cGMP Compliance Design Requirements

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3rd International Summit on

GMP, GCP & Quality Control

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Of Sterile/Aseptic Manufacturing Facilities

cGMP compliance design of Sterile/Aseptic Manufacturing Facilities is a mandatory to meet qualification and validation requirements

HEALTH CANADA EXPERT

SUMMARY

1. CGMP regulation requirements
2. Reminder of URS / Clean Rooms
3. Design of clean rooms
4. Types of contaminants
5. Gowning & means of prevention
6. Classifications of rooms vs standards & applications
7. Types of segregation, of flow, of cascades
8. Building construction and architectural finishes
9. Design of HVAC systems for sterile products
10. Design in the presence of High Potent products
11. PPE, Personal Protective equipment
12. Elements of Commissioning/Validation of Premises & HVAC
13. Many case studies will be presented

Regulatory references?

cGMP / FDA

PDA / APIC /PIC/ PICS

ICH / WHO

HEALTH CANADA GMP

EMA / ANSM GMP

SPECIFIC REFERENCES (Aseptic)

International Guideline Documents for Life Sciences		
Publisher	**Description**	**Reference Document**
ISPE	International Society Pharmaceutical Engineering	HVAC Guidelines
WHO	WHO Expert Committee for Pharmaceutical Preparations	TRS-961
ASHP	Pharmaceutical Compounding-Sterile Preparations	USP-797)
US DOH	USA Department of Health	CGMP
Eurovent		4 10
IEST	Institute Environmental Sciences	IEST-RP-CC001, 007, 021, 034
ASHRAE	American Society Heating, Refrigeration A/C Engineers	Standard 52.2 - filter testing, Guideline 26 In-Situ testing, Standard 180 HVAC Equipment Maintenance , Standard 170 Hospitals
ISO	International Standards Organization	Published: 14644, 29463 HEPA and ULPA Filtration. Coming standards underway: 16890 Filter Testing, Filtration 12249 Life Cycle Assessment , 29462 In Situ Testing
Peaks	Pharmaceutical Inspection Convention	GMP Guide
1822	European Norm for Classification & Testing of HEPA/ULPA Filters	IN-1822 Shares 1-5
IN779	European Norm for Pre filtration testing	IN-779 2012

Clean rooms: regulations

- ✓ **GMP (Good** Manufacturing Practice) ed. 2002, Combined with the european standard
- ✓ **ISO 14644** (Clean rooms and controlled environments)
- ✓ **ISO 14698** « Bio-contamination controls, methods of measurement, principles of estimation and evaluation of data (interpretation) and methods of cleaning and disinfecting of the surfaces "
- ✓ **ISO 13408** " Aseptic processing of health care products"
- ✓ **ASHAE** 1999 (Application) Clean Space chap. 15
- ✓ **ISPE** , vol 3, chap. 4 to 9 & 11
- ✓ ISPE, vol 6, chap. 6 & 13
- ✓ **IEST** (Considerations in clean room) RP cc0012.1

GAP ANALYSIS, Audit & cGMP Requirements Inspection Process

cGMP DESIGN REVIEW & GAP ANALYSIS

Compliance Review for EPCMV projects

Clean Utilities
ASME BPE:
- PuW, WFI
- PS, PCA, N2

Clean Room/
ISO14644:
- Arch. Finishes
- HVAC, FFU
- Flow Analysis
- Cross contamination
- Environmental Room Classification

Process Equipment
ASME BPE:
- Autoclave
- Depyro
- RABS
- Tanks
- Pumps
- Heat Xgers
- CIP
- SIP

Commissioning & Qualification
ICH Q9
- FAT, SAT
- DQ, IQ, OQ, PQ
- Cleaning Validation
- Process Validation

Procedures
- SOP
- QA
- Sampling
- Calibration
- Maintenance
- Manufacturing
- IPC & Analysis
- Cleaning
- Programs

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cGMP DESIGN REVIEW & GAP ANALYSIS

Compliance Review for EPCMV projects

Audit & Independent Compliance Review

- CAPA & Remediation Plan
- Impact & GAP Analysis

Design

- URS & PFD
- BOD

Detailed Engineering

- FDS, P&ID, RAA, CDC
- APD / DD, DR

Project Management

- Control Deadline, Compliance & Quality Control
- Commissioning, FAT, SAT, DQ, IQ, OQ

১। * EPCMV Project, Engineering, Construction Management

- How to reduce the Cost?

২। *AUDIT

cGMP Sanitary DESIGN

- Clean Utilties

- HVAC

৩। *STERILE

- INJECTABLE

- TEAR DROP

৪। * OSD

- High Potent

HP1@5

৫। * OSD

- Flammable & Explosive Compounds

Sugar, Alcohol

ATEX1@3

৬। BIOTECH

VACCINE

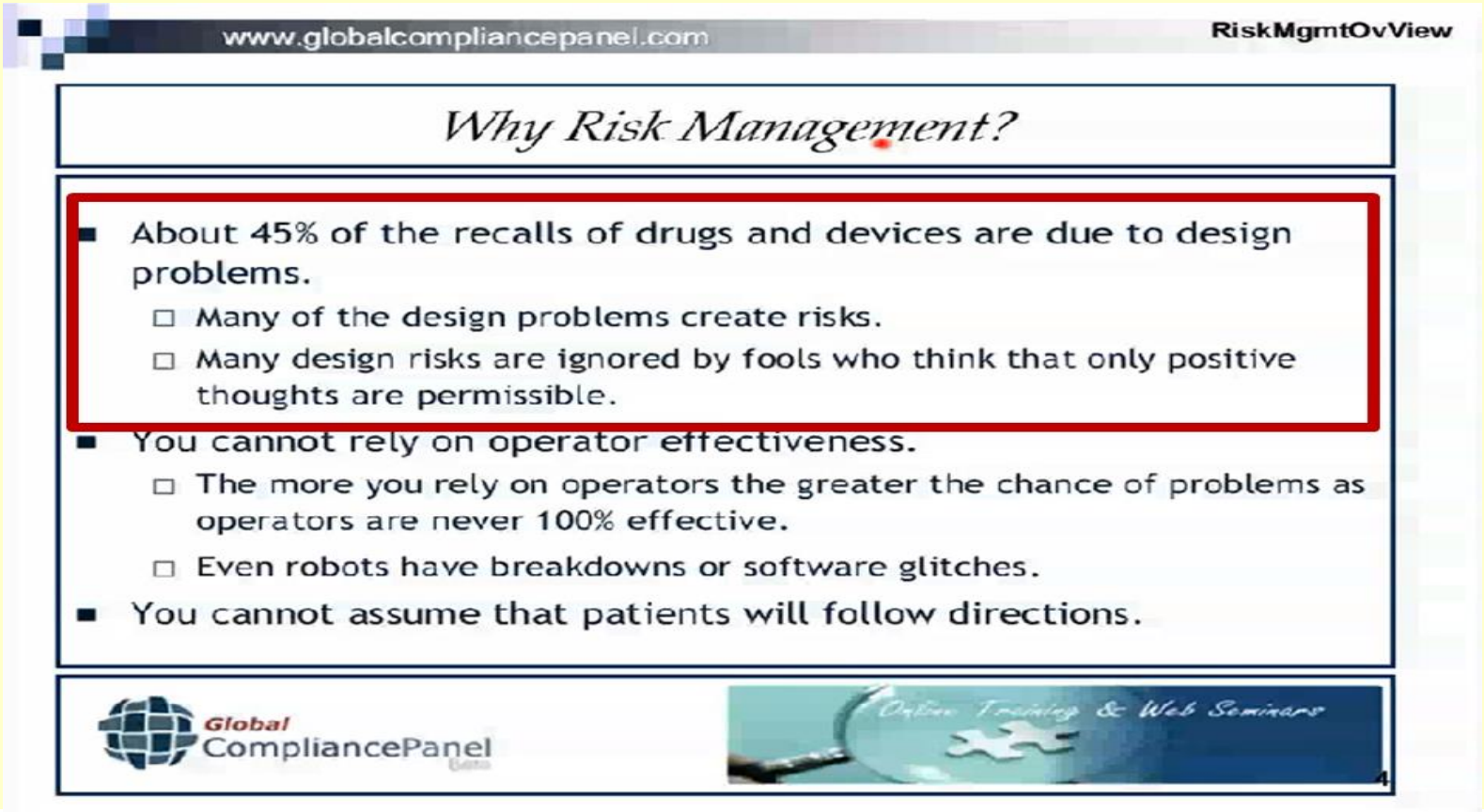
INSULINE

BSL1@4

SKILLED & MULTIDISCIPLINARY HQP REQUIRED

WHY STERILE FACILITIES HAVE TO MEET cGMP REQUIREMENT?

WHY STERILE FACILITIES HAVE TO MEET cGMP REQUIREMENT?



HEALTH CANADA NON-COMPLIANCE INSPECTION

2.2.3 : Éléments du Règlement les plus souvent mentionnés

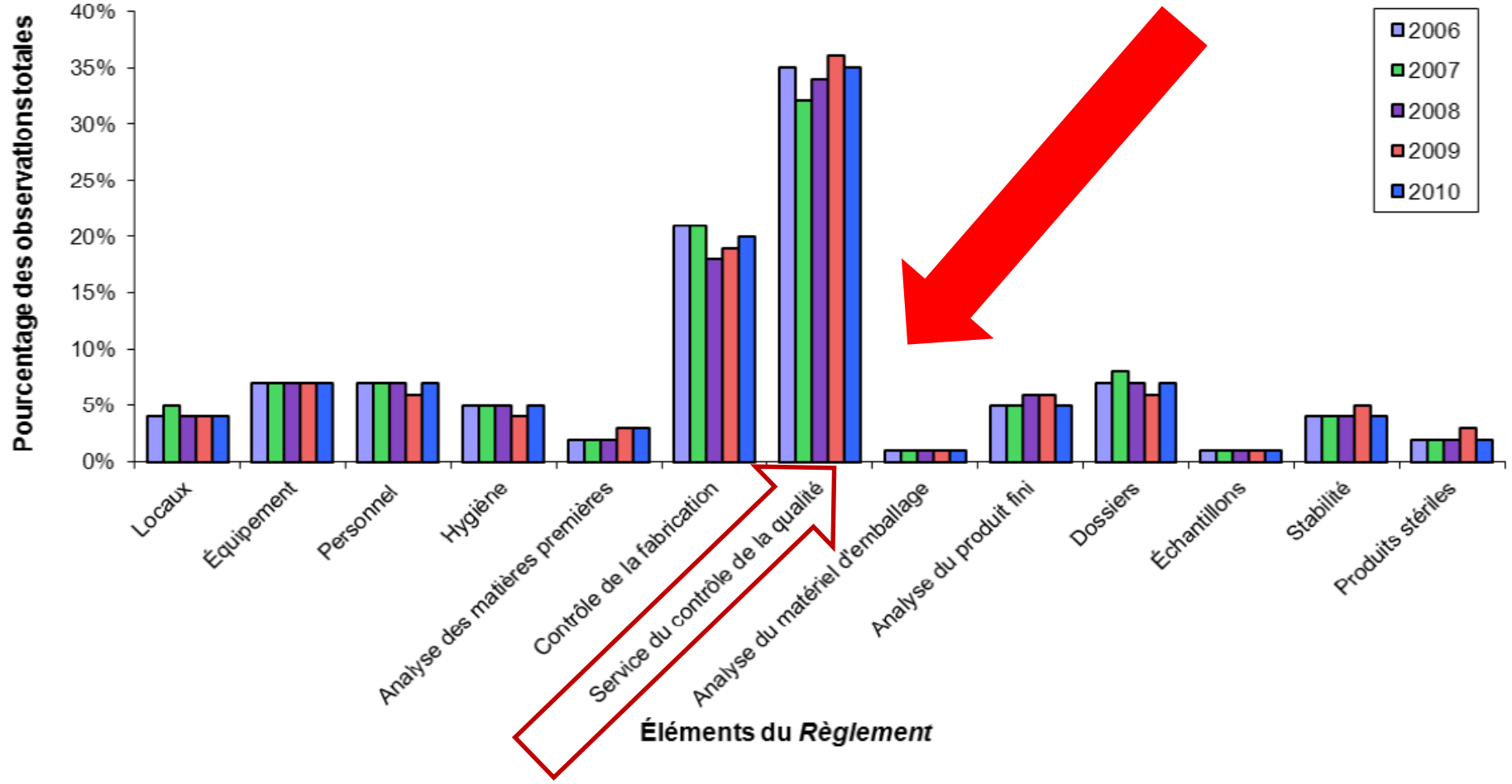
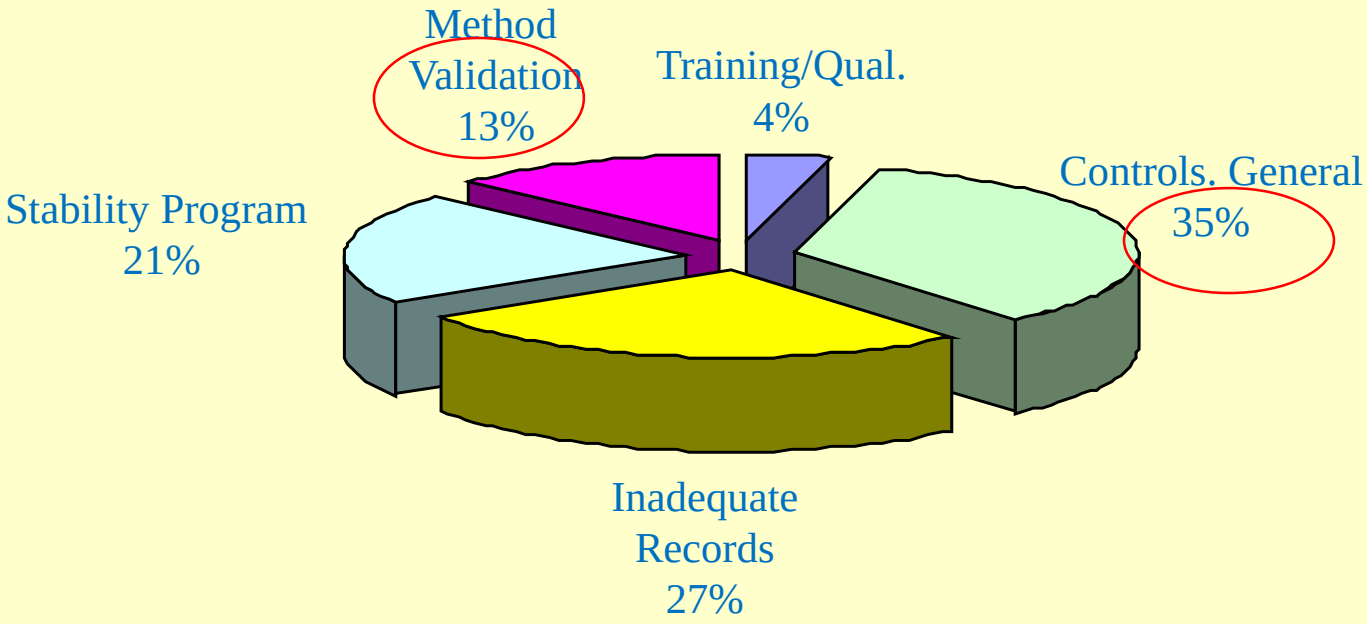


Figure 2.2.3 Éléments du *Règlement* les plus souvent mentionnés par exercice (de 2006 à 2010). Le service du contrôle de la qualité (C.02.015) est toujours l'élément qui est visé par le plus grand nombre d'observations.

