

World Health Organization



*Supplementary Guidelines on
Good Manufacturing Practices for
Heating, Ventilation and Air conditioning (HVAC) Systems
for Non-sterile Dosage Forms*

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1. Introduction

- ◆ *HVAC systems assists in ensuring the manufacture of quality products and also result in operator comfort.*
- ◆ *HVAC systems design influences architectural layouts, with regard to items such as airlock positions, doorways and lobbies.*
- ◆ *The prevention of the contamination and cross-contamination is an essential design consideration of the HVAC system.*
- ◆ *The design of the HVAC system should be considered at the concept design stage.*



2. Glossary ⁽¹⁾

- ◆ *Cleanroom : A room or area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area, and in which other relevant parameters (e.g. temperature, humidity and pressure) are controlled as necessary.*
- ◆ *Containment : A process or device to contain product, dust or contamination in one zone, preventing it from escaping to another zone.*



2. Glossary ⁽²⁾

- ◆ *Contamination : The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediated, during processing, sampling, packaging or repackaging, storage or transport.*
- ◆ *Cross-contamination : Contamination of starting material, intermediated product or finished product with another starting material or material during production.*

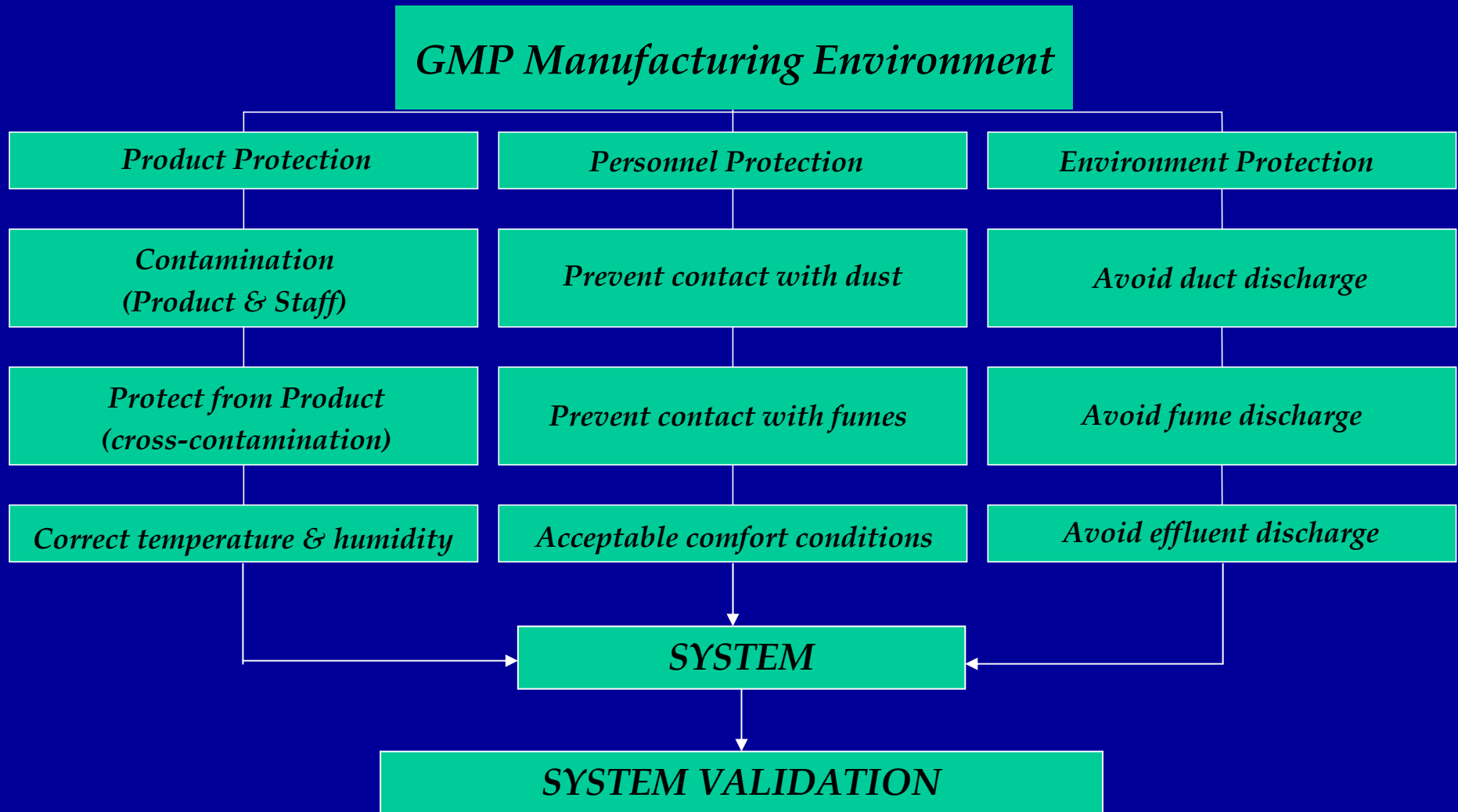


3. Scope

- ◆ *HVAC systems for oral solid dosage facilities*
- ◆ *The three primary aspects addressed in this manual are the role that the HVAC system play in*
 - ❖ *product protection*
 - ❖ *personnel protection*
 - ❖ *enviromental protection*



Protection Aspects



4. Product Protection ⁽¹⁾

4.1 Contamination control

4.1.1 Cleanroom concept

4.1.2 Level of protection

4.1.3 Air filtration to control contamination

4.1.4 Contamination by HVAC plant

4.1.5 Contamination by staff

4.1.6 Airflow patterns

4.1.7 Uni-directional flow protection

4.1.8 Infiltration



4. Product Protection (2)

4.2 Cross-contamination protection

4.2.1 Directional air movement

- Displacement concept*
- Pressure differential concept*
- Physical barrier concept*
- Selecting the segregation concept*

4.2.2 Uni-directional flow protection

4.2.3 Cross-contamination via HVAC supply air

4.2.4 Cross-contamination due to fan failure



4. Product Protection ⁽³⁾

4.3 Temperature and Humidity

4.3.1 General requirements

4.3.2 Product temperature requirements

4.3.3 Product humidity requirements

4.3.4 Microbial growth



5. Personnel Protection

5.1 Protection from dust

5.2 Dust classification

5.3 Uni-directional flow protection

5.4 Point extraction

5.5 Directional airflow

5.6 Air shower

5.7 Protection enclosures

5.8 Operator comfort



6. Protection of the Environment

6.1 Extraction air dust

6.2 Fume removal

6.3 Effluent discharge



7. System and components

7.1 Air distribution

7.2 Air handling unit configurations

7.2.1 Re-circulation system

7.2.2 Full fresh air systems

7.2.3 Additional system components



4. Product Protection (1)

4.1 Contamination control

- ◆ *Through all stages of processing, product should be protected from contamination and cross-contamination.*
- ◆ *These include contamination resulting from*
 - ❖ *inappropriate building finishes*
 - ❖ *plant layout*
 - ❖ *poor cleaning procedures*
 - ❖ *lack of staff discipline*
 - ❖ *poor HVAC system*

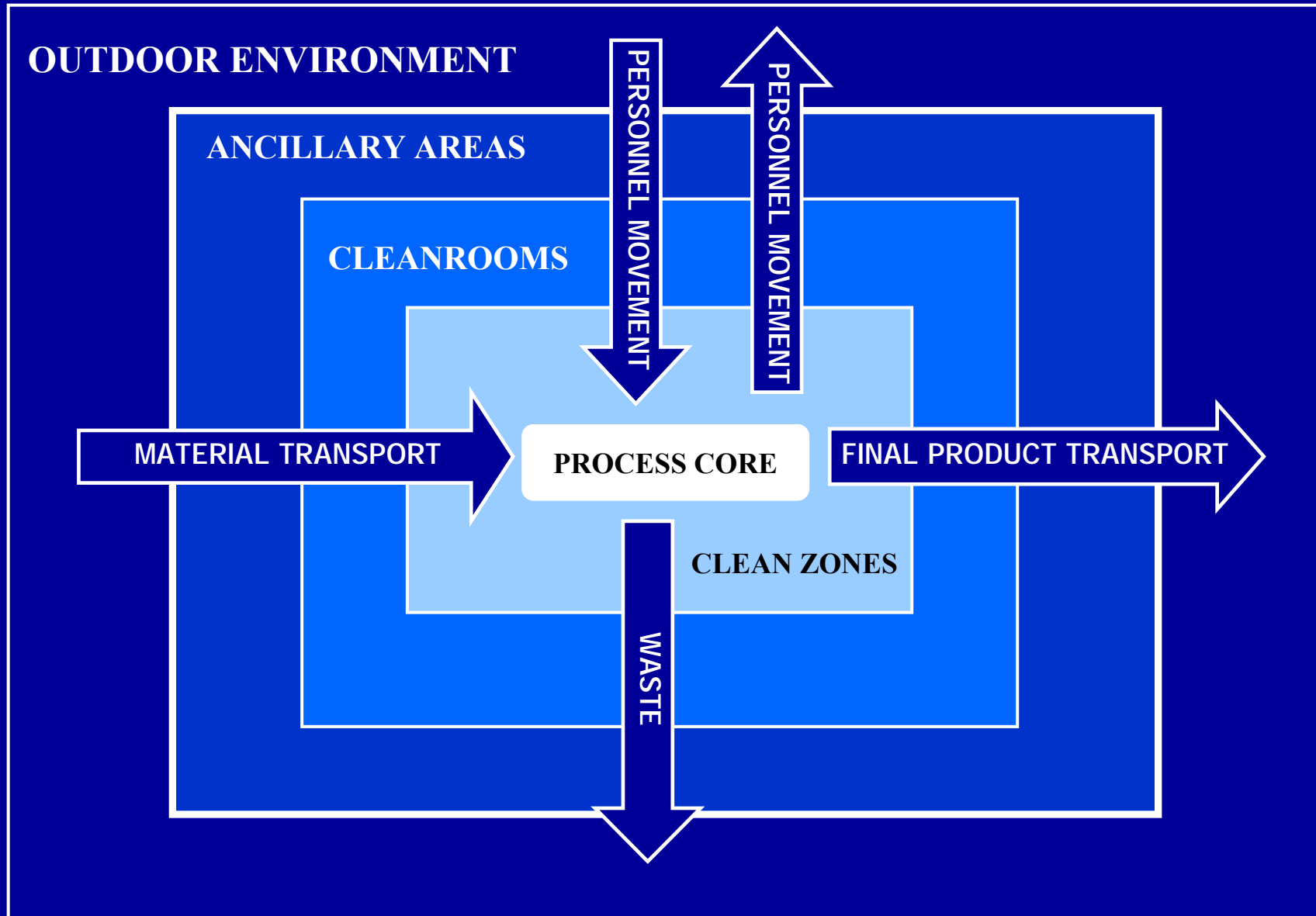


4.1.1 Cleanroom concept

- ◆ *Pharmaceutical manufacturing facilities where pharmaceutical products, utensils and manufacturing equipment are exposed to the environment, should be classified as “cleanrooms”.*
- ◆ *The shell-like containment control concept : The process core is regarded as the most stringently controlled clean zone which is protected by being surrounded by cleanrooms of a lower classification.*
- ◆ *Internal contaminants should be removed by dilution and flushing of contaminants in the room, or by displacement airflow.*



Shell-like containment control concept



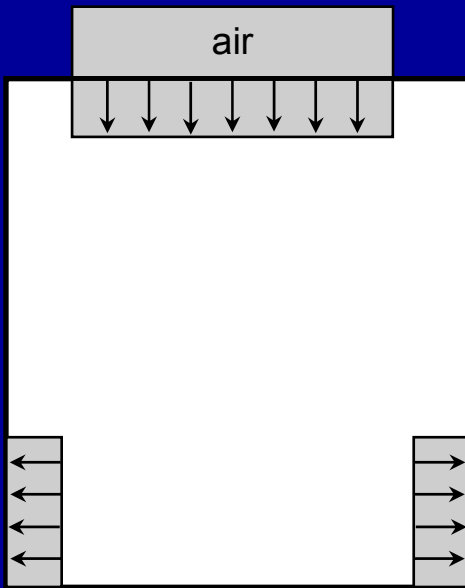
Cleanroom condition

- ◆ *as built : condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel present*
- ◆ *at rest : condition where the installation is complete with equipment installed and operation in a manner agree upon by the customer and supplier, but with no personnel present*
- ◆ *operational : condition where the installation is functioning in the specified manner, with the specified number of personnel and working in the manner agreed upon*

