



EXPERT
SANTÉ CANADA
MAPAQ

Cleanrooms, HVAC, Layouts from Design to Validation ISO-14644

PBE-Expert Inc – CANADA

Training Company Agreement CPMT #0059104

Qualified MAPAQ Consultant

At the measure 2 of the Levier Program

P B E
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PBE, Training Company Agreement CPMT #0059104

Commission des partenaires du marché du travail Québec

CERTIFICAT D'AGRÈMENT

Loi favorisant le développement et la reconnaissance des compétences de la main-d'œuvre

Titulaire : PBE, PHARMA BIO EXPERT INC.

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CHAMPS PROFESSIONNELS

- 01 Administration et commerce
- 03 Alimentation, hôtellerie et tourisme
- 06 Chimie et biologie

Par : Isabelle Benfleur

Le 7 février 2018

La délivrance du certificat est valide en fonction des documents soumis à la Commission des partenaires du marché du travail.

Ministère du Travail, de l'Emploi et de la Solidarité sociale

10-4282 (06-2003)
ENT-0031 (12-2016)



Summary

1. Regulatory framework & requirements.
2. URS / Clean Rooms reminder.
3. Types of contaminants.
4. Clean Rooms Design
5. Dress code & means of prevention.
6. Room classifications vs standards & applications.
7. Types of segregation, flows, cascades.
8. Building elements and architectural finishes.
9. Design of HVAC systems, wet/dry formulation.
10. HVAC design for Injectable & Sterile products.
11. Design in presence of Highly Toxic products (HP/OEL2-6).
12. Design in presence of hazardous biological products (BSL1-3).
13. Design in presence of EXPLOSIVE & Flammable products (ATEX3).
14. Personal protection equipment.
15. OEL containment equipment.
16. Elements of Commissioning / Validation of Premises & HVAC .



HVAC in 9 points

1. What is an HVAC?
2. Benefits of an HVAC?
3. Why use an HVAC?
4. How does an HVAC work?
5. HVAC/AHU/FFU details
6. HVAC system types/formulation
7. Cooling / Expansion Group, GFH Filters
8. Monitoring & Follow-up, Integrity tests
9. Design Considerations



Layouts & clean rooms (ZAC) in 9 points

1. What is a Layout, a Clean Room?
2. Benefits of Layouts, Clean Rooms, PAL, MAL?
3. Why use a Layout, Clean Rooms, PAL, MAL?
4. How does a Clean Room work?
5. Layout & Clean Rooms, PAL, MAL design.
6. Room classification according to ISO-14644, and cGMP.
7. Types of segregation according to needs and processes.
8. Cleaning Cascade & Pressure Cascade.
9. Control and Monitoring of CEP.
10. Design considerations.



Regulatory Framework : Cleaning (cGMP)



Regulatory Framework : (BPF/cGMP)

World Health Organization (WHO)

- http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html

EU - EMEA

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm

United States – FDA 21 CFRs

- <http://www.fda.gov>

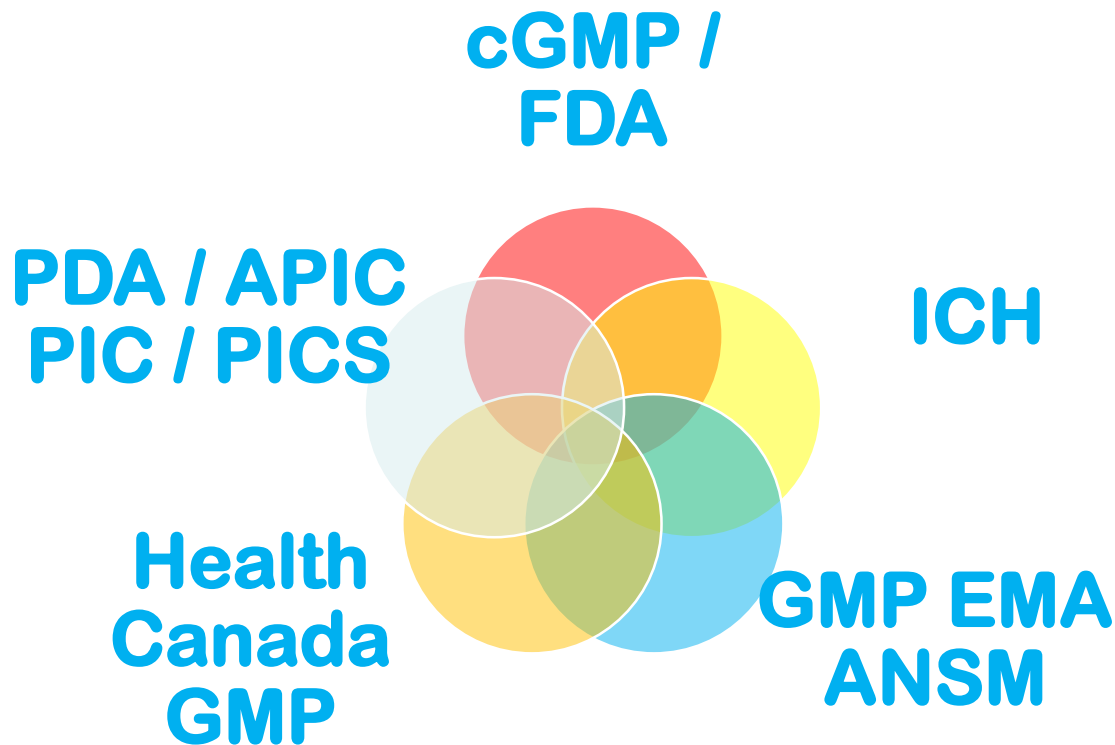
Canada – Health Canada

- <http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/index-eng.php>
- ICH = International Conference on Harmonization

<http://www.ich.org/products/guidelines/quality/quality-single/article/good-manufacturing-practice-guide-for-active-pharmaceutical-ingredients.html>



Laws & Regulatory vs country ?



Normative requirements

- ✓ The European Pharmacopoeia (Ph.Eur.)
- ✓ The French Pharmacopoeia (Ph.F.)
- ✓ Pharmacopoeia Internationalis (Ph.I.)
- ✓ The British Pharmacopoeia (B.P.)
- ✓ The Canadian Formulary (C.F.)
- ✓ The National Formulary (N.F.)
- ✓ The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
- ✓ The United States Pharmacopoeia (U.S.P.)



Clean Rooms: Regulations

GMP (Good Manufacturing Design) ed. 2002, Combined with the European standard ISO 14644 (Clean rooms and associated controlled environments)

ISO 14698 « Control of bio-contamination, measurement methods, principles of data estimation and evaluation (interpretation) and methods of surface cleaning and disinfection »

ISO 13408 « Aseptic treatment of health care products »

ASHAE 1999 (Application) Clean Space chap. 15

ISPE, vol 3, chap. 4 à 9 et 11

ISPE, vol 6, chap. 6 et 13

IENT (Clean Room Considerations) RP cc0012.1

➤ International Conference On Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use



Codes & Standards Requirements



AABC	: Associated Air Balance Council
ANSI	: American National Standards Institute
ASHRAE	: American Society of Heating Refrigerating and Air conditioning Engineers
ASME	: American Society of Mechanical Engineer
CRN	: Canadian Registration Number (Equipment Under Pressure)
CSA	: Canadian Standard Association
NABC	: National Air Balance Council
NEBB	: National Environmental Balancing Bureau
NFPA	: National Fire Protection Association
NEMA	: National Electrical Manufacturers Association
OSHA	: Occupational Health and Safety Administration
NIST	: National Institute Of Standards and Technology
SMACNA	: SMACNA Sheet Metal & Air Conditioning Contractors' National Association
ATEX	: Explosive Atmosphere