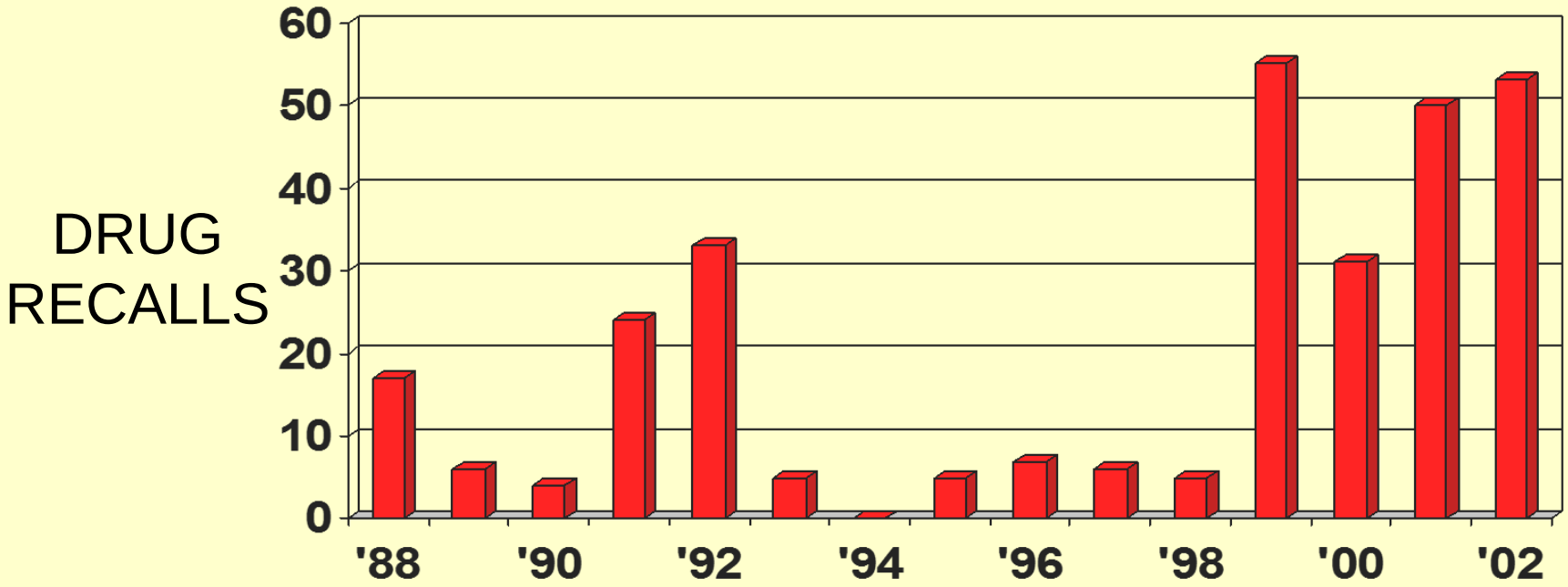
FDA Systems Based Inspection:
Laboratory System

Feb – July 2002: 212 Inspections (US)



* Reference: Albinus D' Sa, FDA, CDER Office of Compliance, from AAPS, Nov. 2002 presentation.

Lack of Sterility Assurance = FDA Drug Recalls



Nearly *all* drugs recalled due to Lack of Sterility Assurance in last 20 years were produced via ASEPTIC PROCESSING / FDA

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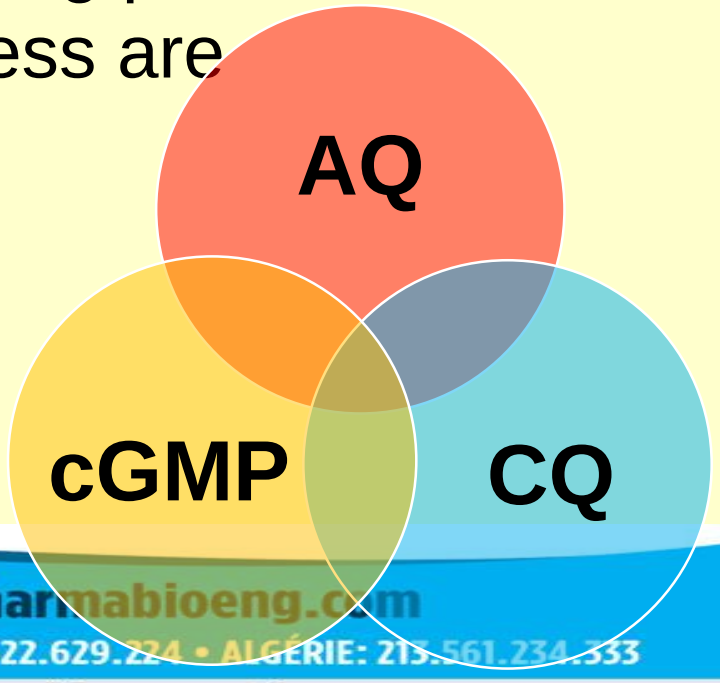
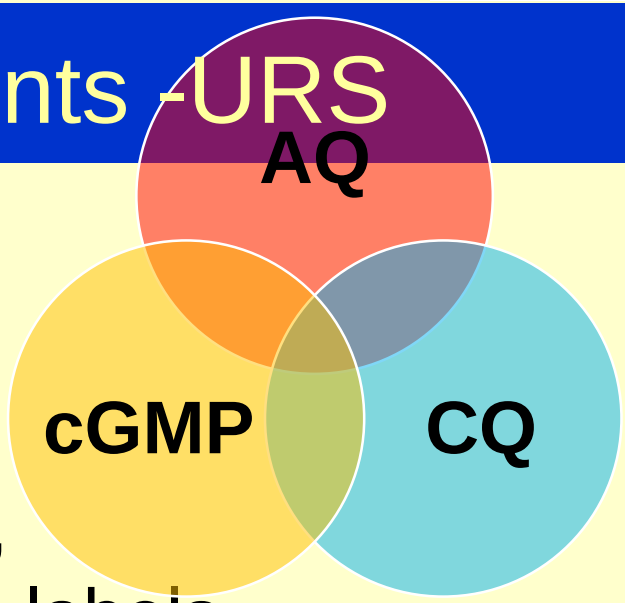
cGMP Regulatory Requirements?

Basic GMP Requirements -URS

1. **Manufacturing processes** are clearly defined and controlled to ensure consistency and compliance with approved specifications;
2. **Critical steps** of manufacturing processes and significant changes to the process are **validated**;



Basic GMP Requirements -URS



3. **Critical GMP requirements** :

-**Qualified** and trained **personnel**,

-**Adequate** premises and **space**,

-Suitable **equipment** and services,

-Correct **materials**, containers and labels,

-Approved **procedures** and instructions,

-Suitable **storage** and transport.

Health Canada / Health Products and Food Branch Inspectorate
Good Manufacturing Practices Guidelines (GMP) 2009 Edition / November 8, 2009
Page 9

cGMP CR GUIDELINES

The rooms where a lot or batch of a drug is:

MANUFACTURED → PACKAGED → LABELED → STORED

ARE

DESIGNED → BUILT → MAINTENED → VALIDATED

IN ORDER TO

cGMP CR GUIDELINES

a) to allow the execution of the manufacturing operations in a manner:

- CLEAN
- HYGIENIC & SANITARY
- NO MIX-UPS
- No CROSS CONTAMINATION

cGMP CR GUIDELINES

3. Prevent cross-contamination (CC)

3.1 **TO SEAL ? to enable CLEANING & reduce CC risks**

3.3 Joints between walls, ceilings and floors are **SEALED.**

FLOORS → WALLS → CEILINGS → DOORS → WINDOWS → SEALS

ATTENTION TO THE SUSPENDED CEILINGS!

cGMP CR GUIDELINES

3.1 **TO AVOID ?**

→ Surface material **which can release particles**.

→ To allow **Cleaning**

& Disinfection

- **VHP** ® Biodecontamination Systems
- **Attention to materials incompatibilities & Corrosion issues by using VHP**

cGMP CR GUIDELINES

3.1 → To allow cleaning

3.2 → **Surfaces** are hard, smooth and free of sharp corners where extraneous material can collect.. **REDUCE**:

- Horizontal Surfaces
- Sharp Corner
- Non Washable Non Drainabale
- Rough Crevice Wholes
- Shedding particles

- FLOORS
- WALLS
- CEILINGS
- DOORS
- WINDOWS

→ **SOFT WALL: Non Acceptable**

Are the drains required in CR ?

3.5 → Floor & Equipment Drains Requirements

Meet :

- **Insurers Requirement (Drainage Water Fire Protection)**
- **Process Requirement / containment HP (Disbursed)**
- **Civil & building Codes**
- **Safety requirement & HSE standards**

Drains of sol vs Classification

3.5 → Floor & Equipment Drains Requirements

- **Fitted with siphons.**
  - **In rooms classified B/A: NON ACCEPTABLE**
  - **In rooms classified C: are closed with disinfectants and automatic priming pumps**
  - **In rooms classified D: may be acceptable + procedure**

How to maintain the air quality in CR

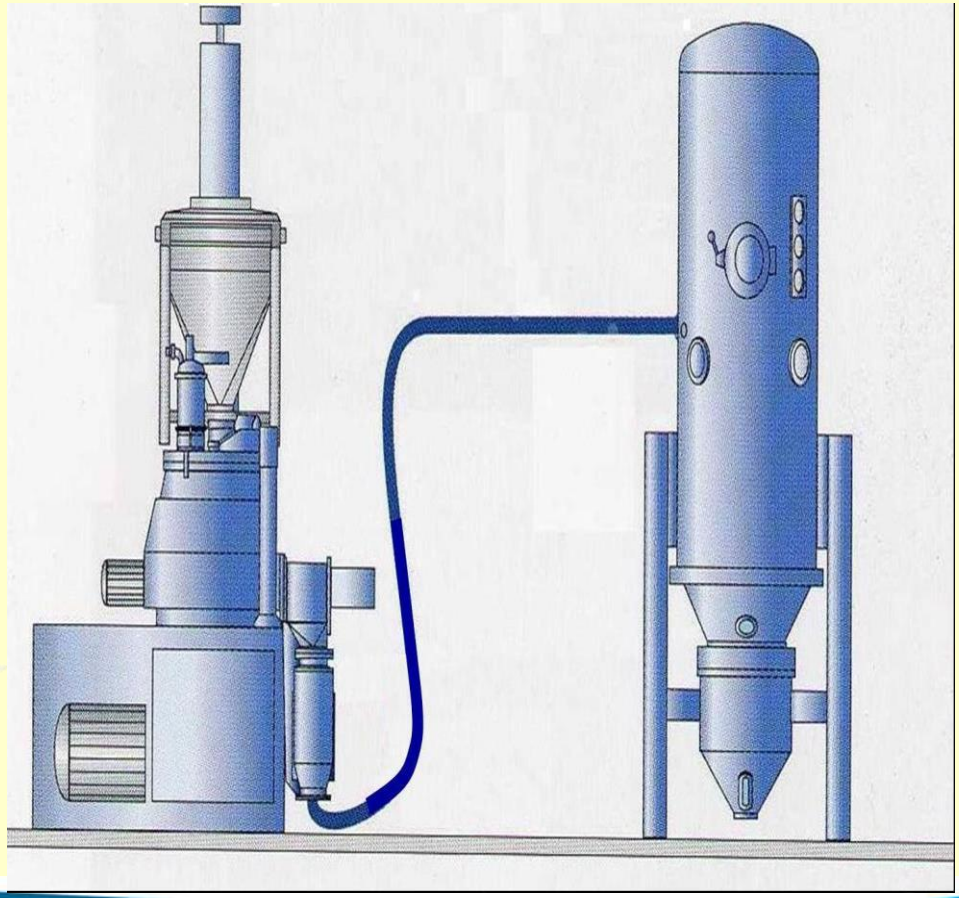
► By **controlling the contaminants**, according:

Three rules:

a. **CE**

b. **CT**

c. **LEV**



LEV : Local Exhaust Ventilation

How to maintain the air quality in CR

► **Control of the contaminants** :

1- ► by monitoring **the pressure cascade** between the adjacent production areas,

2- ► by checking and replacing periodically the air filters

(**HEPA: Integrity Test**).

How to maintain the air quality in CR

→ by suitable **HVAC** designed taking into account:

- **Uni Directional Air Flow : UDAF or NUDAF**
- **HEPA** Filters (Terminal or Central, Integrity Test)
- **Air veocity** or **ACR**, (Volumetric Flow)
- Related **VNV** CR / Air Classification (ISO14644 / cGMP)
- Appropriate **Gowning** **& Flows** (Personal, Material & Prducts)
- Physical & Mechanical Segregations & **Barriers**

NON GMP ISSUES

1- MIX-UPS

2- Failure of Product Quality & Integrity

3- Breakage of GMP & Sanitary Design Consistency

URS - Specifications / Containment / ASEPTIC / ATEX / BSL

Sterile Injectables Facilities

1- Clean Rooms

2- RABS / Sterile

3- ISOLATOR /HP

Definition - RABS

RABS : Restricted **Access Barrier System**

Definition - RABS

RABS provides an **enclosed environment**

- to reduce the risk of **contamination** to **product, containers, closures**, and product contact surfaces
- compared to the risks associated with conventional **our regular** operations.

