part 8: Classification of air cleanliness by chemical concentration (ACC)

Part 9: Classification of surface cleanliness by particle concentration

Part 10: Classification of surface cleanliness by chemical concentration

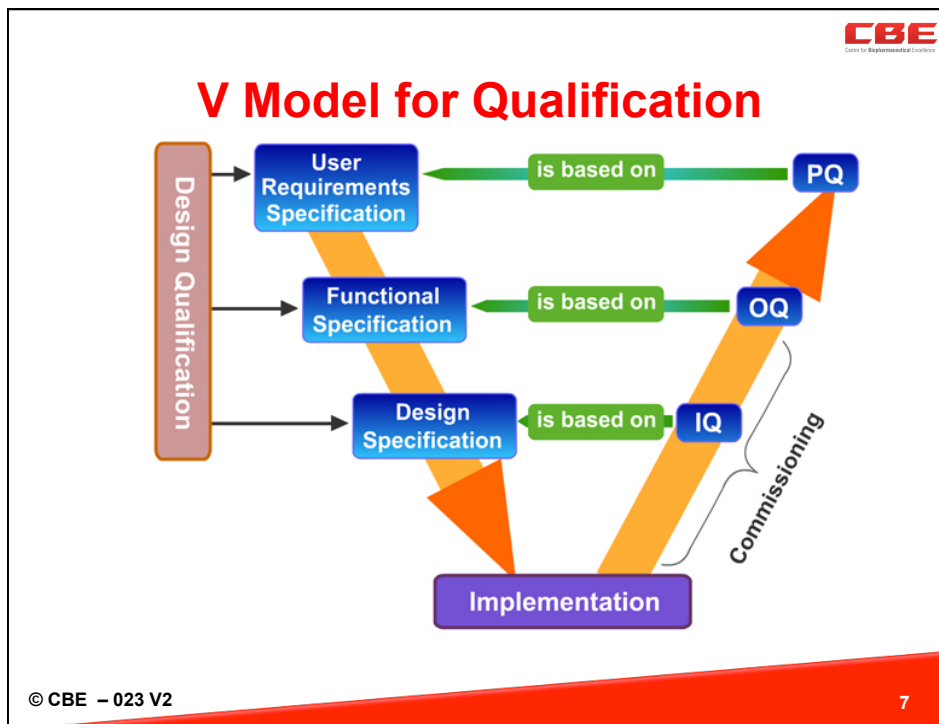
Part 12: Classification of air cleanliness by nanoscale particle concentration

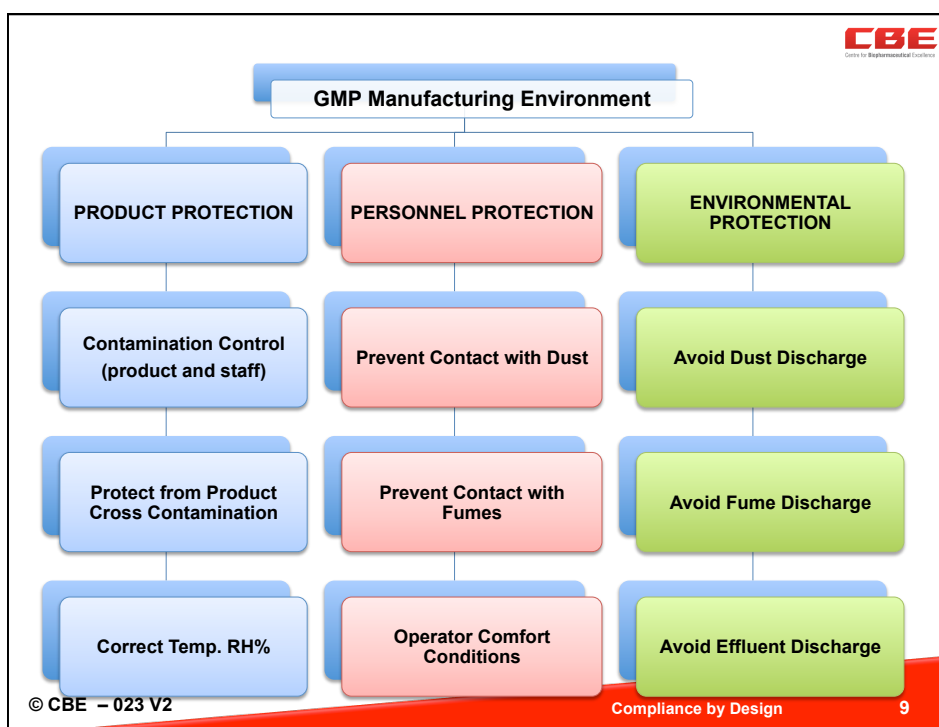
### **ISO 14698 – Cleanrooms and associated controlled environments — Biocontamination control:**

Part 1: General principles and methods

Part 2: Evaluation and interpretation of biocontamination data

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## 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

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## HVAC – what should we consider?