URS

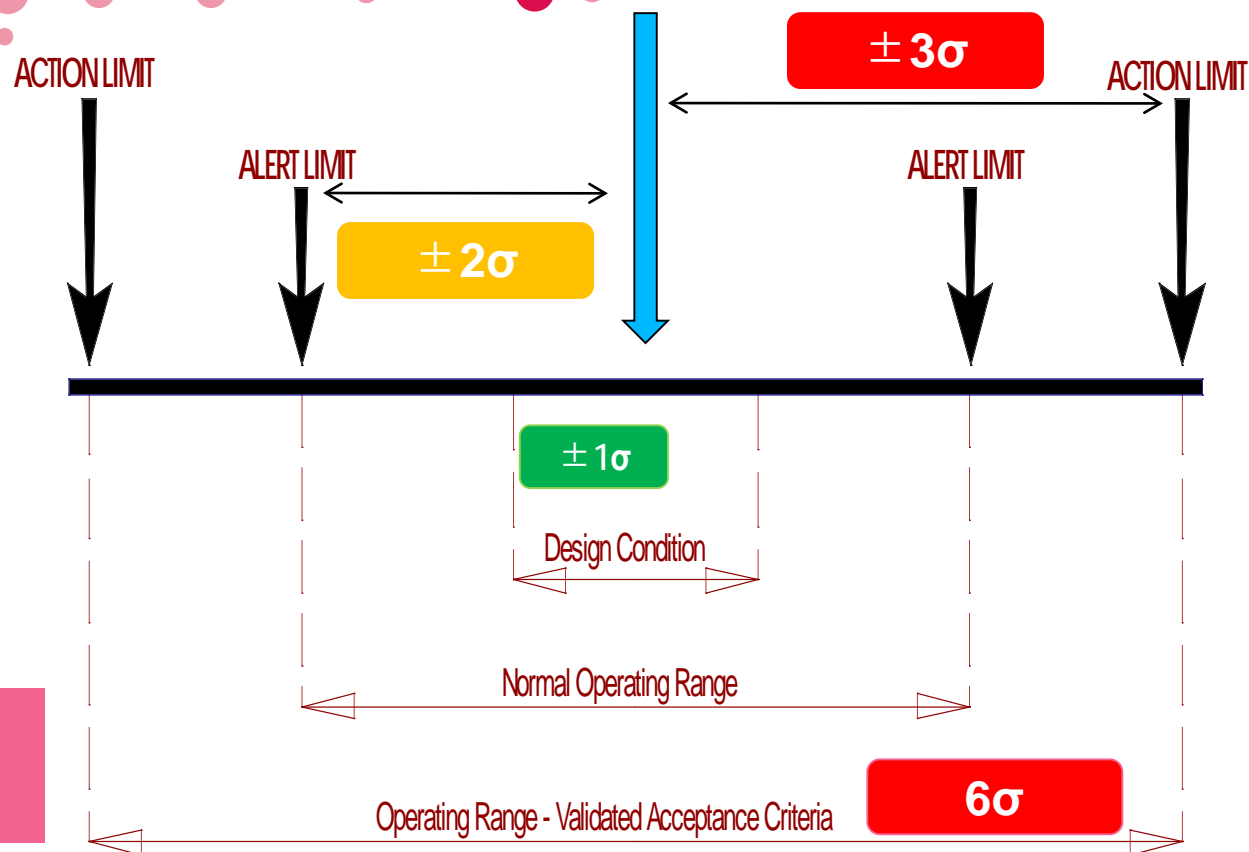
User Requirements Specifications



URS : APPROACH TO DESIGN

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

Action Limit= mean +/- 3 sigma
Alert Limit= mean +/- 2 sigma
Sigma = std deviation/1,128



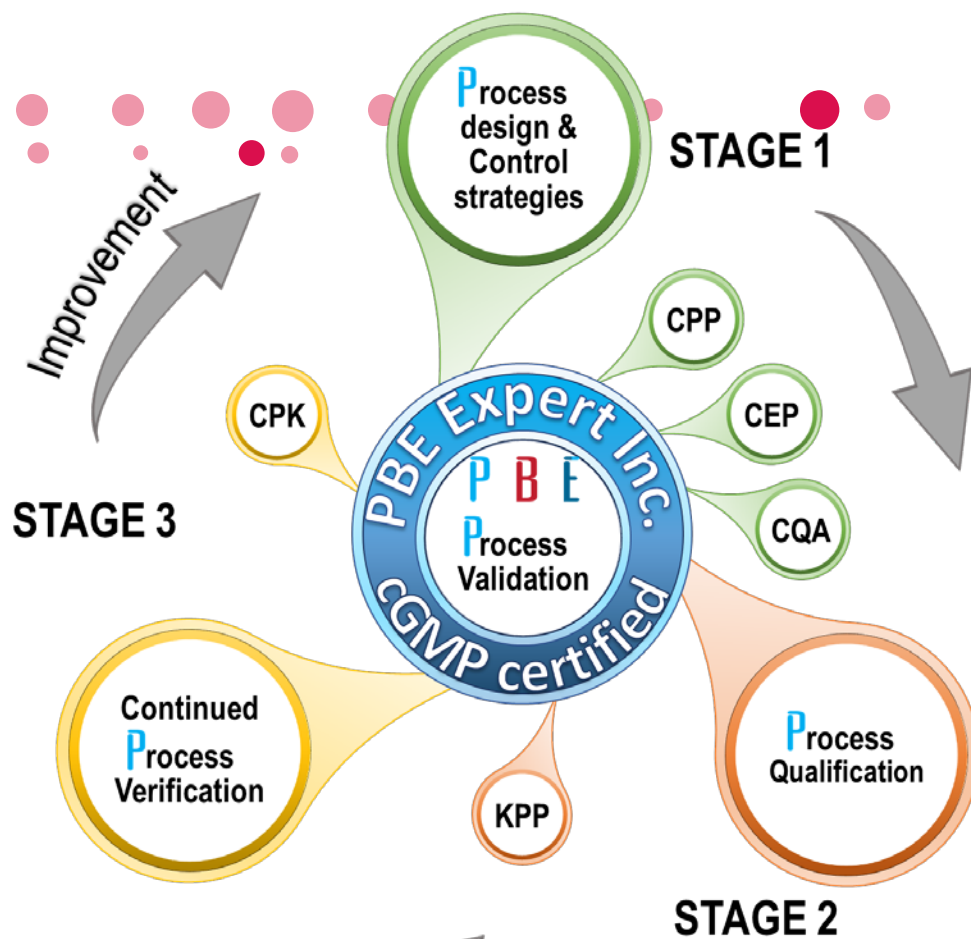


URS : 1- Performance Criteria :

1. Codes, standards and Regulatory Framework
2. Performance Criteria
3. Operation Specifications
4. Installation Specifications
- e. Basic process flow diagrams.
- f. Rational & References.
- g. Tests to be planned.
- h. Execution in :
 - a. IQ/OQ/PQ qualification
 - b. and/or Commissioning: FAT, SAT.



