GMP: ANNEX 1 – PRODUZIONE DI MEDICINALI STERILI

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Giornata di Formazione Acanto – Milano, 20 Settembre 2012

Principi di progettazione di un reparto per la produzione di farmaci iniettabili

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Precedenti 2 anni	Da oltre 2 a 5 anni precedenti	Oltre 5 anni precedenti (facoltativo)
Interessi diretti:					
Impiego in una società					
Consulenza per una società					
Consulente strategico per una società					
Interessi finanziari					
Titolarità di un brevetto					
Interessi indiretti:					
Sperimentatore principale					
Sperimentatore					
Sovvenzioni o altri fondi finanziari					

* Luisa Stoppa, secondo il regolamento sul Conflitto di Interessi approvato dal CdA AIFA in data 26.01.2012 e pubblicato sulla Gazzetta Ufficiale del 20.03.2012 in accordo con la policy 0044 EMA/513078/2010 sulla gestione del conflitto di interessi dei membri dei Comitati Scientifici e degli esperti.

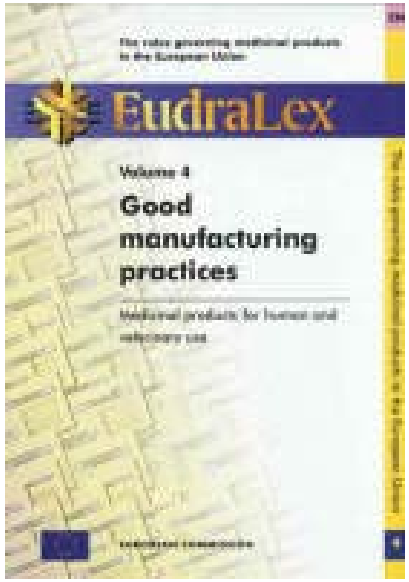
N.B. Per questo intervento non ricevo alcun compenso

SCHEMA

1. Principi base dell'annex 1
2. Requisiti strutturali
3. Monitoraggio ambientale
4. Convalida HVAC
5. Deviazioni ricorrenti (sterili)
6. Conclusioni

1. **Principi base dell’annex 1**
2. Requisiti strutturali
3. Monitoraggio ambientale
4. Convalida HVAC
5. Deviazioni ricorrenti (sterili)
6. Conclusioni

1. PRINCIPI BASE DELL'ANNEX 1



Eudralex: volume 4 – Medicinal products for human and veterinary use: good manufacturing practice

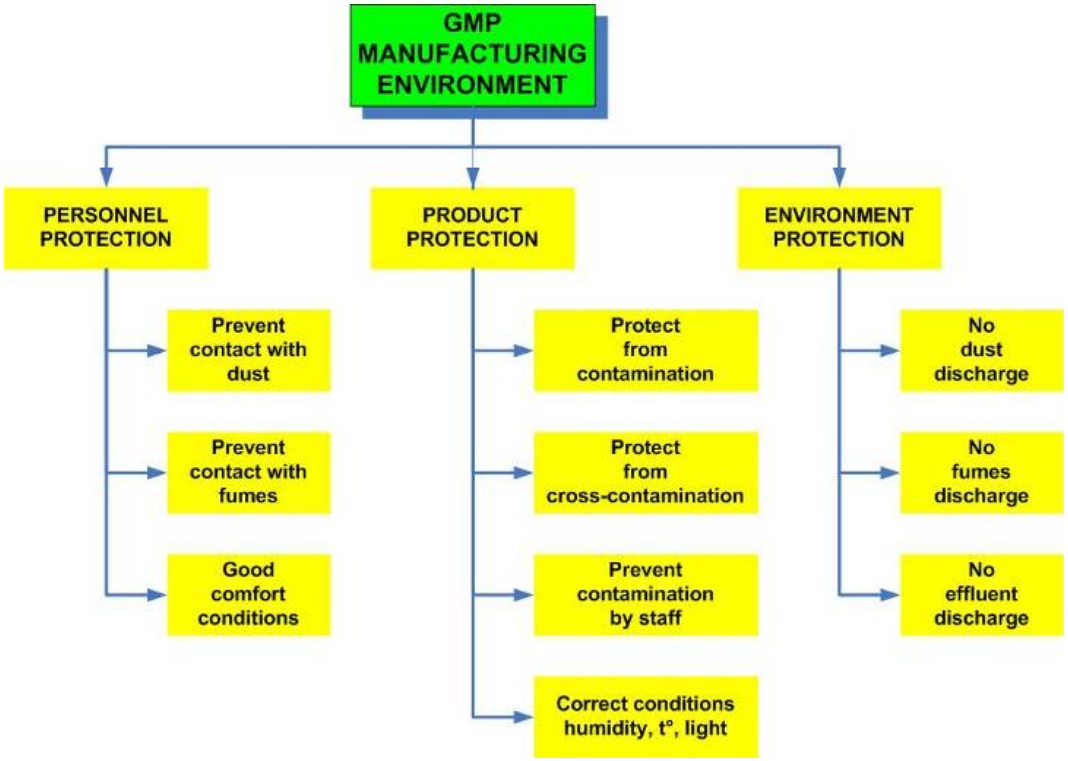
Part I – basic requirements for medicinal products (chapter 1-9)

Annexes: 1-19 (annex 18 → Part II

annex 20 → Part III)

Annex 1 – manufacture of sterile medicinal products

1. PRINCIPI BASE DELL'ANNEX 1



Punti critici:

- Struttura / impianti
- Lay out / materiali
- Manutenzione / pulizia
- Personale / organigramma
- Qualifica / addestramento
- Convalide
- Controlli in process
- Specifiche: delle materie prime, di process, di rilascio, di stasbilità
- Autoispezioni

1. PRINCIPI BASE DELL'ANNEX 1

EU-GMP, annex 1: principle

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination and of particulate and pyrogen contamination

EU-GMP, annex 1: general

The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and material

1. PRINCIPI BASE DELL'ANNEX 1

Cause	Prevenzione
ambiente	progettazione, lay-out, HVAC, flussi personale/materiali, pulizia, manutenzione
personale	indumenti, comportamento, igiene, addestramento, lay-out spogliatoi, POS
processo produttivo	stoccaggio / manipolazione materiali, contenimento, LAF, RABS

1. Principi base dell'annex 1
2. **Requisiti strutturali**
3. Monitoraggio ambientale
4. Convalida HVAC
5. Deviazioni ricorrenti (sterili)
6. Conclusioni

2. REQUISITI STRUTTURALI

2. REQUISITI STRUTTURALI

All exposed surfaces should be smooth, impervious and unbroken ...

... there should be no uncleanable recesses and a minimim of projecting ledges, shelves, cupboards and equipment ... sliding doors may be undesirable ...

False ceiling should be sealed ...

Pipes and ducts and other utilities should be installed so that they do not create recesses ...

Sinks and drains should be prohibited in grade A/B areas ...

… Both airlock doors should not be opened simultaneously ...

2. REQUISITI STRUTTURALI

What is a clean room?

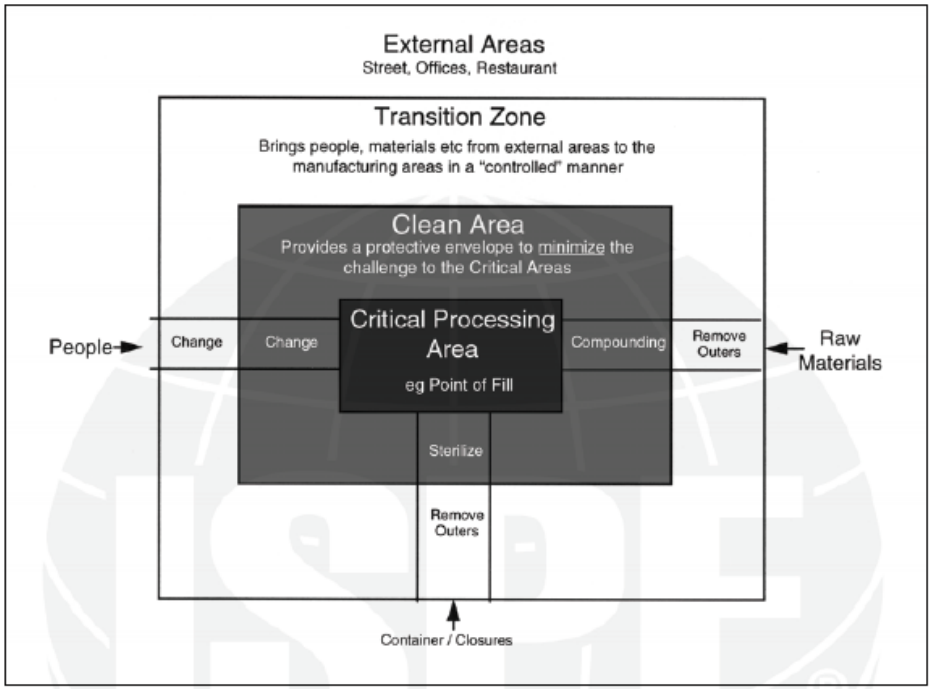
A clean room is a closed room supplied with “filtered (purified) air” in which the particulate and bacterial contamination concentration is below a specified level.

Special guidelines are in place for the room air technology, room furnishings, process equipment, personnel and the procedures.

Pharmaceutical products can be produced in “clean rooms” of different grades, depending on the type of product to be manufactured.

2. REQUISITI STRUTTURALI

Livelli di pulizia: gli ambienti a contaminazione controllati vengono realizzati secondo un modello “a cipolla”: dalla zona più esterna (non controllata o “nera”) verso aree “grigie” fino alle aree più critiche “bianche”



ISPE Baseline Pharmaceutical Guide: volume 3
Sterile Manufacturing facilities

2. REQUISITI STRUTTURALI

4.3 For the manufacture of sterile pharmaceutical preparations, four grades of clean areas are distinguished as follows:

- *grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are achieved by using a unidirectional airflow workstation. Unidirectional airflow systems should provide a homogeneous air speed of 0.36–0.54 m/s (guidance value) at a defined test position 15–30 cm below the terminal filter or air distributor system. The velocity at working level should not be less than 0.36 m/s. The uniformity and effectiveness of the unidirectional airflow should be demonstrated by undertaking airflow visualization tests;
- *grade B*: In aseptic preparation and filling, this is the background environment for the grade A zone;
- *grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products or carrying out activities during which the product is not directly exposed (i.e. aseptic connection with aseptic connectors and operations in a closed system).

2. REQUISITI STRUTTURALI

Grade	Examples of operations for terminally sterilised products
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.
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered
D	Handling of components after washing

2. REQUISITI STRUTTURALI

Contaminazione particellare

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0µm	0.5 µm	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

EU-GMP: annex 1

2. REQUISITI STRUTTURALI

Contaminazione microbiologica

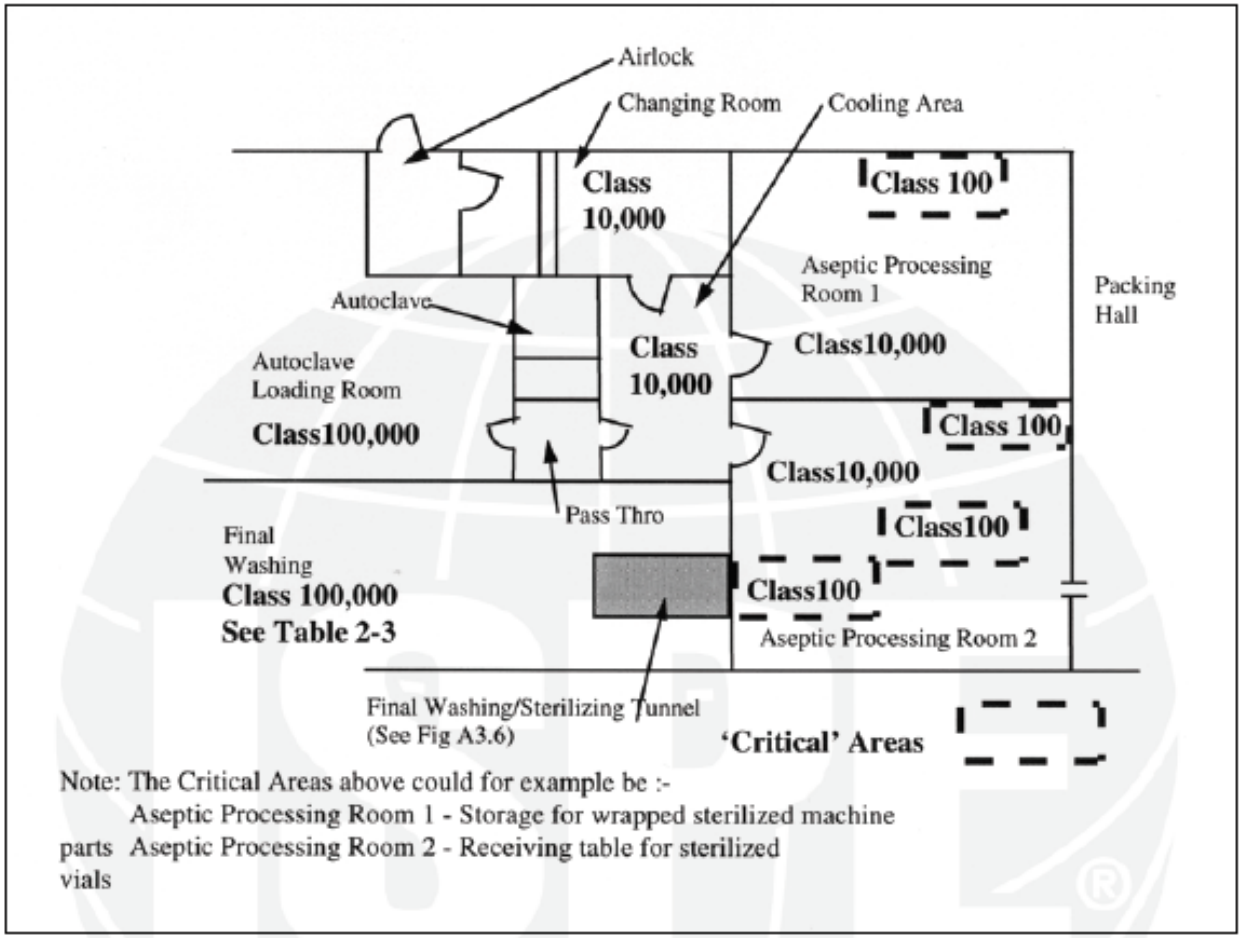
	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.

