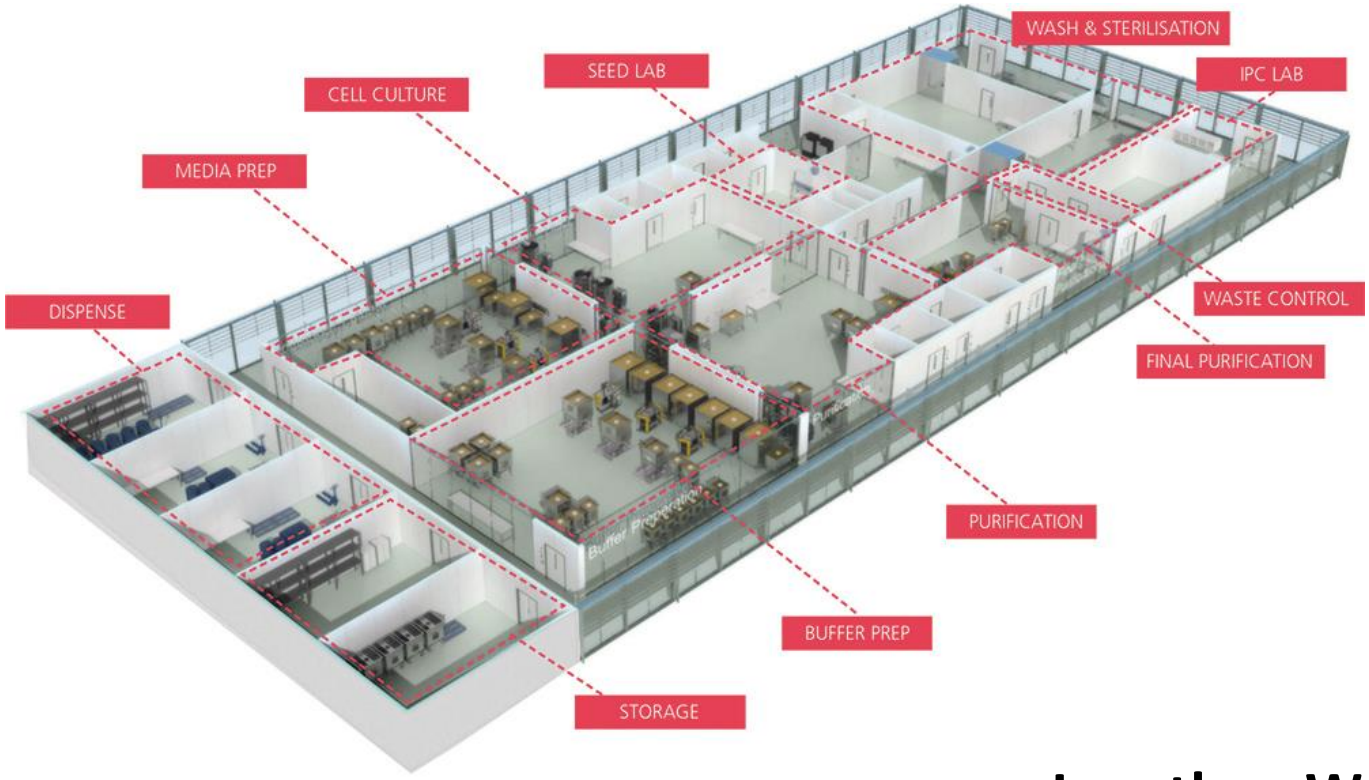
Design, Operation, and Management of GTP/GMP Cell Manufacturing Facilities



Jonathan Wu

2018/05/31

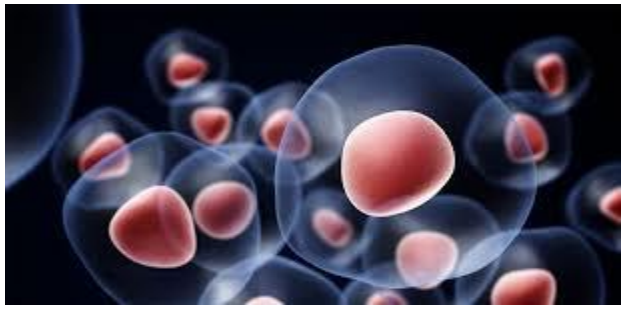
Outline

- General Review: Definition/Market and Regulatory
- GMP Facility Design Principles
- Special Concerns for Bio-containment
- Design Case Study

Regenerative Medicine and Cell Therapy

- "**Regenerative medicine**" is in turn a multidisciplinary area aimed at maintenance, improvement, or restoration of cell, tissue, or organ function using methods mainly related to cell therapy, gene therapy and tissue engineering.

- "**Cell therapy**" is based on transplantation of live cells in order to repair or restore lost or defective functions.



Cell Therapy Market

- The market now is dominated by CMO, while some cell therapy developers have set up in-house manufacturing capabilities. Examples include Adaptimmune, Argos Therapeutics, Cell Medica, Cellular Biomedicine Group, Juno Therapeutics, Kite Pharma and SOTIO.
- North America has the maximum number of cell therapy manufacturing facilities (~ 43%), followed by EU as ~40%.
- In EU, maximum number of manufacturing facilities are located in the UK (~44%). Other emerging pockets for cell therapy manufacturing include Australia, China, Japan, Singapore, South Korea and Israel.
- The market for cell therapy manufacturing is expected to grow at an annualized growth rate of ~42% over the course of next ten years and be worth **over USD 4 billion in 2027**.

cGMP facilities and quality control requirements of cell therapy products

- Any procedure related to CBMPs requires a **strict control** in cGMP facilities.
- Facilities should be designed and organized according to **Good Manufacturing Practice** for Pharmaceutical Manufactures including quality control and quality assurance programs, which established a Quality System approach to control collection, processing, storage and release of cell therapy products.

  a) Facilities (design, access and maintenance);

  b) Equipment (purchase, use and maintenance);

  c) Materials (specifications, qualification, purchase, storage and use);

  d) Quality assurance (quality control, validation, qualification and document control)

  e) Risk-based assessment for process/equipment and facility (FMEA)

CGMP Continuum: Expectations During Development

- GMPs expected throughout clinical studies, though level of control and validation will vary on the process and critical nature of the issue
- Documented control over the facility, equipment, and process
- Expect control to increase as product moves from one phase to the next

Manufacturing and regulatory requirements for cell therapy products

- cGMPs for cell-based therapeutics (CBTs) are based upon practice for pharmaceuticals. US and EU are directed in the first instance to the ICH cGMP guidance [ICH Q7A].
- The legal requirement for CBMPs are set in Regulation 1394/2007/EEC and in revised Annex I Directive 2001/83/EEC GTMP/CTMP → ATMP).
- In compliance with officials standard books such as EP or USP, each batch of a CBMPs or ATPs should pass a very strict and specific test.
- Manufacture of living cells does not allow terminal sterilization. Thus, appropriately tested and qualified starting materials and a validated aseptic manufacturing process are the key factors to ensure microbiological purity of the product.

Other Regulatory Considerations

- IND (Investigational New Drug Application) regulations (21 CFR 312) - patient safety and clinical trials
- Biological Products regulations (21 CFR 600s) – licensing requirements
- CGMPs (21 CFR 210s) – current good manufacturing practices in manufacturing, processing, packing or holding of drugs
- CGMPs (21 CFR 211s) – current good manufacturing practices for drugs/biologics (finished pharmaceuticals)
- Combination products-Medical device (21 CFR 800s)

前言

藥品品質應是在優良系統下“設計製造”出來的

優良系統必須包括合格的:

- **廠房**
- 支援系統(utilities)
- 設備與製程
- 人員(well-trained)
- 原料(supplier audit)
- 品管/品保體系

除微粒之外，尚須注意微生物(病原菌)之管制

廠房設計與考量

汙染控制

- 空調系統設計會影響潔淨室土建工程與空間平面設計:
  - 緩衝室(airlock)位置
  - 門的方向性
  - 門廳位置

- 土建工程的設計亦會對空調系統之表現有影響
  - 各潔淨室間之差壓(Pressure difference)
  - 汙染控制(微粒/微生物)

換言之，(交叉)汙染防治除了考量潔淨室本身與人/物動線之設計外，空調系統之設計扮演相當重要之角色。

潔淨室考量之重點

- 空間規劃、地板、牆面、天花板 (氣體與灰塵)
- 空間平面設計—依據生產流程(functionality)
- 溫度、溼度、微粒、微生物汙染
- 空調氣體量、出風、迴風、排氣
- 空氣換氣率(room classification)
- 氣體流動型態 (laminar or turbulent)
- HEPA 過濾
- 氣壓與氣體平衡(pressure differentiation)
- 層流操作單元 (LFH/BSC or isolator)
- 原料、工具、設備、噪音、震動、照度
- 均勻度 (sensor location?)
- 人員進出與清潔 (gowning and sanitization)
- 其他相關功能測試 (firefighting, alarm…)

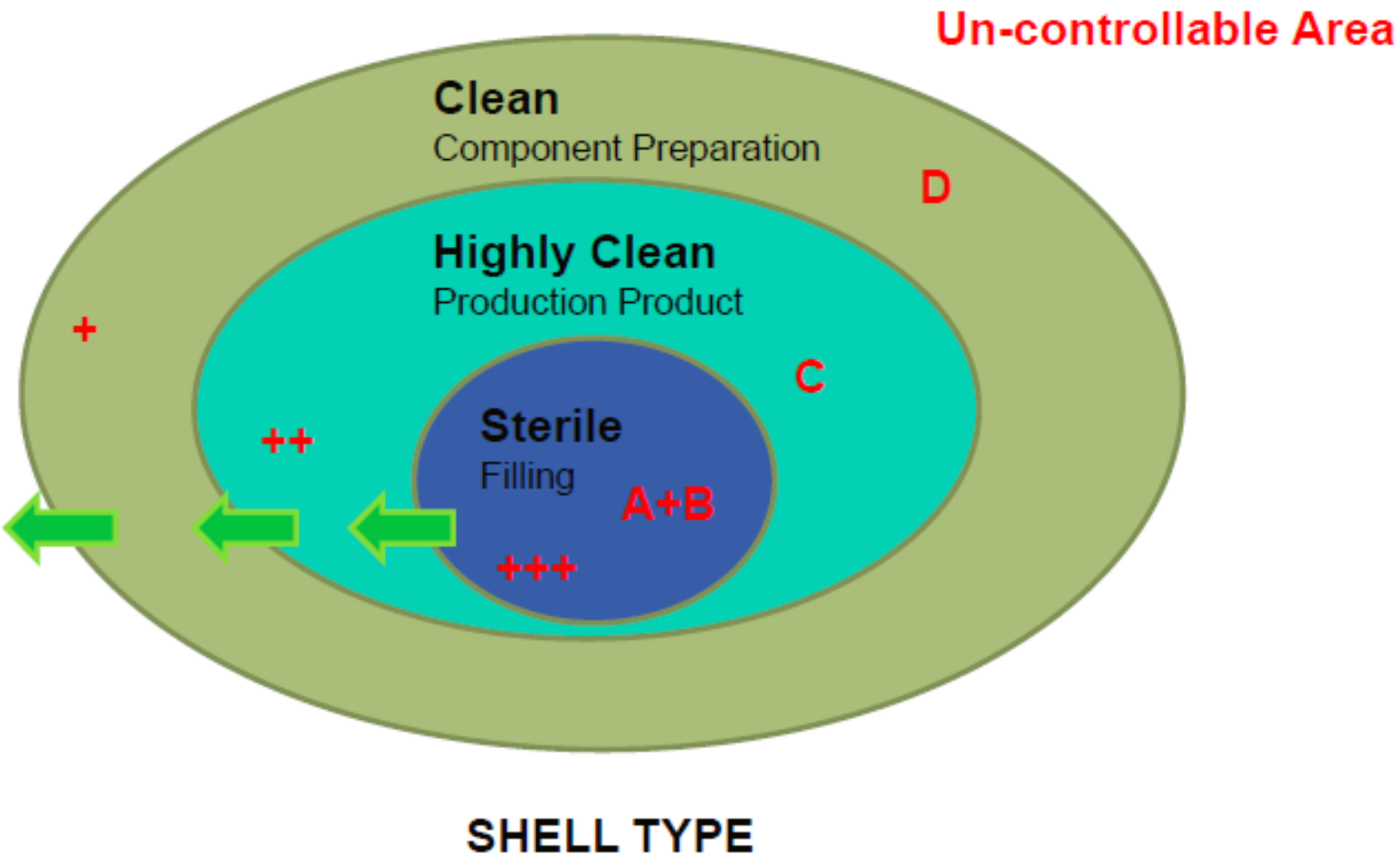
PIC/S GMP Requirements in Premise Design