URS : LIFE CYCLE APPROACH – PROCESS VALIDATION



10 Golden Rules?



Golden Rule #1	Get the facility 1-_____ right from the start	Golden Rule #6	6-_____ and develop staff
Golden Rule #2	2-_____ processes	Golden Rule #7	Practice good 7-_____
Golden Rule #3	Write good 3-_____ and follow them	Golden Rule #8	8-_____ facilities and equipment
Golden Rule #4	4-_____ who does what	Golden Rule #9	Build 9-_____ during design into the whole product lifecycle (APR, PV, QBD)
Golden Rule #5	Keep good 5-_____	Golden Rule #10	Perform regular 10-_____

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10 Golden Rules?

PREMISES in which a lot or a production batch of a drug / medicine is:

MANUFACTURED

PACKED

LABELLED

STORED

are

DESIGNED

BUILT



5.0 Regulations – Premises C.02.004 Interpretation

3. Prevent Cross Contamination (CC)

3.1 **TO BE SEALED?** To allow Cleaning and prevent CC

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



WATCH OUT FOR SUSPENDED CEILINGS!



5.0 Regulations– Premises C.02.004 Interpretation

3.1 → To enable **Cleaning**

3.2 → **AVOID** surfaces where foreign substances may accumulate and free of sharp edges.



→ **Surfaces are hard, smooth (NO SOFT WALL)**



5.0 Regulations– Premises C.02.004 Interpretation

3.4 DESIGN PREMISES & CLEANABLE SURFACES

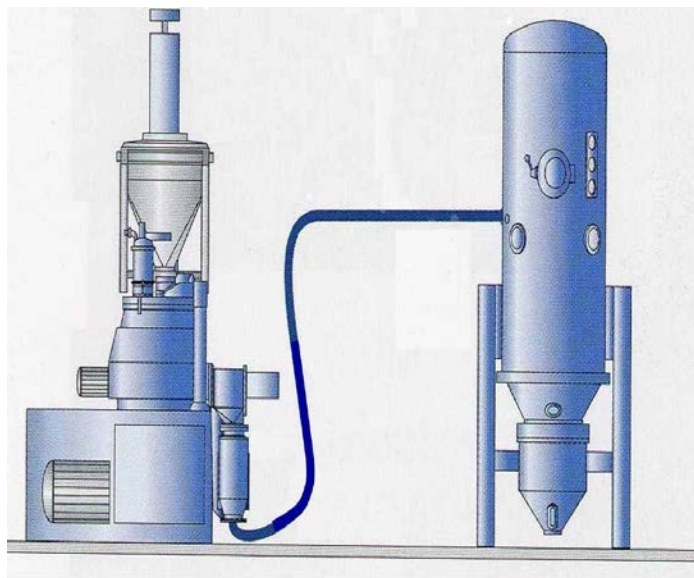


5.0 Regulations– Premises C.02.004 Interpretation

1- ► while **controlling dust**,

Three golden rules to apply :

- a. CE
- b. CT
- c. LEV



5.0 Regulations– Premises C.02.004 Interpretation

2.5 → **HAZARDOUS** production activities,

→ **are isolated & confined.**



- Dedicated premises
- Dedicated access
- Controlled access
- PAL / door interlock
- MAL / door interlock
- Corridors
- Cascade

- 1.
- 2.
- 3.
- 4.
- 5.

- 1.
- 2.
- 3.
- 4.
- 5.

- 1.
- 2.
- 3.
- 4.
- 5.



Types of contaminant & cleaning Systems



Sources of contaminant

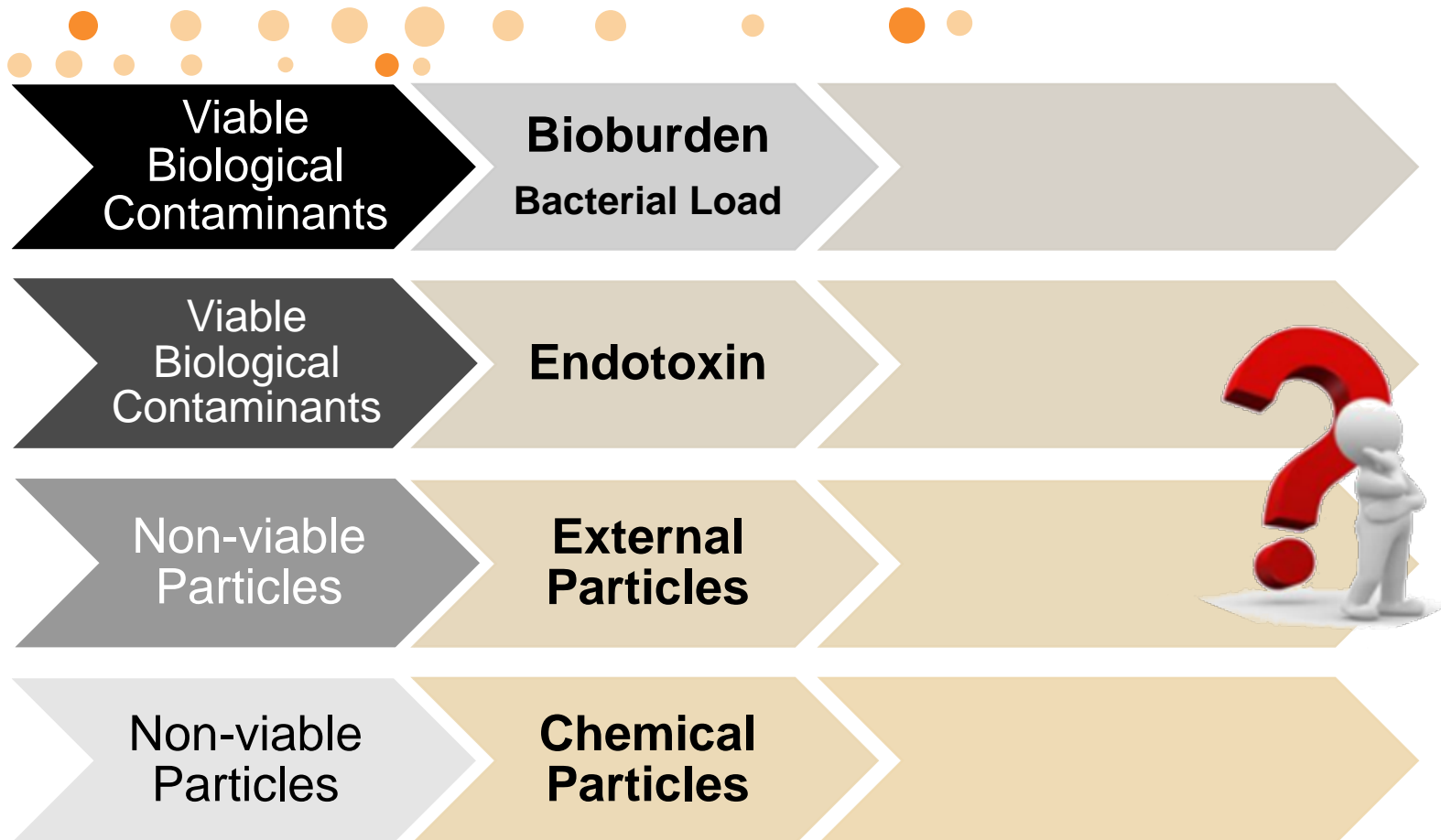
4.1.11 Materials and products should be protected from contamination and cross-contamination during all stages of manufacture (see also section 5.5 for cross-contamination control).

*Note: **contaminants** may result from :*

1. **Inappropriate PREMISES** (e.g. *poor design, layout or finishing*),
2. **Poor CLEANING procedures**,
3. Contaminants brought in *by* **PERSONNEL**,
4. **Poor HVAC system**.