- Should provide a suitable environment for the product and the process staff in terms of temperature, humidity, and air cleanliness.
- Cleanliness means suitable control over particulates, product residues, external contaminants and microbes.
- Removal of airborne contamination by directing it to collection points and return air systems,
- Should be easily (continuously) monitored and maintained at suitable intervals,
- 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 – it's importance

- Supply clean “Pure” air (a known standard) to the production environment via terminal HEPA filters
- Regulates the Room Temperature and Relative Humidity
- Cleanroom airflows should capture airborne particles and direct them away from product and the filling zone
- Exclude microbes and particles from the environment
- Create pressure differentials between different work zones and levels of cleanliness – exclusion and containment options.

## Air Handling Systems (AHUs) and Ductwork



- Separate systems for separate zones controlled by a BMS – must be routinely monitored
- AHUs generally commissioned under GEP
- Must be correctly sized by engineering design and calculations – so the right amount of air is delivered
- The installed ductwork must be cleaned and inspected before putting in the HEPA's – part of IQ record
- Once HEPA's in place the air system can be balanced so the air velocity and relative zone pressures meet the design specification – part of IQ record
- Must have a logical maintenance program designed

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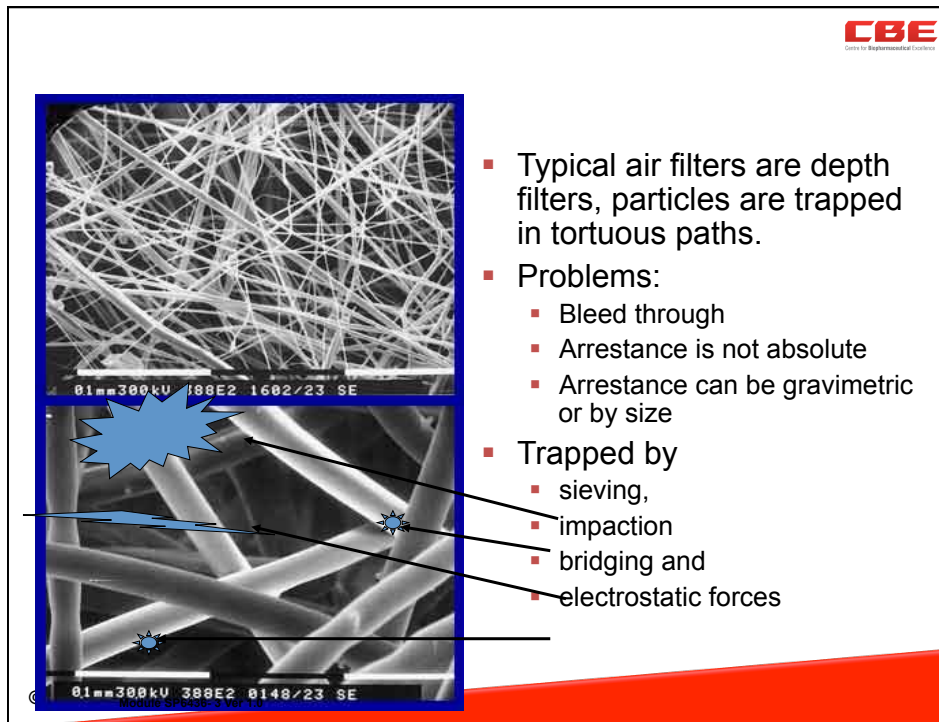
## Air Handling Systems and HVAC Ductwork (what's in the ceiling)



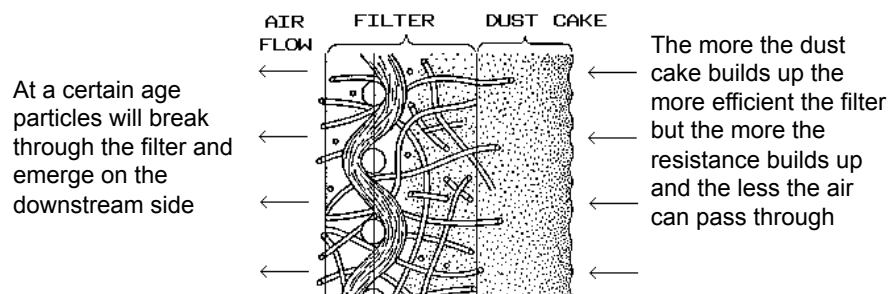
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## Filter Collection Efficiency (Requirement for Maintenance)

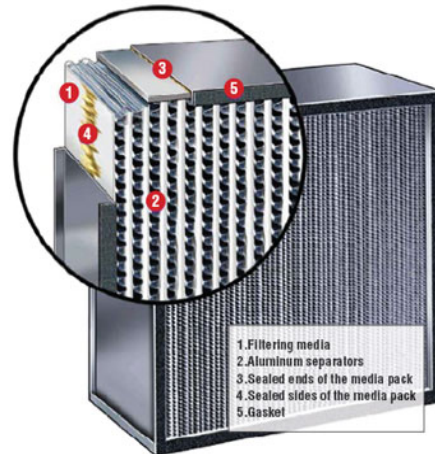


- Filters can remove ONLY a portion of upstream contamination.
- No filter can reduce the amount of contamination introduced DOWNSTREAM of the filter.
- Some particles will break through most filters with time; enhanced by age, wear and vibration.