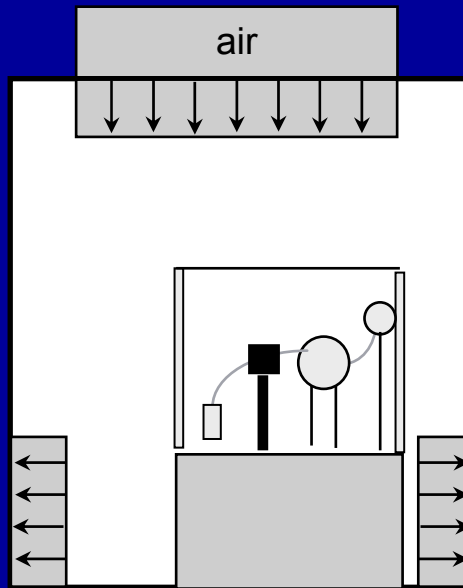


Cleanroom condition

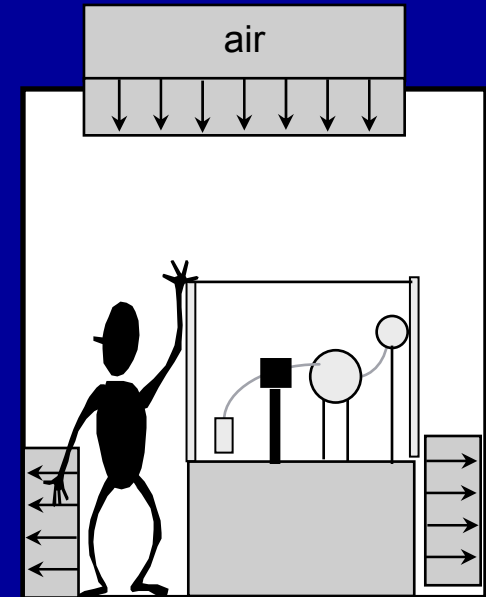
as built



at rest



in operation



4.1.1 Cleanroom concept *(cont.)*

- ◆ *Many multinational pharmaceutical manufacturers have their own minimum air change rate standards for oral dosage facilities, and these typically vary between 6 and 20 air changes per hour.*
- ◆ *Generally a room that is tested for an operational condition, should be able to clean up to a higher at rest cleanroom classification, after a short clean-up condition.*
- ◆ *The clean-up time should normally be in the order of 20 minutes.*



4.1.2 Level of Protection ⁽¹⁾

- ◆ *Level 1 (General) : An area with normal housekeeping and maintenance. (e.g. Warehousing, Secondary Packing)*
- ◆ *Level 2 (Protected) : An area in which steps are taken to protect the exposed drug substance from contamination or degradation. (e.g. Manufacturing, Primary Packing, Dispensing, etc.)*
- ◆ *Level 3 (Controlled) : An area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the drug substance.*



Typical Zone	Level of Protection		Typical Dress Code
	GMP Guides	ISO Class Equivalent	
Street, canteen	External	External	Outdoor clothes
Receipt & dispatch	Level 1 or Unclassified	ISO Class 9	Appropriate to area
Warehousing, offices	Level 1 or Unclassified	ISO Class 9	Appropriate to area
Weighing & dispensing	Level 2 – background Level 3 – open product	ISO Class 8 – background ISO 6 or 7 – open product	Clean garments
Blending	Level 2 or 3	ISO Class 8 or 7	Clean garments
Granulation	Level 2 or 3	ISO Class 8 or 7	Clean garments
Milling	Level 3	ISO Class 8 or 7	Clean garments
Encapsulation & compression	Level 2	ISO Class 8	Clean garments
Coating	Level 2	ISO Class 8	Clean garments
Primary packing	Level 2 or 3	ISO Class 8 or 7	Clean garments
Secondary packing	Level 1 or Pharmaceutical	ISO Class 9	Captive coat, hat and overshoes
Non-sterile processing	Controlled or Class 100000 (in operation)	ISO Class 8	Clean garments
Rooms where filling takes place	Clean or Class 10000 (in operation)	ISO Class 6 or 7	Sterile garments
Point of fill or other aseptic operations	Critical or Class 100 (in operation)	ISO Class 5	Sterile garments
Change rooms & airlocks	The same classification as the area they serve	The same classification as the area they serve	Change to garments for the higher classification



4.1.2 Level of Protection ⁽³⁾

- ◆ *Level 1 protection and Pharmaceutical conditions can be equated with and ISO Class 9 condition.*
- ◆ *The most common applied classification for open product zones in a solid dosage plant is a grade D classification.*
- ◆ *Grade D equates to particulate level classification of ISO 14644-1 Class 8, “at rest”, measured against particles size of 0.5 μm and 5 μm*

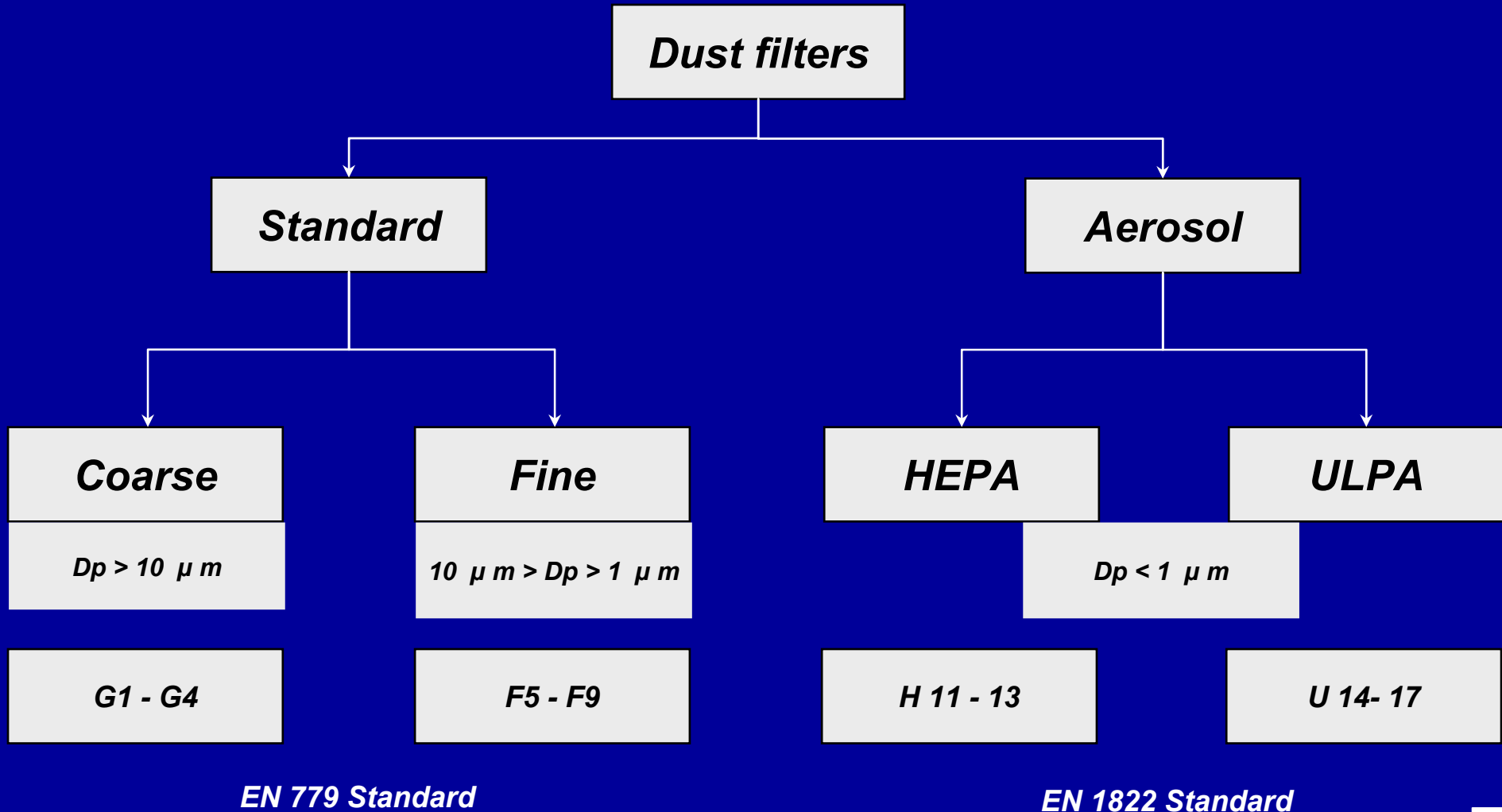


4.1.3 Air filtration to control contamination

- ◆ *Referring to actual filter efficiencies can be very misleading as there are currently many different test methods, and each results in a different value for the same filter.*
- ◆ *Efficiencies of Air Filter*
 - ❖ *Pre-filter (25 - 30 % ARRESTANCE)*
 - ❖ *Medium Filter (90 - 95 % ASHARE 52-76)*
 - ❖ *HEPA Filter (> 99.97 % DOP)*
- ◆ *Back-up HEPA filter*
- ◆ *Good pre-filter extends the life of filters downstream.*



Filter classes



Classification of filters

Classification of filters according to their efficiency

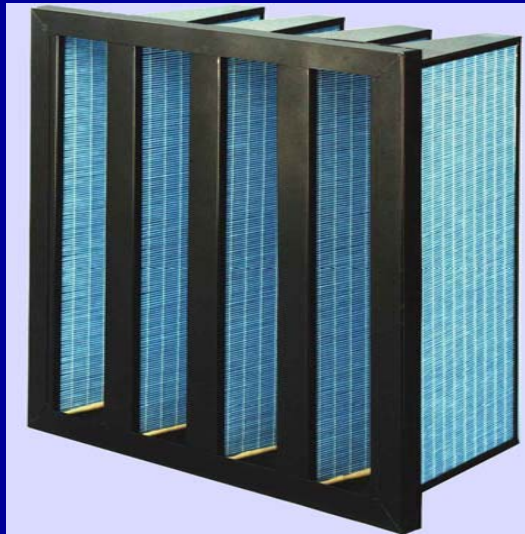
	<i>Average Efficiency Integral Value</i>		<i>Peak Arrestance Local Value</i>	
	<i>Retention in %</i>	<i>Penetration</i>	<i>Efficiency</i>	<i>Penetration</i>
<i>F9</i>	85	0.15		
<i>H11</i>	95	0.05		
<i>H12</i>	99.5	5×10^{-3}	97.5	25×10^{-3}
<i>H13</i>	99.95	5×10^{-4}	99.75	25×10^{-4}
<i>U14</i>	99.995	5×10^{-5}	99.975	25×10^{-5}



Filter



Primary panel filter



Secondary filter

HEPA or tertiary filter



4.1.4 Contamination by HVAC plant

- ◆ *Materials for components of an HVAC system should be selected with care*
- ◆ *Contamination into the air stream should be located upstream of the final filters*
- ◆ *Services are accessible from outside the processing area*



4.1.5 Contamination by staff

- ◆ *Airflows should be planned in conjunction with operator locations, so as to minimize operator contamination of the product and also to protect the operator from dust inhalation.*
- ◆ *Where the product could be harmful to the operator, an alternative arrangement should be made.*
- ◆ *Cosmetics such as facial make-up are a major source of contamination*

