VALIDATION OF CLEAN ROOMS FOR ASEPTIC MANUFACTURING

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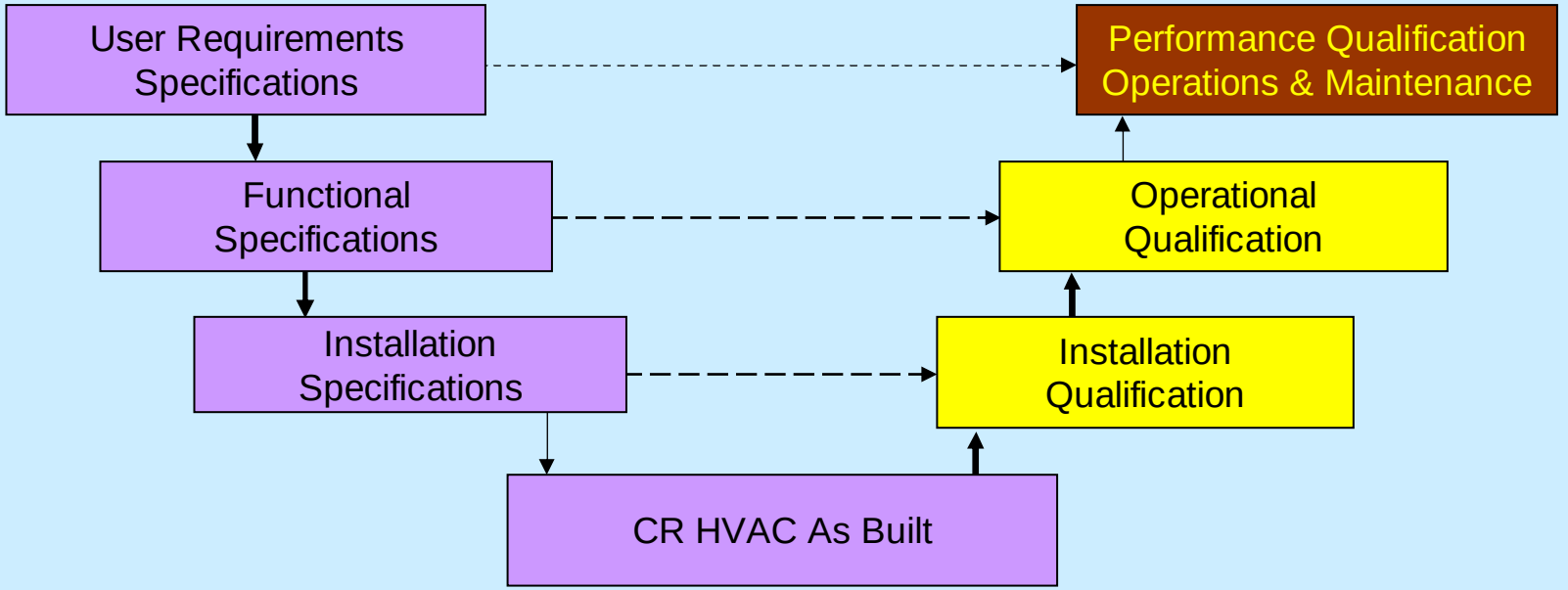
VALIDATION OF CLEAN ROOMS

Proving that the environmental conditions of the clean rooms that have been defined in the HVAC ORDER from the USER PROCESS REQUIREMENTS are ALWAYS reached in the clean rooms Installations

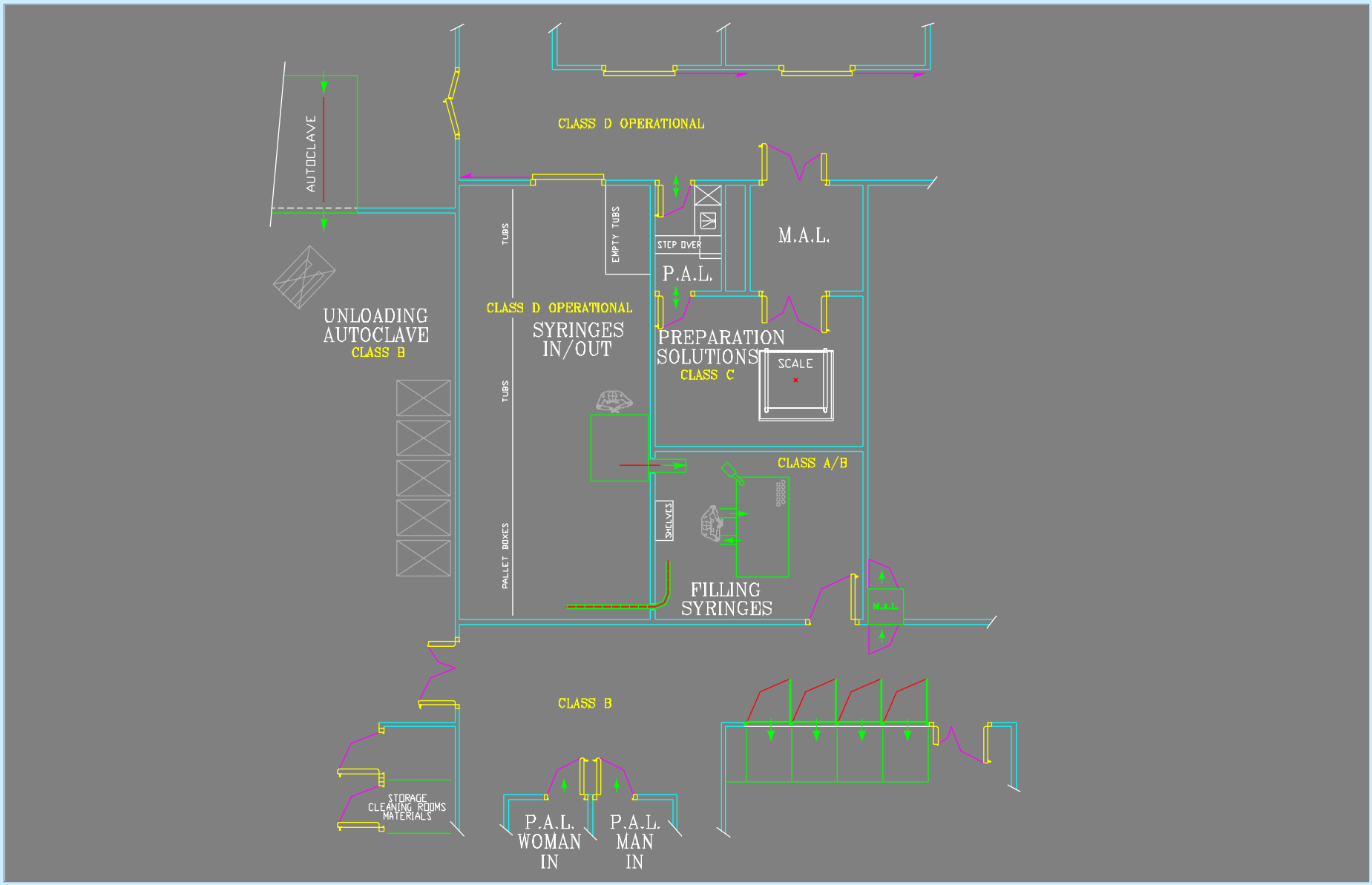
USER/PROCESS REQUIREMENTS FOR CLEAN ROOMS