## High Efficiency Particulate Air

A closer look at a HEPA filter

- Generally Terminally located
- For containment purposes can have HEPA on Returns
- Over time the pressure across the filter increases
- Use of Pre-filters extend the life of HEPA filters
- Must be tested for leakage / integrity on install and periodically
- Should consider a replacement plan



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## 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

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## Manufacturing Cleanrooms 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 into & within the room
- gowning procedures
- equipment movement between zones
- occupancy – how many staff will normally work here?
- cleaning standard operating procedures (SOPs).

## Manufacturing Rooms Key Design Considerations - Facility

- 100% fresh outside air or % re-circulation
- air filtration systems (HEPA or not)
- material and personnel airlocks (MALs and PALs)
- relative room pressures (cascades) & air change/flushing rate
- location of air inlet and exit points and directional airflow
- outside air design conditions (temp. and RH%)
- temperature and relative humidity controls needed for products
- Room & equipment surface finishes and cleanability

## “Once Through” vs Re-circulating HVAC Systems



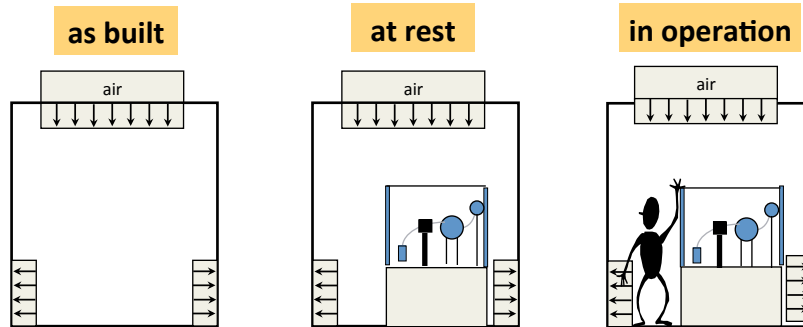
- **Once through systems** do not recirculate the air through the HVAC – air is fresher however are more expensive to run. These can be popular for dispensaries of APIs – but think carefully about the specific reasons for single pass
- **Recirculation systems** are cheaper to run – generally about 5% - 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 <sup>2</sup>	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



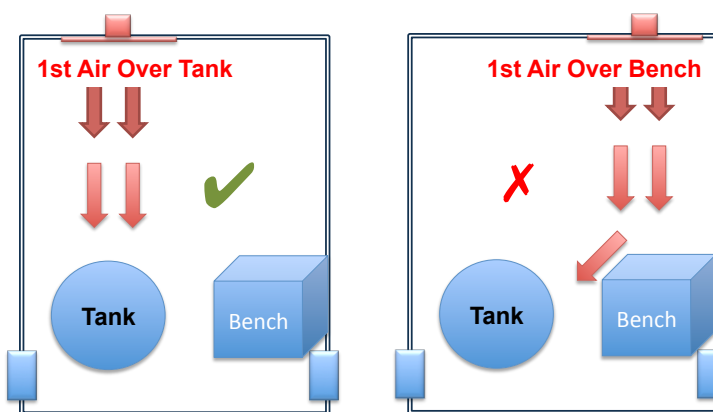
► The "**at-rest**" state is the condition where the installation is installed and operating but with no operating personnel present.

► The "**in operation**" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working

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## Principle of "First Air"



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## 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)

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## PIC/S Annex 1 “Cleanroom” Standards

Grade	Maximum permitted number of particles/m <sup>3</sup> 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 <sup>(a)</sup>				
Grade	Air sample cfu/m <sup>3</sup>	Settle plates (diam. 90 mm), cfu/4 hours <sup>(b)</sup>	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	-

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## Part 1 - Number of Samples

- No longer square root of room area
- Number of samples determined by table A.1
- Determined to ensure “*at least 95% confidence that at least 90% of the locations do not exceed the class limits*”
- Rooms over 1,000m<sup>2</sup> calculated by:

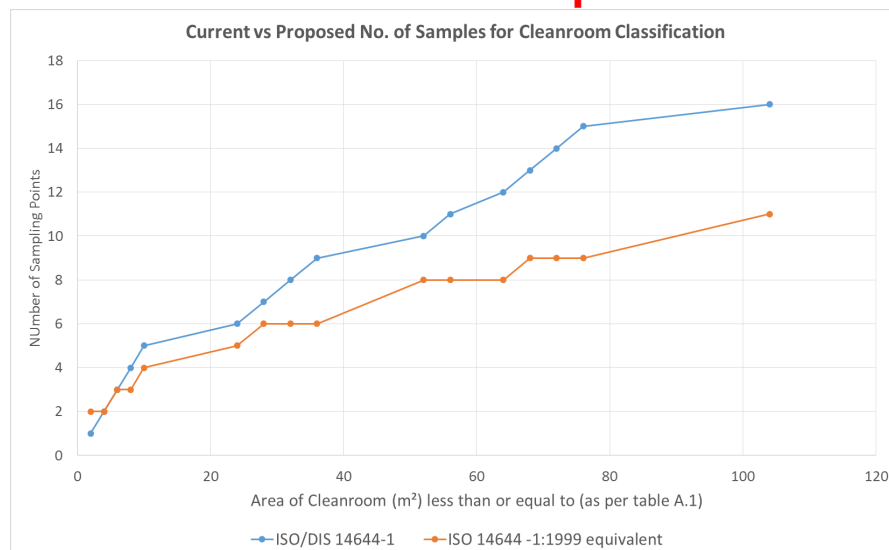
$$N_L = 27 \times (A / 1000)$$

Where:  $N_L$  = minimum number of sample locations to be evaluated

A = area of the cleanroom in m<sup>2</sup>

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## Part 1 - Number of Samples cont.



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

(recommended in ISO14644)

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## 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	<= 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

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## 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)

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## 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

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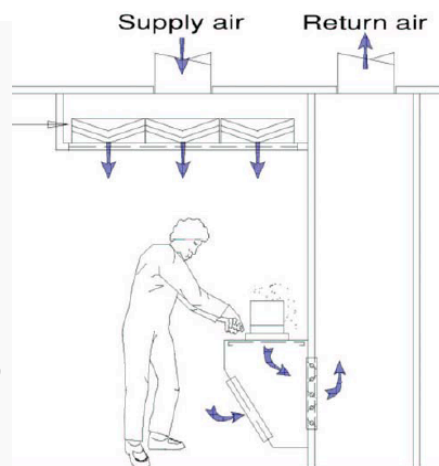
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## PIC/S Guide to Inspection of Utilities (Critical Questions from Inspectors)

- 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.

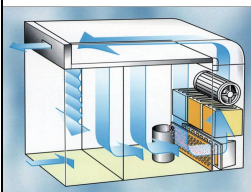


## Sampling and Weighing Booths

- 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.

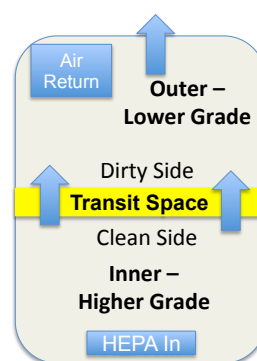
## Sampling and Weighing Booths



## 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

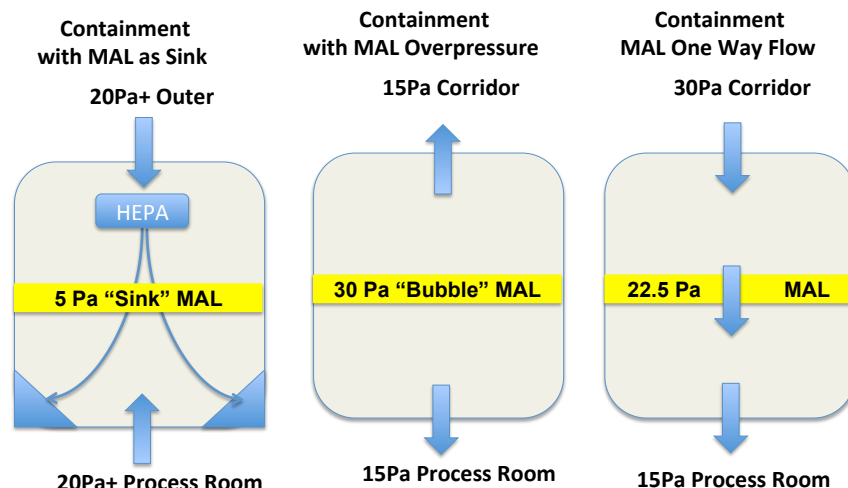


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## Alternative MAL/PAL Designs