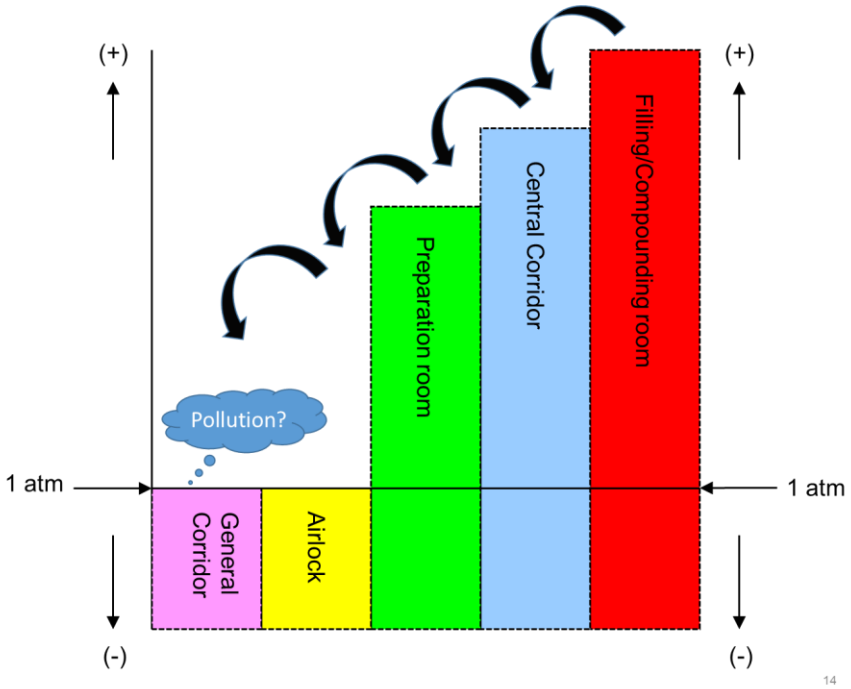
- 生產製程區須藉由空調系統提供有效通氣
- 各潔淨室溫濕度須控制
- 氣體須經過過濾後方可進入潔淨室

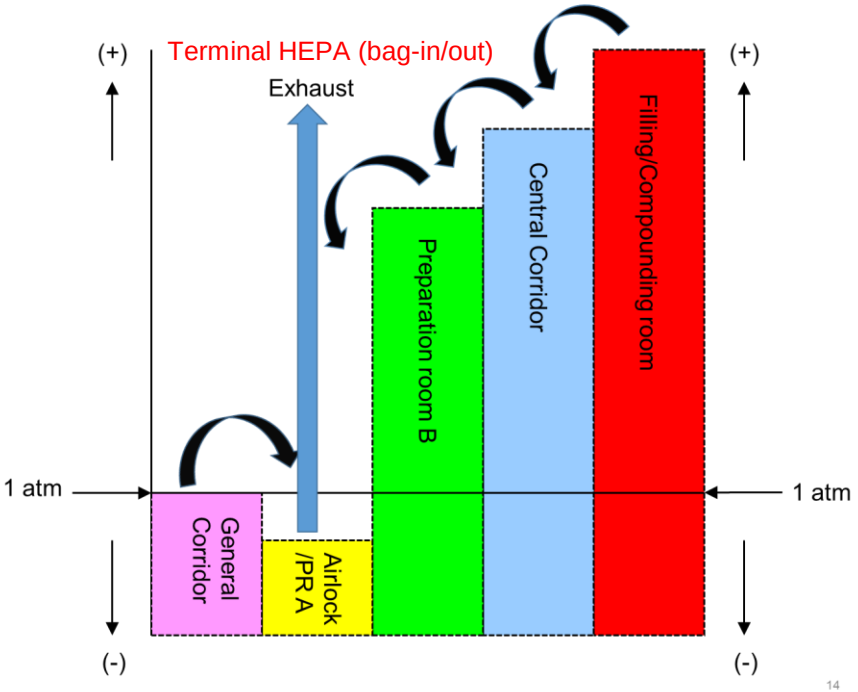
以達到"**產品保護**"與"**外界環境保護**"之目的

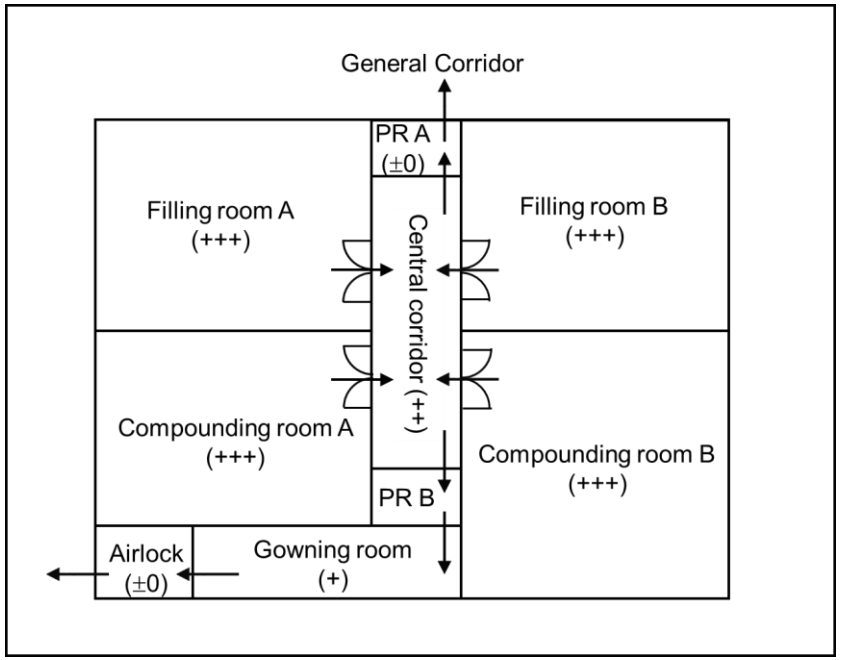
- 產品須於潔淨區生產
- 設備/原料與人員須經過氣閘室(airlock)方可進入潔淨區
- 潔淨區須保持適當的潔淨度
- 潔淨區須提供經過適當過濾後之空氣

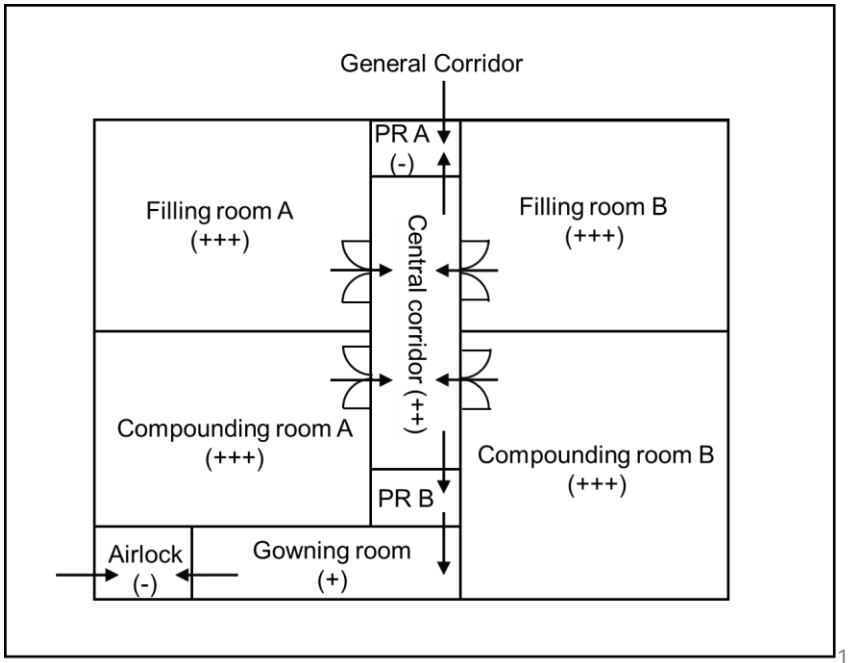
Onion Shell Type Design for Pressure Distribution




(+)
(+)
Filling/Compounding room
Central Corridor
Preparation room
Pollution?
1 atm
1 atm
General Corridor
Airlock
(-)
(-)

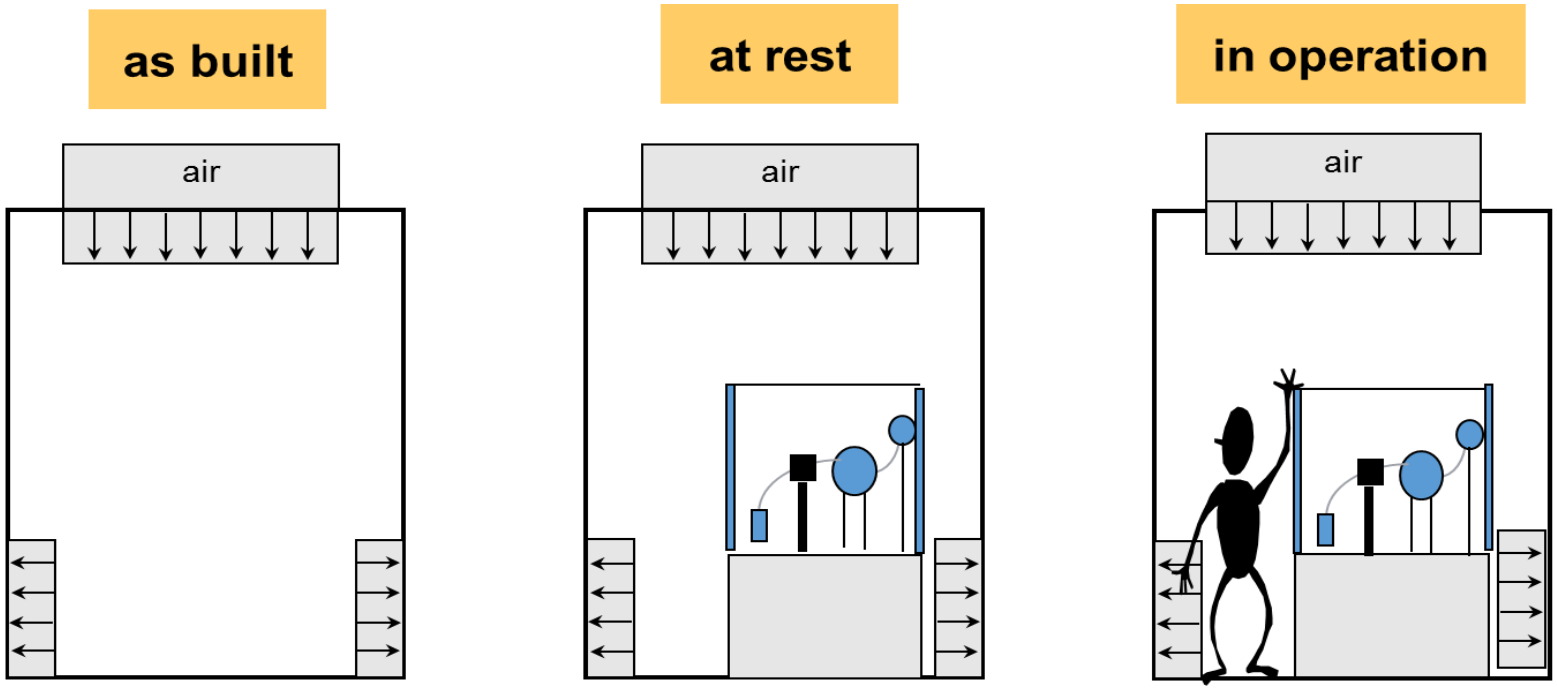

Terminal HEPA (bag-in/out)
Exhaust
(+)
(+)
Filling/Compounding room
Central Corridor
Preparation room B
1 atm
1 atm
General Corridor
Airlock /PR A
(-)
(-)