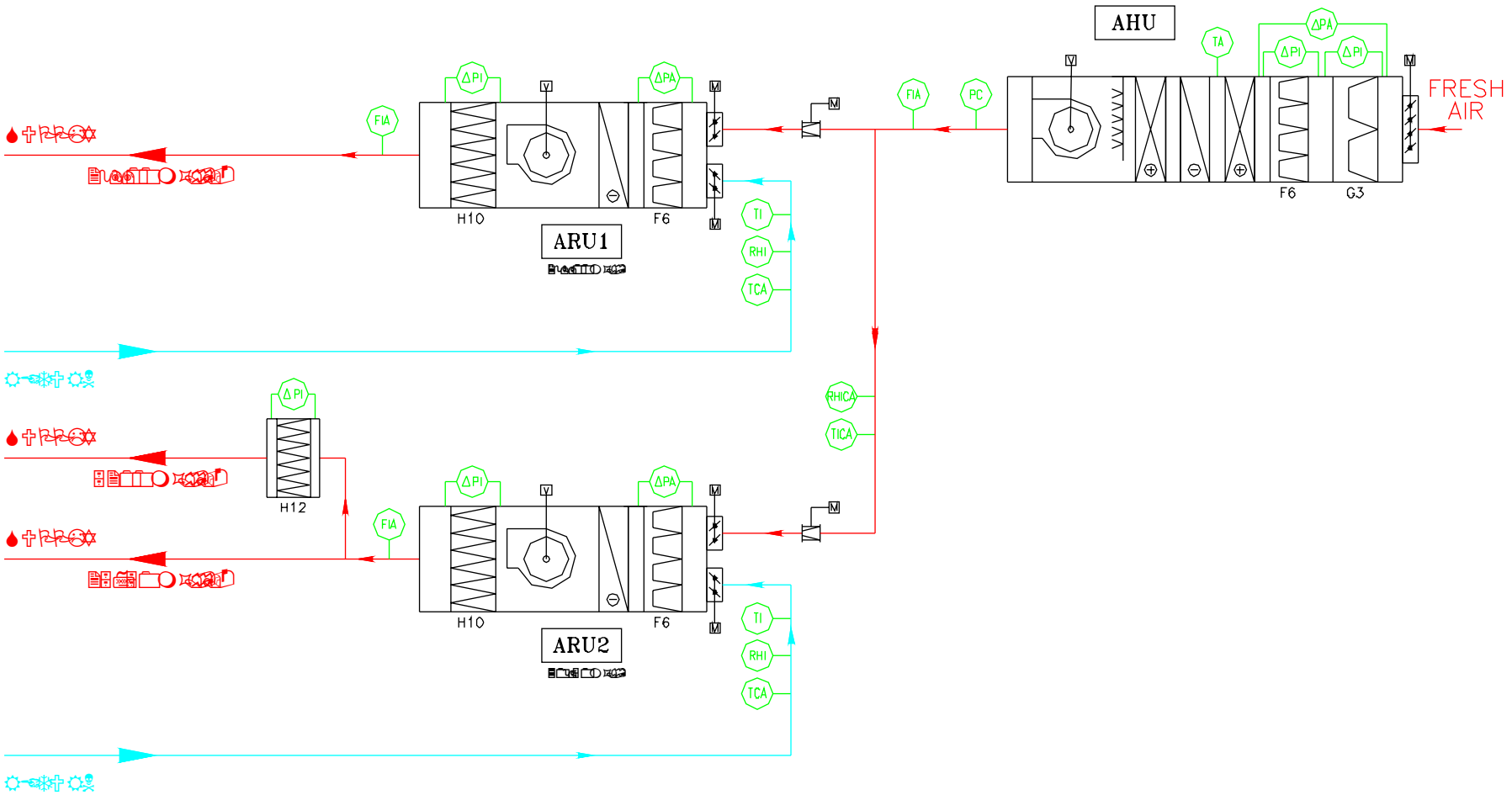
- **Layout and circulations (to avoid contamination and cross contamination)**
- **Environmental Conditions**
- **Automation**
- **Maintenance**
- **Cleaning**

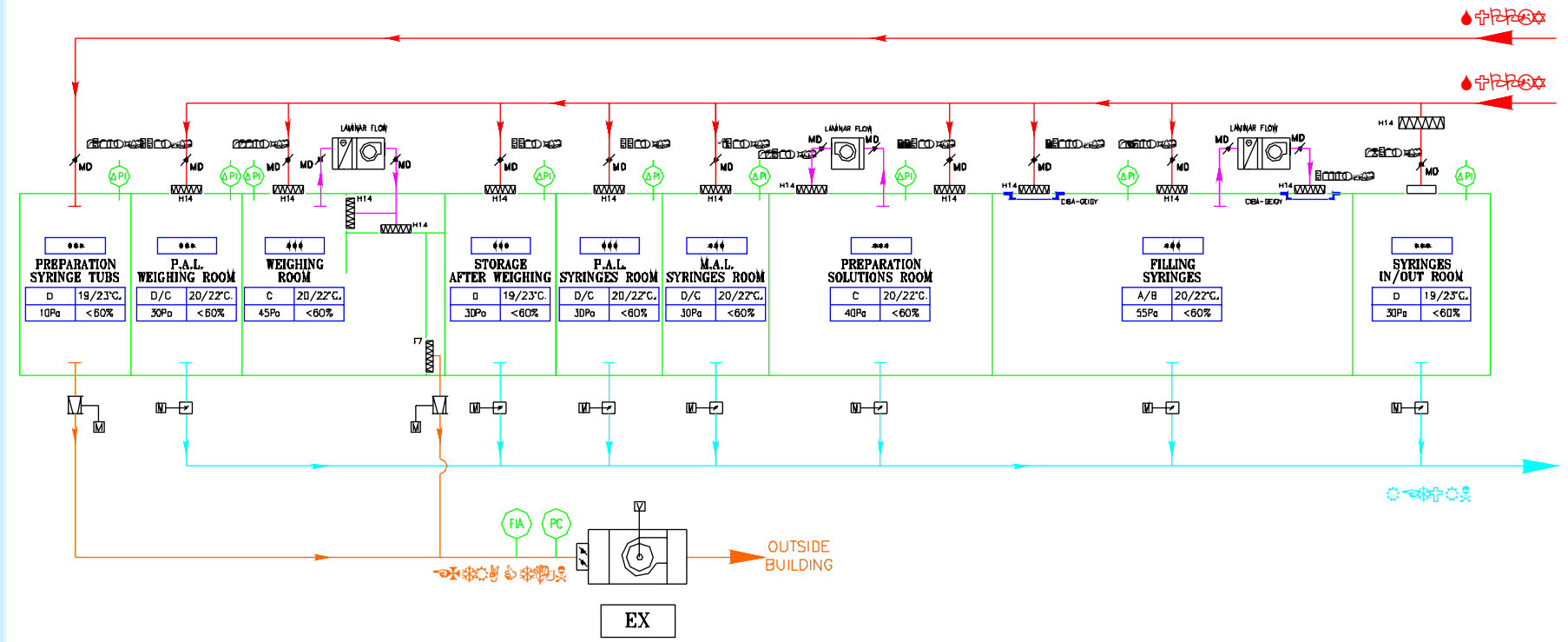
V-MODEL

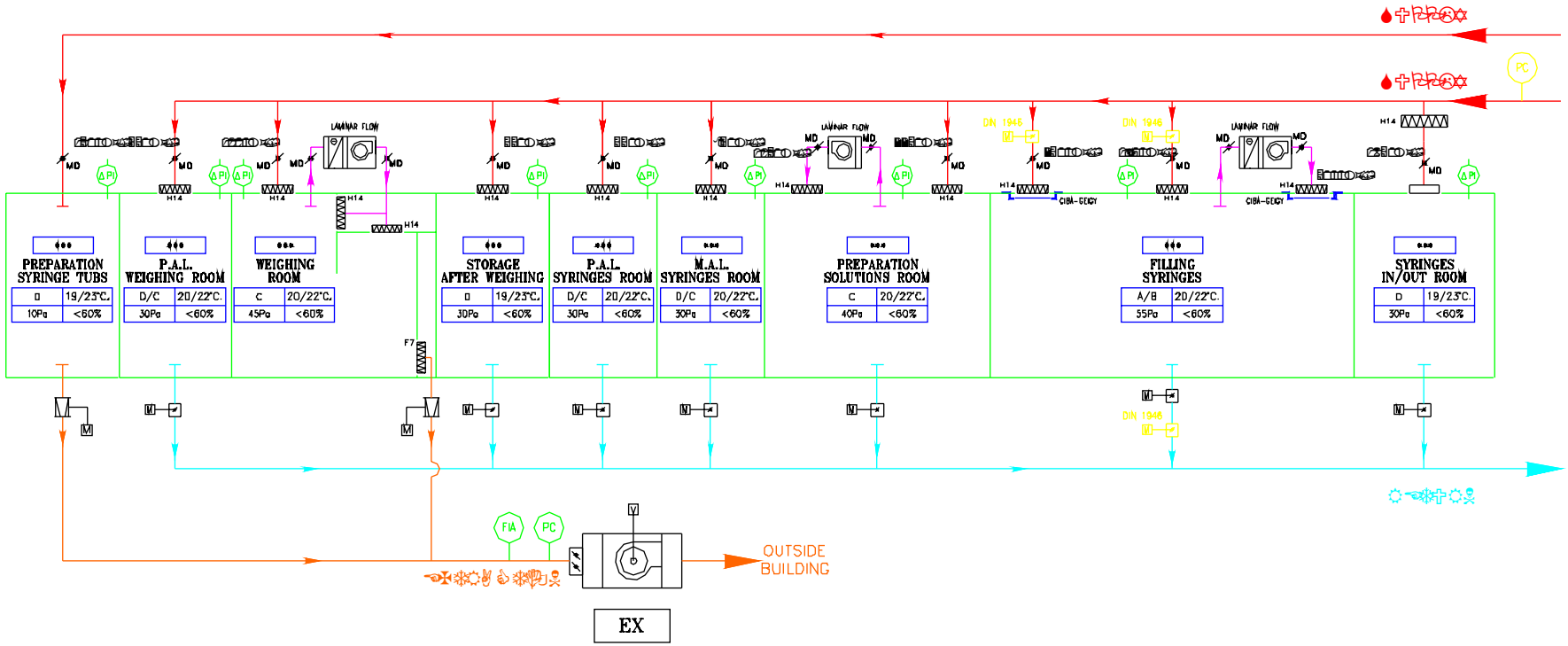

User Requirements Specifications
Performance Qualification Operations & Maintenance
Functional Specifications
Operational Qualification
Installation Specifications
Installation Qualification
CR HVAC As Built

