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CBC’s Inspection Findings and Possible Remedies Thereto

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Contents of this Presentation

- This presentation contains examples for findings which CBC has identified during the inspection of GMP / biosafety facilities
- Most of these inspections were performed in the context of projects to support companies with the WHO prequalification of vaccines
- The presented examples are not intended to embarrass companies, the intention is to share experiences for the benefit of all
- For questions marked in red, the audience is invited to provide answers and suggestions

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CBC's Procedure for Inspections

CBC follows the following procedure to inspect GMP- and/or biosafety-relevant facilities:

- Step 1: Detailed inspection of the facility at site, based on layouts, schematic drawing, etc., and a thorough walk-through of course
- Step 2: Collection of all findings in an inspection report or gap report, etc.
- Step 3: Classification of findings
- Step 4: References to relevant guidelines or standards
- Step 5: Suggestion of appropriate corrective actions

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CBC's Procedure for Inspections

Classification system for findings:

- Critical, minimum requirement (MR), etc.: Findings which directly violate current GMP or biosafety guidelines / requirements. These findings must be corrected to achieve facility compliance

- Advice, not state-of-the-art (SOTA) anymore, etc.: Findings which are related to good engineering practices (GEP), energy efficiency / sustainability, etc., but which do not violate GMP or biosafety requirements. It is recommended to correct these findings, but not mandatory

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CBC's Procedure for Inspections

Example of a gap report for an inspection performed against the **Chinese GMP** guidelines:

#	Topic	Current Situation / Problem	Proposed Solution / Change	Change Classification (MR / SOTA)	Guideline References
10	Floor drains	Floor drains are covered with a simple metal lid without seal => contamination risk	Floor drains need a sanitary design => tight sealing cover, etc.	MR	Chinese GMP (2011), Annex 1, Art29
11	Cold WFI points of use	Point of use heat exchangers to generate cold WFI are plate heat exchangers => no sanitary design	Heat exchangers with a sanitary design are required (e.g. double tube sheet heat exchangers)	MR	Chinese GMP (2011), Art71, Art74
12	Unused equipment	Stopper washing machine in the filling area is not used anymore	The washing machine should be removed from the facility => better for cleaning, no un-qualified equipment in production facilities, etc.	MR	Chinese GMP (2011), Art88

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CBC's Procedure for Inspections

Example of a gap report for an inspection performed against the **WHO GMP** guidelines:

No.	Facility / Topic	Location	Identified Gaps / Issues	Criticality	Suggested Corrective Measures	Comments / References
14	Cell expansion	Air lock XXXXXX	Conflict between AHU zoning, room pressure and biosafety classification. At the moment, potentially contaminated air is transferred to this air lock, but the air lock is connected to an AHU for the bio-negative area	advice	During visit 1, the company explained that this air lock is operated with 100% exhaust air (no recirculation) to avoid biosafety cross-contamination. Although this argumentation is ok, the current design is still a breach of the AHU concept which is valid for the rest of the facilities. If possible, the pressure in air lock XXXXXXXXX should be raised in a way that air is blown to both adjacent rooms	Defined concepts should be implemented consistently
15	Pooling / formulation	e.g. XXXXXX	Design of the grade A areas: Operators enter the grade A areas completely to carry out the required operations	critical	The entry of operators into grade A areas must be minimized. The position of the curtains should be adapted in a way that only the working table is located in the grade A area, operators should sit outside of the grade A area (only their forearms should enter the grade A areas) => a new smoke study and zone classification is required after the change	WHO TRS 961, Annex 6, paragraph 10.8
16	Pooling / formulation	e.g. XXXXXX	Design of the grade A areas: FFUs for the grade A areas take air in at the ceiling of the grade B room	advice	The air intake for grade A areas should be routed to a position near the floor of the grade B room	Good engineering practice