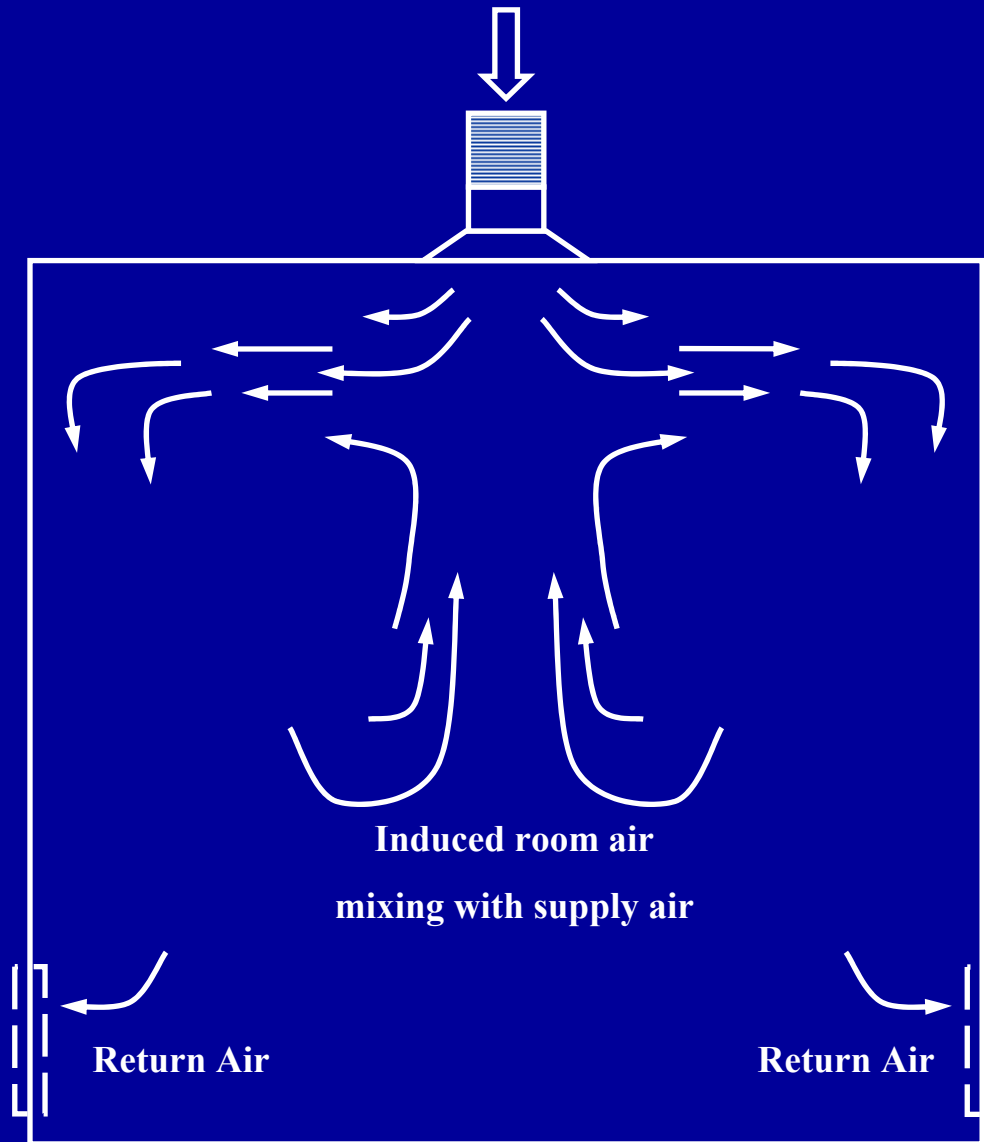


4.1.6 Air flow patterns

- ◆ *Supply air diffusers of the high induction type should not be used in a cleanroom*
- ◆ *Air should be exhausted from rooms at a low level.*
- ◆ *Recommended supply air diffuser*
 - ❖ *Perforated plate diffuser*
 - ❖ *Swirl diffuser*



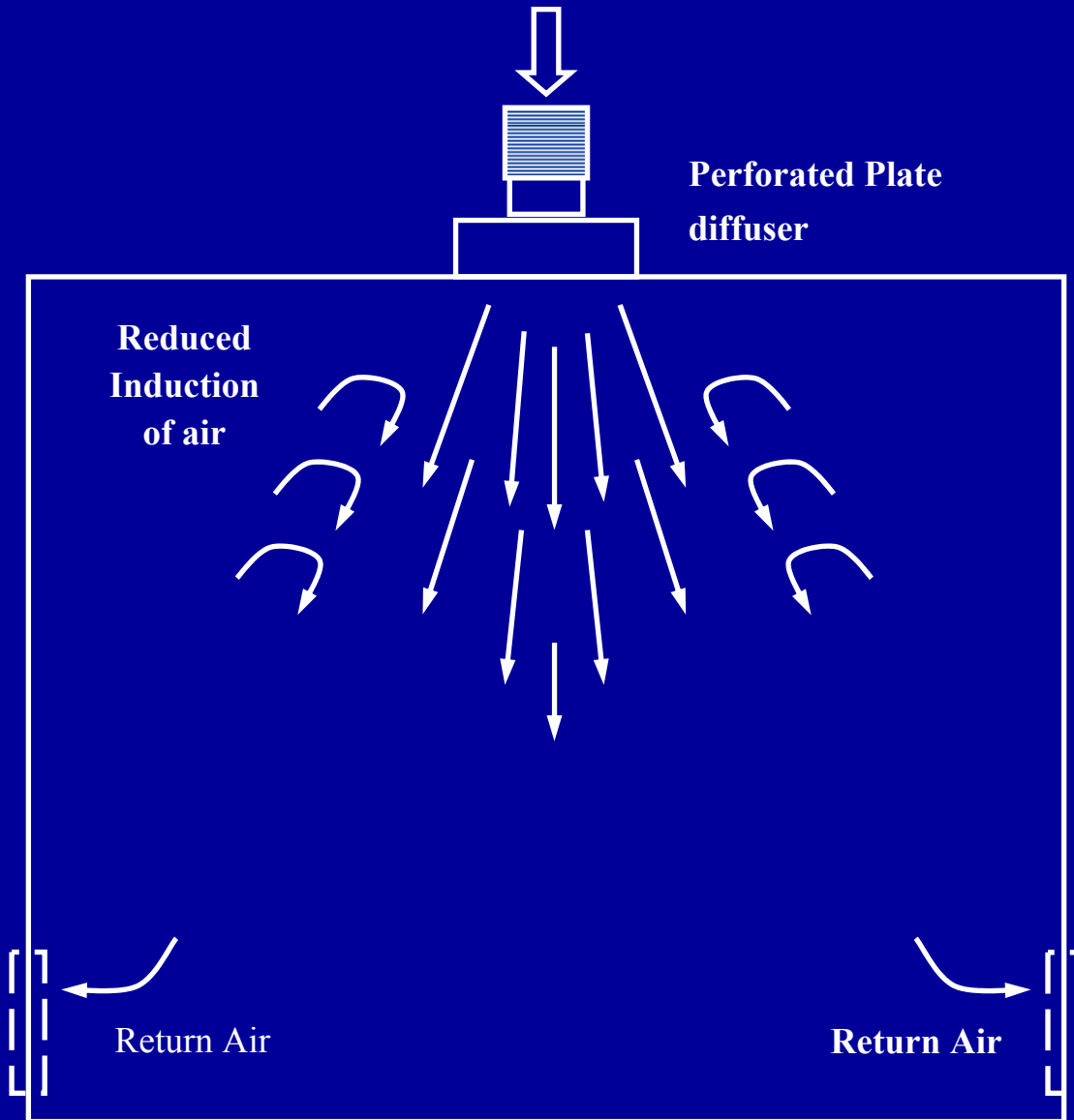
Induction diffuser (not recommended)



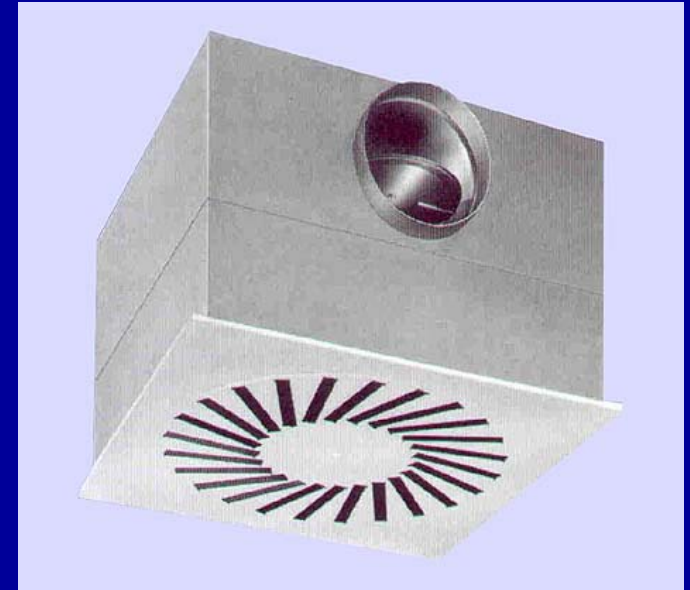
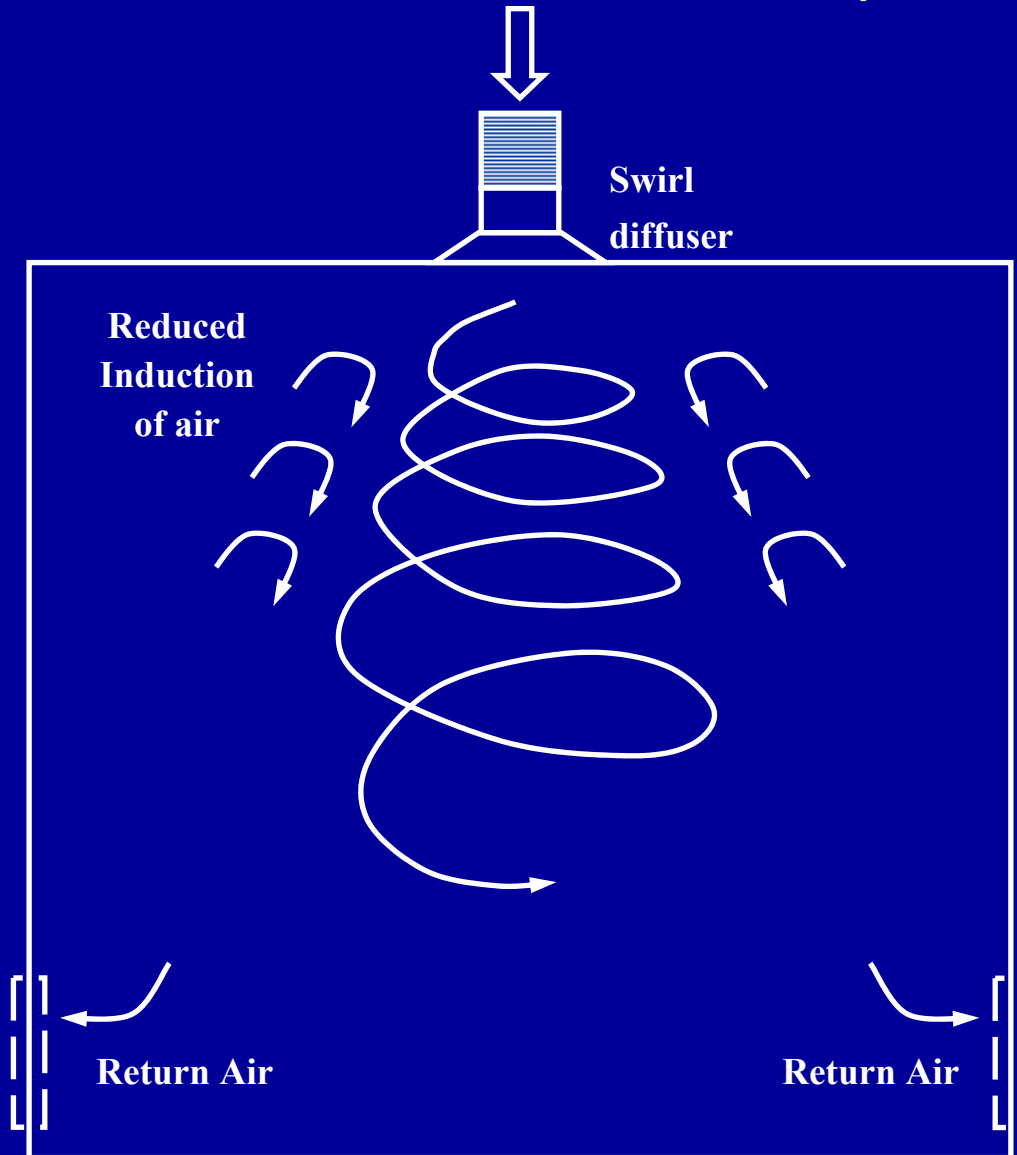
*High induction office type diffuser
(avoid)*