URS HVAC	F.S
- Automated Fumigation	- Dedicated extractor - Stopping HVAC in room with Din 1946 Dampers - Time sequences for Heating plates - Restarting HVAC
Maintenance of filling line without stopping the use of the other clean rooms	- Access door from class D - VAV Boxes
- Absence of contamination cross contamination	- Double HEPA filtration and recirculation - Air shower - PAL and MAL


AUTOCLAVE
CLASS D OPERATIONAL
TUBS
EMPTY TUBS
STEP OVER
M.A.L.
P.A.L.
UNLOADING
AUTOCLAVE
CLASS B
CLASS D OPERATIONAL
SYRINGES
IN/OUT
PREPARATION
SOLUTIONS
CLASS C
SCALE
TUBS
CLASS A/B
SHELVES
PALLET BOXES
FILLING
SYRINGES
M.A.L.
CLASS B
STORAGE
CLEANING ROOMS
MATERIALS
P.A.L.
WOMAN
IN
P.A.L.
MAN
IN


AHU
TA
ΔPA
ΔPI
ΔPI
FRESH
AIR
F6
G3
FIA
PC
ΔPI
ΔPA
H10
F6
ARU1
TI
RHI
TCA
RHICA
TICA
ΔPI
H12
FIA
ΔPI
ΔPA
H10
F6
ARU2
TI
RHI
TCA


LAMINAR FLOW
MD
ΔPI
H14
PREPARATION SYRINGE TUBS
D 19/23°C. 10Pa <60%
P.A.L. WEIGHING ROOM
D/C 20/22°C. 30Pa <60%
WEIGHING ROOM
C 20/22°C. 45Pa <60%
STORAGE AFTER WEIGHING
D 19/23°C. 30Pa <60%
P.A.L. SYRINGES ROOM
D/C 20/22°C. 30Pa <60%
M.A.L. SYRINGES ROOM
D/C 20/22°C. 30Pa <60%
PREPARATION SOLUTIONS ROOM
C 20/22°C. 40Pa <60%
FILLING SYRINGES
A/B 20/22°C. 55Pa <60%
SYRINGES IN/OUT ROOM
D 19/23°C. 30Pa <60%
DBA-GEIGY
F7
M
V
FIA
PC
OUTSIDE BUILDING
EX


PREPARATION SYRINGE TUBS
D 19/23°C. 10Pa <60%
P.A.L. WEIGHING ROOM
D/C 20/22°C. 30Pa <60%
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FILLING SYRINGES
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SYRINGES IN/OUT ROOM
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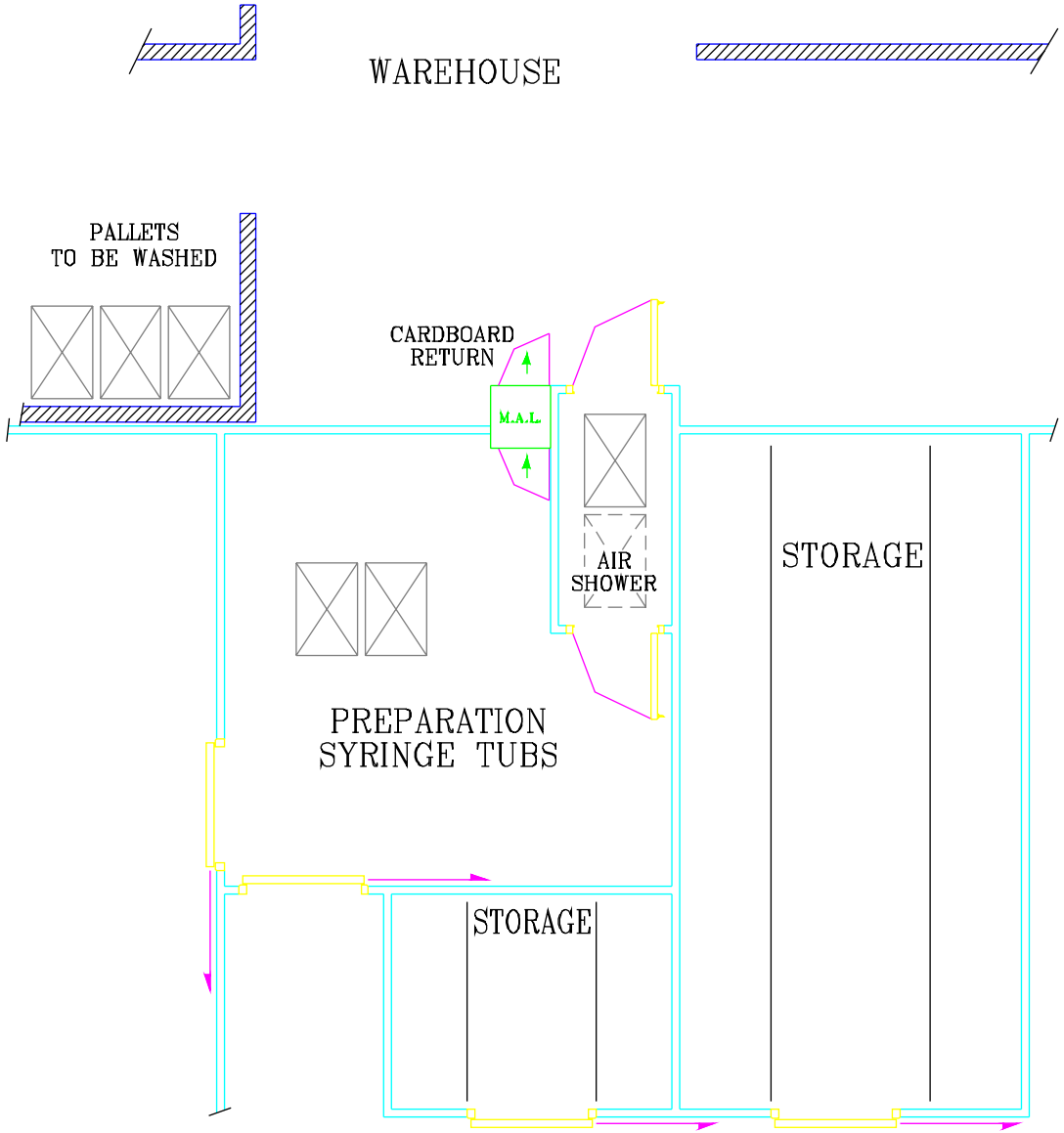
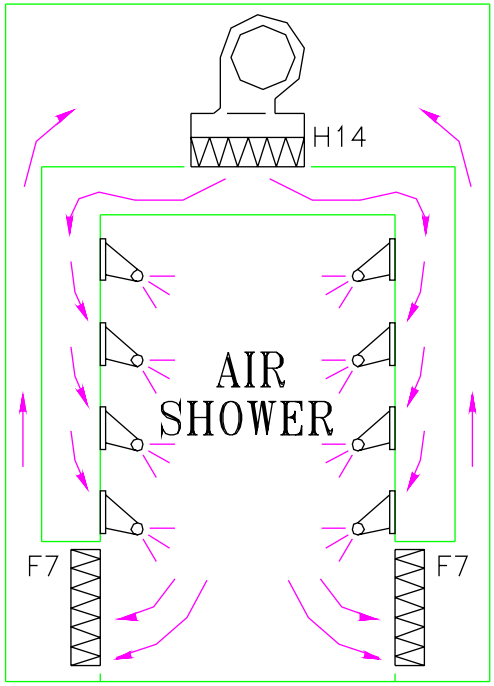
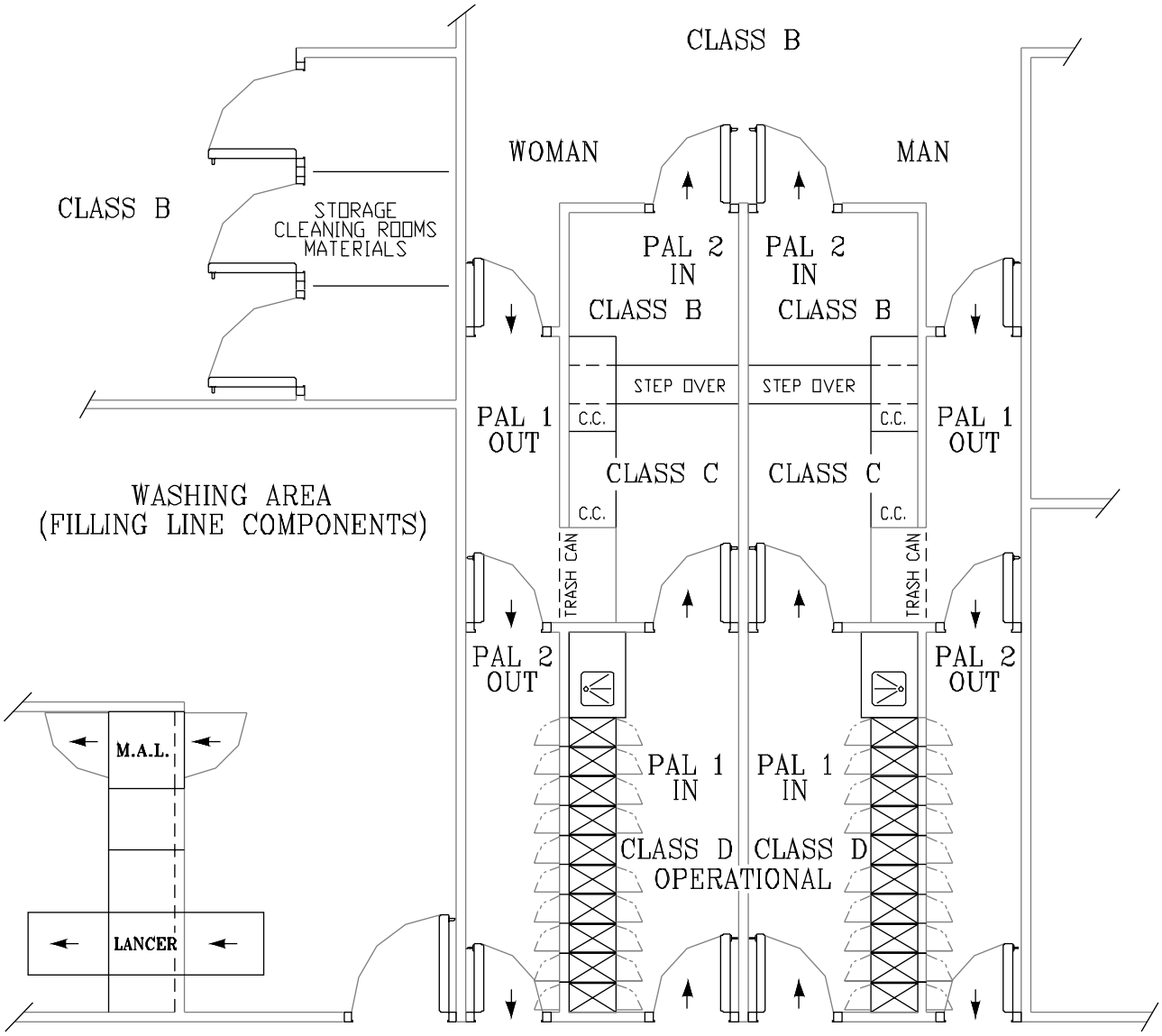
LAMINAR FLOW
DIN 1946
CIBA-GEIGY
MD
H14
F7
PC
FIA
OUTSIDE BUILDING
EX