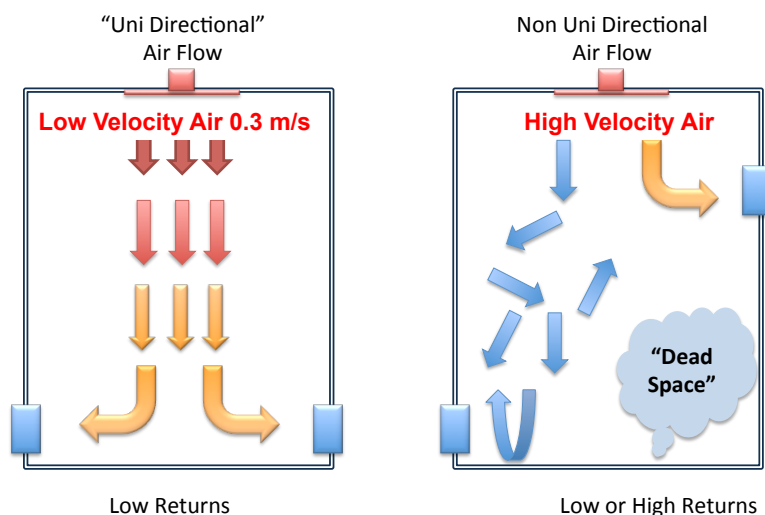
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## Particulate Generation and Removal Grade B Rooms

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## Calculating Actual Air Change Rates

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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
- B, C & D rooms usually require 20 changes per hour

**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**

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## Example of a GMP Processing Room



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## 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 clean hold time

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## 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

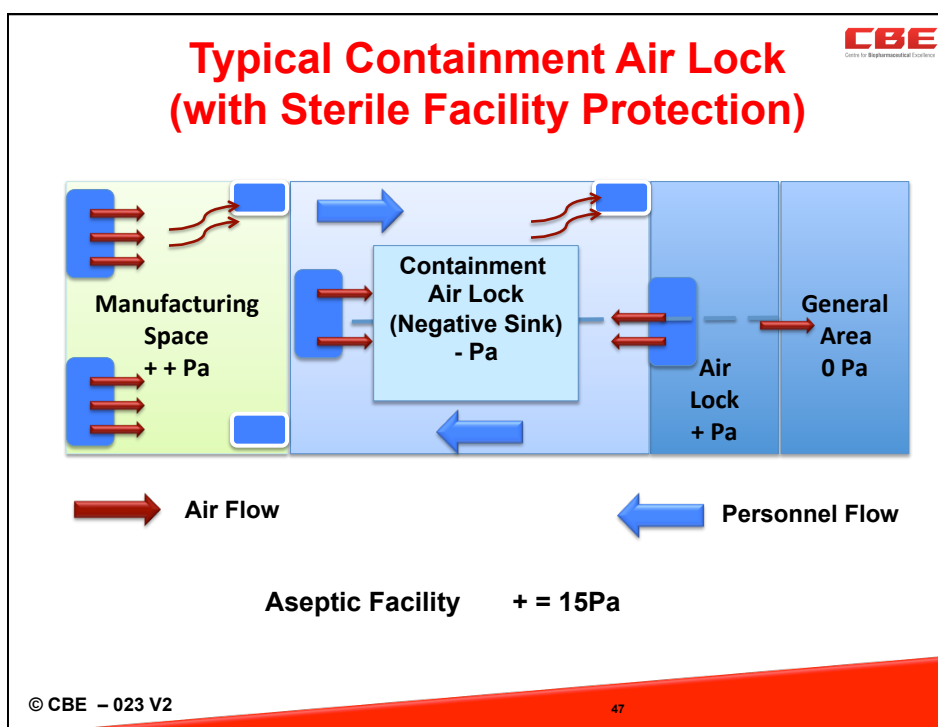
- Gowning is a 3 grade transition  
Grade - D → C → B with transition interfaces
- Doors should be interlocked and alarmed to preserve pressure
- Limit the number of personnel in any one space
- Exit should ideally be via separate route or door
- HEPA's should be located on inner side up high of PAL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

## 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
- Micro testing of gown bioburden and gloves for each operator as they leave the cleanroom



**X** – areas of greatest exposure to the product are monitored



### 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 regularly sanitised and monitored.
- Consider how the doors are activated by the operator

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## Grade B and Grade A Space

- Must conduct air visualisation studies for Grade A space using a written protocol;
- Air flow and turbulence in “at rest” and simulated “in operation” conditions;
- 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  | ✗ Tear open bags                         |
| ✓ Sanitise hands regularly                | ✗ Enter when you're sick                 |
| ✓ Must sanitise pre entry to Grade A      | ✗ Touch face / skin                      |
| ✓ Move slowly and controlled              | ✗ Place forceps on machine               |
| ✓ Wear eye goggles                        | ✗ Work over the top of critical surfaces |
| ✓ Cut open bags                           | ✗ Touch components with hands            |
| ✓ Place forceps in sterile holders        | ✗ Sneeze!                                |
| ✓ Stay out of Grade A as much as possible | ✗ Stay in Grade A                        |
| ✓ Verify room pressures                   | ✗ 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 be available.
- 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

