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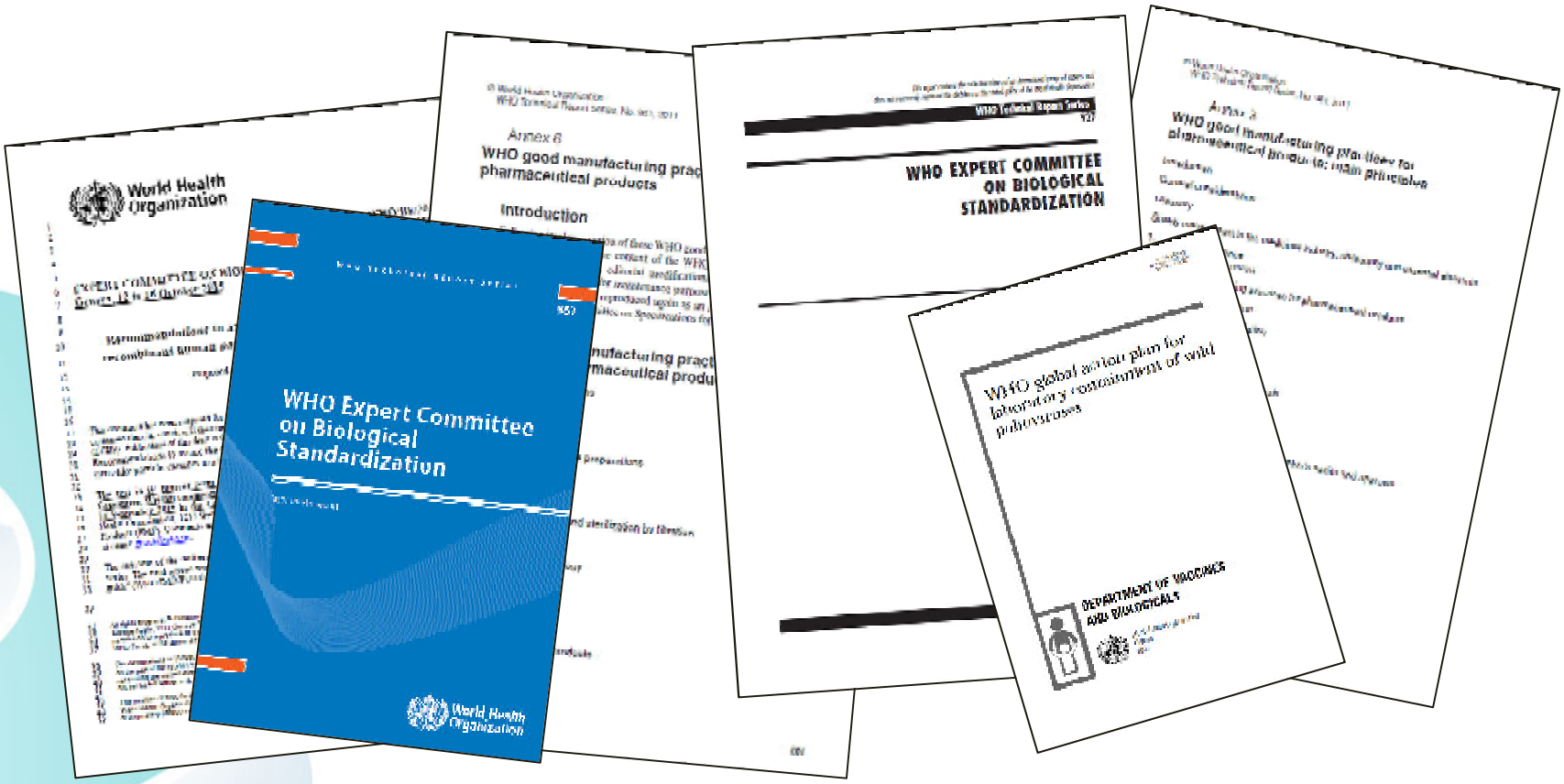

Regulatory Basics for Facility Design (WHO GMP): Current GMP Requirements

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Main Topics of the Presentation

- Clean Room Requirements
- Interior Finishes and Air Tightness of Clean Rooms
- Pressure Cascade Concept
- Design of Personnel Airlocks (PALs)
- Gowning Concept
- Storage Area and Logical Flow of Material from Reception until Final Product Release
- Production Area and Logical Flow of Material, Personnel and Product
- Quality Control Area

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GMP of Pharmaceutical Products

Assurance of:

- Consistently produced products
- Quality standard control
- Decreasing risk in the production
  - → Risk of cross-contamination
  - → Confusion of product

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Design of Premises: General[1] (1)

A facility should be designed to…

- …minimize the risk of errors.
- …permit effective cleaning, maintenance and disinfection.
  - Avoid contamination of material and product
  - Protect manufacturing process
- …facilitate good sanitation in manufacture rooms for the finished products.
- …protect the quality of the product from repair and maintenance operations.

[1] WHO TRS 961, Annex 3, paragraph 12.2 - 12.6

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Design of Premises: General[1] (2)

A facility should be designed to…

- …avoid that electrical supply, lighting, temperature, humidity and ventilation have an effect on the product during manufacturing and storage, or on the equipment.
- …provide the maximum protection against entry of animals from outside.
- …assure a logical flow of material and personnel within the facility.
- …avoid the unnecessary entry of personnel, supervisory and control personnel

WHO TRS 961, Annex 6, paragraph 11.1

[1] WHO TRS 961, Annex 3, paragraph 12.7 - 12.10

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Clean Room Requirements

(Airborne Particles, Microbiology, Air Change Rate)

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Clean Room Requirements[1]

- Ventilation of production areas with an air-control facilities including filtration, control of temperature and, optional, humidity
- Prevent contamination and cross-contamination by filtration
- Regularly monitoring
- Separate air supply of quality control laboratories and production areas
  WHO TRS 961, Annex 3, paragraph 12.35
- Supply of clean rooms with air that has been filtered with the required efficiency
  WHO TRS 961, Annex 6, paragraph 1.1

[1] WHO TRS 961, Annex 3, paragraph 12.30

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Clean Room Requirements: Airborne Particles[1]

	Maximum permitted number of particle per m^3 greater than or equal to the tabulated size			
	At rest [a]		In operation [b]	
Grade	**0.5 µm**	**5.0 µm**	**0.5 µm**	**5.0 µm**
A	3520	20	3520	20
B	3520	29	3520	2’900
C	352’000	2’900	352’000	29’000
D	3’520’000	29’000	Not defined	Not defined

[a] The “at rest” state is the condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.
[b] The “in operation” state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel is present. The areas and their associated environmental control systems should be designed to achieve both the “at rest” and “in operation” states.

[1] WHO TRS 961, Annex 6, paragraph 4.6.1

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Clean Room Requirements: Air Change Rate

- Grade B, C and D: Number of air change should be appropriate for the size of the room and the equipment and personnel which are in it
  WHO TRS 961, Annex 6, paragraph 4.4

- Air filtration and air change rates should be set to ensure that the defined clean area condition is attained
  WHO TRS 961, Annex 5, paragraph 4.1.4

- Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated (in accordance with ISO 14644-3 Annex B13)
  WHO TRS 961, Annex 5, paragraph 8.2.14

- Recovery time from "in operation" to "at rest" limits for particles: 15-20 minutes
  WHO TRS 961, Annex 6, paragraph 4.7.5

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Clean Room Requirements: Air Change Rate, Temperature and Humidity

Design Concept

Room Grade	ISO Class „at rest"	ISO Class "in operation"	Air Exchange Rate [1/h]	Temperature [°C]	Relative Humidity [%]
Grade B	ISO 5	ISO 7	≥ 40	18-22	20-70
Grade C	ISO 7	ISO 8	≥ 20	18-22	20-70
Grade D	ISO 8	n/r	≥ 10	18-22	20-70

- No requirements for grade A (defined according to air flow speed of the laminar flow bench)
- Only for grades C air changes has to be at least 20 times per hour
  FDA Guidance for Industry, paragraph C
- Significant higher air changes needed for higher clean room grades
  FDA Guidance for Industry, paragraph C
- Temperature and relative humidity depend on the product and nature of the operations carried out
  WHO TRS 961, Annex 6, paragraph 4.7.8

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Clean Room Requirements: Microbiology

Only average values

WHO TRS 961, Annex 6, paragraph 4.9

Grade	Air sample (CFU/m³)	Settle plates (diameter 90 mm) (CFU/4 hours) [a]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

[a] individual settle plates may be exposed for less than 4 hours

Result can be influenced by the ventilation system

Result can be influenced by procedures and the discipline of the personnel

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Clean Room Requirements: Pressure Cascade[1]

- Air supply to maintain a positive pressure and an airflow to surrounding area with lower grade
- Adjacent rooms with different grade should have at least 10-15 Pa of pressure differential

[1] WHO TRS 961, Annex 6, paragraph 11.9

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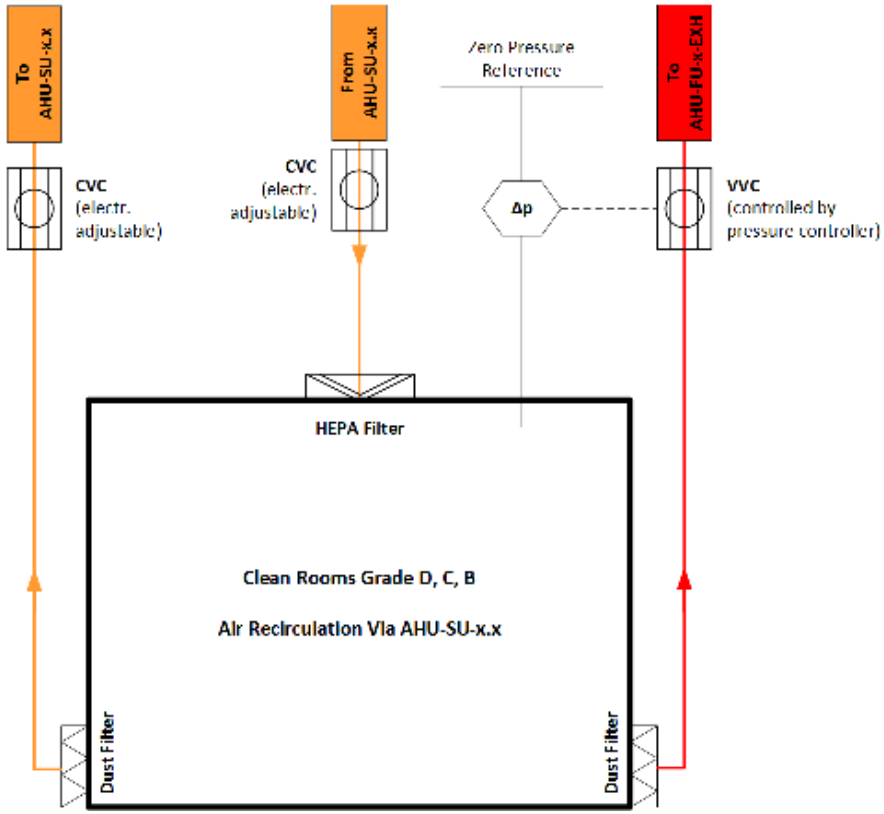
How CBC implements the mentioned Requirements (RQ) (1)

- **Airborne particle and microbiology RQ:** With the HEPA-filtration of the incoming air
- **Air change rate RQ:** A constant volumetric flow controller in each room check the supplied air volume
- **Pressure RQ:** A differential pressure sensor in each room controls a variable air volume controller to achieve a certain pressure

→ Dust filters for outgoing air are not a requirement, but it keeps the pipe system cleaner



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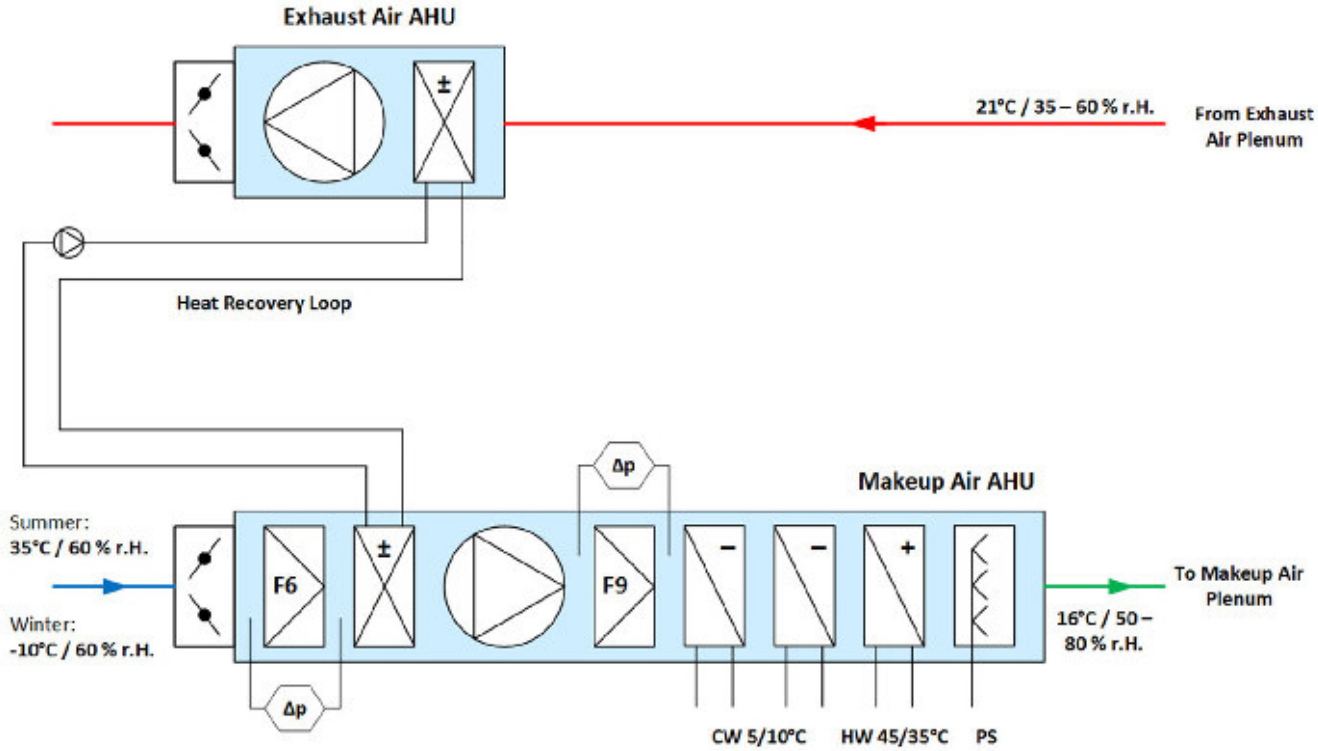
How CBC implements the mentioned Requirements (RQ)

Temperature and Humidity is controlled by the makeup air (air handling unit) with a cooling, heating and humidifying system.