WAREHOUSE
PALLETS
TO BE WASHED
CARDBOARD
RETURN
M.A.L
AIR
SHOWER
STORAGE
PREPARATION
SYRINGE TUBS
STORAGE


H14
AIR
SHOWER
F7
F7


CLASS B
WOMAN
MAN
CLASS B
STORAGE
CLEANING ROOMS
MATERIALS
PAL 2
IN
CLASS B
PAL 2
IN
CLASS B
STEP OVER
STEP OVER
PAL 1
OUT
C.C.
C.C.
PAL 1
OUT
CLASS C
CLASS C
C.C.
C.C.
WASHING AREA
(FILLING LINE COMPONENTS)
TRASH CAN
TRASH CAN
PAL 2
OUT
PAL 2
OUT
M.A.L.
PAL 1
IN
PAL 1
IN
CLASS D
OPERATIONAL
CLASS D
LANCER

DESIGN QUALIFICATION

Checking	**URS → F.S → D.S**
Checking	**cGMP compliance**
Approving For Execution	**Schemes of Principes, P & ID**
	Data sheets

APPROVAL BEFORE CONSTRUCTION

- **SCHEMES OF PRINCIPLES**
- **P & ID ‘S**
- **Ceiling Plan (supplies and returns)**
- **Routing of Air ducts**

F A T

- Air Handling Units
- Automation Acceptance tests
- Electrical Acceptancce Tests

S A T (IQ+ OQ)

- As built Documentation review
- IQ
- CAL + OQ

STANDARD DOCUMENTATION LIST (SDL)

Section	Engineering file sections	Document in file
1	TABLE OF CONTENT	Sections and sub sections as mentioned here
2	BIDDING REQUIREMENTS	Bidding specifications
		Bidding drawings
3	ORDERING DOCUMENTS	Purchase orders
		List of supplier sub contractors
4	"FOR EXECUTION" APPROVED DOCUMENTS	Main components data sheets (Description/ specs)
		Design Calculation
		Control system Specifications
5	"FOR EXECUTION" APPROVED DRAWINGS	P&ID's
		GAD's
		Mechanical drawings
		Electrical drawings
		Connection drawings
		Control system drawings
		Other drawings
6	AS BUILT DRAWINGS	P&ID's
		GAD's
		Mechanical drawings
		Electrical drawings
		Connection drawings
		Control system drawings
		Other drawings
7	AS BUILT DOCUMENTS	General components list an data sheets
		Control system specs
8	INSTALLATION AND INSPECTION DOCUMENTS	Official control inspection reports
		AIB Vinçotte, Apave, TUV
		Installation Instructions
		Risk Analysis (European Directive)
9	OPERATIONS AND MAINTENANCE DOCUMENTATION	Operation and maintenance manuals
		Consumables list
		Spare parts list
		Training Documentation
10	SET POINTS, FUNCTIONAL PARAMETERS	Set points, Alarm values, functional parameters
		Positions of dip switches, etc…

STANDARD DOCUMENTATION LIST (SDL)

Section	Qualification file sections	Document in file
1	TABLE OF CONTENT	Quality Documentation File contents
2	PROJECT CHANGES	Change (control) documents and related documents
3	FACTORY ACCEPTANCE TESTS (FAT)	Supplier pre FAT test reports, FAT Protocols, Report, Raw Data, Punch list
4	INSTALLATION QUALIFICATION TESTS	Electro-mechanical IQ Protocol, Report, Raw data, Punch list
		Control system IQ Protocol, Report, Raw data, Punch list
		IQ certificate
5	CALIBRATION	Calibration certificates
		Calibration Protocols, Report, Raw data, Punch list
		Calibration certificate
6	SITE ACCEPTANCE TESTS (SAT) OPERATIONAL QUALIFICATION (OQ)	Electro-mechanical OQ Protocol, Report, Raw data, Punch list
		Control system OQ Protocol, Report, Raw data, Punch list
		OQ certificate
7	EXTENDED QUALITY DOCUMENTATION PIPING/WELDING DOCUMENTATION	Slopes verification
		Welding procedure and Qualification including Isometric drawings
		Welders Qualification
		Cleaning/passivation procedures and reports
		Pressure leak test reports
8	EQUIPMENT/SUPPLIER CERTIFICATES	Quality Plan, Quality Manual
		Supplier ISO certificates
		CE compliance
		Material certificates
		Pressure/safety valves certificates
		Other certificates

INSTALLATION QUALIFICATION

ATTACHMENT #	TITLE
#01	Test form: Personnel performing IQ
#02	IQ Deviation Form
#03	IQ Information, Observation, Comment Form
#04	Test Form: Documentation Verification
#05	Test form: Piping & Instrumentation Diagram (P&ID) Verification
#06	Test Form: General Arrangement Verification
#07	Test form: Trolleys, Shelves and other ancillary systems verification
#08	Test form: Power, Electrical utilities verification
#09	Test form: Non-electrical utilities verification
#10	Test form: Critical Instrument List and Verification
#11	Test form: Filters and other Consumables list
#12	Test form: Spare part list
#13	Environmental and Safety review
#14	System associated SOP's list and Log-book verification
#15	Installation Qualification Completion and Approval