EU-GMP: annex 1

2. REQUISITI STRUTTURALI

Figure 5-1 Environmental Classifications for an Example Aseptic Facility Layout - Products for USA Supply

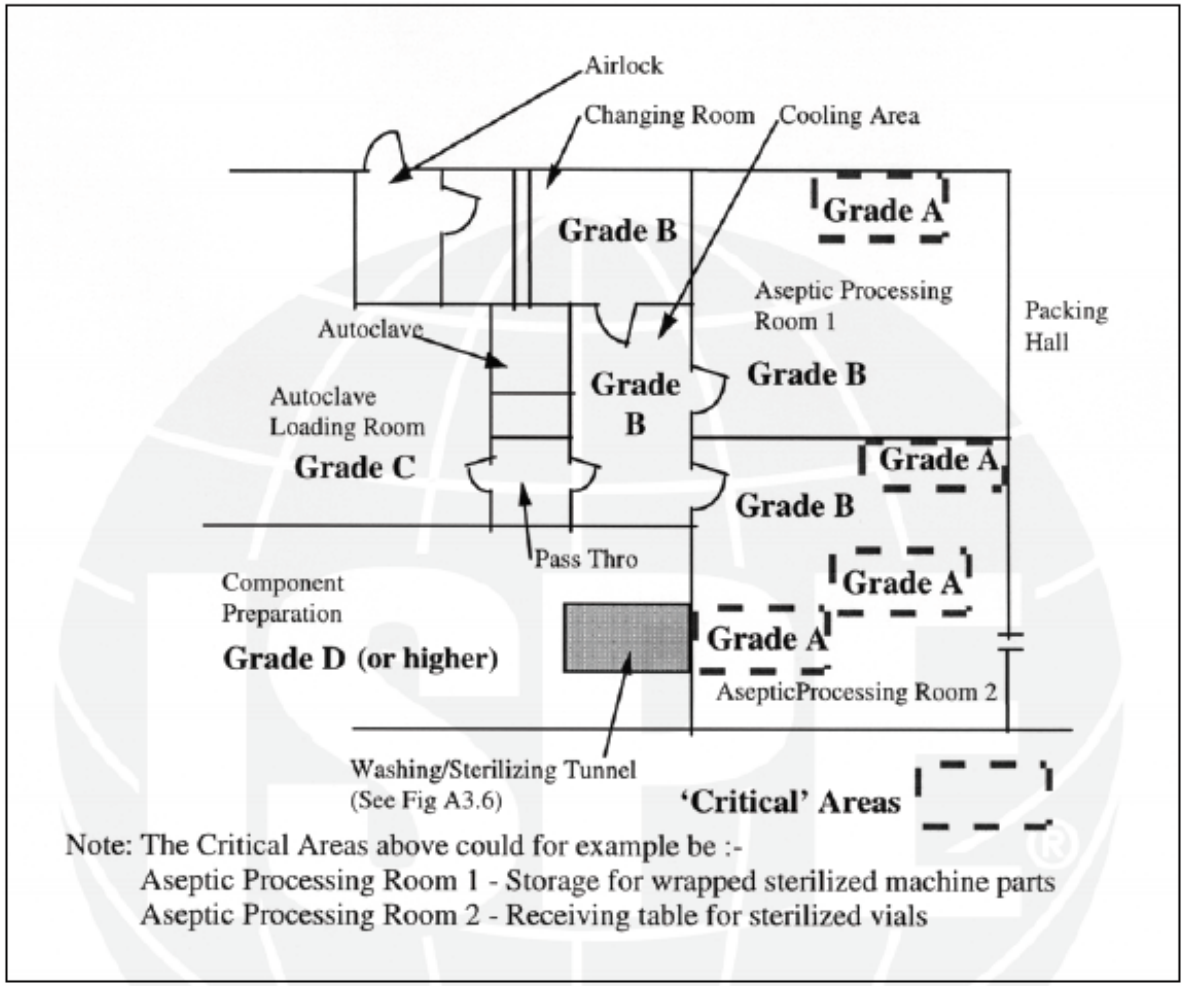


Note: The Critical Areas above could for example be :-
Aseptic Processing Room 1 - Storage for wrapped sterilized machine parts
Aseptic Processing Room 2 - Receiving table for sterilized vials

ISPE Volume 3

2. REQUISITI STRUTTURALI

Figure A2.1 **Typical Environmental Classifications for an Aseptic Facility Layout - Products For European Supply**



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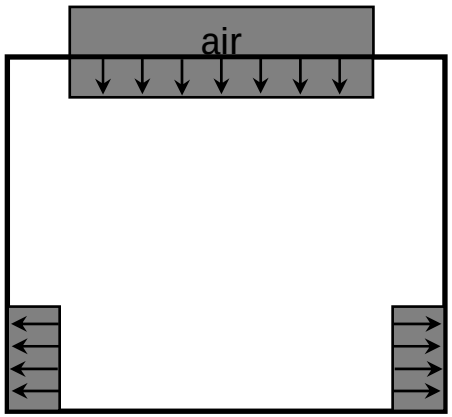
2. REQUISITI STRUTTURALI

Condizioni operative: as built, at rest (unmanned), in operation (manned)

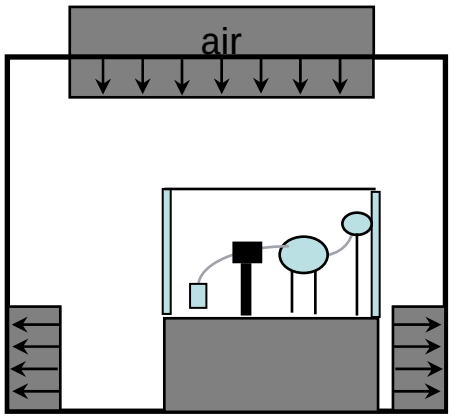
ISO 14644-1

EU-GMP annex 1

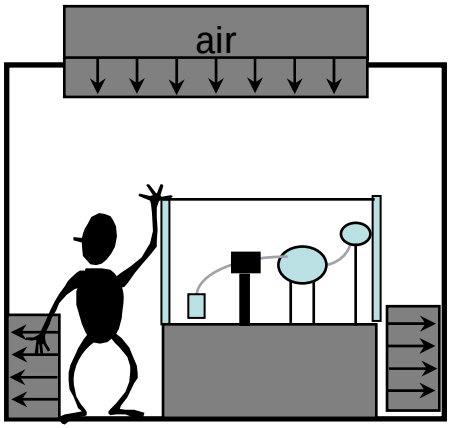
as built



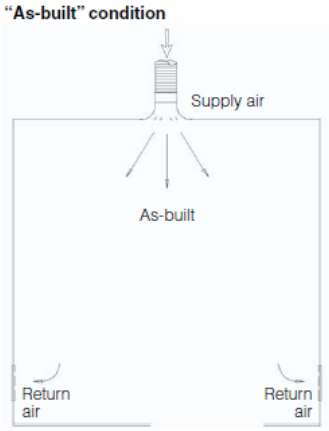
at rest



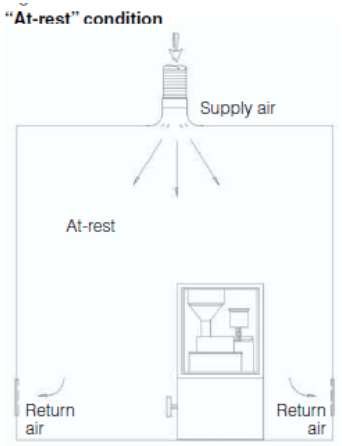
in operation



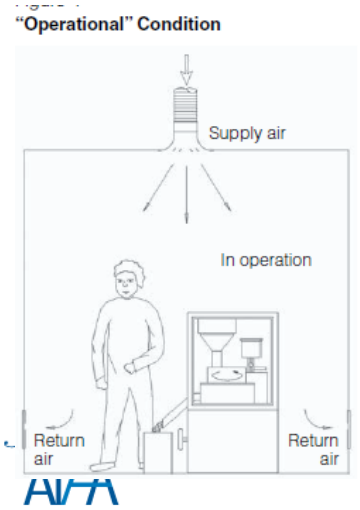
2. REQUISITI STRUTTURALI



Condizione in cui l'installazione è completa con tutti i servizi connessi e funzionanti, ma priva delle attrezzature. Dei materiali e del personale necessari alla produzione



Condizione in cui l'installazione è completa, con le attrezzature installate e funzionanti ma il personale è assente



Condizione in cui l'installazione è completa, con le attrezzature installate e funzionanti ed il personale presente

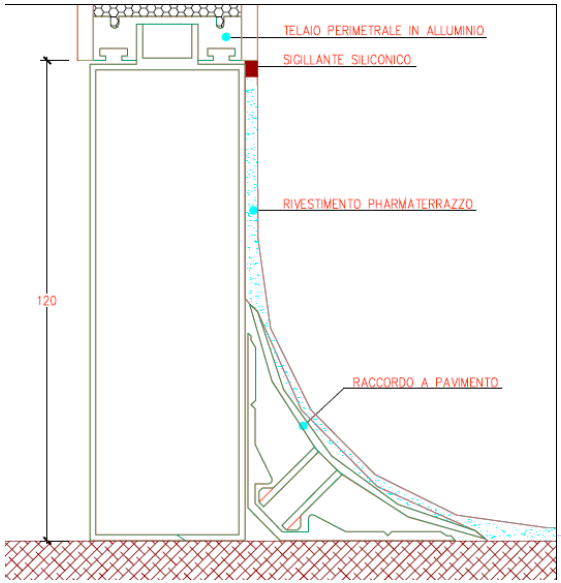
2. REQUISITI STRUTTURALI

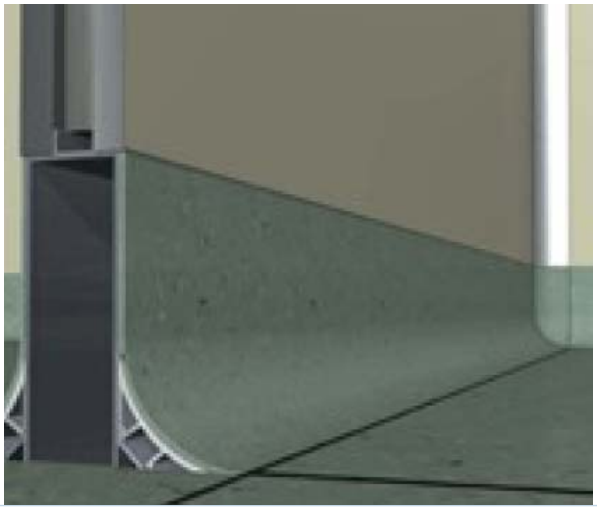
I materiali da costruzione non devono rilasciare particelle, devono avere superfici lisce e facilmente pulibili.

I raccordi devono essere realizzati con spigoli arrotondati; infissi e prese elettriche devono essere complanari con le pareti.

Tubazioni, cavi devono essere ridotti al minimo e possibilmente passare all'esterno dei locali (cavedi facilmente ispezionabili).

Realizzazione a "tenuta" dei locali





2. REQUISITI STRUTTURALI

tubazioni in acciaio

sgusci per facilità di pulizia

superfici lisce, impermeabili e senza rotture

componentistica ad incasso

2. REQUISITI STRUTTURALI

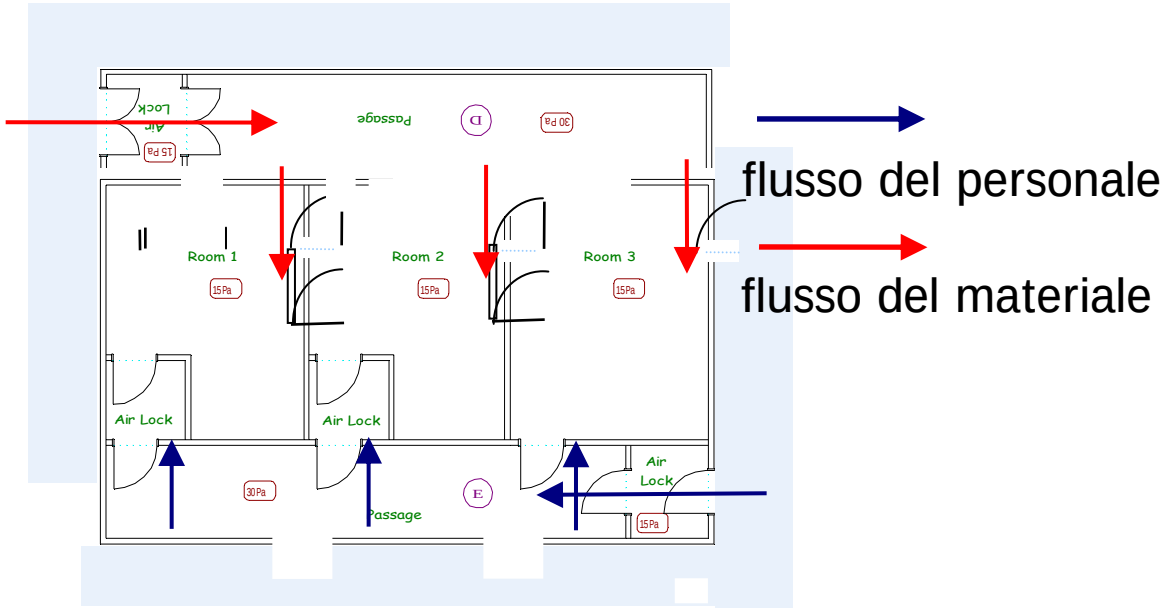
lampada ad incasso

spigoli arrotondati e
assenza di asperità

intelaiature / sigillature complanari

2. REQUISITI STRUTTURALI

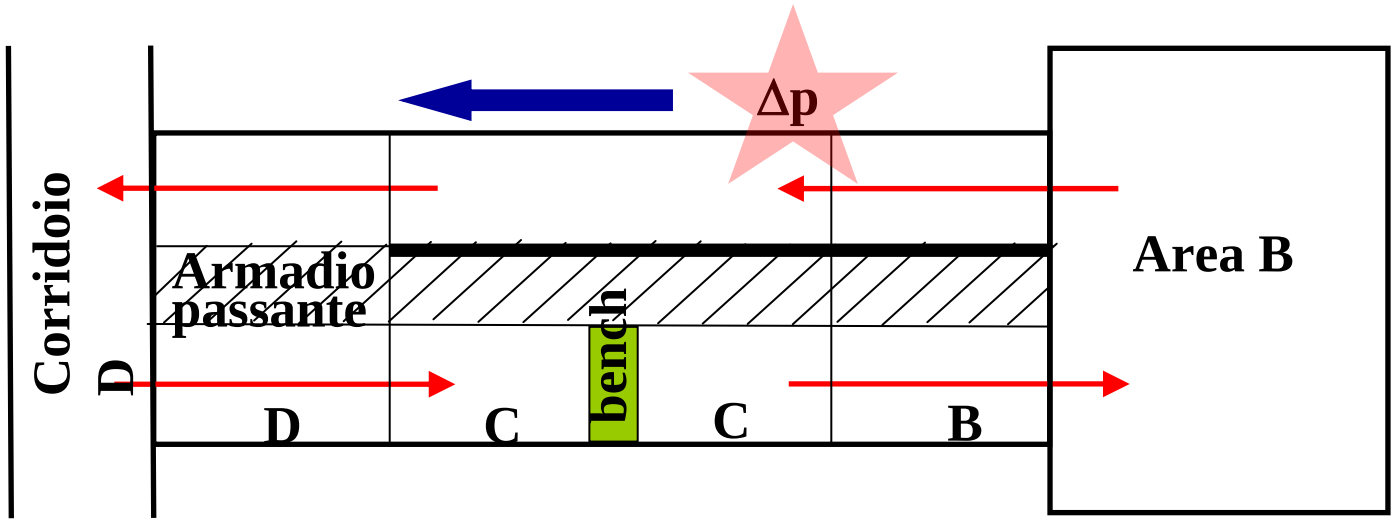
Premises should be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness level (EU-GMP 3.7)



