ISPE
Affiliata Italiana
ENGINEERING
PHARMACEUTICAL
INNOVATION

Convegno:
Innovation in Pharmaceutical Manufacturing

Chiesi
People and ideas for innovation in healthcare

Innovation in Aseptic Manufacturing

RABS versus Isolators

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Main Discussion Topics :

- Why do we use “barriers” in aseptic manufacturing of sterile medicinal products?
- Regulatory Requirements in Aseptic Processing (Which are the basic rules?)
- Design Key Concepts

  (How could we accomplish the objectives?)
- Isolators versus RABS (What does fit better in our process?)
- Case History

Why barriers ? (1)

- Aseptic processing involves more variables than terminal sterilization
- Each process operation step could introduce an error that ultimately could lead to the distribution of a contaminated product
- Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses the greatest risk of contamination

Why barriers ? (2)

- Contamination may take the form of : particulates , microorganisms or endotoxins
- Human operators pose the greatest risk to product contamination during aseptic processing as a source of both viable and nonviable particles
- For instance Staphylococcus are among the most common human associated micro organism identified in clean rooms
- **Why barrier ? First aim :protection of the product, container/closure exposed to the environment ("open" process steps)**

Regulatory Requirements (1)

USA_cGMP[a]	EU_cGMP[b]
Two clean areas are involved in aseptic processing operation : the critical area and the supporting clean areas associated with it.	The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials.
A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility	The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area.

Areas segregation

Regulatory Requirements (2)

USA_cGMP	EU_cGMP
The critical area environment have to be of appropriate quality.One aspect of environmental quality is the particle content of the air	Clean areas are classified according to the required characteristics of the environment. Each operation requires an appropriate environmental cleanliness level in the operational state
Clean area Classification (0,5 p/cft) 100,1000,10.000,100.000	4 grades can be distinguished: grade A, B, C, D
Critical areas has to be class 100. The nature of the activities conducted in supporting clean areas determines its classification	Examples of operations to be carried out in the various grades

Process Environment Quality

Based on airborne particulate (viable and non viable) classification and recommended limits for microbial contamination

Regulatory Requirements (3)

USA_cGMP	EU_cGMP
For Class 100,000 (ISO 8) supporting rooms, 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas.	In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room.
HEPA-filtered air should be supplied in critical areas	HEPA terminal filters for grades A,B,C.
A velocity of 0,45m/s ± 20% maintain unidirectional airflow and air quality under dynamic conditions	range of 0.36 – 0.54m/s (guidance value) of Air speed for unidirectional flows

To reach Environment Quality

Regulatory Requirements (4)

USA_cGMP	EU_cGMP
Clean area separation (airlocks,pressure cascade continuously monitored and alarmed),process flow,material and personnel flow, automation to reduce manual activities,clean rooms construction materials). Temperature and humidity controls (21 CFR 211.42(c))	Premises considerations (exposed surfaces, recesses, sealing ,changing rooms lay-out, interlocking systems, pressure cascade ,areas pressure warning systems) . Comfortably Temperature and relative humidity
Sterile and no shedding personnel gown should provide barrier to prevent contamination from human body (viable and nonviable particles)	The clothing and its quality should be appropriate for the process and the grade of the working area.
Aseptic gowning qualification , personal training (aseptic technique, cleanroom behaviour, microbiology, hygiene,gowning)	Clear SOPs and regular training for personnel (maximum number, hygiene and cleanliness, changing ,clothing treatments, methodical movements)

To maintain Environment Quality

Regulatory Requirements (5)

USA_cGMP	EU_cGMP
Aseptic processing using positive pressure isolation systems separates the external cleanroom environment from the aseptic processing line and minimizes its exposure to personnel.	The utilisation of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination from the environment.
Maintenance concepts are stressed: replacement frequencies and glove integrity	Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system

Isolators : separate operators from product
(false sense of security)

Regulatory Requirements (6)

USA_cGMP	EU_cGMP
Isolators types : open and closed Turbulent flow can be acceptable within closed isolators other aseptic processing isolators employ unidirectional airflow Very high positive air pressure differential (aprox. 17,5 to 50 Pa) for isolator with open portal Local Class 100 (ISO5) for opening protection	There are many possible designs of isolators and transfer devices. Laminar air flow may not exist in the working zone of all such devices
Suitable construction material (durability and resistance to cleaning and decontamination)	Construction materials more or less prone to puncture and leakage

Isolators design

Regulatory Requirements (7)

USA_cGMP	EU_cGMP
The interior of the isolator should meet Class 100 (ISO 5) ; A Class 100,000 (ISO 8) background is commonly used	air classification required for the background environment for aseptic processing should be at least grade D
Open isolator direct interface with other manufacturing equipment (tunnel) RTP (rapid transfer port) decontaminating capability Mousehole with suitable overpressure	Transfer of materials into and out of the unit is one of the greatest potential sources of contamination. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms
Process development and validation studies of Decontamination by chemical agent	Isolators should be introduced only after appropriate validation

Isolators

Design key Concepts (1)

(Conventional Clean Room)

- Aseptic processes facilities are designed to minimize exposure of product and sterile articles to the potential contamination hazards of the manufacturing operation.
- Apply the concepts of nested manufacturing zones (protection around critical area) and integrated design to satisfy both process (material,people,product) and equipment lay out.
- A proper design of the HVAC system (air filtration,air flows patterns ,air change rate ,pressure cascade, etc..) will reduce particulate contamination and maintain air quality

Design key Concepts(2)

(Conventional Clean Room)

- Cleanroom design good engineering practice : turbulent air flow to maintain the background with island of higher environment grade provided by displacement systems
- Carefully designed curtains and rigid plastic shields are among the **barriers** that can be used in appropriate locations to achieve segregation; use of an isolator system further enhances product protection.
- It is important that the high quality reached through a good clean room design is not compromised by entry of potential contamination sources (people clothing, people flow and movements , material flow)

Isolators & RABS

(Advanced Protection Systems)

- The development isolators has been significant. In the last years they have continued to evolve to the more advanced designs we see today (PDA technical report No.34, ISO 13408-6, ISO 14644-7, etc).
- RABS however are less well defined (ISPE/FDA definition_August 2005) but significant development is expected.