OPERATIONAL QUALIFICATION TESTS

AIR HANDLING UNITS (AHU'S)
OPERATIONAL TESTS

- **Frequency Variator Setting**
- **Motor Speed**
- **Absorbed current Intensity**
- **DP AHU in –out**
- **Calculation of Air Flow**
- **Supply and Exhaust Fan Interlocks**

OTHER OPERATIONAL TESTS

- **Heating and cooling Batteries**
- **Steam Humidifier**
- **CAV VAV Box**
- **Dampers**

OPERATIONAL TESTS CONTINUED

- **Temperature and Humidity**
- **Noise levels**
- **Formolation tests**

Operational Qualification

- Testing of Automation System
- Testing of HVAC Operation against Functional Specifications
- Filter Integrity tests
- Air speeds and air flow measurements
- Pressure differentials measurements
- Air flow patterns
- Decontamination time

EN / ISO 14644 and IN SITU HEPA TESTING

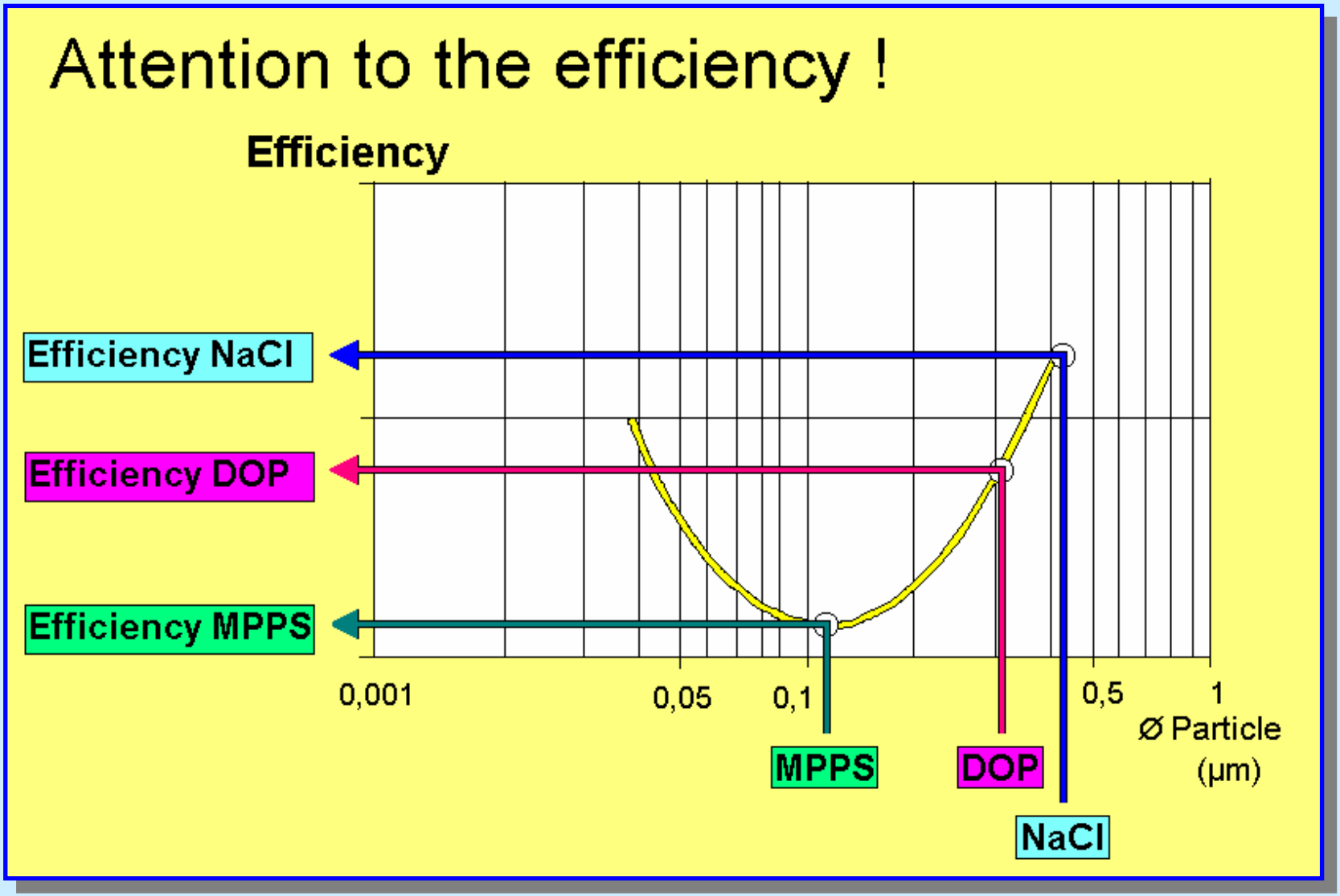
- **14644-3 will allow EMERY 9004 / DURASIN 164, ONDINA EL and other oil aerosol**
- **P ≤ 0,01%**
- **Annex B6: particle counter method satisfies the FDA Aseptic processing guide 87 that requires an adequate challenge level be established for a valid test.**

THE EN 1822-1: 1998 Table 1: Classification of HEPA and ULPA Filters

Filter class		Overall value		Local value 1) 2)	
		Efficiency (%)	Penetration (%)	Efficiency (%)	Penetration (%)
HEPA	H10	85	15	---	---
	H11	95	5	---	---
	H12	99,5	0,5	---	---
	H13	99,95	0,05	99,75	0,25
	H14	99,995	0,005	99,975	0,025
ULPA	U15	99,999 5	0,000 5	99,997 5	0,002 5
	U16	99,999 95	0,000 05	99,999 75	0,000 25
	U17	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

Attention to the efficiency !



EN / ISO 14644 and AIR EXCHANGE RATES

- **14644 - 4 does not specify any requirement**
- **Pharma guides: minimum 20 air changes / h.**