Perforated plate diffuser (recommended)

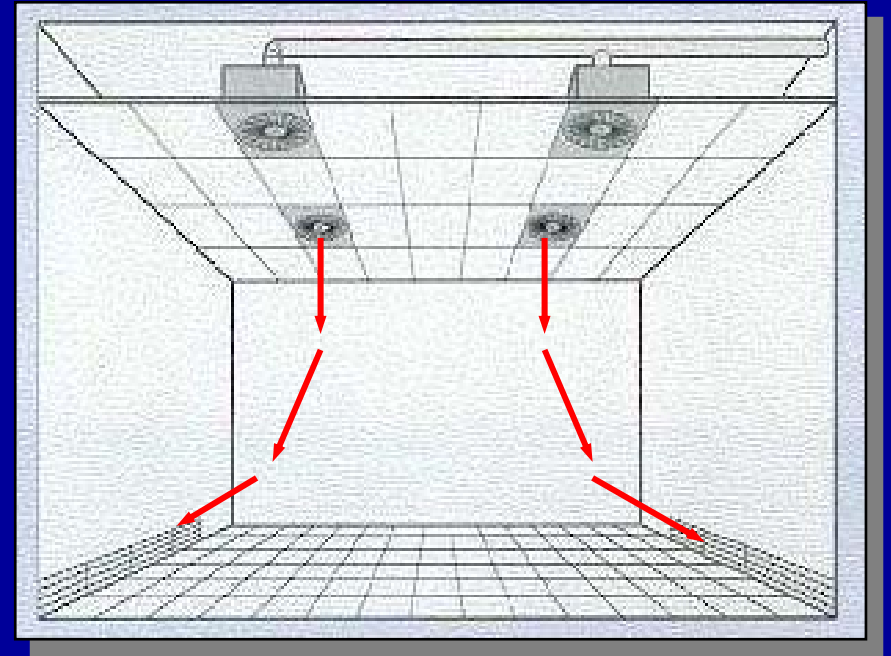
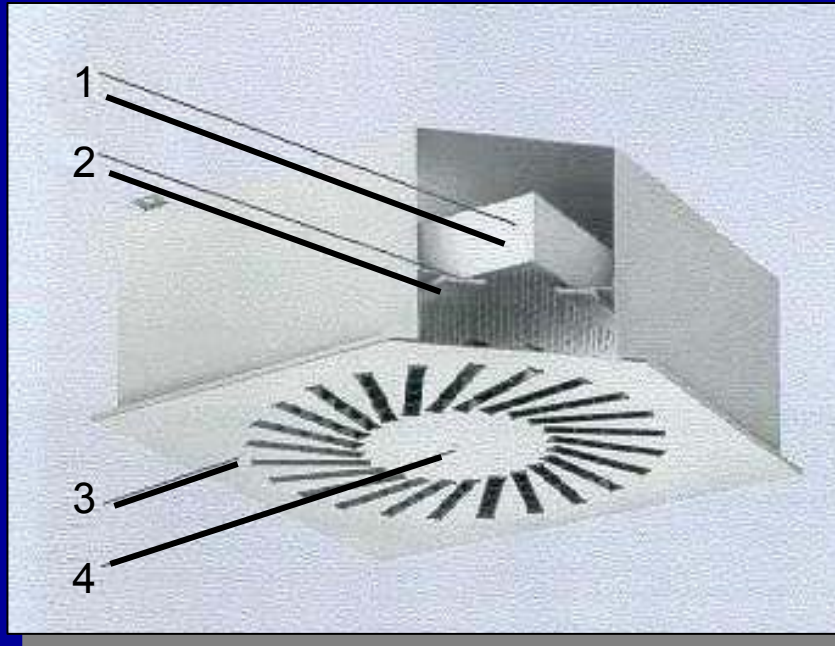


Swirl diffuser (recommended)



*Low induction swirl diffuser
(preferred)*

Swirl Type air diffusers with terminal filters



1 *Filter*

2 *Tightening frame*

3 *Register outlet*

4 *Screw fixation for register*

4.1.7 Uni-directional airflow protection

- ◆ *Sampling should be carried out in the same environmental class that is required for the further processing of the product.*
- ◆ *Sampling should normally be carried out under a uni-directional airflow screen.*

Uni-directional flow can be

- ❖ *Vertical flow ($0.3 \text{ m/s} \pm 20 \%$)*
- ❖ *Horizontal flow ($0.45 \text{ m/s} \pm 20 \%$)*



4.1.8 Infiltration

- ◆ *Manufacturing facilities should be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants.*
- ◆ *Where facilities are to be maintained at negative pressures relative to ambient, in order to prevent the escape of harmful products to the outside (such as penicillin and hormones), then special precaution should be taken.*
- ◆ *Negative pressure zone should, as far as possible, be encapsulated by surrounding area with clean air supplies, so that only clean air can filtrate into the controlled zone.*



4.2 Cross-contamination protection

- ◆ *Through all stages of processing, products should be protect from cross-contamination*
- ◆ *This can achieved with the aid of the following methods.*

4.2.1 Directional air movement

- ◆ *The pressure cascade should be such that air flow from the corridor into cubicles, resulting in dust containment*



4.2.1 Directional air movement ⁽²⁾

- ◆ *In multi-product OSD manufacturing area, the layout normally consists of a corridor with production cubicles located on either side of it. Cross-contamination between products within a single room will not be addressed, as different products should never be processed in the same area at the same time.*
- ◆ *The corridor should be maintained at a higher pressure than the cubicles, and than cubicles at a higher pressure than atmospheric pressure (negative pressure relative to atmosphere, in order to contain hazardous substances, such as penicillin or hormones, etc.)*



4.2.1 Directional air movement⁽³⁾

4.2.1.1 Displacement concept (low pressure differential, high airflow)

- *A low pressure differential can effectively separate clean and less clean adjacent zone, by means of a low turbulent displacement airflow velocity greater than 0.2 m/s.*
- *The air should be supplied to the corridor, flow through the doorway, and should be extracted from the back of the cubicle.*
- *The door containment airflow velocity should be considered a critical parameter.*

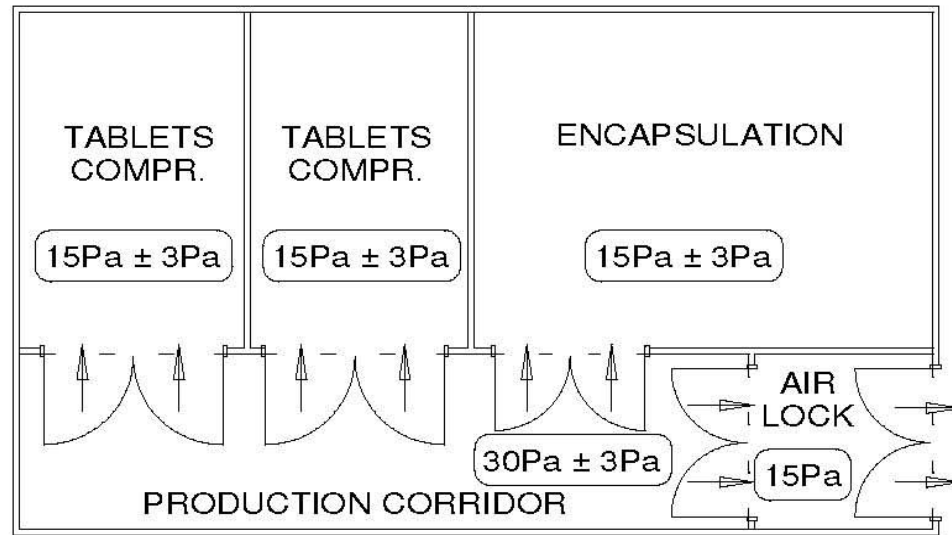


4.2.1 Directional air movement (4)

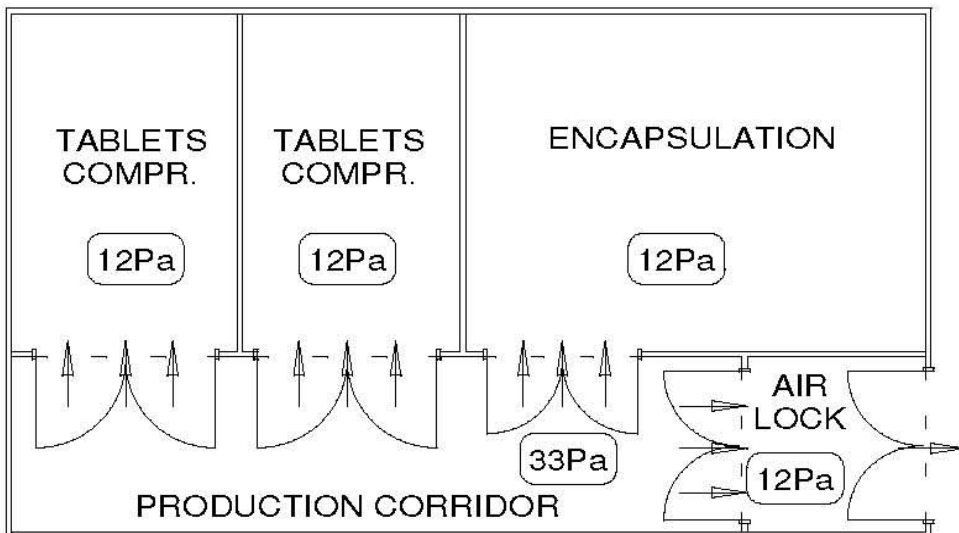
4.2.1.2 Pressure differential concept (high pressure differential, low airflow)

- *The most widely accepted pressure differential between the two adjacent zones is 15 Pa.*
- *But pressure differentials of between 5 Pa and 20 Pa could be acceptable.*
- *A control tolerance of ± 3 Pa is achievable.*
- *The pressure differential between adjacent rooms should be considered a critical parameter.*