Isolators (1)

- ISOLATOR DEFINITION: a Separative Device that provide assured protection by using physical and dynamic barriers to create separation between operation and operator; it is supplied with HEPA filtered air and may be decontaminated in quantifiable and highly reproducible manner
- TYPES: Closed, Open; flexible wall, rigid wall; positive or negative pressurization
- DESIGN & OPERATIONAL SPECIFICATIONS [f]:

✓Feasible both for aseptic and containment applications ✓Construction materials mechanical and chemical resistant ✓Operator interface:gloves,gauntlets,half suites ✓HEPA/ULPA filtered air supplied ✓Either turbulent (closed) or unidirectional air flow (open) ✓Pressure differentials:from 25Pa to 100Pa (monitoring&alarms)	DESIGN

Isolators (2)

✓Air Change rate :don't need to comply with "20V/h minimum" (absence of personnel) for unidirectional airflow could reach very high values ✓Airborne Particulate cleanliness classification : ISO 5 for internal environment ✓Recirculation rate: one through or return air system ✓Leak tightness (0,5% of Volume leak rate acceptance criteria).Even for open (dec. safety and health requirements)	DESIGN
✓Decontamination using a reproducible and validated method ✓Leak testing:pressure decay(closed) & induction leak test(open) ✓Gloves integrity test: oxygen,pressure decay,flow rate methods ✓Monitoring: DP(alarms),T,UR% ✓Environmental controls: viable & non viable,surface&gloves	OPERATIONAL

RABS (1)

(from ISPE Definition paper _August 2005) [i]

- RABS DEFINITION: A Restricted Access Barrier System is an advanced aseptic processing system that provides an enclosed environment to reduce the risk of contamination to product, containers, closures, and product contact surfaces. RABSs are not closed systems and are suitable for applications where process interventions are needed .A RABS provides a level of separation between operator and product that affords product protection superior to traditional systems.
- TYPES: Passive , Active [j] , [l]
- DESIGN & OPERATIONAL SPECIFICATIONS:

✓Rigid Enclosure ✓Unidirectional filtered (HEPA) airflow (ISO5 environment) ✓Suitable entry&exit materials transfer systems	**DESIGN**

RABS (2)

✓Surrounding room classification should be ISO 7 minimum in operation (ACTIVE RABS). ✓When open door interventions are necessary, an ISO 5 (class 100) vertical unidirectional airflow system outside of the RABS reduces risk of a breach in ISO 5 conditions ✓Locked door access or interlocked door access with recorded intervention alarms ✓Positive airflow from the enclosure to the exterior environment while the door is opened. ✓remote or automated sampling for in process control testing (IPC) including monitoring for viable and non-viable particles (design adoptions to prevent door openings)	DESIGN

RABS (3)

✓Sterilization-in-place (SIP) is preferred for contact parts such as fluid pathways. Where this cannot be achieved, such parts should be sterilized in an autoclave, transferred to the RABS via a suitable procedure and aseptically assembled before processing. ✓Product contact parts such should be sterilized in an autoclave and aseptically assembled before processing. ✓Gloves and gauntlets attached to glove ports are required to be sterile when installed; thereafter, gloves should be sanitized or changed as appropriate to minimize the risk of contamination ✓"High-level disinfection" of all non product contact surfaces within the RABS with an appropriate sporicidal agent before batch manufacture ✓ Following an open door intervention, appropriate line clearance and disinfection commensurate with the nature of the intervention are required	**OPERATIONAL**

RABS versus Isolators (1)

Main differences between RABS and Isolator

- DECONTAMINATION:

R Manually disinfected by gowned personnel	***I*** Quantifiable and highly reproducible method performed by automated system

- ASSURANCE OF SEPARATION *(ISO 14644-7)*:

R Do not provide a complete physical separation need a good separation descriptor (*) and a verifiable air overspill	***I*** Quantifiable hourly leak rate (closed) and continuously controlled DP

(*) *(ISO 14644-7)* Separation descriptor is a numerical abbreviation summarizing the difference in cleanliness classification between two areas as ensured by a Separative device : [Aa:Bb]

RABS versus Isolators (2)

Main differences between RABS and Isolator

- SURROUNDING ENVIRONMENT:

R Passive RABS must be positioned in an ISO 5_grade A environment (for Active ISO7_ grade B, could be possible)	***I*** USA-cGMP Class 100,000 (ISO 8) _ EU- cGMP at least grade D

- CONTAINMENT APPLICATIONS :

R Low capability	***I*** Quantifiable leakage tightness [ISO 1410648-2]

Our Case History (1)

- In order to increase capacity and efficiency, Chiesi built a new facility for the production of a sterile **bulk** suspension
- The project was based on a **Quality Risk Assessment**
- We Applied the concept of **Risk reduction** through design to reduce the probability of occurrence of harms and the severity of that harms.
- Additionally several improvements were incorporated as part of our continuous improvement process including state of the art techniques (PAT)

Our Case History (2)

- During our Risk Assesment one of the main hazards we analysed, was of course the potential product contamination by viable and nonviable particles
- One of the objectives of Risk reduction by design was the improvement of product protection
- Ergonomic aspects of our operations, basically drove us to RABS barrier technology
- Chiesi puts a lot of effort into ensuring that the RABS properly fits its process

Our Case History (3)

- FIRST STEP: User Requirement Specification

✓ During this phase we worked close to production people to understand the real operation needs

✓ We used both EU and USA regulatory references to cover cGMP requirements

✓ We used ISPE_RABS definition paper as a guideline

Our Case History (4)

- SECOND STEP: Build of a Full-scale model and mock-up trials

✓ We determined all the locations the operators had to reach in every single detail, and ease of access for al critical manipulations was the base of our barrier design.

✓ Ergonomics are very important with physical barriers;if the operator interface is too demanding or restrictive,or if cycle time become too bogged down , the workers may choose not to use the equipment as it was designed to be used.

Our Case History (5)

- THIRD STEP: Design,Construction and Installation
- ✓ The Restricted Access Barrier System encloses the critical area where the aseptic process takes place.
- ✓ The RAB around the critical zone consists in a U shape rigid wall around a perforated stainless steel working table and a frontal rigid stainless steel wall with glass doors and access hatches.
- ✓ Working table carries on it all the equipment needed for the process.
- ✓ After installation a "Pre testing phase" was accomplished (fine–tuning ,air balances and other adjustments)
- ✓ During this phase, through a smoke patterns pre test, we studied the most representative position for both viable and non viable automatic monitoring probes

Our Case History (6)

- THIRD STEP: Design,Construction and Installation

✓ Doors are utilized during the transfer of sterilized materials on the working table at the beginning and at the end of the process operations ,while the access ports are utilized during process operations (operators use sterile double gloves one with full sleeve)

✓ On top of it a full coverage of the enclosed area with HEPA filters give protection to the entire zone. Air trough the HEPA filters is supplied by the HVAC system (Passive RABS)

✓ Outlet air openings, the perforated working table and bottom air wall returns properly designed assure a correct air flow without stagnation regions or vortexes in the critical points.

Our Case History (7)

- FOURTH STEP: Equipment Validation

  Before starting with the process simulation (Media Fill) , an intensive qualification analysis was accomplished:

- ✓ HEPA filters integrity
- ✓ Environmental conditions : temperature and relative humidity
- ✓ Air volumes change in rooms :
  - ➢ Surrounding ISO 5 (grade A) : ~ 500 Vol/h
  - ➢ Inside RABS ISO 5 (grade A) : ~800 Vol/h
- ✓ Air velocity of unidirectional air flows
- ✓ Differential pressures between areas :

From	To	DP (Pascal)
Inside RABS	surrounding	10
RABS	dissolution/pre-filtration area – (through mouse hole)	30

Our Case History (8)

- FOURTH STEP : Equipment Validation

✓ Air flow patterns visualization test : smoke has been generated during critical operations in order to demonstrate the correct air flow pattern(unidirectional air flow and the sweeping action) including evaluation of the impact of aseptic manipulations and equipment location inside the RAB. These studies have been documented.