Sources of contaminant



Contaminant reduction processes



Sterile Filtration

Reduce

**SIP / SOP
Sterilization**

Reduce

**Depyro,
Thermal/Chemical
Treatment**

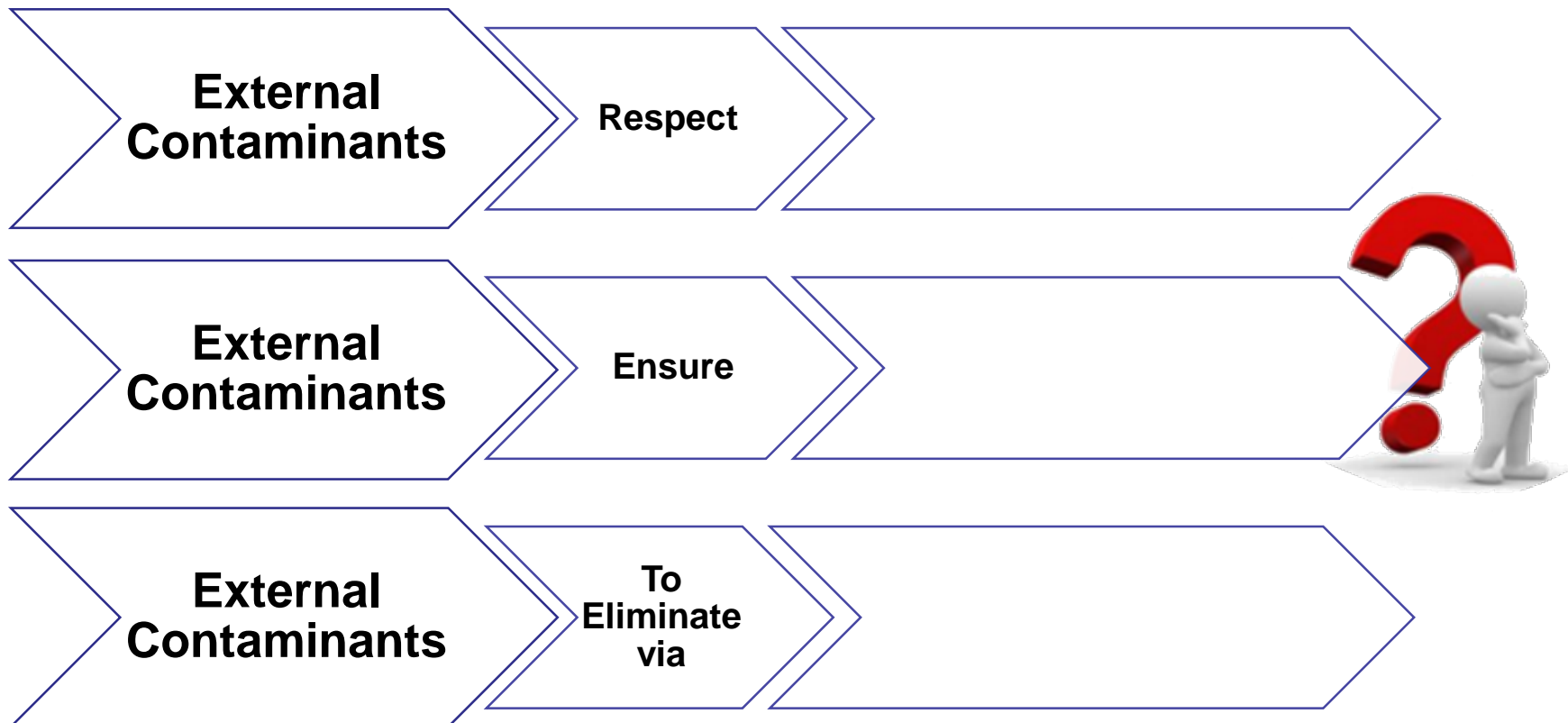
Remove

**Cleaning, CIP
Final rinse / WFI**

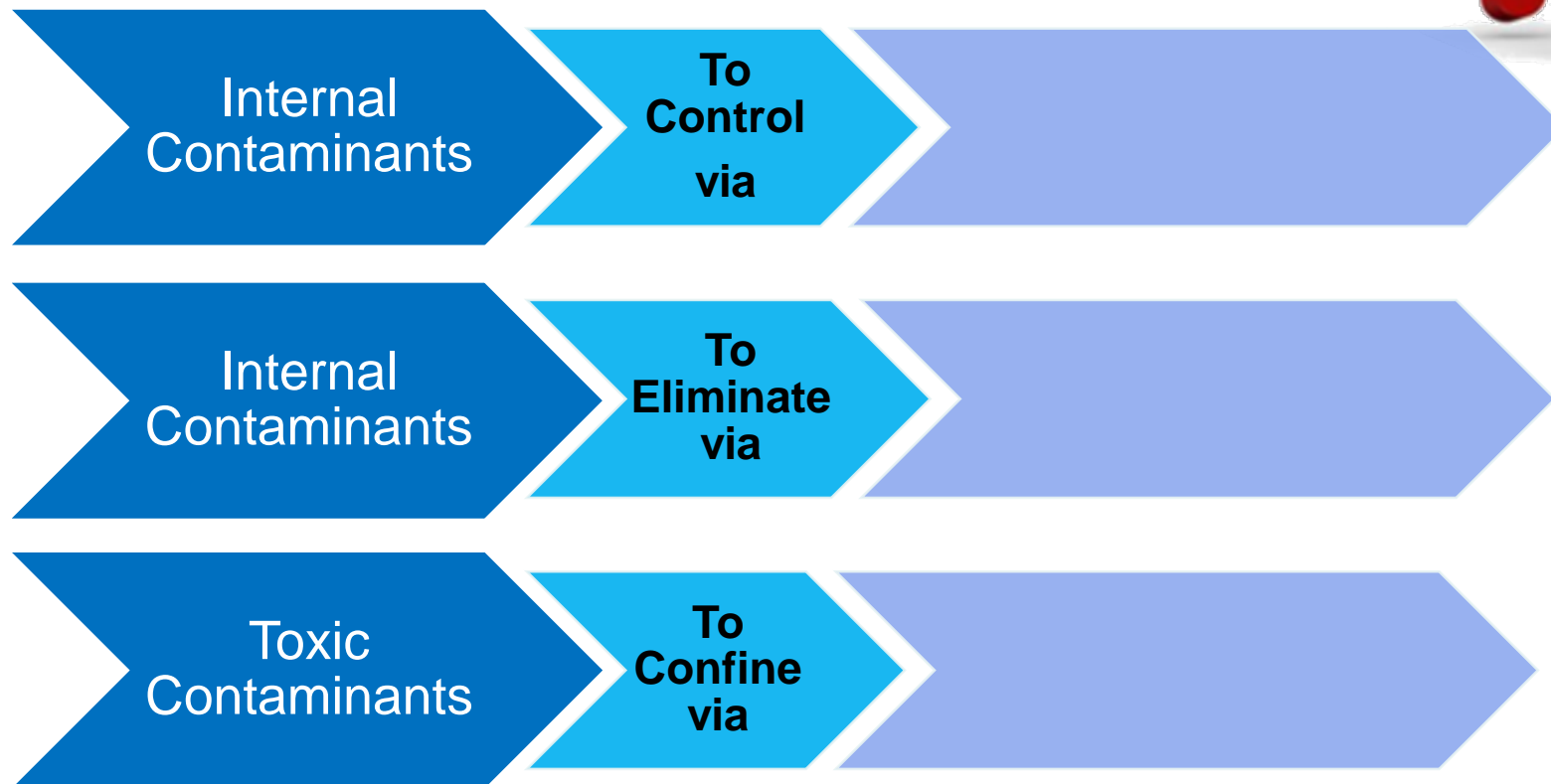
Reduce



Objectives of protection



Objectives of protection



Cleanroom design



Room Design Elements (GMP)

1. Room classification
2. Controlled environmental parameters
3. Selection of construction materials, equipment and aeraulic circuits
4. Selection of cleaning mode for equipment, systems and premises,
5. Flow slope adoption and drainability
6. Choice of internal surface finishes compatible with the process
7. Choice of connection types
8. Selection of sterilization, sanitization, fumigation mode



Prevention technologies in clean rooms (GMP)

1. Process identification.
2. Description of critical process parameters.
3. Air quality % process:
 - a. Classification of the rooms where the equipment is installed.
 - b. Definition of the types of clothing compatible with the asepsis or protection level.
 - c. Quality of air coming into contact with the product.
 - d. Quality of surfaces coming into contact with the product.