AIR FLOW SPECIFICATIONS

Per supply **- 10 %, + 30% of specified Air Flow**

Per room **- 5 %, + 25 % of specified Air Flow**

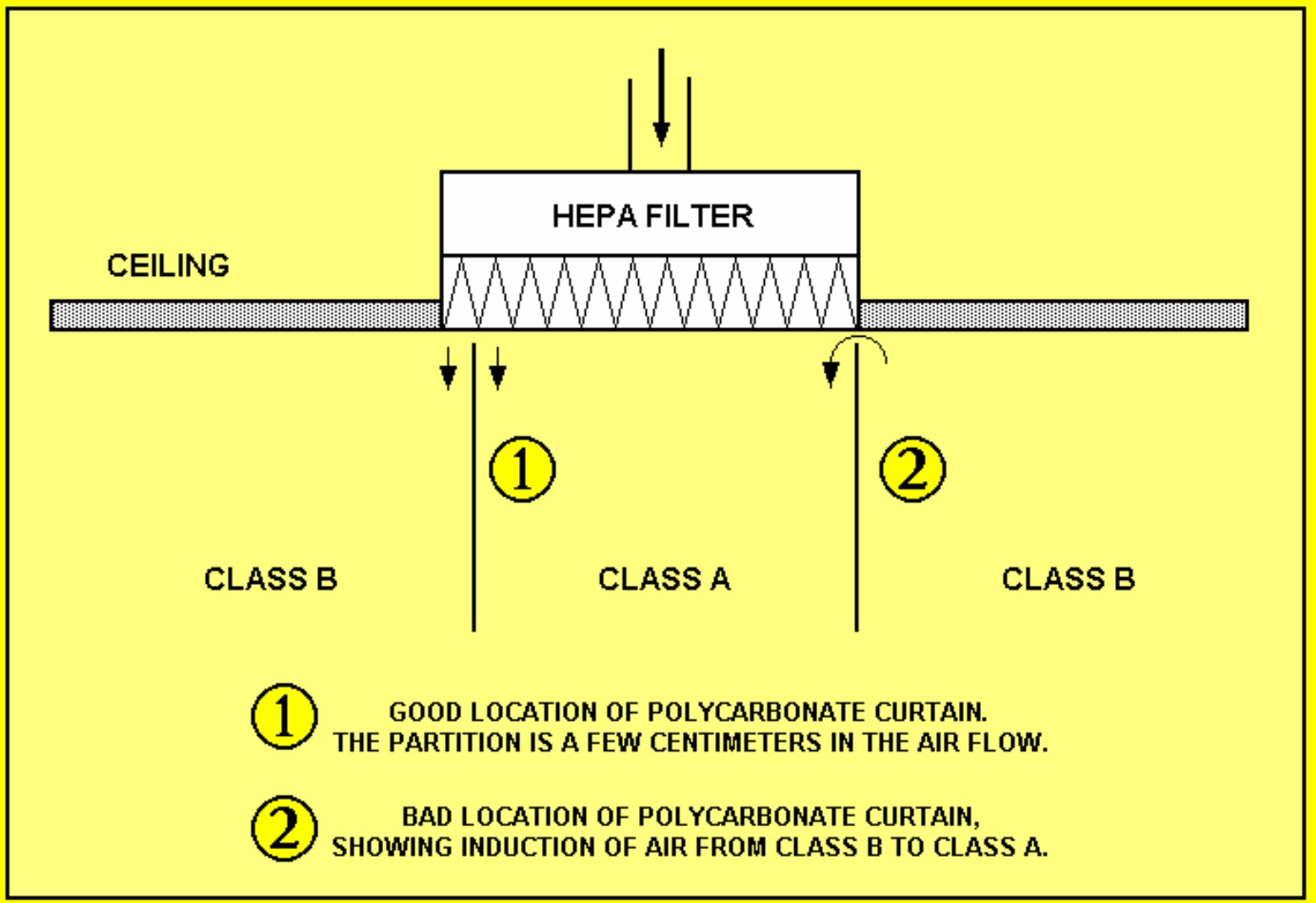
EN / ISO 14644 and AIRFLOW VELOCITY

- **14644 - 4 suggests 0,2 - 0,7 m/s**
  with efficiency demonstrated by performance testing.
- **Pharmacy expectations: 0,45 ± 20%**
  Not always applicable.

AIR SPEED MEASUREMENTS

LAF HOOD	0.45 m/s ± 20 % at working level
LAF with air curtains Or LAF over filling machine	measurement of speeds: -10 cm under filter - at working level (bottom of curtain) No specs : For information ONLY

FIG. 2: CURTAIN LOCATION IN HEPA FILTER ASSEMBLIES



EN / ISO 14644 and ROOM PRESSURE

- 14644 - 4 suggests dp 5 - 20 Pa
  gives guidance on risks on very high pressure
  very low pressure

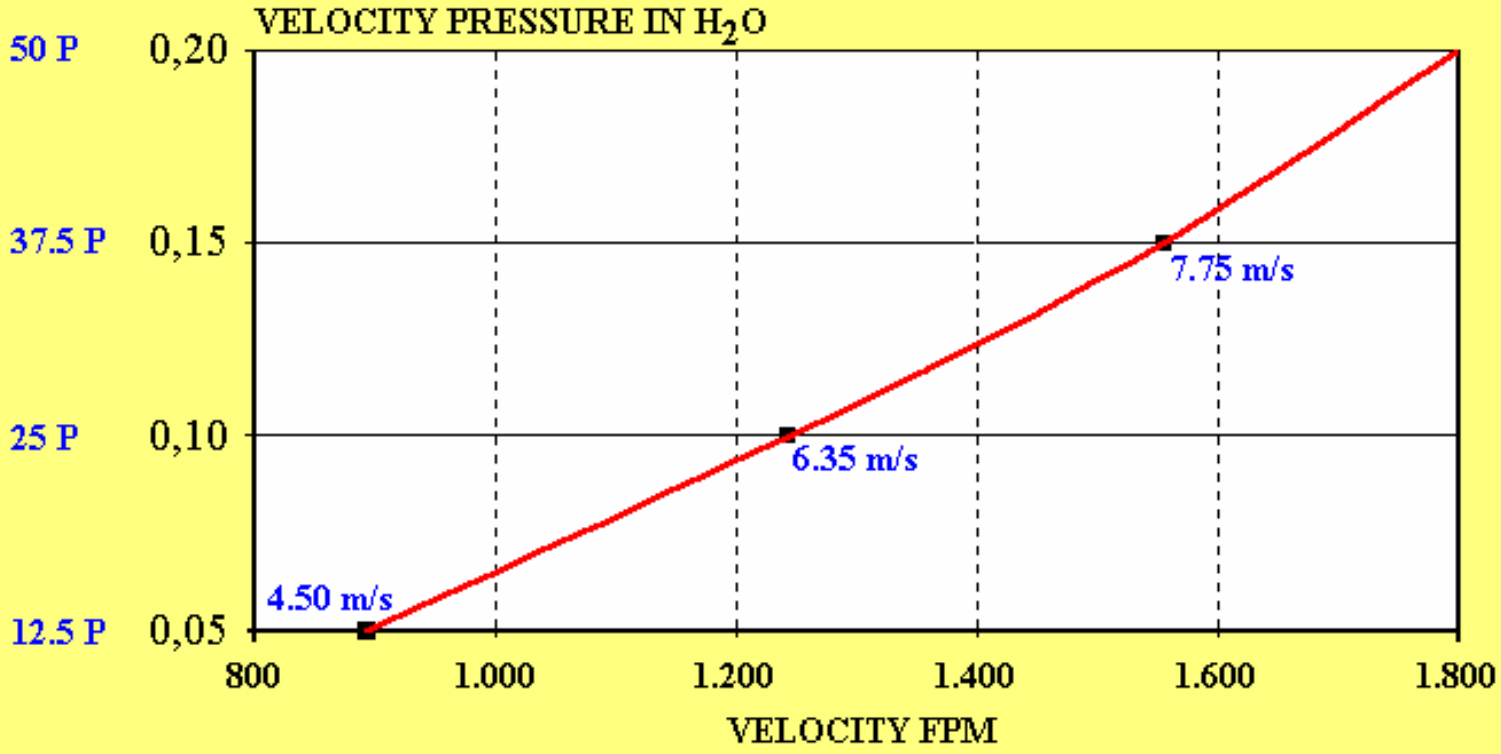
- It accepts
  low pressure differential + Flow through openings

PRESSURE DIFFERENTIAL

Dp ≥ 10 Pa (15 Pa)

with ± 5 Pa tolerance around set point
no overlap

AIR VELOCITY AND VELOCITY PRESSURE



10 P = 4 m/s
20 P =5.7 m/s
25 P = 6.3 m/s
30 P = 6.9 m/s
40 P = 8 m/s
50 P = 9 m/s

$$P_{dyn} = \frac{1}{2} \times \frac{\gamma}{g} \times v^2 \times 10 \text{ (Pascal)}$$

$$= \frac{1}{2} \times \frac{1,2}{9,81} \times v^2 \times 10 \approx \frac{1}{16} \times v^2 \times 10$$

$$P_{dyn} = \frac{10}{16} \times v^2$$

$$v = 4\sqrt{\frac{P}{10}}$$

$\gamma = 1,2 \text{ kg/m}^3$

v = speed m/s

AIR FLOW PATTERNS

Difficulties of performance linked to

- Smoke generation and initial velocity
- Talents of cameraman and film mounting

DECONTAMINATION TIMES MEASUREMENTS

Decontamination Time Procedure

- - Place the probe of the particle counter at a place which is representative for the air flow pattern outside the flow of the HEPA filter (mostly near an extract duct or a place which is poorly ventilated) (particle counting in “Worst case conditions”).

- - Create an artificial contamination in the room using a Dräger smoke generator (along walls, near machine frames, under HEPA filtered air inlets) in order to obtain a contamination level:

  - > 10’000 particles 0.5 ≥ µm per ft^3 (class B)
  - > 100’000 particles 0.5 ≥ µm per ft^3 (class C)
  - > 10^6 particles (class D)

- - Start the particle counter : sampling time = 1 minute ; delay between the samples 1 sec., program the particle counter printer with limits ≥ 0.5 and ≥ 5 µm. Check that the number of particles ≥ 0.5 µm is greater than 10’000/ft^3 (or 100’000, or10^6/ft^3 as applicable).

- - Leave the room and allow to auto-decontaminate until steady conditions are obtained, this is when the contamination level is stable and the possible anomalies have been observed (see BH 77/2 for example where one or more ondulations in the particle counts are obtained).

- - The number of sampling points per area is calculated with the following principle :

- - 1 point per 25 m^2 of floor surface with a minimum of 1 per room.
- - for areas of more than 3 m high : 1 point for each 75 m^3.