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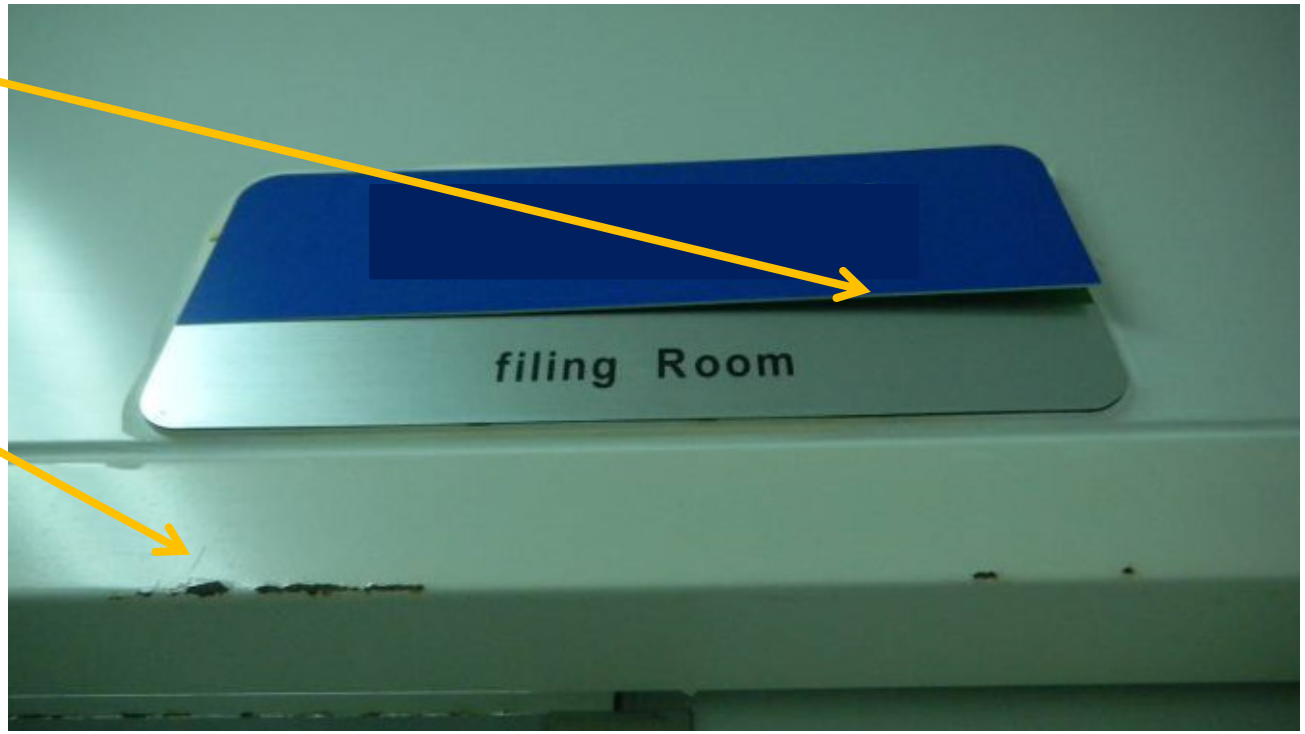
Cleanability – In General

Some examples which are obviously not ok:

Difficult to clean and disinfect

Release of particles, rough surfaces are difficult to clean / disinfect



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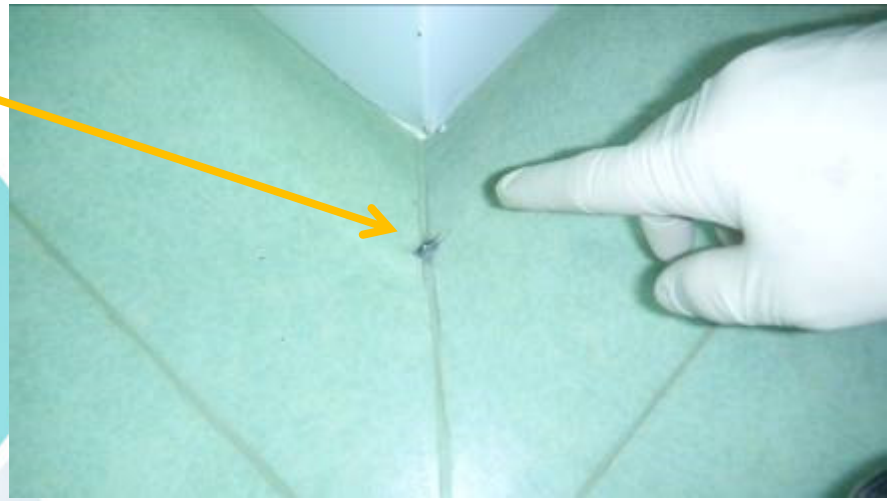
Cleanability – In General