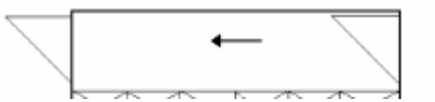
2. REQUISITI STRUTTURALI

Lo spogliatoio o air-lock traverso il quale il personale accede ai locali a contaminazione controllata deve avere la stessa classificazione del locale di produzione

Sono da evitare operazioni di vestizione (ingresso) e svestizione (uscita) in contemporanea: gli spogliatoi one way sono la soluzione ideale



2. REQUISITI STRUTTURALI



L’ air-lock utlizzato per il passaggio materiali tra una zona classificata e un’altra può non avere la stessa classificazione del locale al quale si accede (difficile dal punto di vista gestionale).

Sono da tener presenti i valori del clean-up (recovery time) e la non contemporaneità di apertura delle due porte ed un elevato valore di sovrappressione dalla zona critica.

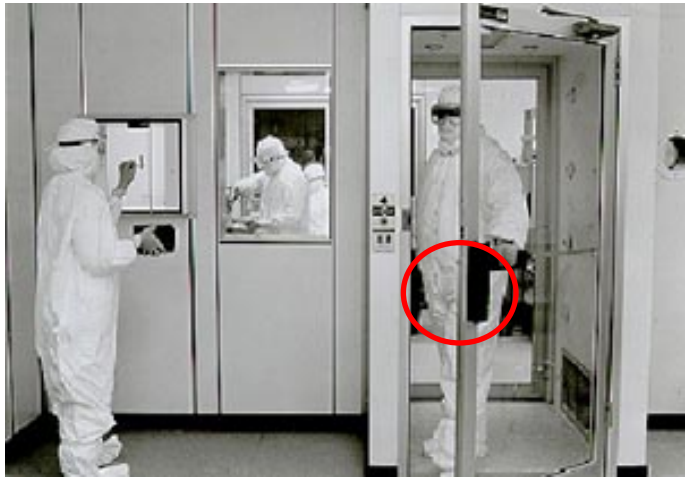
Ref. NCF Aprile 2011

L’equivoco dell’airlock alla luce delle normative vigenti

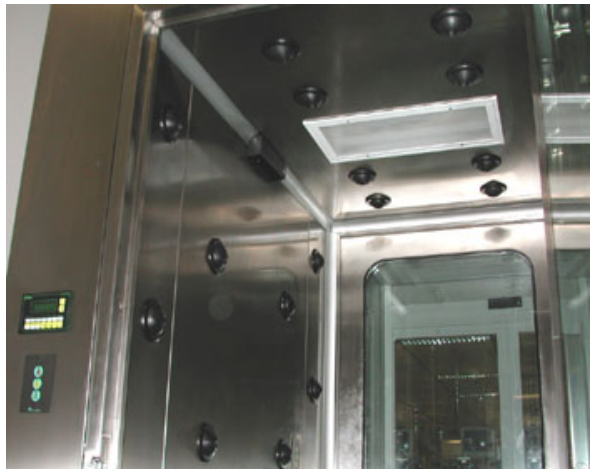
2. REQUISITI STRUTTURALI

Zone di transito per il personale

Air-lock (SAS) / interblocco



Doccia ad aria filtrata



SAS=system air shower

2. REQUISITI STRUTTURALI

Zone di transito per il materiale

Pass-box / interblocco

Autoclave a doppia porta

2. REQUISITI STRUTTURALI

Only the minimum number of personnel required should be present ... (*number of people is established in validation)*

All personnel ... should receive regular training ... (including hygiene and basic elements of microbiology) ... *and behaviour*

High standards of personal hygiene and cleanliness are essential ...

The clothing and its quality should be appropriate for the process and the grade of the working area ... Protective clothing should shed no fibers or particulate matter and retain particels shed byt the body

2. REQUISITI STRUTTURALI

Armadi aspirati

Atomizzatore per la disinfezione delle mani

Shoe-barrier

2. REQUISITI STRUTTURALI

Hair, beard and moustache should be covered

Appropriate shoes and overshoes should be worn

Sterilised, non-powdered rubber or plastic gloves should be worn

2. REQUISITI STRUTTURALI

Protective garments

Abbigliamento per produzioni con materiali altamente attivi (i.e. citotossici)

2. REQUISITI STRUTTURALI

The sanitisation of clean areas is particularly important

Disinfectants ... should be monitored for microbial contamination ...

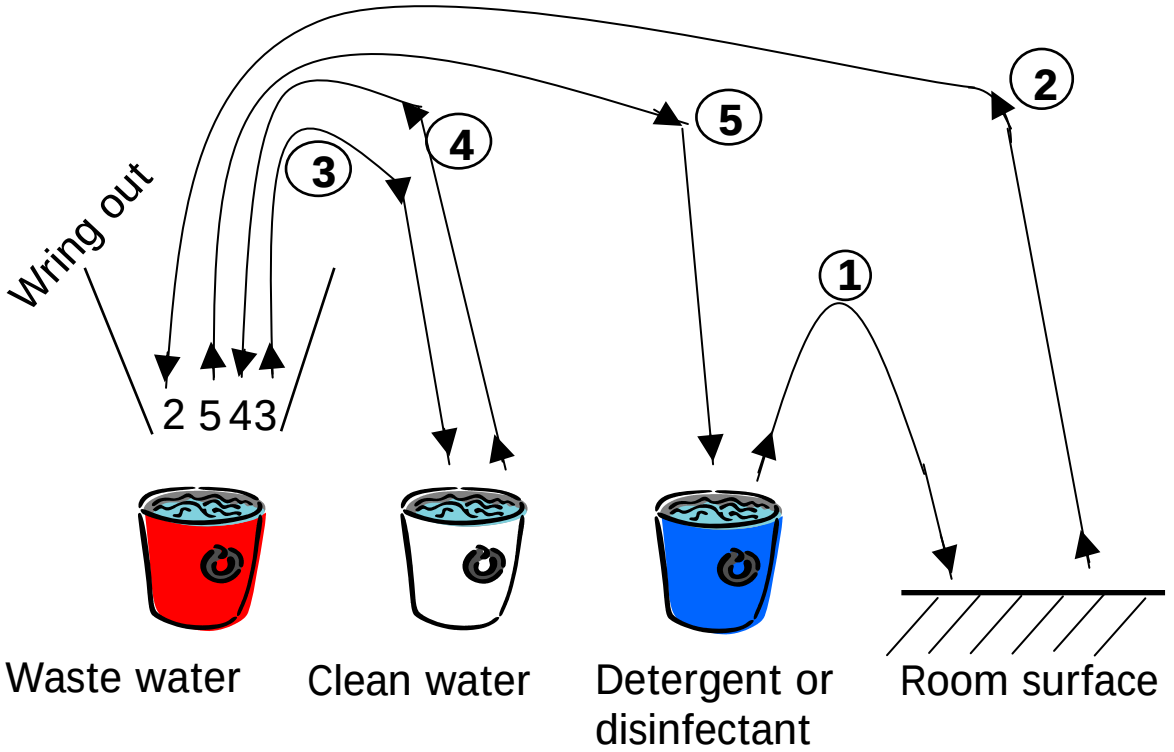
Disinfectants ... used in grade A and B should be sterile ...

... containers and materials liable to generate fibres should be minimised in clean areas

spazzoloni in acciaio inox e materiale che non genera fibre

2. REQUISITI STRUTTURALI

Metodo di lavaggio dei pavimenti con 3 recipienti:



2. REQUISITI STRUTTURALI

Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters* of an appropriate efficiency

Cappa (workstation)

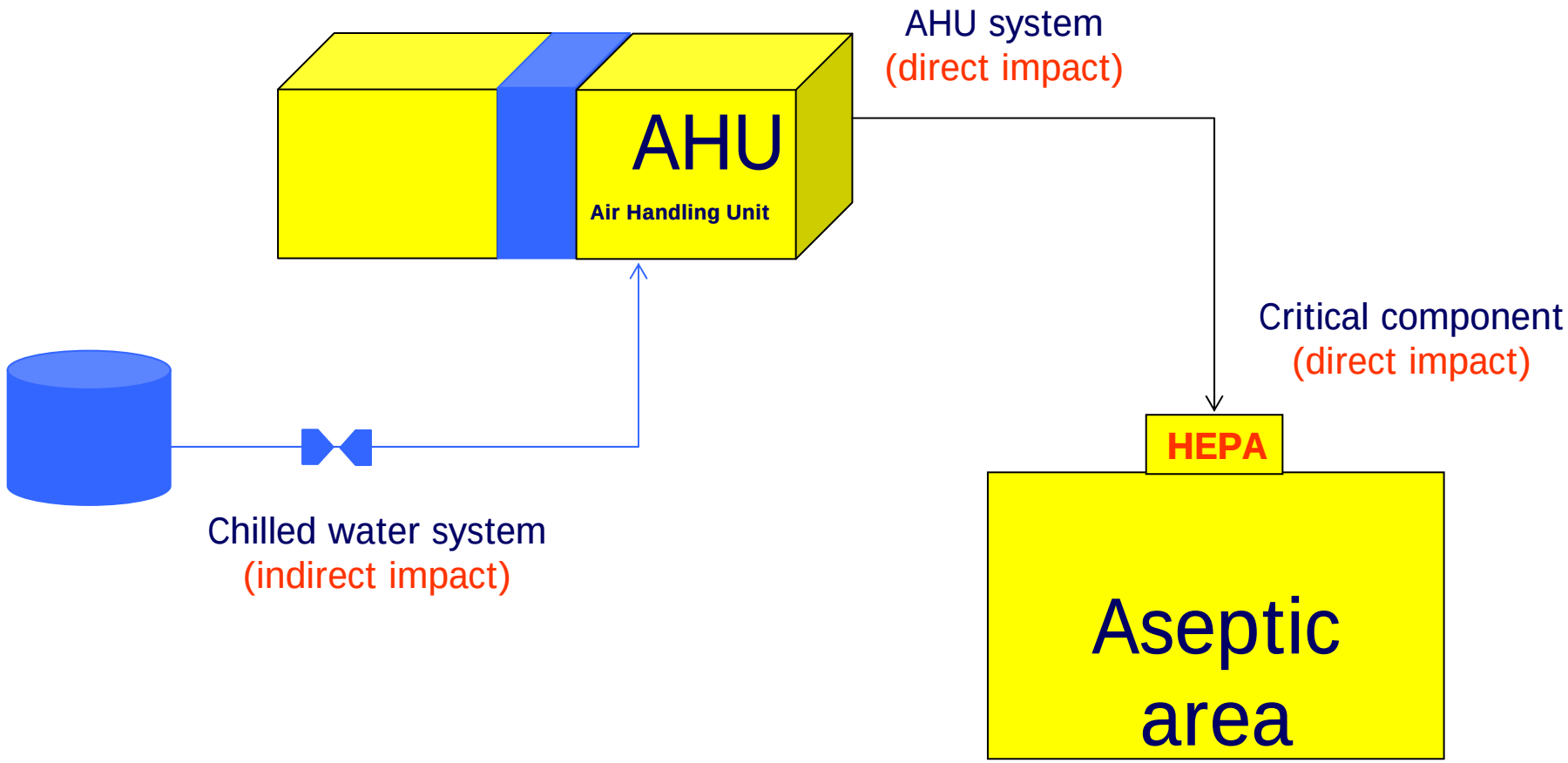
Cappa down-cross

Impianto HVAC

**filtri HEPA: high efficiency particulate air*

filtri ULPA: ultra low particulate air

2. REQUISITI STRUTTURALI



2. REQUISITI STRUTTURALI

Utilities: GMP direct Impact

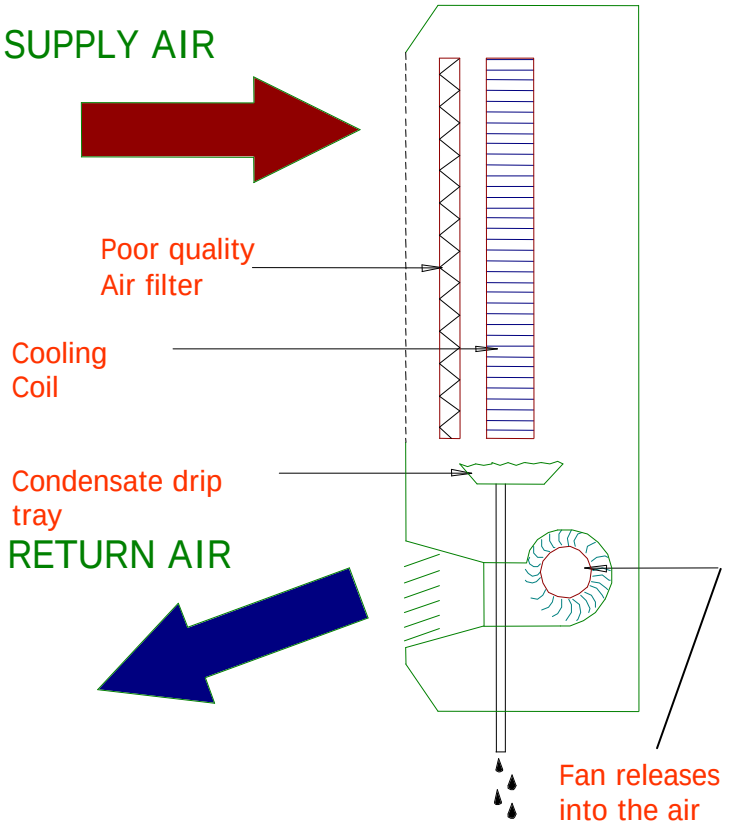
Purified water
WFI
HVAC to clean rooms
Gasses for production
CIP/SIP
Environmental monitoring
Etc.