✓ Room environmental classification : air cleanliness levels in operational in critical areas were confirmed with the maximum permitted number of operators. All tests were done first mocking all activities and then during media fill

✓ Recovery time

Our Case History (9)

- FOURTH STEP : Equipment Validation

✓ Further air pattern analysis were performed on the RABS

Flow Unidirectionality	Overpressure	Backflow absence
Smoke generated inside RAB at 500 mm above the working table in the critical points	Smoke generated •Inside RAB close to the doors, access ports and to the mouse hole •Outside RAB close to doors, access ports and mouse hole	Smoke generated: •Inside under the working table •Outside in proximity of each door •Opening in sequence of each door
Unidirectional flow , without bouncing on the working table, without backflow from adjacent zones	The flow demonstrates that the RAB is in overpressure towards the surrounding and module of the Hood that is connected to the RAB via a mouse hole	Particle counter positioned inside the RAB does not detect any increase of particles (0.5 μm and 5.0 μm) during and after the smoke generation

Our Case History (10)

- FIFTH STEP : Media Fill .

  The validation of aseptic processing simulated all processing operations impacting on sterility

- ✓ Three consecutive runs have been performed
- ✓ Worst cases were introduced with maximum number of operators manipulation and doors openings
- ✓ The Media Fill conducted demonstrated that the aseptic processing operation for the bulk suspension preparation in the new facility is able to exclude contamination.

References (1)

a. **Guidance for Industry_Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice** . U.S. Department of Health and Human Services_Food and Drug Administration/ Centre for Drug Evaluation and Research (CDER)/Centre for Biologics Evaluation and Research (CBER)/ Office of Regulatory Affairs (ORA)_September 2004

b. **EU_cGMP-ANNEX 1_MANUFACTURE OF STERILE MEDICINAL PRODUCTS** _September 2003

c. **ISPE Pharmaceutical Engineering Guides for New and Renovated Facilities**_Volume 3-Sterile Manufacturing Facilities

d. **ISO Standards 14644 Cleanrooms and Associated Controlled Environments**

- 14644-1 : Classification of Air Cleanliness
- 14644-4 : Design, Construction and Start-Up
- 14644-5 : Operations
- 14644-7 : Separative devices (clean air hoods, gloveboxes, isolator and minienvironments)

e. **Institute of Environmental Sciences and Technology (IEST) standards**

- ✓ IEST-RP-CC006.3 -Testing Cleanrooms
- ✓ IEST-RP-CC-002.1 -Laminar Flow Clean Air Device
- ✓ IEST-RP-CC-034.2 -HEPA and ULPA filter leak test
- ✓ IEST-RP-CC-001.4 -HEPA Filters

References (2)

- f. **PDA Technical Report No 34 " Design and Validation of isolator Systems for the Manufacturing and testing of Health Care Products"**
- g. **PIC/S_ PI 014-21 ISOLATORS USED FOR ASEPTIC PROCESSING AND STERILITY TESTING** July 2004
- h. **ISO Standards 13408 "Aseptic processing of health care products "**
- ✓ Part 5 :General requirements
- ✓ Part 6 :Isolator system
- f. **ISO Standards 10648 "Containment enclosures "**
- ✓ Part 1 :Design Principles
- ✓ Part 2 :Classification according leak tightness and associated testing methods
- i. **ISPE definition paper of RABS _August 2005**
- j. **RABS Definitions and Performance levels - http://www.pharmaceutical-int.com/**
- k. **ISPE Vienna Conference, 2006_Practical Aspects of Glove Testing for a Production RABS Application**
- l. **ISPE_PHARMACEUTICAL ENGINEERING** January/February 2007 :"Choosing Technologies for Aseptic Filling .. " J.Agalloco,J.Akers,R.Madsen

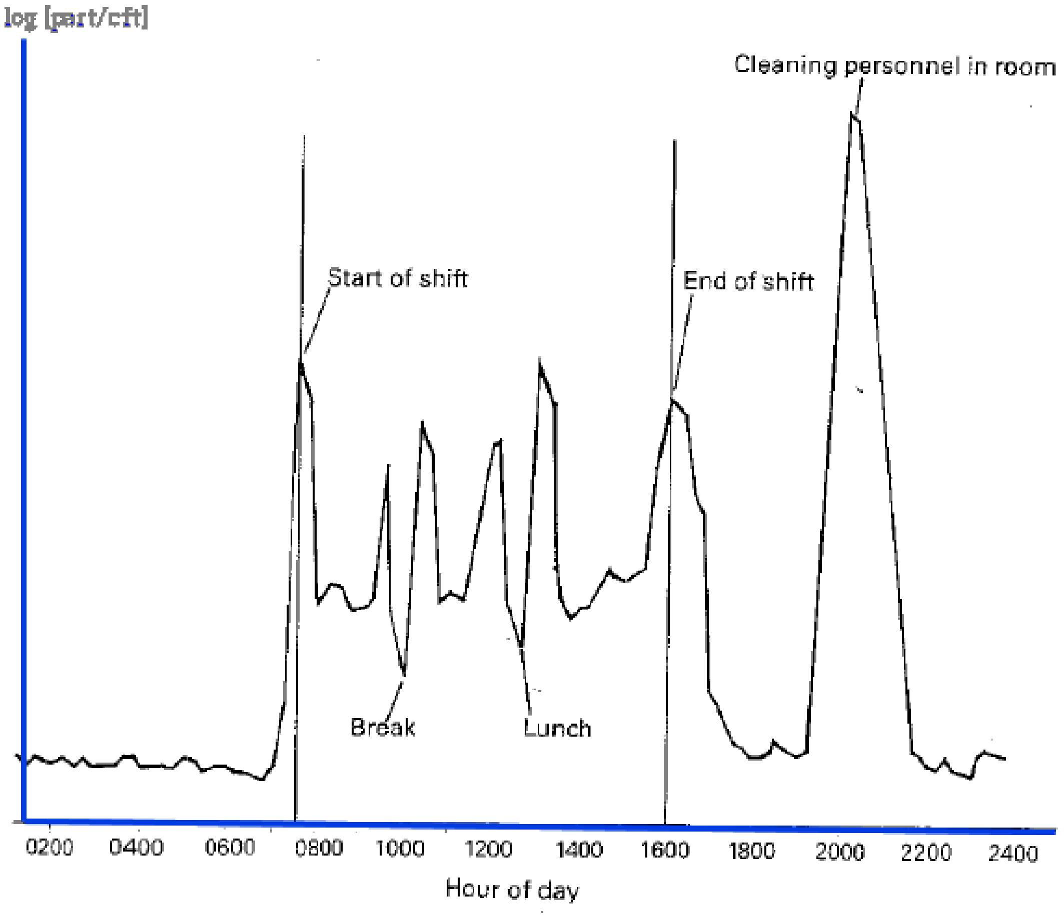
Tank you for your kind attention !!