ISPE definition, August 2005

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Types of Contaminants & Cleanliness Technologies

Sources of contaminants

- ✓ 1.4.11 Materials and products should be protected from contamination and **cross-contamination** during all stages of manufacture
- ✓ *Note:* ***contaminants*** *may result from:*
  1. ***Inappropriate PREMISES (****e.g.* ***Poor design, layout*** or ***finishing***),
  2. ***Poor CLEANING procedures & Equipment***,
  3. *Contaminants brought* in ***by PERSONNEL*** ,
  4. ***Poor HVAC system***

Types of contaminants

Viable Contaminant	Bioburden	CFU= Colony Forming Units
Viable Contaminant	Endotoxin	Pyrogenic Cell Fragments
NON Viable Contaminant	External Particles	Production & Packaging Waste
NON Viable Contaminant	Chemical Particles	Excess Cleaning Agents

Reduction of Contaminant Technologies

Sterile Filtration	**Reduce**	**Viable & Non Viable Content of Particles**
SIP / SOP Sterillization	**Reduce**	**Microbiological Contamination**
Depyro, Thermal Chemical &Treatment	**Remove**	**Endotoxin**
CIP, Disinfection WFI Final Rince	**Remove**	**VNV, Endotoxin Content of Particles**

Objectives of the protections

External Contaminants	Follow	Gowning Procedures
External Contaminants	Ensure	Pre-treatment Components
External Contaminants	Remove	Effective Filtration HEPA, ACR

Objectives of the protection

Internal Contaminants	To Control by	Efficient HVAC
Internal Contaminants	To Remove by	Air Dilution or Displacement
High Potent Contaminants	To be Contained	Physical & Mechanical Barriers

Contaminant & Their Removal Technology

TYPE OF CONTAMINANT	EXAMPLE	DERIVED FROM: (Examples)	DEALT WITH BY: (Examples)
Non-viable (particulates)	- Metal specks - Clothing fiber	- Equipment - People's clothing - Outside air - Water supply	- Airborne particles are HEPA filtered - Contact parts are cleaned and sterilized. - Water purification systems
Viable (micro-organism)	- Bacteria - Yeast molds	- People - Water - Outside air - Equipment, tools - Excipients, active ingredients	- Limit aseptic core interventions - Airborne particles are HEPA filtered - Sterile filtration of solutions (0.2µm) - Steam sterilization or irradiation of components
Endotoxins (Not normally associated with airborne bacteria)	- Arising from cell wall debris from certain organisms (often water borne)	- Wet equipment change parts, or container/closure after a period of time exposure	- Caustic soda solution with heat - High temperature (>200°C) time dependent

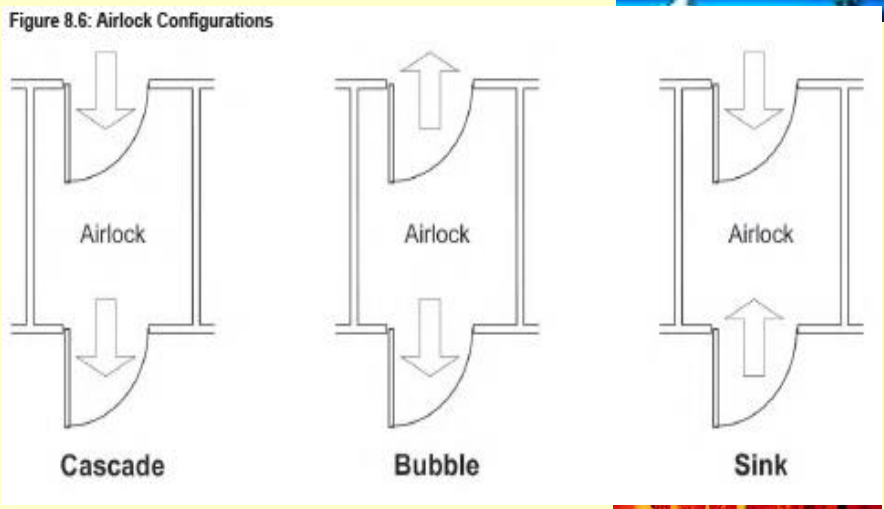
Means of Prevention / Design of rooms

✓ **Segregation and flow** :

1. **<u>Primary Segregation</u>**:

❑Physical Design of the unit of production:

- PAL & MAL,
- Corridors,
- Access Cards,
- Dedicated rooms,
- HVAC,
- Protection Systems,
- Clean Utilities.



2. **<u>Secondary Segregation</u>** :

❑Procedures for controls to reduce the risk of contamination and cross-contamination

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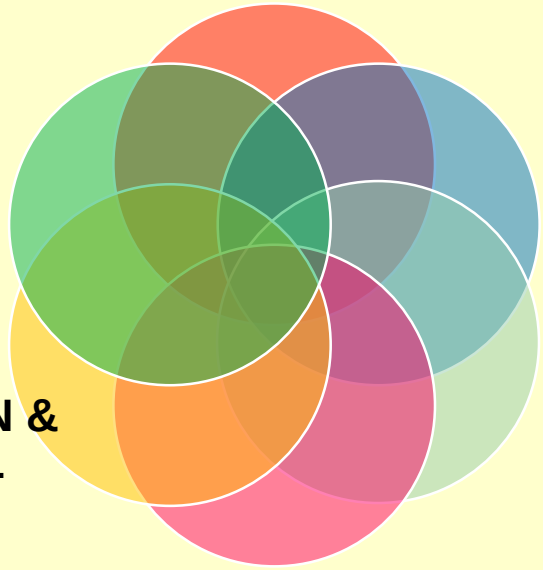
Prevention Technologies Against Contaminants

Means of prevention against contaminants

GOWNING

SANITARY EQUIPMENT, CLEANING & SANITATION

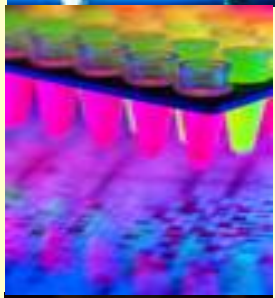
HVAC, EMS, BMS

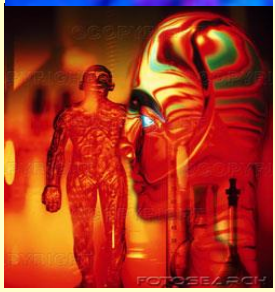


CLEANROOM DESIGN & ARCHITECHTURAL FINISHES

PHYSICAL & MECHANICAL SEGREGATIONS

PROCEDURE





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1- GOWNING Code & Prevention Technologies

GOWNING CODE

Classification	D (ISO8)	C (ISO7)	B (ISO5)
Hair Cover *(Bonnet)*	X	X	-
Beard Cover *(Couvre-barbe)*	X	X	-
Sterile Gloves *(Gants stériles)*	-	-	X
Smock *(Sarrau)*	X	-	-
Coat *(Cagoule)*	-	-	X
Mask *(Masque)*	-	-	X
Shoes or Overshoes *(Couvre-chaussures)*	X	X	-
Jacket & Pants *(Veste & Pantalon)*	-	X	X
Bodysuit *(Combinaison intégrale)*	-	X	X
Boots *(Bottes)*	-	-	X

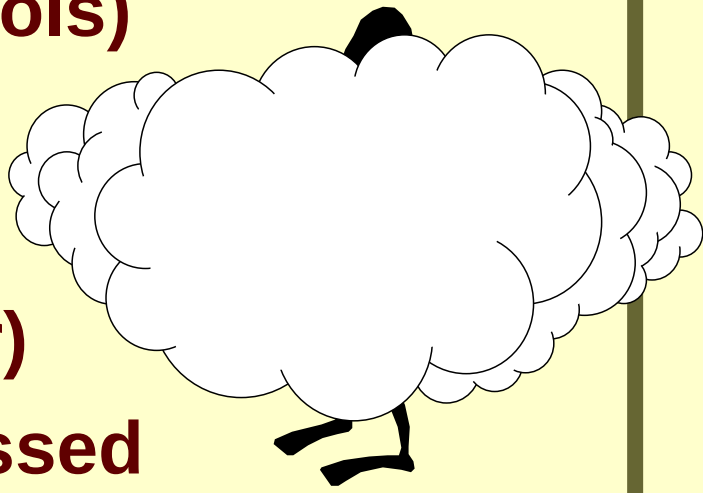
Gowning-Classification Rooms

ISPE vol. 3-p20

Terminology for Air Quality used in this Guide	Typical Area	Example of dress code
External	Street, Restaurant	Outdoor clothes
Unclassified	Laboratories, Offices, Warehouse	Appropriate to area
Pharmaceutical	Packing Hall	Captive coat, hat and overshoes
Class 100,000 (in operation)	Non-sterile processing	Clean garments
Class 10,000 (in operation)	Room where filling takes place	Sterile garments
Class 100 (in operation)	Point of fill or other aseptic manipulations	Sterile garments

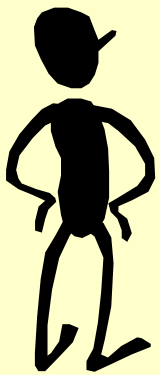
Major contamination vectors

1. **Raw materials (powder, HP, biological material, aerosols)**
2. **Equipment**
3. **Personnel (skin and hair)**
4. **Environment (surface, air)**
5. **Utilities, (Steam, compressed air, water…)**

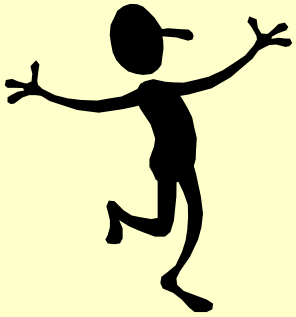


Number of particles > 0.5 µm released/mn

Activity ?

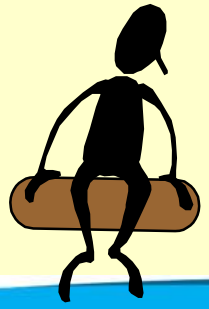


100,000



1,000,000

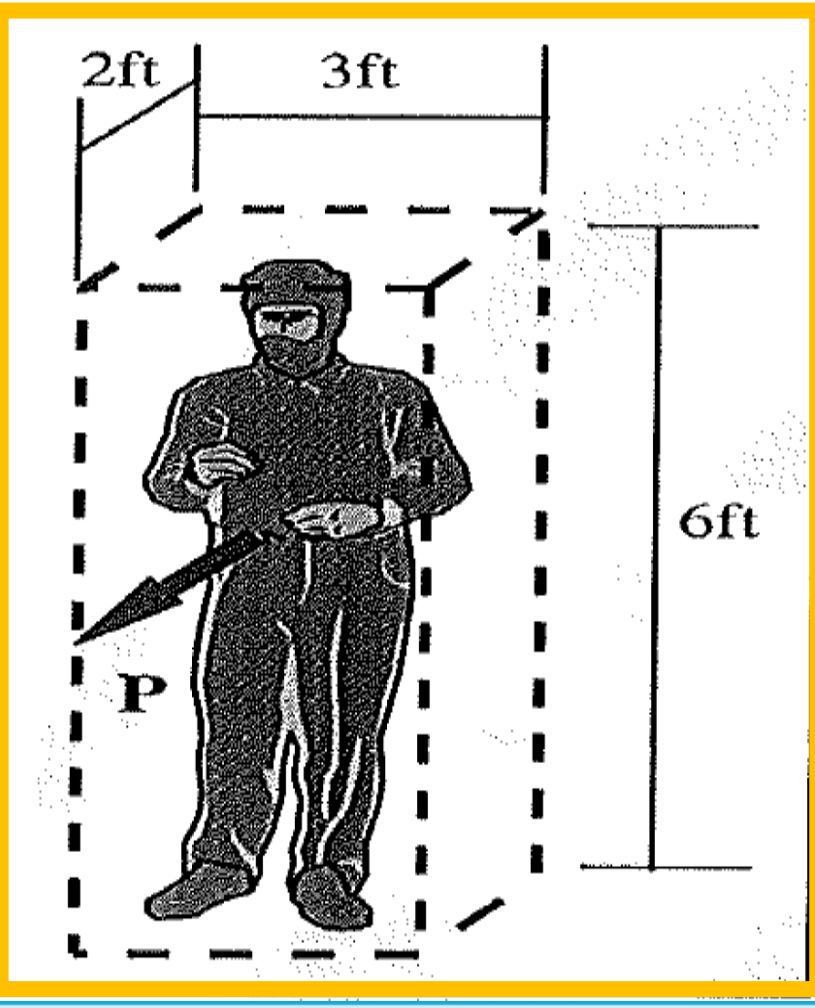
5,000,000



500,000

15,000,000 / 30,000,000

Number of particles released by Clothing



Volume of occupied space equals $36ft^3$ minus the volume of the operator = $18ft^3$

Starting condition assume Class 100.

Therefore, space contains 1800 particles at 0.5µm

Generation rate taken as P = 1 x 104 0.5µm particles per sec.

After 18secs 180,000 particles are released that takes the contained volume over class 10,000.

After 3mins 1,800,000 particles are released that exceeds Class 100,000 within the occupied space.

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Cleanrooms Classification cGMP / ISO-14644

Clean Area Classification - (Viable) ANSM 04/12/2013

Limites recommandées de contamination microbiologique (a)

ansm Agence nationale de sécurité du médicament et des produits de santé

Classe	Echantillon d'air ufc/m^3	boîtes de Pétri (diam.:90 mm), ufc/4heures (b)	géloses de contact (diam. :55 mm), ufc/plaque	empreintes de gant (5 doigts) ufc/gant
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

GMP/ ANSM , p60, &20. **The thresholds of alert and appropriate action must be defined for the results of the monitoring particulate and microbiological** . In case of exceeding these limits, operational procedures must impose corrective measures.

Clean Area Classification - (Viable)

Graph 4.0: Limits of microbial contamination recommended

Limits of microbial contamination recommended (a) (e)				
CLASS	Air sample units forming a colony (cfu) /m 3	Plates of sedimentation (90 mm diameter), units forming a colony (cfu) /4 hours (b)	Contact plates (diameter 55 mm), units forming a colony (cfu) /plate (c)	Imprint of glove 5 Fingers units forming a colony (cfu) /glove (d)
HAS	**< 1**	**< 1**	**< 1**	**< 1**
B	**10**	**5**	**5**	**5**
C	**100**	**50**	**25**	**-**
D	**200**	**100**	**50**	**-**

Clean Area Classification - (Viable) ANSM 04/12/2013

FDA U.S. Food and Drug Administration

TABLE 1- Air Classifications[a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c][d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

Clean Area Classification - (Non-Viable) ANSM 04/12/2013

GMP/ ANSM -14. The particulate limits indicated in the table " **AT REST** " must be reached after a short time of purification of **15 to 20 minutes** (guide value)

Classe	Nombre maximal autorisé de particules par m^3 de taille égale ou supérieure aux tailles précisées.			
	Au repos		*En activité*	
	0.5 µm (d)	*5 µm*	*0.5 µm (d)*	*5 µm*
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Non défini	Non défini

Equivalence Air Classification % BPFs % cGMP

Table 5-1 Airborne Environmental Requirements

ISPE Sterile Guide Grade (N.B. refer to In-operation state)	FDA, CDER June 1987 Guideline on Sterile Drug Products by Aseptic Processing			Draft USP (1116) February 1997 Microbiology Evaluation of Cleanrooms and Other Controlled Environments		European Commission Annex 1, 1997 - Manufacture of Sterile Medicinal Products					
	In Operation [note 1]		Descriptive	In Operation		Descriptive	At Rest [note 4]		In Operation		
	Acceptable particulate quality per ft.³	Maximum number of colony forming units		Maximum permitted number of particles per ft.³	Maximum number of colony forming units per ft.³		Maximum permitted number of particles per m³ equal to or above (per ft.³)		Maximum permitted number of particles per m³ equal to or above (per ft.³)		Maximum number of colony forming units per m³ (per 10ft³)
	0.5µm and larger	CFU/10ft³		0.5µm and larger	CFU/ft.³ (CFU/m³)		0.5µm	5µm	0.5µm	5µm	CFU/m³ (CFU/10ft³)
Class 100	100 [note 2]	No more than 1	Critical Areas	100	Less than 0.1 (less than 3)	Grade A [note 5]	3500 [note 6] (100)	None	3500 (100)	None	Less than 1 (0.3)
Class 10,000	-	-	-	10,000	Less than 0.5 (less than 20)	Grade B	3500 (100)	None	350000 (10000)	2000 (57)	10 (3)
Class 100,000	100000 [note 3]	25	Controlled Areas	100,000	Less than 2.5 (less than 100)	Grade C	350000 (10000)	2000 (57)	3500000 (100000)	20000 (570)	100 (30)
Pharmaceutical (with local monitoring)	-	-	-	-	-	Grade D	3500000 (100000)	20000 (570)	-	-	200 (57)
Pharmaceutical	-	-	-	-	-		-	-	-	-	-

ISO 8 Activity = D Rest = C Activity

ISO 8

Means of prevention / design of rooms

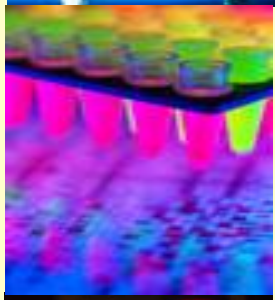
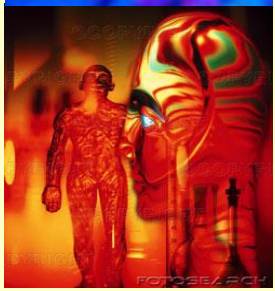
- ✓ **Segregation and flow** :

1. **<u>Primary Segregation</u>** :

❑Physical Design of the manufacturing plant:
- PAL & PAL airlocks,
- Corridors,
- Access Cards,
- Dedicated manufacturing rooms,
- HVAC,
- Protection Systems,
- Cclean Utilities

2. **<u>Secondary Segregation</u>** :

❑Procedures for controls to reduce the risk of contamination and cross-contamination

Facility Design & Prevention Technologies

2.3 → **Manufacturing areas** are **separated from non-manufacturing areas.** (Attention to **SUSPENDED CEILINGS**!)