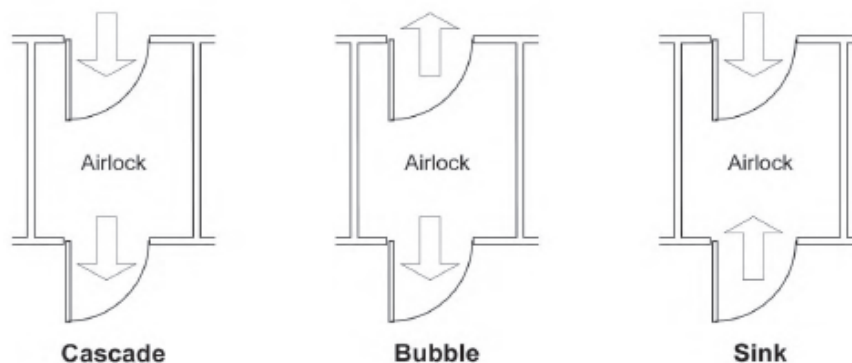
Prevention technologies in clean rooms (GMP)

Segregation and flow :

a. Primary Segregation:

- a. Design and physical & mechanical segregation:
- b. Personal material SAS,
- c. Corridors,
- d. Access cards & interlock,
- e. Dedicated rooms,
- f. HVAC,
- g. Protection systems,
- h. Clean Utilities

Figure 8.6: Airlock Configurations



b. Secondary Segregation :

- a. Control procedures to reduce the risk of contamination and cross-contamination



Prevention technologies in clean rooms (GMP)

Segregation and flow

1. Definition of GMP, aseptic, sterility level:
 - **GMP, aseptic design, sterile, etc.**
2. Definition of containment level:
 - **BSL 1 to 4.**
3. Definition of the level of protection:
 - **HP 1 to 6, BiBo vs Non BiBo.**
 - **ATEX 1 to 3.**
4. Process type & equipment definition (Open/**Closed**).
- 5. Mono vs Multi-product** (Operation by campaign).
6. Definition of the type of **clothing & signaling**.



Prevention technologies in clean rooms (GMP)

1. Dress code
2. Classified rooms
3. Physical / mechanical segregation
4. HVAC Systems
5. Procedures
6. Cleaning & Disinfection



Dress code & means of prevention



GMP dress code



Classe	D (ISO8)	C (ISO7)	B (ISO5)
Hat			
Beard-Cover			
Sterile Gloves			
Frock			
Hood			
Mask			
Shoe-Cover			
Jacket			
Trousers and Coveralls			
Boots			



Room classifications vs standards & applications



Cleanrooms Classification (Viable)

EMA-ANSM 04/12/2013



Recommended microbiological contamination limits (a)				
Class	Air Sample ufc/m ³	Petri Dish (D=90mm) ufc/4heures (b)	Contact Agar (D=55mm) ufc/plaque	Glove Prints (5 fingers) ufc/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

BPF/[ANSM](#), p60, &20. **Appropriate ALERT and ACTION thresholds should be defined for particulate and microbiological monitoring results..** If these limits are exceeded, operational procedures must impose corrective measures.



Cleanrooms Classification

Viable Count cGMP FDA



TABLE 1- Air Classifications^a

Clean Area Classification (0.5 μm particles/ ft^3)	ISO Designation ^b	$\geq 0.5 \mu\text{m}$ 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.



Building Elements & Architectural Finishes



Building Elements & Architectural Finishes

Physical Make-up/Room Finish		Classification Levels				
Parameter	Minimum Requirements	A/B	C	D	E	
Ceiling	<ul style="list-style-type: none"> Drywall with epoxy, plastic polyester (at least two coats) To be smooth and cleaning agent resistant 	R	R	R	R	
Walls	<ul style="list-style-type: none"> Plastic, epoxy coated plaster, drywall, or panel systems so as to provide and maintain a smooth acid and cleaning agent resistant surface. 	R	R	R	R	
Floors	<ul style="list-style-type: none"> Coved, seamless Coving, such that no dust collecting ridges are found Floors in areas where operations discharge water liquid product waste onto floor must be sloped to a drain and sealed to facilitate cleaning 	R	R	R	R	
Windows	<ul style="list-style-type: none"> Required for monitoring purposes and communication Must be flush, no ledges If ledges present, must be slanted 	R	R	N/A	N/A	
Doors	<ul style="list-style-type: none"> Framing to be flush (hardware should be stainless or equivalent). Any hardware should have a minimum of protrusions Weather stripping may be required for differentials (non-shedding or particulate producing) No panic bars are allowed 	R	R	R	NR	
Lighting	<ul style="list-style-type: none"> Shadowless and uniform intensity at 100 to 150 foot candles at work surface 70 to 100 foot candles at work station Light fixtures should be sealed to prevent air leaks. Flush mounted are preferred 	R	R	N/A	N/A	
Electrical Design	<ul style="list-style-type: none"> Electrical panels, distribution equipment, panels, and starters/related components that do not have to be used for daily operation in the cleanroom should be installed in unclassified areas. Conduits entering the cleanroom should have seal fittings attached to them just ahead of the entrance point. This prevents outside air and vermin from coming into a cleanroom through race ways of electrical components. Light switches should be installed outside cleanrooms If present, all switches and receptacles should have gasket weather proof SS/anodized aluminum covers, and located high enough above the floor as possible, out of reach of hose-down-cleaning activities 	R	R	R	R	
General	<ul style="list-style-type: none"> No protrusions, ledges, or exposed piping are allowed Access doors in walls and ceilings should be limited No drains Those drains, if present, should be designed with atmospheric break, or check valve to prevent back flow (trap seal primer is required) Process' drains and "sanitary" drains should be separated with a running trap Cross connections between "process and sanitary" systems should be avoided All process pipe lines or service lines whose contents come in contact with product or product contact surface (such as steam and compressed air) should be sloped back to the source, or to a planned low point drain outside of controlled area. 	R	R	NR	NR	
		R	R	NR	NR	
		R	R	NR	NR	
		R	R	NR	NR	
		N/A	N/A	R	R	
		N/A	N/A	R	R	
		R	R	R	R	



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Building Elements & Architectural Finishes

- ✓ Suspended ceiling?
- ✓ Is this acceptable:
 1. D class Production premises
 2. D class Corridor & SAS
 3. D class Washing Area
 4. Warehouse CNC



Design of HVAC / AHU AIR TREATMENT CENTRALS



HVAC Design Elements

Different types of clean room models in the pharmaceutical industry:

- ▶ **H**_____ Ventilation.
- ▶ **Tu**_____ Flow.
- ▶ **Un**_____ # **La**_____ Flow.
- ▶ Air **F**_____ rate (recirculation, Risk analysis% cross conta).
- ▶ Air inlet **Qu**_____.
- ▶ Particles **Co**_____.
- ▶ Premises **Dim**_____.
- ▶ HVAC **Ef**_____ (contamination removal efficiency).