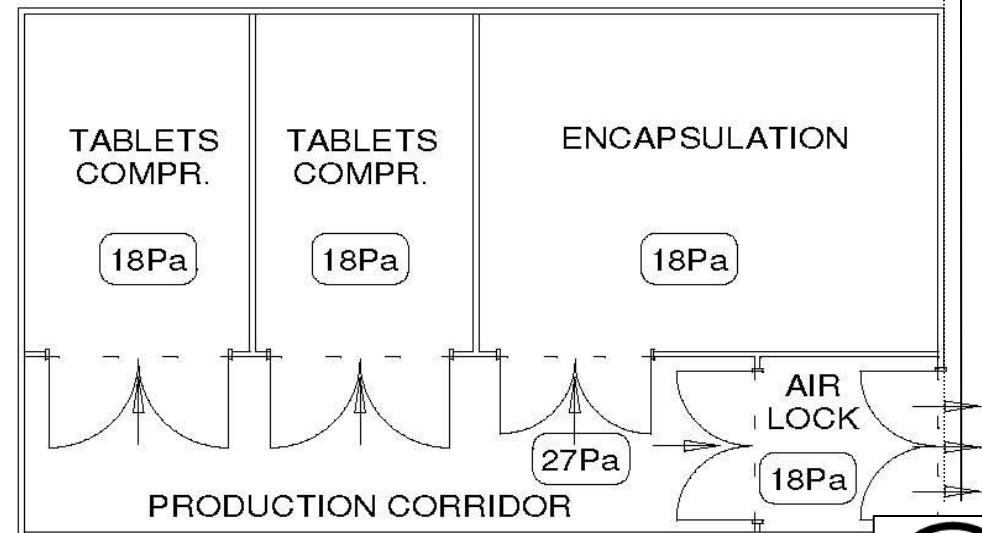




DESIGN CONDITION



MAXIMUM DIFFERENTIAL

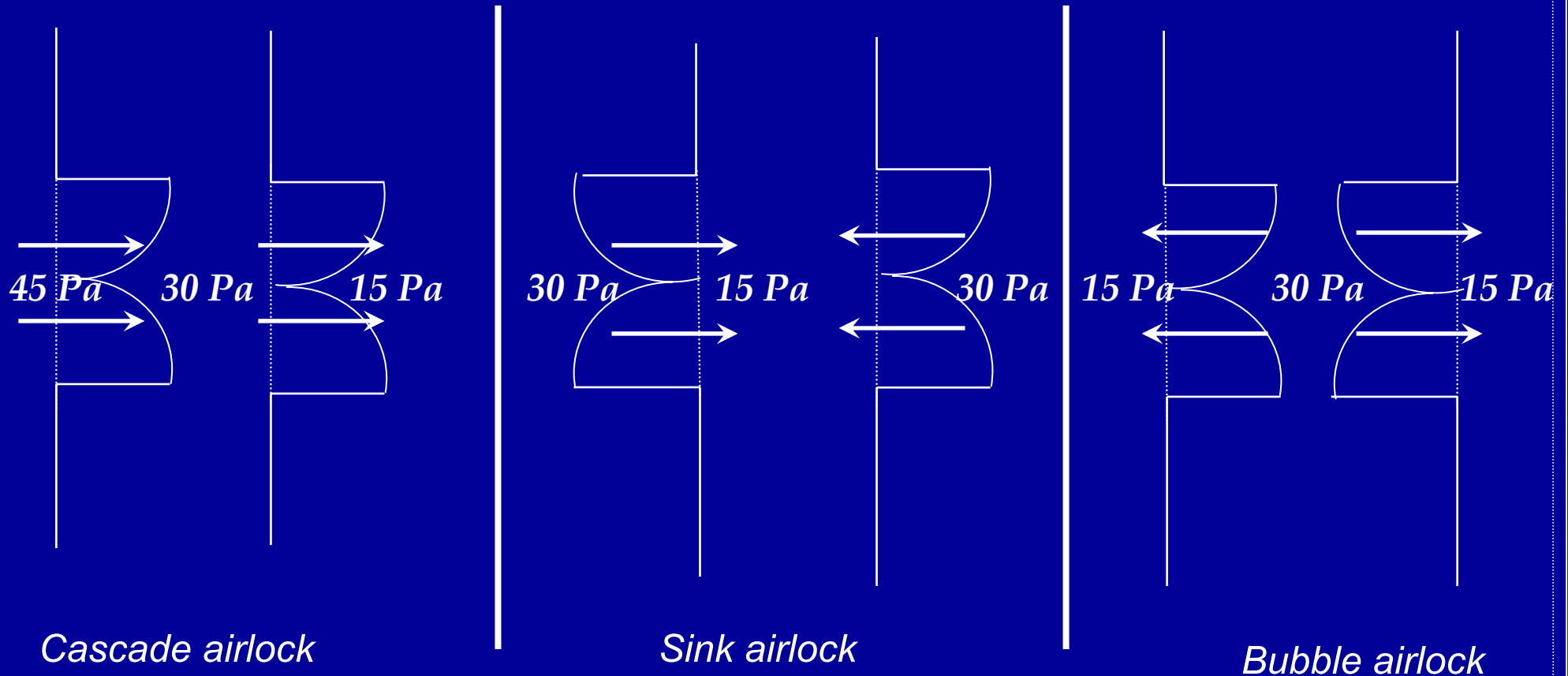


MINIMUM DIFFERENTIAL



4.2.1 Directional air movement (5)

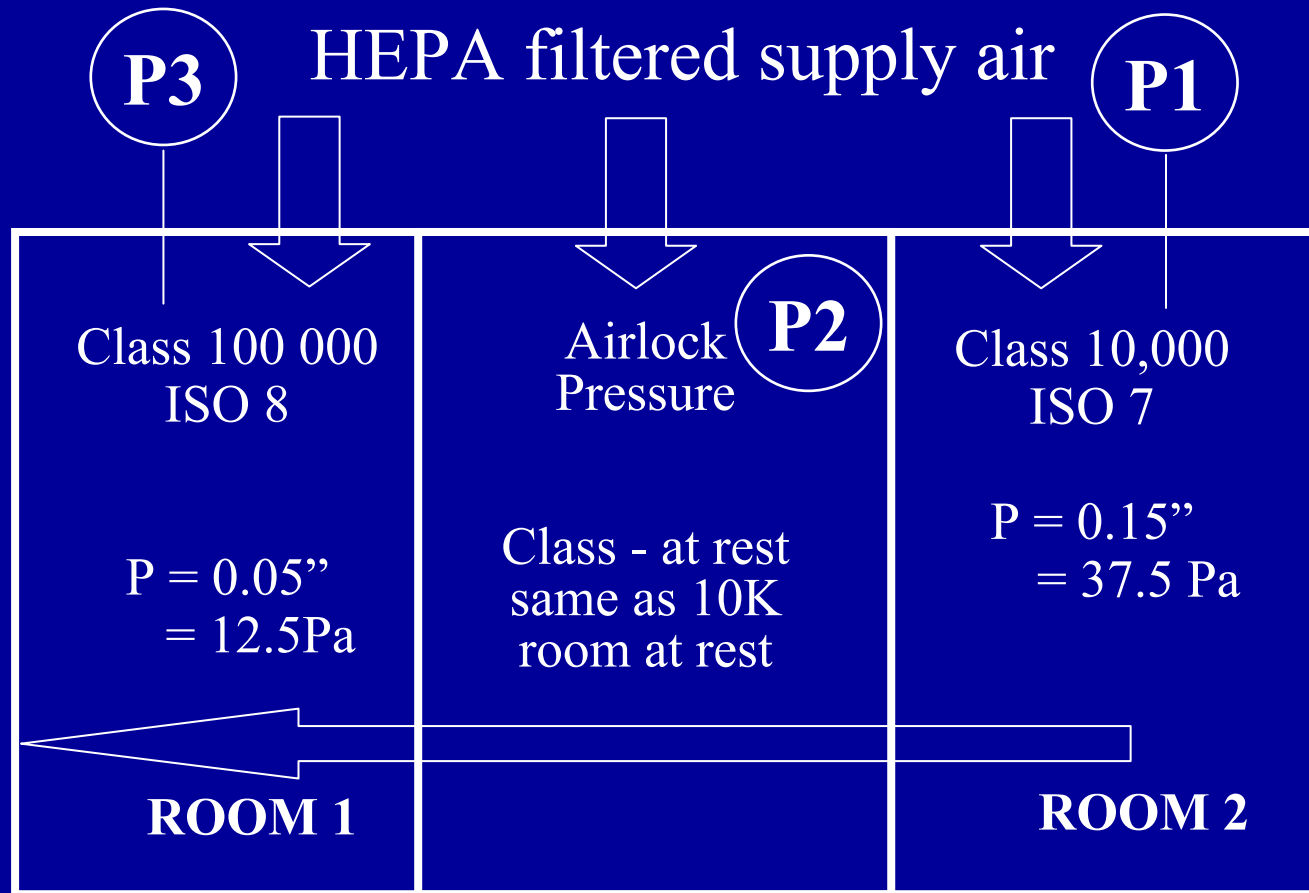
Classification of airlock



The door swing on airlocks should be such that opens to the high pressure side



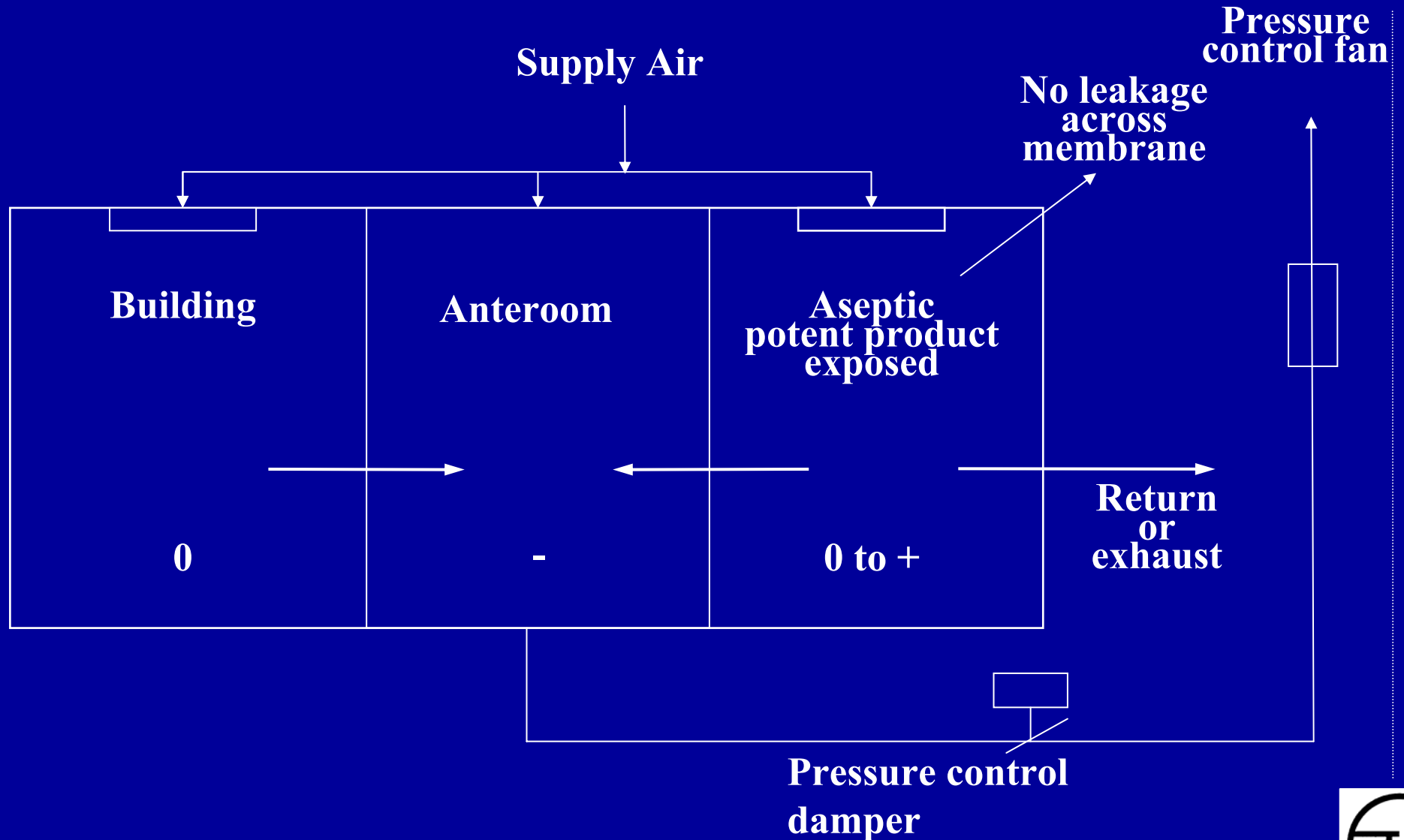
Typical Pressure Cascade Airlock



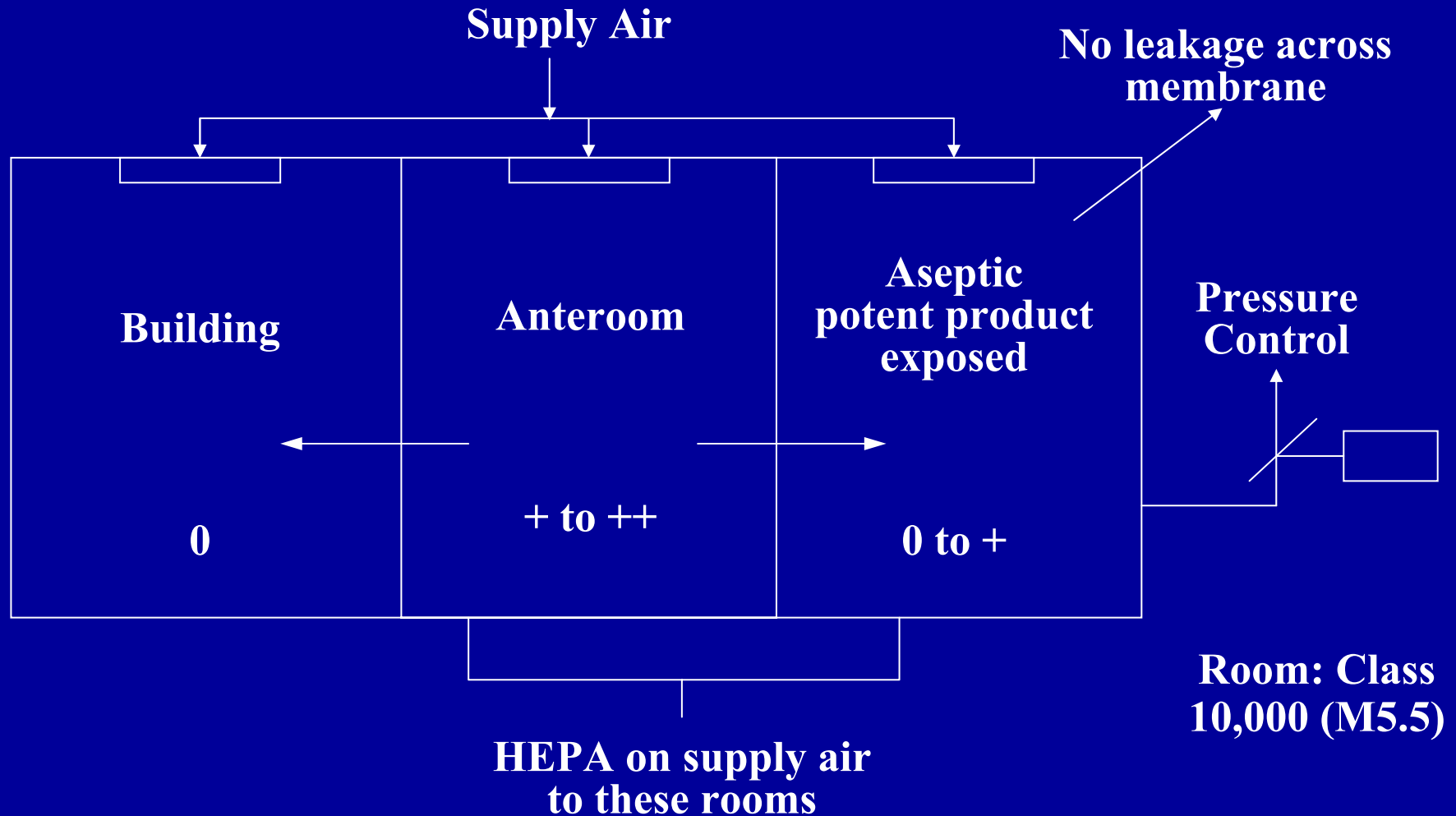
$P2 - P3 = 0.05''$
 Airlock is most common between Class 10,000 and Class 100,000. Also used Class 100,000 to building
 $P1 - P2 = 0.05''$



Pressure Sink for Containment



Pressure Bubble for Containment



4.2.1 Directional air movement ⁽⁶⁾

4.2.1.3 Physical barrier concept (barrier isolator)

- *The use of an impervious barrier to prevent cross-contamination between two zones is the third segregation concept (the case where a barrier isolator, or pumped transfer of materials, is used)*
- *Not practical in an oral solid dosage facility.*



4.2.1 Directional air movement (7)

4.2.1.4 Selecting the segregation concept

- *The displacement concept should ideally be used in production process where large amounts of dust are generated.*
- *The pressure differential may normally be used in zones where there is little or no dust being generated.*
- *High potent products should be manufactured under a pressure cascade regime that is negative to atmospheric pressure*



4.2.2 Unidirectional airflow protection

- ◆ *A dispensary weigh booth should be provided with unidirectional airflow for product and operator protection*
- ◆ *Sampling and dispensary booth for oral solid dosage form may not be required unidirectional flow provides Class A (ISO 5)*



4.2.3 Cross-contamination via HVAC supply air

- ◆ *Dust laden air, returned to air handling unit, increases the possibility of cross-contamination in a multi-product plant.*