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Interior Finishes and Air Tightness of Clean Rooms

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Interior Finishes and Air Tightness of Clean Rooms

- Smooth, impervious and unbroken surfaces
  WHO TRS 961, Annex 6, paragraph 11.2
- No uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment
  WHO TRS 961, Annex 6, paragraph 11.3
- Sealed ceilings to prevent contaminations
  WHO TRS 961, Annex 6, paragraph 11.4
- Avoid creation of recesses, unsealed openings and surfaces in the installation of pipes and ducts from utilities
  WHO TRS 961, Annex 6, paragraph 11.5
- Avoidance of recesses at pipework, light fittings and ventilation points (should be accessible from outside)
  WHO TRS 961, Annex 3, paragraph 12.28
- Adequate size of drains, prevent back-flow, designed to facilitate cleaning and disinfection
  WHO TRS 961, Annex 3, paragraph 12.29

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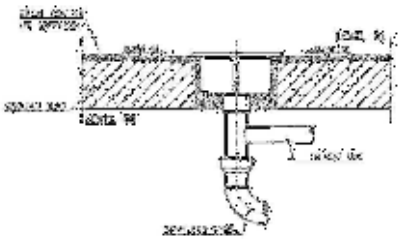
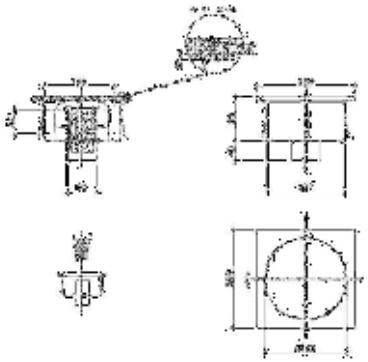
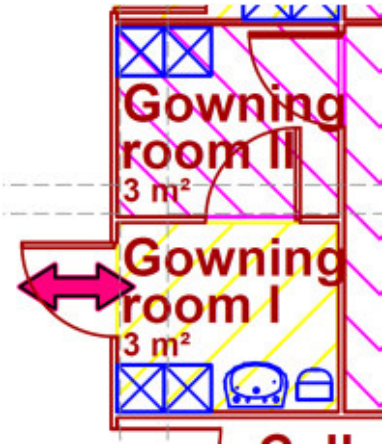
Interior Finishes and Air Tightness of Clean Rooms

- Installation flush to the clean room floor
- Drains must be closable with a lid that is fully sealed with a gasket
- Top of the lid must be smooth, easy to clean, etc.
- Drains itself easy to clean and disinfect
- Sinks placed in the personnel airlock with the lower clean room classification







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Interior Finishes and Air Tightness of Clean Rooms, Chamfers

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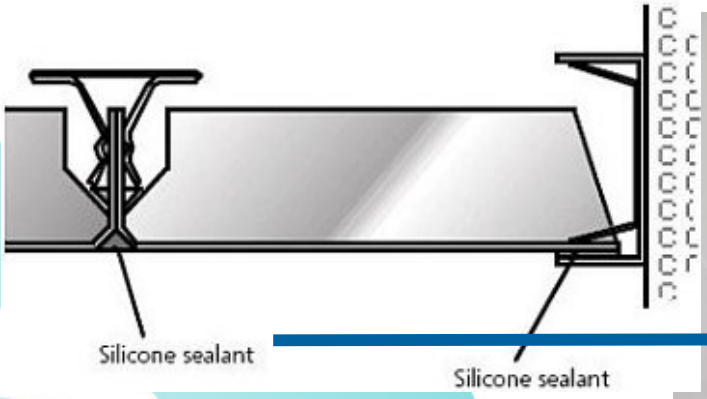
Interior Finishes and Air Tightness of Clean Rooms



Mouse hole

Silicon sealant

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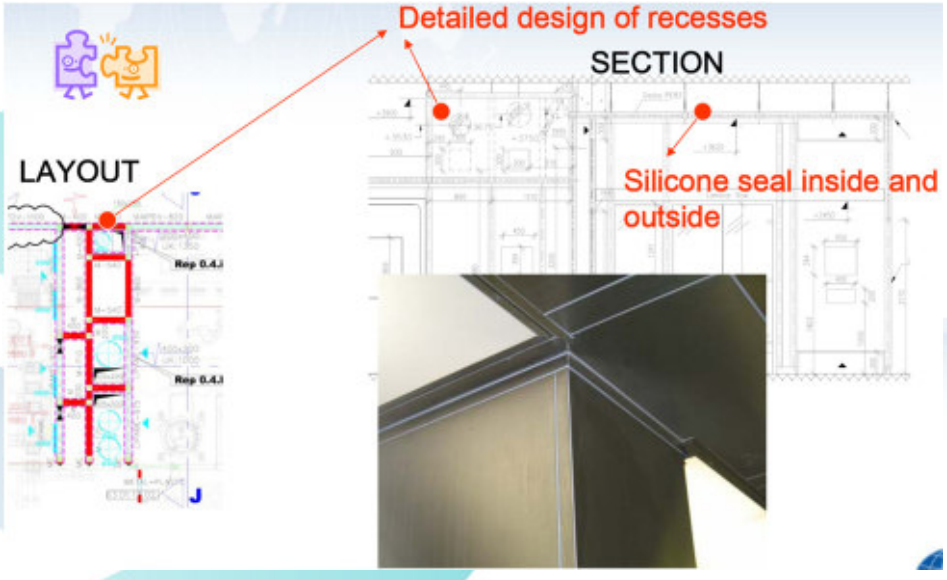
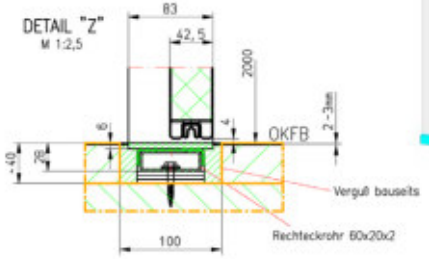
Interior Finishes and Air Tightness of Clean Rooms



Clean Room Construction

Detail: clean room doors, floor connection for door sealing



Doors with inflatable seals for VHP locks

More about VHP decontamination systems will follow in the next presentation

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Special Air Tightness of Bio-Positive Clean Rooms with Negative Pressure

- Designed to allow decontamination of the rooms with VHP
- Resistant material
- Air-tight room as far as possible to…
  - …minimize the release of VHP during decontamination.
  - …minimize the diffusion of potentially contaminated air.
  - …minimize the ingress of "dirty" air due to negative pressure.

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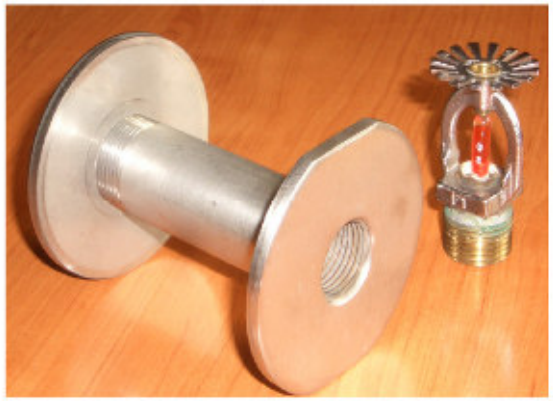
Special Air Tightness of Bio-Positive Clean Rooms with Negative Pressure

Air-Tight Panel Penetrations for Pipes:

The ceiling panel will be squeezed “sandwich-like” between the two discs. The edge of the two discs are then sealed inside and outside of the clean room ceiling.



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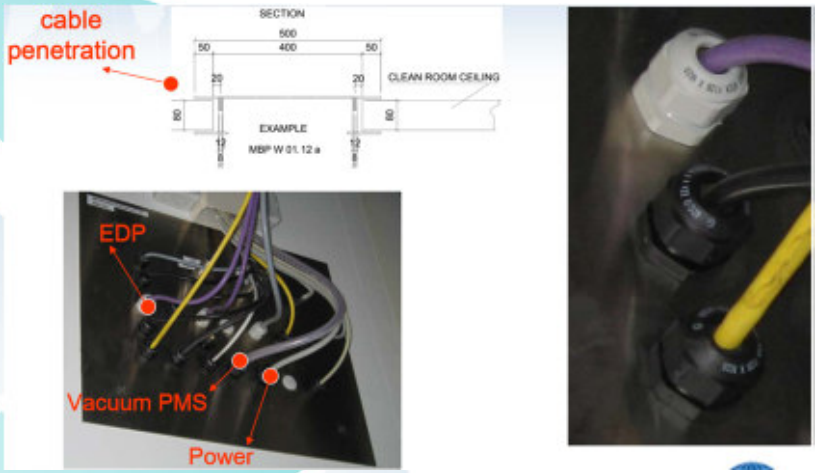
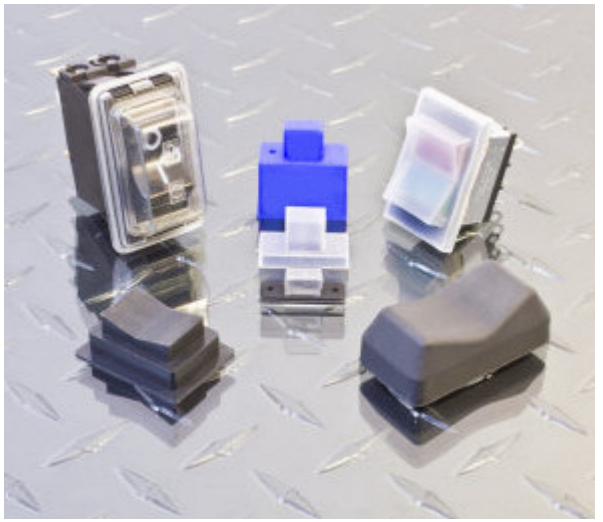
Special Air Tightness of Bio-Positive Clean Rooms with Negative Pressure



Air-tight cable penetration



Air-tight switch

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Special Air Tightness of Bio-Positive Clean Rooms with Negative Pressure

EE for bio-positive areas needs to be designed with the follow conditions:

- Permit an easy use in case of disaster
- Properly sealed to prevent air to flow from areas of lower grade into areas with higher grade.

Emergency exit (EE) panel

In case of disaster, the handle is pulled to remove the sealing holding the door in position, then the door can be pushed out of the door frame

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Pressure Cascade Concept

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Pressure Cascade Concept: General Philosophy (1)

- Critical cases: minimum pressure difference of 15 Pa (upper level of the demanded value)
  - → Between production rooms of different grade
  - → Between a barrier airlock and the adjoining rooms
- Uncritical cases: minimum pressure difference of 7-8 Pa
  - → In airlocks that connect areas or corridors of different GMP room grades

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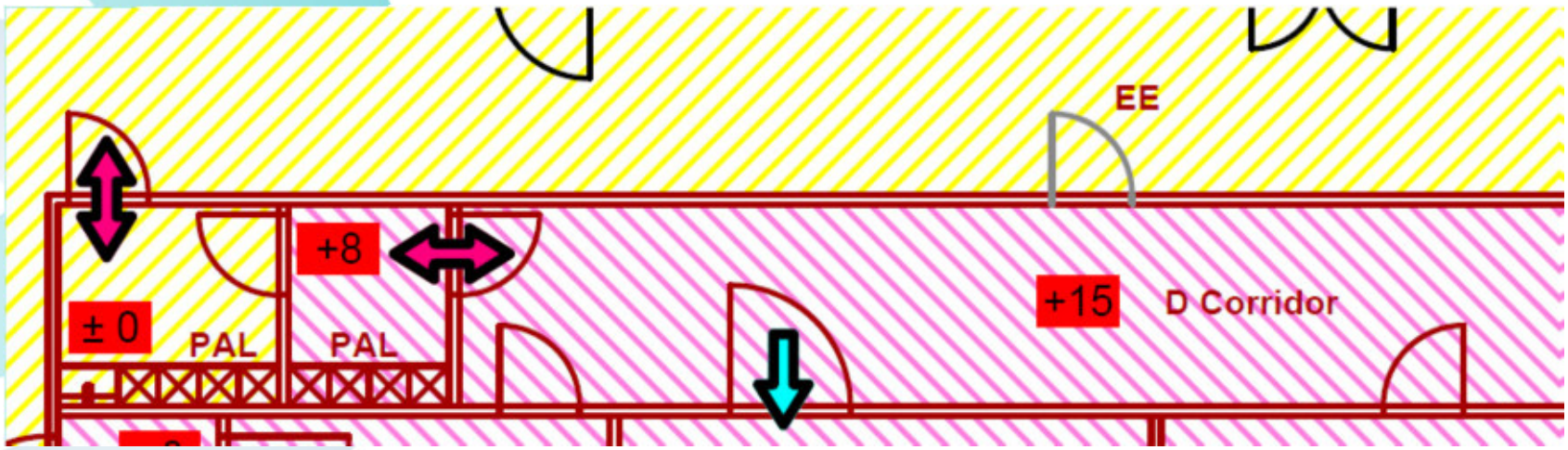
Pressure Cascade Concept: General Philosophy (2)

Why a pressure differential of 7-8 Pa is still efficient in the design of PALs and its pressure cascade?