URS & HVAC prerequisites?

- 1• Classified ZACs vs Protection Level (I @ IIIa vs IIIb)
- 2• Total Volume Flow & TCA.
- 3• Type of flow (T_____ vs L _____) & (U _____ vs M _____).
- 4• A_____ Rate vs r_____ Time
- 5• P_____ & c_____ Cascade
- 6• _____range & _____
- 7• _____ counts VNV
- 8• Flow of _____, _____, PSO, _____ ...
- 9• Type of a_____ and p_____



URS & HVAC prerequisites?

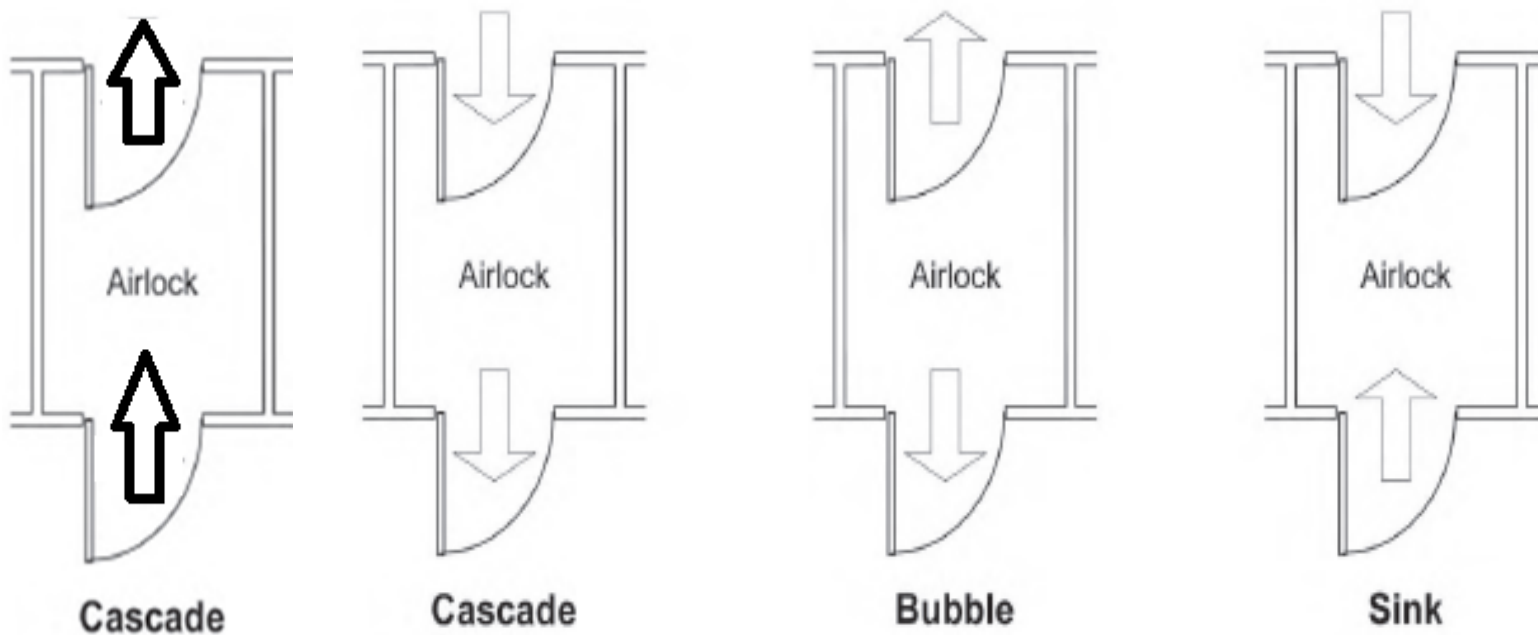


- 10• W_____ & P_____ Conditions
- 11• Number of P_____ inside the room
- 12• Filtration type (Cascade: _____, _____, _____)
- 13• C_____ filtration vs T_____ (T_____, P_____
& N_____ of filters).
- 14• Air D_____ in the room vs b_____ air, q_____ air and
l_____ (leakage check : Input – Output).
- 15• System with direct E_____ vs C_____ water/air, cooling
T_____.
- 16• Dispersion control and control of highly active contaminants and
impact on personnel, the environment



Means of prevention / Physical segregation / Pressure cascade / PAL & MAL

Figure 8.6: Airlock Configurations



FS mo	?
FS mu	
FS Eff	
CR	
HP	
INJ	
BSL ₂	
HP+ INJ	

A



B

C



D



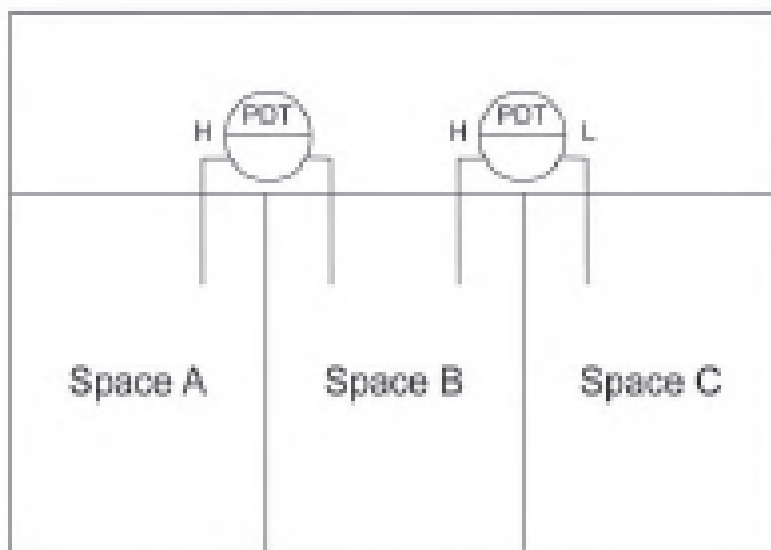
DIFFERENTIAL PRESSURE CASCADES



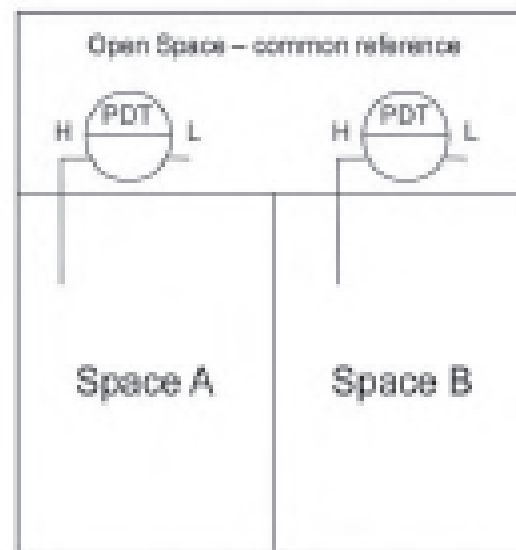
Differential pressure measurement configuration