Sources of Contamination

(ISPE Baseline-Vol.3 Sterile Manufacturing Facilities[c])

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

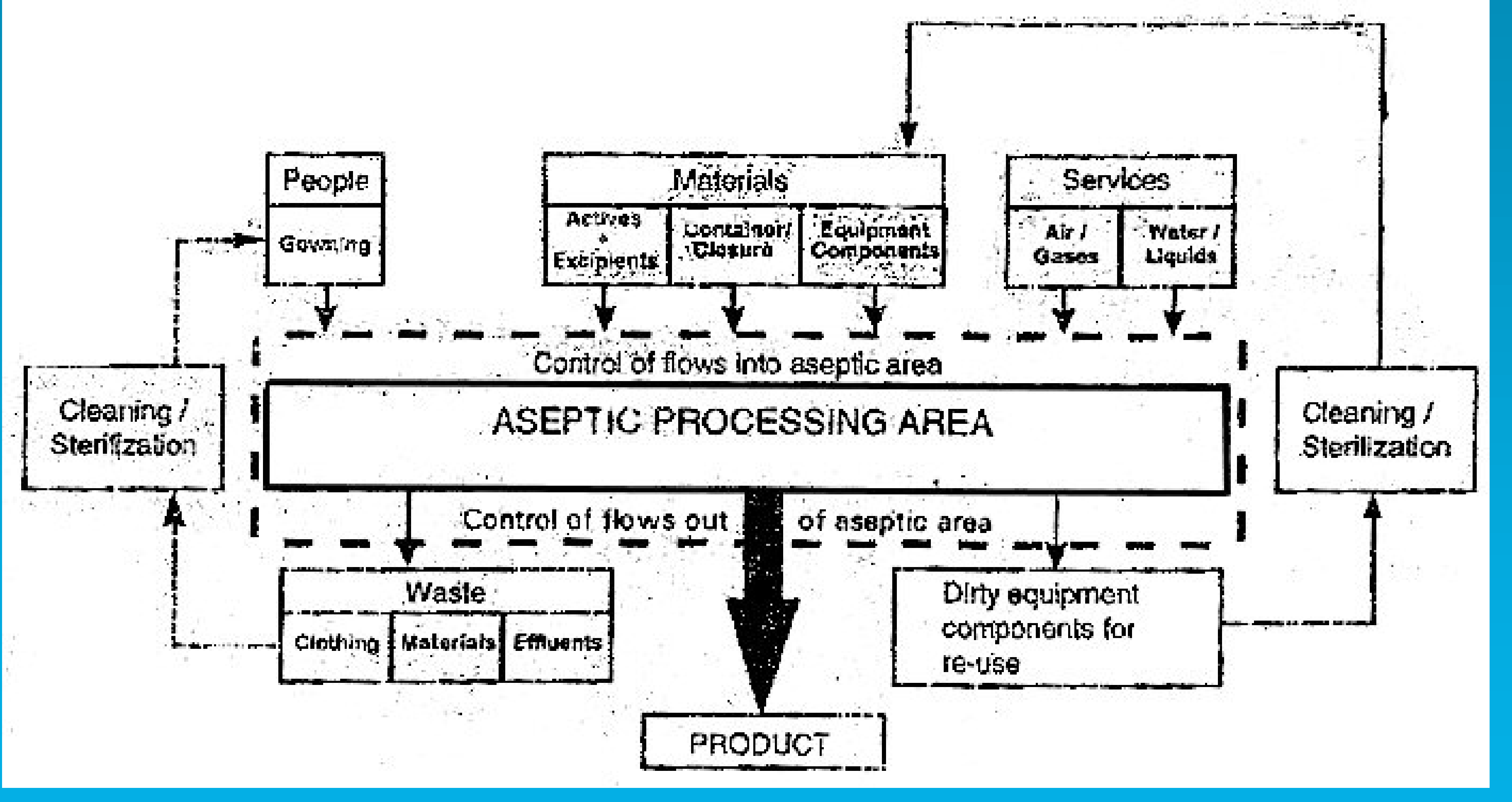
Number of particles generated by operators activity in a cleanroom



The people effect in the cleanroom (Source: NASA)

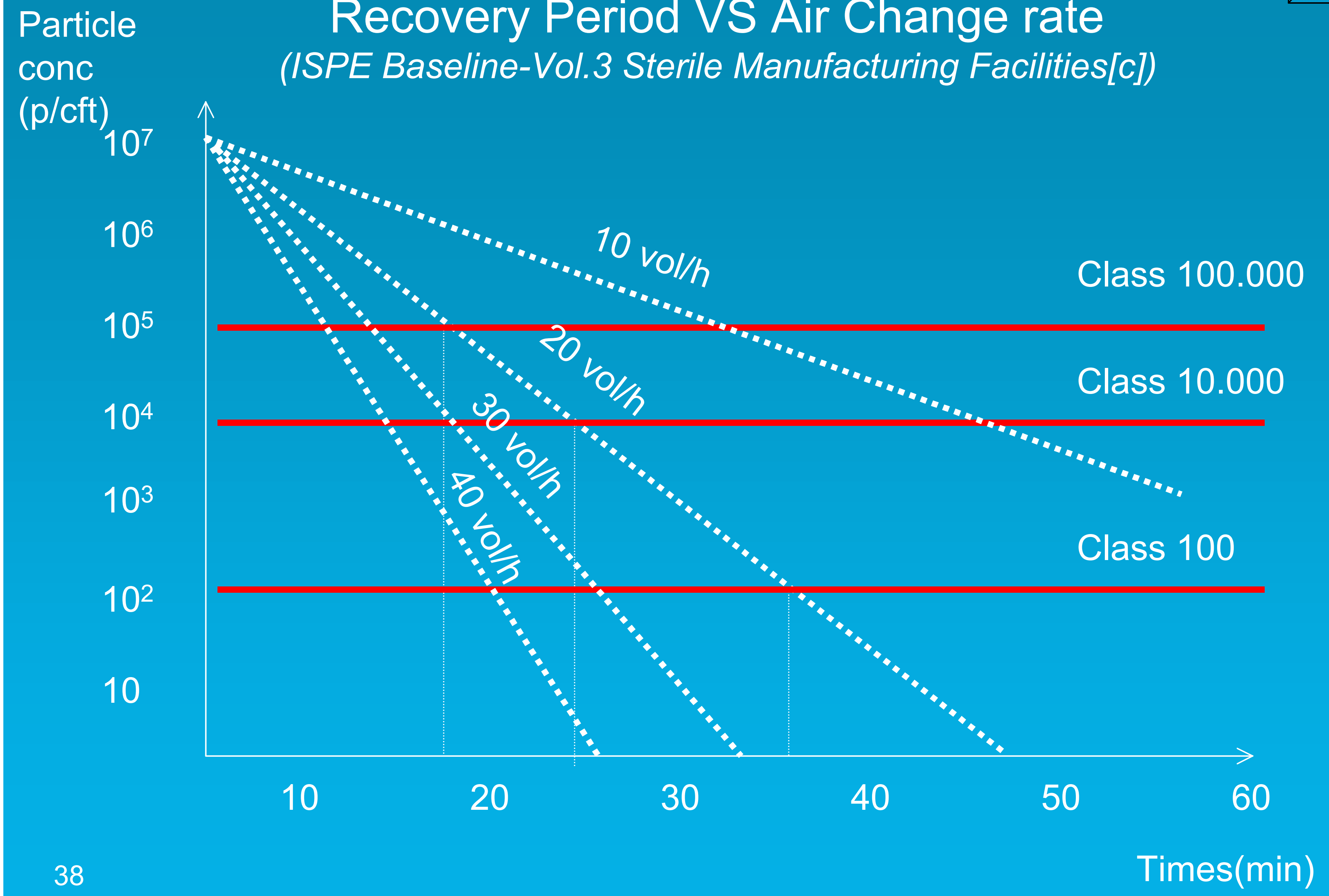
Aseptic Manufacturing Flowchart

(ISPE Baseline-Vol.3 Sterile Manufacturing Facilities[c])