Operational tests Conclusions

- **PUNCH LIST (List of Deviations)**

  Accepted without remarks
  Accepted with remarks
  Not accepted

PL Nber	Description	Action By	Critical Y/N
	Retest	Verified By	Closing Date
PL Nber	Description	Action By	Critical Y/N
	Retest	Verified By	Closing Date

PERFORMANCE QUALIFICATION

- PARTICULATE COUNTINGS
- CONTAMINATION CURVES

NOTICE OF CANCELLATION OF FED-STD-209

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NOTICE OF CANCELLATION

FED-STD-209NOTICE 1

November 29, 2001

FEDERAL STANDARD

AIRBORNE PARTICULATE CLEANLINESS CLASSES

IN CLEANROOMS AND CLEAN ZONES

Federal Standard 209E dated September 11, 1992 is hereby canceled and superseded by International Organization for Standardization (ISO) Standards. International Standards for Cleanrooms and associated controlled environments, ISO 14644-1 Part 1: Classification of air cleanliness; and ISO 14644-2 Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1.

Application for copies of ISO Standards 14644-1 Part 1, and 14644-2 Part 2; may be addressed to the Institute of Environmental Sciences and

THE EU GMP 5µ Particle Number Problem

Nber of Particles	EC	EC	EC	EC	ISO	ISO	ISO
	A	B	C	D	5	7	8
≥5µ	0	0	2,000	20,000	29	2,930	29,300

PROCEDURE, PARTICLE COUNTS

- Determine the number of particle counting points with (locations) respect to the recommendations of the
  - *EN ISO 14644-1 : 1999 (E)*
  - *"The rules governing medicinal products in the European Community (Eudralex Volume IV, Annex 1, 1998)"*
  - *"FDA guideline on sterile drug products produced by aseptic processing",1987*

- Make a drawing of the room and locate the measuring points (preferably at the most critical points).
- At each point, place the probe of the particle counter parallel to the flow (vertically or horizontally) with the opening towards the HEPA filter (isoaxial sampling).

- The particle counter is used following the recommendations of the manufacturer. Each time the counter probe is moved in the room, the “initial delay” must be programmed with a time appropriate for the cleaning of the tube. The time between two successive readings without transferring the probe is programmed at 1 sec. (“delay time”).

- Sample the air at the height of the work activity (quite often between 0,8 to 1.2 m), unless impossible due to the presence of equipment.

PROCEDURE, PARTICLE COUNTS

- Sample the air once at each location except if :
  - *There is only 1 sampling point in the room : sample the air thrice at the same location*
  - *The result of the 1st sampling is out of the specifications range.*
    Then confirm or refute the reading by 3 successive readings

- For class C and D at rest or operational, sample time is 1 min and sampling volume is 1ft³

- For class A at rest or operational or B at rest the sampling time will be at least 5 min and could be more if the results are in between Pass and Failed values of the Table F.1 of the Annex F of the EN ISO 14644-1 : 1999, describing the sequential sampling procedure (see next page)

- The statistical calculations of classification are performed in accordance with the recommendations of the "EN ISO 14644-1" at the upper confidenc level of 95 %.

EN ISO 14644-1

EN ISO 14644-1 : 1999 (E) Sequential sampling procedure

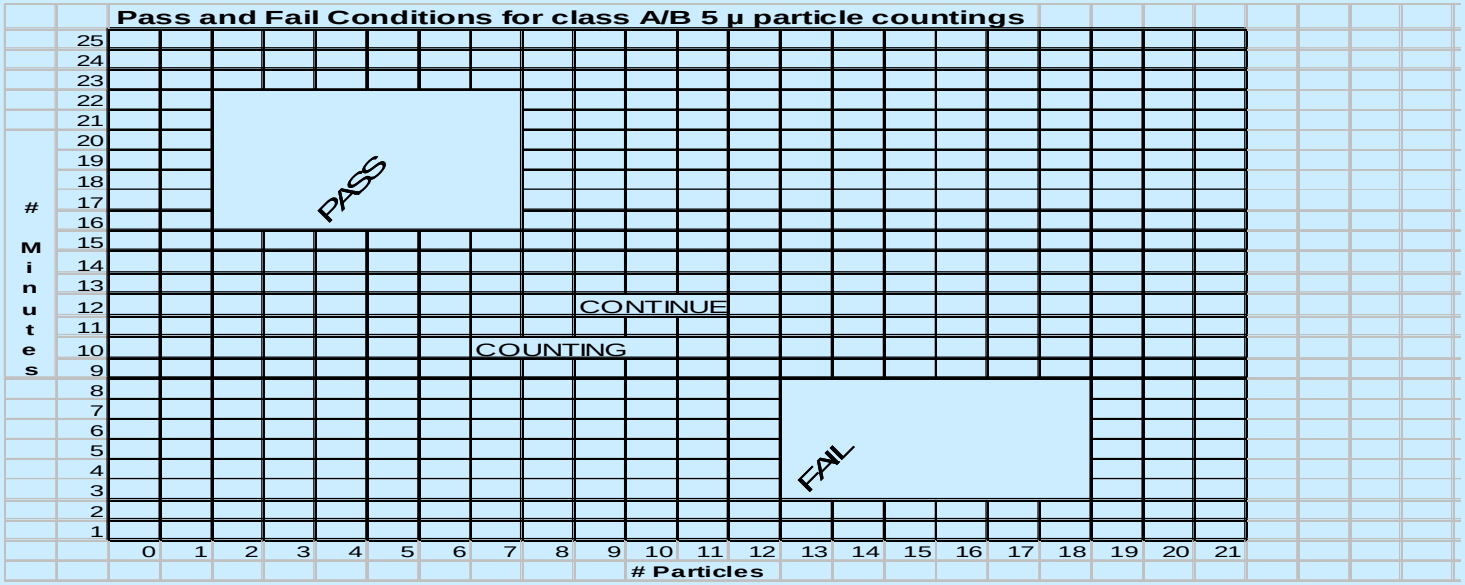
Table F.1 – upper and lower limits for time at which C observed counts should arrive

FAILS IF COUNT, C, COMES EARLIER THAN EXPECTED		PASSES IF COUNT, C, COMES LATER THAN EXPECTED	
Fractional time, t	Observed Count	Fractional time, t	Observed Count
0,001 9	4	0,192 2	0
0,050 5	5	0,240 7	1
0,099 2	6	0,289 3	2
0,147 6	7	0,337 8	3
0,196 1	8	0,386 4	4
0,244 7	9	0,434 9	5
0,293 2	10	0,483 4	6
0,341 7	11	0,532 0	7
0,390 2	12	0,580 5	8
0,438 8	13	0,629 1	9
0,487 3	14	0,667 6	10
0,535 9	15	0,726 2	11
0,584 4	16	0,774 7	12
0,633 0	17	0,823 3	13
0,681 5	18	0,871 8	14
0,730 0	19	0,920 3	15
0,778 6	20	0,968 9	16
1,000 0	21	1,000 0	17

NOTE Fractional times are given as the fraction of total times (t = 1,000 0 at the class limit)

Total times t = 1,000 0 at the class limit represents 24,3 minutes at the limit of class A,B (class A at rest or operational, class B at rest) for particles ≥ 5 microns

PASS AND FAIL CONDITIONS FOR CLASS A/B 5µ PARTICLE COUNTINGS



ACCEPTANCE CRITERIA

Particle counting, classification of rooms

- Particle counts are within specifications at a upper confidence level of 95 % following the statistical calculation of the "EN ISO 14644-1: 1999 E".
- The specifications for the airborne particulate classification of cleanrooms, as defined in the Eudralex Volume IV, Annex 1, 1998

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	At rest		**In operation**	
GRADE	**Maximum permitted number of particles/m³ equal to or above**			
	0.5 µm	**5 µm**	**0.5 µm**	**5 µm**
A ISO Class 5	3.500 3.520	0 29	3.500 3.520	0 29
B ISO Class 5	3.500 3.520	0 29	350.000 352.000	2.000 2.930
ISO class 6	35.200	293	352.000	2.930
C ISO Class 7	350.000 352.000	2.000 2.930	3.500.000 3.520.000	20.000 29.300
D ISO Class 8	3.500.000 3.520.000	20.000 29.300	Not defined, depends on nature of operations	

- **Any change of hereabove acceptance criteria must be mutually agreed upon by ICCE and** (see Annex 1: Sheet for change of acceptance criteria).
- **Note the discrepancy between Eudralex and EN ISO 14644-1 : 1999 for class A, B particles ≥ 5µ where Eudralex admits 0/m³ and EN ISO admits up to 29.**
  29 should be considered because of the electronic noise of the counter and other considerations.