## 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.

## Some Questions to Discuss



## Example HVAC Qualification Task List



- |                                                         |                              |
|---------------------------------------------------------|------------------------------|
| 1. URS and DQ signed off                                | Company and HVAC Contractor  |
| 2. Clean ductwork and inspect ducts/seals               | Contractor / Company Witness |
| 3. Attach HEPAs** and test / certify them in place      | Contractor / Company Witness |
| 4. HVAC IQ Protocol and Report                          | Contractor/ Company Witness  |
| 5. Balance System and Witness by Company***             | Contractor/ Company Witness  |
| 6. Assess change over rates                             | Contractor/Company approve   |
| 7. Checklist Rooms against Specifications               | Contractor/Company Witness   |
| 8. Final Clean of room to meet Grade – verify particles | Contractor                   |

### Fumigation / VHP/Ozonation ?

- |                              |                             |
|------------------------------|-----------------------------|
| 1. Check Temp. / RH% via BMS | Contractor /Company Witness |
|------------------------------|-----------------------------|

### Handover to Company from Contractor

- |                                                                        |                                 |
|------------------------------------------------------------------------|---------------------------------|
| 1. EMS Install and qualify                                             | Contractor / Company            |
| 2. Clean and Sanitise Cleanroom / Equipment                            | Company issues SOPs             |
| 3. OQ Qualify “at rest” (Micro, Particles, Physical/air flow (3 X)     | Company: Production/Micro. Lab. |
| 4. Clean/sanitise in between each OQ qualification                     | Company Production              |
| 5. PQ - Micro, physical. particles “in operation” (concurrent with PV) | Company QA/QC                   |

\*\* Need manufacturers certificates and serial numbers for each HEPA before they install them

\*\*\* need to conduct post balance velocity measures through HEPAs as this is used for calculating room air change rates

## Physical Monitoring Requirements per PICs – Annex 1 and ISO 14644.



- Environmental cleanliness - Airborne particles
  - Pressure differentials between rooms >10 - 15Pa
  - Air-change rates (>20) and recovery time (<15min)
  - Uni-directional airflow velocities in Grade A – air visualisation
  - Airflow patterns in Grade A – air visualisation studies
  - Air filtration (final filters) requirements – generally HEPA
- 
- **ISO 14644 – 1 Requirements**
  - **Number particle samples per room:** Square root of the area of the clean-zone in m<sup>2</sup>, rounded up to nearest integer.
  - **Sample Size Calculation** – ISO 14644-1 (Annex B)



## How often should HEPA filters and Cleanrooms be Re-Certified ?



- ISO 14644 recommends frequency – Tighter the Grade the more frequent re-certification. (Grade A 6 months)
- Need to be clear about “at rest” vs simulated “in operation” re-certification conditions
- Locations of sampling points in room - need to be justified
- # room samples is per ISO 14644
- Airflow visualisation studies – maybe every 3 years and certainly when considering any significant change to the room or equipment layout

## Alarming of Cleanrooms



- Automated EMS monitoring systems enables Alarm Conditions to be recognised (Alerts & Actions).
- Alarm Conditions