→ **Segregation** :

PHYSICAL SEGREGATION	MECHANICAL SEGREGATION	SPECIFIC GOWNING	PROCEDURE QA
• Dedicated rooms • Controlled access • PAL & MAL airlocks • Interlocked doors • Corridors	• HVAC, • AHU • FFU • RABS • ALF • Biological Safety Cabinet	• Appropriate to CR • Clean Garments • Steriel GArments • Scaphandre	• cGMP / Training • Gowning • Flows & Access • Cleaning • Sanitation • HSE • Maintenance

→ They are clearly defined and isolated.

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Dr. Aziz Chraibi , eng.

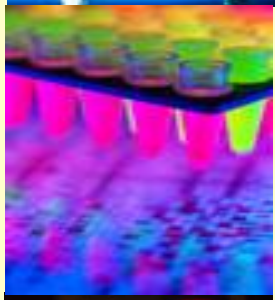
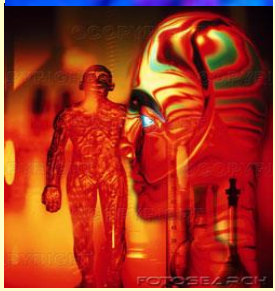
HEALTH CANADA EXPERT

PBE, Pharma Bio Expert Inc.
President

Cleanrooms Architectural Finishes

Needs HVAC & Architectural

- ✓ Layout the cleanrooms & building
- ✓ Air cleanroom classification according to ISO-14644, FDA, EMA, Health Canada
- ✓ Construction Materials
- ✓ Architectural Finishes

ARCHITECTURAL MATERIALS/FINISHES GUIDE - ISPE vol. 3, p. 52

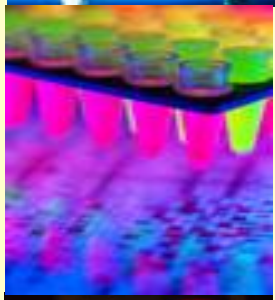
ENVIRONMENTAL STANDARD ARCHITECTURAL ELEMENT	UNCLASSIFIED	PHARMACEUTICAL	CLASS 100.000	CLASS 10.000 AND 100
Floors	**Standard construction practice is generally appropriate. Typical materials include concrete sealed gold coatings with a high level of wear resistance.**	**Standard construction practice is generally appropriate. Typical materials include sealed concrete, epoxy coatings, VCT, seamless vinyl, terrazzo.**	**Surfaces should be smooth and cleanable. Typical materials include sealed concrete, epoxy coatings, VCT seamless vinyl, CALUX) resistant coatings, and terrazzo floors. Capped With floor drains.**	**Should not have seals gold seams where microbial growth may occur. Should provide a solid, non-porous, clean and sanitizable surface. Typical materials include sheet vinyl and epoxy floor systems. Coved bases wall integral with the floor system. Floor drains and sinks are not permitted.**
Interior walls	**Not required to separate operations, if installed typical materials include wire mesh, gypsum board, CMU.** Note that as a method of separating stored materials, devices such as stanchions, chains and moveable partitions are acceptable if proper production materials identification procedures are in place.	**Standard construction practice is generally appropriate. Typical materials include CMU, gypsum board, metal panels (with a finish material appropriate to the durability and cleanability requirements), glazed tile.** Note that softer materials such as plastic aussi al-noor curtains can be used as a secondary method for preventing contamination, e.g. in conjunction with HVAC systems.	**Wall construction should provide a solid, non-porous surface. Typical substrate materials include CMU, gypsum board, metal panels (finished with epoxy paint), resinous coatings, gold metal type PVC cladding.**	**Should not have seals of seams where microbial growth may occur. Should provide a smooth, solid, non-porous surface. Typical materials include gypsum board, finished with paints of CALUX) resistant coatings, sheet vinyl gold sprayed on wall finishes, panel systems with gold metal vinyl surface finishes. Curved/rounded corners are used to enhance cleanability.**
Ceilings	**Ceilings are generally not required in thesis areas if material gold product is not exposed (e.g. normalement bas in a warehousing environment). A lay-in type ceiling is recommended for staff areas where room**	**Ceilings are generally required in these areas. Typical materials included suspended grid systems (mylar, PIB, metal or other cleanable, non-porous surfaces).**	**Should provide required level of protection from contaminants from non-environmentally controlled areas, i.e. above ceiling space. Typical materials include sealed (i.e. caulked in place) suspended grid systems (mylar, PIB, metal or other cleanable, non-porous surfaces) gypsum board, metal room pressure.**	**Should not have seals gold seams where microbial growth may occur. Should provide a smooth, solid, cleanable, sanitizable, non-porous surface. Typical materials include gypsum board, finished with paints of chemical resistant coatings, sheet vinyl gold sprayed-on wall finishes, panel systems with gold metal vinyl surface finishes. Fixtures (lights, or not have any horizontal surfaces**

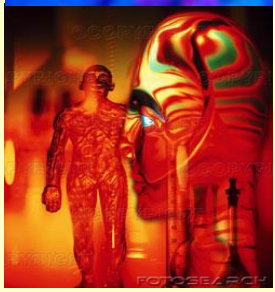
ENVIRONMENTAL STANDARD ARCHITECTURAL ELEMENT	UNCLASSIFIED	PHARMACEUTICAL	CLASS 100.000	CLASS 10.000 AND 100
Junction Details Floor/Wall Wall/Wall Wall/Ceiling	Standard construction details are generally appropriate.	Coved splayed gold full floor bases are not required, baseboards are suggested to protect wall bases, particularly when materials such as gypsum board are used. Rounded wall/wall and wall/ceiling details are not required.	Coved splayed gold full floor bases are not required, but are suggested to enhance cleaning ease and to protect wall databases particularly when materials such as gypsum board are used. Rounded wall/wall and wall/ceiling details are preferred.	Coved and splayed full floor databases should be provided. In addition wall/wa and wall/ceiling covings should be provided .
Doors and Windows	Should meet general building code requirements.	Should meet general building code requirements.	Typical materials include metal with a painted finish, PIB in high washdown or corrosive areas. Vision panels may be glass (regular gold reinforced), Plexiglas, Lexan, or equivalent materials. Horizontal surfaces should be accessible for easy cleaning. Flush glazing is not required, but should be considered to enhance cleanability. Meet building codes. Drop sills there doors not needed if HVAC can accommodate leakage.	Devrait meet building codes. Typical materials include metal, vinyl, PVC, or similar finish. Vision panels may be glass (regular gold reinforced), Plexiglas, Lexan, or equivalent material. All surfaces should be designed and designed an artificial to be accessible fo cleaning. Stainless steel may be used for construction of the door, hardware and kick/mop platforms, aim is not mandatory.
Hardware	General purpose hardware, as required to comply with building and related codes. Suitability for any for industrial use is recommended.	General purpose hardware, as required to comply with building and related codes. Suitability for any for industrial use is recommended.	Designed to promote and provide access for cleaning. Typically, plated metals gold stainless steel.	Recessed and comes, where possible, accessible for cleaning. Typically, plated metals gold stainless steel.
Penetrations (through walls, floors and ceilings, into the room space)	Sealing is generally not required, except as necessary for fire resistance and thermal requirements.	Should be sealed with caulk to prevent contamination between areas, with escutcheon platforms suggested.	Should be sealed with caulk (Silicon caulk normalement bas acceptable) to prevent contamination between areas, with escutcheon recommended platforms. Fis has fire resistant sealant is required, it should be installed with silicon (or similar) caulking installed over its surface, gold covered by year flat escutcheon if tea fire resistant material does not provide a smooth finish.	Penetrations should be sealed. Silicon caulking is generally acceptable. Fis has fire resistant sealant is required, it should be installed with silicon (or similar) caulking installed over its surface, gold covered by year flat escutcheon if tea fire resistant material does not provide a smooth finis

Architectural Finishes

- ✓ Is this acceptable:
- ✓ **Suspended Ceiling / CLASS D**?

1. Manufacturing aera
2. Corridor & SAS
3. Washing area
4. Warehouse CNC





Architectural Finishes

Architectural Finishes

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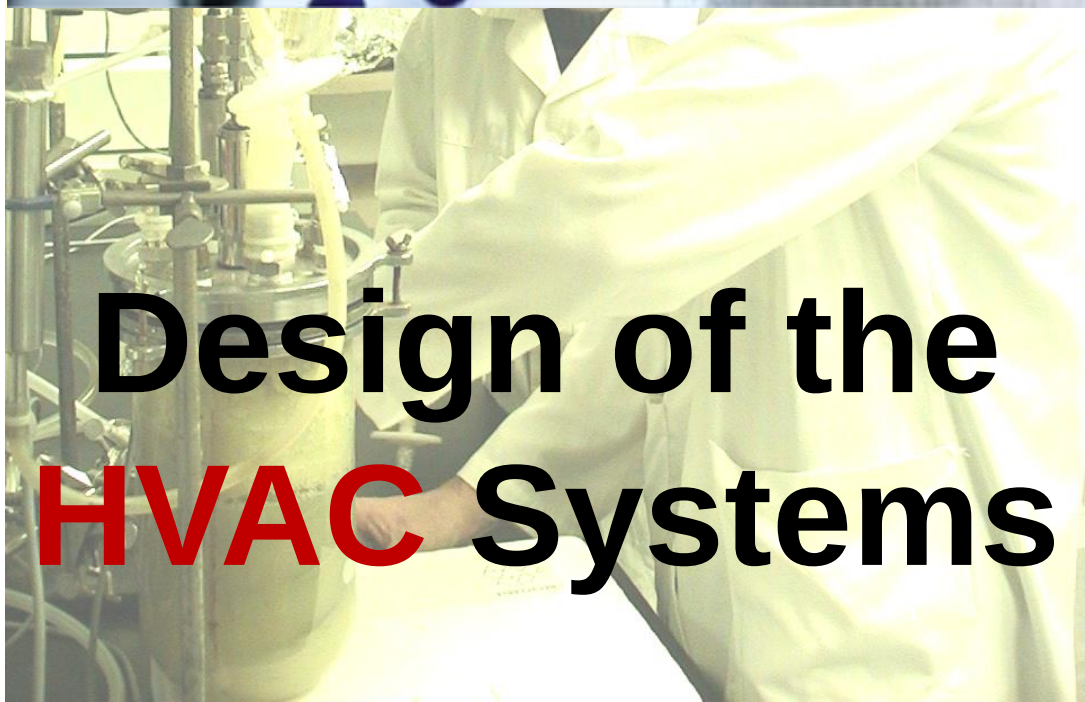
Dr. Aziz Chraibi , eng.

HEALTH CANADA EXPERT

PBE, Pharma Bio Expert Inc. President



Design of the HVAC Systems

HVAC & AHU

Different types of models of cleanrooms in the pharmaceutical industry:

- **HVAC** ventilation,
- **Turbulent Flow,**
- **Unidirectional vs Laminar**

- **Recycling Air Flow Rate ?**
- **Air supply Flow Rate ?**
- **Particles content ?**
- **Sizes of the rooms?**
- **HVAC system for contaminants removal effectiveness**

Critical items / Clean Rooms / HVAC WHO-TRS-961-2011

1. Architectural finishes, structures
2. Air Filtration, Air Change Rate, Recycling, Direct Exhaust
3. Psychrometric conditions of the atmospheric air
4. Pressure & air classification cascade between rooms
5. Position of the terminal filters and airflow direction
6. Temperature & Relative Humidity RH% range
7. Material, Peronnel, RW, FG Flows
8. Gowning, Cleaning, Disinfection procedures
8. Open vs Closed Systems vs products MSDS, HP, HSE, ATEX