Grade D
Grade CNC

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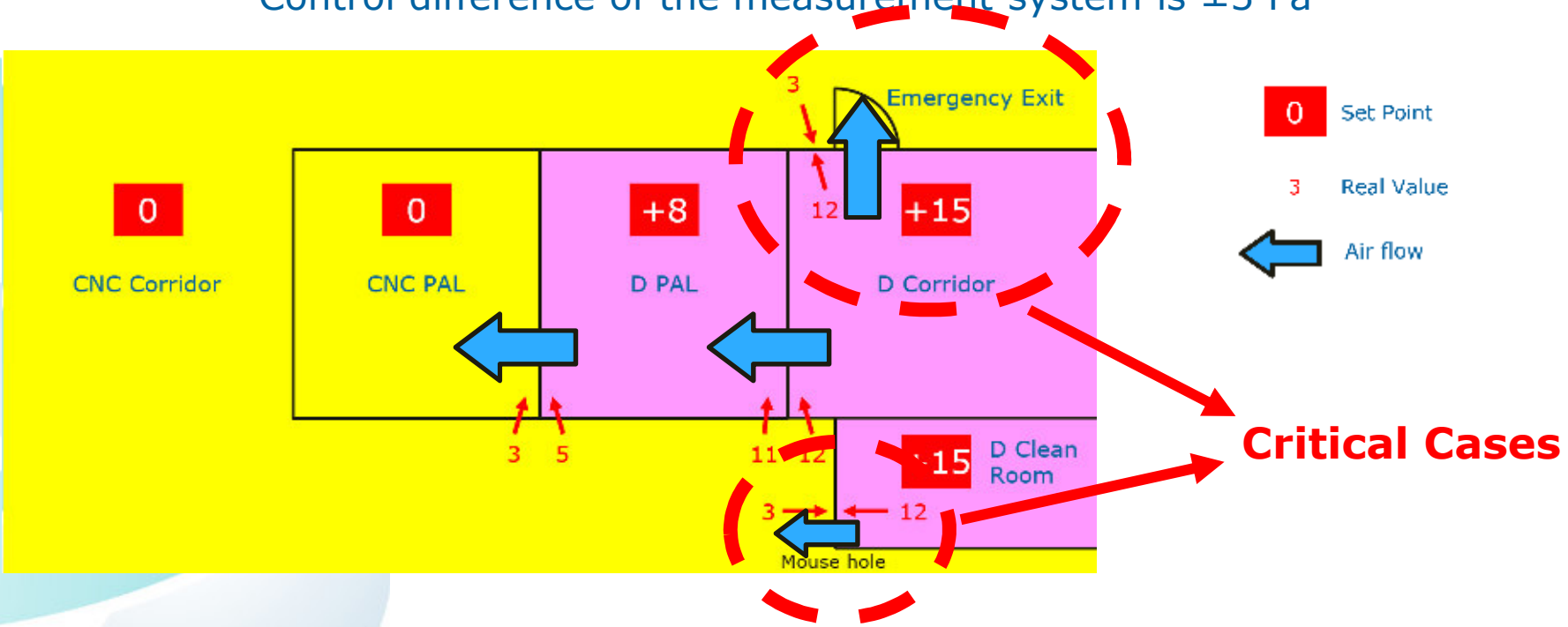
Pressure Cascade Concept: Measurement Inaccuracy

Control difference of the measurement system is ±3 Pa



Taking into consideration the control difference, the air flow is **still guaranteed in the critical cases**

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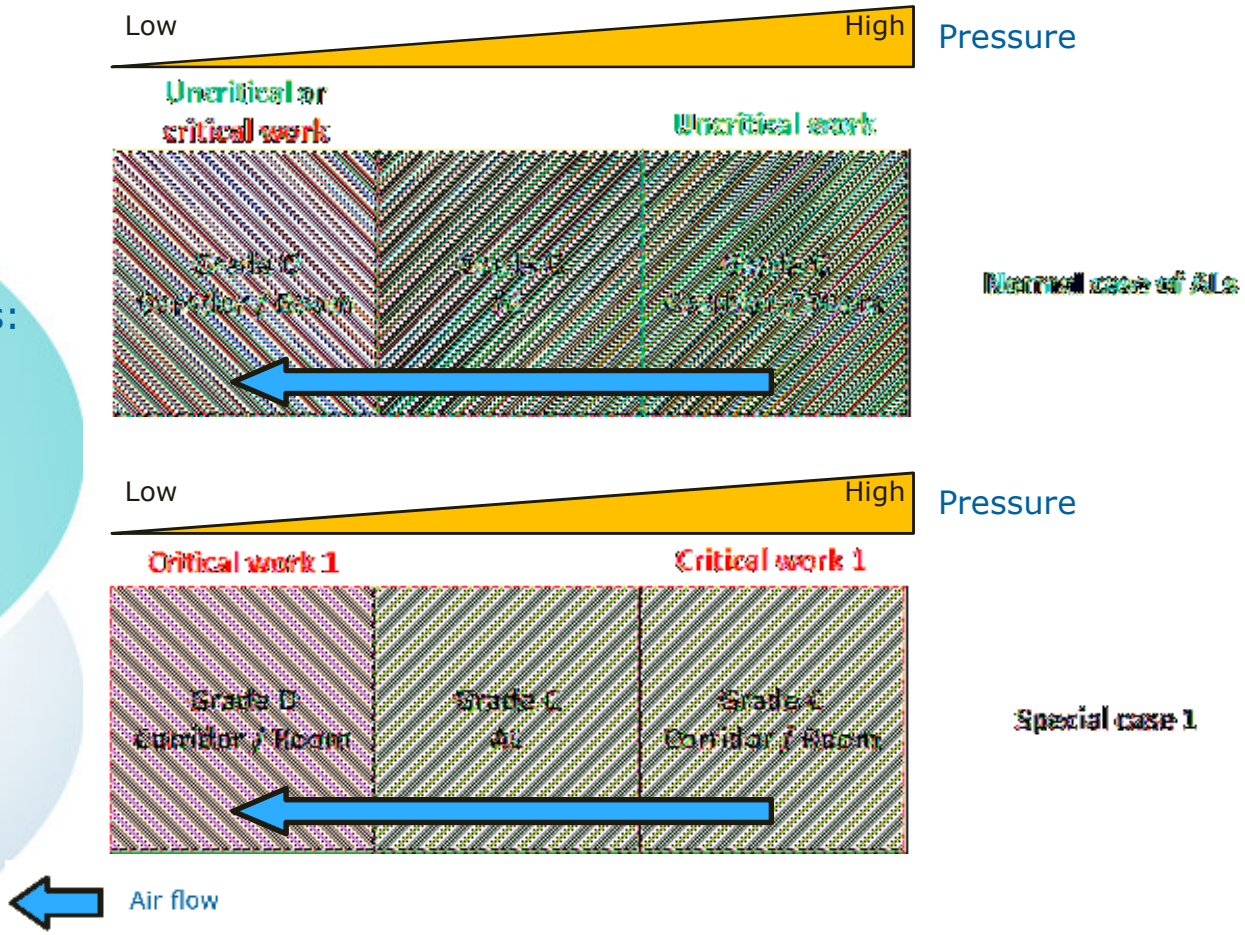
Pressure Cascade Concept: Critical and Uncritical Cases in ALs

Uncritical/critical cases:

- Biosafety
- ATEX
- OSD
- "Virus-risk"



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Pressure Cascade Concept: Critical and Uncritical Cases in ALs

Uncritical/critical cases:

- Biosafety
- ATEX
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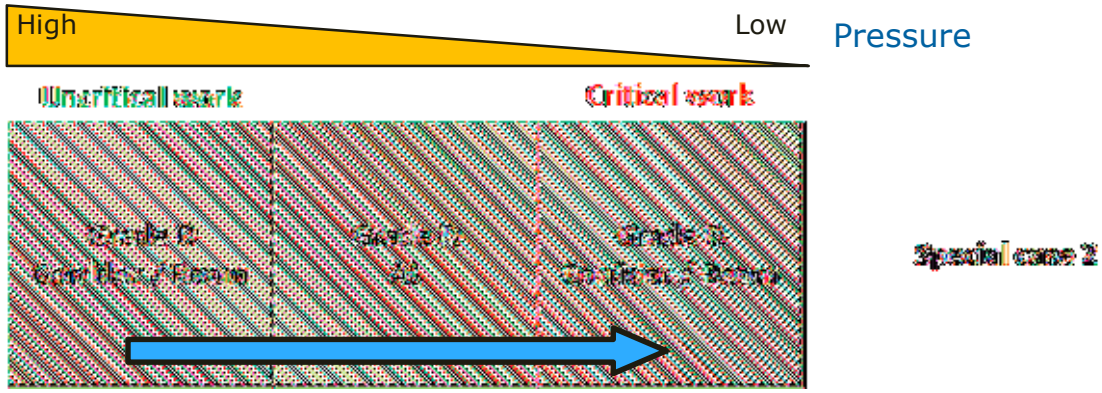

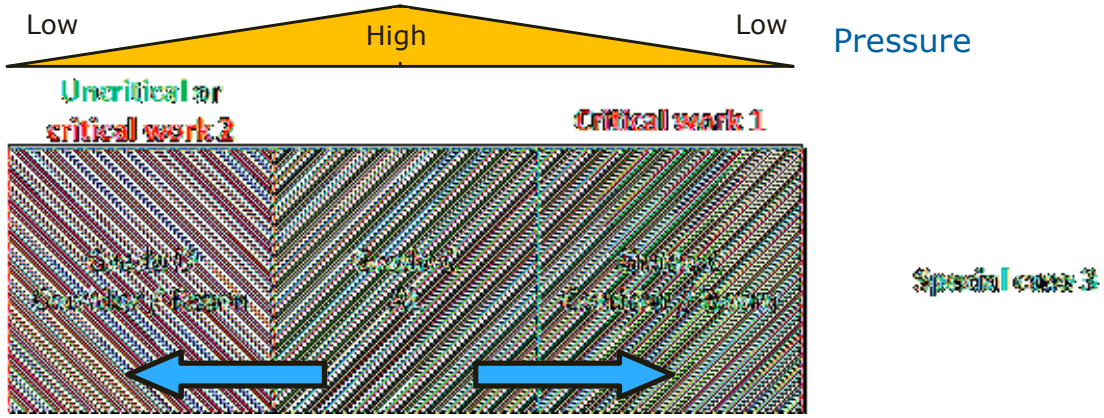

Air flow

= Barrier AL / Bubble AL

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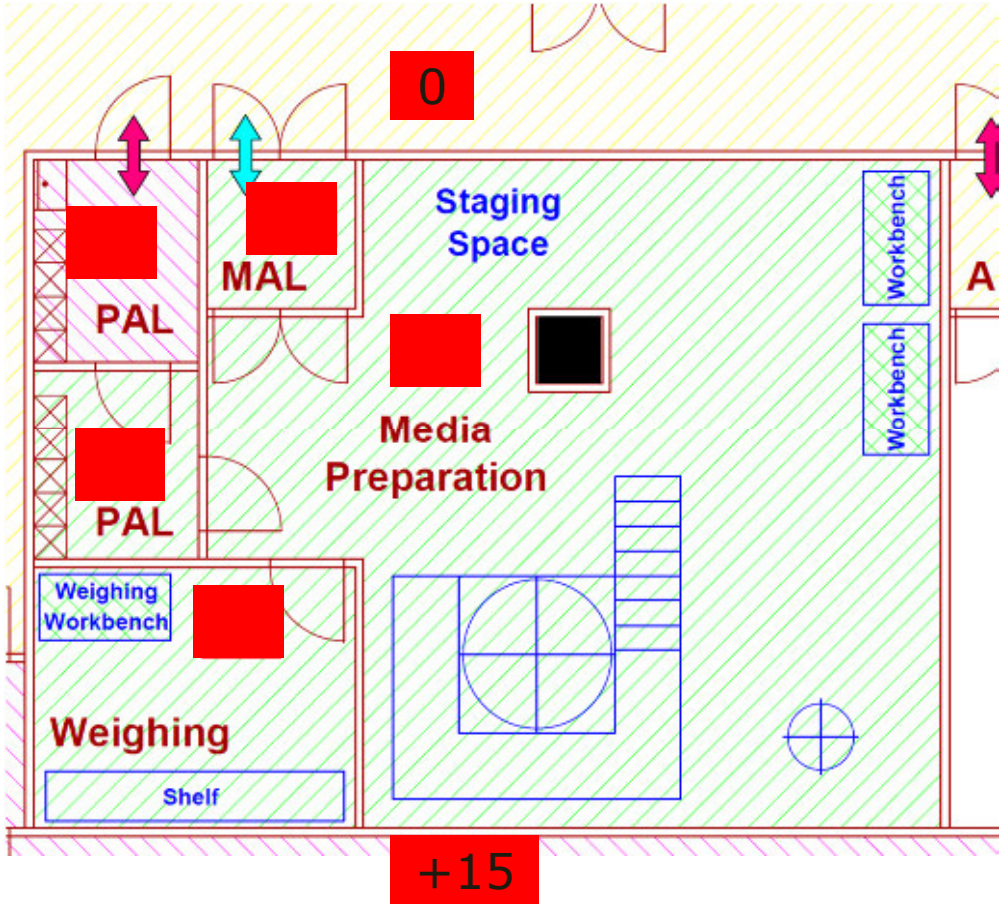
Exercise 1:

How is the pressure cascade and the air flow from CNC corridor to grade C clean rooms? (uncritical case)



Grade C
Grade D
Grade CNC

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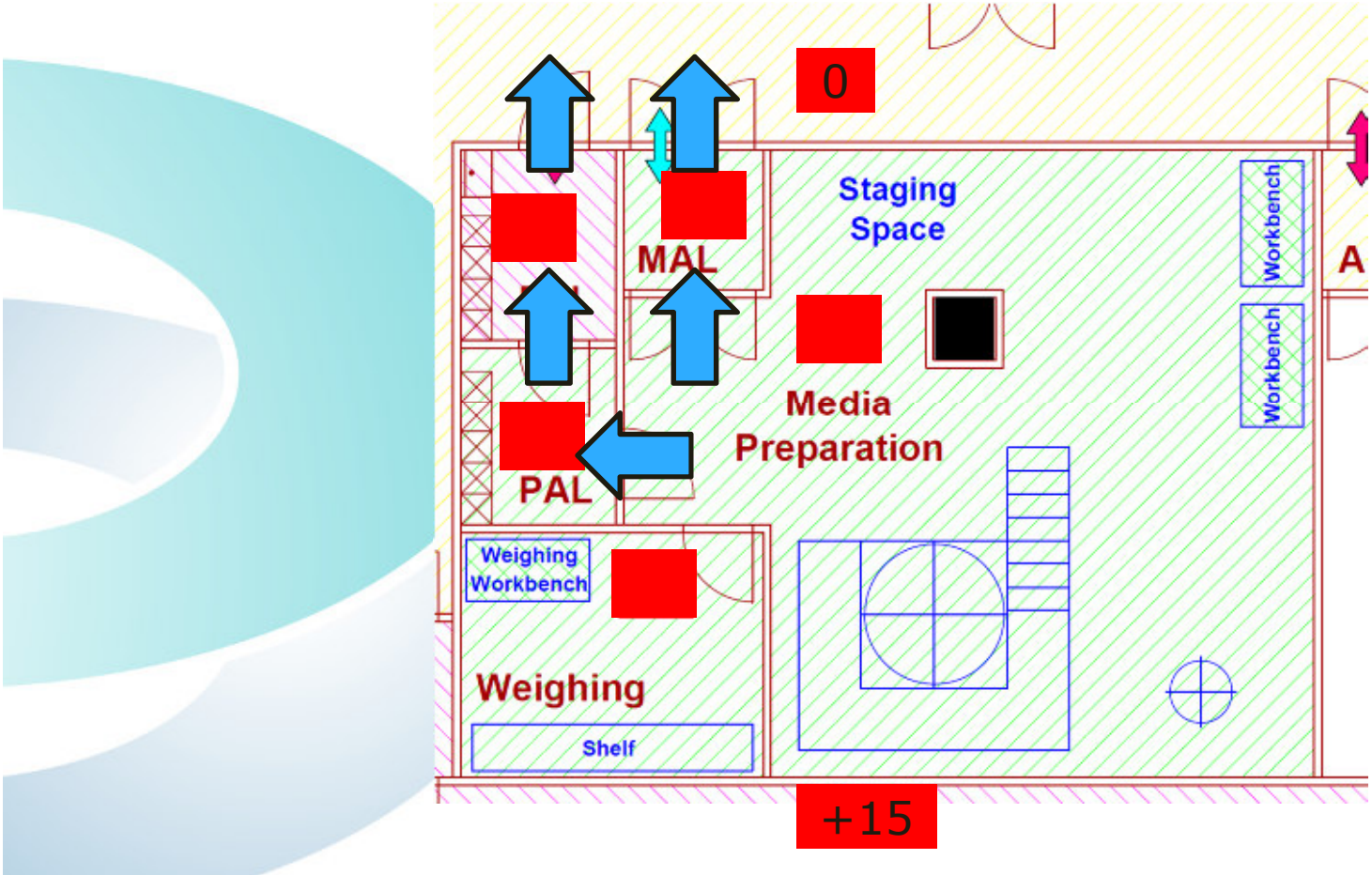
Solution 1