TEST RESULTS : PARTICLE COUNTINGS ACCORDING EN ISO 14644-1 : 1999(E)

TEST RESULTS: PARTICLE COUNTINGS ACCORDING EN ISO 14644-1 : 1999 (E)

Particle countings class A,B (ISO 5) : A at rest or operational
B at rest only

Sampling time ≥ 5 min **Sampling Volume ≥ 5 ft³**

Number of sampling point (SP)/room = 1 **Sequential sampling**

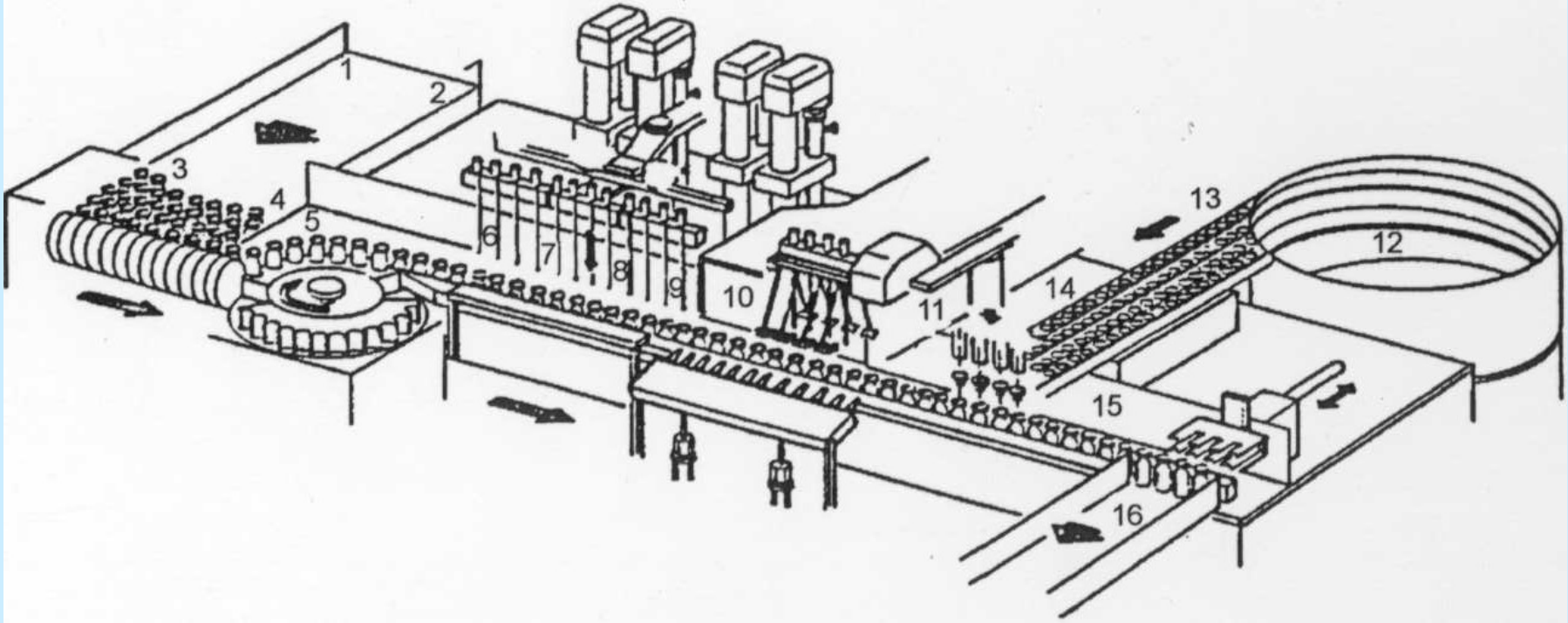
Room ID : **Class B at rest**

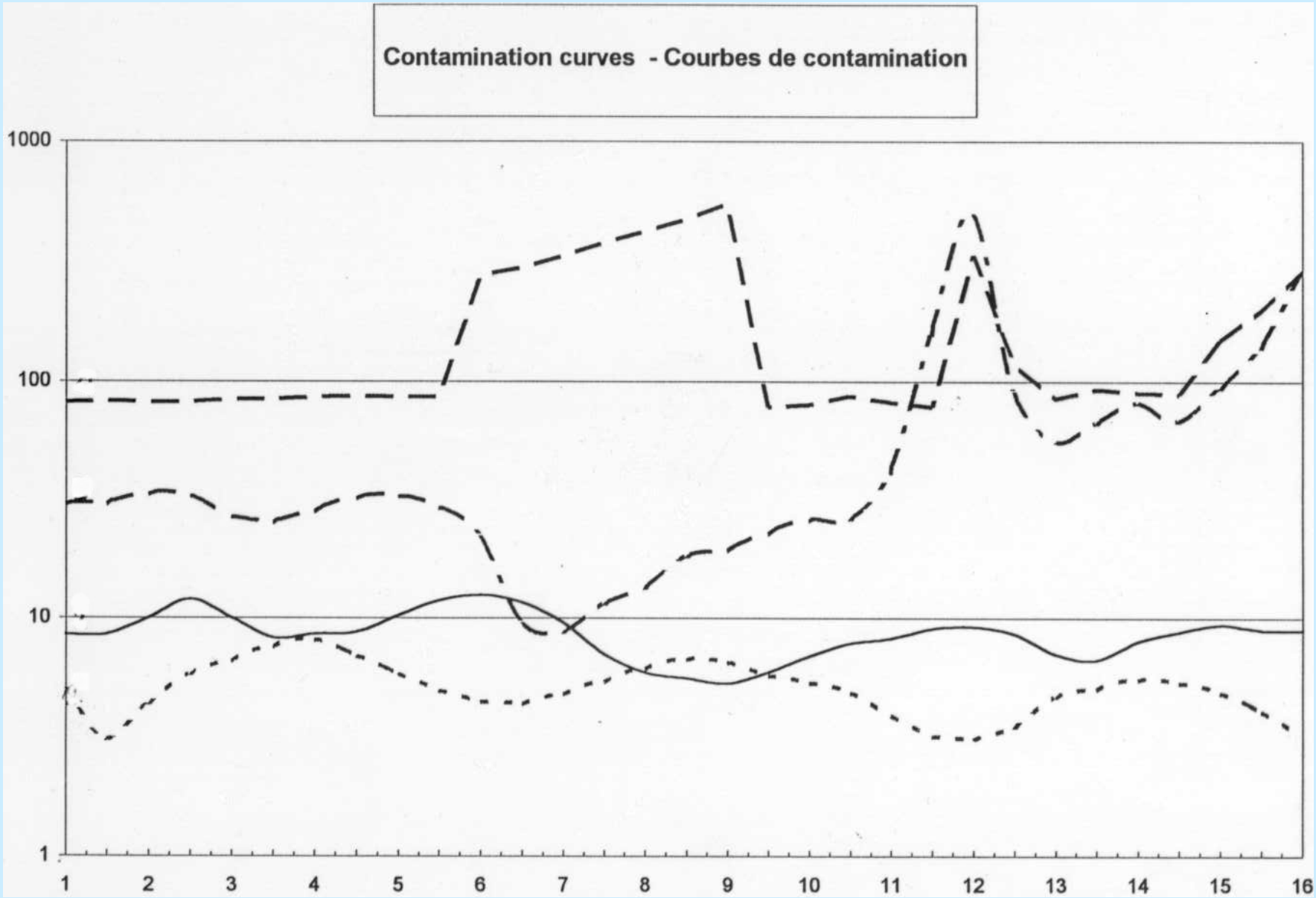
Particle counts ≥ 0.5 µ/ft³				
Sampling Point ID	Particle counts/ft³			
	1	2	3	Avg 0.5
Part ≥ 0.5 µ				
Acceptance criteria				<100
In compliance Y/N				

Particle counts ≥ 5 µ			
Counting time : (minutes)	Particle counts (observed)	Acceptance criteria	Fails
5		0	≥ 8
6		≤ 1	≥ 9
7		≤ 2	≥ 10
* (1)	* (1)	(2)	(3)
In compliance with acceptance criteria of table F1 Y/N			

(1) Enter first value which is in compliance with counts of table F1 or which fails
(2) Enter relevant acceptance criteria (from table F)
(3) Enter relevant fail value (from table F1)

CONTAMINATION CURVE - COURBE DE CONTAMINATION
Recommendations BH 77/1A - Recommandations BH 77/1A




Contamination curves - Courbes de contamination
1000
100
10
1
1
2
3
4
5
6
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14
15
16

REFERENCES

- The Rules governing Medicinal Products in the European Community
  (Eudralex Volume IV Annex 1, 1998)
- EN ISO 14644-1-7 on Clean Room Standards
- ISPE Baseline Pharmaceutical Guide :
  Sterile Manufacturing Facilities
- ISPE Baseline Pharmaceutical Guide :
  Commissioning and Validation

CONCLUSIONS

All the validation steps are important
(start well to finish well)

It is not possible to validate a poor Design

It is not possible to validate a poor Field Installation