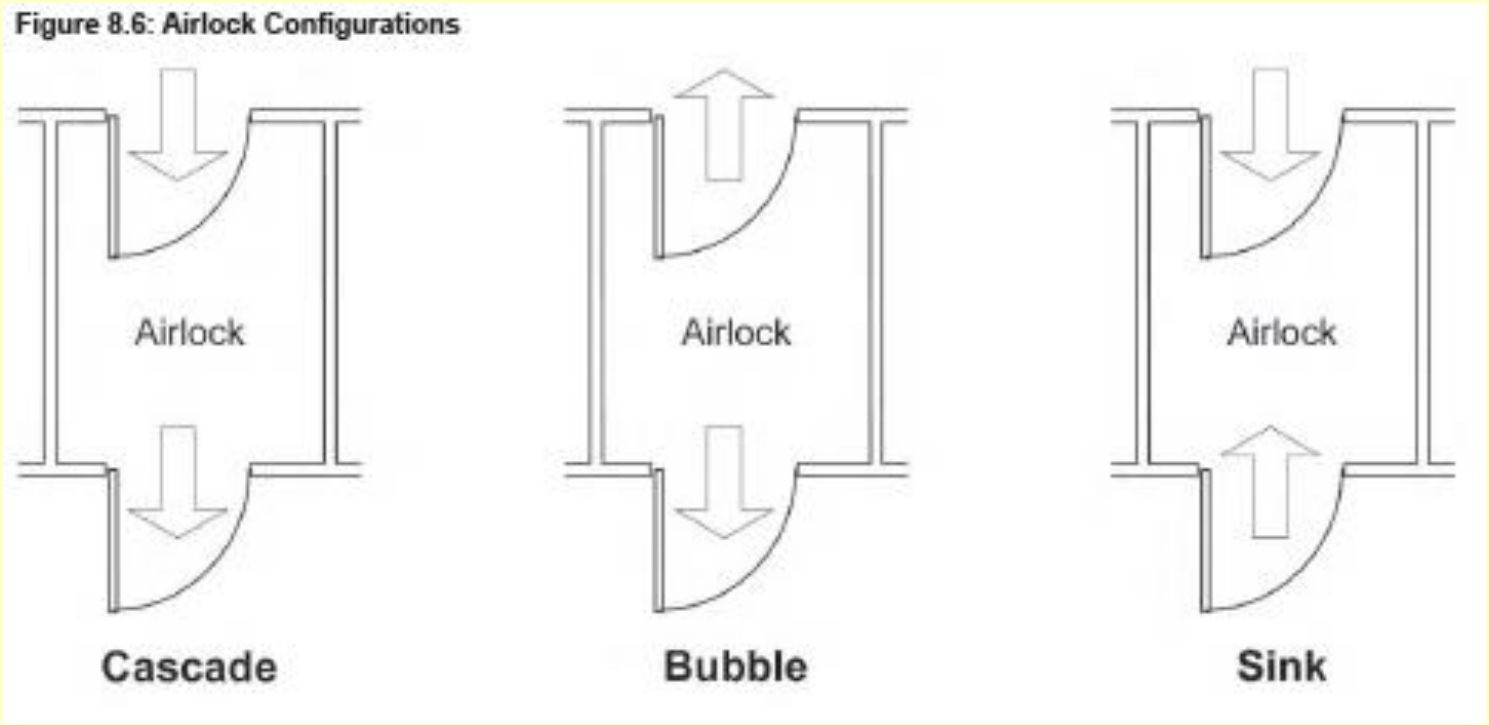
Description of the HVAC and Classrooms

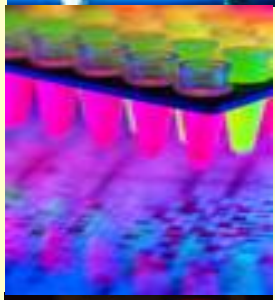
- **Fresh Air Rate** (HSE requirement)
- Air Change Rate : **ACR** (Cleanliness issues)
- **Recovery Time** of level of cleanliness (**Interlock** of PAL & MAL doors)
- **VNV** Particle count

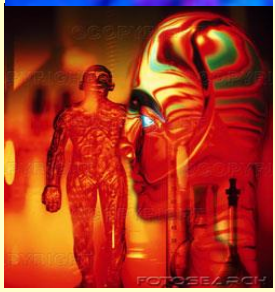
Recovery Time / WHO - TRS 937, page 65/478

- ✓ Normalement Bas has room that is tested for year "operational " condition should be able to be cleaned up to the " **at-rest** " clean area classification after a short clean-up time.
- ✓ The clean-up time should be determined through validation and is generally of the order of **20 minutes** .

Prevention Technology / Physical Segregation / Cascade of pressure / PAL & MAL

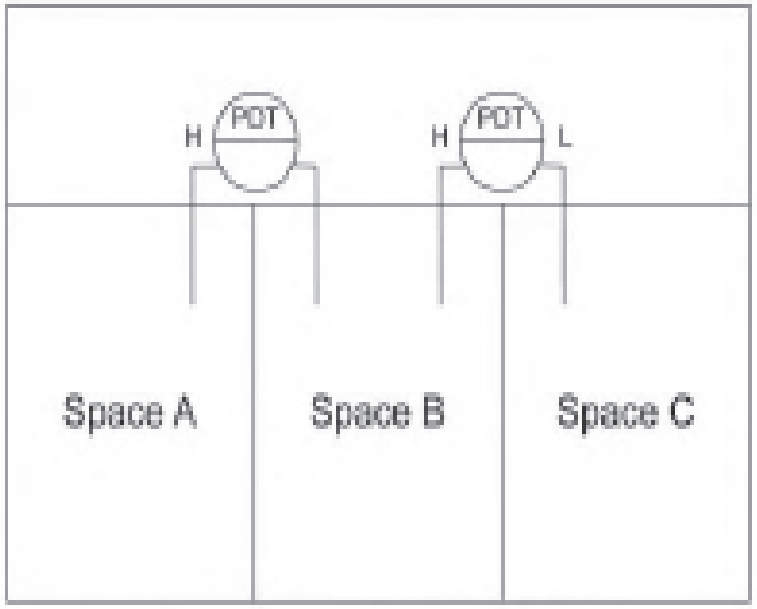




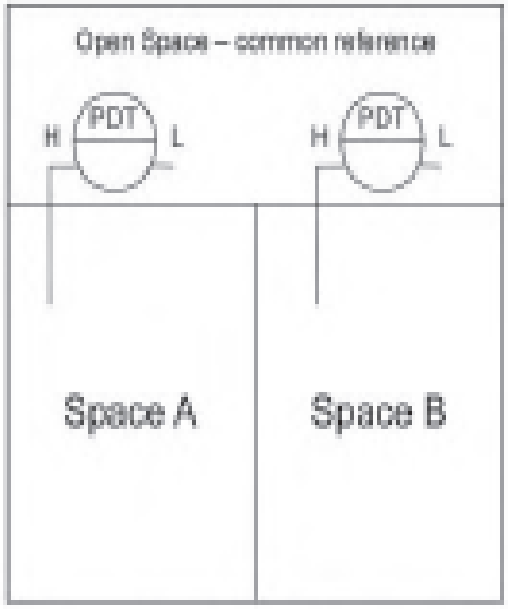


Configuration of differential pressure measurem

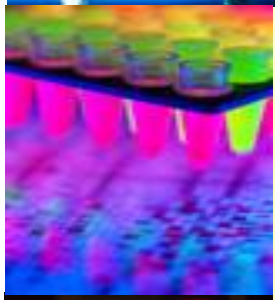
Figure 8.10: DP Sensor Locations

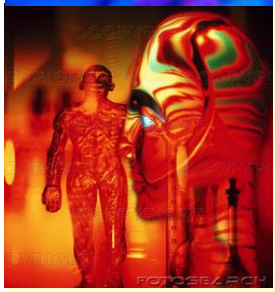


Room-to-Room Monitoring



Common Reference Monitoring





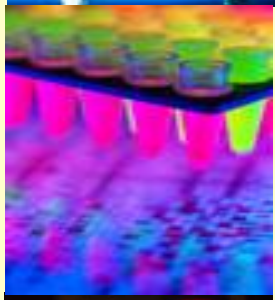
Air supply system (HVAC)

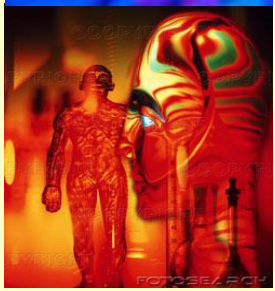
Based on what the design?

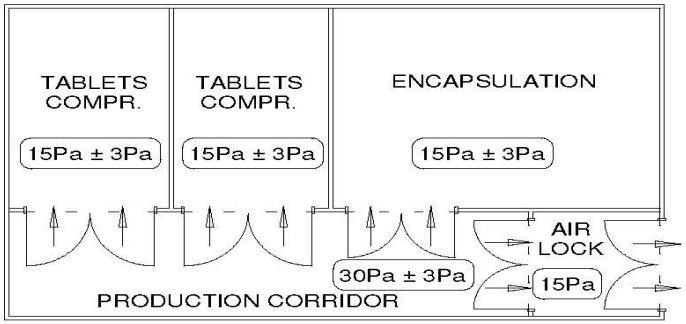
✓ NEBB / BPF EMA : require cascade of pressure a pressure differential of 0,05" / 0.06inwc = 12.5 / 15Pa)

between each level of air classification

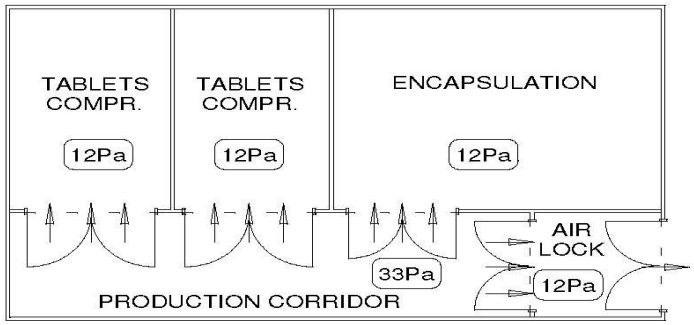
Prevention Technology / Cascade of pressure



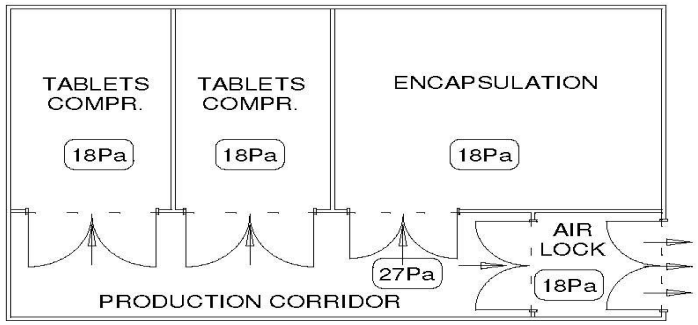




DESIGN CONDITION



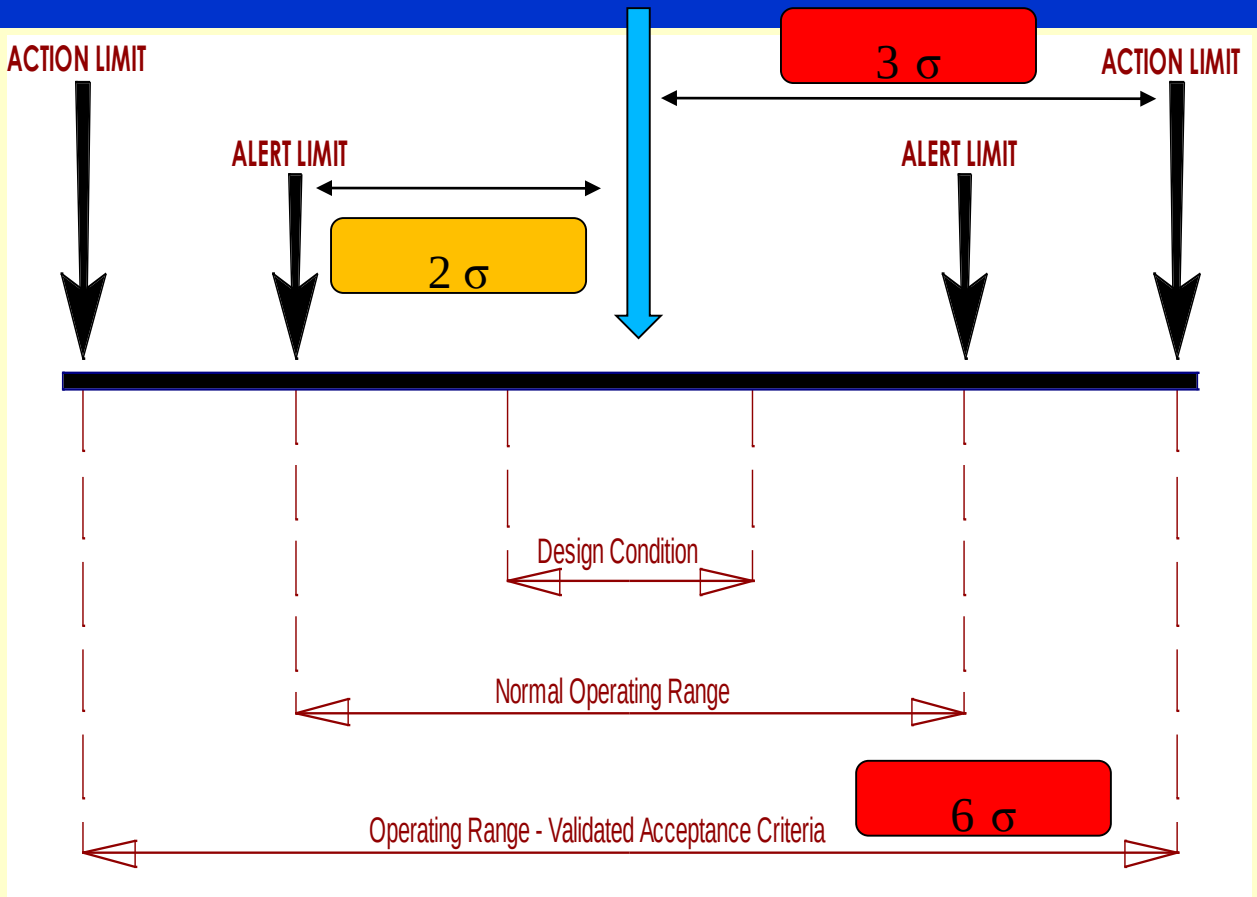
MAXIMUM DIFFERENTIAL



MINIMUM DIFFERENTIAL

URS : DESIGN APPROACH

- *Design conditions (±1 * Sigma)*
- *Normal operating ranges set to achievable limits*
- ***Alert Points** (±2 * Sigma) **OOT***
- ***Action Points** (±3 * Sigma)*
- ***OOS** results recorded*
- ***CAPA***



Action Limits = Average + /- 3 sigma
Warning limits = Average + /- 2 sigma
Sigma = gap type/ 1.128