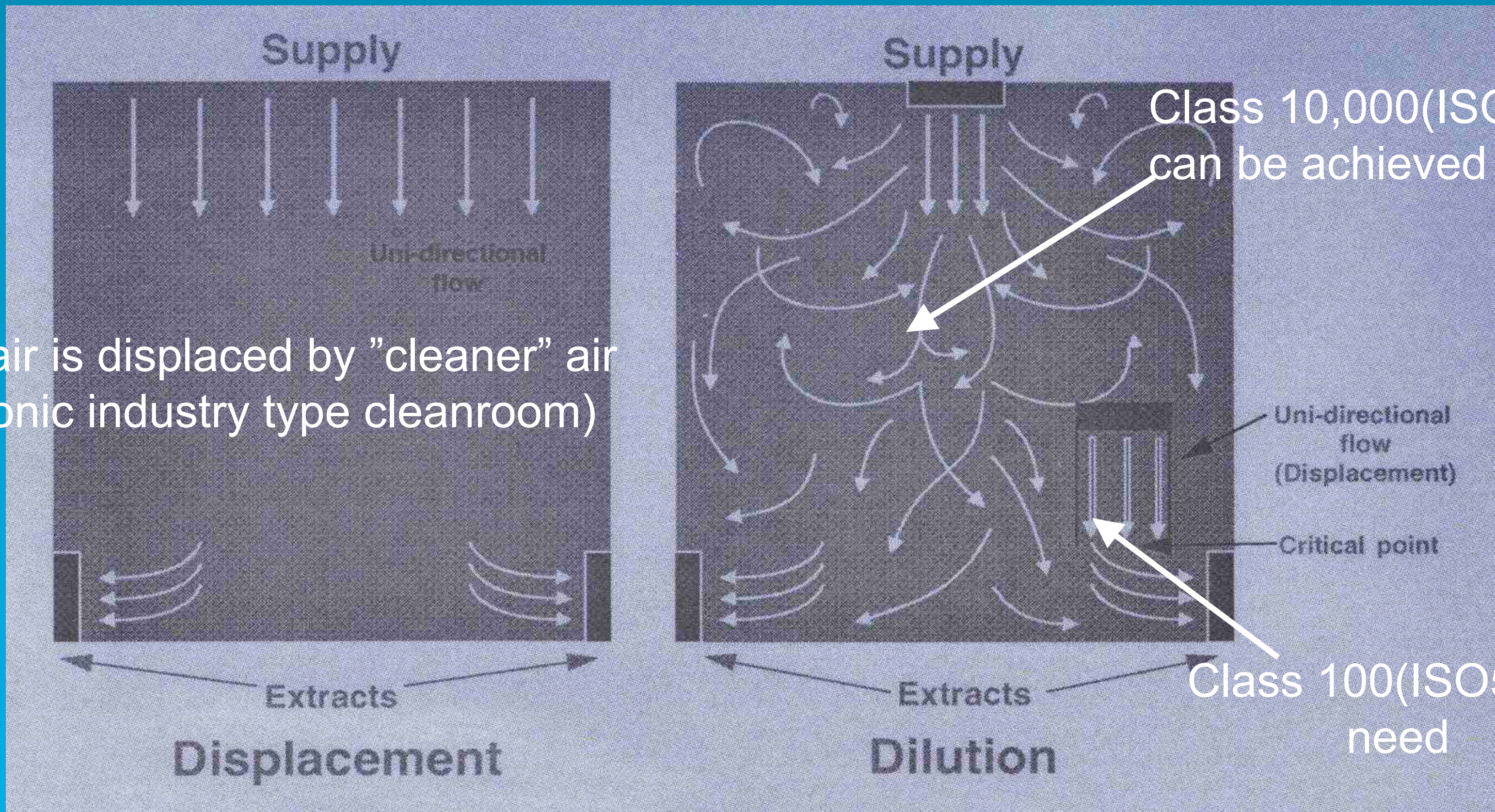
Recovery Period VS Air Change rate

(ISPE Baseline-Vol.3 Sterile Manufacturing Facilities[c])



Conventional Clean room design Key concepts

(ISPE Baseline-Vol.3 Sterile Manufacturing Facilities[c])