General Corridor
PR A
(±0)
Filling room A
(+++)
Central corridor (++)
Filling room B
(+++)
Compounding room A
(+++)
Compounding room B
(+++)
PR B
Airlock
(±0)
Gowning room
(+)


General Corridor
PR A
(-)
Filling room A
(+++)
Central corridor (++)
Filling room B
(+++)
Compounding room A
(+++)
Compounding room B
(+++)
PR B
Airlock
(-)
Gowning room
(+)

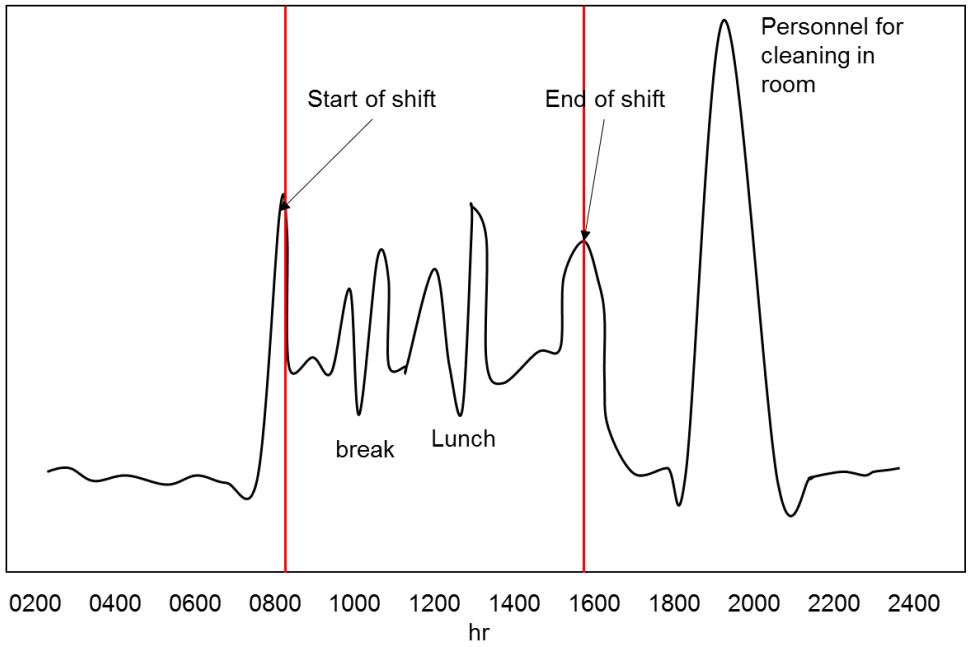
潔淨等級需求

- 製程區之潔淨等級依據所需要的環境特性來區分;
- 每一個潔淨製程區在"操作狀態(in operation)"下均須保持一定潔淨等級，以降低來自產品與原料汙染之風險;
- 人員離開後15-20min內，潔淨等級須由in-operation恢復到at-rest狀態。



人是最大汙染來源

- ✓ 靜坐潔淨室之人員每分鐘可釋出15,000粒子;作業時會增加10倍;
- ✓ 人身上會同時釋出粒子與細菌比例為6,000-7,000;
- ✓ 人員著無菌衣每小時會釋出600-1,300粒子
- ✓ 其中含可形成多達40菌落之好氧性細菌



Clean Room Classification

等級A:高風險操作區域

如:細胞株準備區/產品充填區/裝塞區與無菌連接操作等

- ✓ 一般於層流操作台(Laminar flow hood)/生物安全櫃(biosafety cabinet)/isolator內作業;
- ✓ 在操作位置提供均勻0.34-0.45m/s氣流線性速度;
- ✓ 須隨時證明/確認並維持層流狀態;

等級B:為無菌準備與充填區

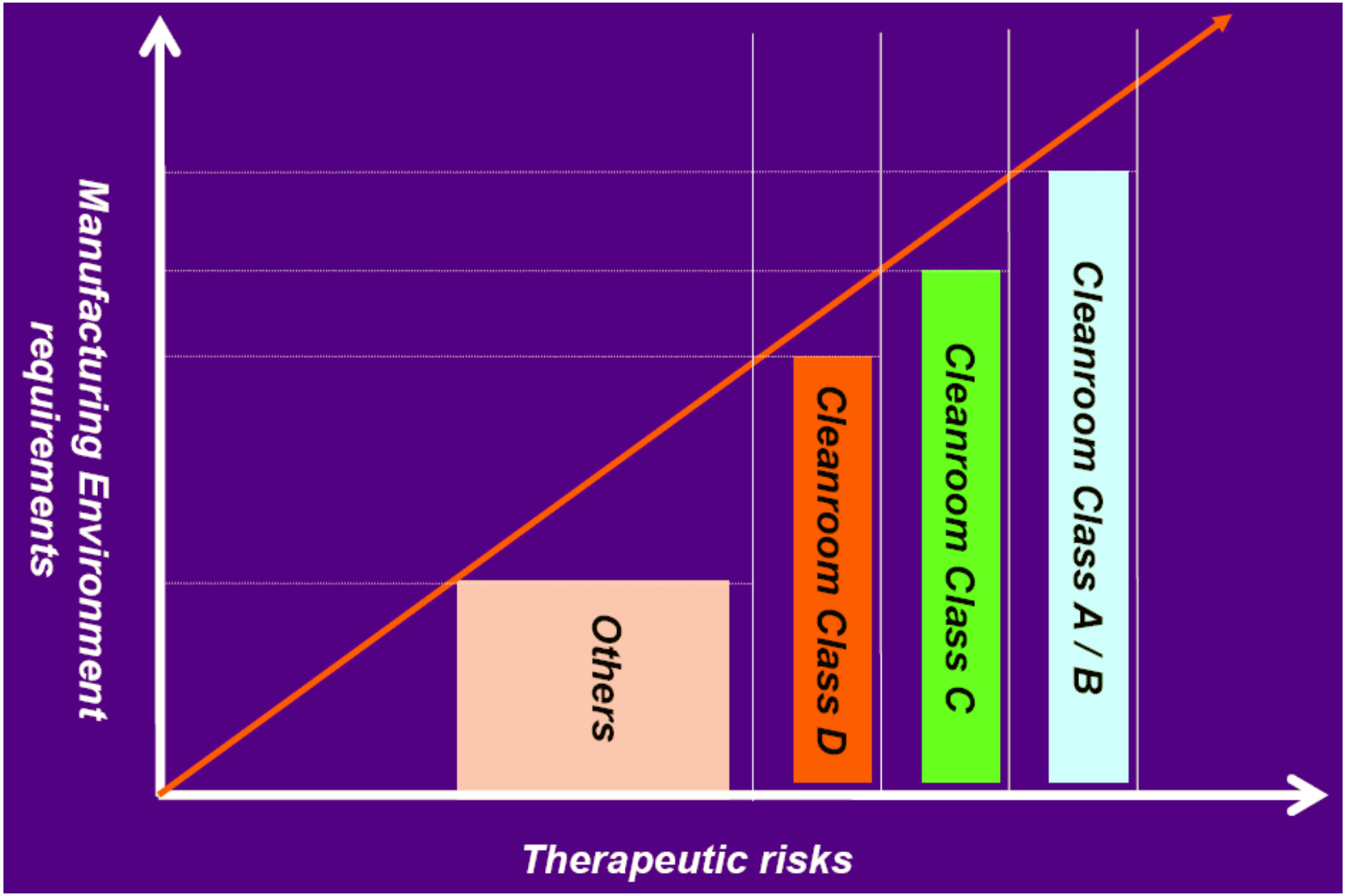
- ✓ 為潔淨等級A之背景環境

等級C/D:

- ✓ 用於非無菌要求之製程區

針對潔淨等級A/B/C ，空調系統須裝設適當的終端過濾器(e.g. terminal HEPA)

Therapeutic Risks for Various Cleanness

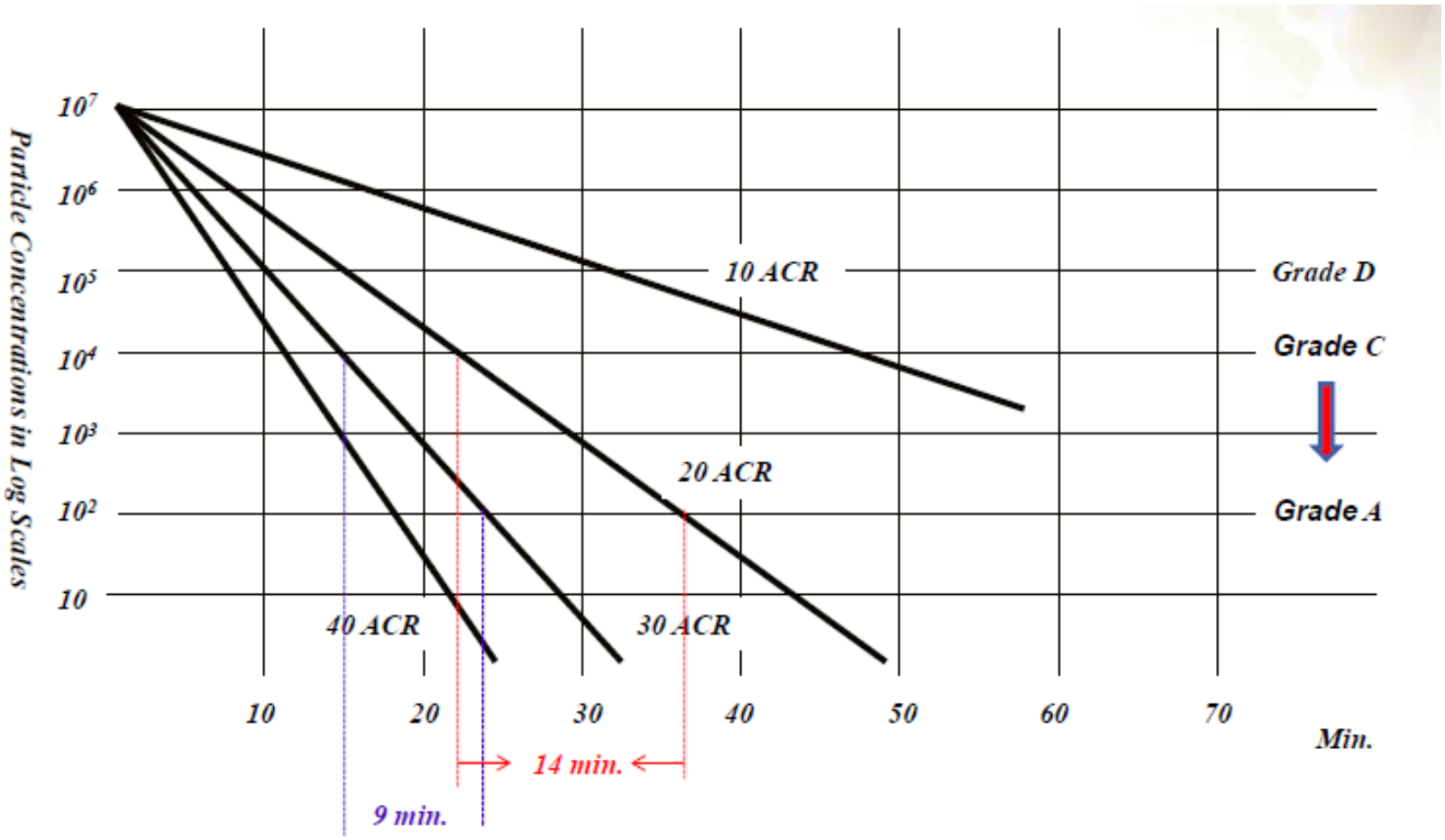


Recommended Average Airflow Velocity, ACH and Ceiling Coverage

Class ISO 14644-1 (Federal Standard 209E)	Average Airflow Velocity m/s (ft/min)	Air Changes Per Hour (ACH)	Ceiling Coverage
ISO 8 (Class 100,000) D	0.005 – 0.041 (1 – 8)	5 – 48	5 – 15%
ISO 7 (Class 10,000) C	0.051 – 0.076 (10 -15)	60 – 90	15 – 20%
ISO 6 (Class 1,000)	0.127 – 0.203 (25 – 40)	150 – 240	25 – 40%
ISO 5 (Class 100) A/B	0.203 – 0.406 (40 – 80)	240 – 480	35 – 70%
ISO 4 (Class 10)	0.254 – 0.457 (50 – 90)	300 – 540	50 – 90%
ISO 3 (Class 1)	0.305 – 0.457 (60 – 90)	360 – 540	60 – 100%
ISO 1 – 2	0.305 – 0.508 (60 – 100)	360 – 600	80 – 100%

Note: The larger ceiling coverage, the more unidirectional air flow can deliver.