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Exercise 2: Air Locks & Pressure Cascade in a mAb Facility

Installation of **barrier airlocks** to avoid contamination of the supply corridor:

- Clean air must be driven into both directions (towards supply corridor and towards production room)
- Clean room grade of barrier airlock equal to the highest grade of the adjoining rooms
- Not required between production rooms and return corridor (standard GMP rules can be applied)

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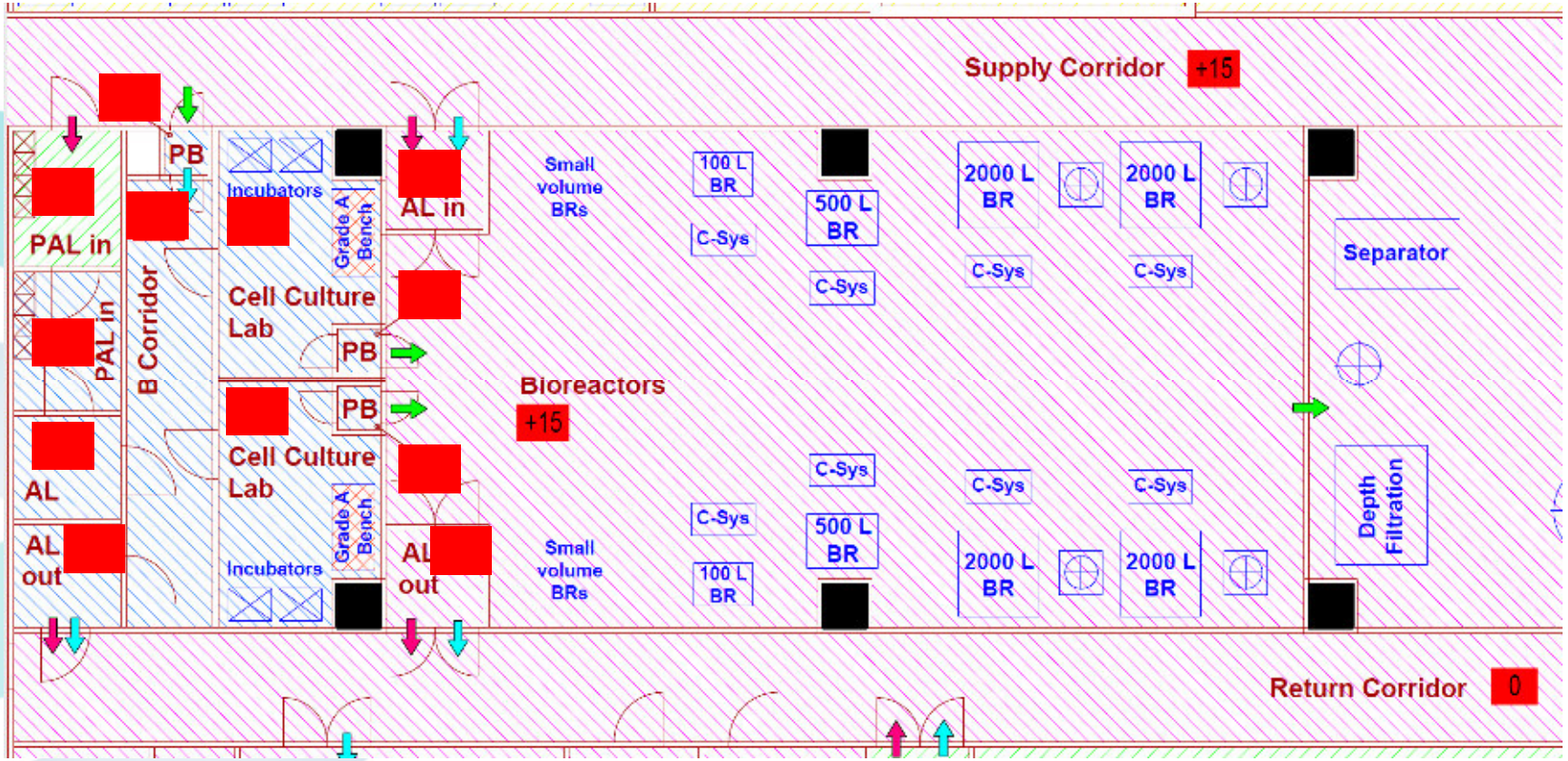
Exercise 2:

Which are the barrier airlocks and which pressure should they have? How is the air flow in general?



Grade B Grade C Grade D

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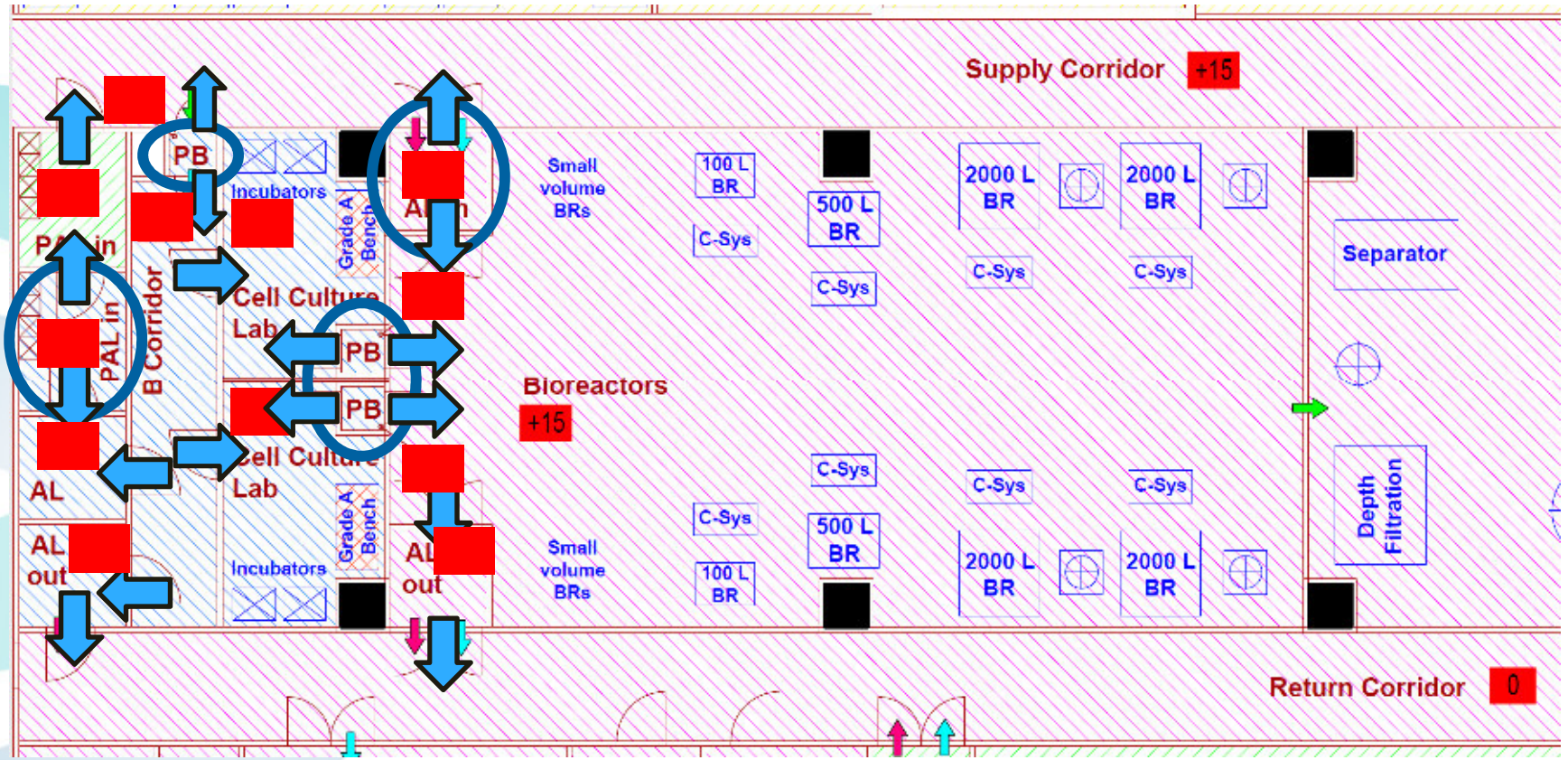
Solution 2: Barrier Airlocks and Air Flow



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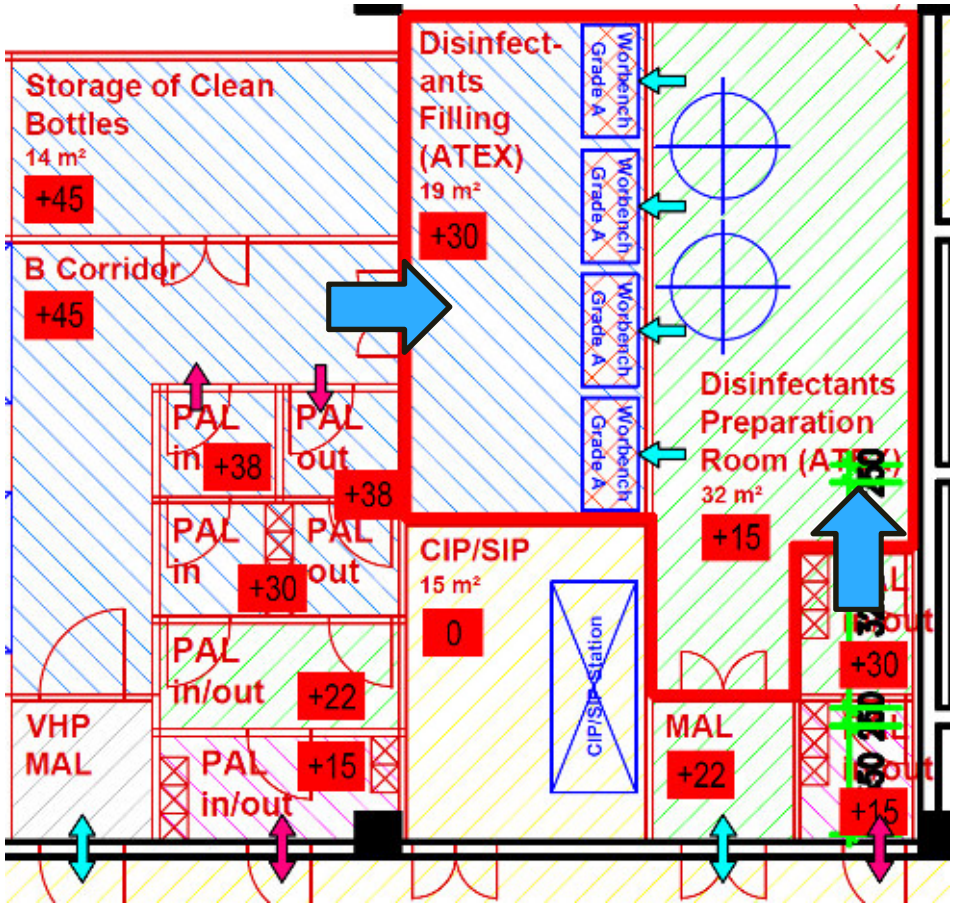
Pressure Concept for ATEX Area



Grade B Grade C Grade D Grade CNC Air flow

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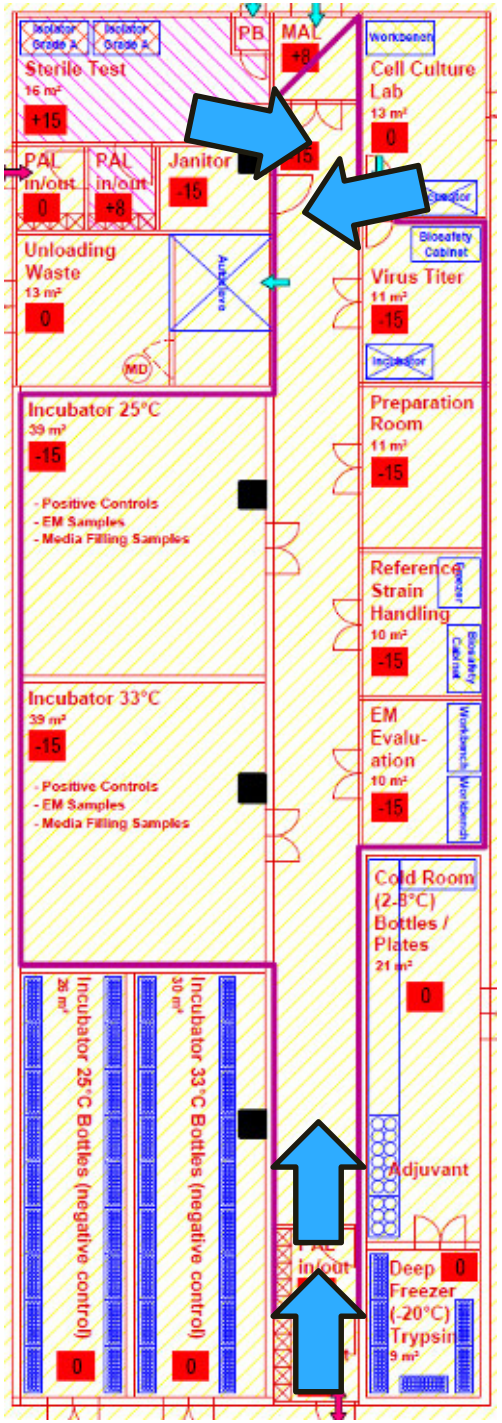
Pressure Concept for QC Area (Biosafety)

Grade D Grade CNC

Air flow



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Design of Personnel Airlocks (PALs)

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Design of PALs: General Requirements (1)

- Changing rooms and toilets → easily accessible (toilets no direct connection with production or storage areas)
  WHO TRS 961, Annex 3, paragraph 12.12
- Changing & washing → follow a written procedure which minimize clean areas and clean-area clothing contamination
  WHO TRS 961, Annex 6, paragraph 10.5
- Appropriate for the process and the clean room grade
  WHO TRS 961, Annex 6, paragraph 10.5
- Grade A/B: clean sterile protective garments (provided at each work session)
  WHO TRS 961, Annex 6, paragraph 10.6
- Mask and gloves: change at least every work session
  WHO TRS 961, Annex 6, paragraph 10.6

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Design of PALs: General Requirements[2] (2)

- Designed as airlocks
- Physical separation of different stages of changing
- Minimize microbial and particulate contamination
- Flushed with filtered air
- Last airlock should have the same grade as the corridor/room it leads into
- Only one grade of difference between airlocks
- Sufficient size
- Equipped with mirrors to confirm correct fit of clothes

[1] WHO TRS 961, Annex 6, paragraph 11.7

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Design of PALs: General Requirements (3)

- Avoidance of simultaneous door opening (implementation of interlocking system, visual and/or audible warning system)
  WHO TRS 961, Annex 6, paragraph 11.8
- Higher airlocks have higher pressure compared to lower grade airlocks
  WHO TRS 961, Annex 6, paragraph 11.9
- Protection of the zone with greater risk (for example immediate environment in which product or cleaned components are handled openly)
  WHO TRS 961, Annex 6, paragraph 11.9

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Design of PALs: General Requirements (4)

- Prove that airflow patterns are without contamination risk (avoidance of particle flow from particle-generating person / operation / machine to zone of higher risk for the product)
  WHO TRS 961, Annex 6, paragraph 11.10
- Doors should open to high-pressure, with self-closer (changes are allowed based on exits and environmental, health or safety requirements)
  WHO TRS 961, Annex 6, paragraph 11.3

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Design of PALs: General Design

- Different possibilities to design PALs

  → Bidirectional: Personnel enters and leaves the production rooms though the same PALs. The PALs are separate rooms

  → Unidirectional: Personnel enters into the production rooms through the PAL IN. After they leave the production rooms through other PALs, the PAL OUT.