Utilities: GMP no direct Impact

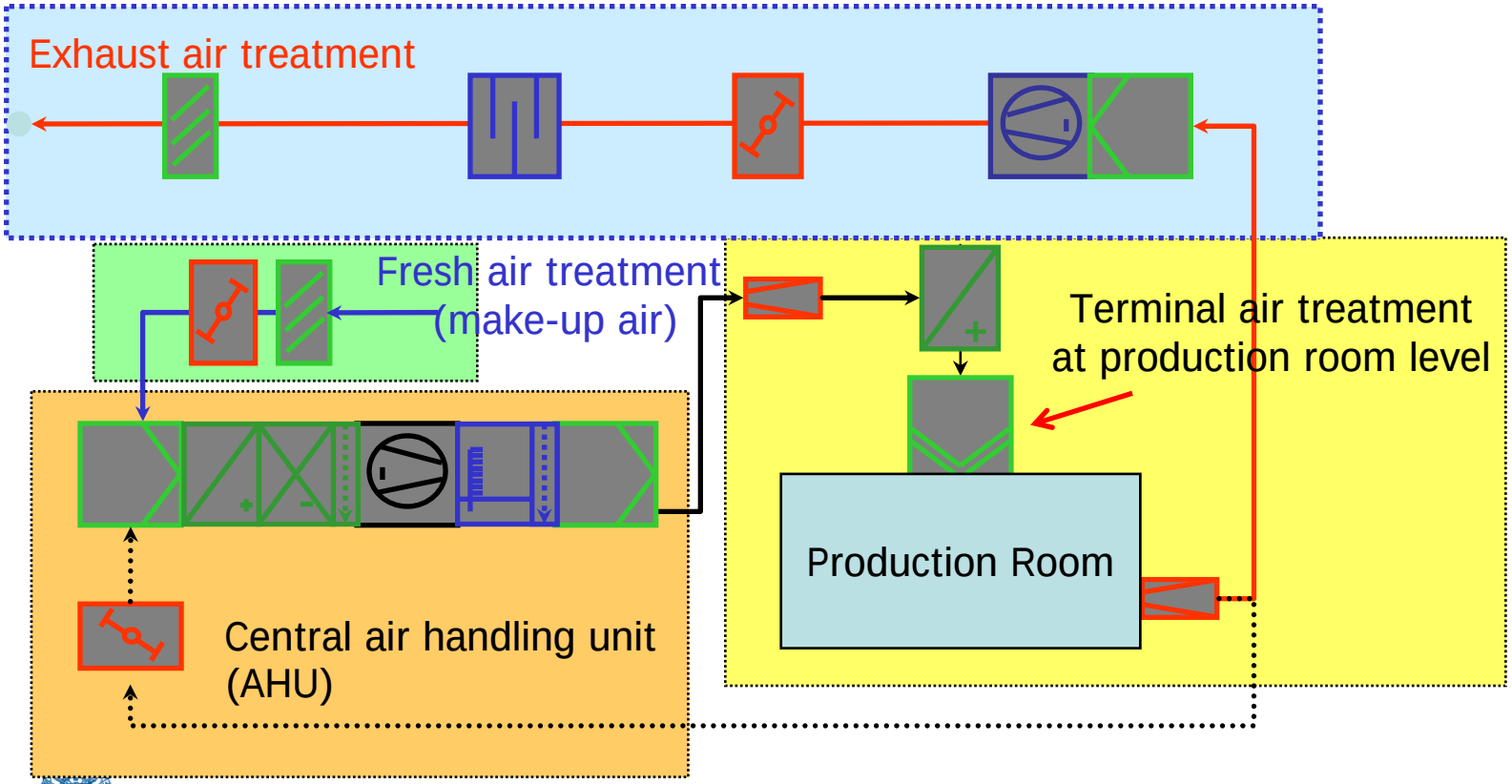
Heating systems
Potable water
Fire systems
Effluent treatment
General HVAC
Lighting
Cooling water
Etc.

2. REQUISITI STRUTTURALI

Air handling systems (poor design):



Air handling systems (good design):



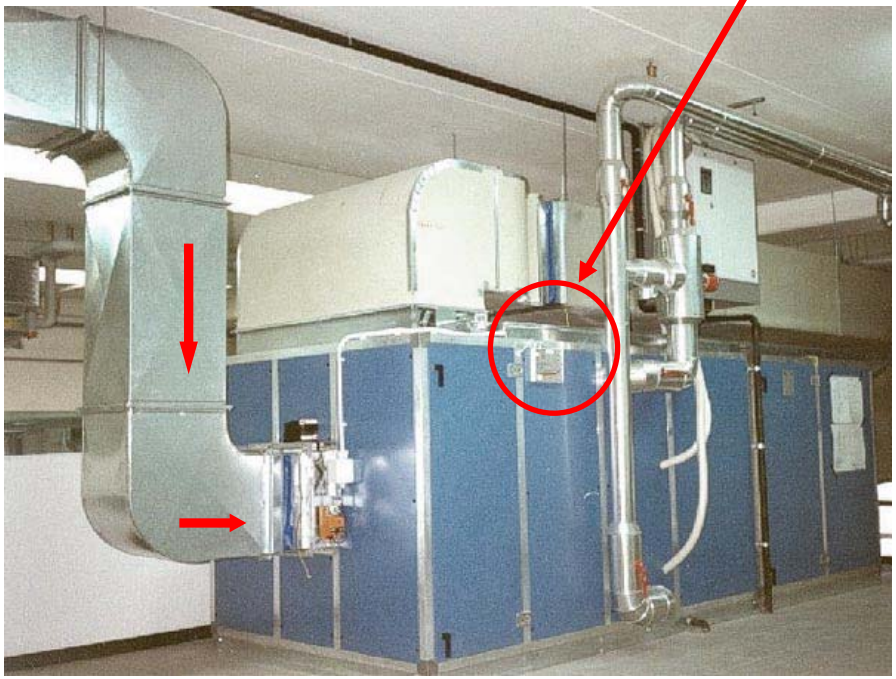
2. REQUISITI STRUTTURALI

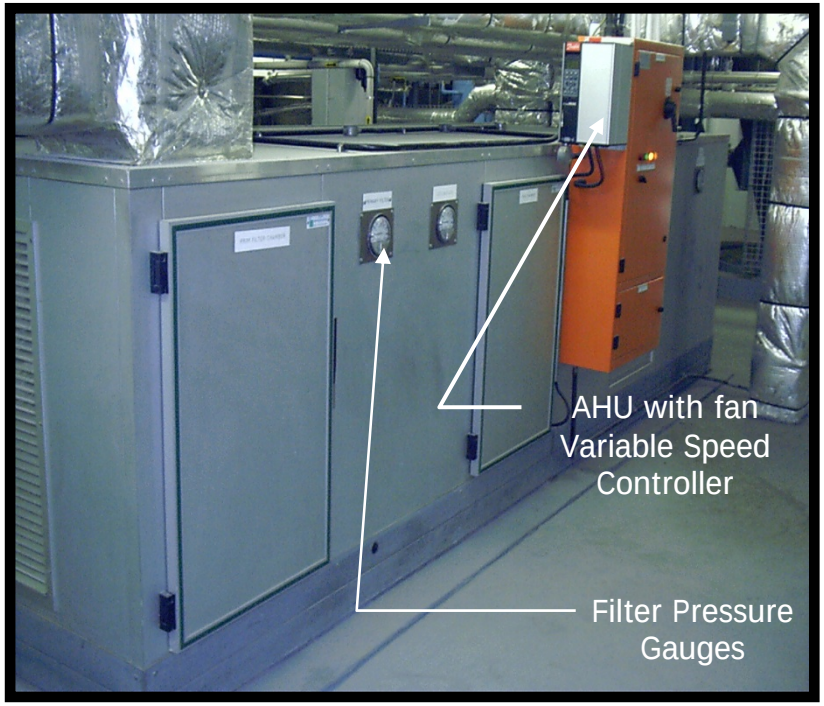
Air Handling Unit: fresh/make-up air is filtered through the outside air assembly (left) featuring easy to replace high efficiency pre-filters, which is ducted to packaged air conditioning units (right).

Dominant and seasonal wind direction should be taken into account when positioning exhaust and supply points.

2. REQUISITI STRUTTURALI

Liquid column manometer

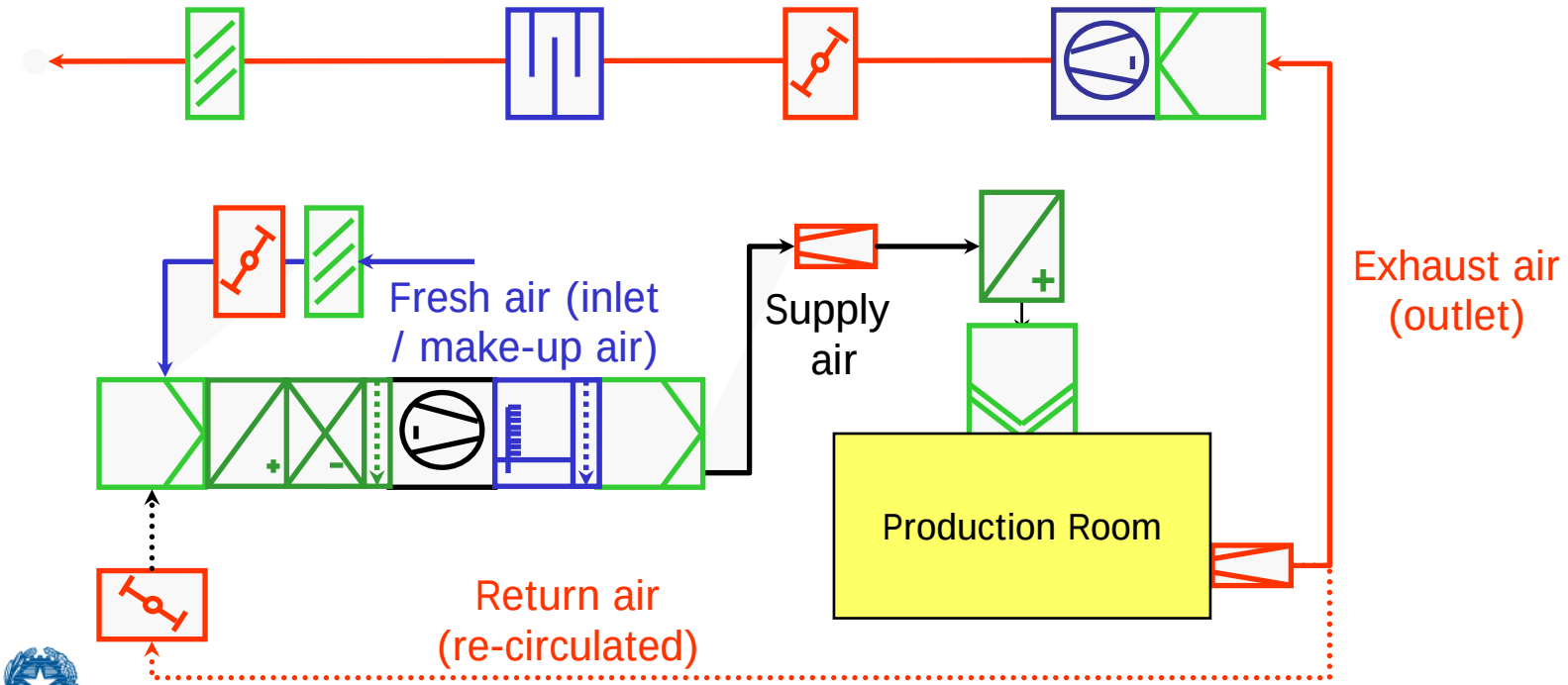




Air handling unit

2. REQUISITI STRUTTURALI

Air types: fresh, supply, return, exhaust air



2. REQUISITI STRUTTURALI

Characteristics of air handling system:

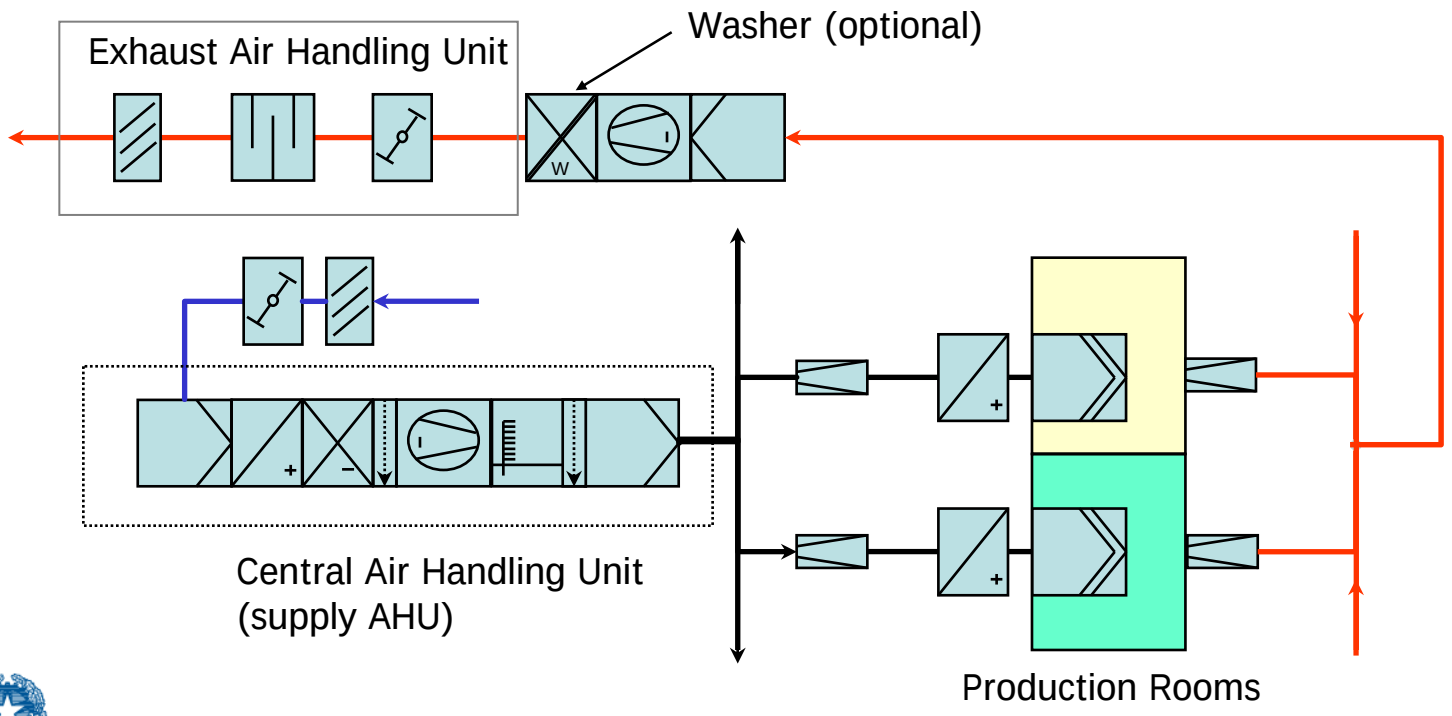
- 100% fresh air versus air re-circulation,
- local extraction system (de-duster, canister),
- position return air system (low-wall air returns),
- room grade or air cleanliness (air change, pressure differentials),
- turbulent or uni-directional airflows (air flow patterns),
- filters position (terminal filters).

2. REQUISITI STRUTTURALI

- Full fresh air system (100% outside air supply):
  - It is used in a facility dealing with toxic products where re-circulation of air with contaminants should be avoided.
  - The required degree of filtration of the exhaust air depends on the exhaust air contaminants and local environmental regulations.
  - Energy recovery, via crossover plate heat exchangers and water coil heat exchangers, may be used in a multiproduct facilities.
  - The potential for air leakage between the supply air and exhaust air should be prevented. The relative pressures between supply and exhaust air system should be such that the exhaust air system operates at a lower pressure than the supply system.

2. REQUISITI STRUTTURALI

Ventilation with 100% fresh air (no air re-circulation):

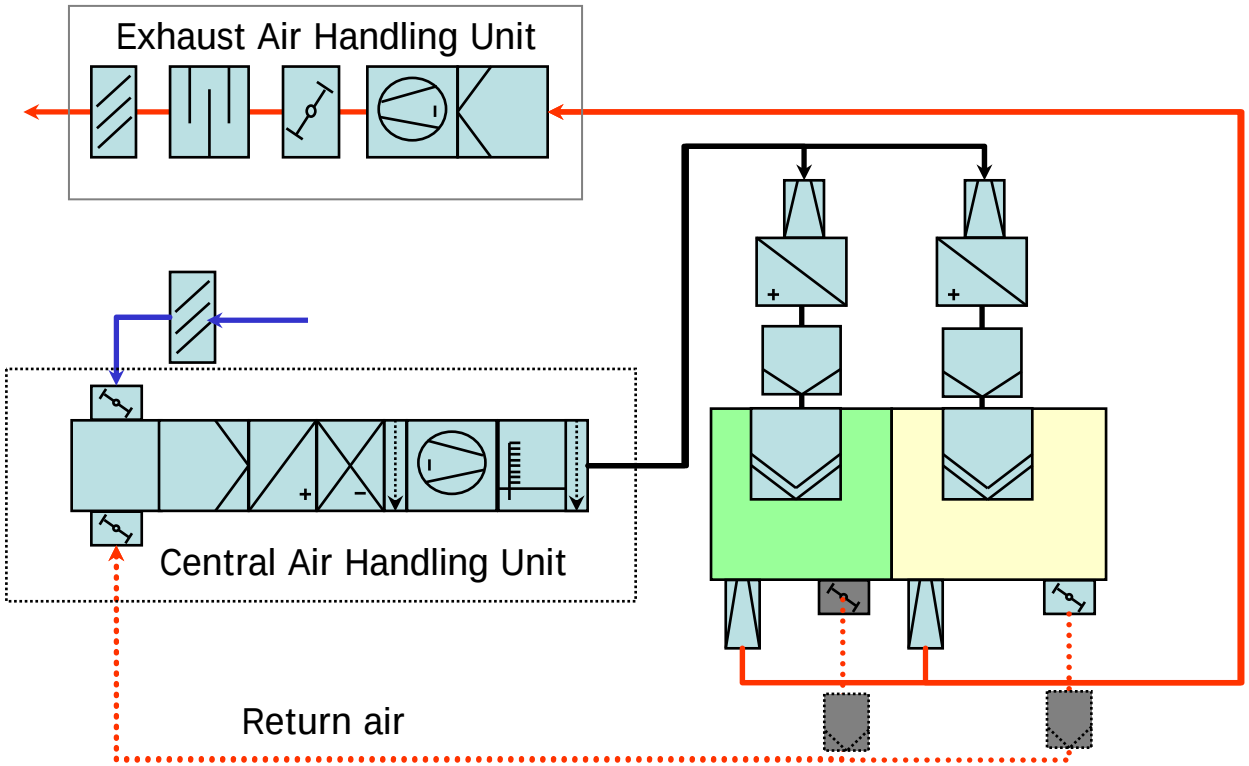


2. REQUISITI STRUTTURALI

- Re-circulation system:
  - It may be acceptable to use re-circulated air provided that HEPA filters are installed in the supply air stream to remove contaminants and prevent cross-contamination (HEPA filters should have a classification of H13).
  - HEPA filters may not be required where the air-handling system is serving a single product facility and there is evidence that cross-contamination would not be possible.
  - HEPA filters may be located in the air-handling unit or placed terminally.
  - Air containing dust from highly toxic processes should never be re-circulated to the HVAC system.
  - The share of “fresh/external air” and “recirculating air” can be fixed or variable according to the external temperature, to the number of people working.

2. REQUISITI STRUTTURALI

Ventilation with re-circulated air + make-up air:



2. REQUISITI STRUTTURALI

La filtrazione dell'aria per classi A, B e C deve avvenire attraverso filtri HEPA terminali di grado H14 (>99,995%).

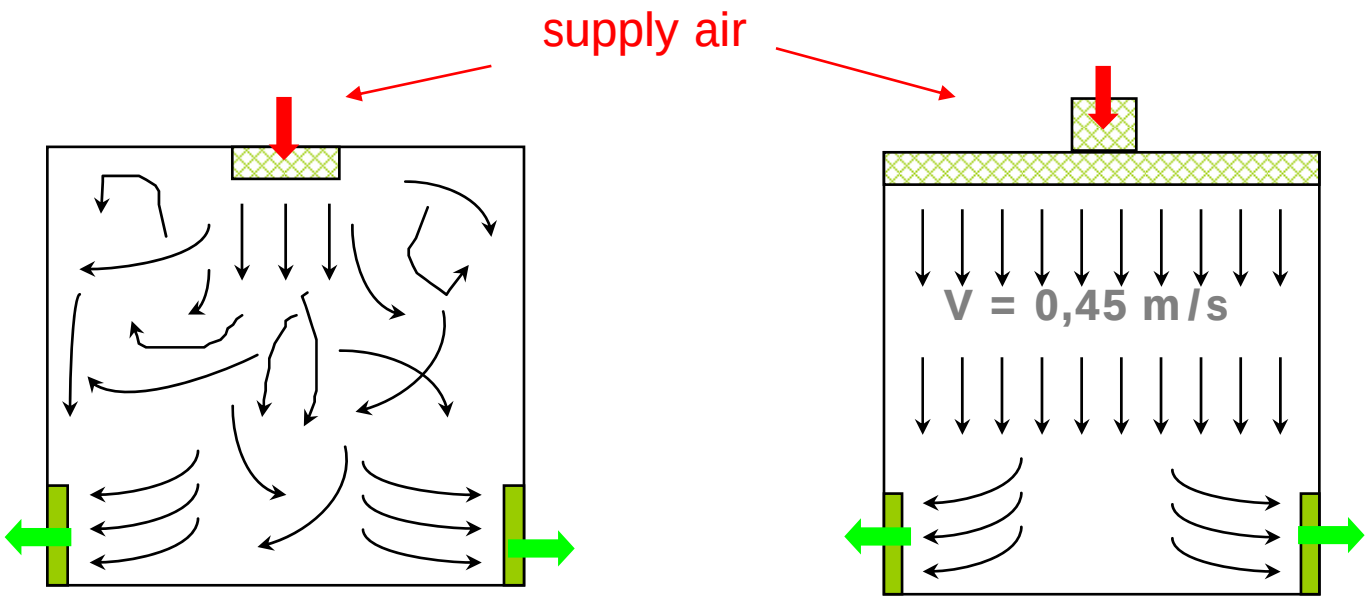
Per le classi D è consigliabile installare filtri HEPA terminali per proteggere le classi più pulite.

I filtri terminali di immissione aria filtrata devono essere sigillati con il controsoffitto del locale.

Nelle riprese "non" sono richiesti dalle EU-GMP filtri HEPA (eccetto se presenti prodotti tossici). La normale pratica industriale usa filtri HEPA nel return-grill per prevenire la contaminazione dei condotti delle strutture multi-purpose.

2. REQUISITI STRUTTURALI

Air flow pattern: internal contaminants should be controlled by dilution or by displacement airflow



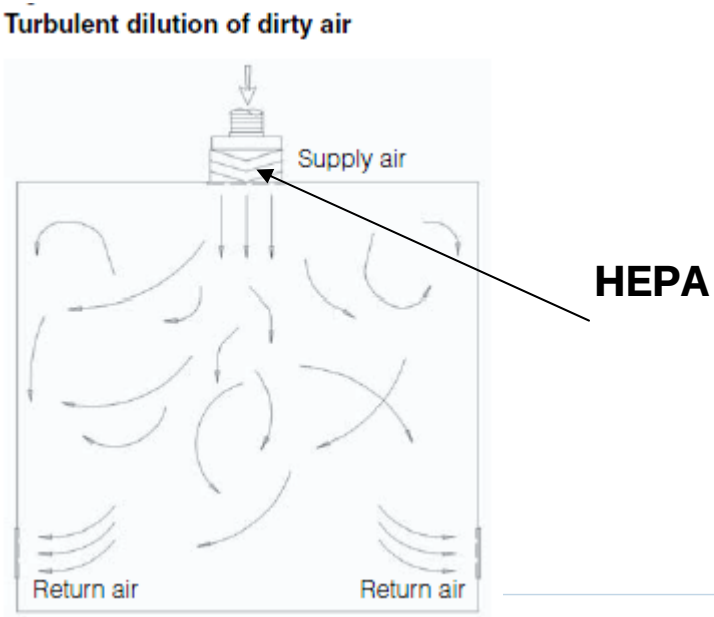
Turbulent (dilution of dirty air)

Laminar / unidirectional (displacement of dirty air)

2. REQUISITI STRUTTURALI

Flusso turbolento:

Il sistema di immissione genera nell'ambiente una turbolenza tale da assicurare la massima omogeneizzazione della concentrazione dei contaminanti tale da ottenere una diluizione inizialmente presente e/o generata da sorgenti interne al locale: la diluizione è tanto più efficace quanto maggiore è la portata di aria immessa nel locale (numero di ricambi orari)

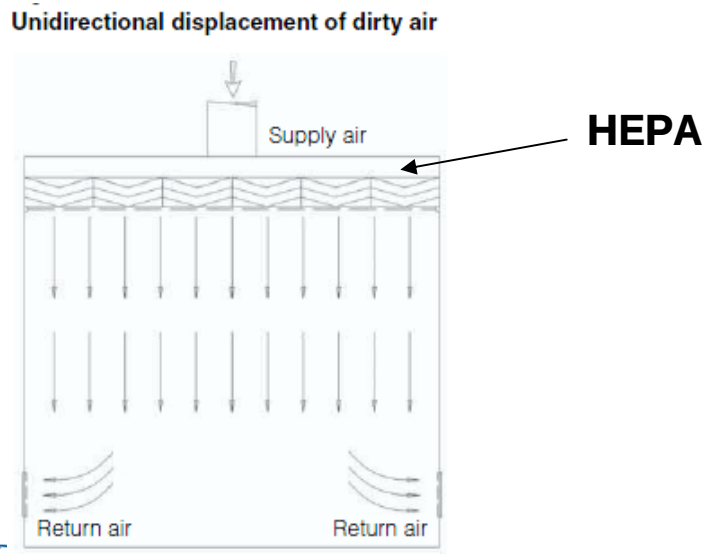


2. REQUISITI STRUTTURALI

Flusso laminare:

Il flusso d'aria viene immesso in modo uniforme seguendo una unica direzione nell'ambiente, con linee di flusso parallele e con velocità tale (ca. 0.36-0.54 m/s oppure 0.45 m/sec ± 20%) da avere un'assenza di vorticosità.

I contaminanti vengono così trascinati lungo la direzione del flusso (lavaggio continuo).