Air Quality Recovery via Air Change



硬體操作考量

空調系統:

- ✓ 提供潔淨空氣以維持製程區內適當溫度與濕度;
- ✓ 持續提供阻絕性空氣以杜絕外界微生物汙染;
  - ➢ 專屬系統
  - ➢ 差壓控制
- ✓ 持續維持封閉性空氣以避免環境汙染;
  - ➢ 藥理活性
  - ➢ 生物性
  - ➢ 放射性
- ✓ 妥善處理排氣;
- ✓ 作業結束後須進行除汙措施(fumigation if necessary)

硬體操作考量

風管:

- ✓ 依個別作業區風量需求適當調整閘門(damper);
- ✓ 定期檢查風管:結構良好/絕緣妥當/無洩漏;
- ✓ 如必要定期使用消毒劑處理;
- ✓ 作業區內出迴風口須定期清潔;

作業區:

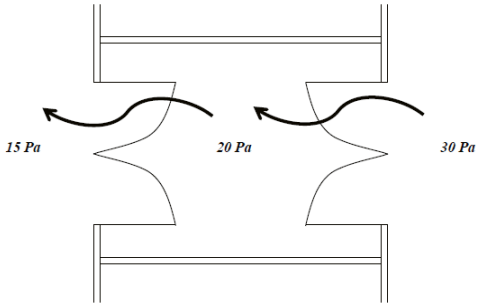
- ✓ 妥善規劃出迴風口位置—提高空氣置換幅度
- ✓ 盡可能移出室內物品—空氣流通/易清理
- ✓ 隨時關閉作業區之門—維持室壓與空氣流向，避免汙染物逸散

良好保養/儀表校正/環境監控(HVAC trail & T/H monitoring)

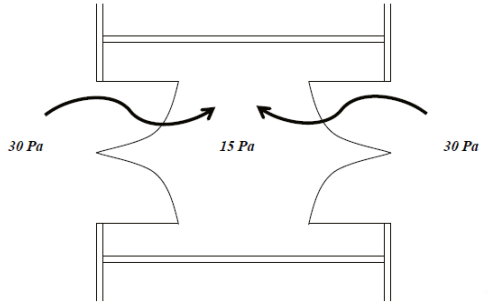
氣閘室/緩衝室/車間(Airlock)

- 在各潔淨室間，有兩個或多個門以上，用來控制人員或物料進出的空間;
- 一般在某一時間僅能開啟一道門，以控制氣體流動與壓差;
- 依據不同的壓力分佈狀況可分為以下三種:

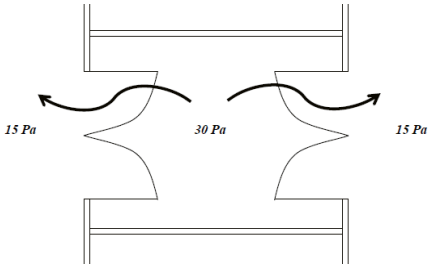
(1) Cascade airlock 順向車間



(2) Sink airlock 匯氣車間



(3) Bubble or Source airlock 氣源車間



Facility Design Considerations: Product Issues

- Will the entire manufacturing process be performed in the facility?
- Nature of the starting material – cell culture vs. recombinant cell line vs. virus → biosafety level issue
- Nature of the process – open vs. closed systems (MU vs. SU); fermentation/cell culture, purification, etc.→ room classification and clean validation
- Multi-product or multi-patient manufacturing? Cross-contamination → personal/material flows.
- Facility intended to be licensed or limited to IND products (commercial plant or clinical trial only)?

Facility Design: Multi-Product Issues

- Campaign vs. concurrent production will impact on design and operation of the facility

  How to segregate USP from DSP ? in which step? HVAC segregation? Cross personal/material flows?

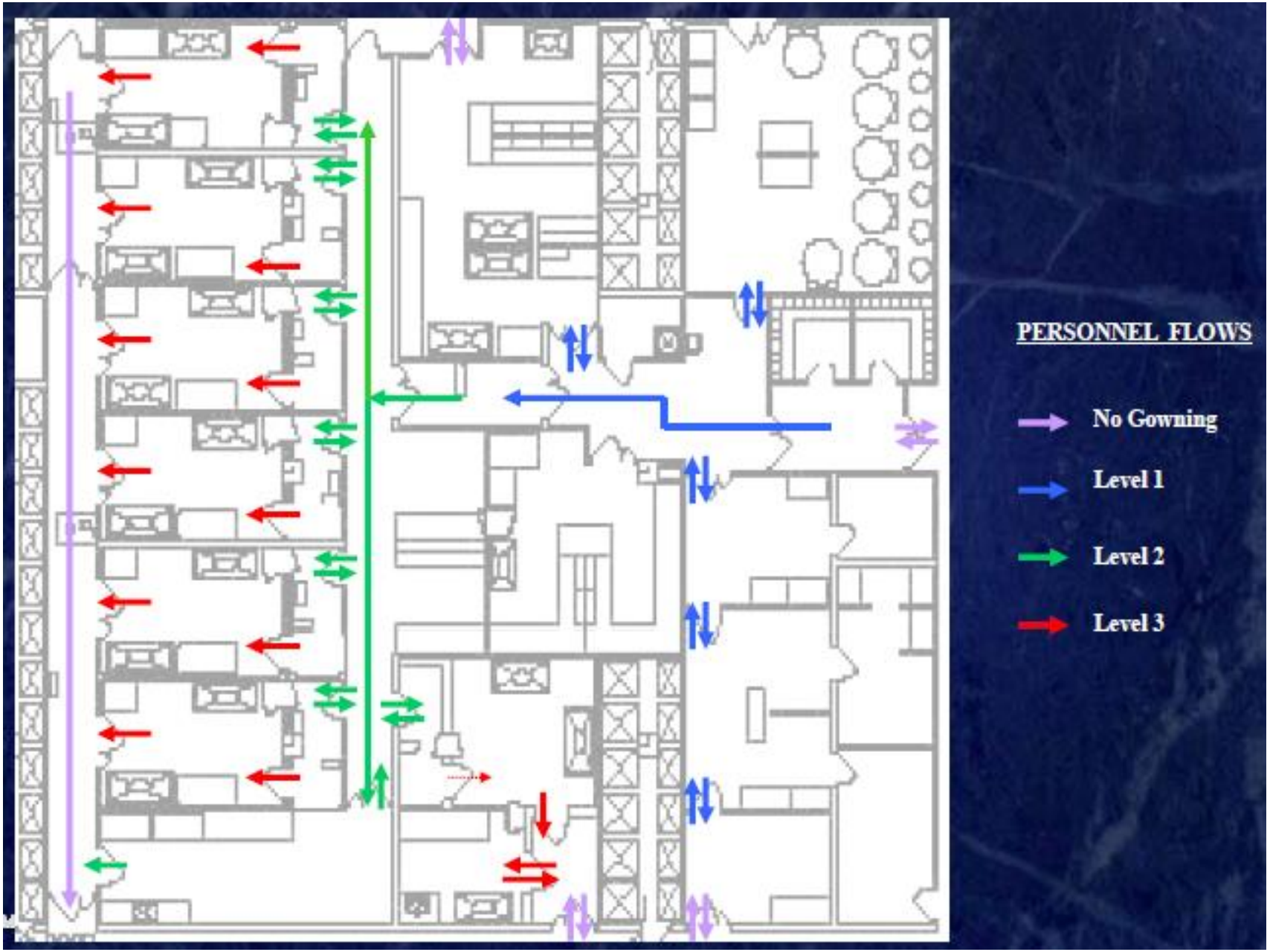
- Commercial vs. investigational product manufacturing
- Dedicated vs. shared equipment (clean validation?)
- Multiple patient cells

Facilities/Personnel

- Personnel practice universal precautions when processing biological materials such as cells or tissues
- Unidirectional flow of personnel and processed material
- Temporal segregation of processing activities
- Gowning program designed to protect the product from contamination and keep airborne particulates away from the product and prevent the transfer of particulates from one manufacturing environment to another environment of higher classification

Basic Design Concepts for cGMP Facility

- Sequential segregation of manufacturing areas based on PFD
- One way through personnel/material flow
- Separate HVAC air handling systems for areas with different functionalities
- Differential pressure control (from clean to dirty) 10~15pa
- Use airlock for room classification separation and buffering requirement
- BSC/LFH/isolator for living microorganism operation and sterile operation


PERSONNEL FLOWS
No Gowning
Level 1
Level 2
Level 3

Bio-Containment Facility

- **Facilities within which Human or Animal Pathogens or Infectious Agents are grown for Research or Development Purposes**
- **Minimize or Eliminate Potential Hazardous Agents to: Laboratory Workers, Outside Environment and Community**

Biosafety Level 1 – Basic

Biosafety Level 2 – Basic Containment

Biosafety Level 3 – Containment

Biosafety Level 4 – Maximum Containment

Containment Barriers

- **Primary Barrier**

  Facility inside Equipment (BSC/isolator/PPE)