Figure 8.10: DP Sensor Locations



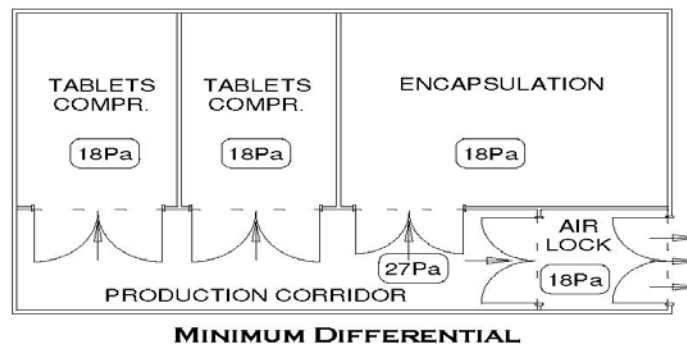
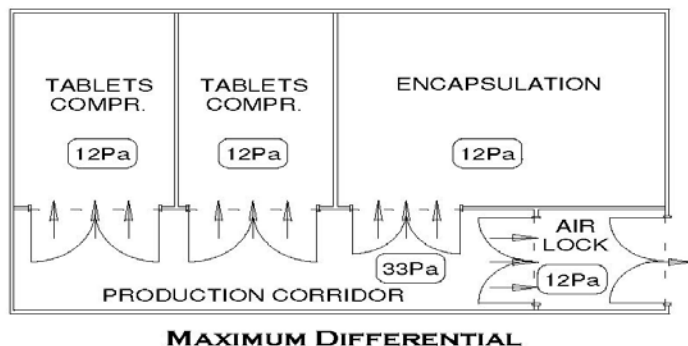
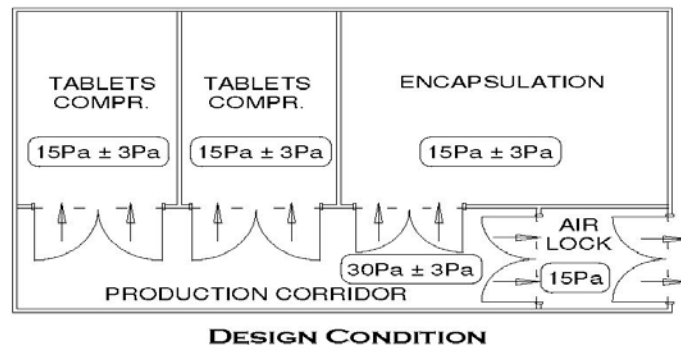
Room-to-Room Monitoring



Common Reference Monitoring

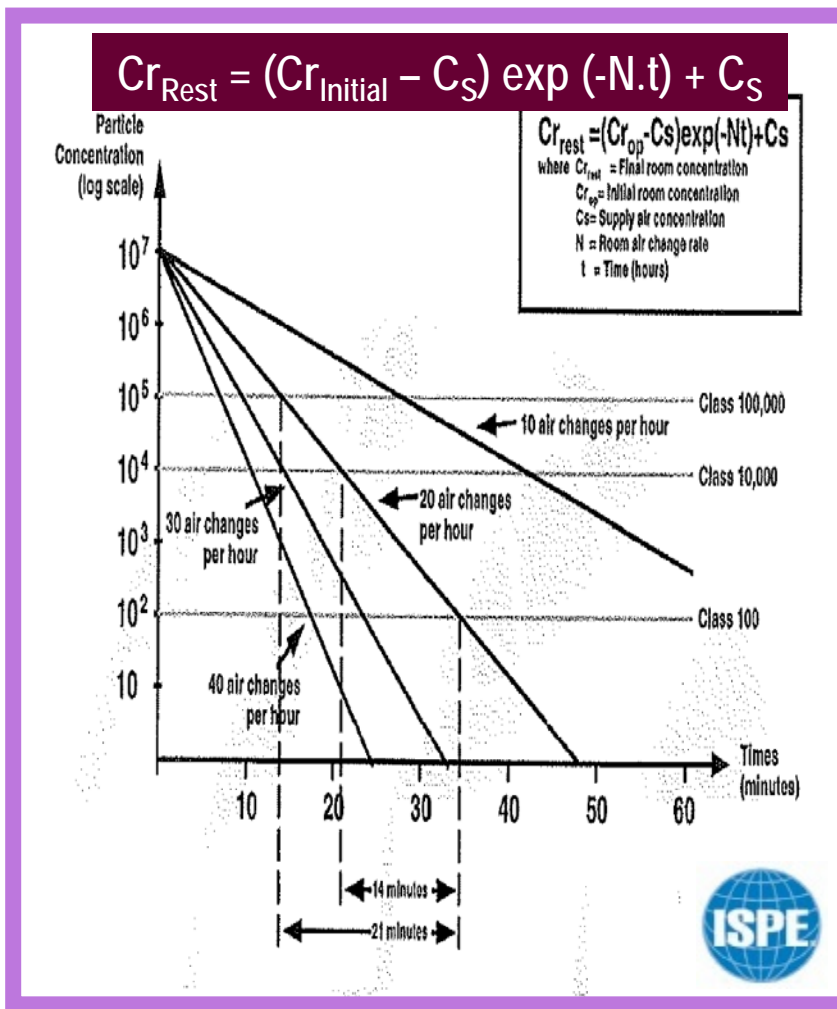


Prevention means / Differential pressure cascade





Air quality recovery time: ISPE, ISO-14644-3 (B12)



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



DIFFERENTIAL PRESSURE CASCADES



HVAC Design vs Protection & Classification Level

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 or product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing , first stage change 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 or product, e.g. where product, starting materials and components are exposed to the room environment; plus equipment wash and storage areas for equipment product contact parts.



HVAC Design vs Protection & Classification Level

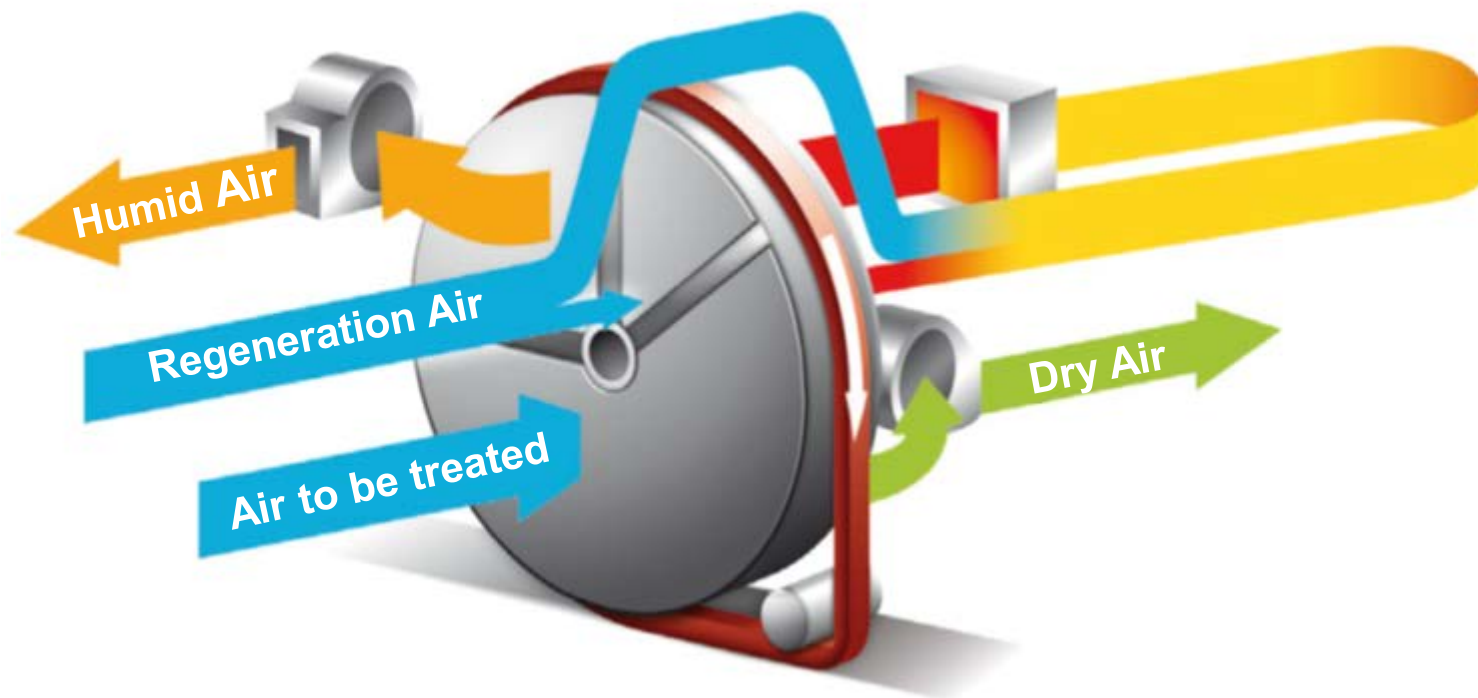
TABLE 6-1 - Suggested minimum design values (see text for details/exceptions)

