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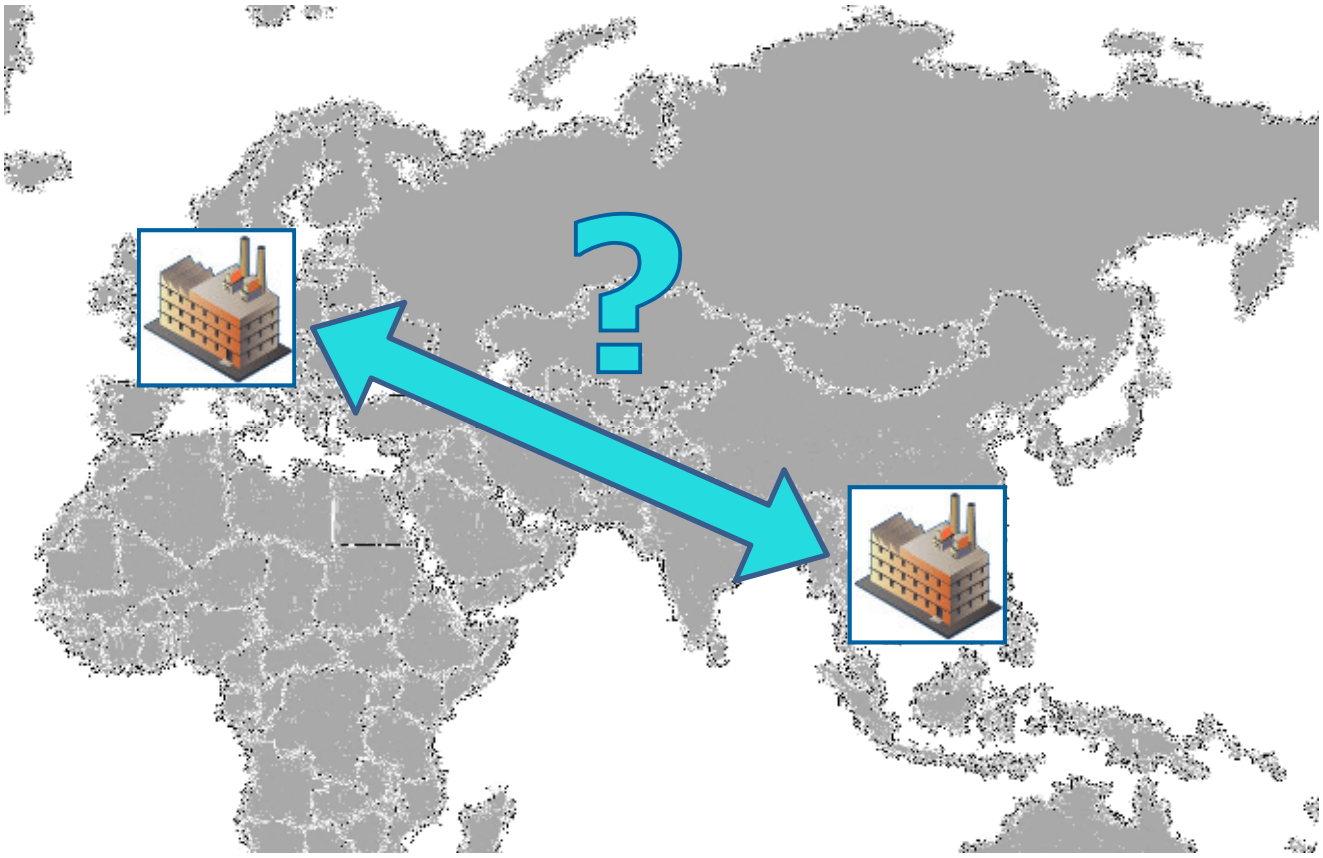

Differences in the Facility Design, Europe & Asian Developing Countries

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Presentation Contents

Facility design differences between Europe and Asian developing countries will be discussed based on some examples:

- Personnel / material air lock design
- Clean room floor construction options
- UAF areas for autoclave unloading
- Design of aseptic filling facilities (room arrangements, RABS / isolator design)
- Design of exhaust HEPA filter housings
- Design of technical areas
- Project schedule / realization time

For questions marked in red, the audience is invited to provide answers and suggestions

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Personnel Air Lock Design

Regulatory requirements:

- Required to separate different areas (e.g. different clean room grades, bio-positive & bio-negative areas, etc.)
- Different clean room grades must be cascaded
- Door interlock
- Furniture requirements: Hand wash sinks, hand disinfection, mirror, locker cabinets, etc.
- Step-over bench (for shoes change) to divide rooms into a «clean» and «less clean» side

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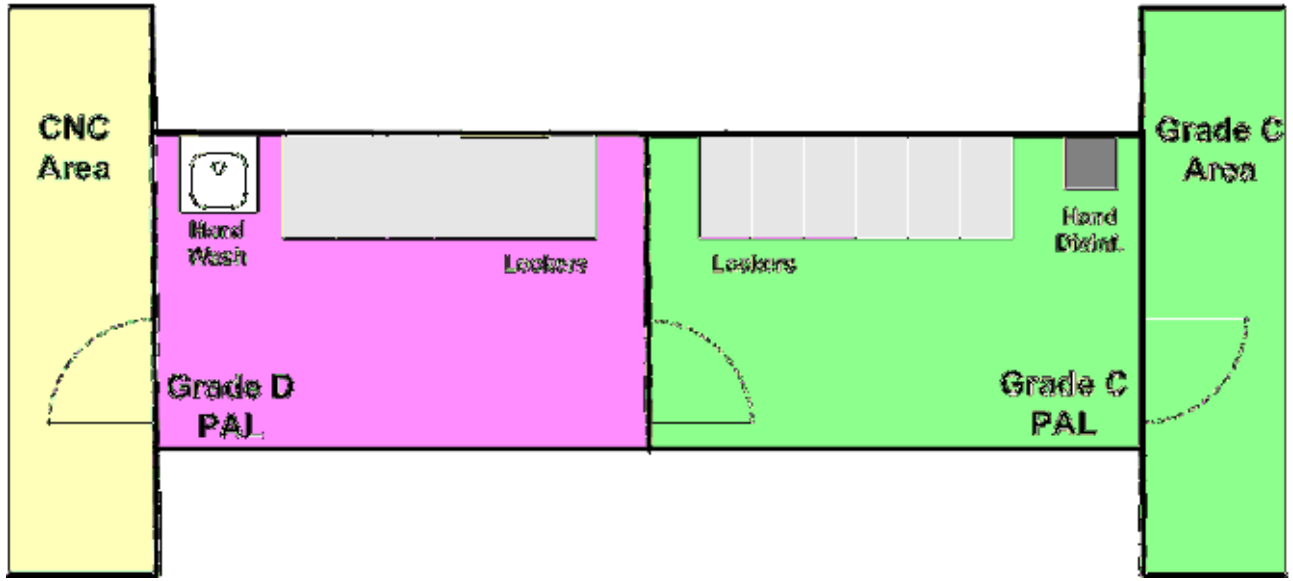
Personnel Air Lock Design

Typical design example found in Asian facilities:



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Personnel Air Lock Design

Typical design example found in Asian facilities:

- Room grades are cascaded: CNC => D => C
- One room to take off the CNC garments, one room to don the grade C garments
- One clean room grade per room

=> The big question: Where shall the step-over bench be placed…?

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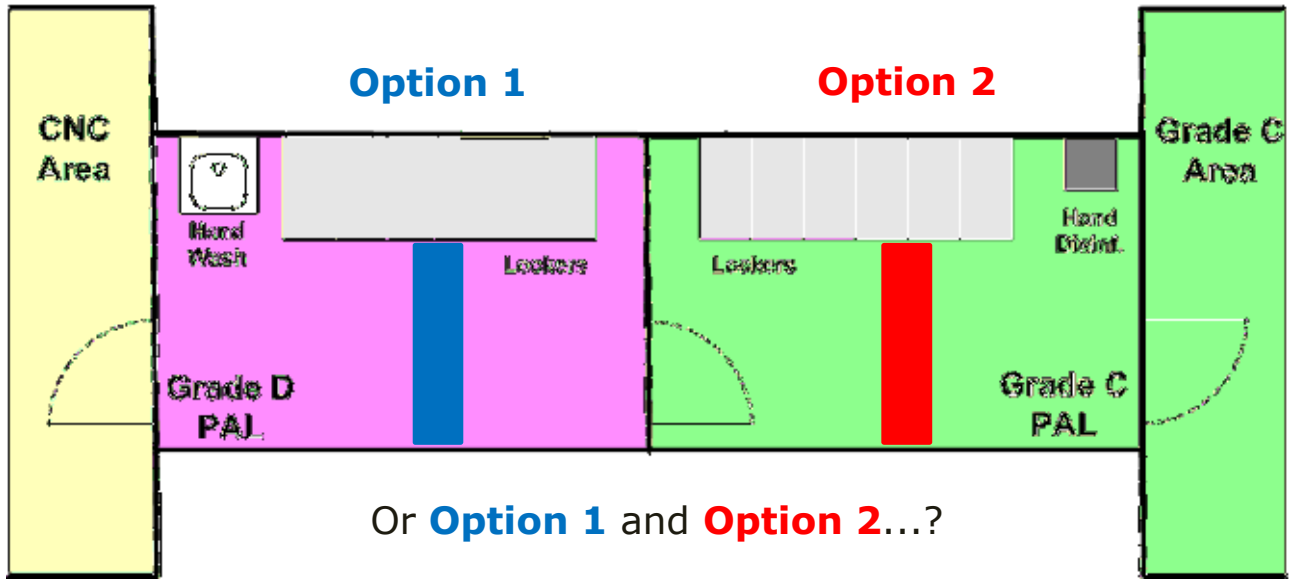
Personnel Air Lock Design

Position of the step-over bench:



Or **Option 1** and **Option 2**...?

Which is the best solution, and why...? Suggestions...?

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Personnel Air Lock Design

Problems with placing the step-over bench:

- According to the guidelines, a step-over bench (shoes change) should be used to separate the clean area from the less clean area
- However, the requirements for grade D or C are strictly defined, there is e.g. no "grade C less clean" classification
- Since the shoes should be changed while crossing the step-over bench, the following problems exist with option 1 and/or option 2 on the slide before:

=> Surface contamination (bioburden) is transferred via the shoes from CNC to D and from D to C

Suggestions to solve this problem…?

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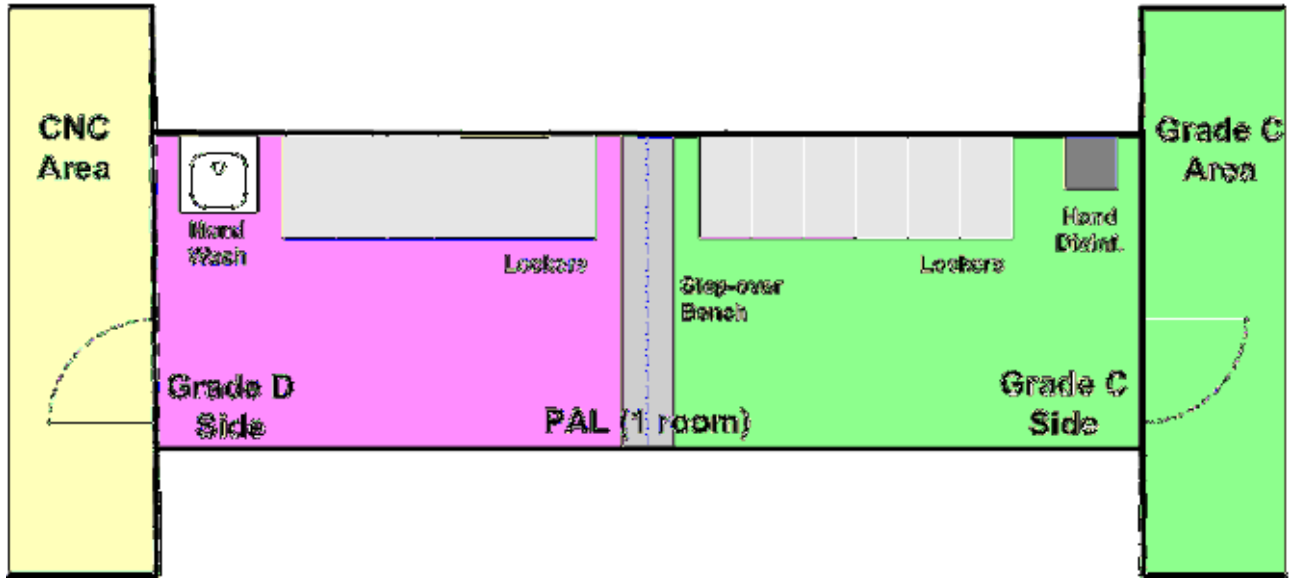
Personnel Air Lock Design

Typical design example found in European facilities:



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Personnel Air Lock Design

Typical design example found in European facilities:

- Room grades are cascaded (CNC => D => C), but in one common PAL room
- The PAL room is separated into a D side (less clean) and a C side (clean) by the step-over bench
- CNC garments are left on the D side, C garments are donned on the C side

=> How can one room be classified with 2 different clean room grades...?