- **Secondary Barrier**

  Engineering System Design

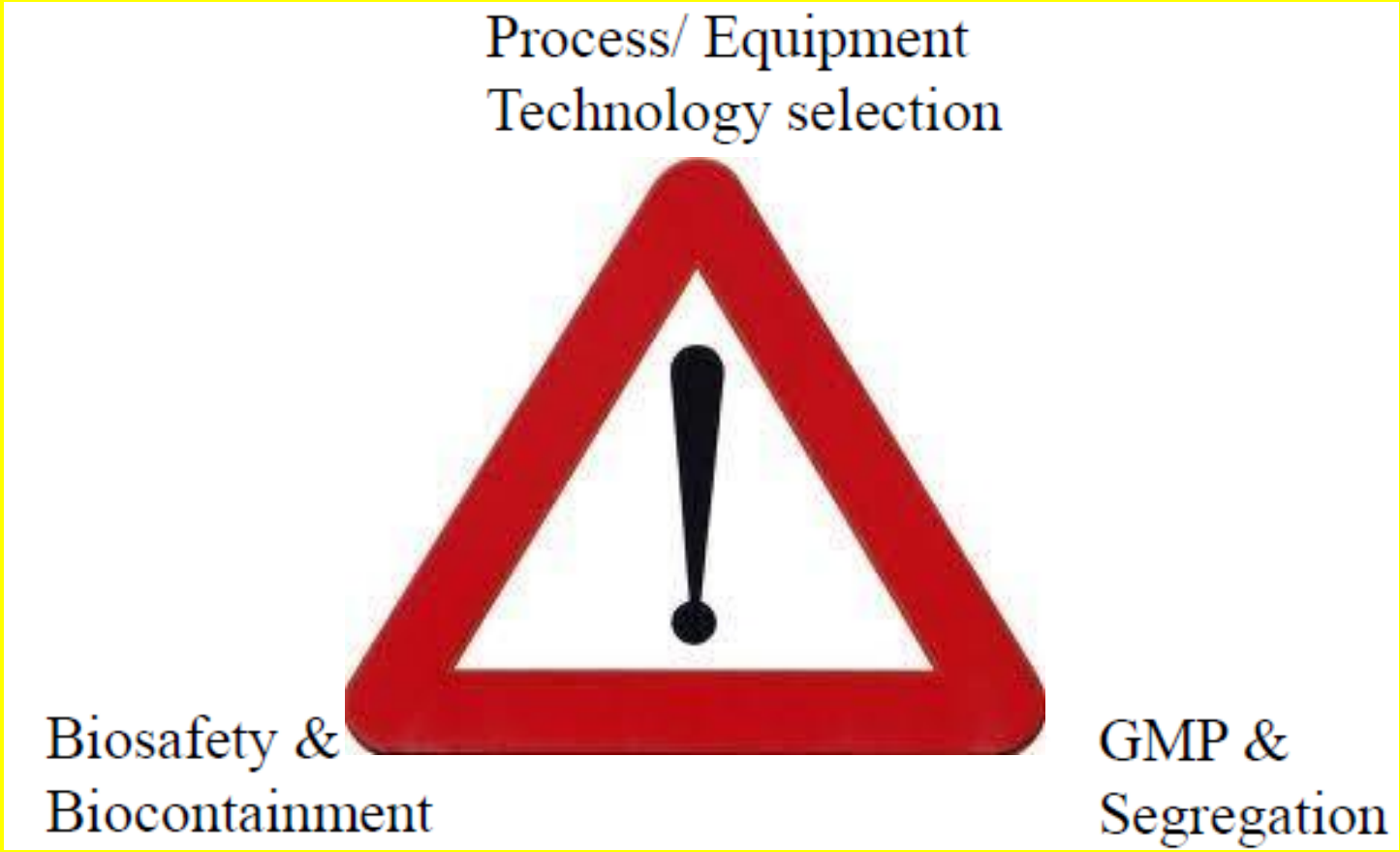
- **Tertiary Barrier**

  Building Envelope

Biocontainment

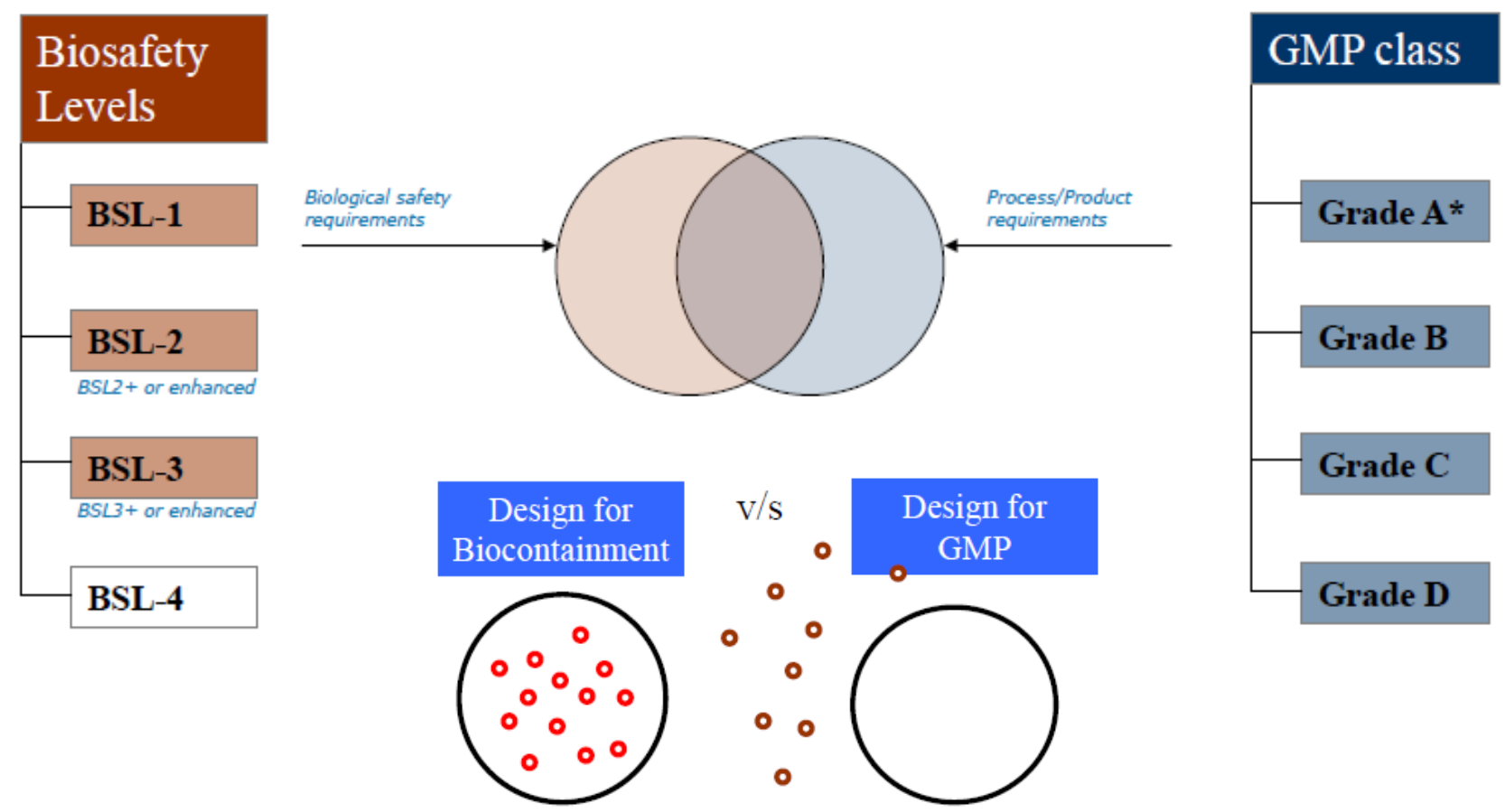
- **Biocontainment is the control of biohazards through**
  - **Practices & procedures, including administrative controls**
    - Good lab/facility practices
    - Written SOPs for research activities, specialized equipment, etc
    - Required training
    - Access requirements
  - **Primary barriers (safety equipment)**
    - Biosafety cabinets (BSCs)/isolators
    - Lab equipment (pipetting devices, waste containers, safety centrifuge cups)
    - Personal protective equipment
  - **Secondary barriers (engineering & architectural controls)**
    - Building & room construction – the floor plan
    - HVAC issues – directional airflow, filtration
    - Waste treatment

3 principal facets of biocontainment facility design



Key complexities in biocontainment facility design

- Establishing level of “biocontainment” & defining barriers.
- Resolving design conflicts: BSL v/s GMP.



Key complexities in biocontainment facility design

- Establishing level of “biocontainment” & defining barriers.
- Resolving design conflicts: BSL v/s GMP.

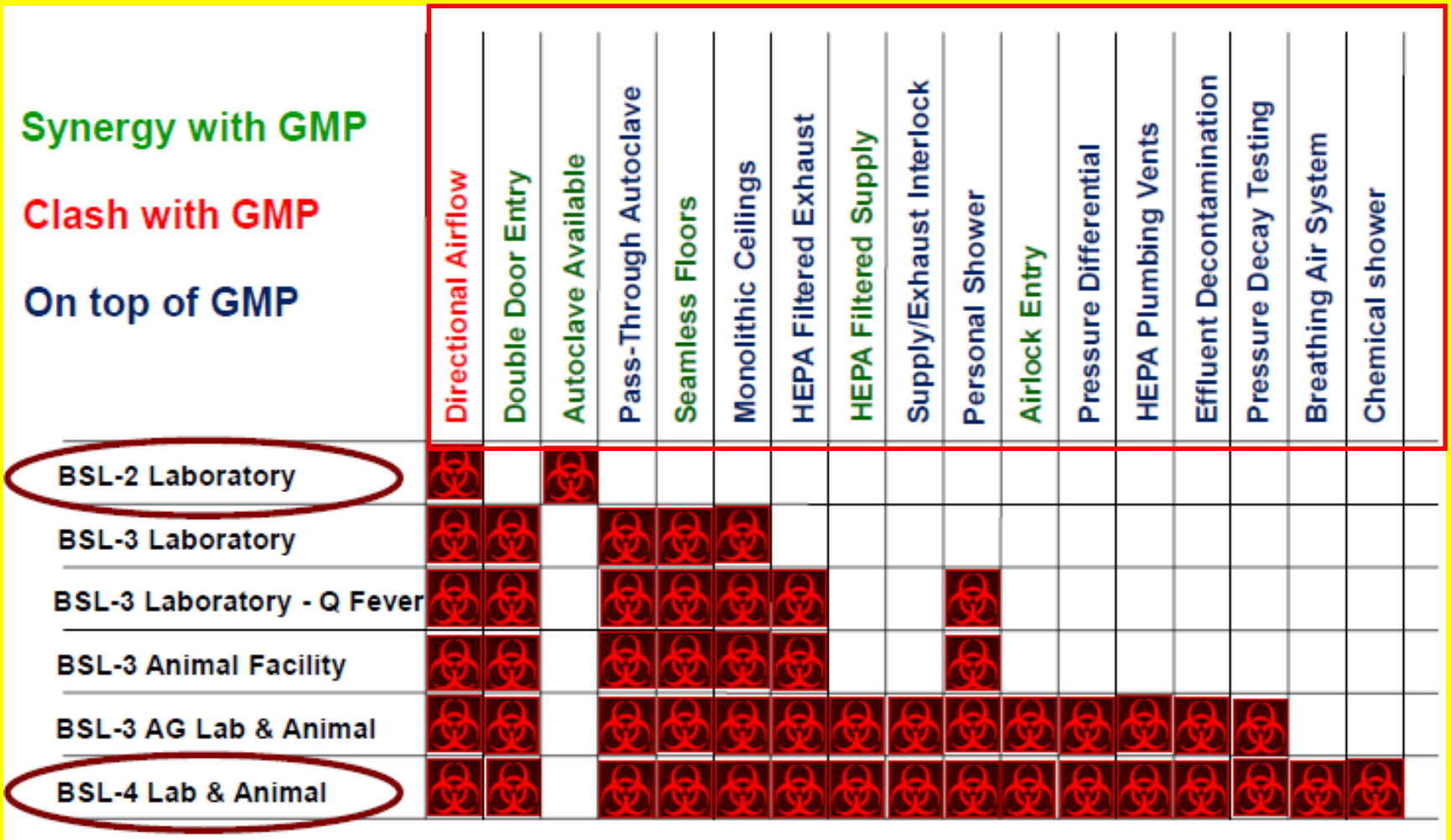
  - ✓ **HVAC Design (direction of flows, pressure differentials)**
  - ✓ **Room pressures**
  - ✓ **Doors (door swings, type of doors, e.g. inflation gasket)**
  - ✓ **Cleaning rooms (dedicated cleaning rooms)**
  - ✓ **Kill systems (handling of waste, decontamination of waste water, solid waste, gowning etc.)**