- ◆ *A re-circulation system may be acceptable, provided that suitable filtration and there are no contaminants (such as fumes and volatile) which cannot be removed by normal filtration.*
- ◆ *A re-circulation system should be provided with HEPA filters to ensure the removal of return air contaminations.*



4.2.4 *Cross-contamination due to fan failure*

- ◆ *Appropriate airflow alarm system.*
- ◆ *Central dust extraction systems should be interlocked with the appropriate air handling systems.*
- ◆ *Air should not flow from the room with the higher pressure to the room with the lower pressure, via the dust extract ducting.*



4.3 Temperature and Humidity ⁽¹⁾

◆ General requirements

- ❖ product manufacturing requirements*

- ❖ operator comfort*

◆ Product temperature requirements

- ❖ minimum and maximum should not be made too close*



4.3 Temperature and Humidity (2)

◆ Product humidity requirement

- ❖ < 45 % RH at 22 °C may require chemical driers*
- ❖ Humidifiers should be avoided (microbial growth)*
- ❖ Silica gel or Lithium chloride*

◆ Microbial growth

- ❖ High T° and % RH cause perspiration from operator*



5. Personnel Protection ⁽¹⁾

5.1 Protection from dust

- ◆ *Operator health should not be put at risk by being exposed to harmful products.*
- ◆ *Airflow should be carefully planned, to ensure that*
 - ❖ *the operator does not contaminate the product*
 - ❖ *the operator is not put at risk by the product.*



5.2 Dust classification

Dust can be roughly classified by size according to :

- ◆ *Coarse dust with size range of 50 to 500 μm (settles rapidly)*
- ◆ *Fine dust with size range of 1.0 to 50 μm (settles slowly)*
- ◆ *Ultra fine dust with size range $< 0.5 \mu\text{m}$ to $1.0 \mu\text{m}$ (remains constantly suspended)*
- ◆ *Particles $< 0.05 \mu\text{m}$ are considered to be vapors and not dust*

Only dust particles that are greater than 10 μm are visible to the naked eye with good lighting and good eyesight