- **Generally** the PALs are designed for a **bidirectional flow** of the personnel

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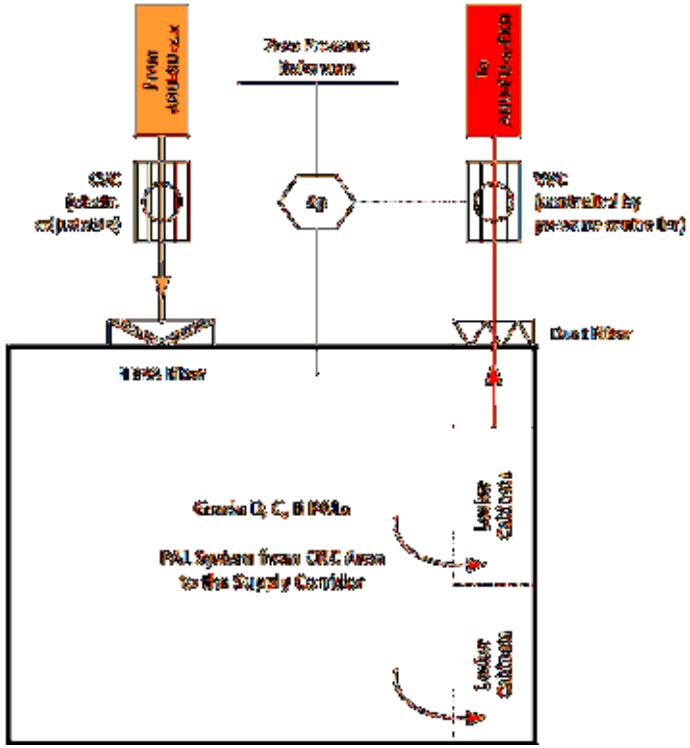
Design of PALs: Room Typicals

100% of air exchange, because of the smell of the clothes and shoes.



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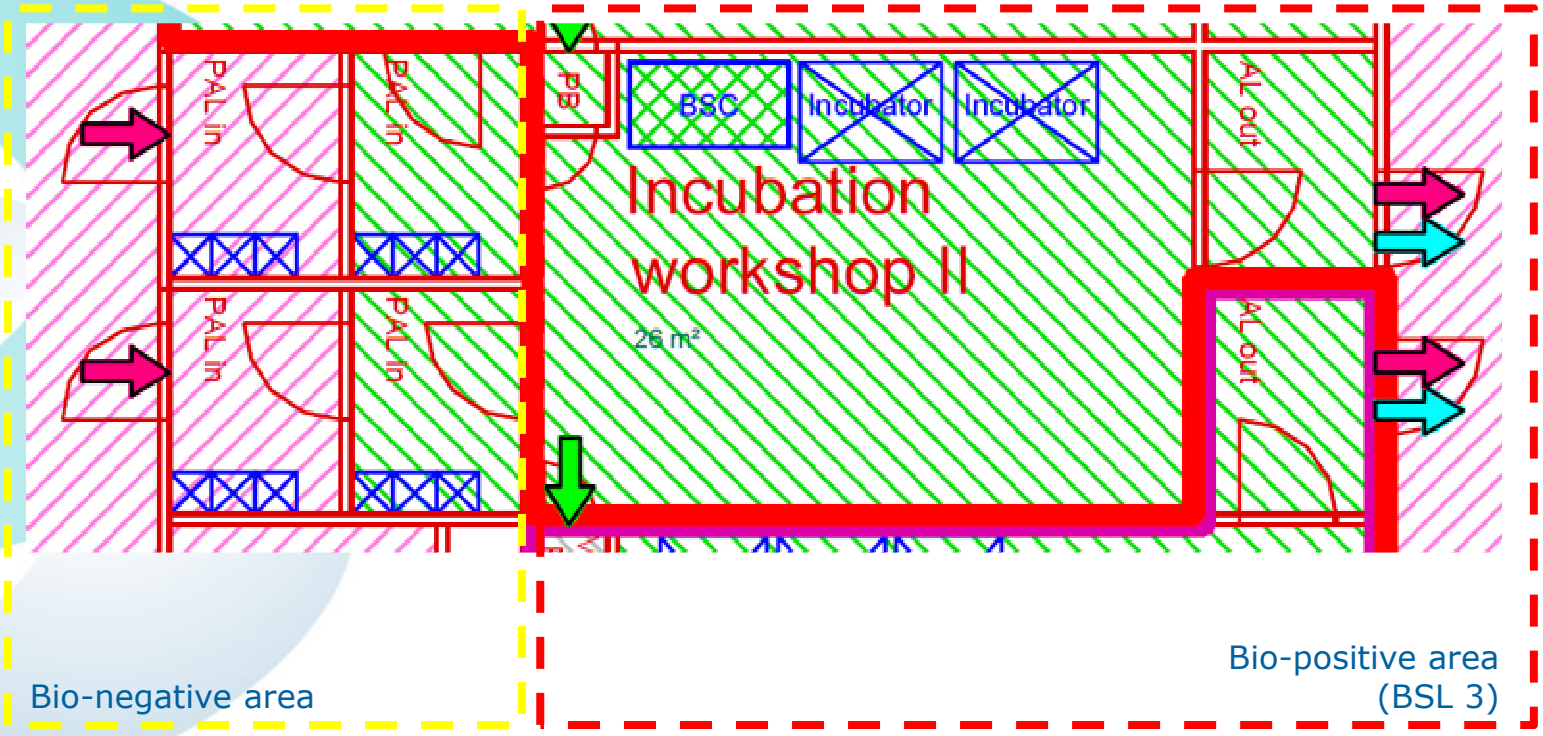
Design of PALs: Exception 1

One exception of the bidirectional design of PALs is the **bio-safety area**, in which PALs are designed in an unidirectional way.



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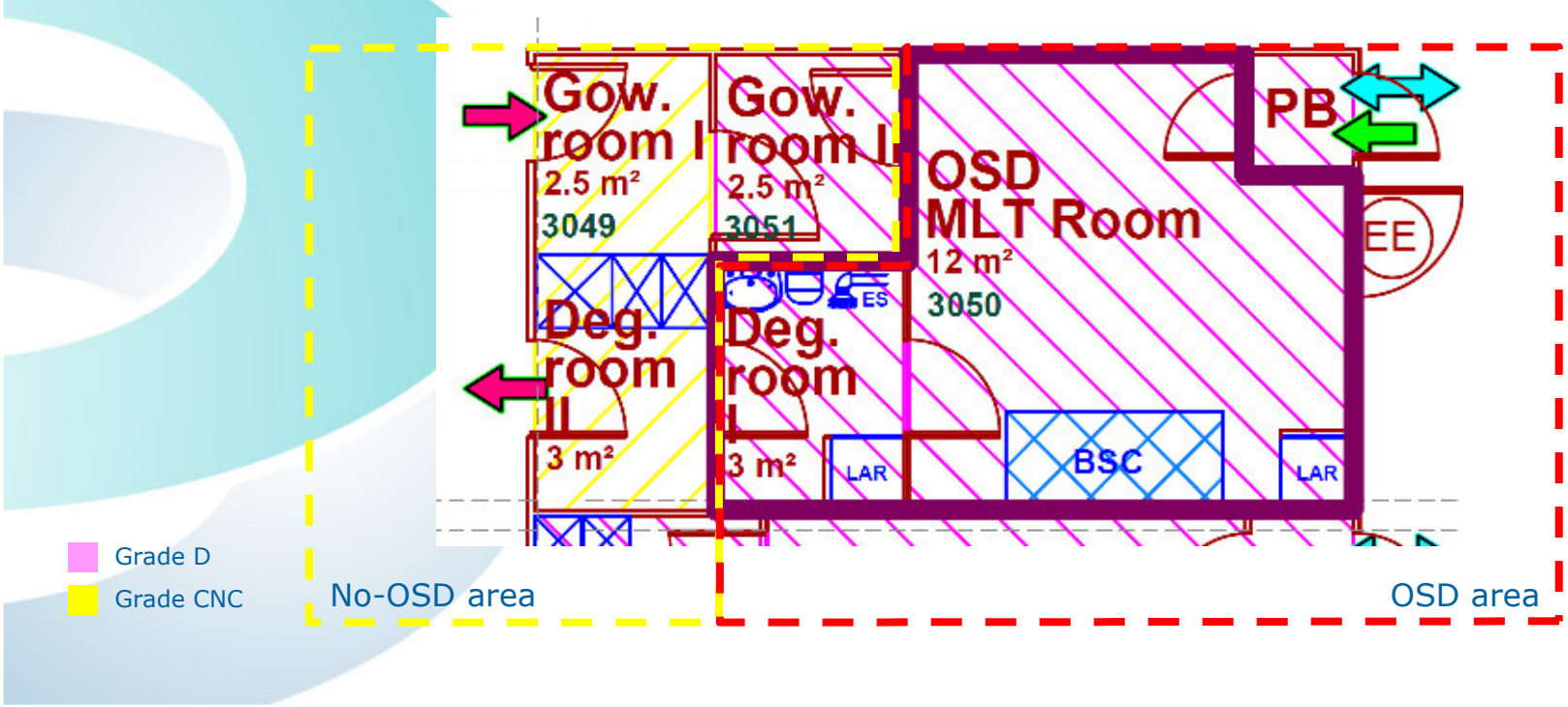
Design of PALs: Exception 2

Exception 2 of the bidirectional PAL concept is the **production of OSDs**, in which PALs are designed in an unidirectional way.



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Gowning Concept

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Gowning Concept (1)

- Garments, which are marked in grey colour (see next slide),…

  → …shall not be removed when changing.

  → …is worn under the new clothes.

- Two possibilities
  - Gowning and degowning in the same PAL. Lockers are provided for the changed clothes.

    → **not recommended for critical cases (e.g. entering grade B)**

  - Separated rooms for gowning and degowning

    → **preferred option**

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Gowning Concept (2)

Room Grade	Garment	Illustration / Example
CNC / D / C / B (Layer 1, underwear for all areas)	Socks Long underpants Sweatshirt / t-shirt	
CNC (Layer 2)	Socks Long underpants Sweatshirt / t-shirt CNC-overcoat CNC-trousers Safety shoes CNC Hair net (optional for CNC)	
D (Layer 2)	Socks Long underpants Sweatshirt / t-shirt Grade-D-overcoat Grade-D-trousers Safety shoes grade D Gloves Hair net / cover Face mask (optional, e.g. for OEL protection) Beard cover (for those wearing a beard)	

Room Grade	Garment	Illustration / Example
C (Layer 2)	Socks Long underpants Sweatshirt / t-shirt Grade C one-piece jumpsuit Safety shoes grade C Gloves Hair net / cover Face mask Beard cover (for those wearing a beard)	
B (Layer 2)	Socks Long underpants Sweatshirt Safety shoes Grade B (see picture) Full-body protective overall for Grade B (see picture) Gloves (see picture) Head cover (see picture) Safety goggles (see picture) Face mask (see picture)	

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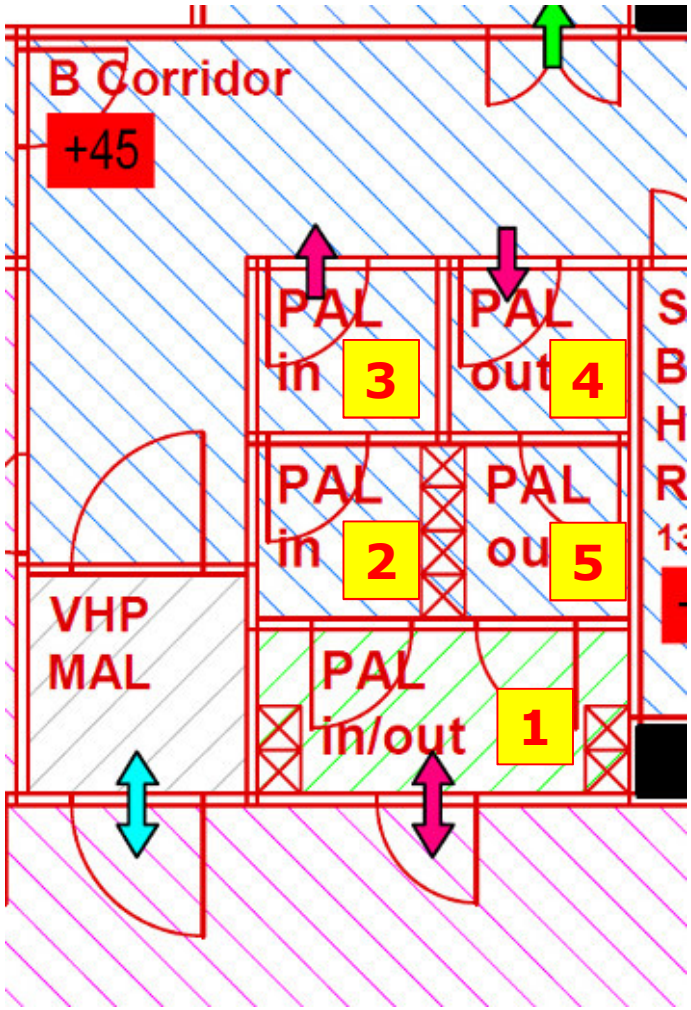
Gowning Concept: Example from grade D to grade B and backwards

PAL No.	Grade	Gowning procedure
1	C	**Entering grade B:** Taking off layer 2 for grade D **Leaving grade B:** - Putting on layer 2 for grade D - Verification of clothing in the mirror
2	B	- Putting on layer 2 for grade B out of pass-through locks - Verification of the clothing in the mirror - Glove disinfection
3	B	Walk through into grade B corridor
4	B	Walk through into grade B PAL out, leaving grade B corridor
5	B	Taking off layer 2 for grade B and put in pass-through locks