2. REQUISITI STRUTTURALI

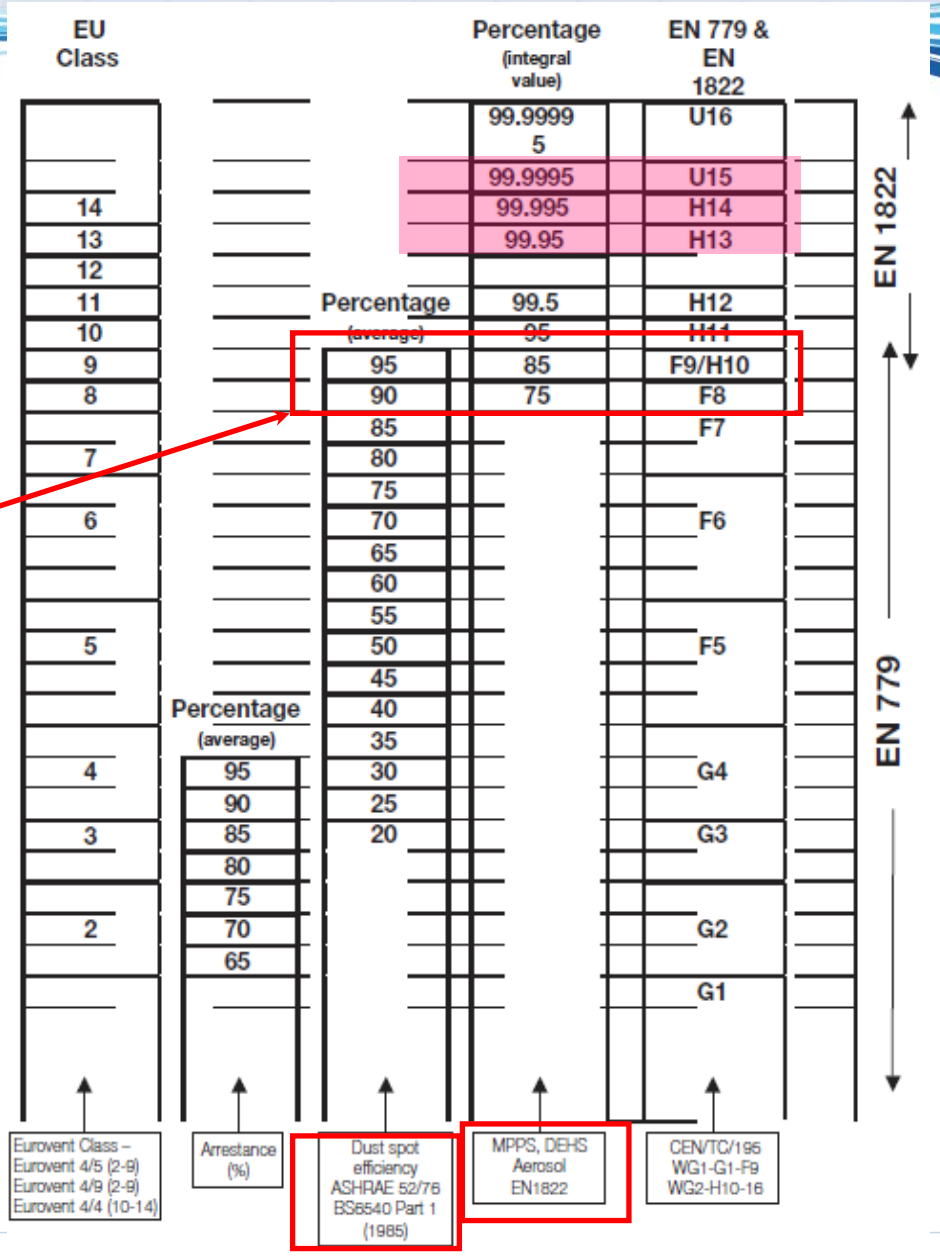
Filter classes:

they should always be linked to the standard test method because referring to actual filter efficiencies can be very misleading (as different test methods give results in a different value for the same filter) – *see comparison aside-*

EN European norm (euro norm)

EU European Union

(*by WHO guideline*)



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AIFA

2. REQUISITI STRUTTURALI

Table 5.4: Filter Comparisons – HEPA/ULPA

These comparisons of filter rating systems are only approximate as the test methods are different.

EU Type	EN 1822 HEPA/ULPA*		IEST Type (RP-CC001.4)	
Designation	Designation	Efficiency	Efficiency	Designation
EU 10	H10	85% @ MPPS		
EU 11	H11	95% @ MPPS		
EU 12	H12	99.5% @ MPPS		
			99.97% @ 0.3 mm**	A, B, E
EU 13	H13	99.95% @ MPPS	99.99% @ 0.3 mm**	C
EU 14	H14	99.995% @ MPPS	99.999% @ 0.3 mm**	D, K
	U15	99.9995% @ MPPS	99.999% @ 0.1 – 0.2 mm**	F
	U16	99.99995% @ MPPS	99.9999% @ 0.1 – 0.2 mm**	G
	U17	99.999995% @ MPPS		

*All EN 1822 tests at MPPS H = HEPA; U = ULPA
HEPAs = H10-H14, A, B, E, C, D, K; ULPA = U15-17, F, G
**All tested with thermally generated DOP aerosol (0.3 mm MMD; i.e., CMD is near MPPS). F, G and K type filters are tested at either 0.1 – 0.2 or 0.2 – 0.3 mm. K type filters are 99.995%.

(by ISPE guideline)

2. REQUISITI STRUTTURALI

Filter classes:

MPPS = minimum separation rate; the particle size with the highest penetration for a defined filter medium flow velocity is called the Most Penetration Particle Size (EN1822 uses single or discrete particle-counting instrument)

Table 1: Classification of HEPA and ULPA filters (extracted by EN 1822-1)

Filter class	Overall value		Local value[1)2)]	
	Efficiency (%)	Penetration (%)	Efficiency (%)	Penetration (%)
H 10	85	15	---	---
H 11	95	5	---	---
H 12	99,5	0,5	---	---
H 13	99,95	0,05	99,75	0,25
H 14	99,995	0,005	99,975	0,025
U 15	99,999 5	0,000 5	99,997 5	0,002 5
U 16	99,999 95	0,000 05	99,999 75	0,000 25
U 17	99,999 995	0,000 005	99,999 9	0,000 1

1) see 6.5.2 and prEN 1822-4
2) local values lower than those given in the table may be agreed between supplier and purchaser

Efficiency based on MPPS (Most Penetration Particle Size)

Overall efficiency: the efficiency, averaged over the whole superficial face area of a filter element under given operating conditions of the filter

Local efficiency: the efficiency, at a specific point of the filter element under given operating conditions of the filter

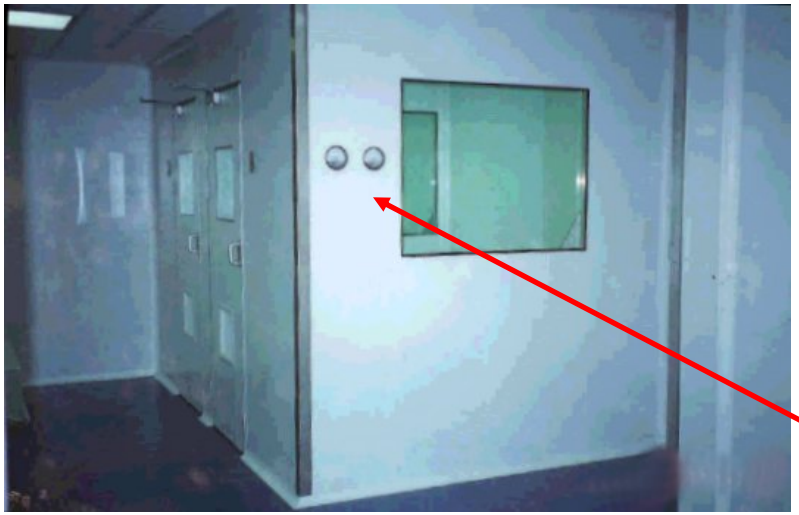
Pressure Cascade:

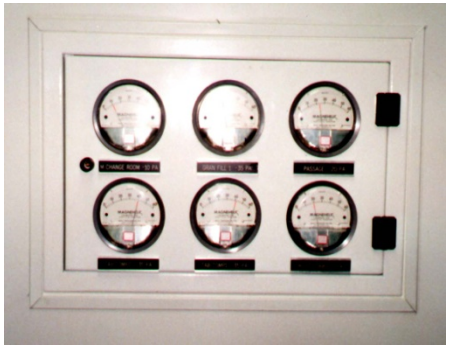
A process whereby air flows from the cleanest area, which is maintained at the highest pressure to a less clean area at a lower pressure in order to:

- prevent cross-contamination between areas;
- prevent ingress of contaminants from outside;
- separate areas of different cleanliness.

2. REQUISITI STRUTTURALI

The pressure differential over the doorway is measured with a magnehelic gauge or liquid manometer.

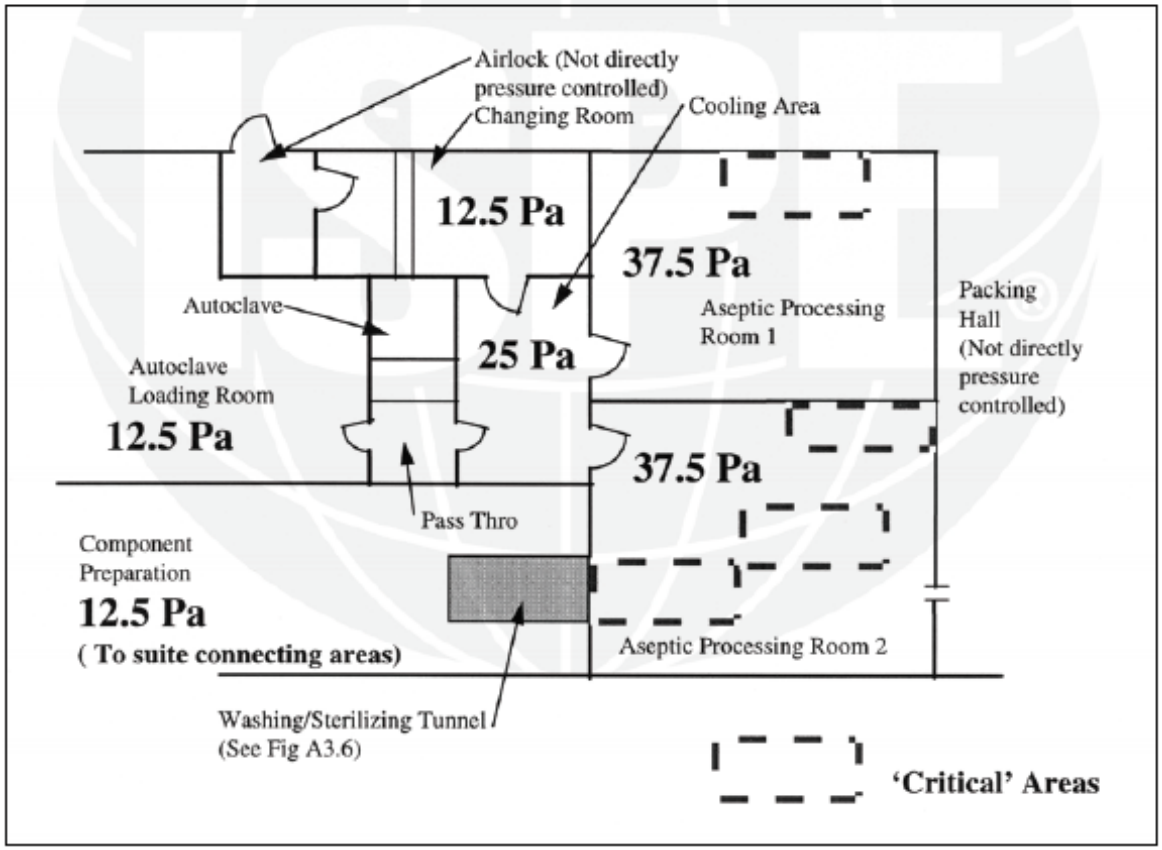




Permanently installed gauges: indication panel.

2. REQUISITI STRUTTURALI

Figure 5-4 Resultant Pressure Cascade for an Example Aseptic Facility Layout

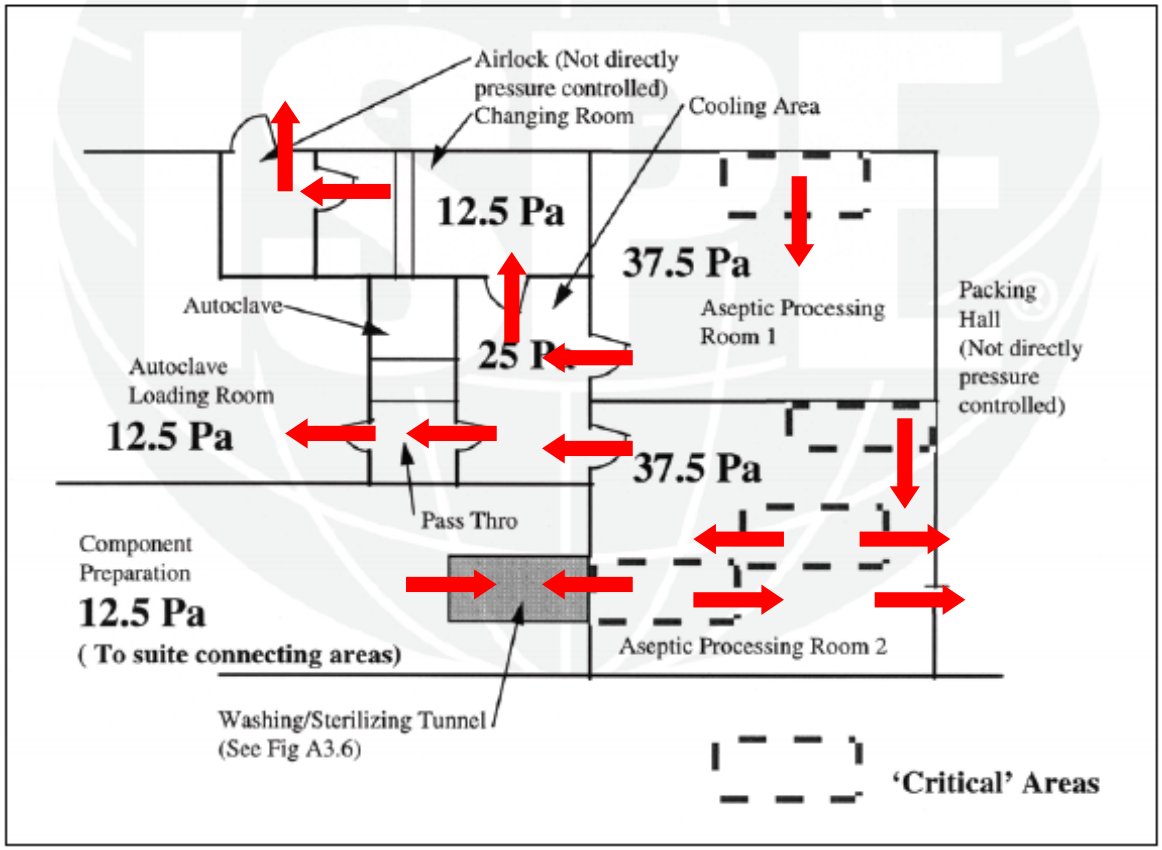


ISPE Volume 3

2. REQUISITI STRUTTURALI

air flows

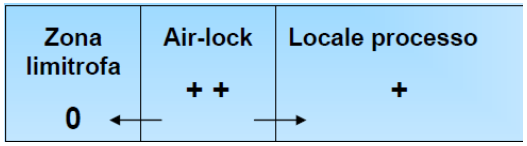
Figure 5-4 Resultant Pressure Cascade for an Example Aseptic Facility Layout