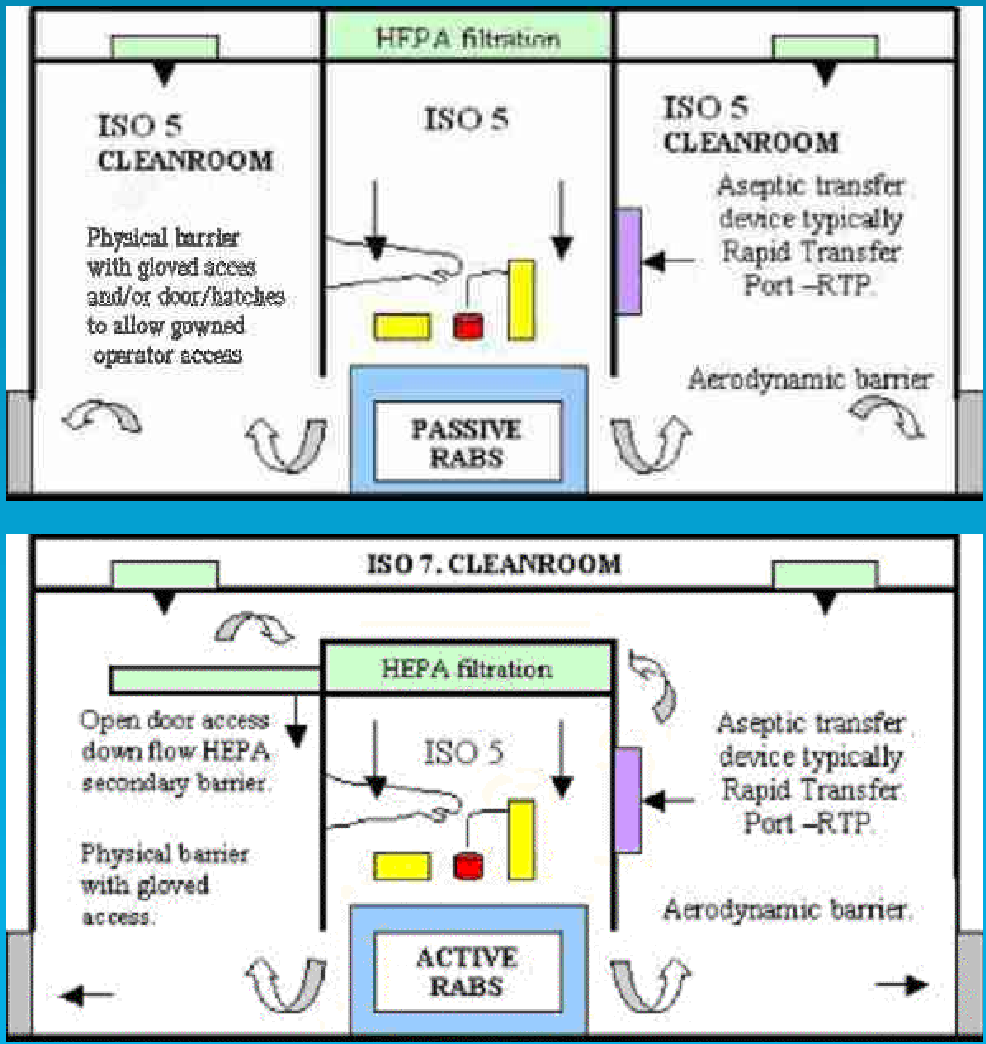
Class 10,000(ISO7) op. can be achieved

“dirty” air is displaced by ”cleaner” air (Electronic industry type cleanroom)

Class 100(ISO5) op need

“dirty” air is mixed continuously with ”clean” air to reduce particulate load (Pharmaceutical industry type cleanroom)

RABS design Key concepts [j]



RABS versus Isolators (1)
evaluation criteria – features and functions

	RABSs		ISOLATORs	
	PASSIVE	ACTIVE	OPEN	CLOSED
CAPITAL COSTS	• Higher than conventional clean room • Reduced capital costs with renovation and retrofit application	• Higher than conventional clean room • Reduced capital costs with renovation and retrofit application	High equipment costs	High equipment costs
OPERATING COSTS	Higher than conventional cleanroom	Higher than conventional cleanroom	Cost saving in energy consumption (HVAC) and clothing	Cost saving in energy consumption (HVAC) and clothing
SET UP TIME& FACILTY START UP	Building infrastructure time consuming similar of conventional cleanroom	Equipment more complex but facility simpler	Equipment more complex but facility simpler	Equipment more complex but facility simpler
CHANGE OVER FLEXIBILITY	High	High	Medium	Medium

RABS versus Isolators (2)
evaluation criteria – features and functions

	RABSs		ISOLATORs	
	PASSIVE	ACTIVE	OPEN	CLOSED
TOXICS CONTAINMENT	Not usable	Low capability	Complex feasibility	Good Reliability *(Complex feasibility for sterile toxic)*
PERSONEL IMPACT EXTENT	Minimal Separation (physic barrier and restricted air overspill)	Aerodynamic separation is upgrade with a controlled differential pressure	Medium Separation (physic barrier and openings aerodynamic barriers)	High Separation (physic barrier and overpressure
ERGONOMICS	• Less complex than isolators • suitable for applications where process interventions are needed	• Less complex than isolators • No open doors are permitted	Process Line preparation slow due the access constraints	Process Line preparation slow due the access constraints
BACKGROUND ENVIRONMENT	ISO 5, class 100 ,GRADE A *(gowning, Env.Monitoring commiserate with manned cleanroom)*	ISO 7, class 10000 ,GRADE B	• USA-cGMP Class 100,000 (ISO 8) • EU- cGMP at least grade D	• USA-cGMP Class 100,000 (ISO 8) • EU- cGMP at least grade D

Regulatory requirements

RABS versus Isolators (3)
evaluation criteria – features and functions

	RABSs		ISOLATORs	
	PASSIVE	ACTIVE	OPEN	CLOSED
AIR DOWFLOW	Unidirectional	Unidirectional	Unidirectional	Unidirectional or Turbulent
PRESSURE DIFFERENTIAL (to the surrounding environment)	Difficult to control	Independent air system: DP easy to control	• Independent air system: DP easy to control • ISO5 HEPA air sweep in conjunction with Mousehole • DP monitored continuously (alarms)	• Independent air system: DP easy to control • From 25 Pa to 100Pa typical set range • DP monitored continuously (alarms)
TRANFER SYSTEMS	Transfer doors / hatches	Suitable transfer system (RTP)	Continuous or semi continuous material ingress/egress	Suitable transfer system (RTP)
ENVIRONMENTAL SANITIZATION	• Manual disinfection by gowned personnel • Reproducibility and validation uncertain	• Manual disinfection by gowned personnel • Reproducibility and validation uncertain	decontaminated while closed (Sealing need before GSIP)	GSIP gas/vapors sanitization in place
LEACK TESTING	Induction leak testing*(ISO14644-7)* or L-R method*(PDA TR 34)*	Induction leak testing	• Hourly leak rate for GSIP safety&healt aspect • Induction leak testing	Hourly leak rate (*In-process pressure decay test _ Tf (h^{-1}) of 0,5% or 8 Pa/min)*

Separation Continuum Concept

(ISO 14644-7 : annex A [d])