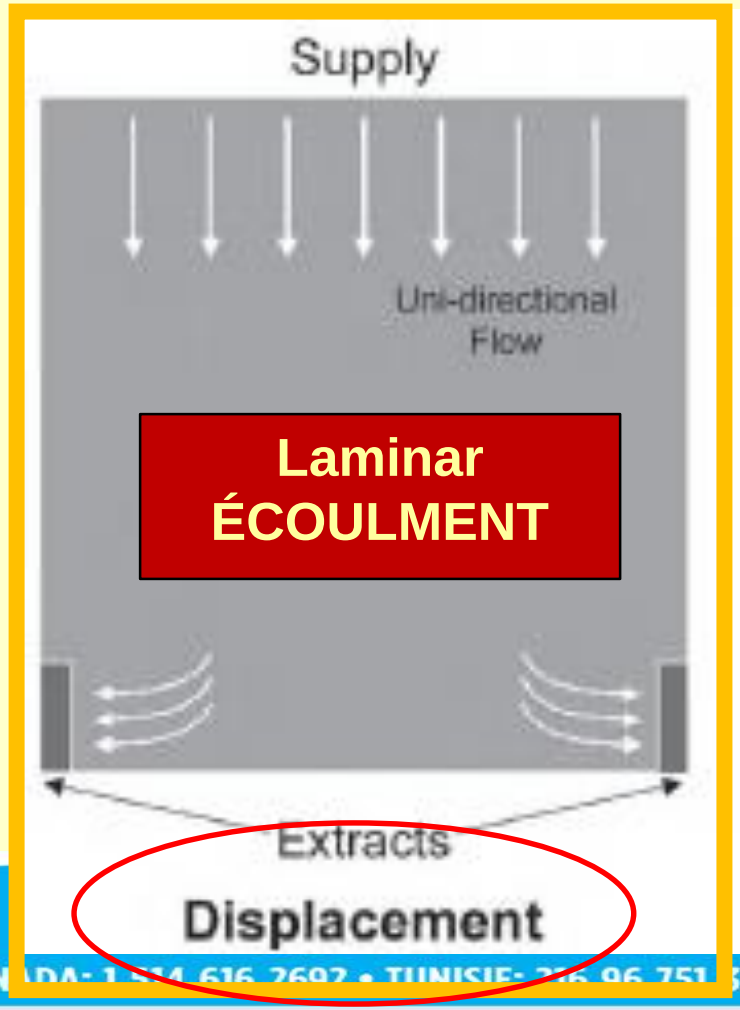
Facility Design

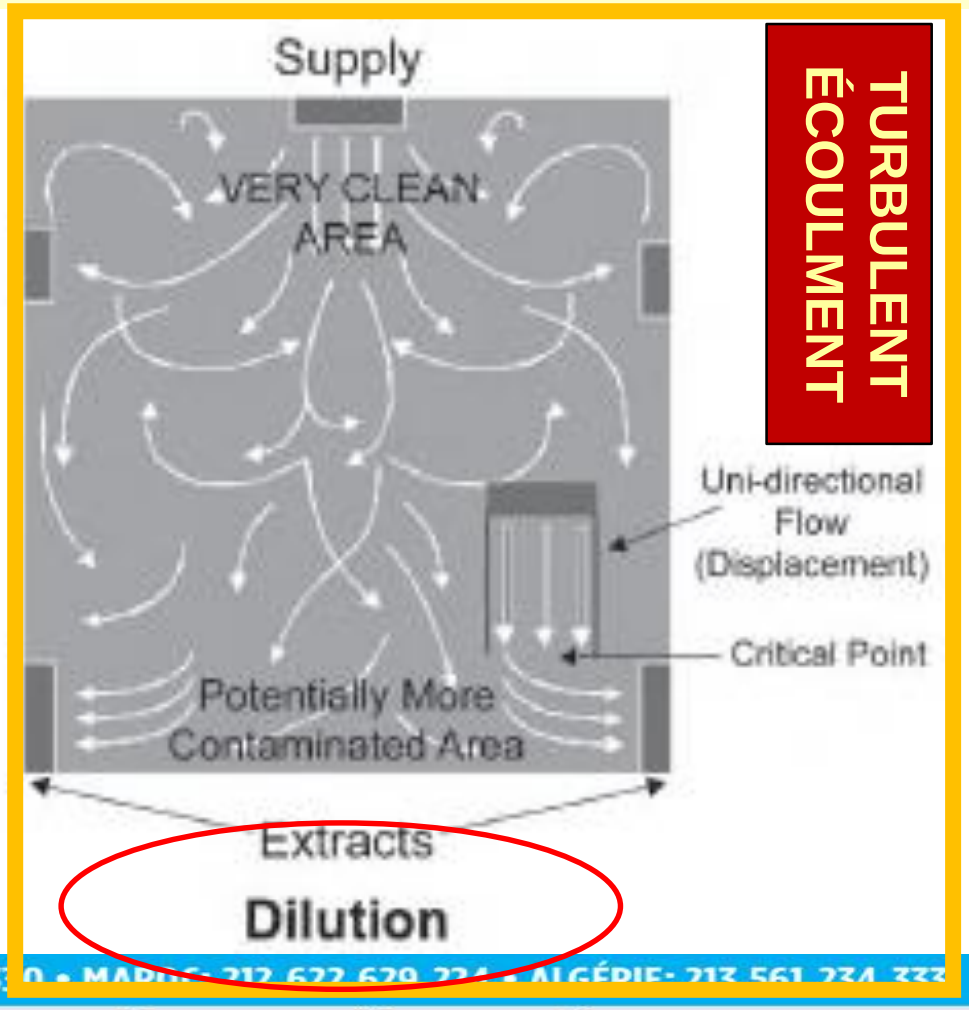
Nom du lient

Classification des locaux - Bâtiment

Nom du Local	Local No.	DIMENSIONS (m) * approx.			Surface	Volume	Degré de risque	Aseptique (IIIb) Ispe	CLASSIFICATION			Temps maximum de récupération (< 15 mn / EMEA)	Taux de Changement d'Air minimum (ACR)	Pressurisation		Température	Humidité	Capteurs	Désinfection :	Liquide Poussière Solvant Vapeur	Chaeur dégagée	Remarques	
		L	P	H	(m^2)	(m^3)	1 / 2 / 3 / 4	Oui / Non	FDA	ISO 14644-1	Repos / Activité	(mn)	(/h)	signe vs local adjacent	(Pa)	(°C)	(% HR)	T ΔP RH% CP N2	VHP (V), Formol (F), Alcool ou Anios (A)	L, P, S, V	KwH	Code habillement G1 à G6	Nombre maximal de personnes dans le local
Aire de Production	**1**									8			20										
	2									7			30										
	3									6			90										
	4									5			150										

Air Flow Pattern : Air Diffusion or by Displacement





UDAF vs LAF Sampling & Weighing Booth

- ✓ 4.3.3 **Sampling of materials**
- ✓ Such as **starting materials,** **WHO_TRS-937 p71**
- ✓ **Primary packaging materials and products ,**
- ✓ **Should be carried out**
- ✓ **In the same environmental conditions**
- ✓ **That are required for**
- ✓ **The further processing of the product .**

UDAF vs LAF Sampling & Weighing Booth

- ✓ 4.3.4 In a **weighing booth** situation,
- ✓ The aim of the design using **UDAF**
- ✓ **Should be** to provide **dust containment'** .

WHO_TRS-937 p71

Required? CDP under Laminar Flow?

- ✓ 4.3.5 A **dispensary or weighing booth**
- ✓ **Should be** provided with
- ✓ **Unidirectional airflow**
- ✓ For protection
  - ❖ Of the **product**
  - ❖ And operator

Safe Operation under a Booth

Laminar Flow?

UDAF vs Laminar Air Flow

Minimum required	UDAF	Laminar Air Flow
1- HEPA Filter	Yes	Yes
2- Integrity Test	Yes (12 Months)	Yes (6 to 12 Months)
3- Speed	0.2 to 0.45 m/s ± 20% 15-30cm under HEPA	0.45M/s ± 20% (Less 4 RABS) 15-30cm under HEPA
4- Unidirectional Flow	Yes + Air Flow Test (Smoke)	Yes + Air Flow Test / Smoke
5- Air Classification Particles	ISO7, C (+ If Aseptic)	ISO5, A
6- Continuous Monitoring of particles account	Non	Yes (A + Critical Processes)
7- Operators may work under the booth	Yes	Non
8- Differential Pressure	+	+
9- Protection of	Product & Personnel	Product

AIR SHOWER

To be Installed Where ?

When Required ?

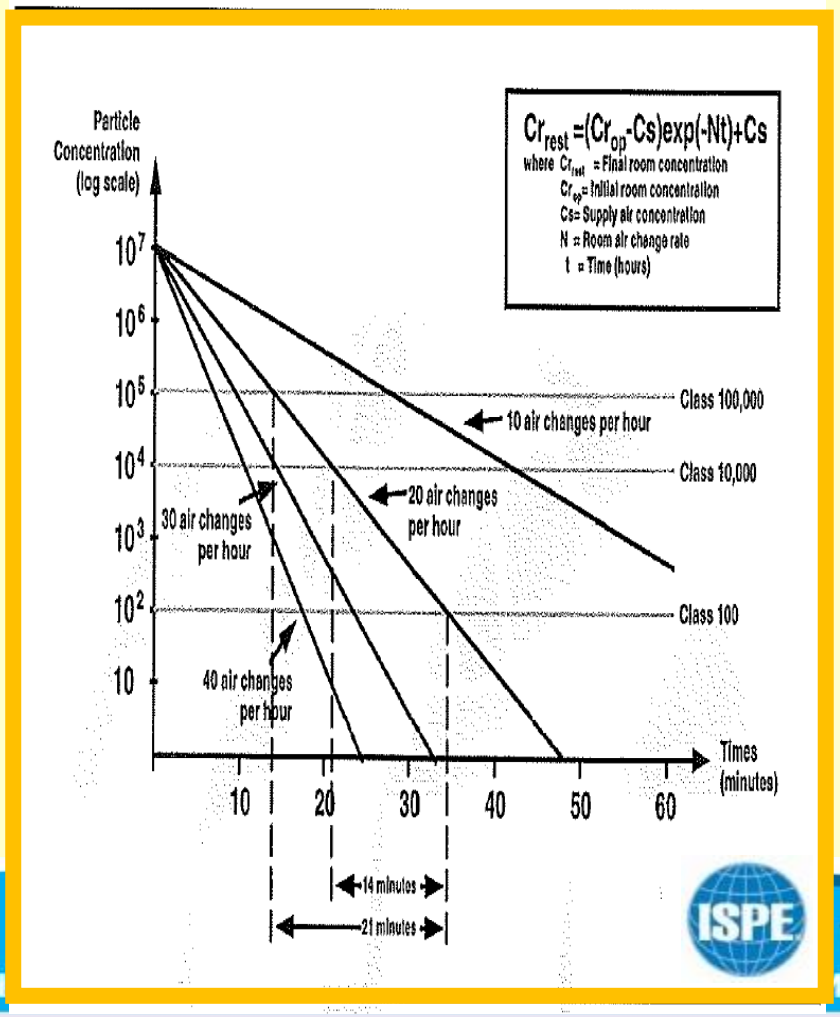
Air supply system Capacity (HVAC)

The sizing of the HVAC unit (its Cost $$$) will depend :

1. Internal contaminant loads
2. Dissipated heat by the equipment
3. Number of working personnel
4. Cleanroom air classification
5. Type of filtration (HEPA)
6. Loses of the pressure on the Filters
7. Hourly ACR : air change rate
8. Temperature & RH% difference between Fresh air and CR.

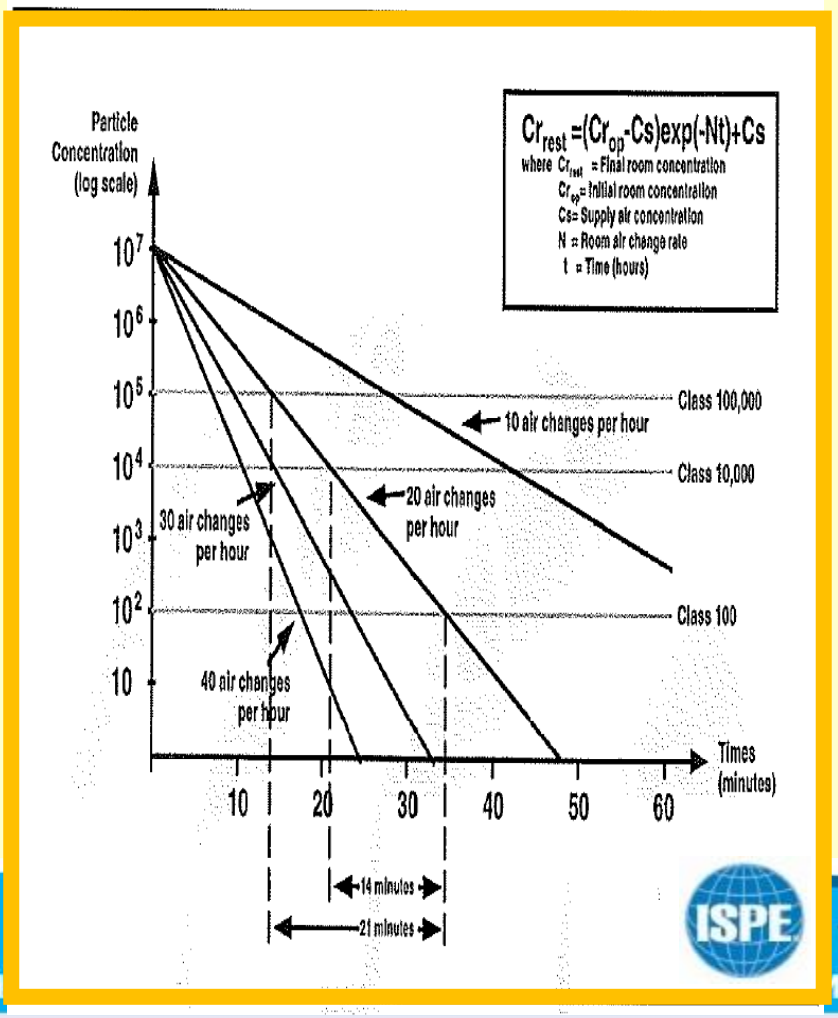
$$Cr_{Rest} = (Initial\ Cr - C_S)\ exp(-N.t) + C_S$$

RECOVERY TIME of the air quality
ISPE, ISO-14644-3 (B12)



Recovery Time (mn)	ISO8/D @ ISO7/C	ISO7/C @ ISO 5/A	ISO8/D @ ISO 5/A
ACR10			
ACR20	7	14	21
ACR30			
ACR40			
ACR60			
ACR120			
ACR240			

Recovery Time of the Air Quality ISPE, ISO-14644-3 (B12)



The " **clean-up** " or " **recovery** " test should demonstrate a change in particle **concentration** by a factor of **10 to 100** Within the prescribed time.
(WHO, Annex 4, Sterile)
(ISO 14644-3 clause B. 12)

Maximum permitted airborne particle concentration

	Maximum permitted number of particles per m^3 greater than or equal to the tabulated size			
	At rest[a]		In operation[b]	
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

[a] The "at rest" state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

[b] The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the "at rest" and "in operation" states.

HVAC Design vs Level Protection & Classification / ISPE

Level	Condition	Example of area
Level 1	**General**	Area with normal housekeeping and maintenance where there is no potential for product contamination, e.g. warehousing.
Level 2	**Protected**	Area in which steps are taken to protect the pharmaceutical starting material gold product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing, first stage changed rooms.
Level 3	**Controlled**	Area in which specific environmental conditions are defined, controlled and monitored to prevent contamination or degradation of the pharmaceutical starting material gold product, e.g. where product, starting materials and components are exposed to the room environment; more equipment wash and storage areas for equipment product contact parts.

Levels of protection and recommended filtration / ISPE

Level of Protection	Recommended Filtration
Level 1	Primary filters only (e.g. IN 779 **G4** filters)
Level 2	Protected areas operating on 100% outside air: primary more Secondary filters (e.g. IN 779 **G4** more **F8** or F **9** filters)
Level 3	Production facility operating it recirculated more ambient Air, where potential for cross-contamination exists: Primary plus secondary more tertiary filters (e.g. IN 779 **G4** more **F8** more 1822 **H13** filters) for full fresh air system , without Recirculation, **G4** and **F8** or F **9** filters are acceptable)

Note: The filter classifications shallbe referred to above relate to the 1822 and in 779 test standards (IN 779 recounted to filter classes G1 to F9 and 1822 recounted to filter classes E10 to U17). Refer to Figure 8 for comparative classifications of other filter standards.