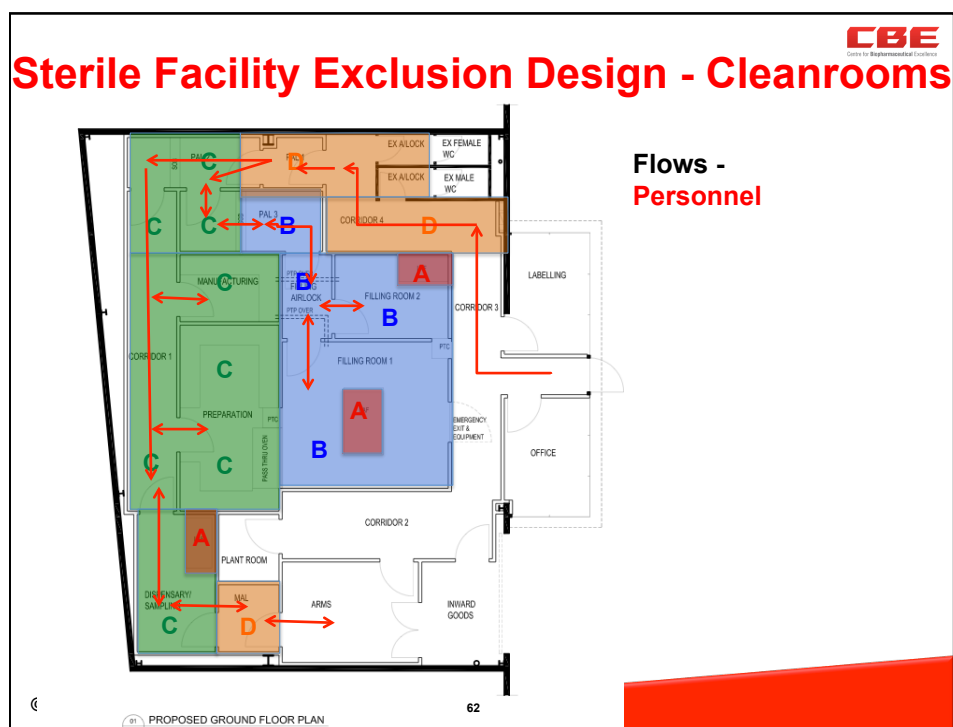
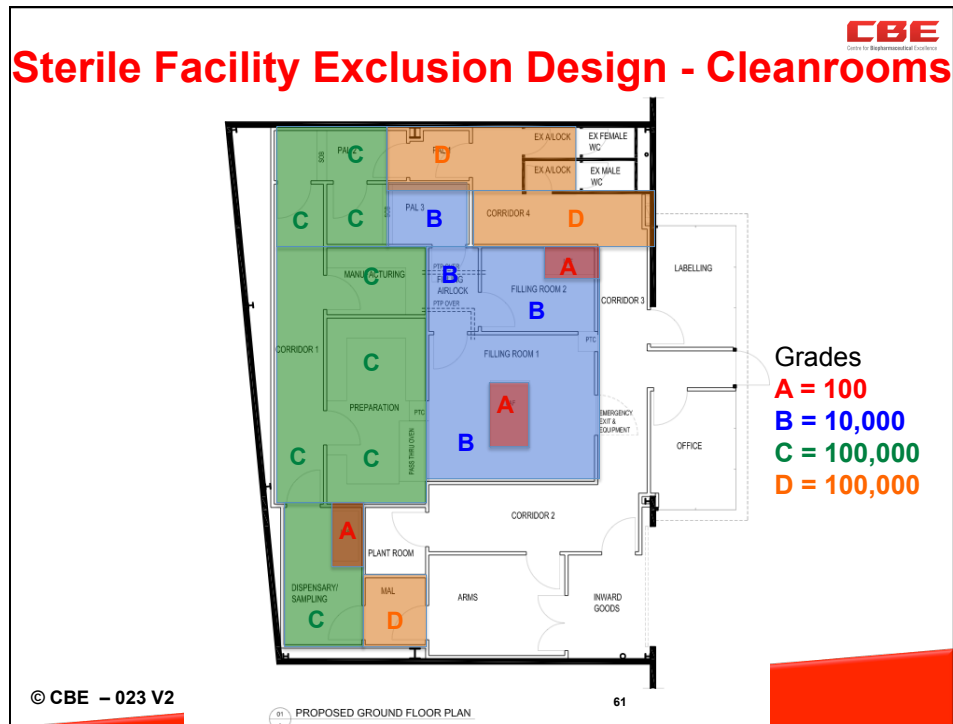
### ALERT