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Storage Area and Logical Flow of Material from Reception until Final Product Release

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Logical Material Reception and Release Flow: Storage Area[1]

- Sufficient size to allow orderly storage (material and product)
- Proper separation of all the different categories of material and products
- Ensure good storage conditions
- Clearly marked quarantine area
- Isolation of rejected, recalled or returned material/product
- Separate sampling area for starting materials

[1] WHO TRS 961, Annex 3, paragraph 12.15 - 12.22

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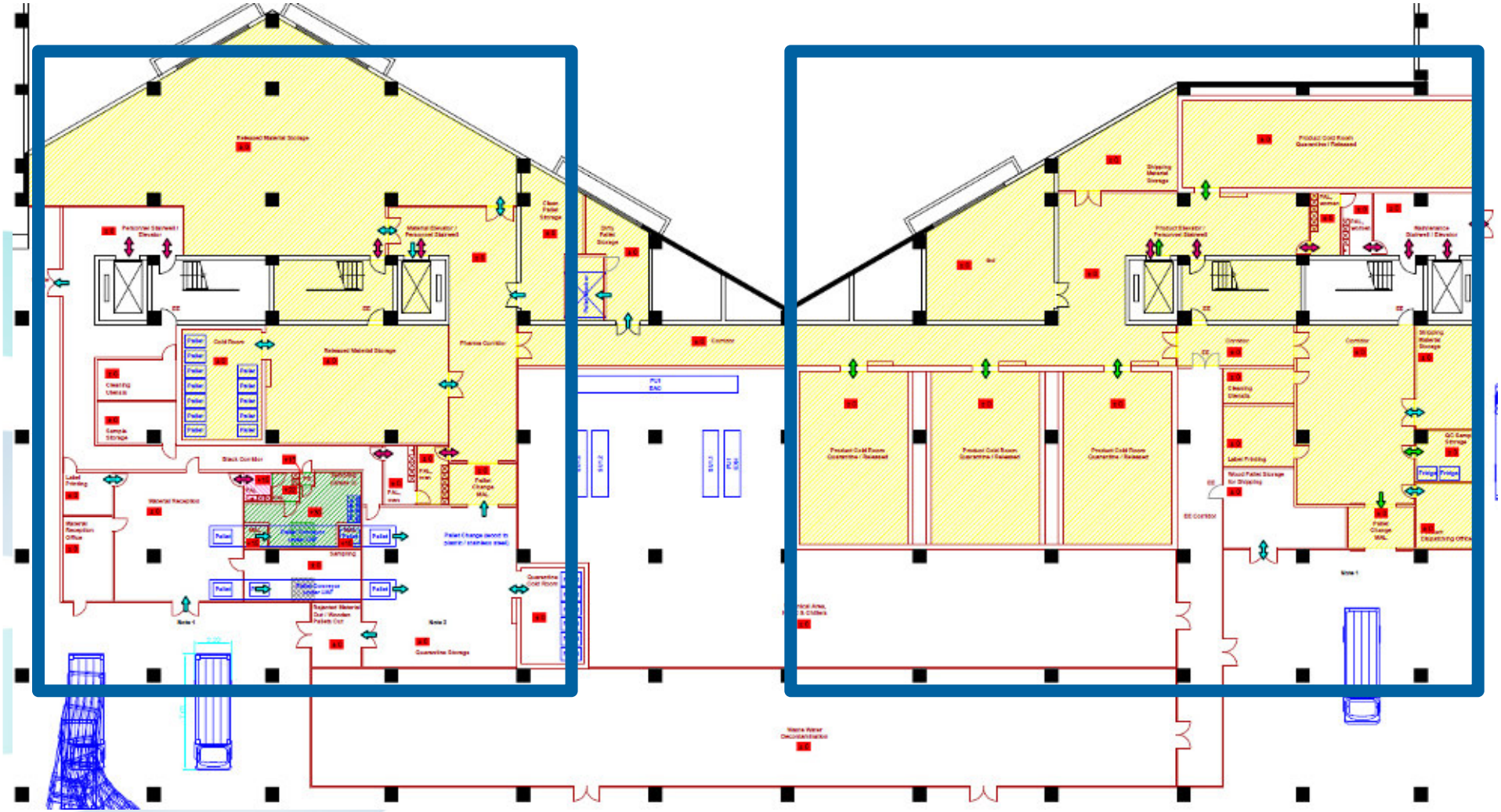
1. Material Reception

2. Quarantine

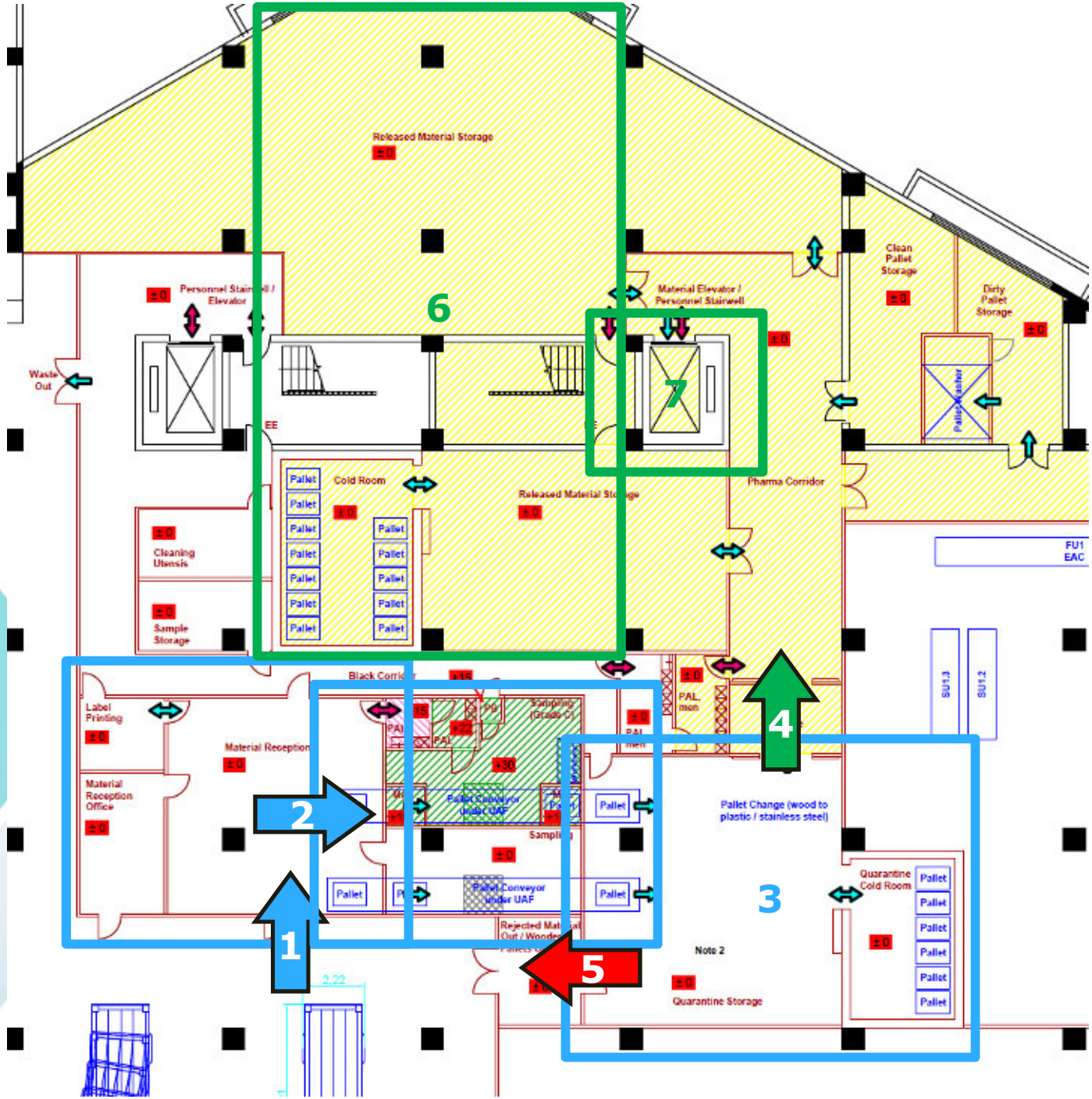


Grade CNC

1. Warehouse:

From the reception until the release of material

1. Material arrives and is labelled.
2. Samples are taken.
3. Material is stored in the quarantine area.
4. Material which fulfils requirements → transport into CNC released zone
5. Material which are out of specification are rejected and moved out of the facility.
6. Storage until use
7. Released material for production is brought to the production levels via elevators



Grade C
Grade D
Grade CNC

2. Quarantine Area:

From the final product to the shipping.

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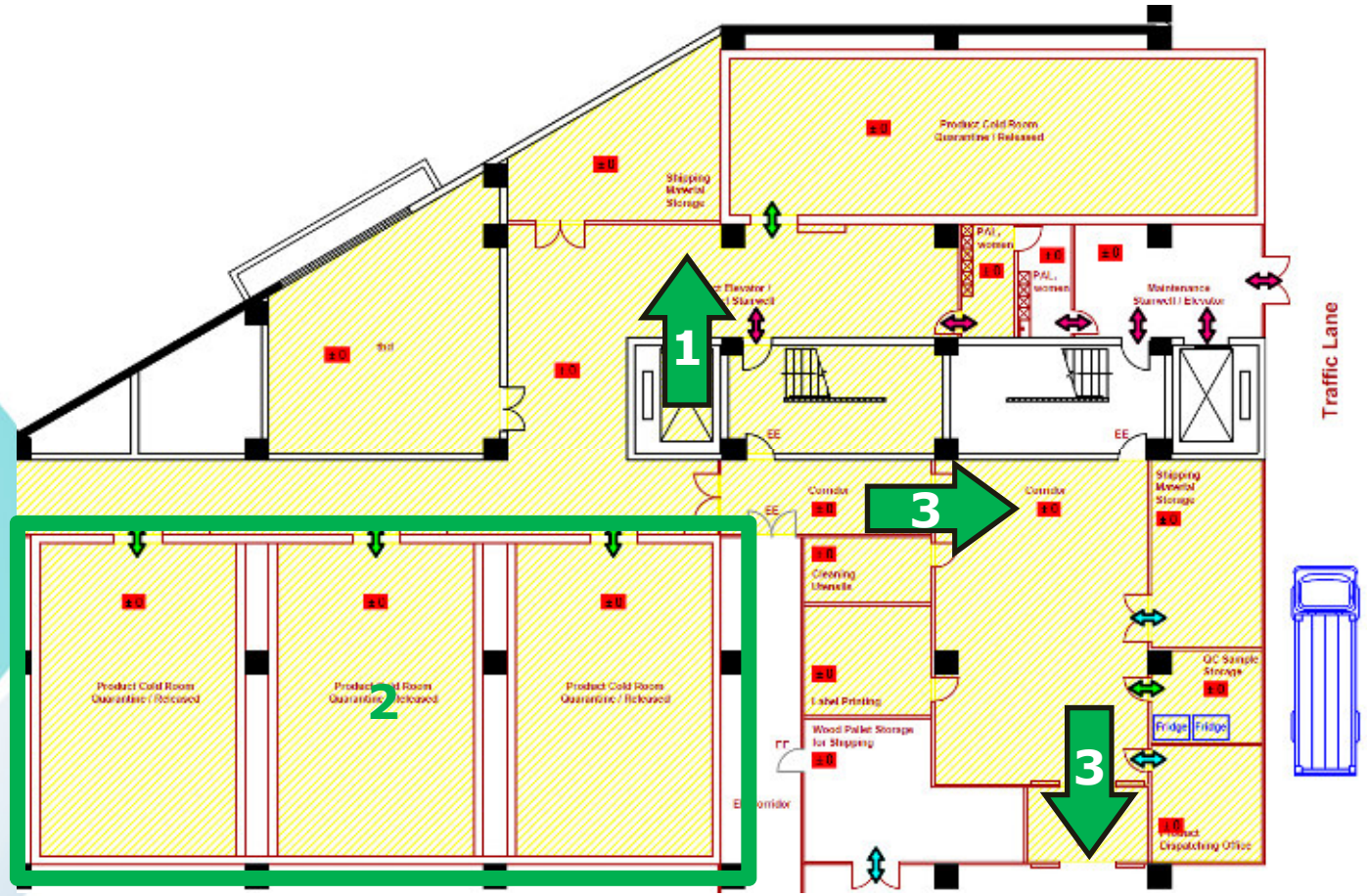
1. Product is brought from the production levels via elevators to the quarantine area.
2. Product is kept for the quarantine time in the appropriate room.
3. Product is prepared for shipping (labelled, etc.) and transported for selling.