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 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*.



Air dehydration



Influence of HVAC components on the cleanliness of classified cleanrooms

Equipment	Temperature	Humidity RH%	Prussure Static/Room	Air Flow(AHU)	Air cleanliness
AHU / FFU					
Blow & Return Fan					
Direct Extraction Fan					
Heating Battery					
Battery & Cooling Unit					
Air Filter					
Humidifier					
Dehumidifier					
Aeraulic Network					
Register & Component					
Air Diffusers Grilles Recovery					
UV Lights					



**22 CHECKS TO PLACE?
On 60**



HOURLY AIR CHANGE RATE - ACR



CRITICAL EQUIPMENT IN AN HVAC UNIT



ENERGY SAVING & HQ SUBSIDY, ...



HEPA FILTERS & INTEGRITY TESTS



ISO-14644 & FREQUENCY TESTS

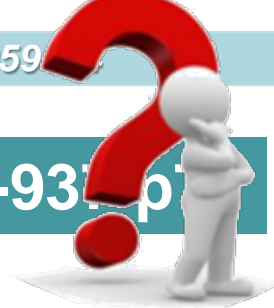


BIMODULAR CLEAN ROOMS



UDAF vs LAMINAR FLUX





UDAF vs LAMINAR FLUX

WHO_TRS-93

Minimum requirement	UDAF	Laminar Flux
1- HEPA filter		
2- Integrity Test		
3- Speed		
4- Unidirectional flow		
5- Particle class		
6- Particle count continuous monitoring		
7- Operators under		
8- Differential Pressure		
9- Protection		



DUAL REDUNDANCY, WHEN IS IT REQUIRED?



CAPTURING SYSTEMS AT THE SOURCE? LOCAL VS. CENTRAL



FLOW TYPES FILTER/DIFFUSER POSITION



CASE STUDY #1: Wet & Dry Forms.



CASE STUDY#2: Injectables & Steriles.



CASE STUDY #3: Highly Toxic Products– OEL 2-6



CASE STUDY #4: Biological Products BSL2-3



CASE STUDY #5: Explosives products & Flammable Solvents. ATEX 1-3



Staff protection equipment



OEL Containment Equipment

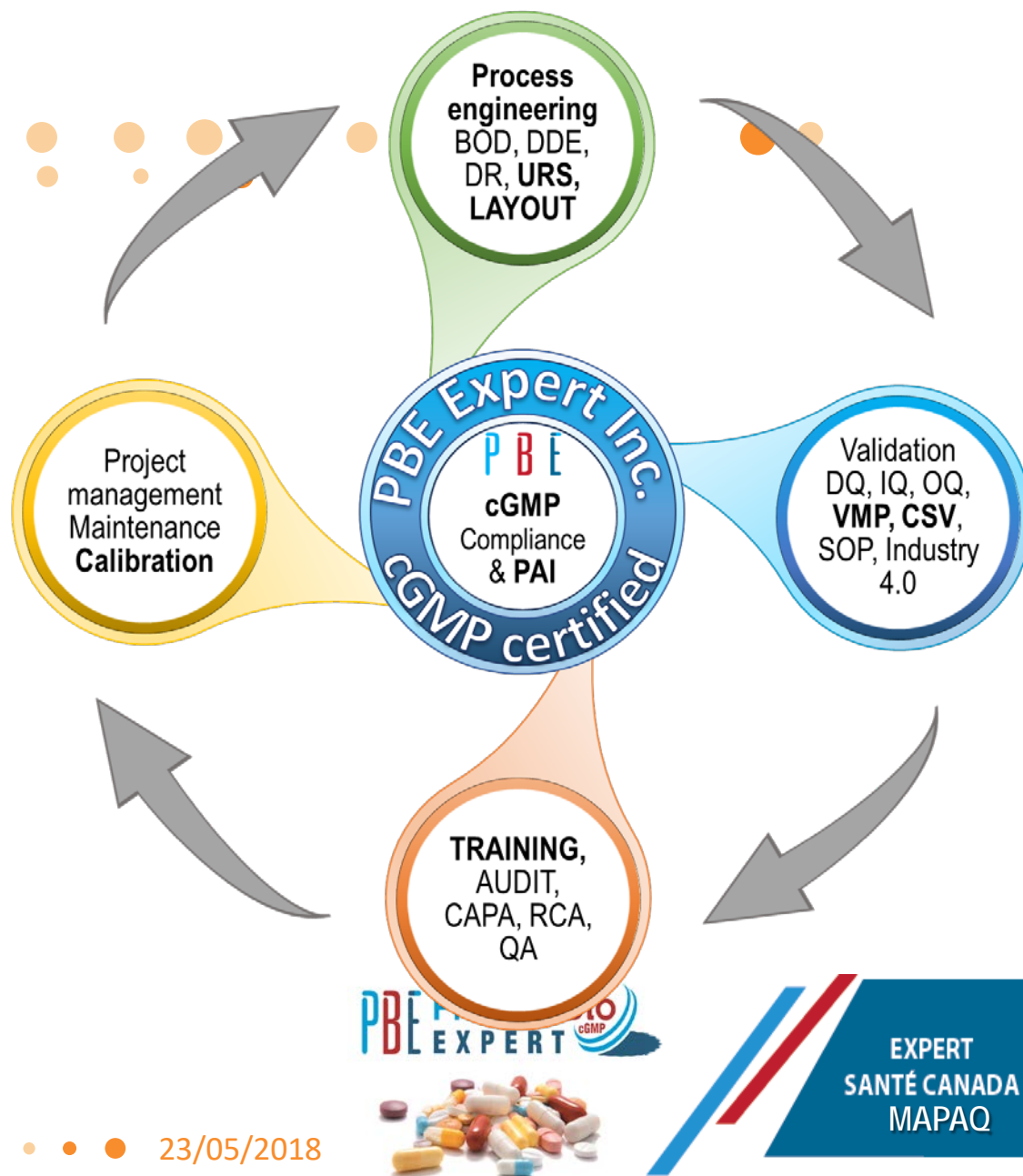


Commissioning / Premises Validation & HVAC



Part 7 – Quiz - Evaluation







**PBE Expert Inc. Your
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