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Personnel Air Lock Design

Typical design example found in European facilities, monitoring limits:

	D Side	C Side
Air quality, particles	Grade C limits	Grade C limits
Air quality, microbio. contamination	Grade C limits	Grade C limits
Surface cleanliness, microbio. contamin.	**Grade D** limits	Grade C limits

To achieve a grade C air quality in the whole room, also on the D side, is relatively easy. This mainly depends on the kind of HEPA filter used, the **air change rate** and the pressure cascade

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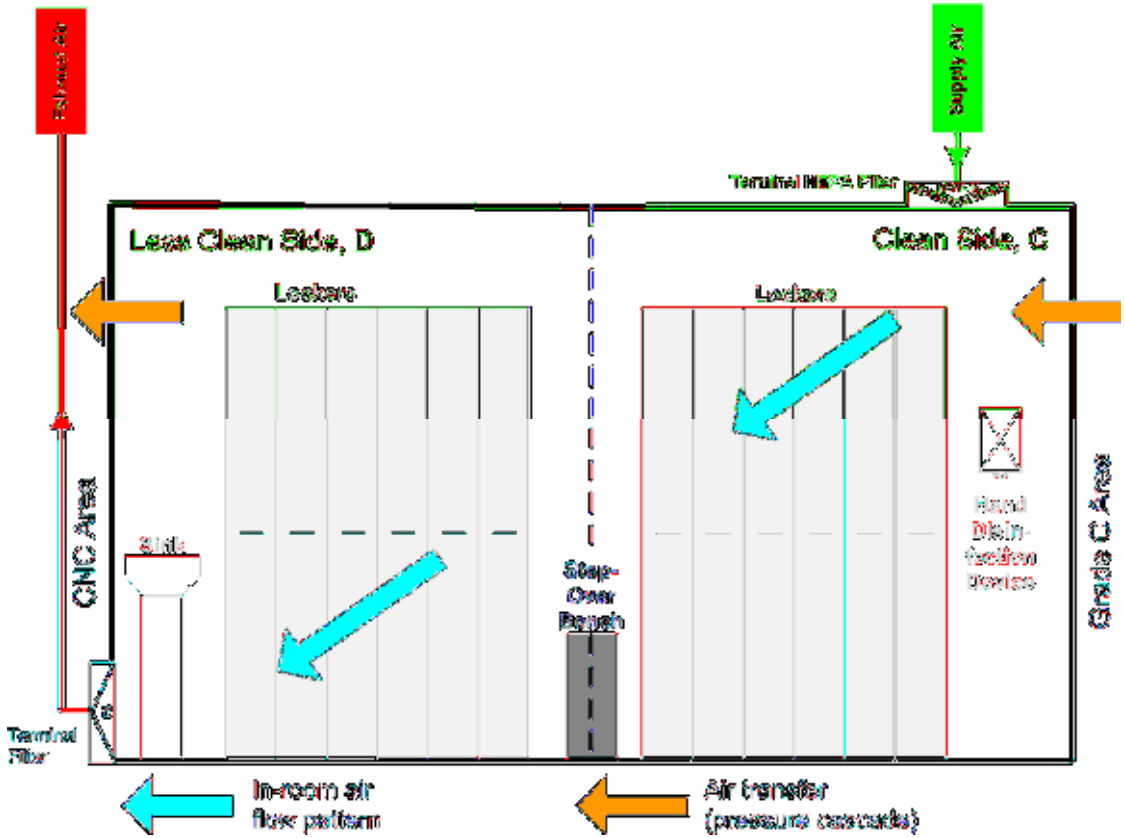
Personnel Air Lock Design

Keeping grade C air quality on the D side:



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Personnel Air Lock Design

Surface cleanliness, microbiological contamination:

- While maintaining a grade C air quality in the whole room is relatively easy, the true challenge is to control the surface cleanliness (because personnel transfers contamination from one area to another)
- In the example above, bioburden is transferred from CNC to the D side (e.g. via the shoes), which has been accepted (less critical bioburden requirements for D)
- The transfer from D to C has been realized with regard to minimization of the bioburden carry-over risk (position of the step-over bench, C is the critical production area)

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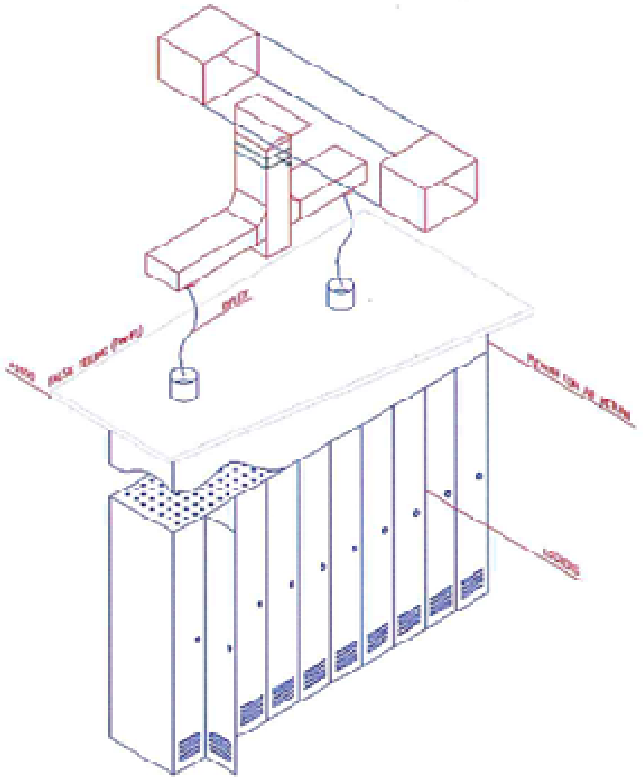
Personnel Air Lock Design

Locker cabinets connected to the exhaust air, for smelly shoes or wet clothes:



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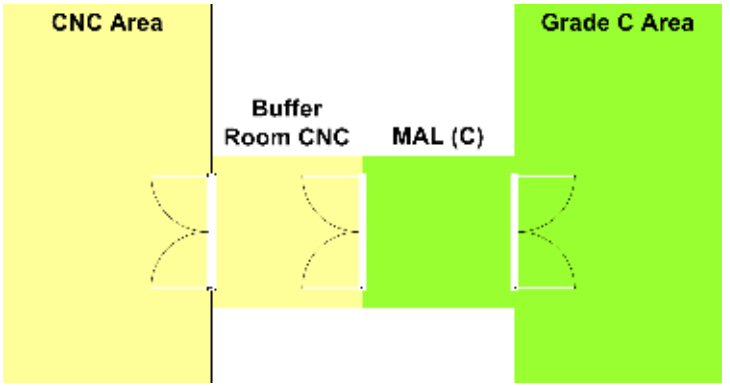
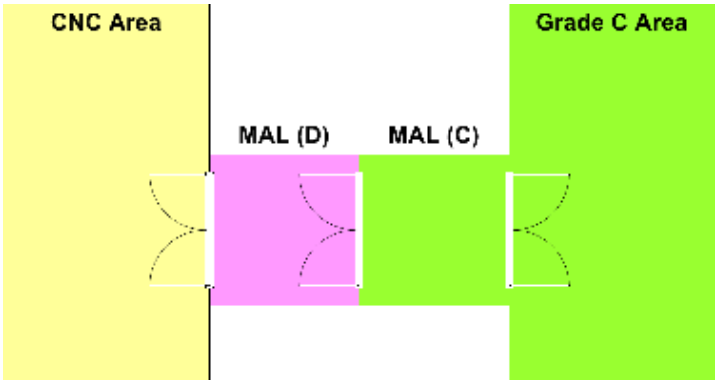
Material Air Lock Design

Typical examples found in Asian facilities for transfers from CNC to C:

What are the advantages...





...and disadvantages of these design options?

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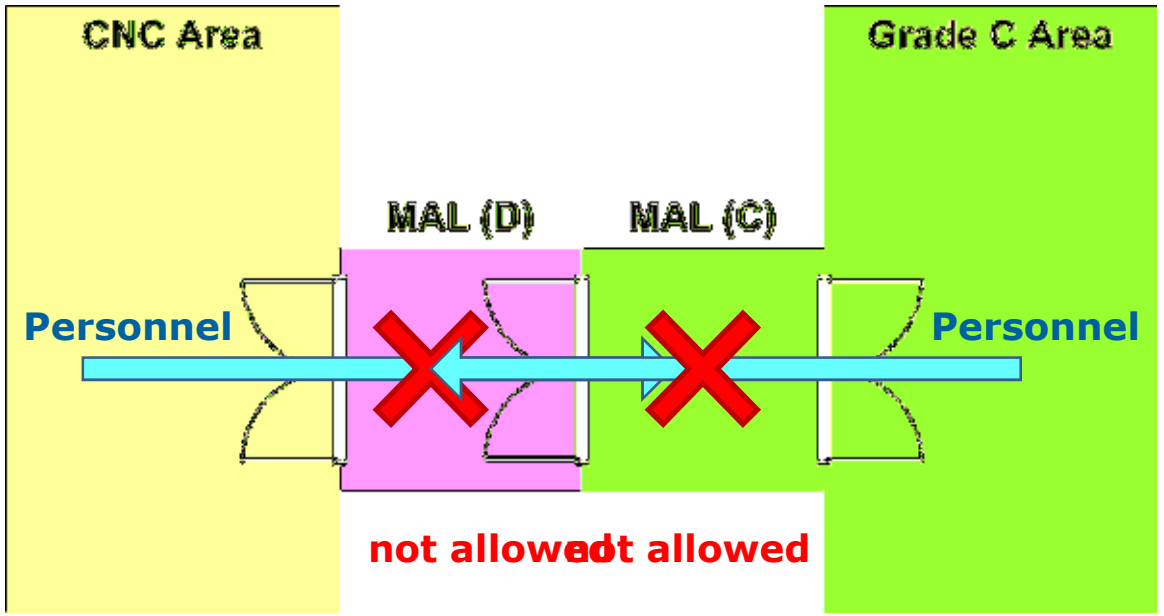
Material Air Lock Design

Problems with example 1, CNC => D => C:



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Material Air Lock Design

Problems with example 1, CNC => D => C:

- Personnel should not enter the grade D MAL from the CNC side (different grades, no PAL)
- Personnel should not enter the grade D MAL from the C side (different grades, no PAL)
- The only option would be to realize the transfer **without personnel entering the D MAL** (only the material enters the D MAL, which may be difficult to realize)
- In this case, the number of disinfection steps has to be discussed then: Two? From CNC to D and from D to C?

=> Suboptimal solution

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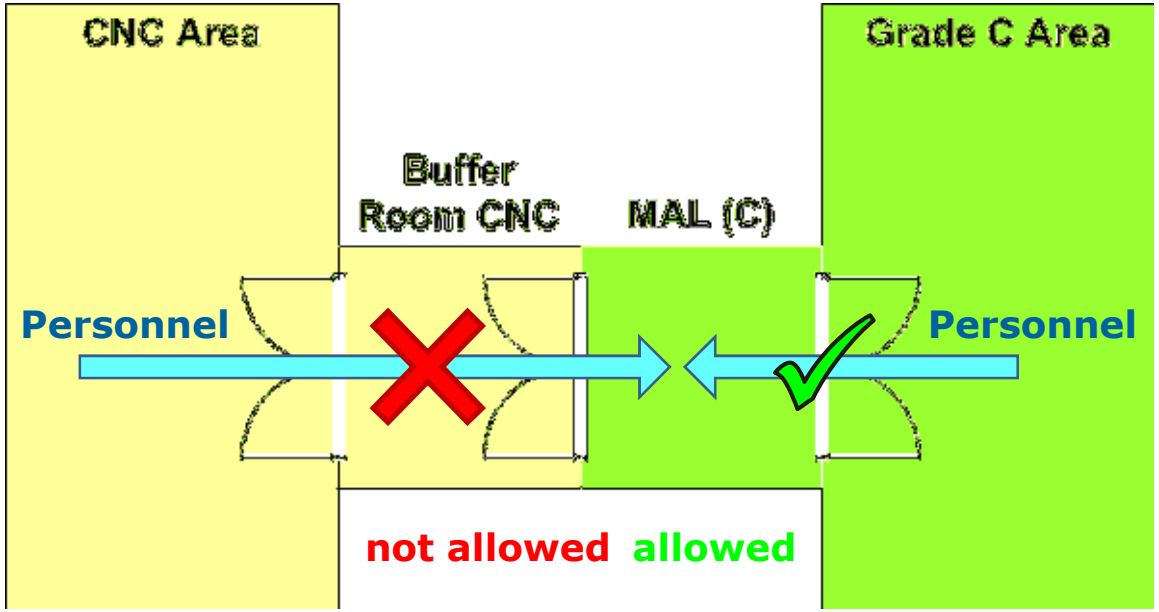
Material Air Lock Design

Problems with example 2, CNC => CNC => C:



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Material Air Lock Design

Problems with example 2, CNC => CNC => C:

- Personnel should not enter the grade C MAL from the CNC side (different grades, no PAL) => material has to be loaded / unloaded from the MAL without personnel entering the MAL
- Personnel can enter the grade C MAL from the C area to load / unload material
- The need for a buffer room should be questioned, because it has the same classification as the rest of the CNC area (which is even no formal clean room grade)
- The buffer room does not contribute to the prevention of contamination carry-over, only complicates the material transfer procedure

=> Better, but still suboptimal solution

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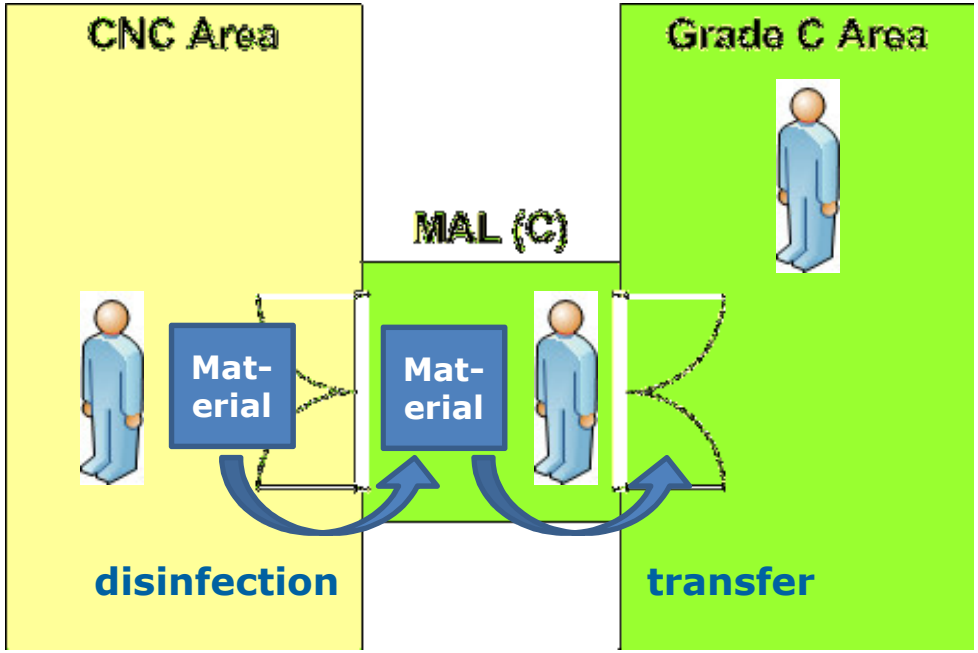
Material Air Lock Design

Optimized solution CNC => C in one MAL:



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Material Air Lock Design

Optimized solution CNC => C in one MAL:

- Again, to achieve grade C limits (particles and bioburden) for the air in the MAL is not a problem. This mainly depends on the HEPA filter used, air change rate and the interlock time for air flushing
- The true challenge is again to control the bioburden on the surfaces
- An adequate disinfection procedure is needed for material transfers from CNC to C
- For critical transfers (e.g. CNC directly to B, or materials with complicated surfaces which are hard to disinfect manually), e.g. VHP fumigation should be considered

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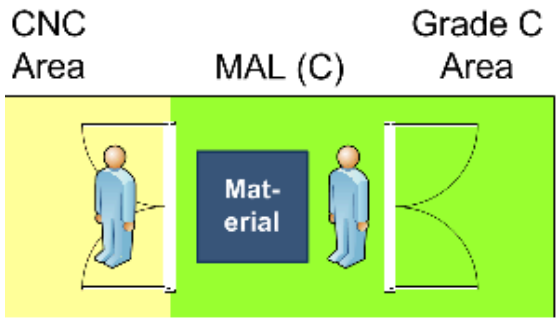
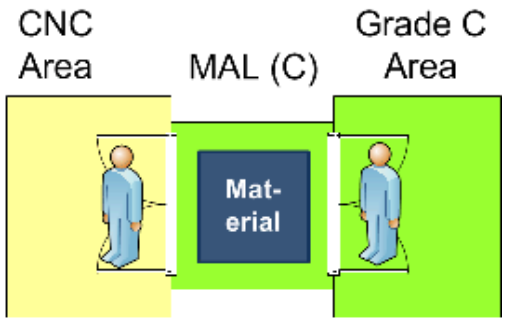
Material Air Lock Design