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Production Area and Logical Flow of Material, Personnel and Product

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Logical Production Process Flow: Production Area (1)[1]

Production premises:

- → Laid out in a logical way for the production process (logical connection of different areas)
- → Logical position of working and in-process storage space (avoid the risk of cross-contamination, confusion or mistakes in the control measures)
- → Adequate space for working and in-process storage to place the equipment logically

[1] WHO TRS 961, Annex 3, paragraph 12.24 - 12.26

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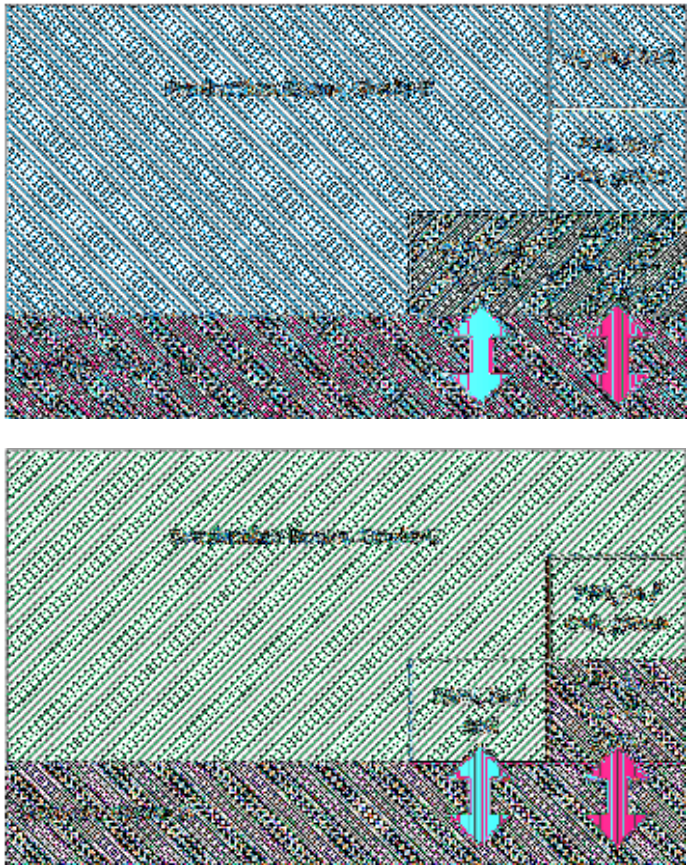
Logical Production Process Flow: Example
Normal Flow in Production Rooms

- Bidirectional flow of personnel and material
- Material and personnel airlocks are separated
- Airlocks for the flow between different clean room grades
- If the change is from grade D to grade B, instead of a normal MAL, an VHP MAL can be installed (VHP decontamination follows in few slides)



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Logical Production Process Flow: Example
mAb Production Facilities (Virus Risk Area)

Since upstream processing is based on cell culture fermentation, contamination of the mAb / protein product with viruses is one of the major production risks to be considered. Examples for potential sources of virus contamination can be:

- The use of an already contaminated master or working cell bench
- Introduction of virus contamination into the process by operators
- Residual (retro-) viral activity from the cell line design

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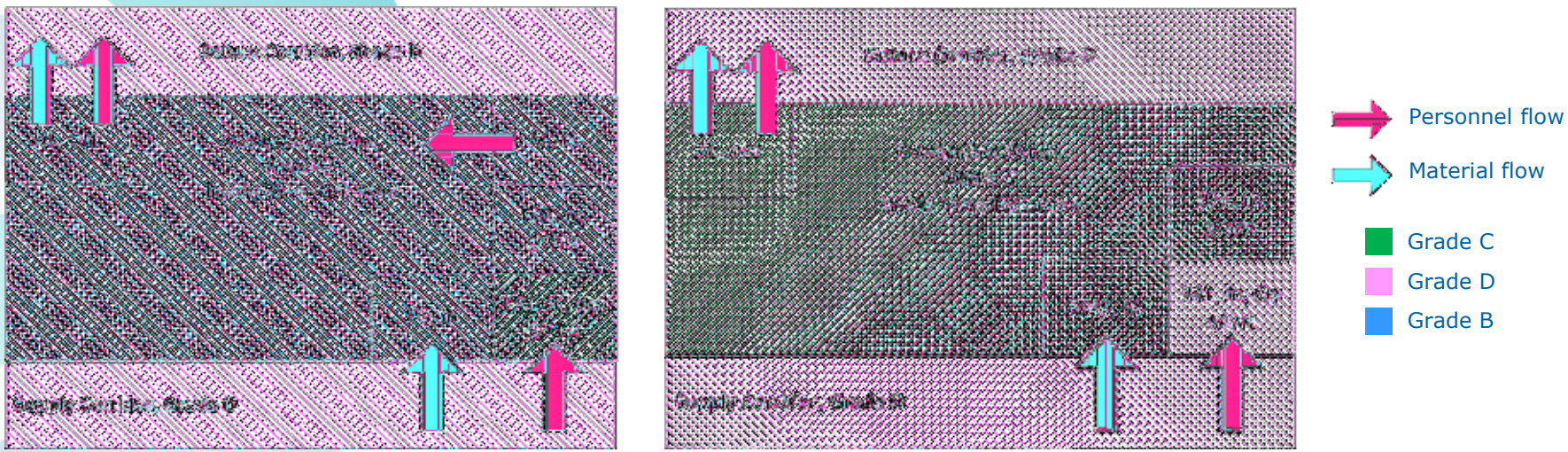
Logical Production Process Flow: Example
mAb Production Facilities (Virus Risk Area)

Material and Personnel Flow:

Minimize the risk of virus contamination by unidirectional flows (material and personnel) → splitting production facility into a supply and a return side



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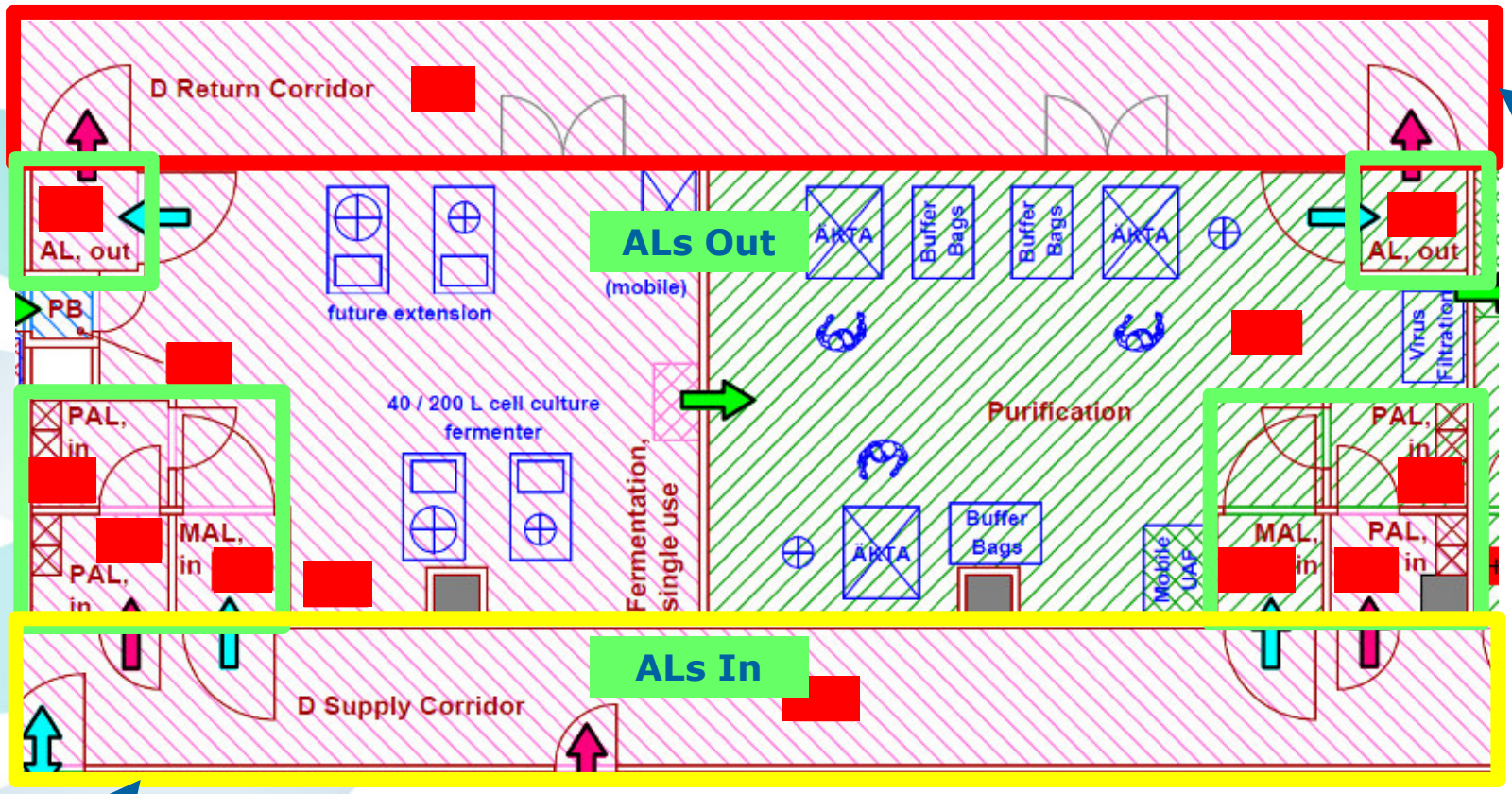
Logical Production Process Flow: Example
mAb Production Facilities (Virus Risk Area)



Return corridor

Supply corridor

Grade C

Grade D

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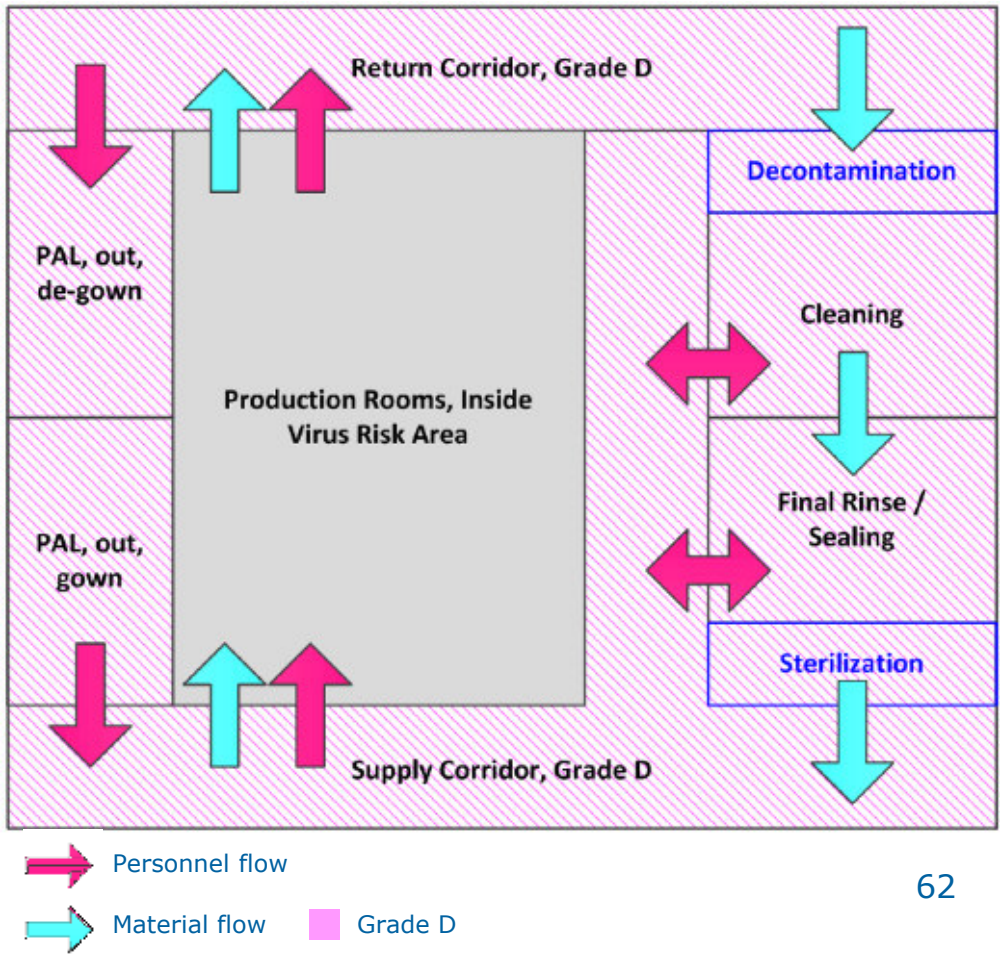
Logical Production Process Flow: Example
mAb Production Facilities (Virus Risk Area)

Material and Personnel Flow:

Flow back from return to supply side

- Personnel goes through separate PALs OUT back to the supply side
- Material goes via autoclave or decontamination chamber through a washing area to the supply side



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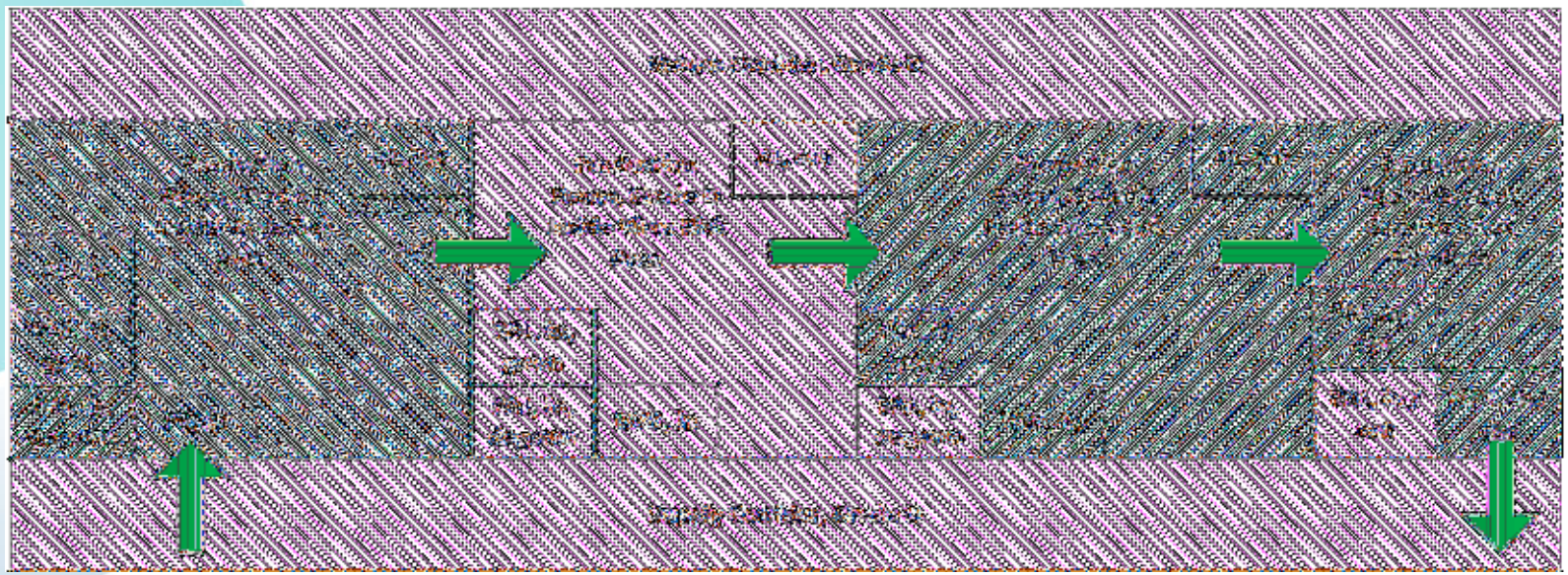
Logical Production Process Flow: Example
mAb Production Facilities (Virus Risk Area)

Product Flow:

The product never leaves the production rooms inside the virus risk area into the return corridor. It always stays in the production rooms, and the transport is through the walls (e.g. via pass boxes or via piping)