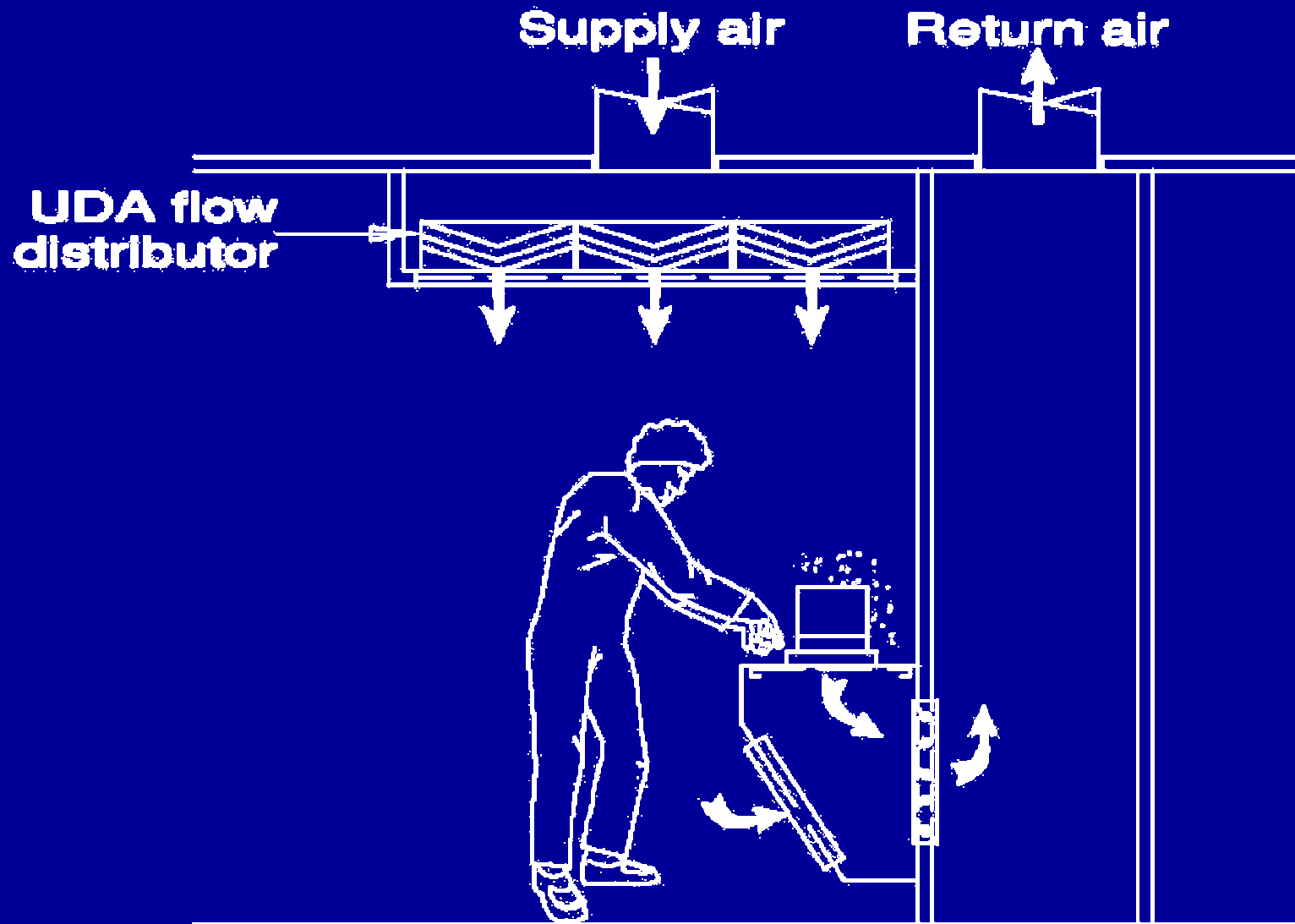


5.3 Unidirectional flow protection

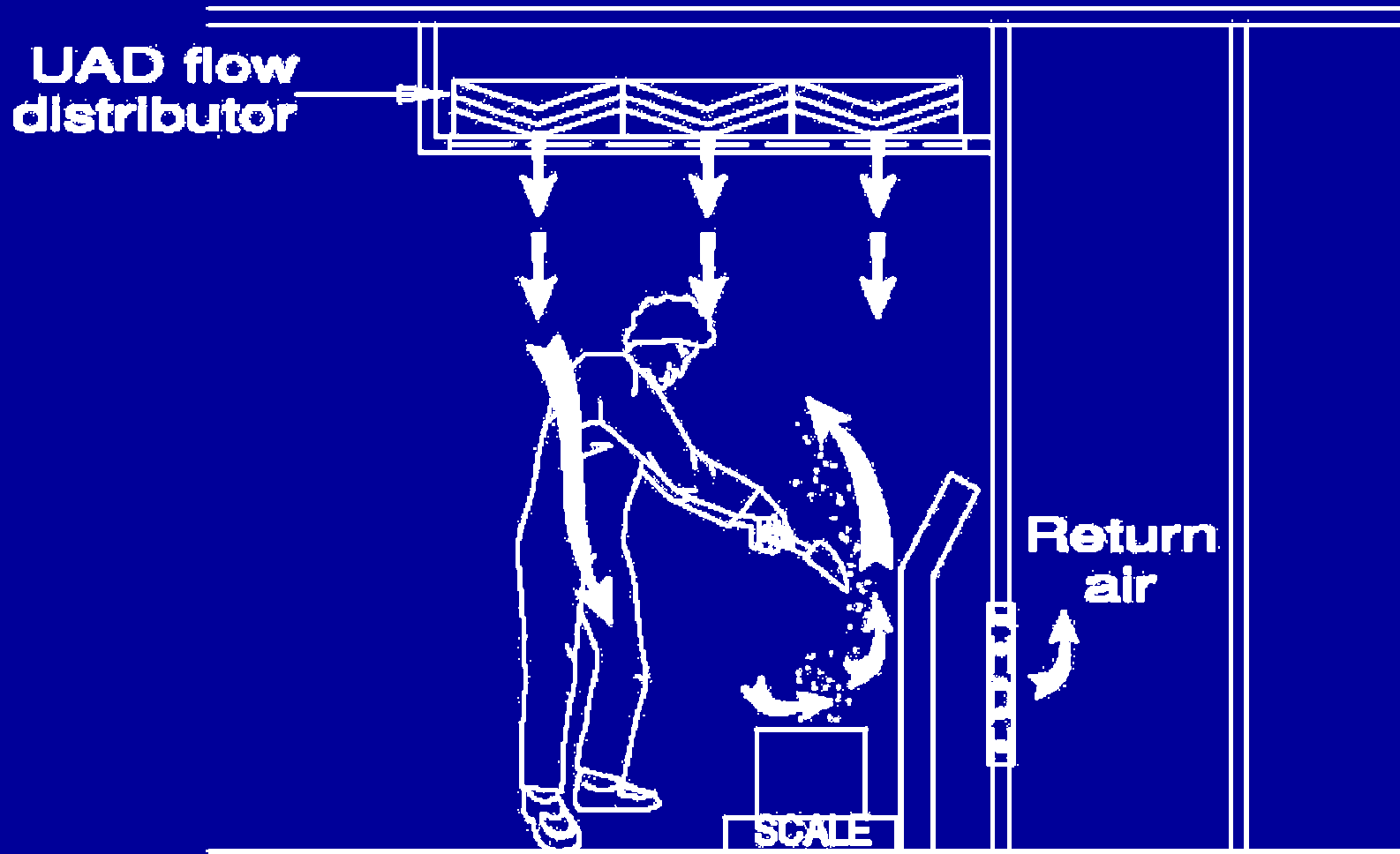
- ◆ *Unidirectional flow velocity of the dispensary weigh booth should be considered with regard to the possible disruption of sensitive scale readings*
- ◆ *Operator is not in the path of an airflow that could lead to contamination of the product.*
- ◆ *The back of the scale should not block the return air path.*



Operator protection at weighing station



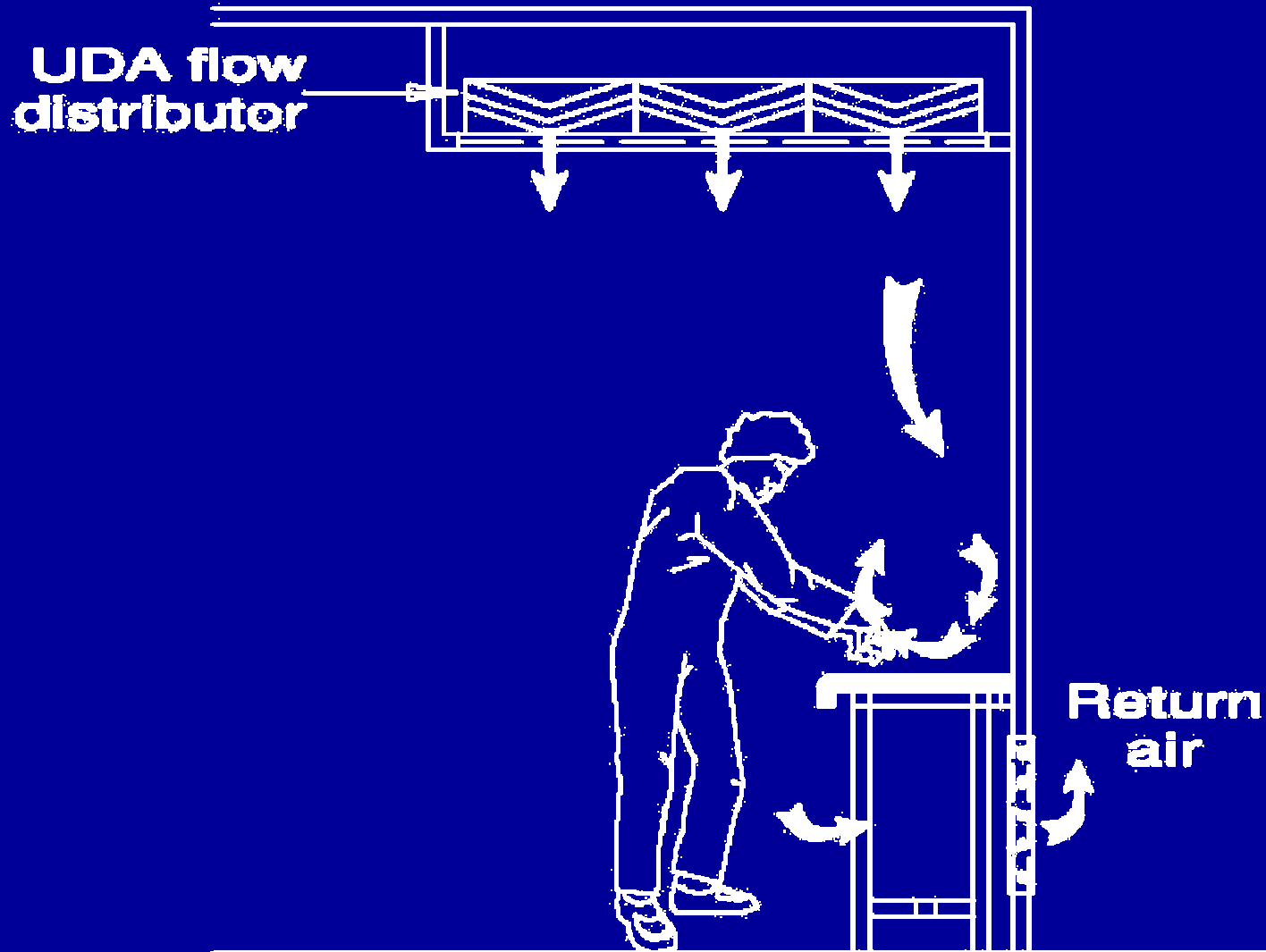
Operator subject to powder inhalation due to obstruction



Operator subject to powder contamination due to air flow reversal in bin



Operator subject to powder inhalation due to worktop obstruction



5.4 Point extraction

- ◆ *As closed as possible to the point where dust is generated.*
- ◆ *Transfer velocities for pharmaceutical dust should be 18 – 20 m/s.*

Air velocities for dust transport	
Type of dust or vapor	Duct velocity (m/s)
Paint and varnish fumes	8 – 10
Textile lint and sawdust (dry)	10
Asbestos and limestone dust	13
Metal fumes and dusts	15
Grain and flour	18 – 20
Grinding, shot- and sand-blasting	18 – 22
Pulverized coal, stone cutting	20
Wood chips and shaving	20 – 25
Lead dust	28



5.5 Directional airflow

- ◆ *The air should be introduced from ceiling diffusers and is extracted from the room at low level. (Turbulent airflow)*
- ◆ *Vapor is lighter than air, extract grilles should be at high level.*

5.6 Air shower

- ◆ *Operators could pass through an air shower, prior to entering the change room, on leaving the production area.*
- ◆ *Should be validated*



5.7 Protection enclosures

- ◆ *For products such as hormones or highly potent, operators should wear totally enclosed garments.*
- ◆ *Breathing air system should be provide a supply of filter.*

5.8 Operator comfort

- ◆ *Recommended humidity comfort level of 20 - 60 % RH should be maintained where required.*
- ◆ *Typically comfort condition of 21 to 22 °C should be applicable in oral solid dosage facility.*



6. *Protection of the Environment* ⁽¹⁾

6.1 *Extraction air dust*

- ◆ *On systems where harmful substances such as penicillin, hormones, toxic powders and enzymes are exhausted, the final filters should be HEPA filters.*
- ◆ *When handling hazardous compounds, safe change filter housing, also calls “bag-in-bag-out” filters, should be used*
- ◆ *All filter banks should be provided with pressure differential indication gauges, to indicate the filter dust loading.*



6. Protection of the Environment (2)

6.2 Fume removal

- ◆ *Wet scrubbers (chemicals added to water to increase the adsorption efficiency)*
- ◆ *Dry chemical scrubbers or deep bed scrubbers (activated carbon filters, chemical adsorption granular media)*

6.3 Effluent discharge

- ◆ *Should be design to ensure the systems like wet scrubbers, which could discharge contaminants into the drainage system, do not become sources of possible risk or contamination.*



7. *Systems and components* ⁽¹⁾

7.1 *Air distribution*

- ◆ *HEPA filter may be located in the air handling unit or terminally*
- ◆ *Normally, system having Class A or B and possibly C should have final filters terminally located.*
- ◆ *A cleanroom should be designed with low-level return.*
- ◆ *Where ceiling return air grilles are used a higher air change rate may be required to achieve a specified cleanroom classification.*



7. *Systems and components* ⁽²⁾

7.2 *Air handling unit configurations*

◆ *Re-circulation system*

- ❖ *Having a percentage of fresh air make-up*
- ❖ *Re-circulated should not be used if there are no HEPA filter installed in the system, unless the air handling system is serving a single product facility and there is evidence that there is no possibility of cross-contamination.*



7. System and components (3)

7.2 Air handling unit configurations

- ◆ *Full fresh air system (100 % fresh air)*

- ❖ *apply to toxic products*

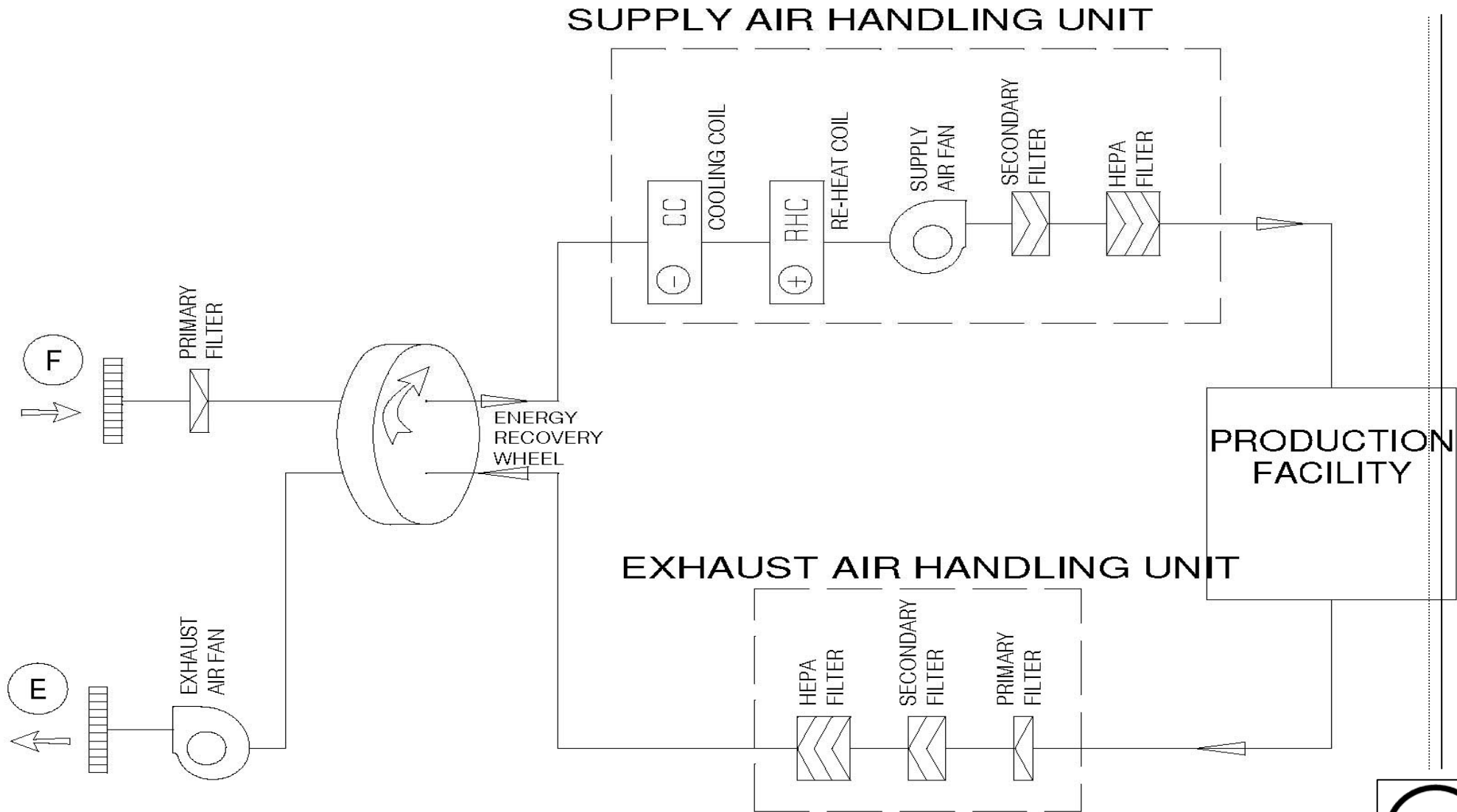
- ❖ *achieved air cleanliness in most oral solid dosage*