TABLE 6-1 - Suggested minimum design values (see text for details/exceptions)

CONTROLLED VARIABLE	LEVEL I	LEVEL II	LEVEL IIIa Non - aseptic	LEVEL IIIb Aseptic
Temperature	50-105F (10-40.6°C)	Product reqmt	Product reqmt	Product reqmt
RH	20-60% recomm	Product reqmt	Product reqmt	Product reqmt
Room classification	none → 60%	none	none	Class 10,000 EC Grade B
Supply air filter	30% ASHRAE	30% ASHRAE*	85% ASHRAE*	HEPA 99.97%
Room air changes	Codes & NFPA	Codes & NFPA	Codes & NFPA	20 (Unidirectional flow ** at product)
Differential Pressure	none	protect the product	controlled airflow	0.05 or 0.06 inch wg (12.5 or 15 Pascal) positive
Differential Pressure (potent)	none	negative	negative or positive to anteroom	Pressure buffer at 0.05 or 0.06 inch wg (12.5 or 15 Pascal)
Outdoor air	code & ASHRAE62	code & ASHRAE62	code & ASHRAE62	As required for pressurization §
Duct material	galvanized steel, aluminum	galvanized steel, aluminum	galvanized steel, aluminum	Stainless steel, plastic, or cleanable equivalent where exposed to room
Duct leakage	This is an economic decision, follow SMACNA standards			
Validation	none	Product req.◆	Product req.◆	Product req.◆ + air changes + HEPA**

*	For once through air. Recirculated air may require additional treatment
**	Pinhole scanned 99.99% HEPA filtration of air in direct contact with product, air class 100 or better at product, unidirectional flow at nominal 90 ft/min (0.46m/s). EC Grade A. See ASHRAE Applications, ISO/IES or forthcoming ISPE Guide on aseptic production facilities.
§	It is assumed that the volume of makeup air for pressurization will provide more outdoor air than required by ASHRAE 62.
◆	Sensors / indicators / alarms / recorders for Critical Product Parameters

For details of American Society of Heating, Refrigeration, and Air Conditioning Engineering (ASHRAE) and Sheet Metal & Air Conditioning Contractors' National Association (SMACNA) standards see Chapter 12 *References*.

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HEALTH CANADA EXPERT

PBE, Pharma Bio Expert Inc. President

Detailed Design of HVAC Components

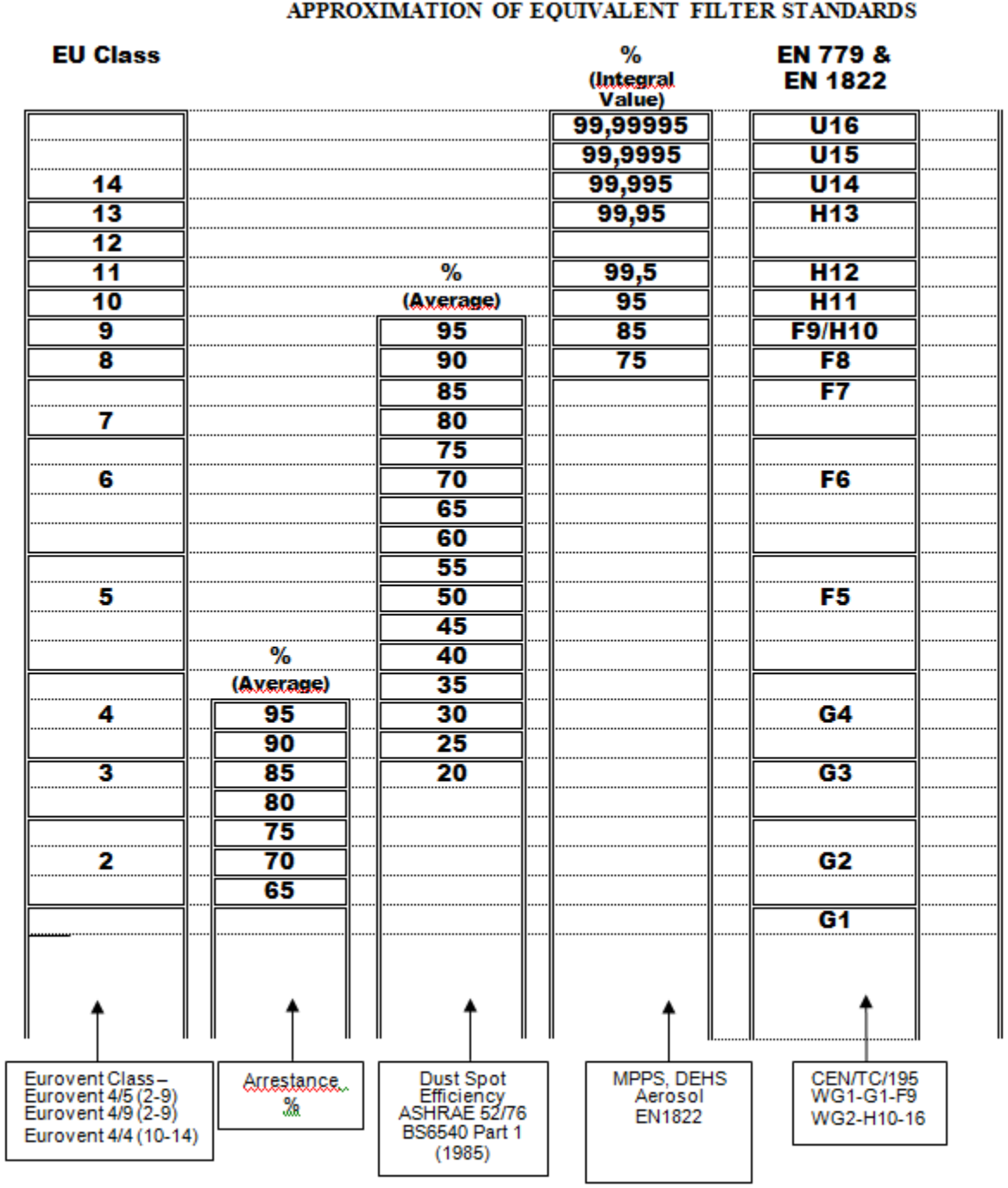

Fig. 4.7 Comparison of filter test standards

WHO TSR937 Page 69

Table 1: Values ASHRAE 52.2 &779 HEPA Filters

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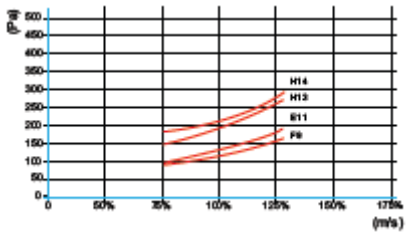
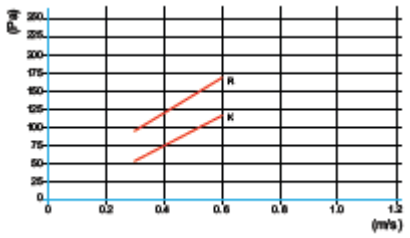
Filter Value ASHRAE 52.2 (Eurovent IN779)	Loss of load Initial maximum (Inches of col. of water/Pa)	Loss of load The recommended Filter change (Inches of col. of water/ Pa)
Merv 8 (G4)	0.10 / 25	0.20 / 50
Merv 11 (G4)	0.32 / 80	0.65 / 160
Merv 13 (F7)	0.40 / 100	0.80 / 200
Merv 15 (F9)	0.50 / 125	1.0 / 250
HEPA Filters online	0.60 / 150	1.2 / 300
Filters HEPA / ULPA	0.50 / 125	1.0 / 250

HEPA Filters

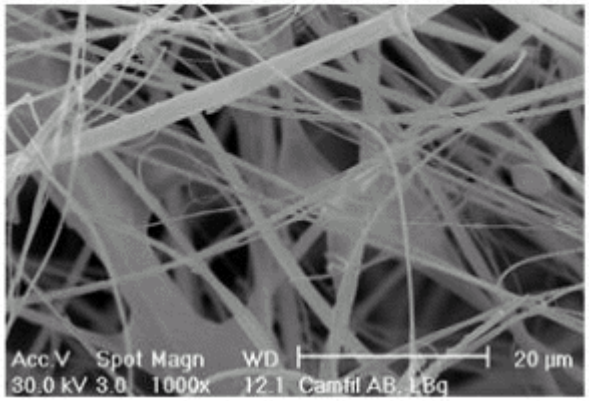
HEPA Filters



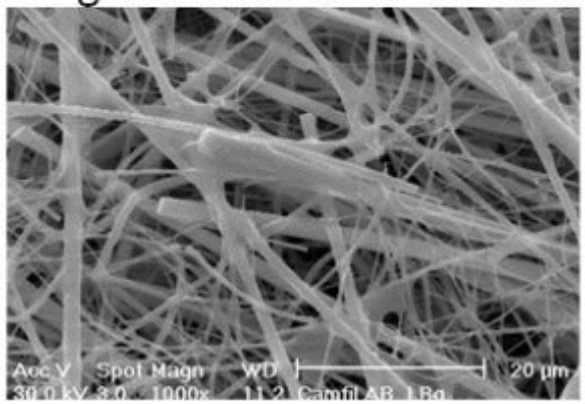


↗ Ø fibres ⇒ ↘ efficacité
↗ Densité de fibres ⇒ ↗ efficacité

Hi-Flo F7 Fibres

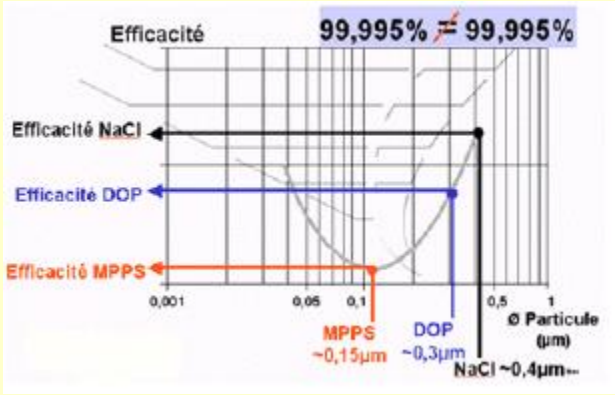


Megalam H14 Fibres

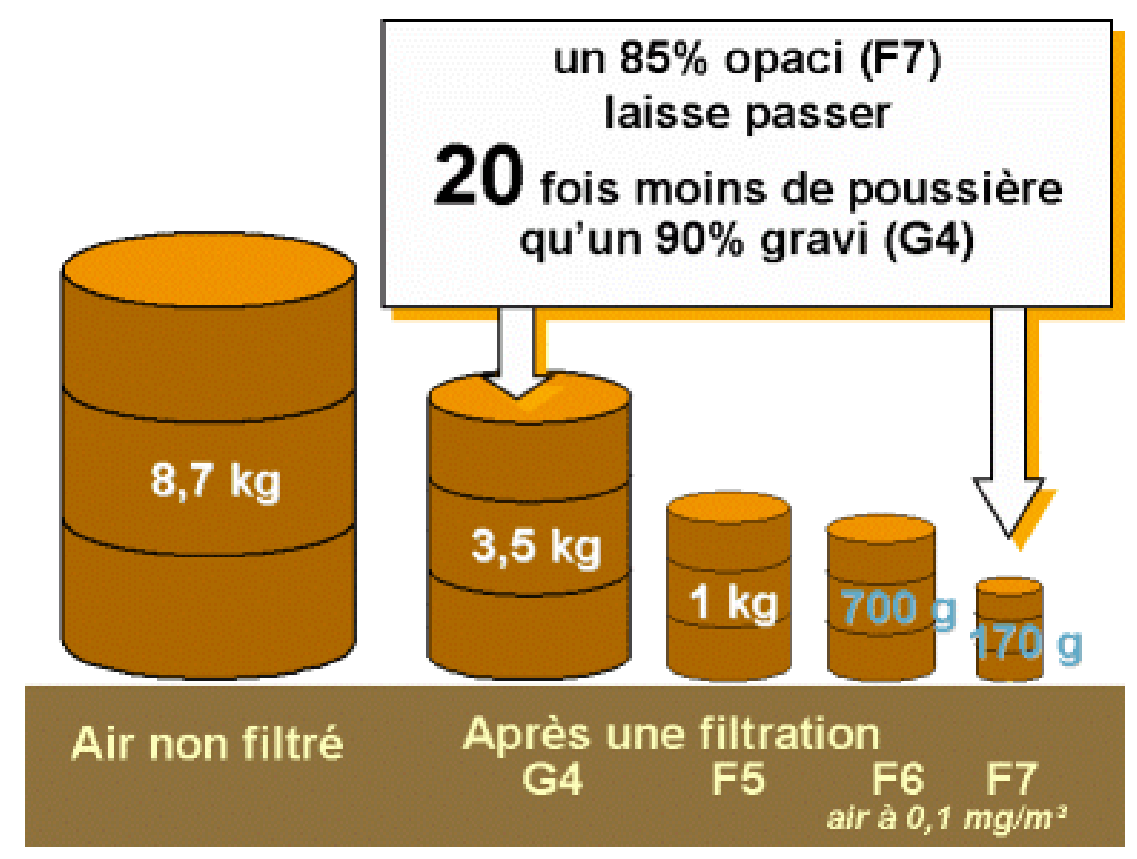


Integrity Test HEPA Filters

Challenge Aerosols Frequently Used for HEPA Testing	
DEHS (DOS), a liquid	Di-ethyl hexyl sebacarte
DOP, liquid	Di-octyl phthalate
Emery 3004, liquid	Product name for a type of PAO
PAO, liquid	Poly-alpha olefin
PSL	Poly-styrene latex spheres
Shell Ondina EL, liquid	Refined mineral oil
Total Finaveston A80B, liquid	Refined mineral oil



What Filter category Should I install ?



ABSOLUTE FILTERS

What reference for validation?

1.Effectiveness overall MPPS?

1.Effectiveness local MPPS ?

ABSOLUTE HEPA FILTERS

Standards

Two standards govern the filters:

- **1822: this standard deals with testing of performance of the filters to very high efficiency (HEPA) and very low penetration (ULPA)**

Note:

The value of **the overall MPPS efficiency** is the one being searched for the qualification tests .