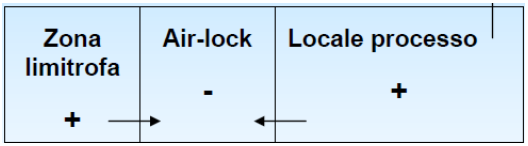
ISPE Volume 3

2. REQUISITI STRUTTURALI

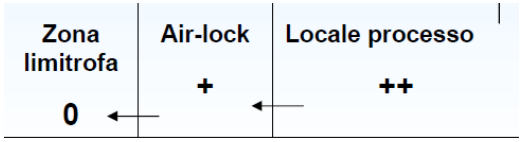
Per mantenere le condizioni di pulizia esistenti, per evitare cross-contamination e per proteggere l'operatore si mantiene un differenziale di pressione (valore consigliato tra classi differenti ΔP=10-15 Pascal)



Sistema a "bolla d'aria" (bubble)



Sistema a "pozzo" (sink)

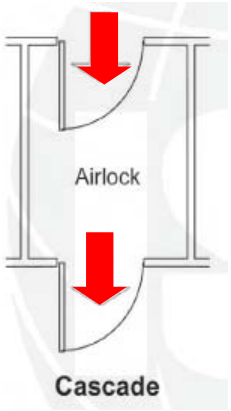


Sistema a "cascata" (cascade)

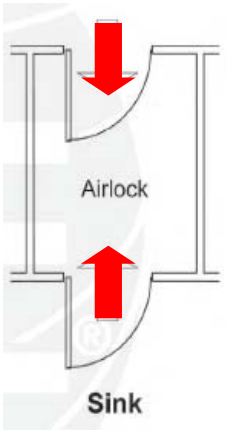
2. REQUISITI STRUTTURALI

Pressure Cascade: airlocks

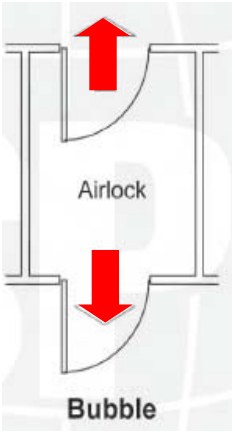
Three scenarios: cascade airlock, sink airlock and bubble airlock



High pressure on one side of the airlock and low pressure on the other.



Low pressure inside the airlock and high pressure on both outer sides.

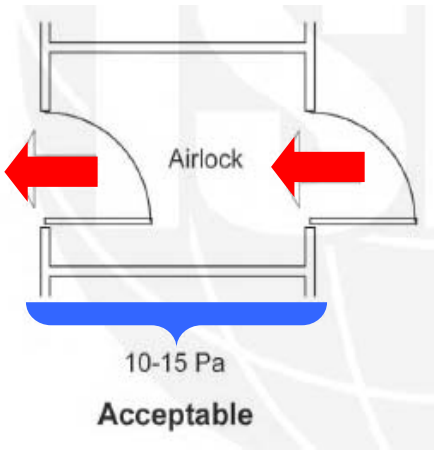


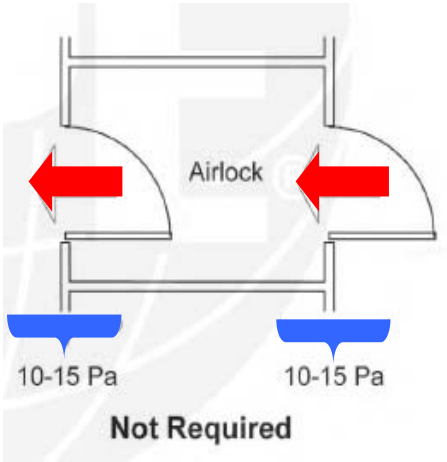
High pressure inside the airlock and low pressure on both outer sides.

2. REQUISITI STRUTTURALI

Differenziali di pressione attraverso gli airlocks

La guidalinea ISPE HVAC suggerisce che il differenziale di pressione vien misurato attraverso l'interlock "in toto" e non attraverso le singole porte.





2. REQUISITI STRUTTURALI

The materials and personnel have to access into clean areas through air locks: “material air lock (or pass box) ” and “changing rooms (or gowning rooms)”.

Air locks must always fulfill the relevant requirements in terms of minimizing microbiological and particulate contamination.

Air locks should have the same cleanliness grade as the work area.

Only one door can be opened at a time.

Ventilation and pressure differential are required.

Ventilation in cupboards used for the storage of clothes should be ventilated.

2. REQUISITI STRUTTURALI

The personnel lock is generally divided by a step-over-bench (or sit-over bench) that divides the areas corresponding to the adjacent cleanliness grades.

The design for personnel entering in a grade B class is:

- air lock in cleanliness grade non classified / D;
- air lock in cleanliness grade D / C;
- air lock in cleanliness grade C / B.

2. REQUISITI STRUTTURALI

The materials entering a high cleanliness grade via the air-lock must be cleaned and disinfected appropriately.

A residence time in the lock following the disinfection has to be established (validation should take into account the clean-up period).

1. Principi base dell'annex 1
2. Requisiti strutturali
3. **Monitoraggio ambientale**
4. Convalida HVAC
5. Deviazioni ricorrenti (sterili)
6. Conclusioni

3. MONITORAGGIO AMBIENTALE

8.2.17 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that should be qualified may include:

— temperature
— relative humidity
— supply air quantities for all diffusers
— return air or exhaust air quantities
— room air change rates
— room pressures (pressure differentials)
— room airflow patterns
— unidirectional flow velocities
— containment system velocities
— HEPA filter penetration tests
— room particle counts
— room clean-up rates
— microbiological air and surface counts where appropriate
— operation of de-dusting
— warning/alarm systems where applicable.

Fonte: WHO TR 937

3. MONITORAGGIO AMBIENTALE

- temperature (19-25 °C),
- relative humidity (40-65 % RH),
- supply air quantities for all diffusers,
- return air or exhaust air quantities,
- room air change rates (20 ac / hour is generally accepted for controlled areas),
- room pressures (pressure differential of 10-15 Pa as guidance value between different classes),
- room airflow patterns (smoke studies),
- unidirectional airflow velocities (range of 0.36-0.54 m/s at the working position in open clean room applications is given as guidance value),
- HEPA filter penetration tests (> 0,01 % leak; upstream concentration: 20 μg/l or 20 mg/m^3),
- room particle counts,
- room recovery (the particle limits given in the table for “at rest” state should be achieved after a short “clean up” period of 15-20 minutes – guidance value),
- microbiological air and surface counts (where appropriate),
- warning / alarm systems, where applicable.

3. MONITORAGGIO AMBIENTALE

Part A: schedule of tests to demonstrate compliance (for reference purposes only)

Schedule of tests to demonstrate continuing compliance			
Test parameter	Clean room class	Max. time interval	Test procedure
Particle count test (Verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5*
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13*
Airflow velocity (To verify laminar flow or containment conditions)	All Classes	12 Months	Air velocities for containment systems and laminar flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4*

Fonte: WHO TR 937 / ISO

3. MONITORAGGIO AMBIENTALE

Part B: recommended optional strategic tests (ISO 14644)

Schedule of tests to demonstrate continuing compliance

Test parameter	Clean room class	Max. time interval	Test procedure
Filter leakage tests (To verify filter integrity)	All classes	24 months	Filter penetration tests to be carried out by a recognized authority to demonstrate filter media and filter seal integrity. Only required on HEPA filters. In accordance with ISO 14644-3 Annex B6*
Containment leakage (To verify absence of cross-contamination)	All classes	24 months	Demonstrate that contaminant is maintained within a room by means of: • airflow direction smoke tests • room air pressures. In accordance with ISO 14644-3 Annex B4*
Recovery (To verify clean-up time)	All classes	24 months	Test to establish time that a clean room takes to return from a contaminated condition to the specified clean room condition. This should not take more than 15 min. In accordance with ISO 14644-3 Annex B13*
Airflow visualization (To verify required airflow patterns)	All classes	24 months	Tests to demonstrate airflows: • from clean to dirty areas • do not cause cross-contamination • uniformly from laminar flow units. Demonstrated by actual or videotaped smoke tests. In accordance with ISO 14644-3 Annex B7*

Fonte: WHO TR 937 / ISO

3. MONITORAGGIO AMBIENTALE

Si definisce ambiente a contaminazione controllata (camera bianca, clean room) un ambiente tale da garantire che l'aria, con cui il prodotto stesso viene o può venire a contatto, abbia un contenuto di agenti inquinanti (microorganismi o particelle) inferiore a un determinato numero per unità di volume.

Il "determinato numero (numero magico)" è stabilito dall'allegato 1 delle NBF (limiti di contaminazione particellare e contaminazione microbiologica per diversi livelli di "contaminazione (pulizia)" definiti con le lettere dell'alfabeto)

3. MONITORAGGIO AMBIENTALE

particellare (non vitale):
airbone non viable particles

- particelle aerotrasportate

microbiologica (vitale) o
biocontaminazione: viable particles

- microorganismi

particelle ⇔ microorganismi ⇔ pirogeni

- le particelle trasportano i microorganismi
- i microorganismi (gram negativi) generano endotossina batterica

3. MONITORAGGIO AMBIENTALE

particellare

numero di particelle con un dato diametro presenti in un dato volume di aria

microbiologica

numero di UFC presenti in un dato volume di aria, e/o su una data superficie

NUMERO MAGICO

"nr. di particelle" – "diametro" - "volume" – "nr. di UFC":

"pharma" guidelines:

- EC Guide, GMP, vol. 4 annex 1
- Code of Federal Regulations 21, parts 210 & 211
- FDA Guidance for Industry – Sterile Drug Products, Sept. 2004

"no pharma" guidelines:

- Federal Standard 209 E
- ISO serie 14644, serie 14698 (biocontamination)

3. MONITORAGGIO AMBIENTALE

Grade A a minimum sample volume of 1 cubic meter per sample location

For classification purposes EN/ISO 14644-1 defines both the minimum number of sample locations and the sample size

Portable particle counter with a short lenght of sample tubing

Isokinetic sample heads shall be used in unidirectional airflow system

...routinely monitored in operation

For grade A zones, particle monitoring .. For the full duration of critical processing

.....

3. MONITORAGGIO AMBIENTALE

Contaminazione particellare

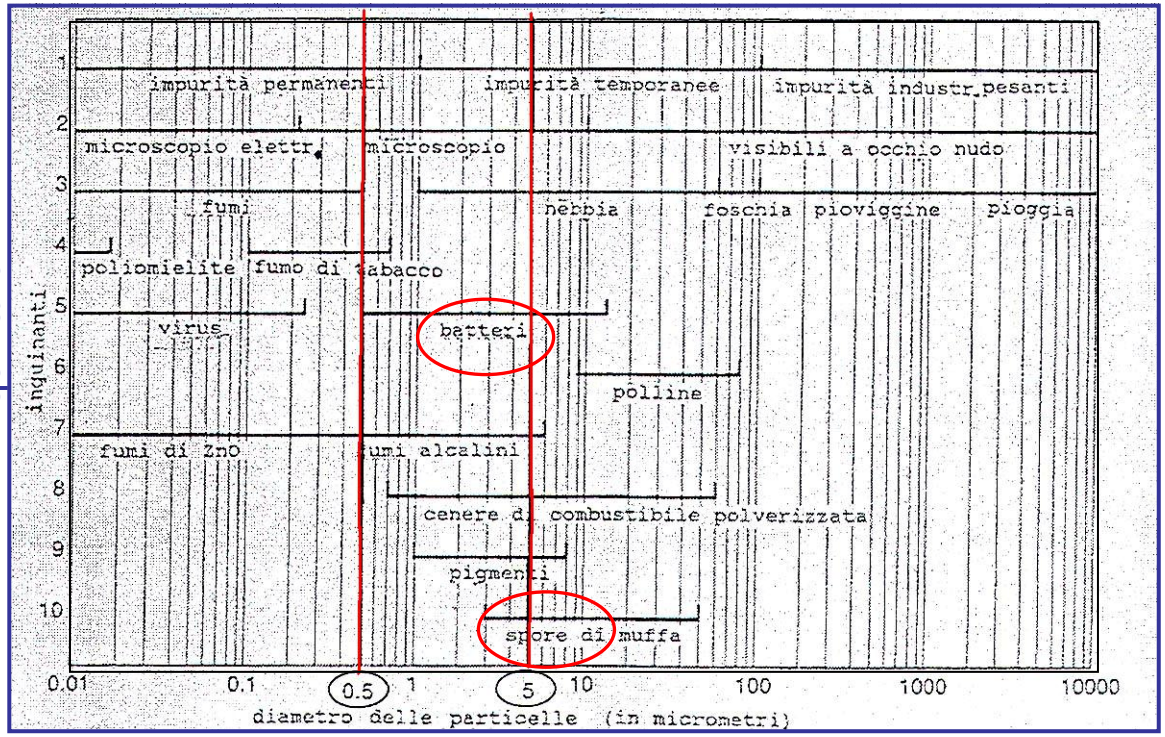
	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

EU-GMP: annex 1

Numeri magici

3. MONITORAGGIO AMBIENTALE

0,5 & 5 μm ?



inquinanti

diametro delle particelle dei particolati (μm)

3. MONITORAGGIO AMBIENTALE

Contaminazione particellare

Sensori

Contatore particellare

Software

3. MONITORAGGIO AMBIENTALE

Contaminazione microbiologica

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 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	-

Notes
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.