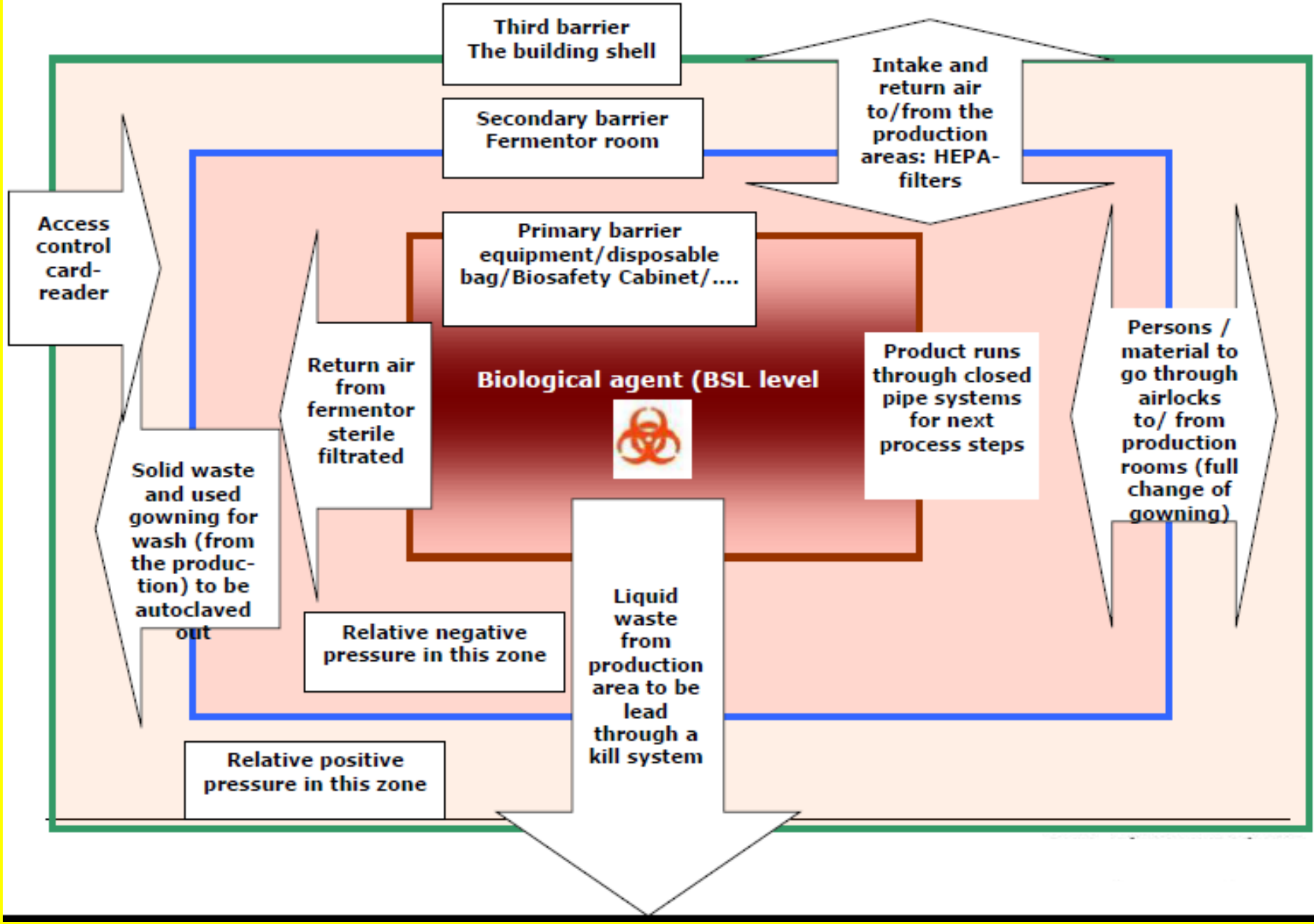
Overview of BSL recommendations

Synergy with GMP

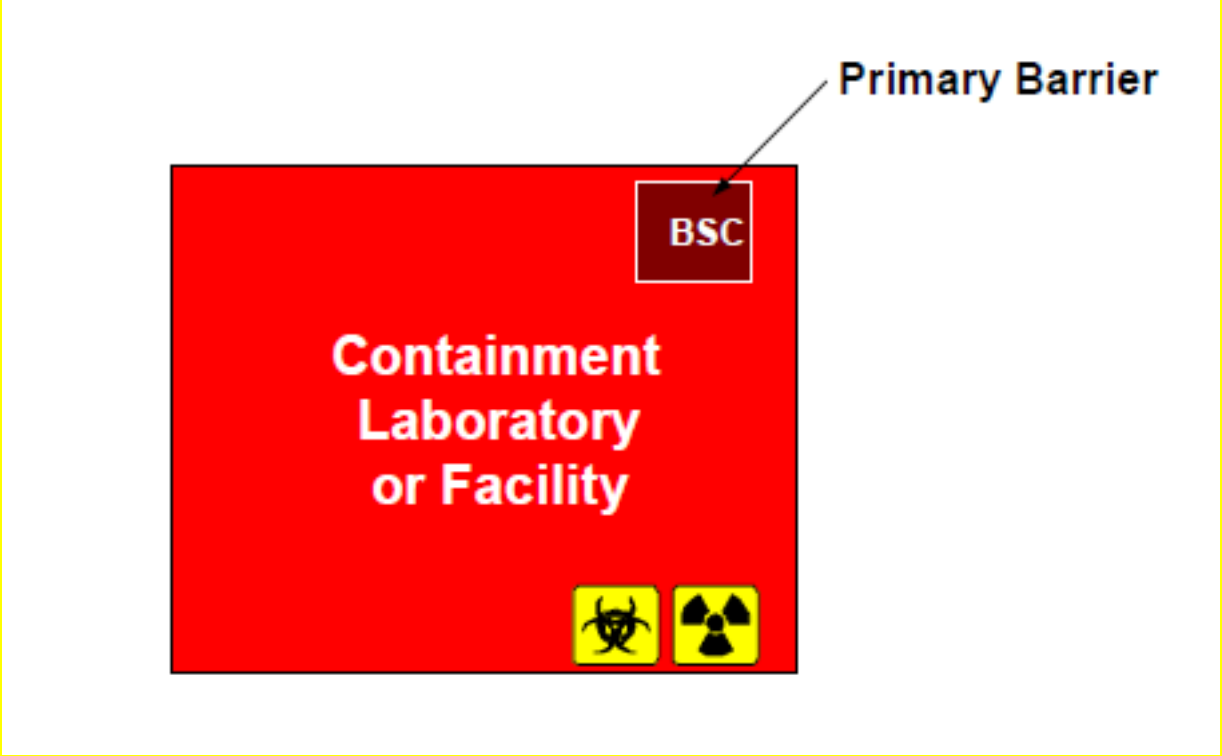
Clash with GMP

On top of GMP

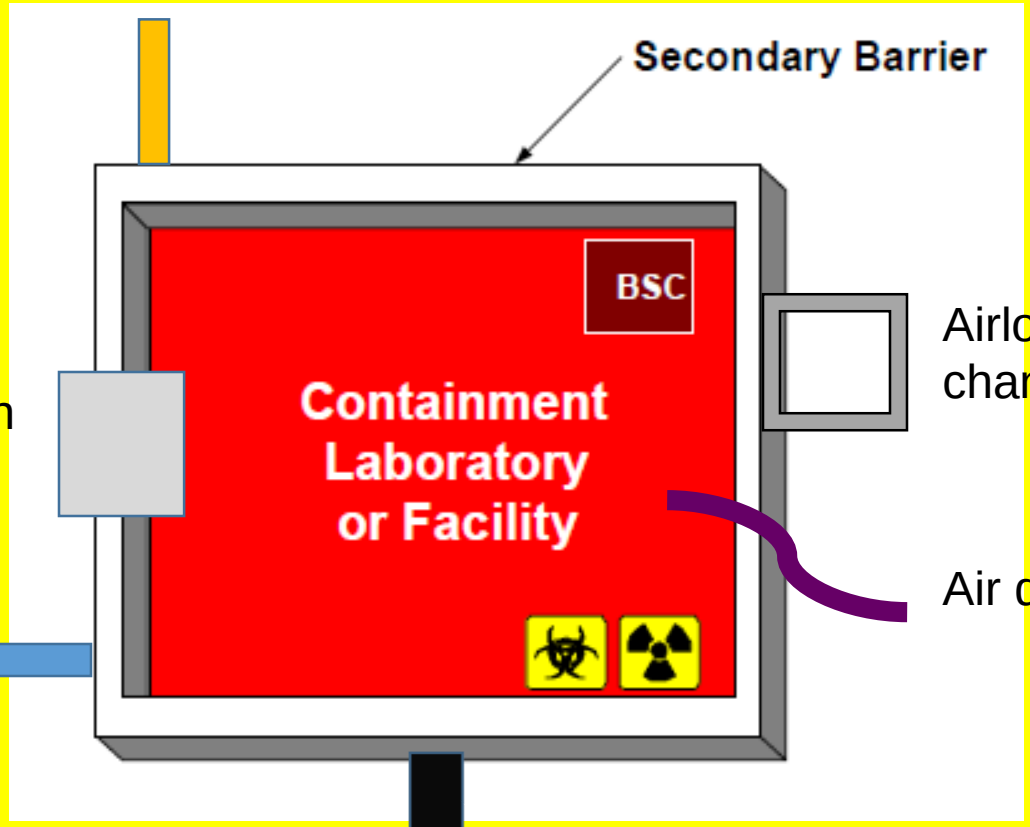



Third barrier
The building shell
Secondary barrier
Fermentor room
Primary barrier
equipment/disposable
bag/Biosafety Cabinet/....
Biological agent (BSL level
Intake and
return air
to/from the
production
areas: HEPA-
filters
Access
control
card-
reader
Return air
from
fermentor
sterile
filtrated
Solid waste
and used
gowning for
wash (from
the produc-
tion) to be
autoclaved
out
Relative negative
pressure in this zone
Relative positive
pressure in this zone
Liquid
waste
from
production
area to be
lead
through a
kill system
Product runs
through closed
pipe systems
for next
process steps
Persons /
material to
go through
airlocks
to/ from
production
rooms (full
change of
gowning)