MAL sizes for material transfer:

- Generally, the smallest possible MAL size is the best => minimization of the contamination carry-over risk
- The risk is lowest for e.g. a small pass-through box because in such a box, all the inner surfaces can be disinfected easily as well



OK



Better

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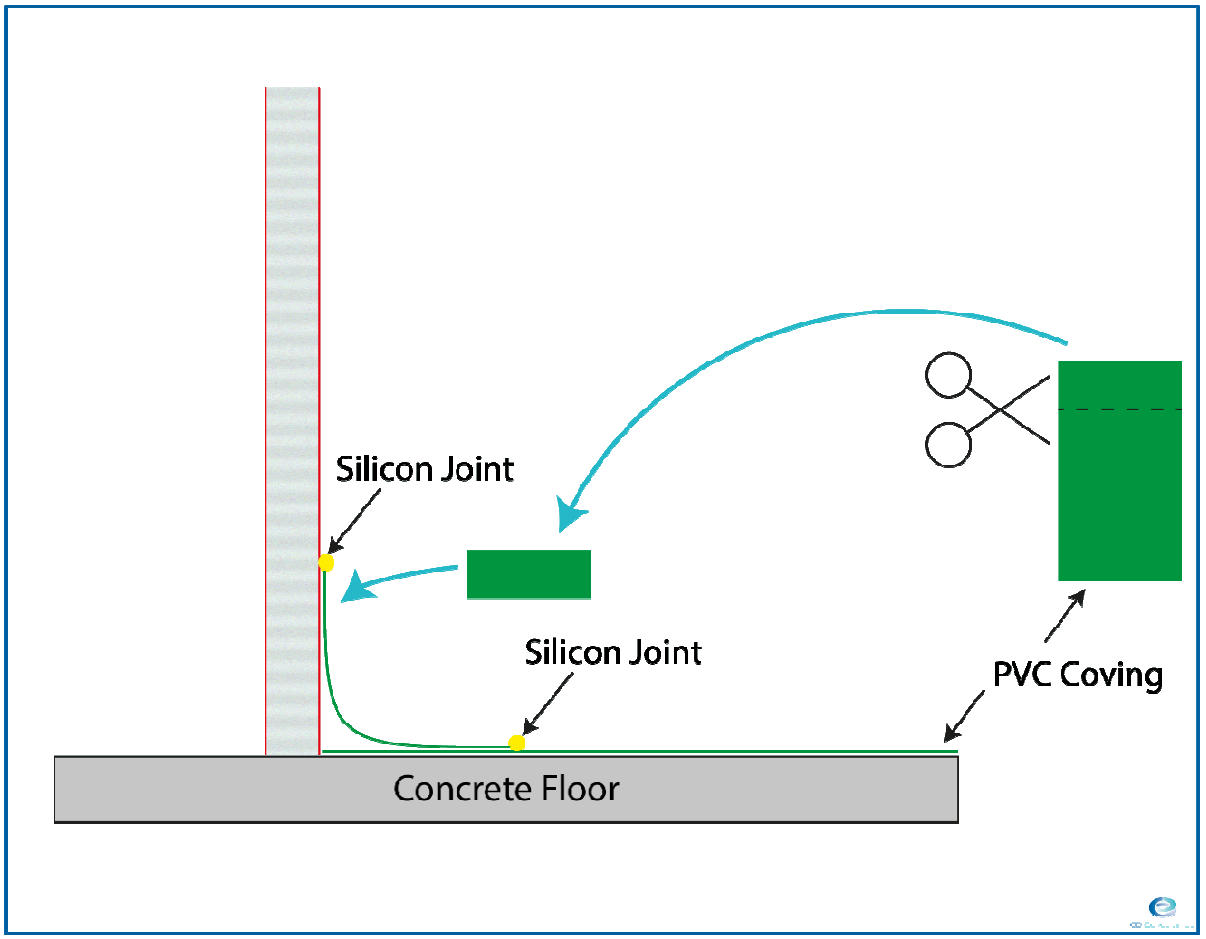
Clean Room Construction

1. Option from Asia:

1. Concrete floor
2. Clean room walls
3. PVC floor cover / coving
4. Cut a piece of the PVC floor cover to serve as coving, and put it close to the clean room walls
5. Close the gaps with silicon joints



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Clean Room Construction

1. No chamfer (support below the coving)
2. Not really easy to clean because of irregularities
3. Easy to damage
4. Complicated construction
5. Floor cover is not continuous

Why is this option suboptimal?

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Clean Room Construction – Examples Option 1

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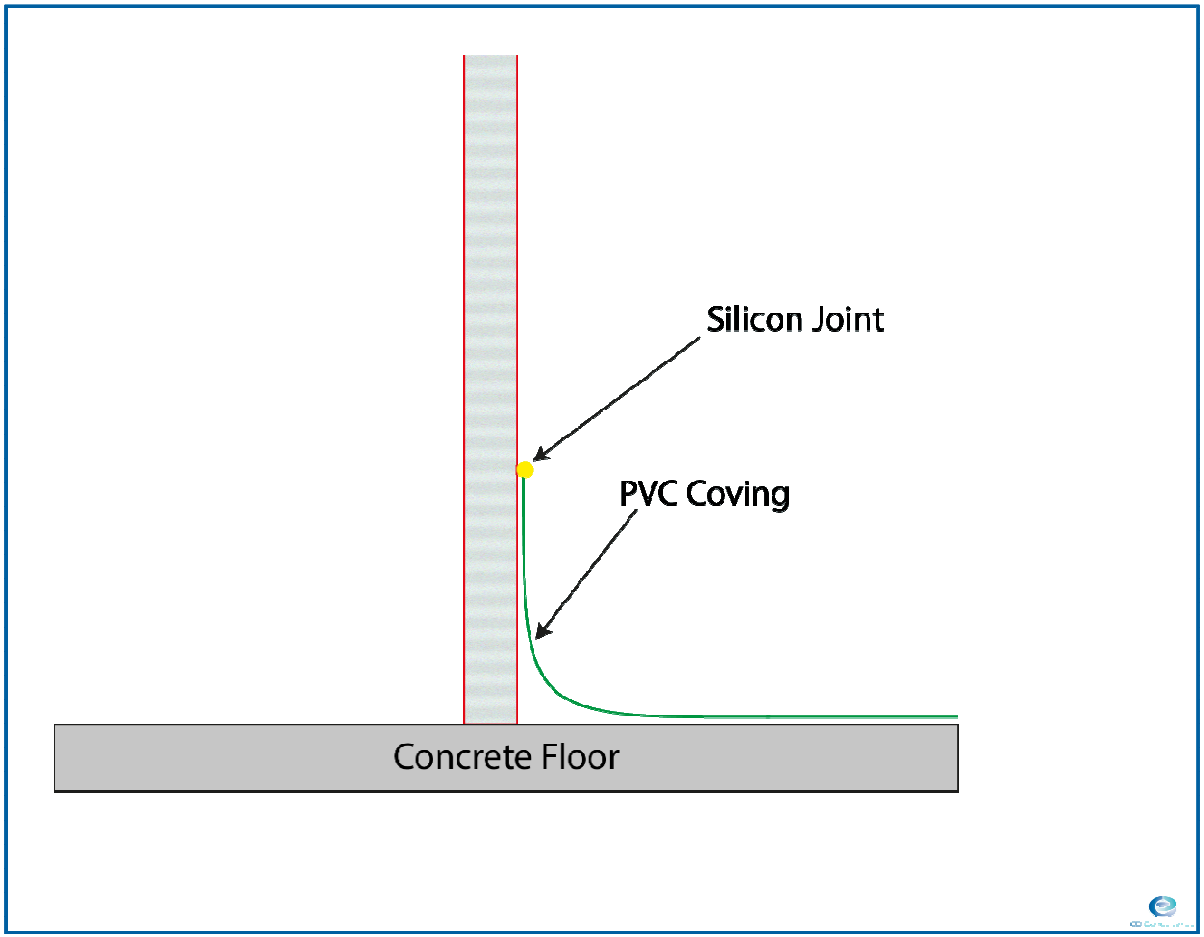
Clean Room Construction

2. Option from Asia:

1. Concrete floor
2. Clean room walls
3. PVC coving → one piece overlapping the clean room wall (the floor cover directly covers a part of the wall panels)
4. Close the gaps with silicon joint



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Clean Room Construction

Less worse than option 1 because the floor and coving is one piece, but…

1. No chamfer (support below the coving)
2. May not be easy to clean because of irregularities
3. Easy to damage (no support below coving)
4. Difficult corner construction
5. Floor cover is not continuous

Why is this option suboptimal?

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Clean Room Construction – Examples Option 2

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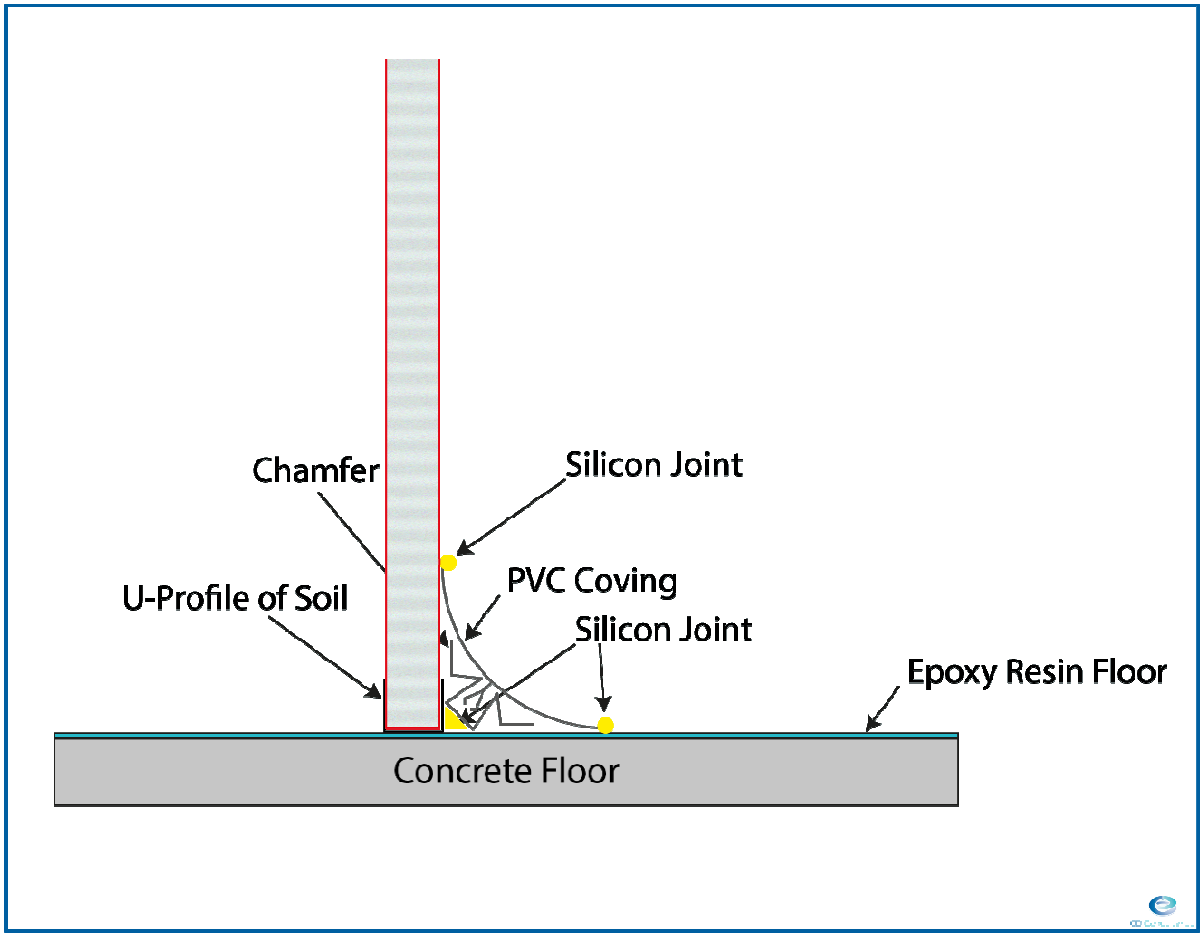
Clean Room Construction

3. Option from EU:

1. Concrete floor
2. Epoxy floor
3. Install U-profile for clean room walls
4. Fix clean room walls into U-profile
5. Put silicon joint between wall and floor
6. Fix chamfer onto silicon joint
7. PVC coving for covering chamfer
8. Close the gaps with silicon joint



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Clean Room Construction

Better because…

- Stability of the construction, chamfer (support) below the coving
- Continuous floor cover in one piece
- Can be cleaned / decontaminated / disinfected to a high degree