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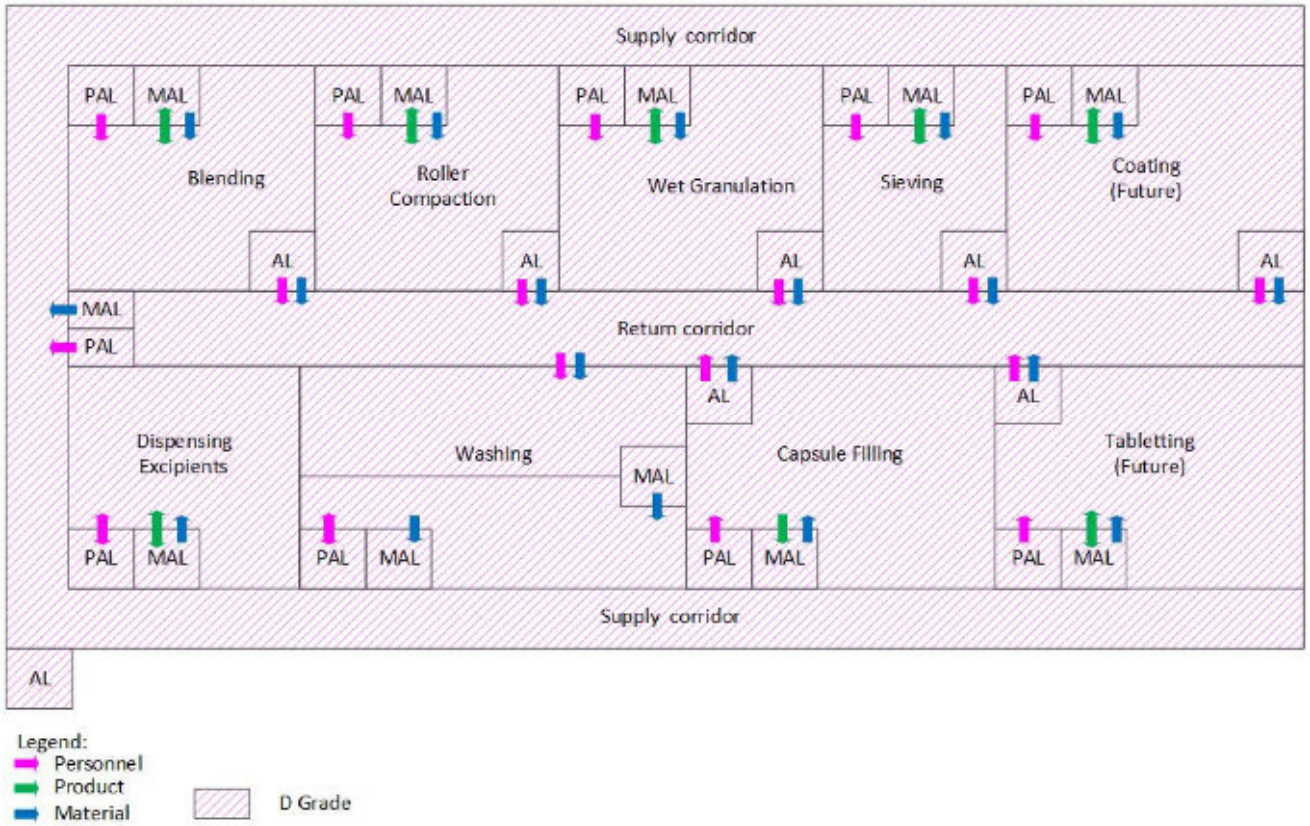
Logical Production Process Flow: Example
OSD (OSD = oral solid dosage) Facilities

Material/Personnel/ Product Flow:

Speciality of an OSD facility is that the **product** is always **going back** from the production rooms **into the supply corridor (in closed IBCs)**. Only material and personnel have to go through the facility in an unidirectional way.



Supply corridor

Grade D

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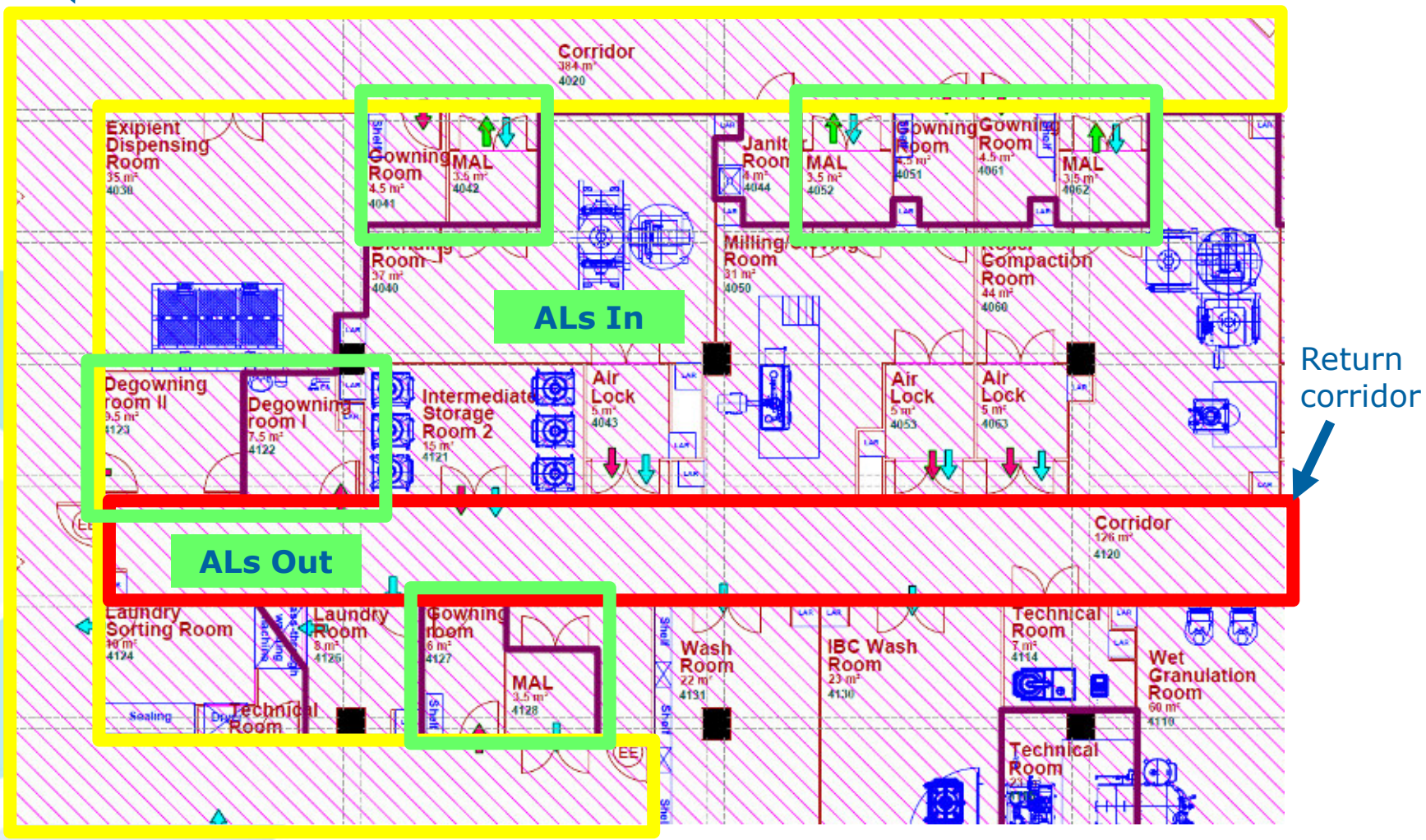

Logical Production Process Flow: Example OSD (OSD = oral solid dosage) Facilities

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Quality Control Area

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QC Area: General

- Separated from production area
  WHO TRS 961, Annex 3, paragraph 12.33

  → no definition of the meaning “separated”

- Sufficient space to avoid mix ups and cross-contamination
  WHO TRS 961, Annex 3, paragraph 12.34

- Appropriate storage space
  WHO TRS 961, Annex 3, paragraph 12.34

- Separation of air supply from laboratories and production area
  WHO TRS 961, Annex 3, paragraph 12.35

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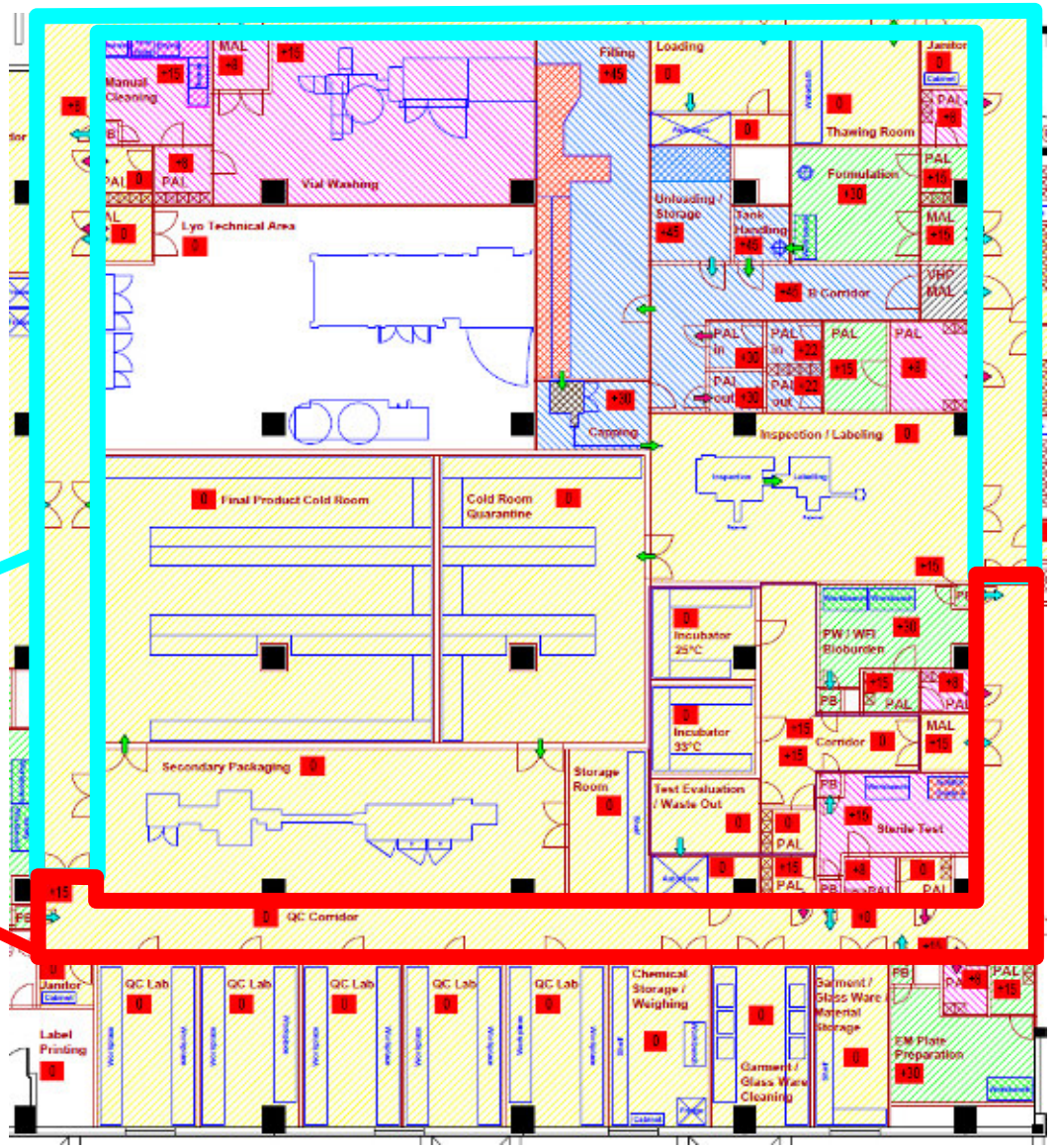
Example:
Separation QC & Production Area (Spatial Separation)

Minimum of separation:

Two different corridors connected by doors

Production Area Corridor

QC Area Corridor



- Grade C
- Grade D
- Grade CNC

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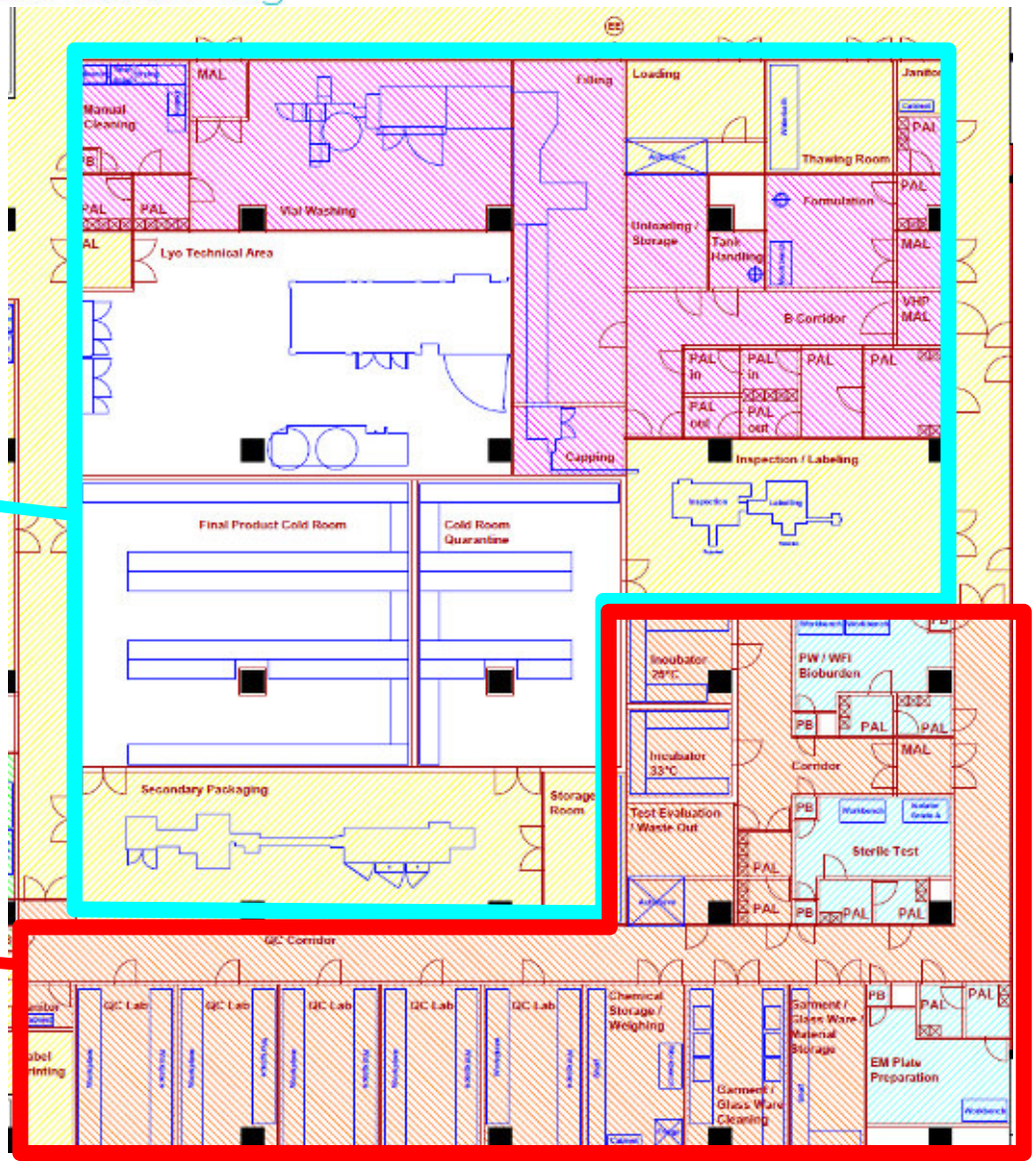
Example:
Separation QC & Production Area (Separation of Air Supply System)



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Further Questions?