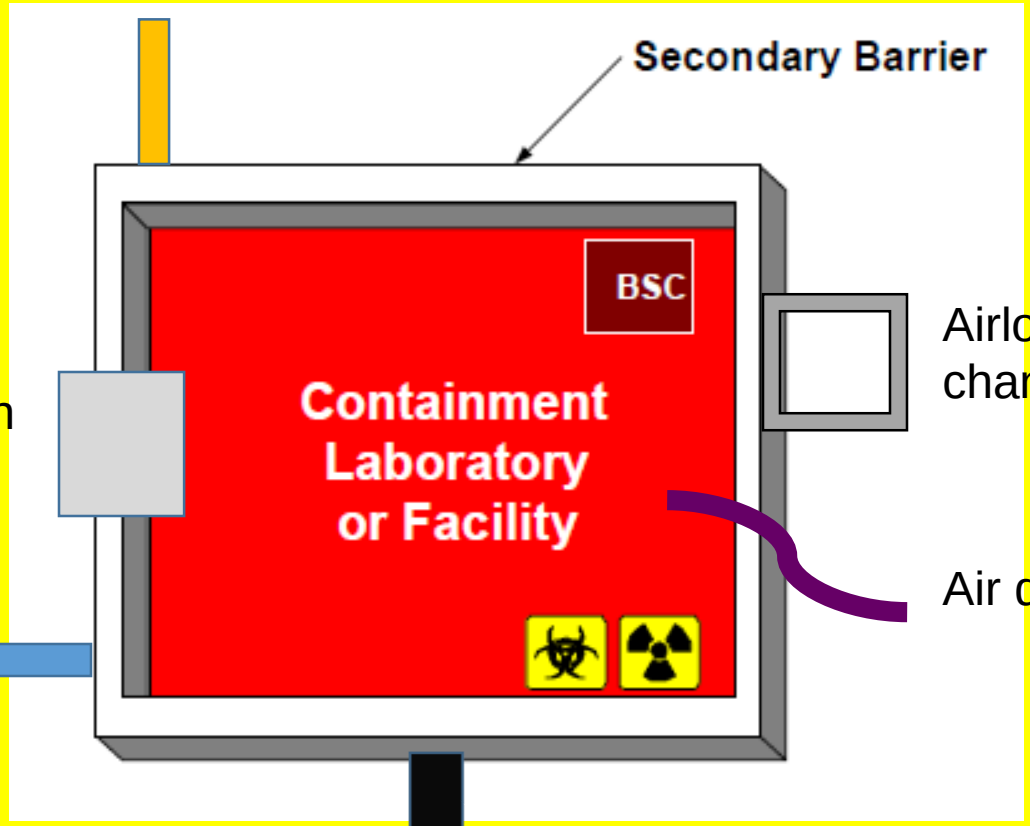
Primary Barriers



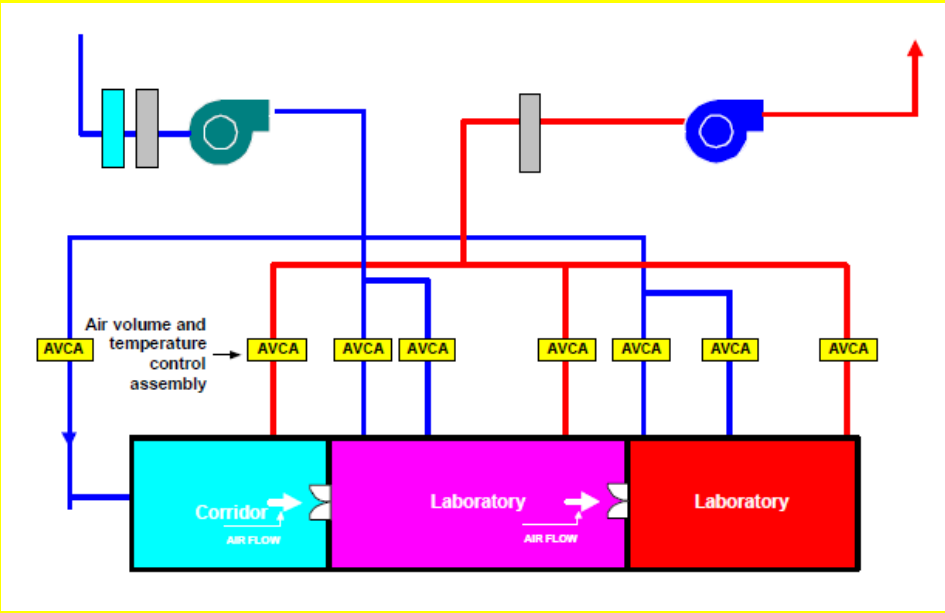
Secondary Barriers



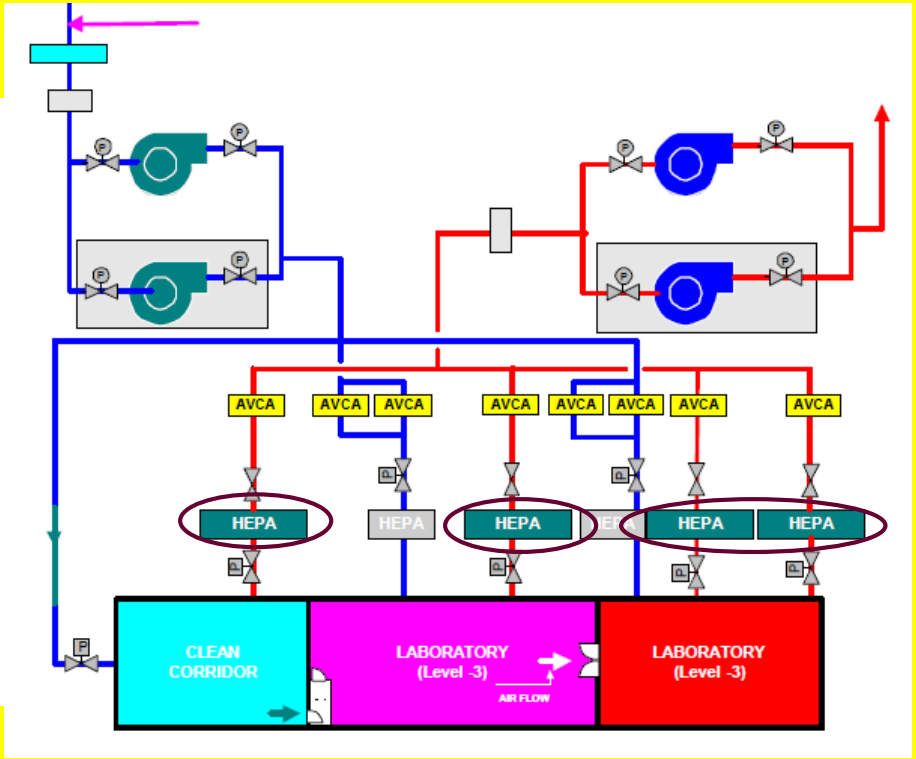
Tertiary Barriers



Tertiary Barriers-Ventilation Design



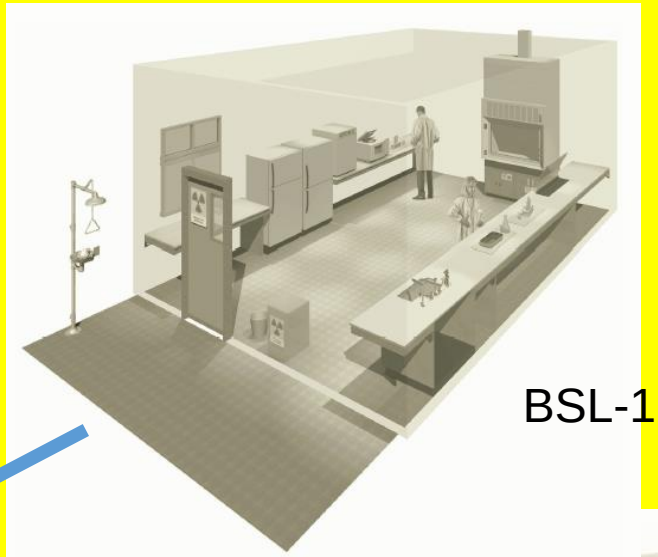
BSL-1/BSL-2



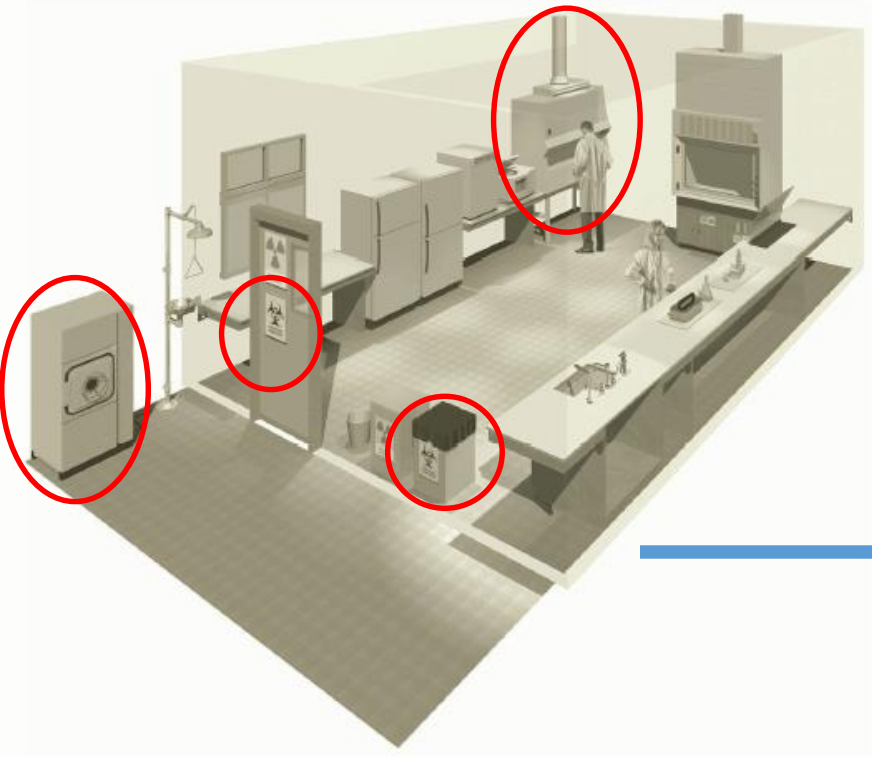
BSL-3

AVCA: air volume and temperature control assembly

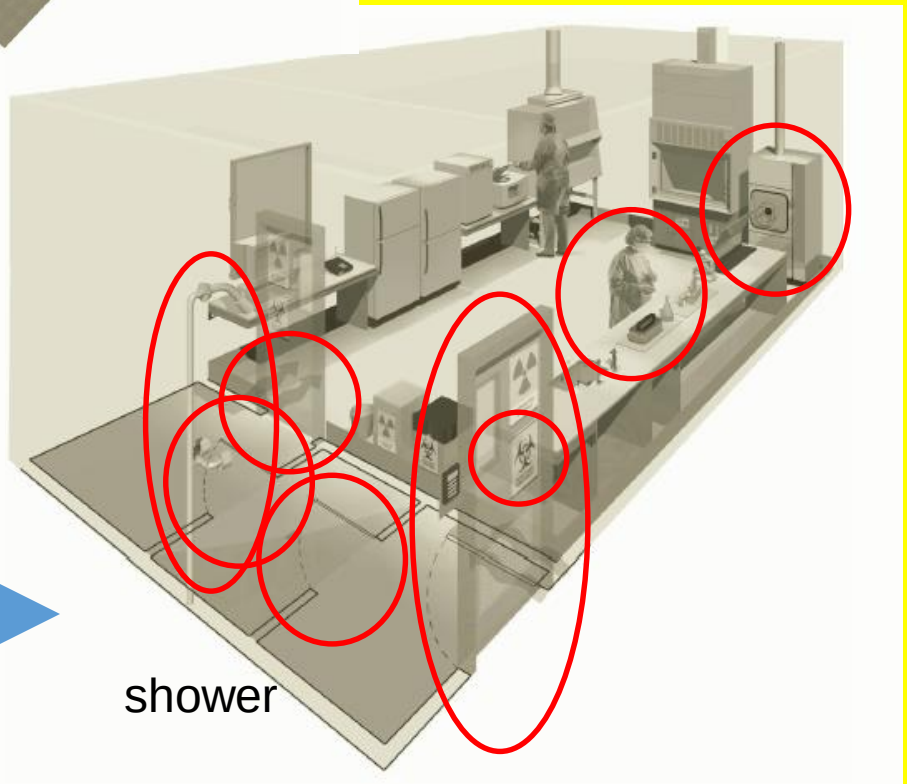
HEPA filter to avoid possible emission!



BSL-1

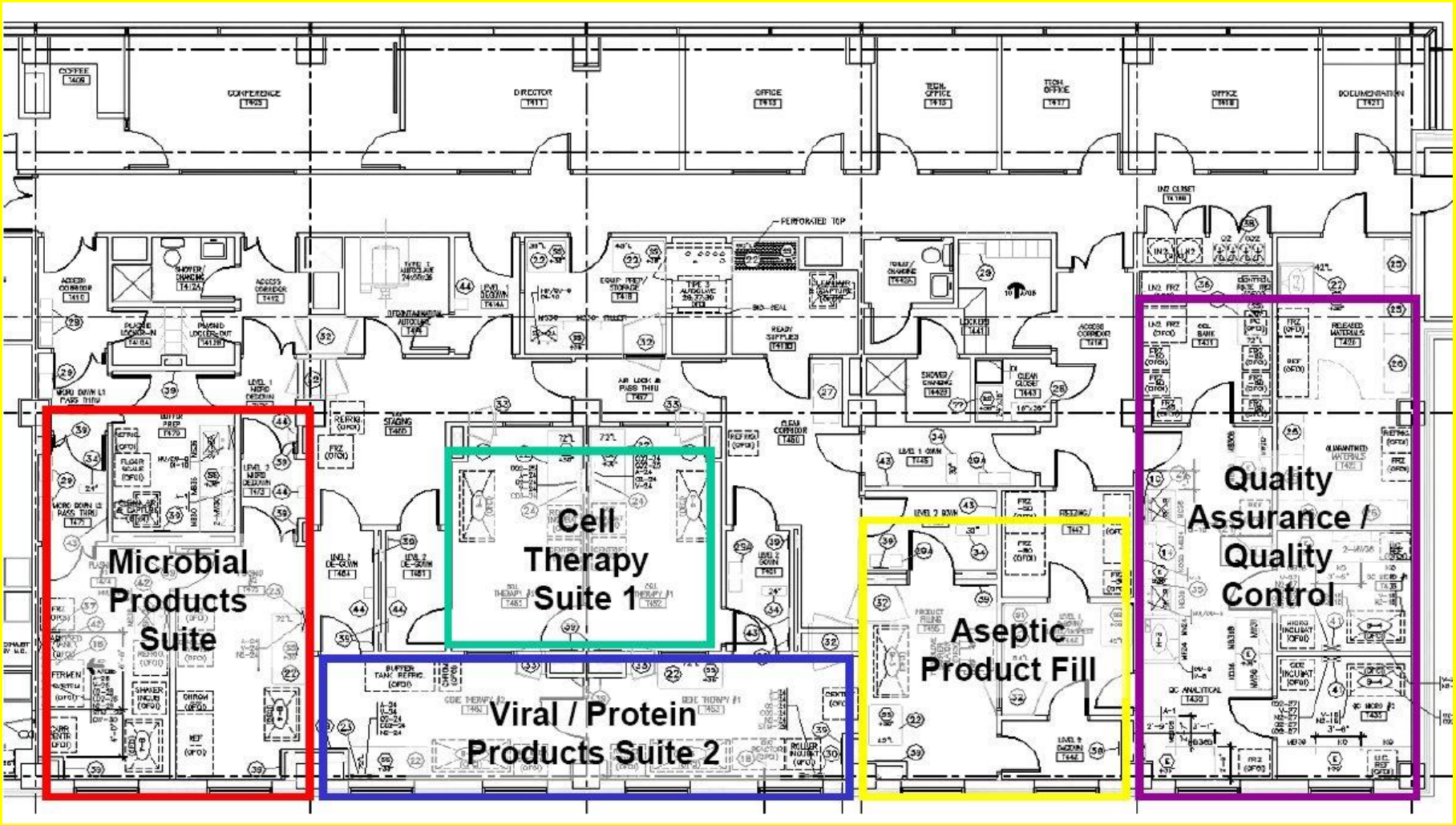


BSL-2



shower

BSL-3


Microbial Products Suite
Cell Therapy Suite 1
Viral / Protein Products Suite 2
Aseptic Product Fill
Quality Assurance / Quality Control