EU-GMP: annex 1

Numeri magici

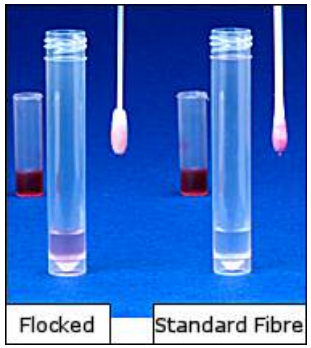
3. MONITORAGGIO AMBIENTALE

Contaminazione microbiologica

- Aria (campionatore / piastre a sedimentazione)
- Ambienti: pavimenti / pareti (piastre a contatto)
- Superfici: attrezzature (piastre a contatto / tamponi)
- Personale (piastre a contatto)

Campionatore d'aria

Piastre



Tampone

3. MONITORAGGIO AMBIENTALE

• Conte particellari: volume di campionamento / numero di punti da campionare / installazione di campionatori continui

• Velocità dei flussi unidirezionali / portata e ricambi orari / traccianti fumogeni (air flow patterns)

• Controlli microbiologici: punti da campionare / metodi di campionamento / definizione dei limiti / efficacia dei sanitizzanti / impiego di test microbiologici rapidi

• Test di simulazione (media fill): dimensione dei runs / worst case / criteri di accettazione

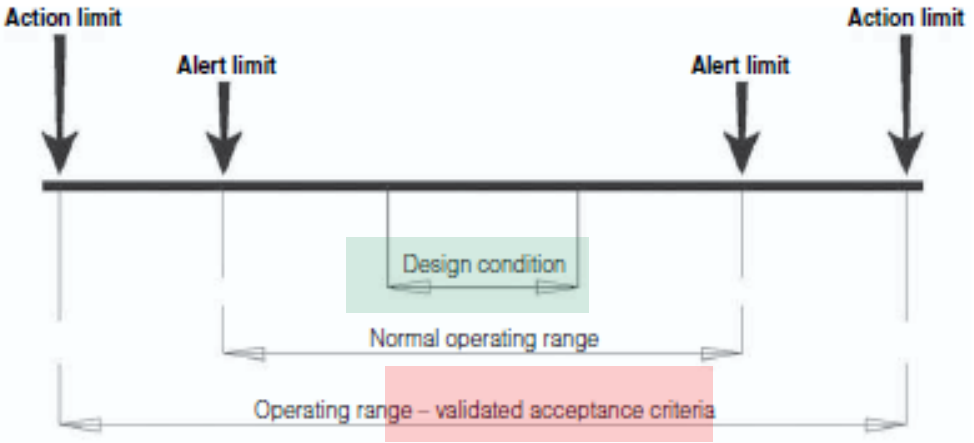
1. Principi base dell’annex 1
2. Requisiti strutturali
3. Monitoraggio ambientale
4. **Convalida HVAC**
5. Deviazioni ricorrenti (sterili)
6. Conclusioni

4. CONVALIDA HVAC

- The qualification of the HVAC system should be described in a validation master plan.
- Stages of the qualification of the HVAC system should include DQ, IQ, OQ and PQ.
- Any parameter that may affect the quality of the pharmaceutical product should be considered as a critical parameter.
- All critical parameters should be included in the qualification process:
  - i.e. the humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. Thus the humidity sensors should be qualified;
  - i.e. a room cleanliness classification is a critical parameter and therefore the room air change rates and HEPA filters should be critical parameters and require qualification.

4. CONVALIDA HVAC

- Non-critical system and components should be subject to GEP and may not necessarily require classification.
- Acceptance criteria and limits should be defined during the design stage.
- The manufacturer should define design conditions, normal operating ranges, operating ranges and alert and action limits.
- The relationship between design conditions, operating range and qualified acceptance criteria is the following:



4. CONVALIDA HVAC

- DQ: design of the system according to URS
  (e.g. components, type of air treatment needed, materials of construction).
- IQ: verification of installed components; it is a static verification
  (e.g. relevant components, ducting, filters, controls, monitors, sensors etc.) / includes calibration where relevant.
- OQ: confirm HVAC is well designed and is working in “at rest conditions” – no personnel - (it has to be done prior the room qualification).
- PQ: confirm HVAC is working in operating condition (with personnel).
- Periodical re-qualification of parameters should be done at regular intervals (i.e. annually).
- Re-qualification should also be done when any change, which could affect system performance, takes place.

4. CONVALIDA HVAC

Tests:

- Filter pressure drop or differential pressure on filters.
- Differential pressure between rooms.
- Determination of air flow velocity.
- Measurement of air volume and uniformity – air exchange rate -.
- Determination of airflow patterns.
- Filter installation leak test.
- Determination of the recovery time.
- Determination of room classification (airborne particle count).
- Temperature / humidity level and uniformity test.

4. CONVALIDA HVAC

Mobile particle monitoring or discrete particle counter:

the particle counter is taken from one sampling point to another, according to a fixed sampling plan (SOP).

Only one sampler is needed

to monitor sequentially the sampling points.

4. CONVALIDA HVAC

Stationary on-line monitoring:
the particle counter is installed in a fixed position and is permanently connected to its sampling probe.
The sampling is continuous, without interruptions.
Every sampling point needs its own sampling probe/counter.
An automatic data transfer is needed.
The system requires low personnel.

4. CONVALIDA HVAC

Is stationary or mobile particle monitoring recommended?
There is not a fixed rule....the rationale comes from GMP guideline.

A areas: stationary ... because continuous measurements are required.

B areas: ... continuous measurements are recommended.

C/D areas: mobile measurements are acceptable.

1. Principi base dell’annex 1
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5. **Deviazioni ricorrenti (sterili)**
6. Conclusioni

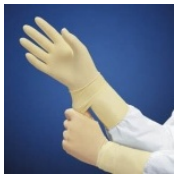
5. DEVIAZIONI

Interblocchi non funzionanti / periodo di interblocco non basato sul recovery

Sovrappressioni senza allarmi (sonori) / registrazione dei valori non puntuale (solo una volta al giorno durante la lavorazione)

Cascata delle classi a contaminazione controllata non rispettata (soprattutto in airlock, spogliatoi)

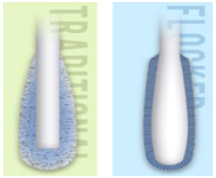
Frequenza di monitoraggio negli spogliatoi diversa da analoga classe nei reparti operativi / monitoraggio non eseguito



5. DEVIAZIONI

Rotazione del personale per l'esecuzione periodica del media fill non tracciata

Qualifica di classe A eseguita con un prelievo di volume inferiore al metro cubo



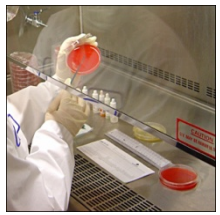
Basso recupero e/o basso rilascio dei tamponi utilizzati per la pulizia

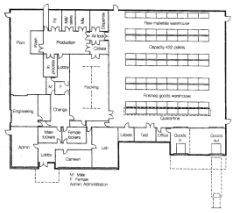
Controlli di sterilità non eseguiti separatamente sui "sub-batches" dei carichi di autoclave

5. DEVIAZIONI

Approccio overkill non dimostrato in concomitanza a una non esecuzione del controllo del bioburden su tutti i lotti (per farmaci sterilizzati terminalmente)

Controllo del bioburden non eseguito su tutti i lotti (per farmaci prodotti in asepsi)





Nr. punti / locazione dei punti / volumi campionati / frequenza di campionamento / limiti di allerta non definiti

Non evidenza della verifica dei dati di monitoraggio particellare e microbiologico ai fini del rilascio del lotto

5. DEVIAZIONI

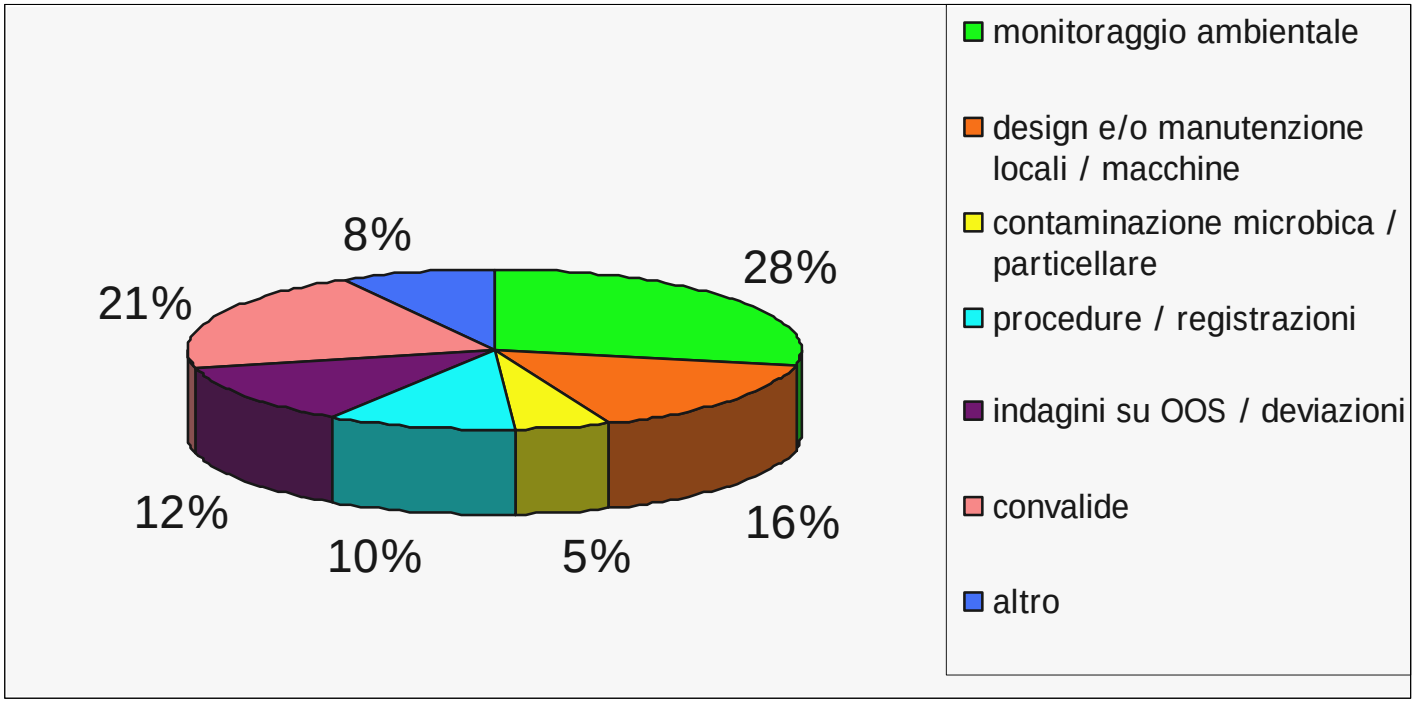
Data review dei monitoraggi non eseguiti in modo critico per tempi lunghi / “media” dei risultati microbiologici nei limiti

Batch production record non compilati contestualmente

Piani di manutenzione di UTA (prefiltri, filtri) carenti / attività non tracciate

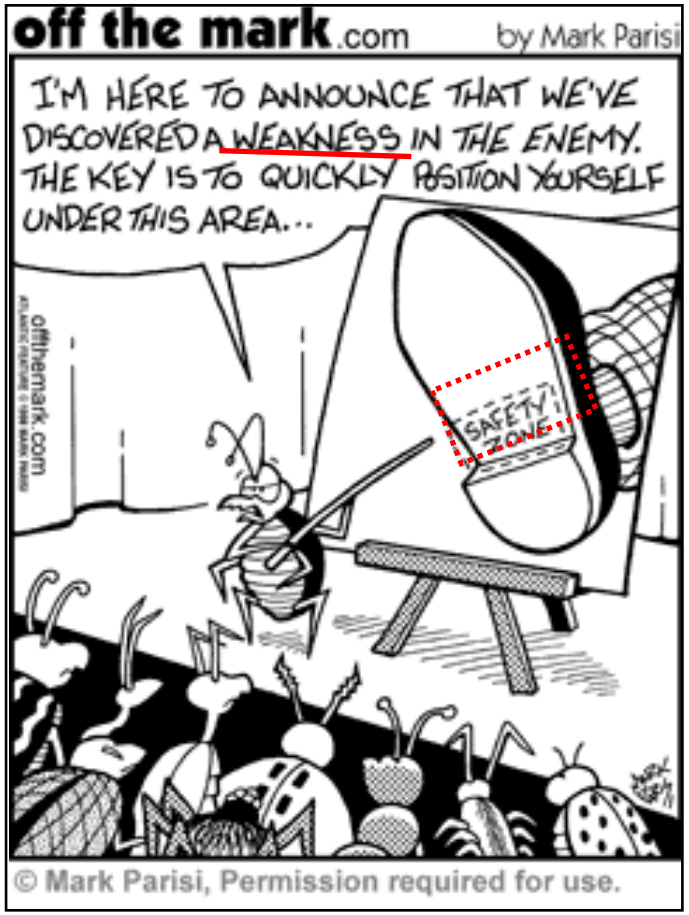
Riconvalida non effettuata a seguito di modifiche dell’impianto (up-grading) WFI / P&ID’s non aggiornati a seguito di modifiche

5. DEVIAZIONI (DRUGS - 2011)

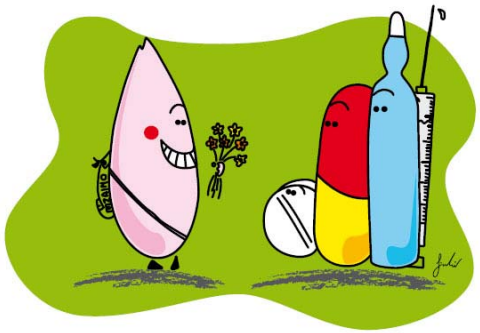


6. CONCLUSIONI

Attenzione ai punti deboli !



Grazie



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