- manufacturing facilities without the use of HEPA filters.*

- ❖ *Energy recovery wheel*



Full fresh air system with energy recovery



7. System and components (4)

7.2 Air handling unit configurations

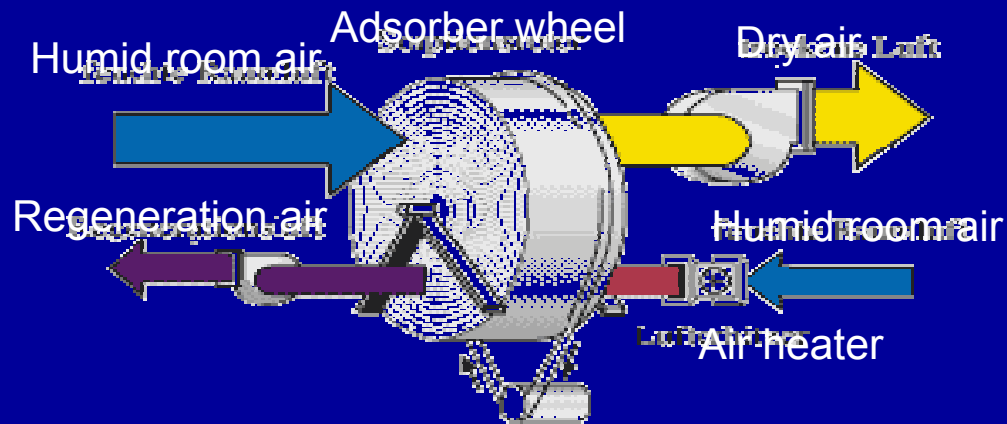
◆ Additional system components

- ❖ Frost coils on fresh air inlets to preheat the air.*
- ❖ Snow eliminators to prevent snow entering air inlets.*
- ❖ Dust eliminators on air inlets in arid and dusty locations.*
- ❖ Moisture eliminators in humid areas with high rainfall.*
- ❖ Fresh air pre-cooling coils for very hot climates.*

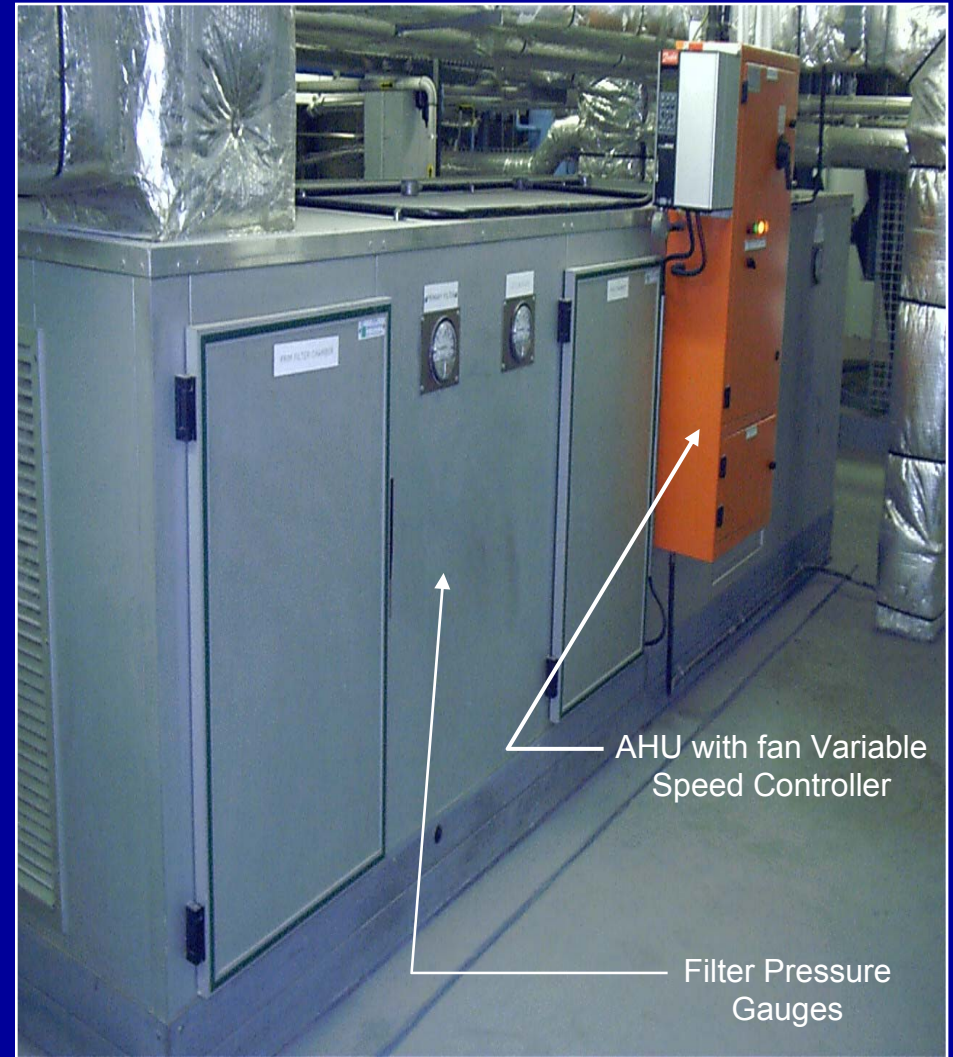




Control damper for air flow



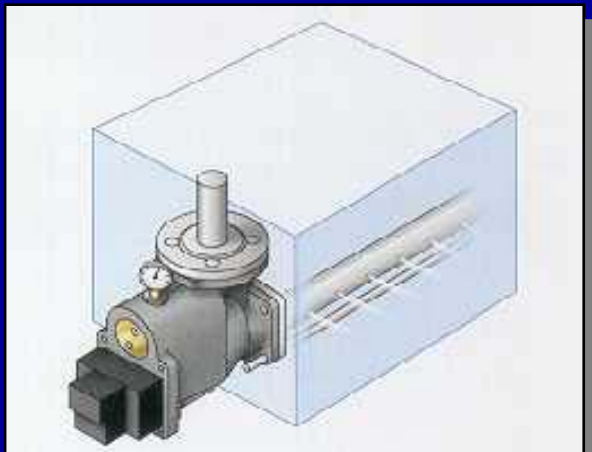
De-humidification



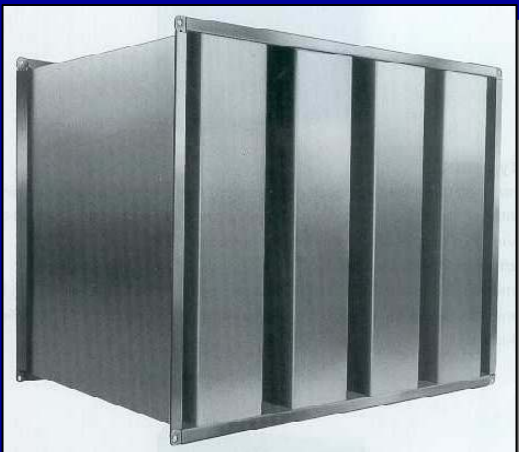
Air handling unit



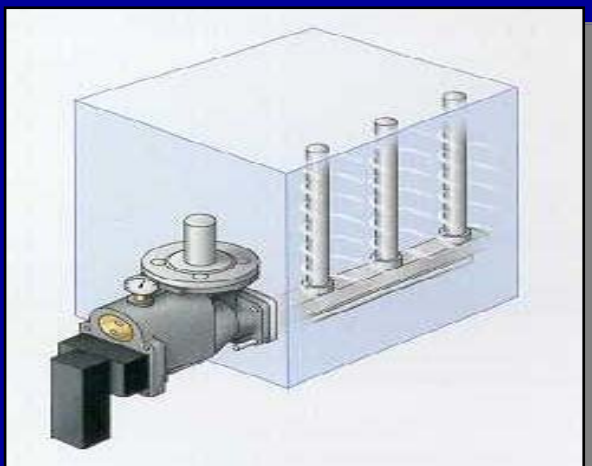
Humidifier



Silencer



Heating and cooling units



8. *Commission, Validation and Maintenance* ⁽¹⁾

A good design is essential, but it has to be complemented by

- ◆ *Qualification of air handling systems*
- ◆ *Process validation*
- ◆ *Maintenance and periodic re-qualification*
- ◆ *Adequate documentation*



Qualification (OQ, PQ) ⁽¹⁾

Test	Uni-directional airflow / LAF	Turbulent / mixed airflow	Description
Differential pressure on filters	2	2	1 := As built (ideally used to perform IQ) 2 = At rest (ideally used to perform OQ) 3 = Operational (ideally used to perform PQ)
Room differential pressure	N/A	2, 3	
Airflow velocity / uniformity	2, 3	Optional	
Airflow volume / rate	2	2	
Parallelism	2	N/A	
Air flow pattern	2	3	

Annex 1, 17. 4

IQ tests are not mentioned on this slide



Qualification (OQ, PQ) ⁽²⁾

Test	Uni-directional airflow / LAF	Turbulent / mixed airflow	Description
Recovery time	N/A	2	1 := As built (ideally used to perform IQ) 2 = At rest (ideally used to perform OQ) 3 = Operational (ideally used to perform PQ)
Room classification (airborne particle)	2	2,3	
Temperature, humidity	N/A	2,3	

Annex 1, 17. 4

IQ tests are not mentioned on this slide



8. Commission, Validation and Maintenance (4)

Strategic test (ISO 14644)

Schedule of Test to Demonstrate Continuing Compliance			
Test Parameter	Cleanroom Class	Max. Time Interval	Test Procedure
Particle Count Test (Verification of Cleanliness)	\leq ISO 5 $>$ ISO 5	6 Months 12 Months	ISO 14644-1 Annex B
Air Pressure Difference (To verify non cross-contamination)	All Classes	12 Months	ISO 14644-3 Annex B5
Airflow Volume (To verify air change rates)	All Classes	12 Months	ISO 14644-3 Annex B4
Airflow Velocity (To verify unidirectional flow or containment conditions)	All Classes	12 Months	ISO 14644-3 Annex B4



8. Commission, Validation and Maintenance (5)

Recommended Optional Strategic test (ISO 14644)

Schedule of Test to Demonstrate Continuing Compliance			
Test Parameter	Cleanroom Class	Max. Time Interval	Test Procedure
Filter leakage Test (To verify filter integrity)	All Classes	24 Months	ISO 14644-3 Annex B6
Containment leakage (To verify non cross-contamination)	All Classes	24 Months	ISO 14644-3 Annex B4
Recovery (To verify clean up time)	All Classes	24 Months	ISO 14644-3 Annex B13
Airflow Visualization (To verify required air flow patterns)	All Classes	24 Months	ISO 14644-3 Annex B7



Reference

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