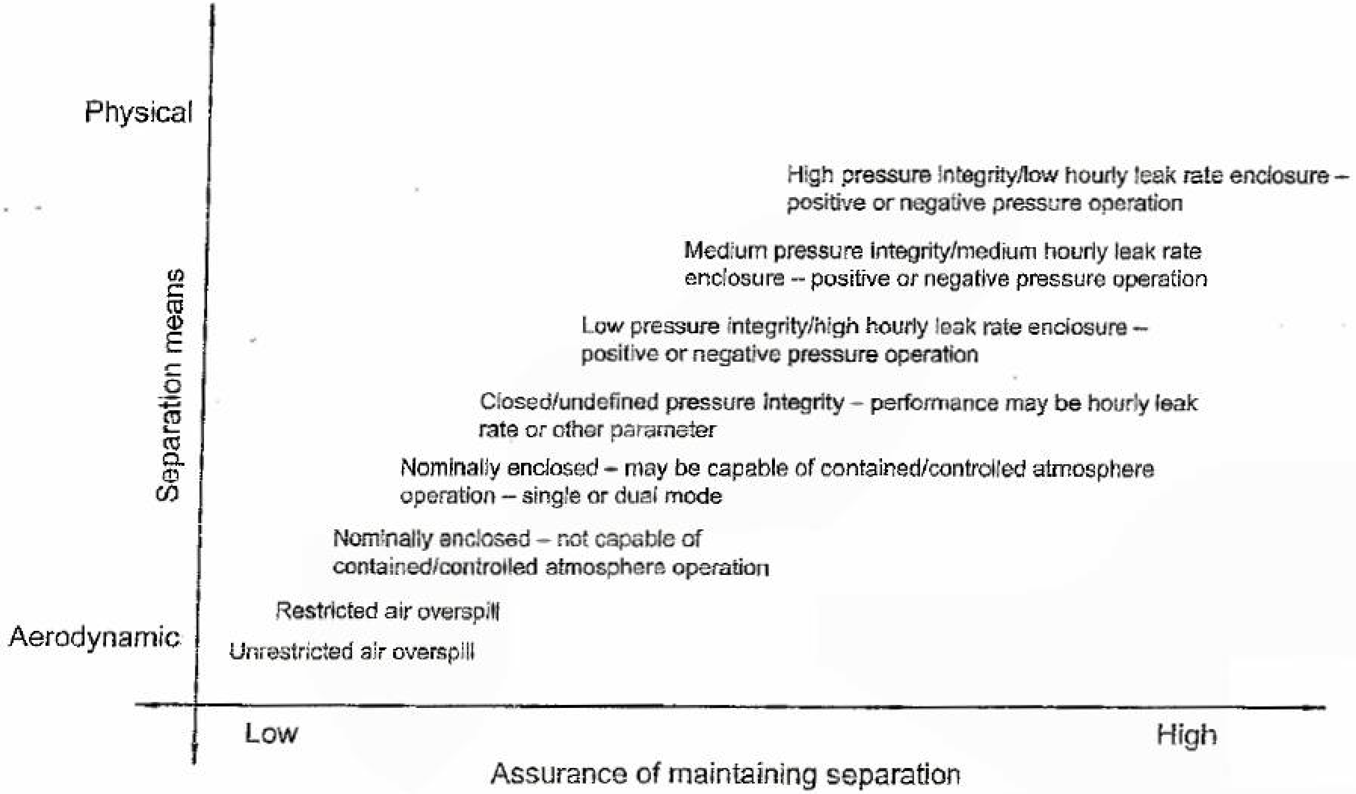


Figure A.1 — Schematic of the separation continuum illustrating increasing assurance of maintaining separation as the separation ranges from aerodynamic to physical means with overlapping separation approaches as a parameter

Chiesi Aseptic Process steps

STERILE BULK PROCESS AREA

Sterilization of Solvents and of Chloroform solution by filtration

Evaporation of Solvents

Drying of the Sterile Purified Paste

- 0.1 μm Filters
- Vacuum rotating evaporator
- ➢Sterilized connections
  ➢Depyrogenated glass containers

Suspension in Sodium Chloride Solution 0.9%

Emulsification by stirring, recirculation & sonication

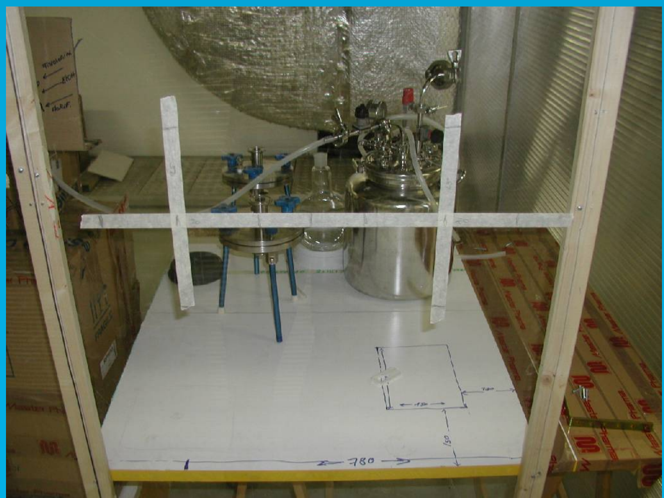
pH adjustment and final sonication

- Magnetic stirrer
- Sonicator
- Peristaltic pump
- Aseptic connections

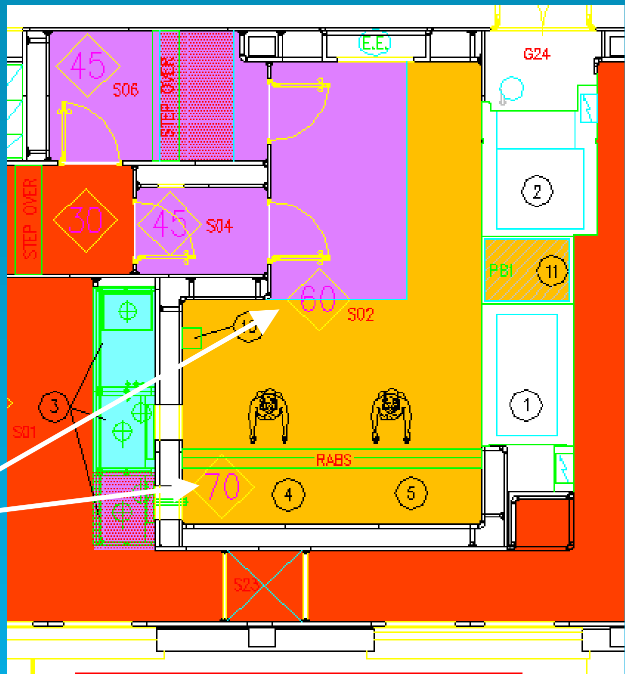
Filling of 2L suspension bottles
Using peristaltic pump, aliquots of Sterile bulk suspension is filled into the 2 L bottles. The bottles are blanketed with Nitrogen