But…

- Complex installation

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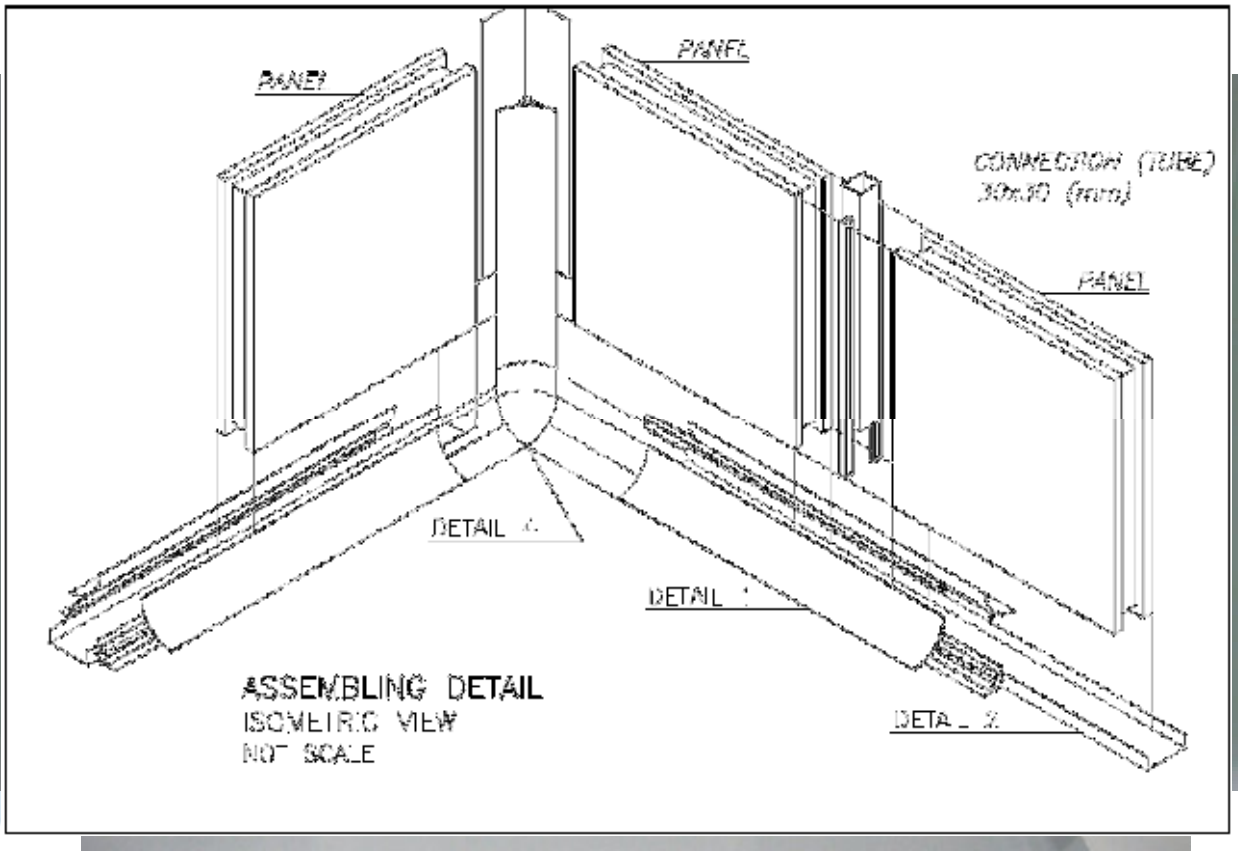
Clean Room Construction – Examples Option 3



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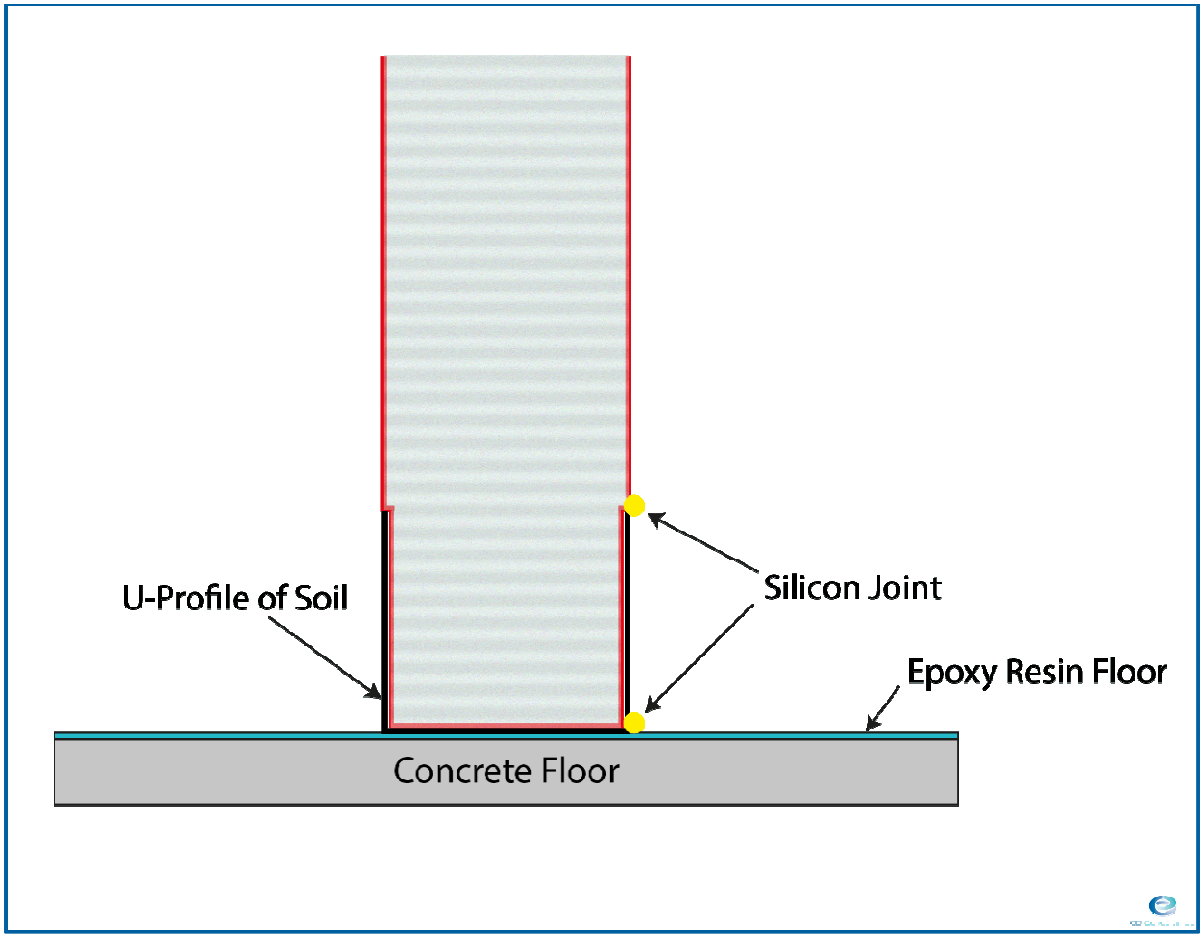
Clean Room Construction

4. Option from EU:

1. Concrete floor
2. Epoxy floor
3. Install U-profile for clean room walls
4. Fix clean room walls into U-profile
5. Put silicon joint between the U-profile and the floor, and between the U-profile and the wall panel



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Clean Room Construction

The best option because…

- Simple construction
- Easy to clean as well, although there is no coving
- Air-tight to a high degree if silicone joints are made properly
- Continuous floor cover in one piece
- Modification of the clean room structure (repositioning of walls) is relatively easy

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Clean Room Construction – Examples
Option 4, Walls and Windows

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Clean Room Construction – Examples
Option 4, Stainless Steel Wall Panels

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Clean Room Construction – Examples
Option 4, Glass Wall Panels

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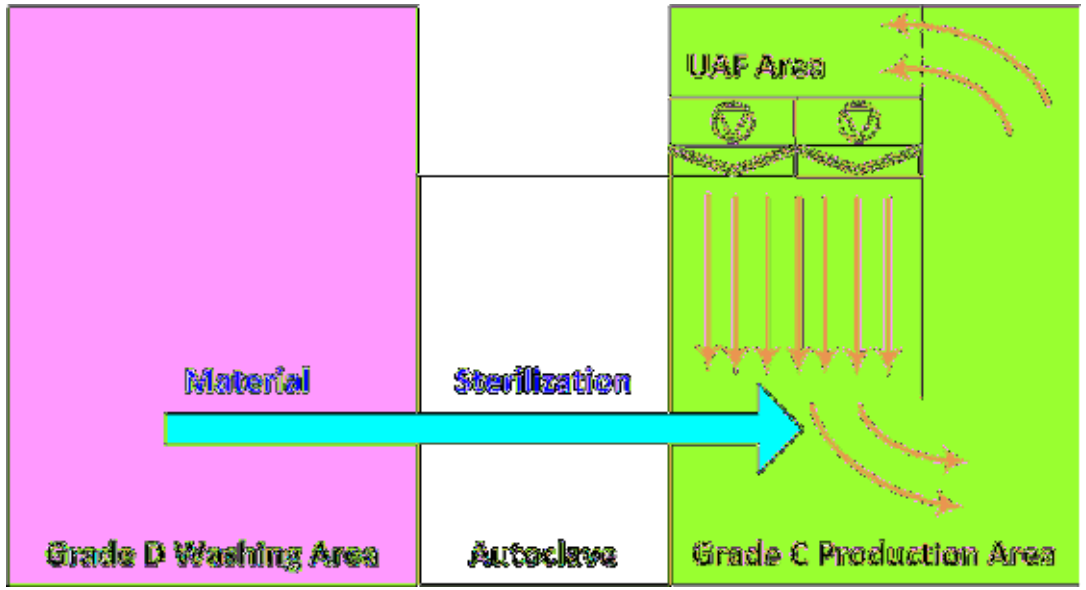
UAF for Autoclave Unloading

Situation sometimes found in Asian facilities:



What is the purpose of the grade C UAF area…?

(or similarly, unloading in B / B UAF)

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UAF for Autoclave Unloading

Purpose of the UAF for autoclave unloading:

- Is the UAF used to handle sterile goods openly (e.g. assembling operations or closing of bottles)?
- Is a grade C UAF suitable to handle sterile goods (aseptically)?

- Problem: If sterile goods really must be handled aseptically, an A in B area would be required. This area might be quite large to unload an autoclave, with operators having to walk into this area, which should not be the case for grade A
- Better solution: Prepare the goods to be sterilized in a way that they will remain sterile if unloaded into a standard clean room (without UAF)

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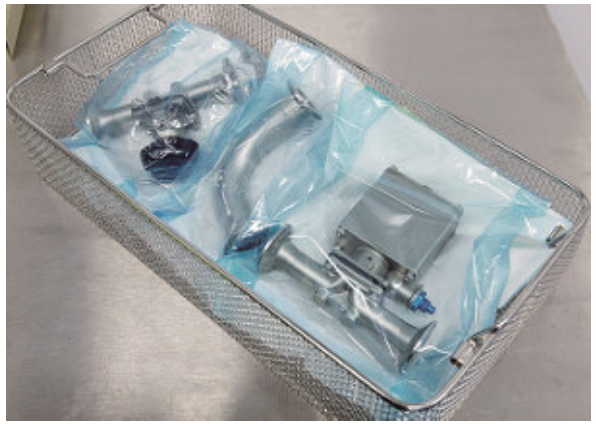
UAF for Autoclave Unloading

Examples for proper preparation of goods for sterilization:



Packing and sealing of goods in steam-permeable bags

Pre-assembling with vent filters which are gas-permeable

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Design of Filling Lines (Grade A/B)

Typical design found in Asian facilities:

- One independent clean room compartment per filling line (with dedicated airlocks, corridor, washing area, etc.)
- Each process step (e.g. vial washing / sterilization, filling, capping) is performed in a separate room
- Different environment (clean room grade) for different process steps

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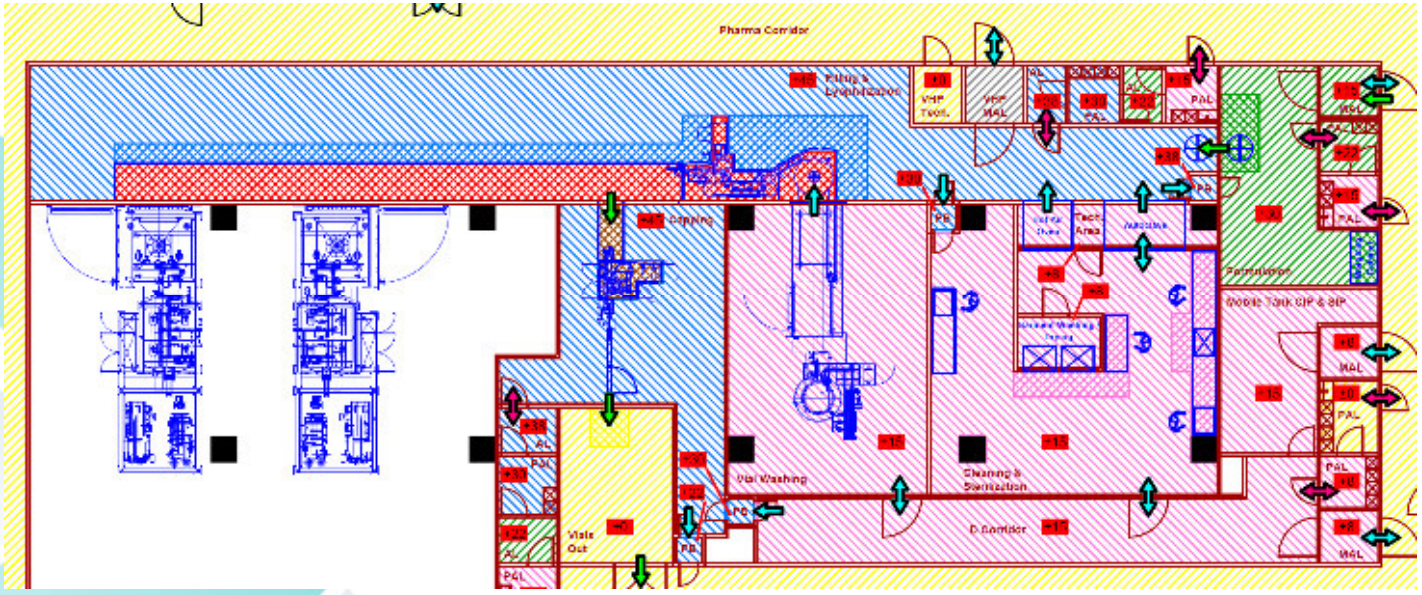
Design of Filling Lines (Grade A/B), Layout Example Asia



Lyo-Line, Grade A/B Design, 5 Rooms

Each process step has its own room with different clean room grades

→ Designed in this way a large area / many rooms are needed

→ More complex material, product and personnel flows result

Room No.	Process	Grade
1	Washing / Steri.	D
2	Filling	A/B
3	Capping	B
4	Vials out	CNC
5	Lyo technic	Black