MPPS : Most Penetrative Particle Size

Tests: ISO-14644 vs Classification

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Table 2: Required Testing (ISO 14644-2)

Schedule of Tests to Demonstrate Continuing Compliance			
Test Parameter	**Class**	**Maximum Time Interval**	**Test Procedure**
Particle Count Test	<= ISO 5	6 Months	ISO 14644-1 Annex A
	> ISO 5	12 Months	
Air Pressure Difference	All Classes	12 Months	ISO 14644-1 Annex B5
Airflow	All Classes	12 Months	ISO 14644-1 Annex B4

Optional Tests: ISO-14644 vs Classification

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Table 3: Optional Testing (ISO 14644-2)

Schedule of Additional Optional Tests			
Test Parameter	**Class**	**Maximum Time Interval**	**Test Procedure**
Installed Filter Leakage	All Classes	24 Months	ISO 14644-3 Annex B6
Containment Leakage	All Classes	24 Months	ISO 14644-3 Annex B4
Recovery	All Classes	24 Months	ISO 14644-3 Annex B13
Airflow Visualization	All Classes	24 Months	ISO 14644-3 Annex B7

HVAC Components Design

22. **Supply diffusers** :

- By **induction**
- By **perforated plate**

Elements of HVAC design - WHO - TRS-929 (Annex 3)

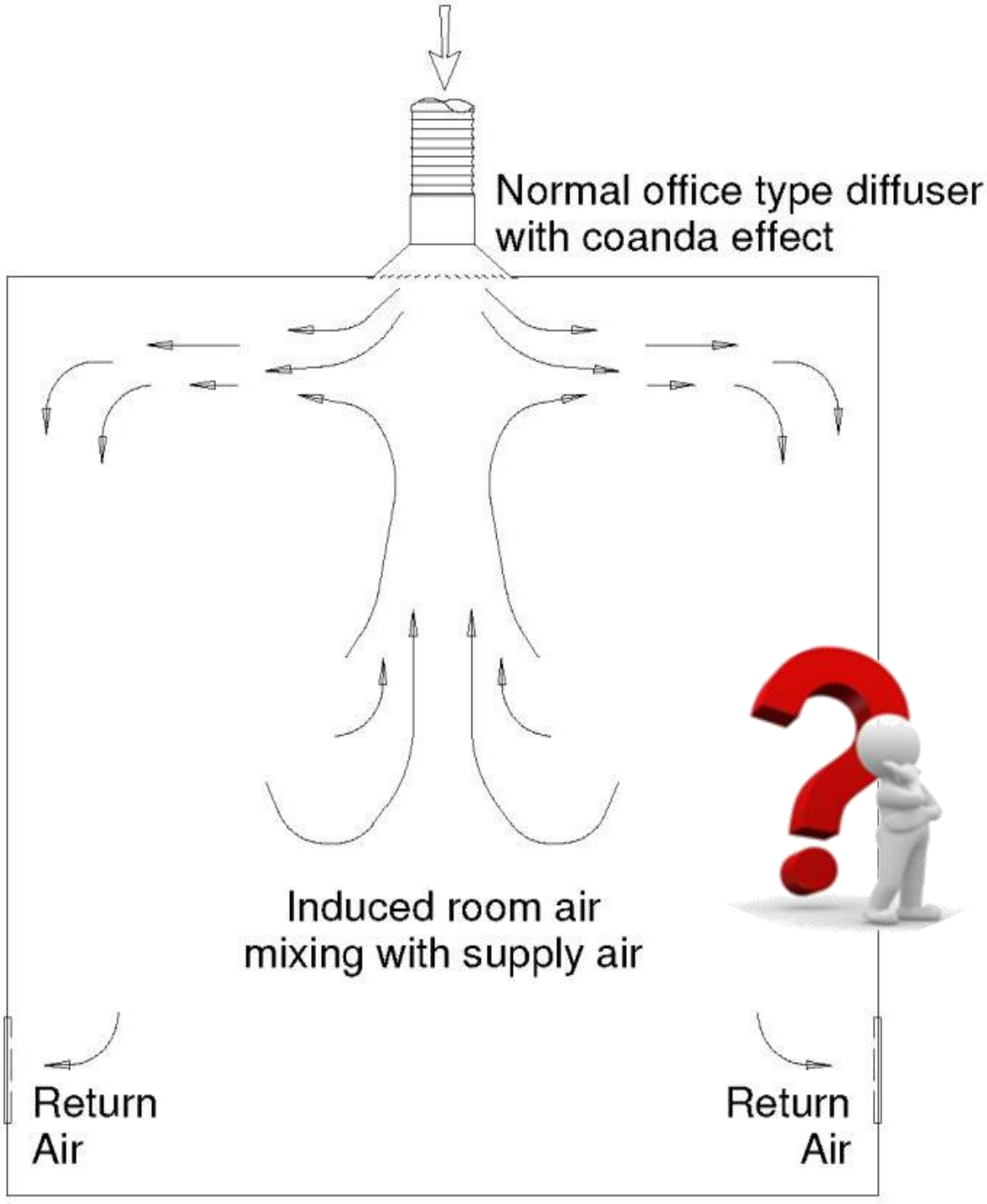
- ✓ 4.2.9 Supply air **DIFFUSERS** of the high **INDUCTION type** (e.g. those typically used for office-type air-conditioning) should where possible **not be used in clean areas** where dust is liberated.
- ✓ **Air diffusers should be of the non-induction type**, introducing air with the least amount of induction so as to maximize the flushing effect

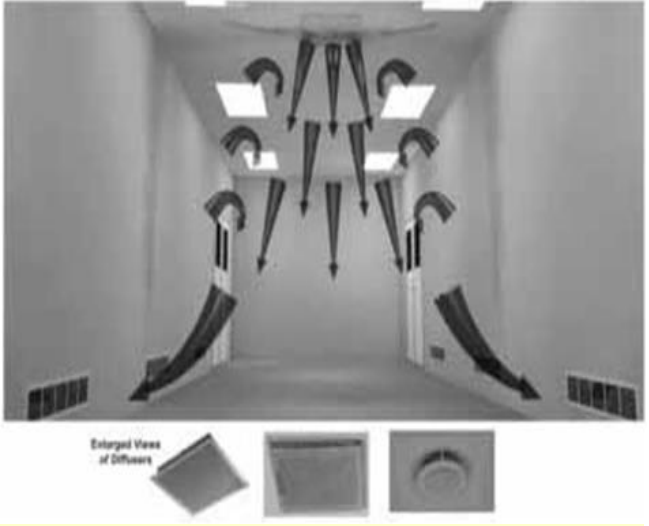
Induction diffuser

✓ Fig. 4.8 (WHO-Working document QAS/02,048 /Rev. 1)

Induction diffuser

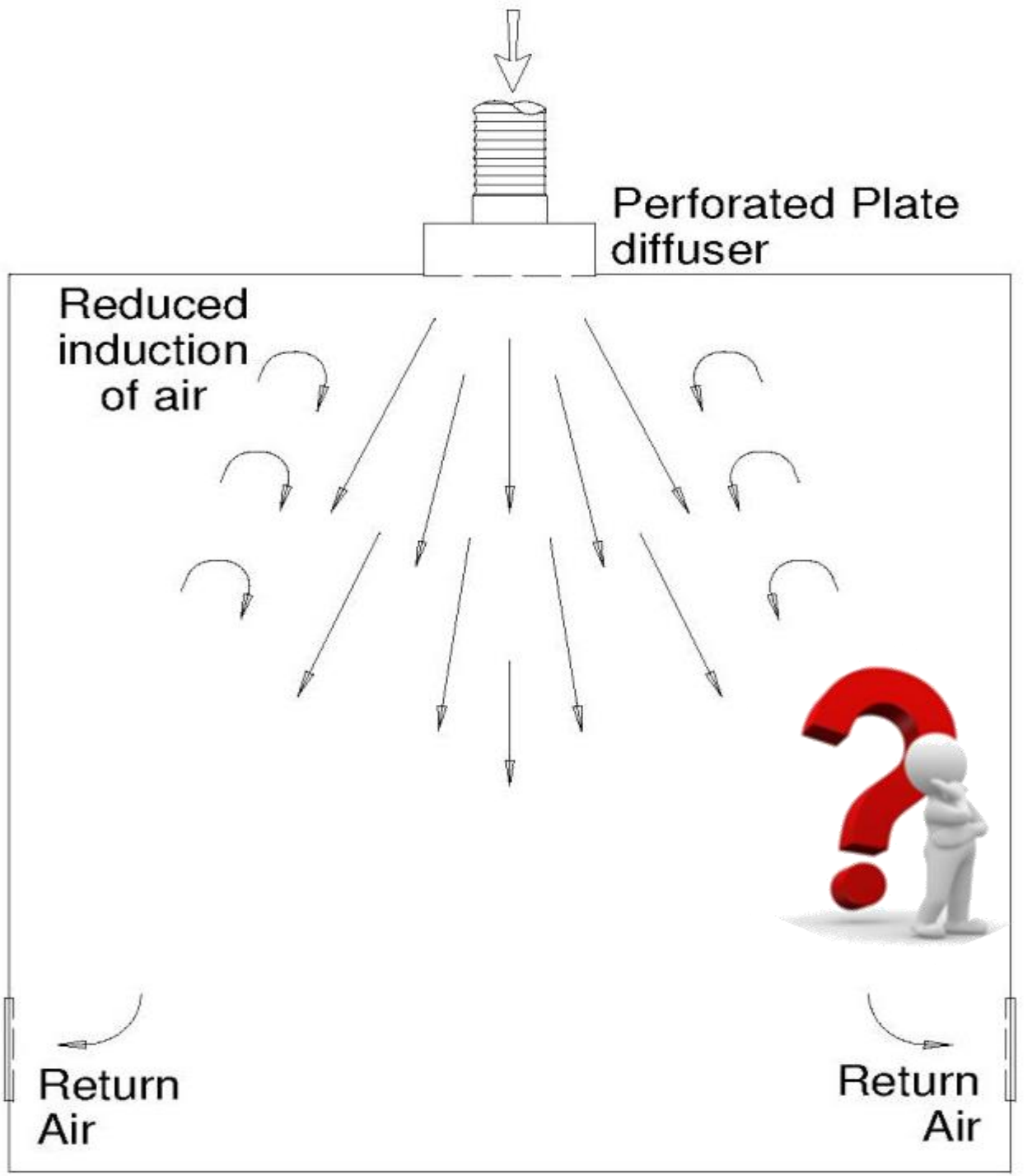
(Not recommended)





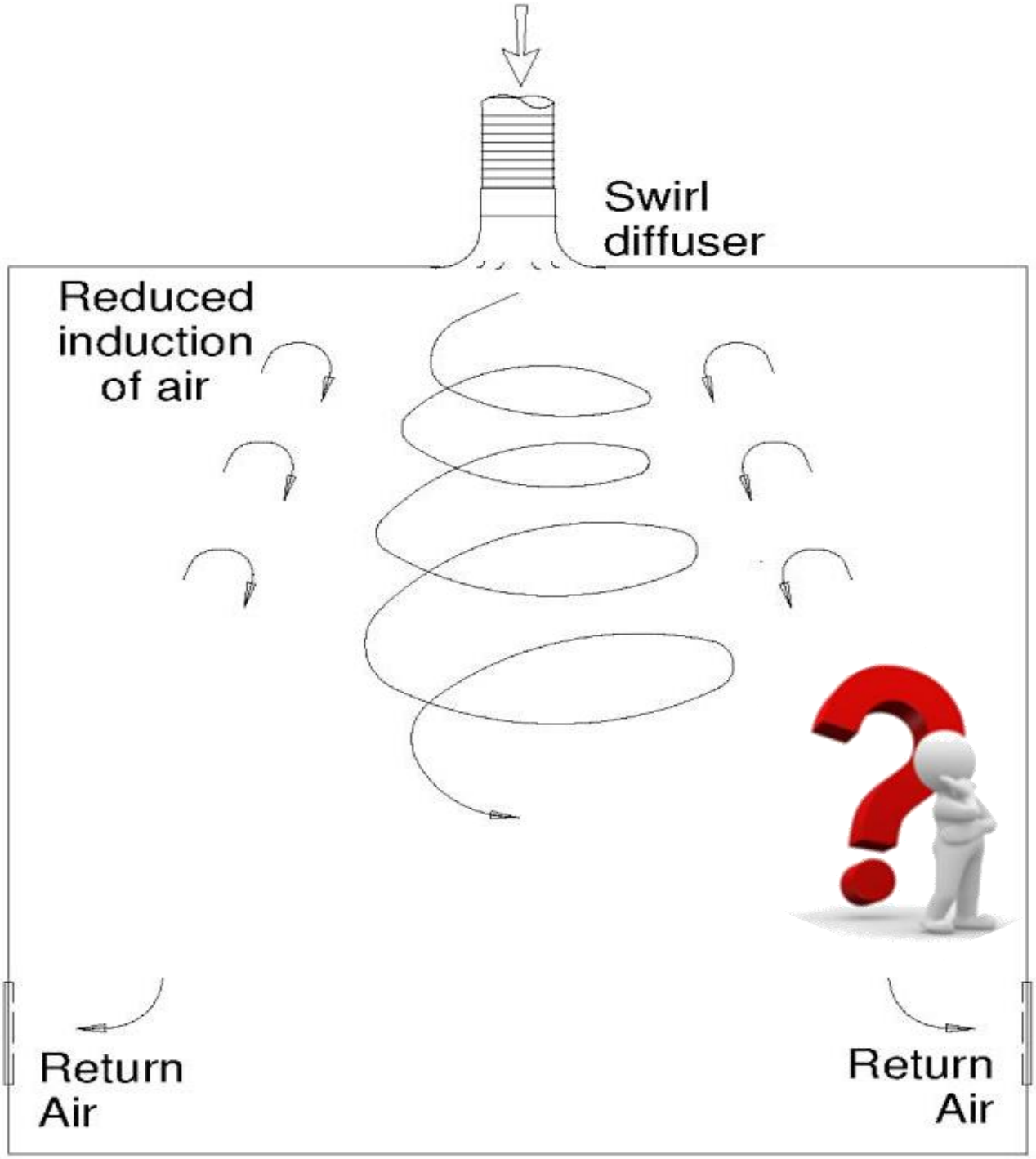
- ✓ Fig. 4.9 (WHO-Working document QAS/02,048 /Rev. 1)

Perforated plate diffuser (Recommended)



- ✓ Fig. 4.10 (WHO-Working document QAS/02,048 /Rev. 1)

Swirl diffuser (recommended)



HVAC Design Elements - API / OSD / RH %

WHO-2011-06 / TRS 961

4.9.4 Cubicles, or suites, in which products requiring low relative humidity are processed, should have **well-sealed walls and ceilings** and should also be **separated** from adjacent areas with higher relative humidity by means of suitable airlocks.

Design Elements - API / OSD / RH %
WHO-2011-06 / TRS 961

4.9.9 **Humidifiers** should be **avoided** if possible as they may become a **source of contamination** (e.g. microbiological growth).

…

A product-contamination assessment should be done to determine whether **pure or clean steam** is required for the purposes of humidification.

Éléments de conception – API / OSD / RH %
WHO-2011-06 / TRS 961

4.9.9 **Humidifiers** should be **avoided** if possible as they may become a **source of contamination** (e.g. microbiological growth).

…

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Application of GMP

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GMP, GCP & Quality Control
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HEALTH CANADA EXPERT

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President

CASE STUDY

ASEPTIC (STERILE) DESIGN