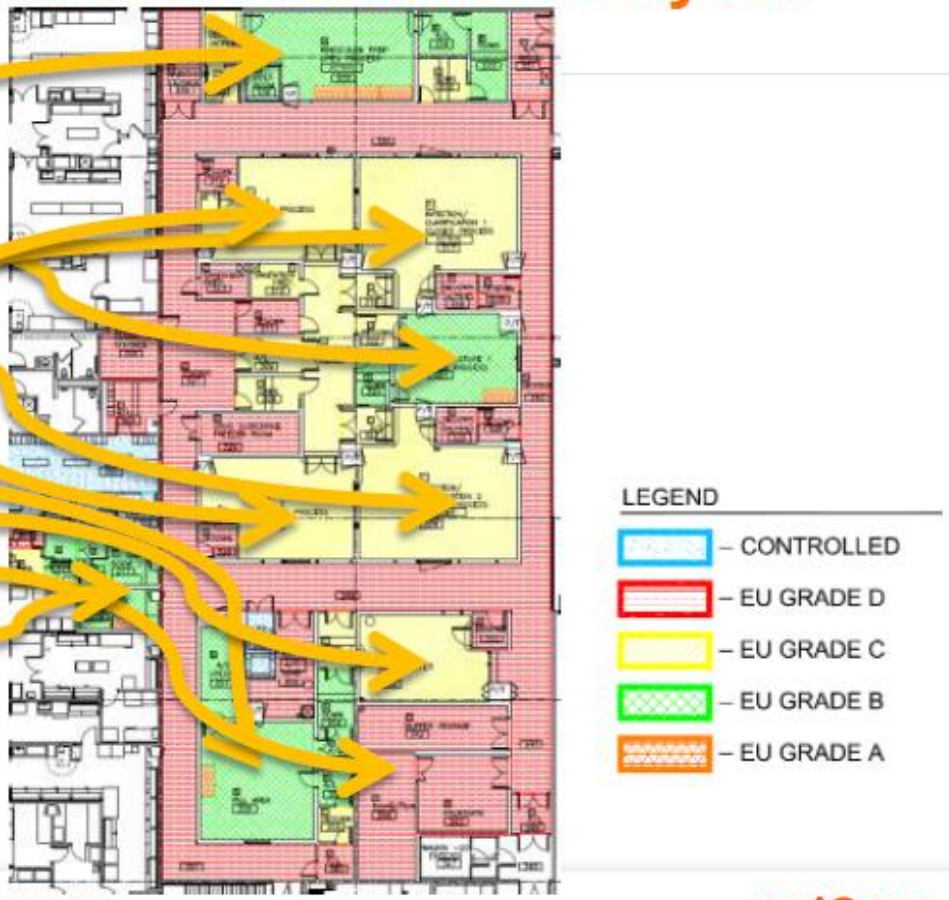
Lexington Site Layout

uniQure

LEXINGTON, MA (USA)

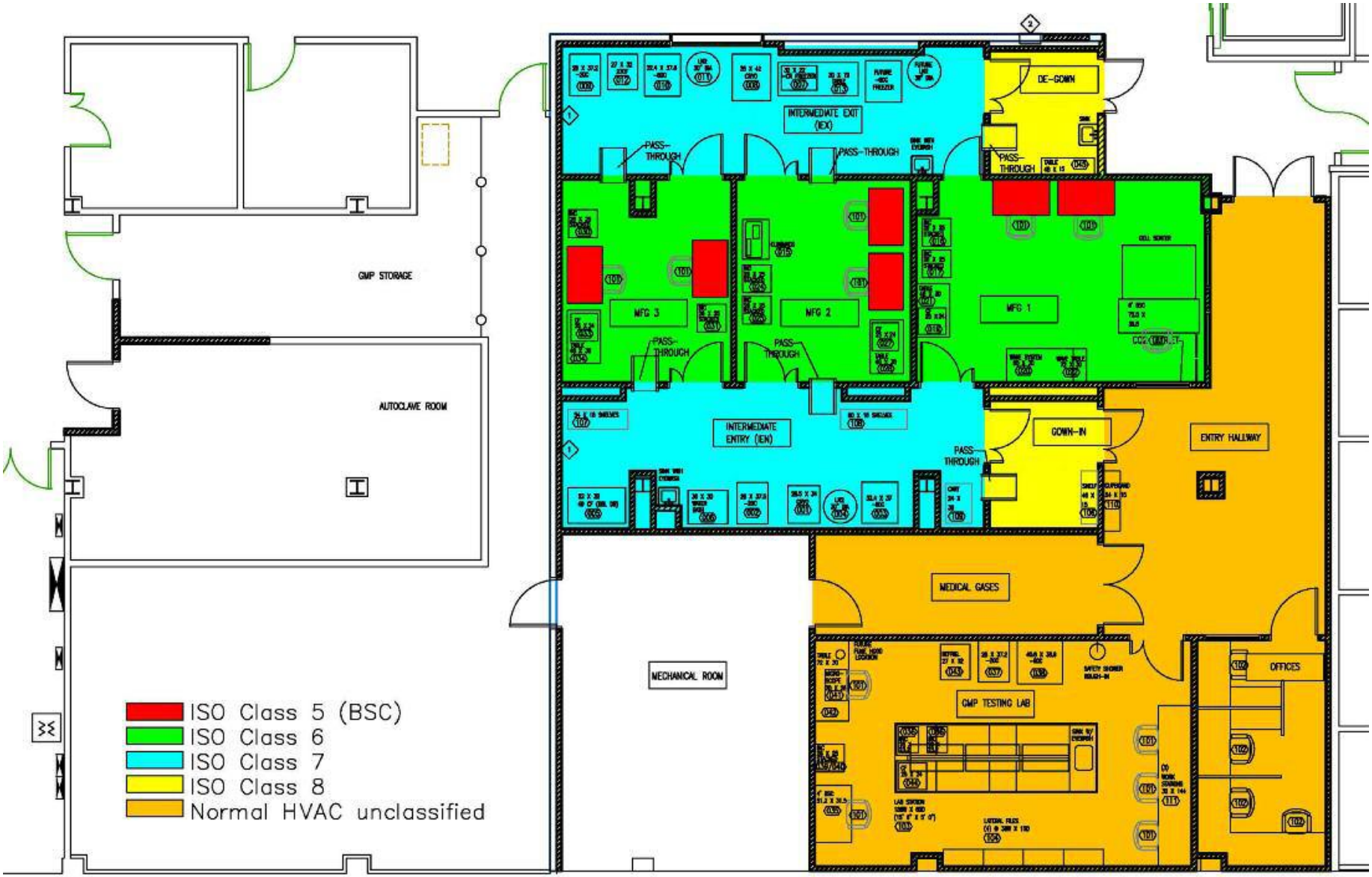
Manufacturing and Controlled Lab Area Layout

- INOCULUM PREP Grade B
- PRE CULTURE ROOM Grade B
- UPSTREAM 1 & 2 Grade C
- DOWNSTREAM 1 & 2 Grade C
- FILL AREA Grade B
- SOLUTION PREP AND SUPPORT Grade C
- INSPECTION, LABELING, & PACKAGING Grade D
- QC SAMPLING Grade B



uniQure

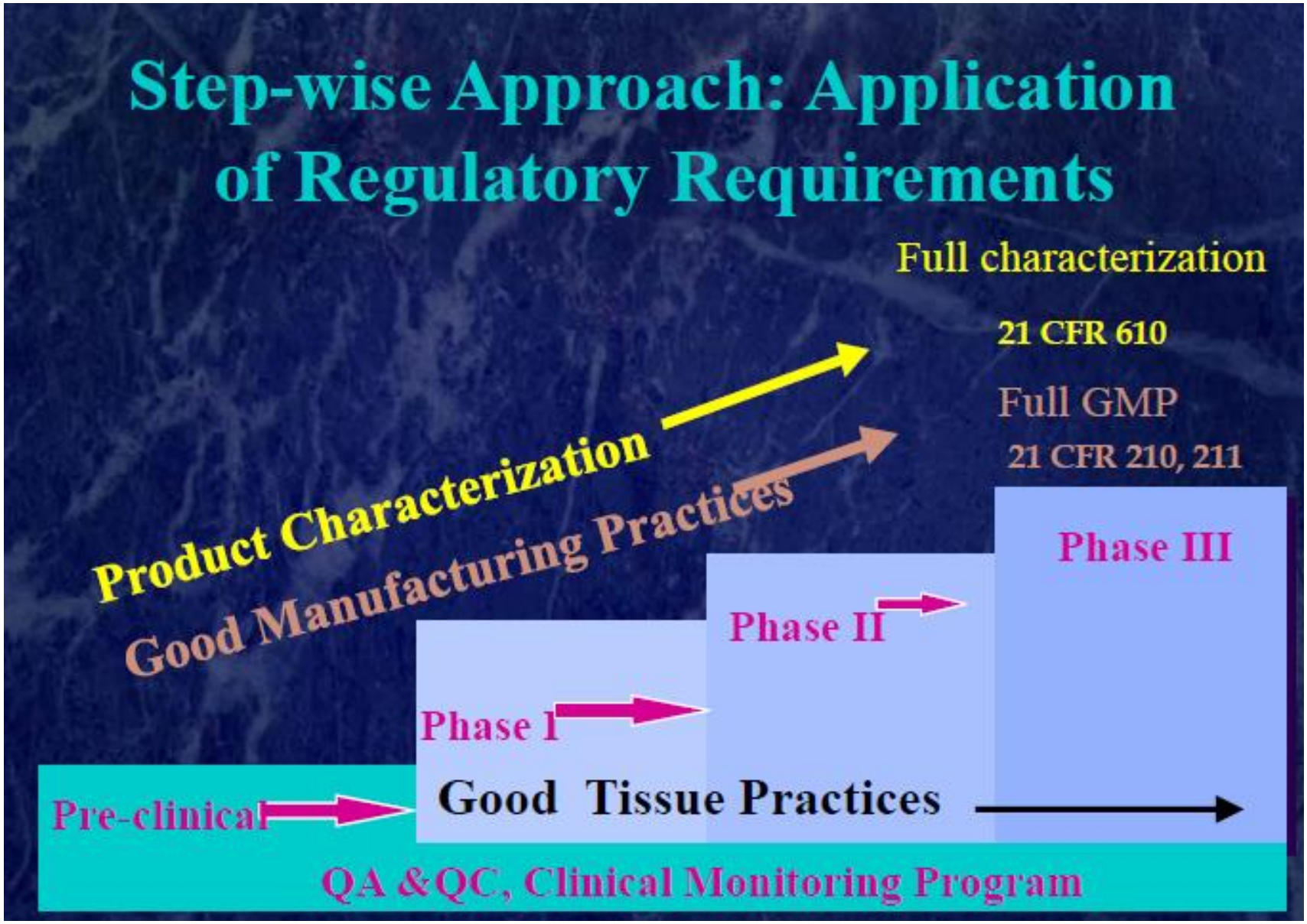
LEXINGTON, MA (USA)


GMP STORAGE
AUTOCLAVE ROOM
MECHANICAL ROOM
INTERMEDIATE EXIT (IEX)
PASS-THROUGH
DE-GOWN
MFG 3
MFG 2
MFG 1
INTERMEDIATE ENTRY (IEN)
GOWN-IN
ENTRY HALLWAY
MEDICAL GASES
GMP TESTING LAB
OFFICES
ISO Class 5 (BSC)
ISO Class 6
ISO Class 7
ISO Class 8
Normal HVAC unclassified

In Summary….

- FDA recognizes changing nature of clinical studies; need for sliding scale approach to meeting cGMPs
- Key production steps, equip. and facilities need to be under documented control
- Patient safety cannot be compromised
- Testing alone does not assure a quality product
- QC/QA needed at early stages

Step-wise Approach: Application of Regulatory Requirements



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Thank You

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Sartonets Taiwan Ltd.

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