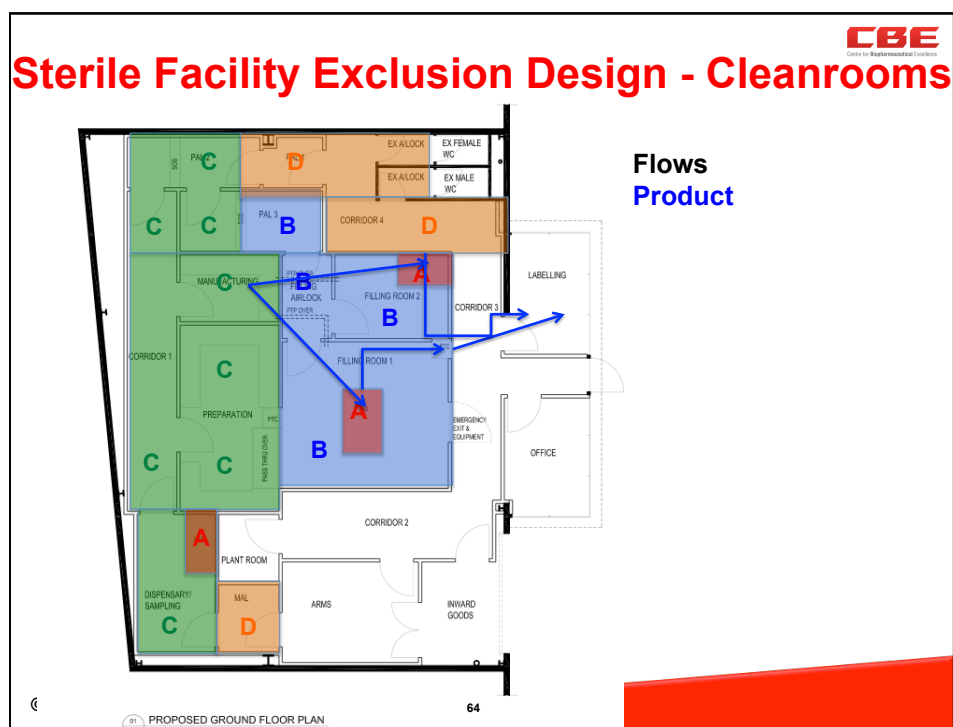
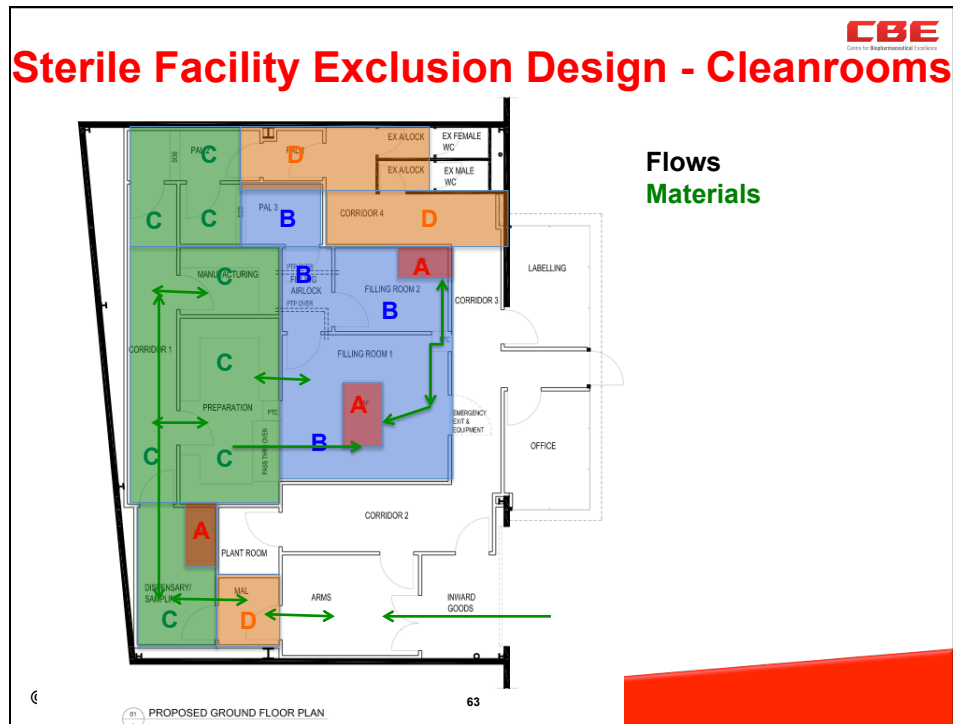
- Set to give early warning as we deviate from normal
- Allows time to intervene and correct time before failure occurs

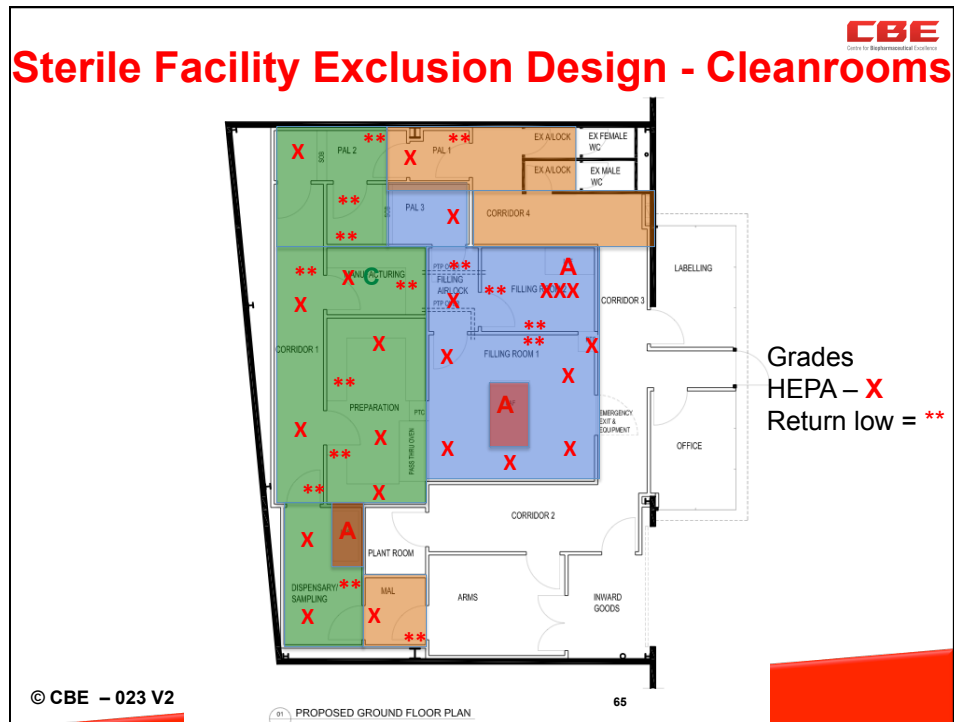
### ACTION

- Set to give warning that we have deviated from “validated state”

- Separate alarms into “Critical” vs “Routine” – Need an SOP for responses







## 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.





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