- 0.2 μm nitrogen filter
- ➢Depyrogenated bottles
  ➢Aseptic connections

MOCK UP development



Concept of nested critical processing area



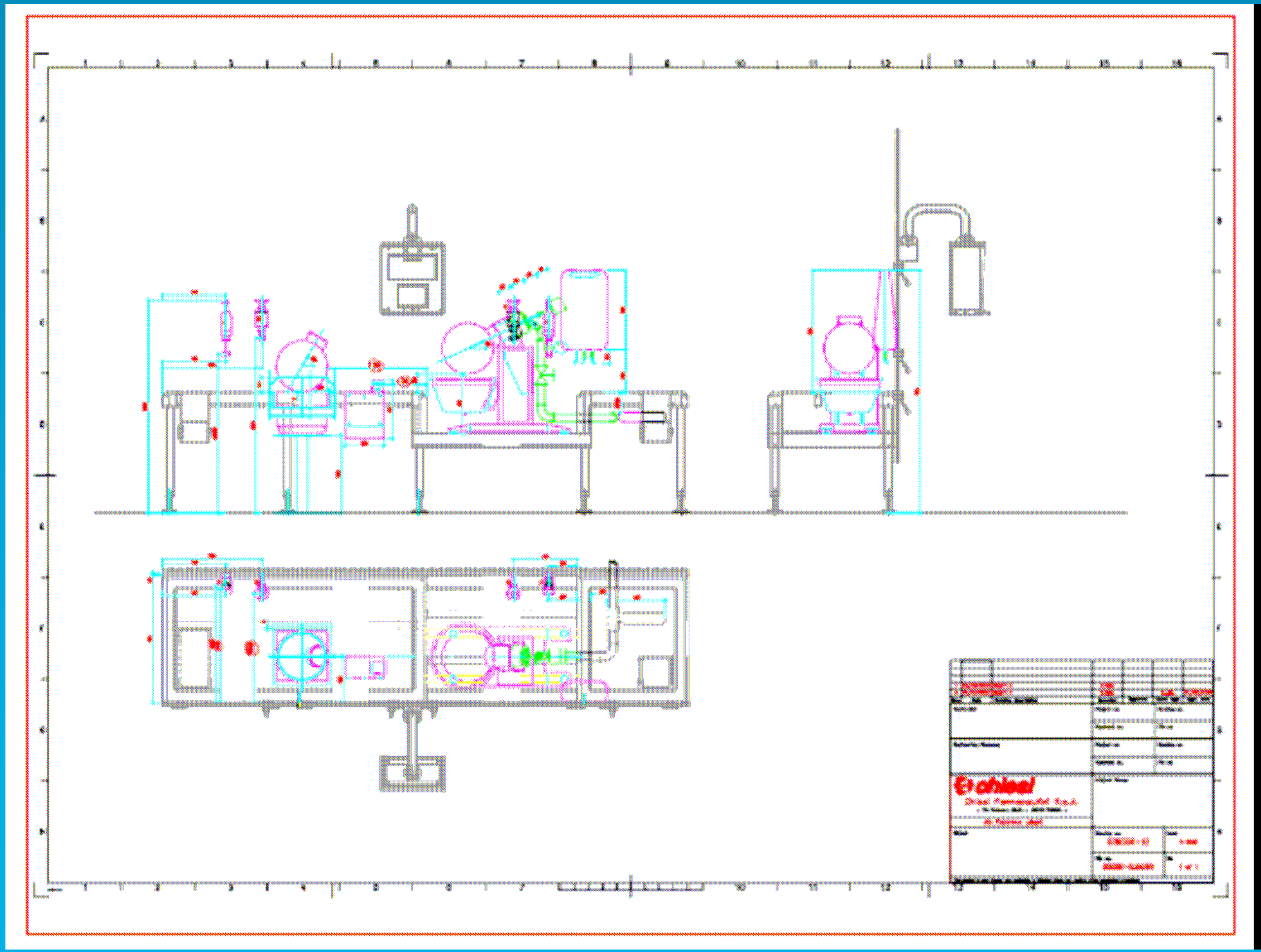
Differential pressure between areas

AREA CLASSIFICATION			
	GMP – FDA IN OPERATIONAL 0,5µm PARTICLES/ft³	ISO 14644-1	GMP EC
	CLASS 100	5	A
	CLASS 10,000 WITH UNIDIRECTIONAL AIR FLOW	5 AT REST	B
	CLASS 10,000	7	B
	CLASS 100,000	8	C
	PHARMACEUTICAL (WITH LOCAL MONITORING) (*)	8 AT REST	D
	LOCAL UNIDIRECTIONAL AIR FLOW PROTECTION	5 AT REST	
	PHARMACEUTICAL		
	PASS BOX PB1 – CLASS 100 AFTER RECOVERY TIME		
	PASS BOX PB2 – CLASS 100,000 AFTER RECOVERY TIME		

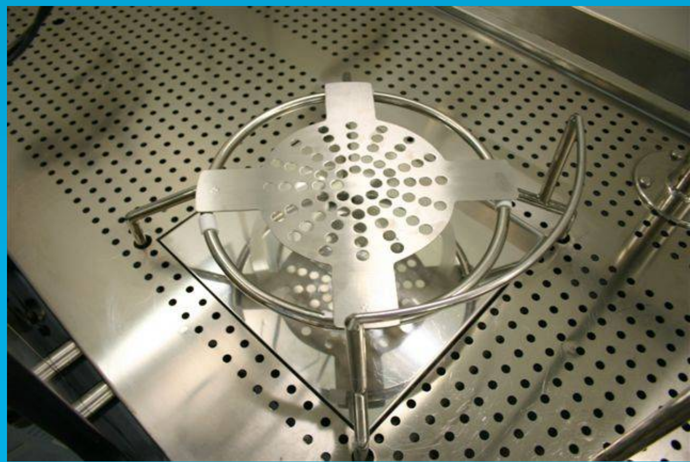
1
2
3
4
5
XX
(*)

Areas environmental classification

RABS design: “as built” drawing



RABS installation: process equipment details



Rabs Design concepts

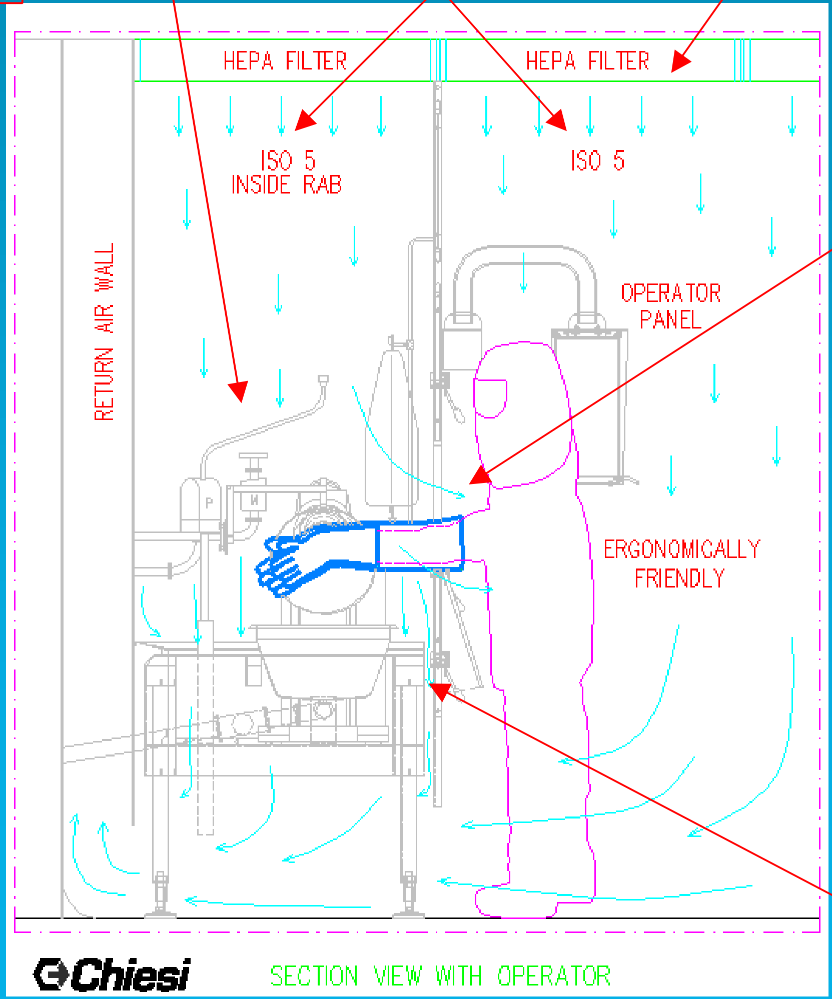
continuous particulate monitoring systems and active air sampling with gelatines filtration method

Separation descriptor
$[5_{0,5} : 5_{0,5}]$

open-hatches overhead HEPA downflow protection barrier to improve protection against potential contamination from operators

Outward airflow from RABS with the hatch open

Air overspill



Equipment Validation: Induction Test

(ISO 14644-7 : annex E_ Induction leak test _ to determine if there is an intrusion of contaminated air into the clean zones from surrounding areas)