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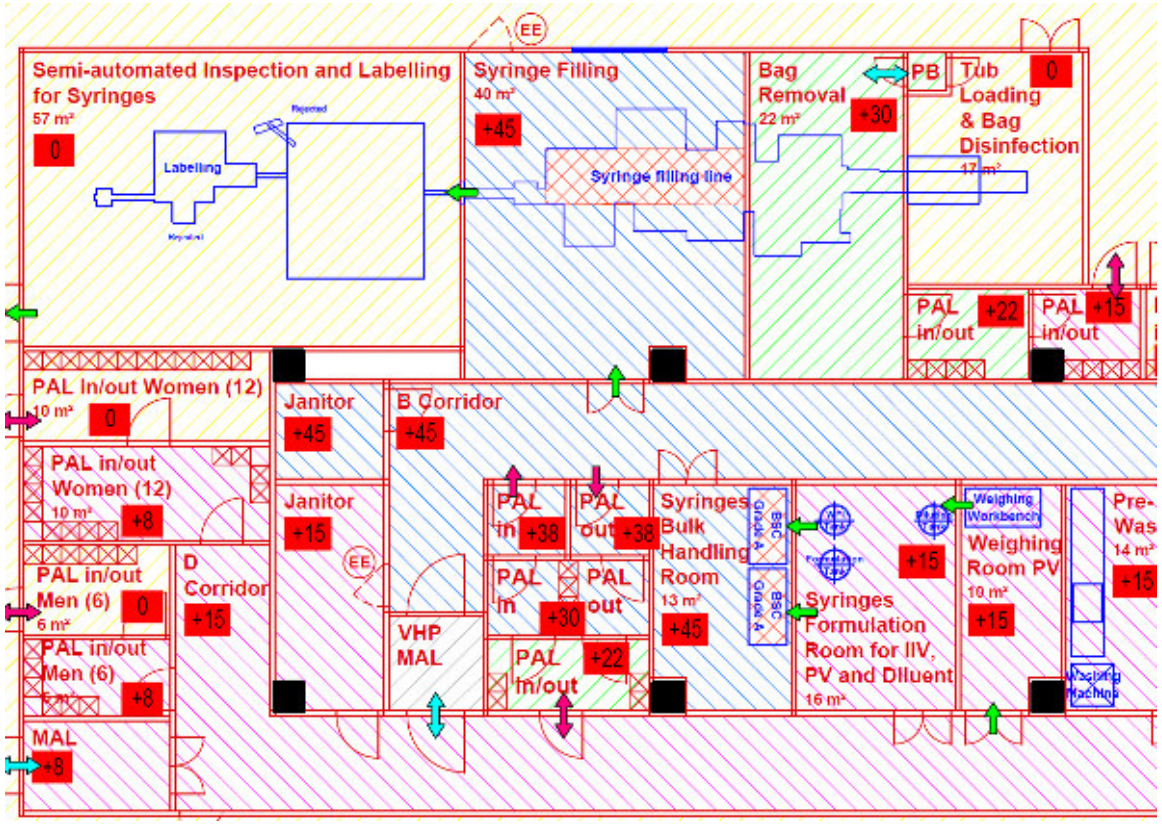
Design of Filling Lines (Grade A/B), Layout Example Asia

Syringe Filling Line, A/B Design, 4 Rooms

Same points as mentioned above apply

Room No.	Process	Grade
1	Loading	CNC
2	Bag removal	C
3	Filling	A/B
4	Syringes out	CNC



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Design of Filling Lines (Grade A/B)

Design option found in European facilities:

- Multiple filling lines (different products) are located in the same clean room compartment (common corridor)
- Product separation is achieved by a dedicated AHU per product / filling line, and by a suitable pressure cascade
- Multiple process steps can be performed in the same room, particularly if there is no open product handling involved (e.g. vial washing, unloading of capped vials)
- Segregation by appropriate equipment design (e.g. enclosure around the vial washer, connected to the exhaust air)

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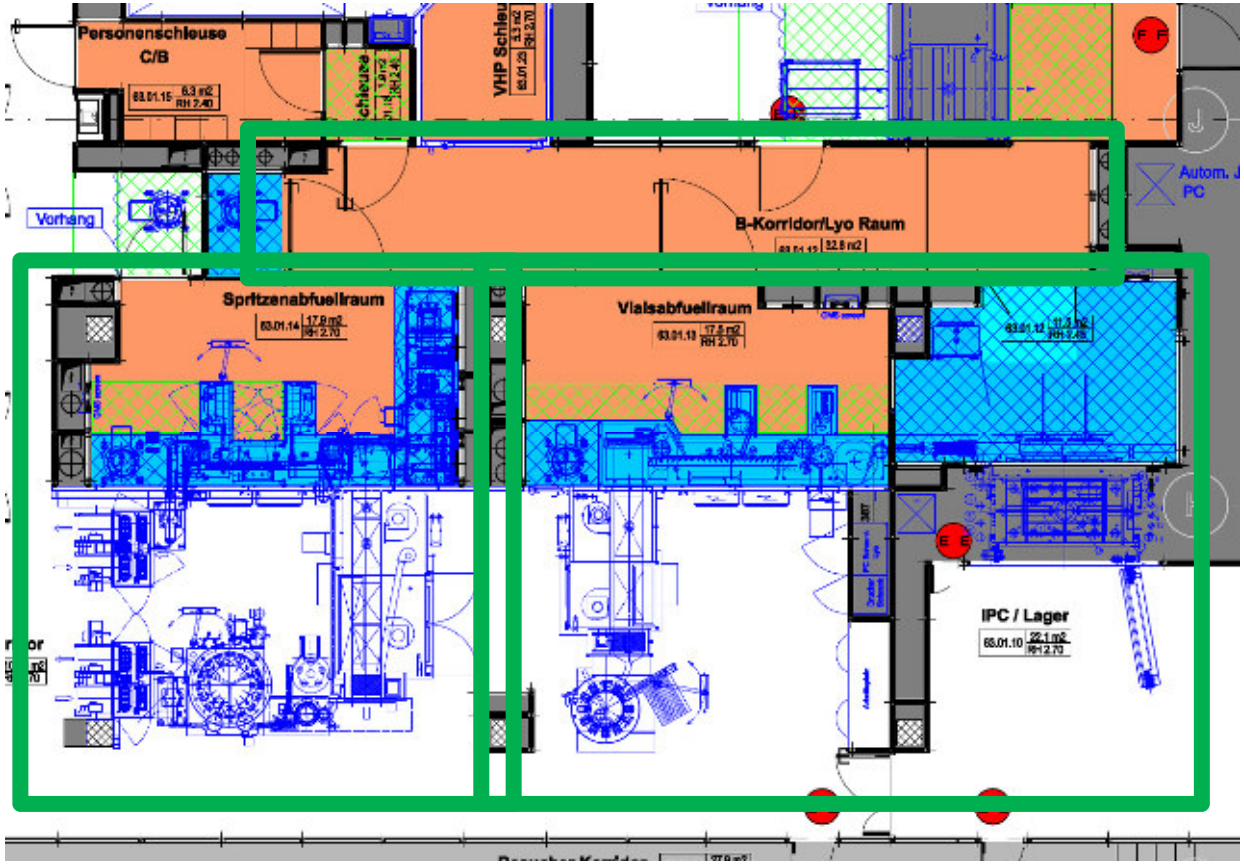
Design of Filling Lines (Grade A/B), Layout Example EU

Syringe- & Lyo-Line, A/B Design, in the same clean room compartment

Room No.	Process	Grade
1	Loading, Washing, vials/syringes out (shared)	C
2	Filling syringes (dedicated)	A/B
3	Filling vials (dedicated)	A/B
4	Lyophilization (dedicated)	A/B

Connected by one corridor



Vial Filling Line / Lyo Syringe Filling Line Grade A Grade B Grade C

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RABS vs. Isolator

Different options exist to design the environment / enclosure for aseptic filling processes. The most used ones are:

- Grade A in B, open, air flow guided with e.g. curtains (not state-of-the-art anymore)
- Restricted access barrier system (RABS), open, passive
- RABS, open, active
- RABS, closed, active
- Isolator enclosure

Open RAB systems are currently found in a lot of Asian facilities, and are most likely the preferred option in Asia (currently)

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RABS vs. Isolator

Open RABS

Isolator

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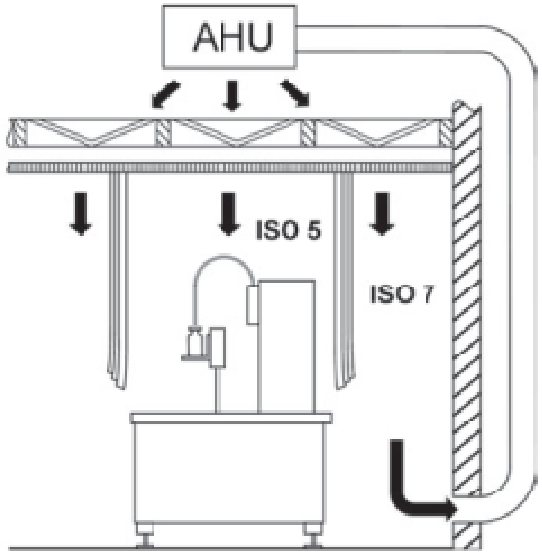
RABS vs. Isolator

Open processing, grade A in B, filling line placed in a clean room:



- Air flow guided by curtains around the filling line
- ISO No. reflect the state «in operation»
- Curtains can be opened at any position for interventions
- Not state-of-the-art anymore, limited product protection only

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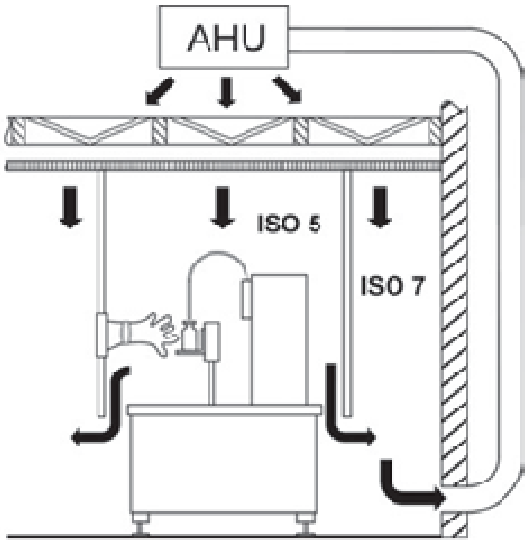
RABS vs. Isolator

Open, passive RABS:



- The filling line is enclosed by rigid cladding (RABS)
- Interventions only possible via glove ports
- Air is provided to the grade A area via the AHU / FFUs installed as part of the clean room (passive RABS)
- Air recirculates via the grade B clean room (open RABS)

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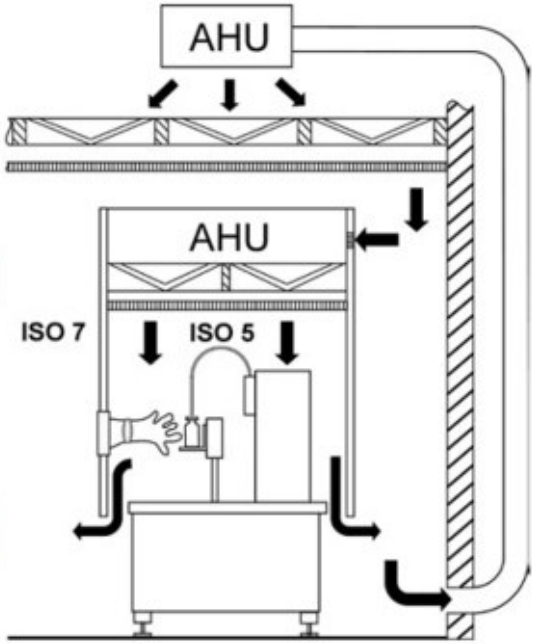
RABS vs. Isolator

Open, active RABS:



- The filling line is enclosed by rigid cladding (RABS)
- Interventions only possible via glove ports
- Air for the grade A area is provided by a dedicated AHU / FFUs (active RABS)
- Air recirculates from the grade A area via the grade B clean room (open RABS)

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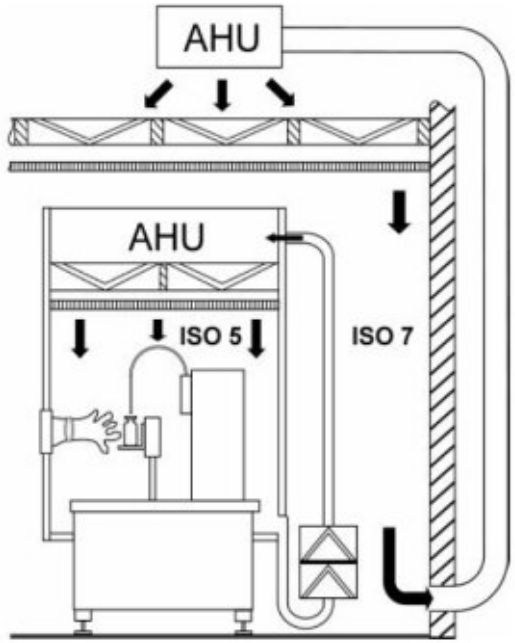
RABS vs. Isolator

Closed, active RABS:



- The filling line is enclosed by rigid cladding (RABS)
- Interventions only possible via glove ports
- Air for the grade A area is provided by a dedicated AHU / FFUs (active RABS)
- Air recirculates from the grade A area via dedicated ducts (closed RABS)

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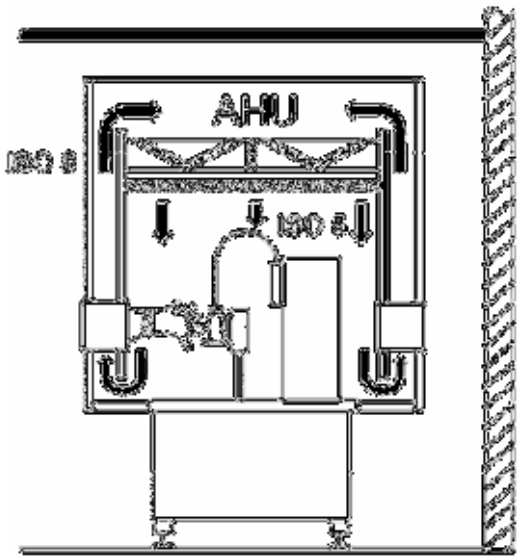
RABS vs. Isolator

Isolator:



- The filling line is enclosed by rigid cladding, sealable for fumigation
- Interventions only possible via glove ports
- Air for the grade A area is provided by a dedicated AHU / FFUs
- Internal air recirculation
- Lower requirements for the surrounding clean room (ISO 8, C in operation, or no requirement, D)

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RABS vs. Isolator

Closed RABS / Isolator:

- A closed RABS is already quite similar to an isolator in terms of the line enclosure, the required AHU, investment costs, etc.
- However, a closed RABS does not provide the critical advantage of an isolator which can be operated in a grade D or C room
- Thus, the trend is that western companies go for isolator solutions for new filling line projects

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RABS vs. Isolator

Comparison of main features:

Feature	A in B	oRABS	cRABS	Isolator
Product protection (sterility)	Basic	Better	Best	Best
Operator protection (e.g. biosafety)	No, open	No, open	Good	Best
Negative pressure operation	No	No	No	Possible
Interventions	Direct	Glove ports	Glove ports	Glove ports
Environment for enclosure	B	B	B	min. D
Opening of the enclosure during processing	Allowed	Allowed	Allowed	Not allowed*

*e.g. alpha / beta ports or VHP ALs to be used for all transfers

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RABS vs. Isolator

Comparison of main features:

Feature	A in B	oRABS	cRABS	Isolator
Procedure after enclosure opening in specified environm.	Disinfec-tion / n/a	Disinfec-tion / n/a	Disinfec-tion / n/a	Fumiga-tion
Environmental monitoring efforts (bioburden / particles)	High (B)	High (B)	High (B)	Low (D)
Personnel hygiene / gowning efforts	High (B)	High (B)	High (B)	Low (D)
Relative initial qualification / validation efforts	Low	Low	Medium	High
Relative investment costs	Lowest	Low	High	Highest

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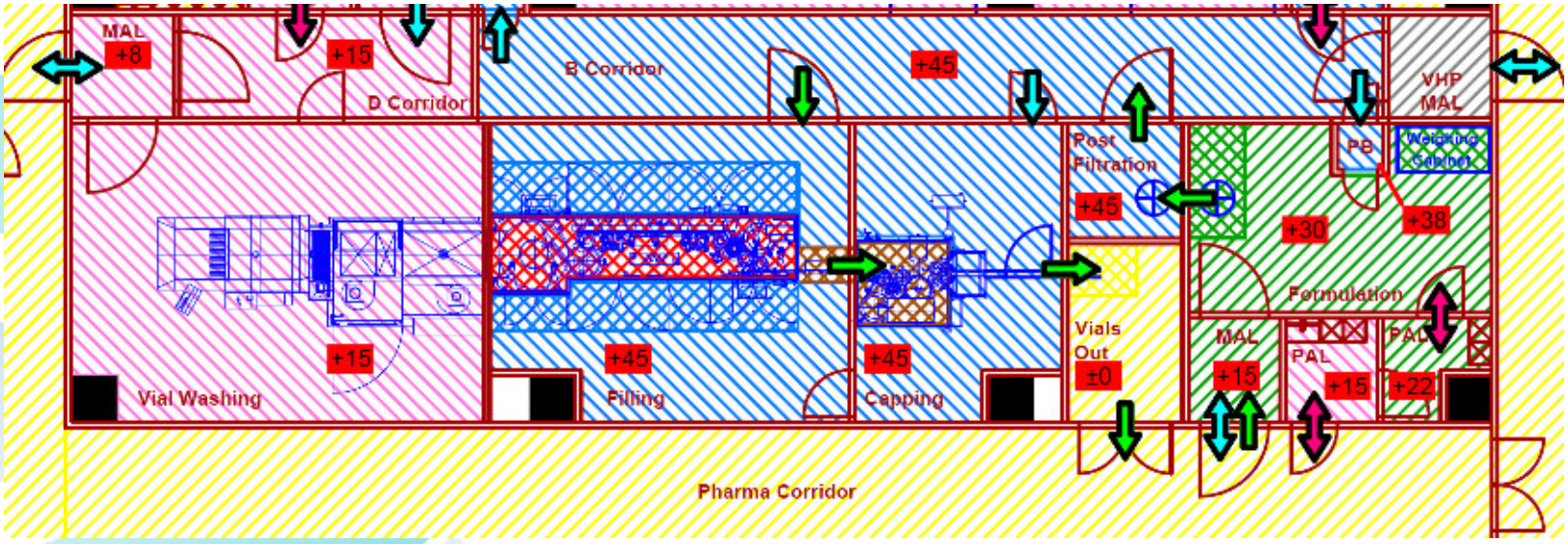
RABS vs. Isolator, Layout Example Asia



Vial Filling Line, RABS, 4 Rooms

Each process step has its own room with different clean room grades

- → Optimization potential for space, energy (air exchange rate) and gowning/degowning between the different rooms
- → Machine has to match perfectly with the walls (installation challenge)
- → Higher monitoring frequencies (grade B has to be monitored each day)
- → Cheaper equipment

Room No.	Process	Grade
1	Washing / Steri.	D
2	Filling	A/B
3	Capping	B
4	Vials out	CNC

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RABS vs. Isolator, Layout Example EU

Vial Filling Line, Isolator, 1 Room

The room includes a filling line with an isolator.

→ Space, gowning efforts and energy saving → optimized option

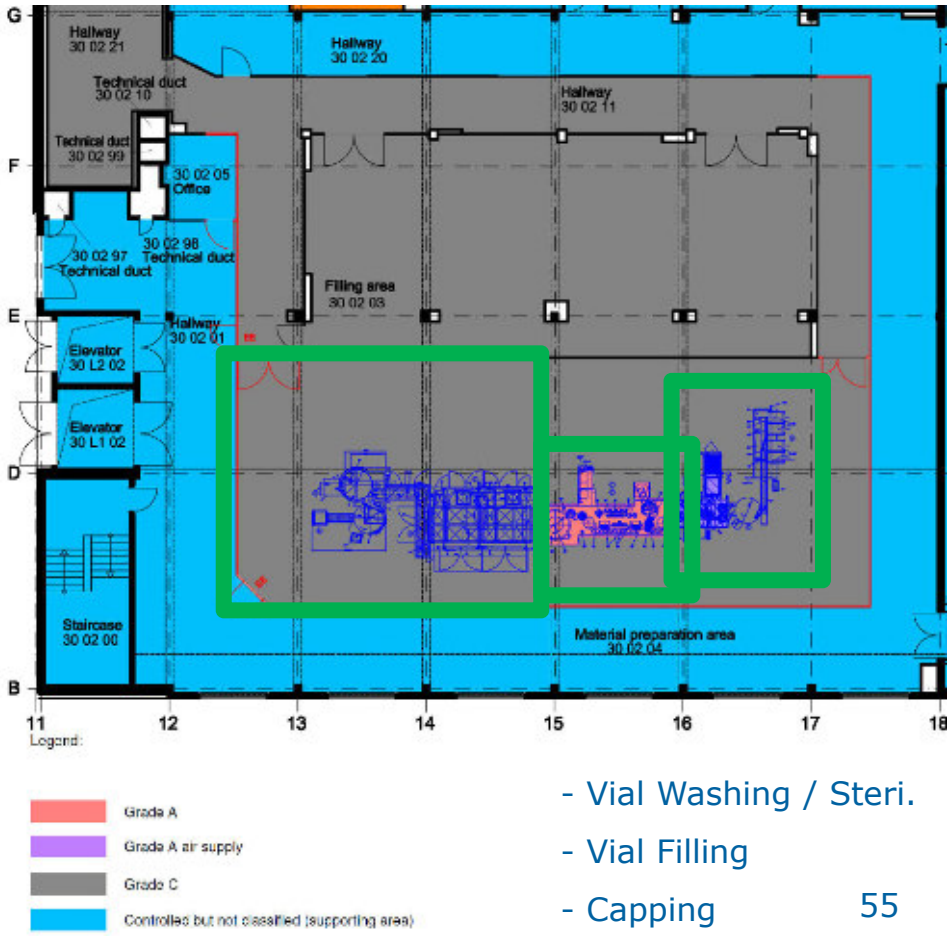
→ Easier installation (machine does not penetrate walls)

→ Lower monitoring frequencies

→ More expensive equipment

…but the investment in an isolator is worth it because of the easy handling of the overall filling process.

Room No.	Process	Grade
1	Washing / Sterilization, Filling, Capping	C, A isolator



- Vial Washing / Steri.
- Vial Filling
- Capping

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RABS vs. Isolator, Layout Example Asia

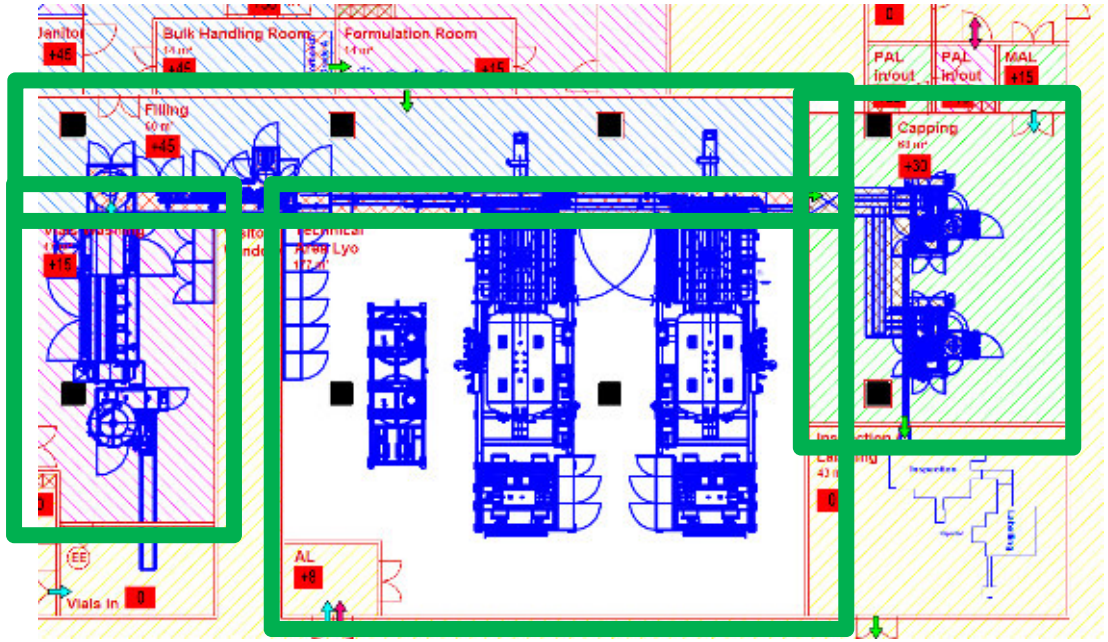
Lyo-Line, RABS, 6 Rooms

Each process step has its own room with different clean room grade.

→ Same points than described before

→ Lyos need an extra separate room for the technique

Room No.	Process	Grade
1	Vials In	CNC
2	Washing / Steri.	D
3	Filling / Lyo	A/B
4	Capping	C
5	Vials out	CNC
6	Lyo technic	Black



- Vial Washing / Steri.
- Vial Filling
- Lyophilisation
- Capping

Grade A
Grade B
Grade C
Grade D
Grade CNC

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RABS vs. Isolator, Layout Example EU

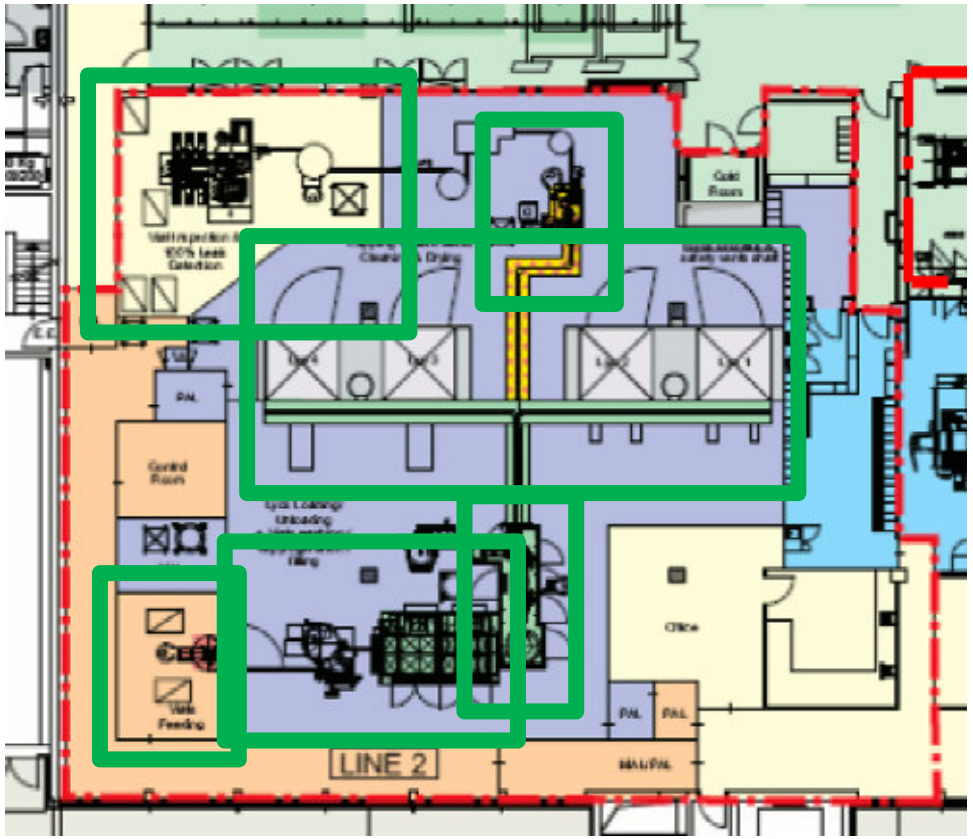
Lyo-Line, Isolator, 3 Rooms

→ Technique of lyos is accessible from the intermediate ceiling

→ Lyos and technical area go over multiple levels

Room No.	Process	Grade
1	Vials Feeding	D
2	Washing / Sterilization, Filling, Lyophilisation, Capping,	C, A isolator
3	Vials out	CNC

- Vial Feeding & Testing
- Vial Washing / Steri.
- Vial Filling
- Lyophilisation
- Capping



Grade A Grade C Grade D Grade CNC

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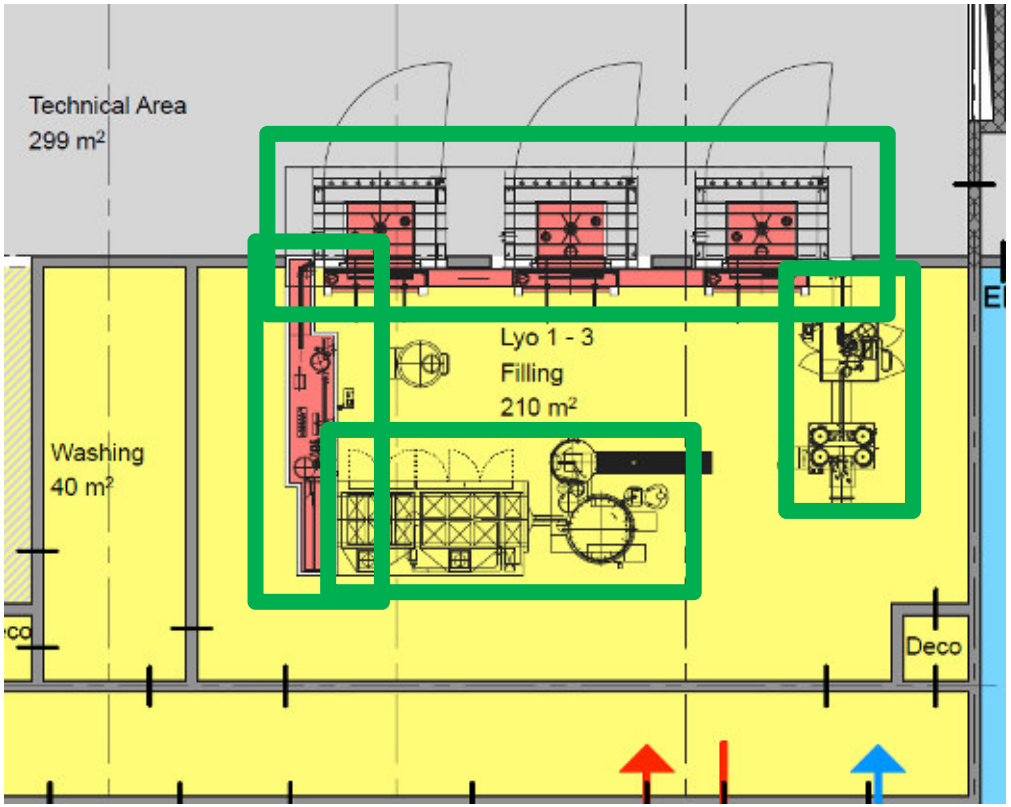
RABS vs. Isolator, Layout Example EU

Lyo-Line, Isolator, 2 Rooms

→ The lyos have its own technical area which is accessible from the black area for maintenance

Room No.	Process	Grade
1	**Loading, Washing / Sterilization, Filling, Lyophilisation, Capping**	**C, A isolator**
2	**Lyo technic**	**Black**

- Vial Washing / Steri.
- Vial Filling
- Lyophilisation
- Capping



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Terminal exhaust HEPA Filter Housings

Situation:

- Exhaust HEPA filters in production rooms are e.g. required in OSD facilities (for highly active APIs) or in some biosafety relevant facilities
- Exhaust HEPA filters have to be tested regularly for integrity (similar to the requalification of clean room supply air HEPA filters)
- This requires a special design for exhaust HEPA filter housings
- We found that Asian manufacturers are sometimes unaware of this situation / requirement

=> How are exhaust HEPA filters tested, while they are mounted in the housing?

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Terminal exhaust HEPA Filter Housings

Integrity testing for terminal exhaust filters:

- The testing procedure is similar to e.g. the DOP or DEHS test for supply air HEPA filters
- Raw gas, containing aerosol particles, is applied from the clean room side
- Clean gas has to be sampled downstream of the HEPA filter, i.e. in the housing or exhaust duct
- The particles are counted in both, the raw and clean gas
- The leakage or retention rate for particles is calculated

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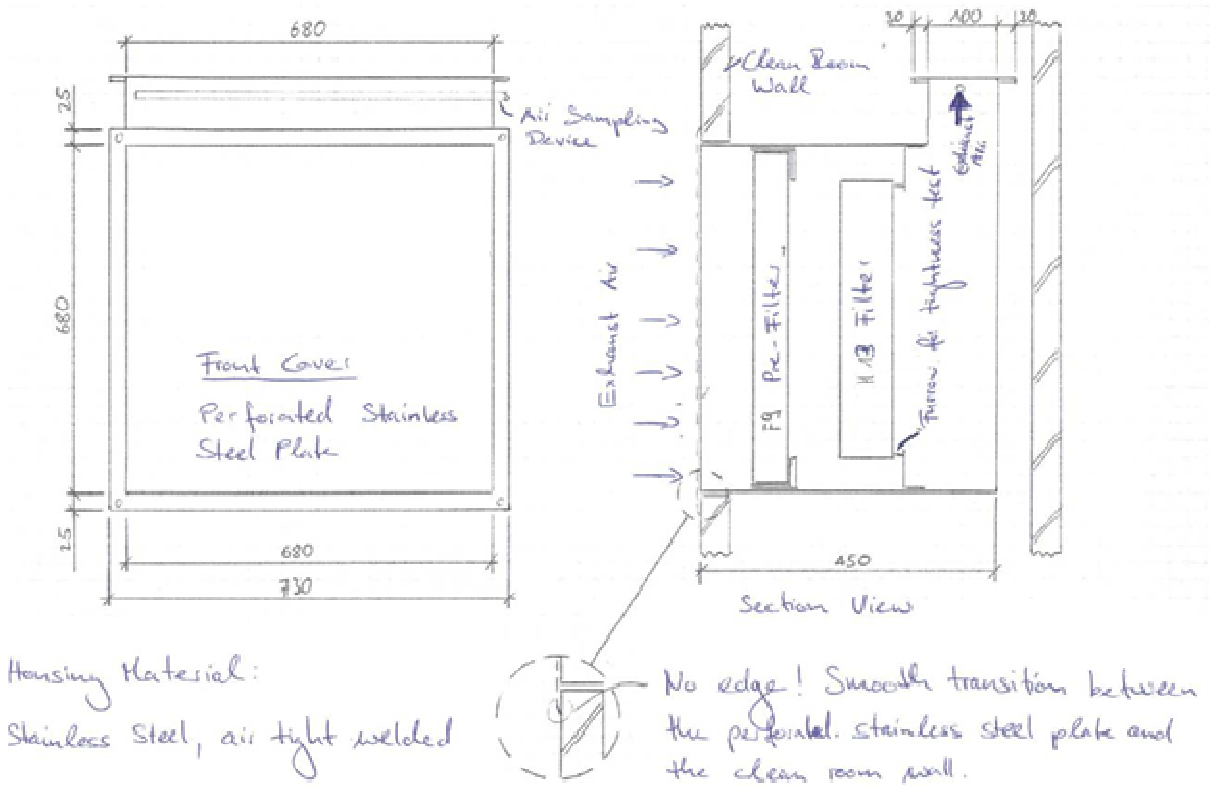
Terminal exhaust HEPA Filter Housings

Simple example for an exhaust filter housing:



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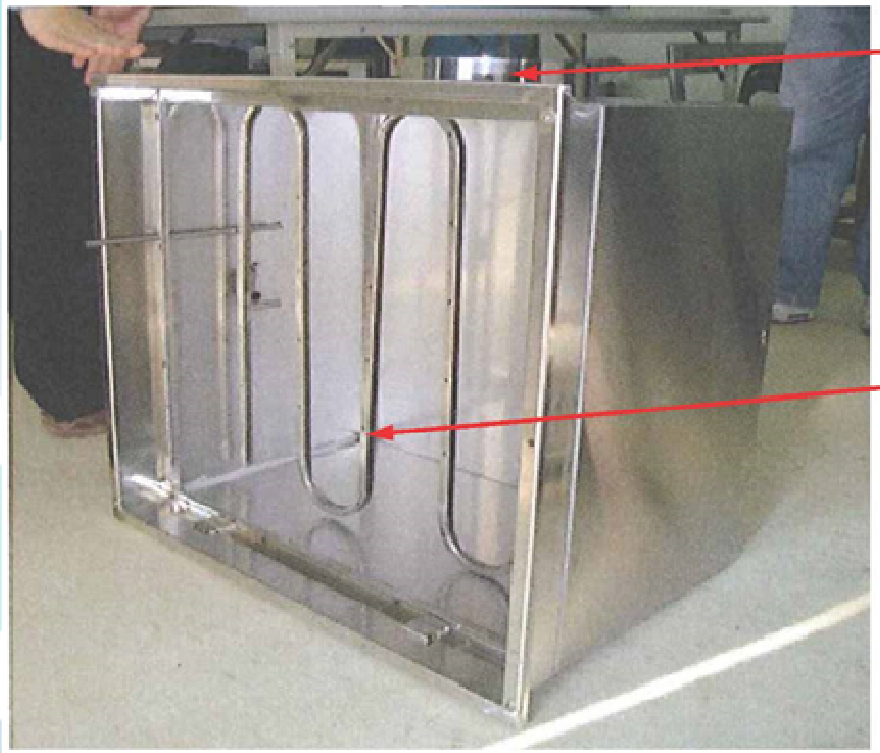
Terminal exhaust HEPA Filter Housings

Simple example for an exhaust filter housing:



- Problems with this design: Only air from part of the filter surface is sampled (incomplete filter scanning)
- Better solution: Extraction of a homogenous sample further downstream from the filter, in the duct (for integral filter testing)

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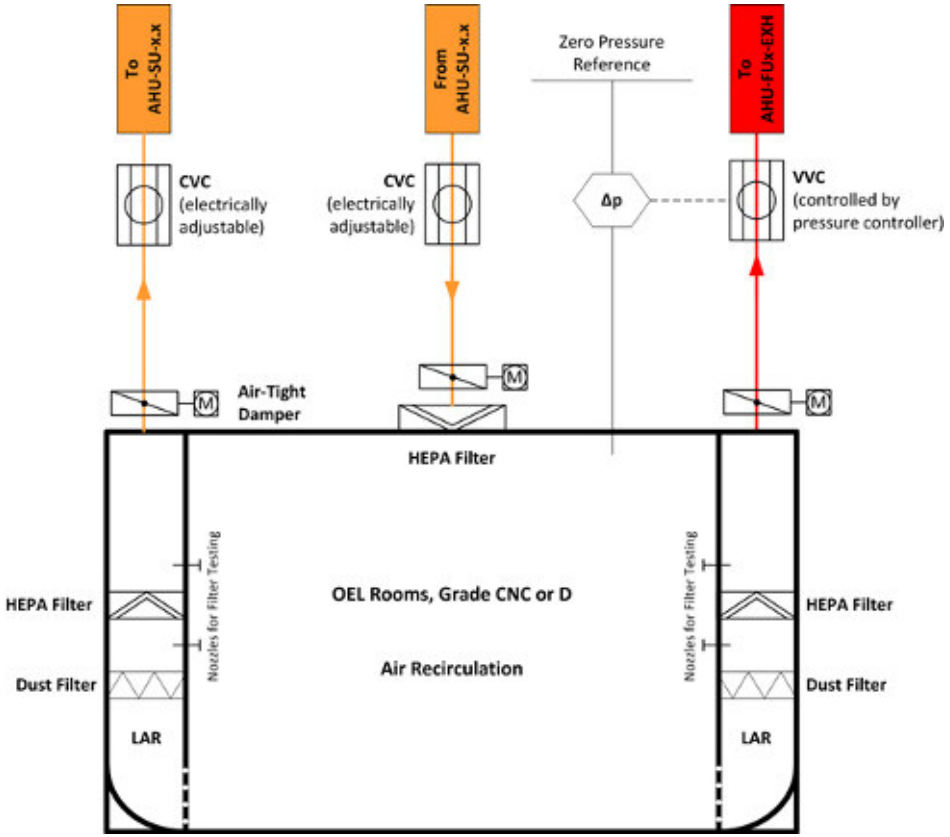
Terminal exhaust HEPA Filter Housings

Hi-tech example for an exhaust filter housing:



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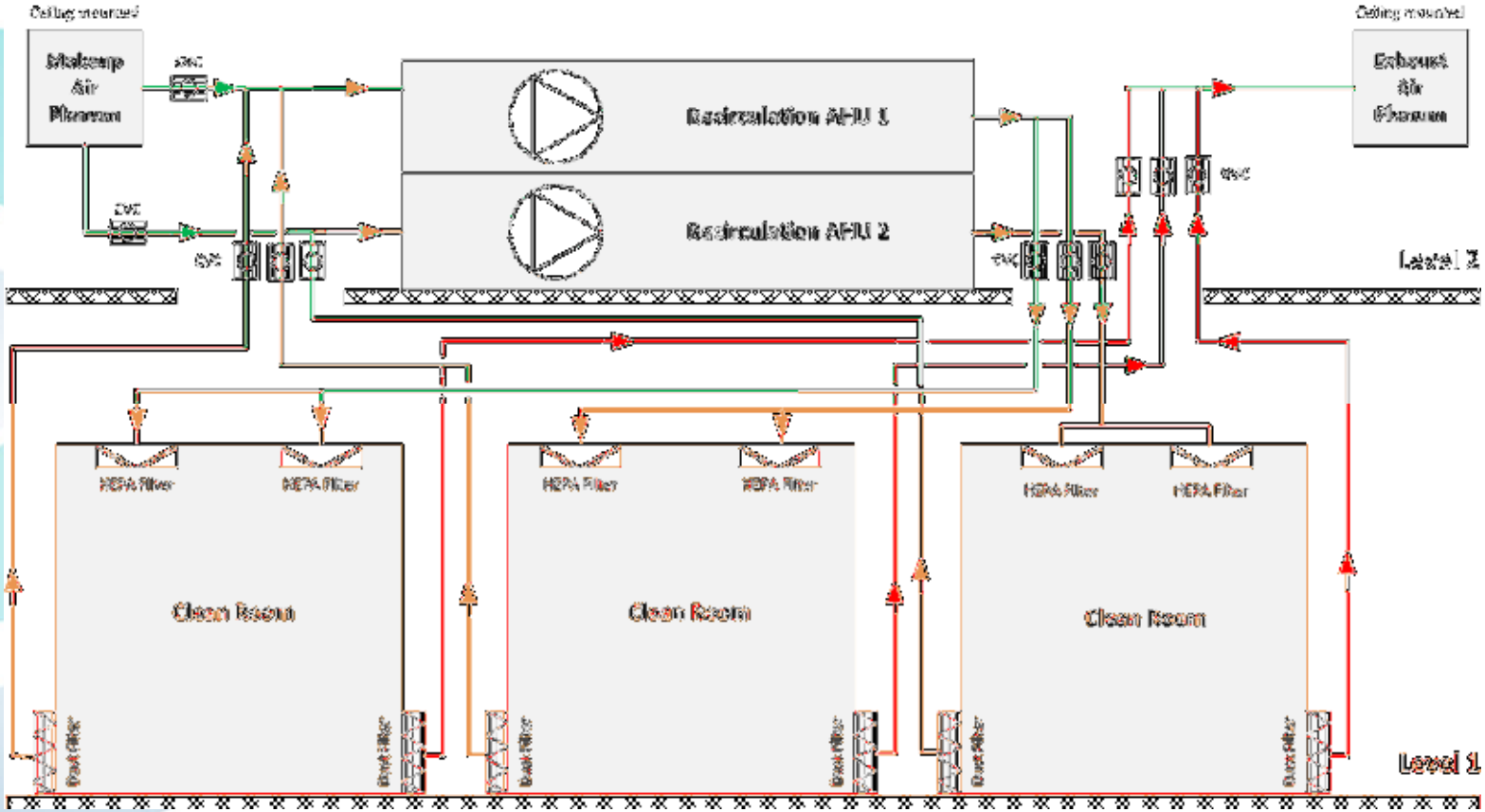
Technical Area & HVAC Design

Preferred design in Europe, technical level on top, section view:



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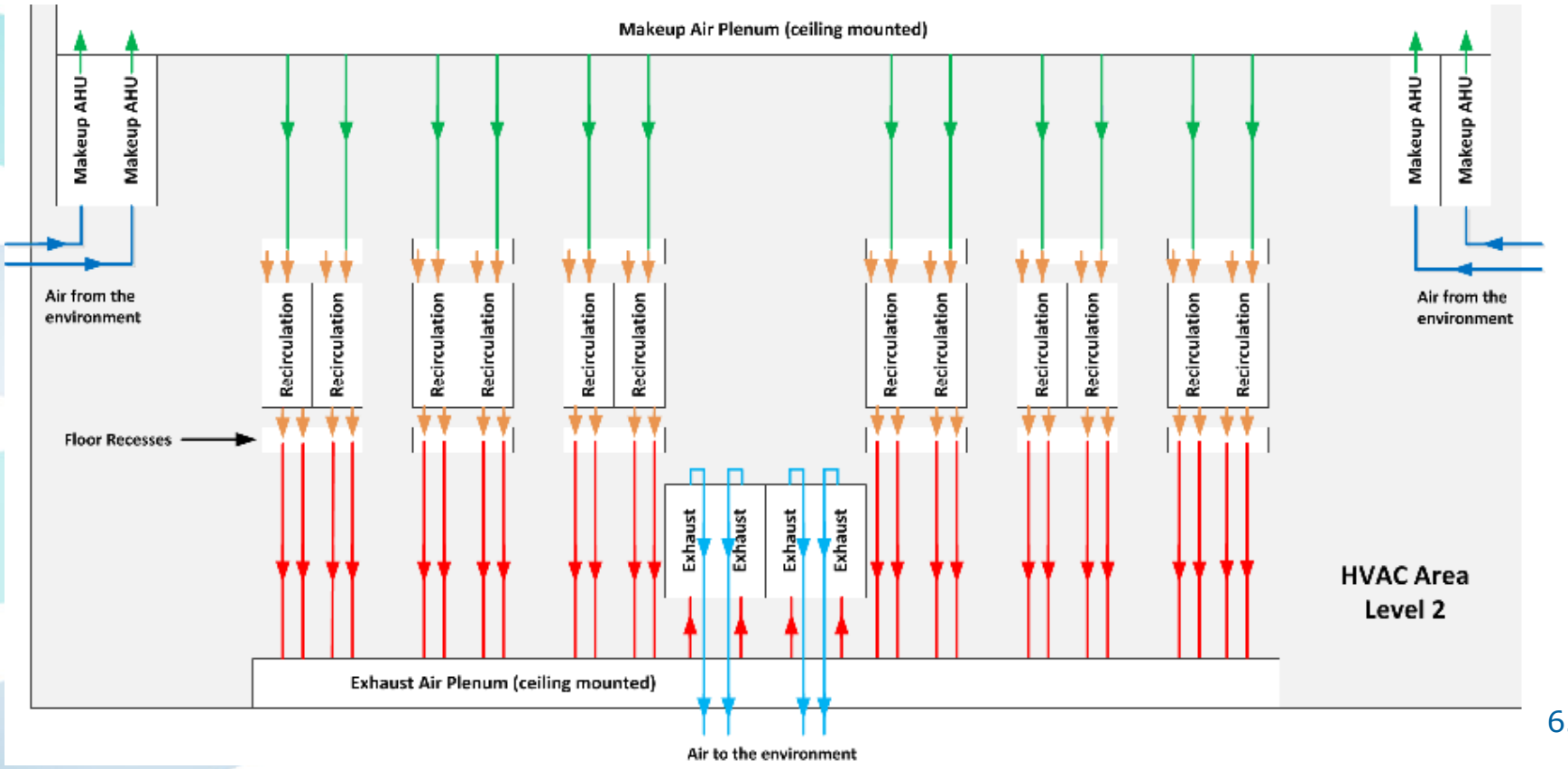
Technical Area & HVAC Design

Preferred design in Europe, technical level on top, top view:



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Technical Area & HVAC Design

Preferred design in Europe, technical level on top, advantages:

- Optimized duct routing, ductwork minimized in length
- AHU and all other components requiring maintenance / calibration (sensors, CVC / VVC, dampers, etc.) are installed close together, on the same level => efficient installation, minimization of wiring, etc.
- Easy access because there is a full dedicated building level for HVAC installations
- For makeup air and exhaust air in the example above: Partial redundancy allows for continuous operation during maintenance

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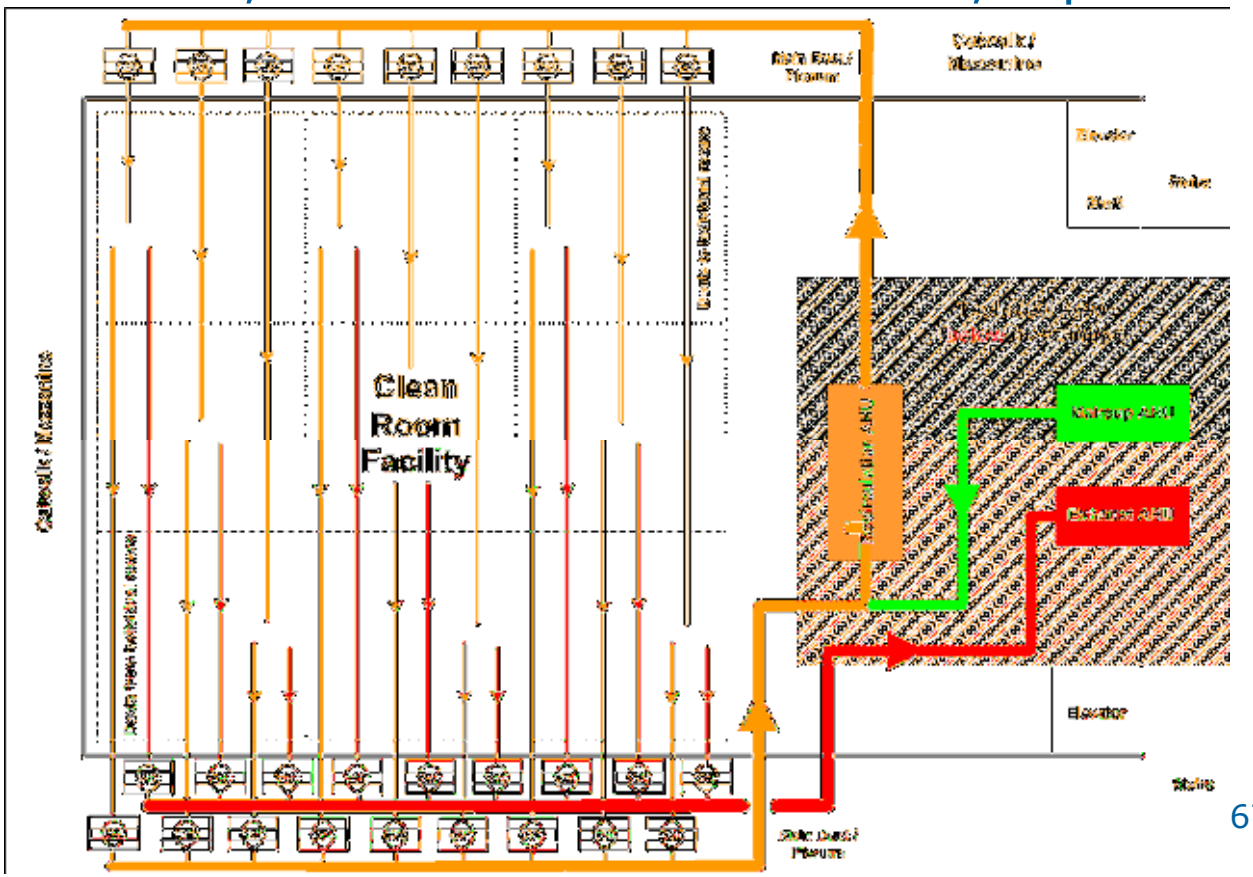
Technical Area & HVAC Design

Alternative found in Asia, technical area on the side, top view:



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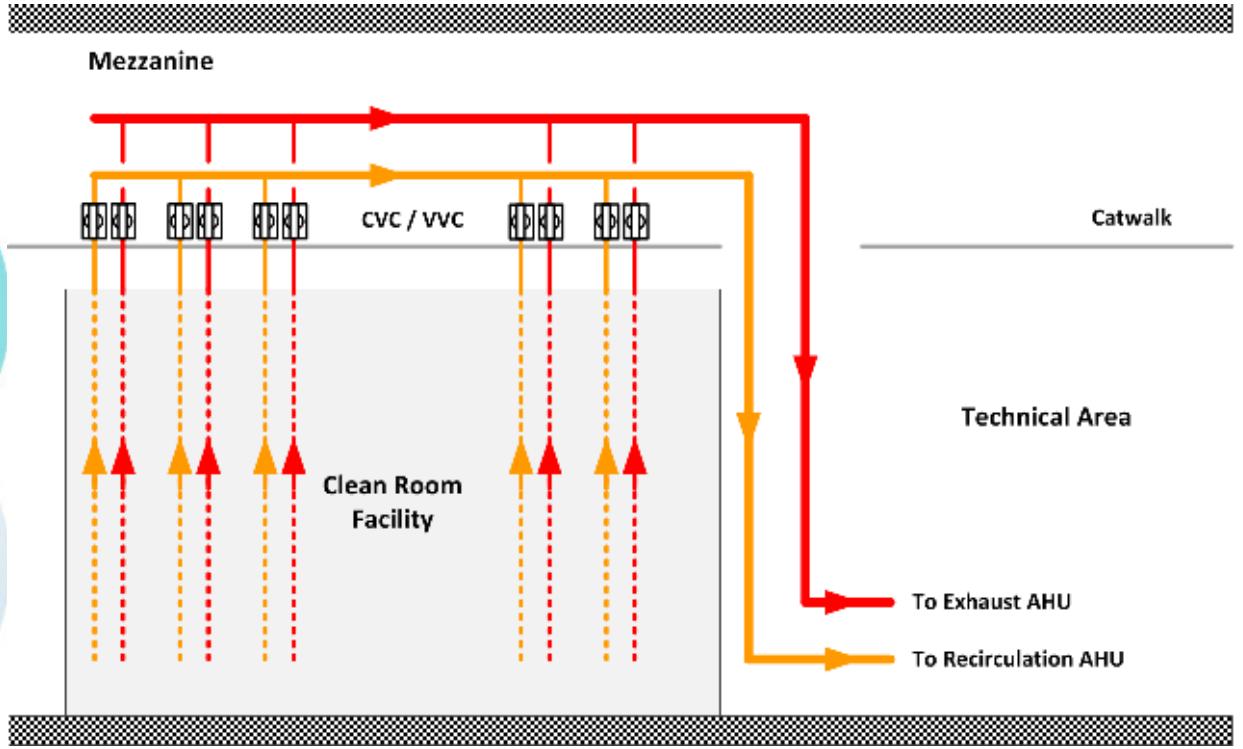
Technical Area & HVAC Design

Alternative found in Asia, technical area on the side, section view:



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Technical Area & HVAC Design

Alternative found in Asia, technical area on the side, features:

- Longer ductwork system compared with the other option presented
- Components requiring maintenance / calibration (sensors, CVC / VVC, dampers, etc.) should be installed along a catwalk for easy access, and to minimize walking on the clean room ceiling
- The AHU and field elements for control are distributed within a larger area => more wiring, etc. is required accordingly

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Technical Area & HVAC Design

If there is no space / not enough height for a mezzanine / catwalk (not recommended):

- All components requiring maintenance / calibration (sensors, CVC / VVC, dampers, etc.) should be installed in the technical area, before the ducts “vanish” above the clean room ceiling
- Thus, the ducts leading to individual rooms must be separated in the technical area already, making the ductwork even longer

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Project Schedule and Realization

Comparison of the time required for planning and realization of a project:

- On the following slide, 2 project schedules have been compared
- One project was realized in Europe, the other in Asia
- Both projects are similar (installation of a filling line, including clean rooms, HVAC, etc.)

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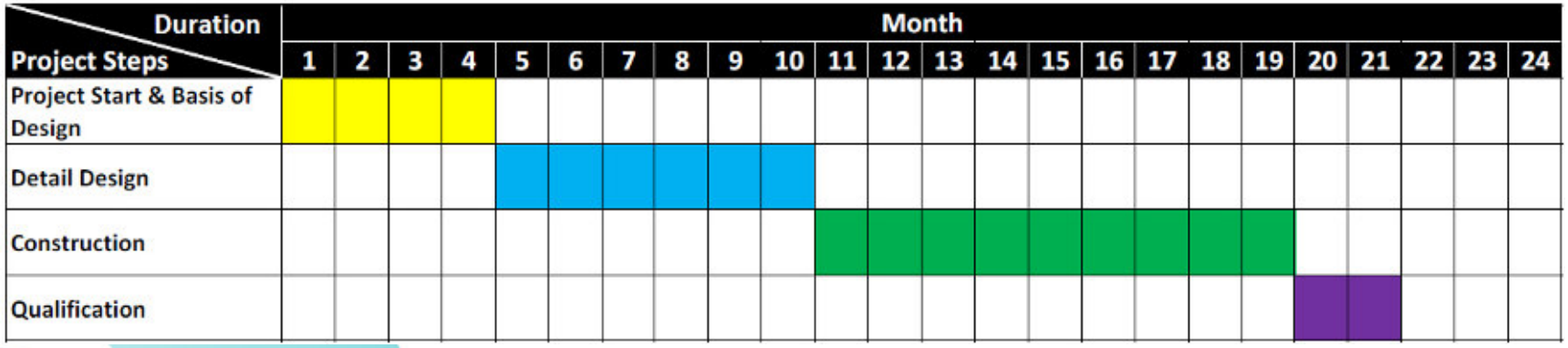
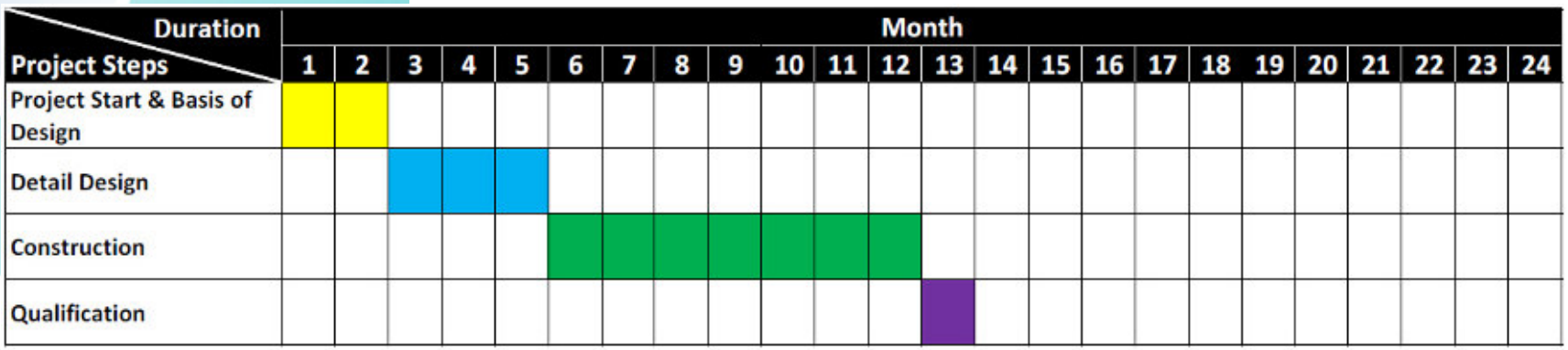
Which Time Schedule belongs to which Continent?



Example of an EU Time Schedule



Example of an Asian Time Schedule

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Difference in Time Schedule

- Generally the time for the same project phase is shorter in Asia than in EU (not always an advantage)
- EU: higher time investment in quality control and therefore less investments later for error corrections
- Asia: basis designs and detail design appear → could lead to misunderstandings later

Why does this time difference appear?

- Construction phase is the most similar one regarding duration
- Also qualification takes longer in the EU, due to a thorough and detailed testing
- Long leadtime-equipment should be ordered as early as possible to avoid delays

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Further Questions?