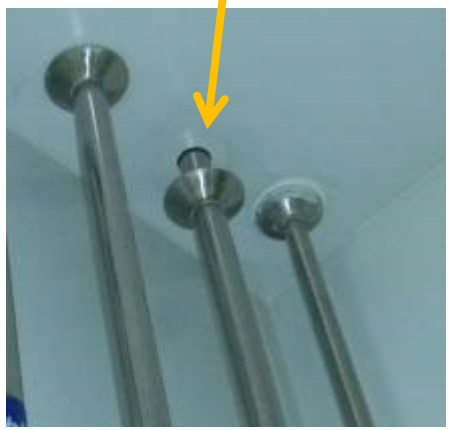
Some examples which are obviously not ok:

Damaged floor covering, difficult to clean / disinfect



Difficult to clean, corrosion leads to particle release

Difficult to clean, ingress of dirty air in negative pressure clean rooms



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Cleanability – Clean Room Structure

What about this situation? Ok or not?

This spot is badly accessible for cleaning / disinfection

Better solution:

Complete integration of the pass-through box into the clean room structure, flush with the wall panels on both sides (maintenance access to be considered)

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Cleanability – Grade B Room Furnishing

What about this situation? Ok or not?

Top and inside of the cabinet are difficult to clean

Release of particles through the ventilation opening

Electrical cabinet in the grade B filling room

Better solution:

Electrical cabinets should be installed in a technical area, or a CNC room, etc., but not in a grade B room

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Cleanability – Grade A Area Furnishing

What about this formulation room? Ok or not?

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Cleanability – Grade A Area Furnishing

Some requirements for grade A areas, WHO TRS 961, Annex 6. These requirements are related to potential risks:

- Unidirectional air flow, 0.36-0.54 m/s
- Continuous particle monitoring during operation
- Personnel should not enter grade A areas
- Good cleaning and disinfection properties are especially important
- Only the minimum amount of operations should be carried out
- Only the minimum amount of goods, equipment, etc. should be placed in grade A areas

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Cleanability – Grade A Area Furnishing

Quality by design risk assessment:

- Requirement: Unidirectional air flow, 0.36-0.54 m/s. Measures?
- Curtains to guide the air flow, minimize installations which could disturb the unidirectional air flow, monitoring of the air speed

- Requirement: Continuous particle monitoring during operation. Measures?
- Monitoring with a mobile particle counter during the time of operation, or installtion of a fix online particle monitoring system

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Cleanability – Grade A Area Furnishing

Quality by design risk assessment:

- Requirement: Personnel should not enter grade A areas. Measures?
- Minimization of the grade A area, the design should enable that operators can perform the aseptic operations without entering the grade A area physically (only with the forearms)

- Requirement: Good cleaning and disinfection properties are especially important. Measures?
- Minimization of installations in grade A areas, smooth and even surfaces, no corners, etc.

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Cleanability – Grade A Area Furnishing

Quality by design risk assessment:

- Requirement: Only the minimum amount of operations should be carried out. Measures?
- Processes and equipment should be designed to minimize the grade A area use

- Requirement: Only the minimum amount of goods, equipment, etc. should be placed in grade A areas. Measures?
- Minimization of installations in grade A areas, optimization of the processes / operations in a way to minimize the amount of transfers to the grade A area

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Cleanability – Grade A Area Furnishing

Problems with this grade A area setup:

- The whole UAF area was defined as grade A, no curtains
- Installations are difficult to clean / disinfect
- Difficult to maintain uni-directional air flow in the whole area
- Personnel has to enter the defined grade A area

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Cleanability – Grade A Area Furnishing

Possible solutions:

- Define the rest of the FFU area as grade B UAF
- Limit the grade A definition to the area where aseptic operations take place (tank lid)
- Install curtains to separate grade A from grade B UAF, and the grade B UAF from the grade B room

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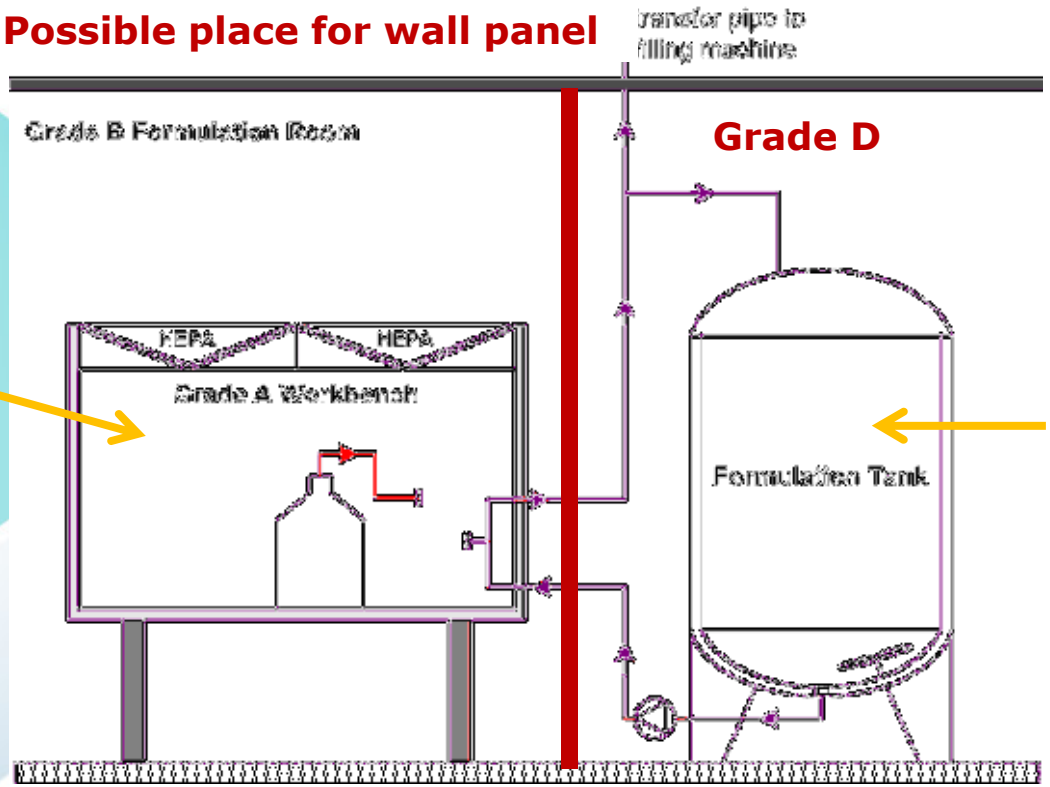
Cleanability – Grade A Area Furnishing

Better solution:

Grade A workbench to make aseptic connections



The tank does not need a grade A area then, could even be located in a room of lower grade (e.g. D for closed systems)

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Technical Room Adjoining Clean Rooms

What about this situation? Ok or not? Problems?

Autoclave in clean room

Maintenance access and technical room for autoclave, no controlled ventilation, no regular cleaning, no monitoring, etc.

Grill to cover the maintenance opening

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Technical Room Adjoining Clean Rooms

Problems with the design shown before

- Without a controlled ventilation, regular cleaning and monitoring, the technical room must be considered an unclassified area
- If the grill is removed and technicians enter the technical room, the clean room will be contaminated => maintenance can only be performed during shut-downs
- The grill allows air to pass. Without control and monitoring of the differential pressure, there is a risk for contamination to be carried over from the technical area to the clean room
- Even if the differential pressure is controlled, the air loss through the grill would be quite high

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Technical Room Adjoining Clean Rooms

Possible solutions:

- Design, construction and operation of the technical room as clean room, incl. cleaning and monitoring (only reasonable for grade D, and maybe grade C)
- Installation of a maintenance door to provide a tighter closure => maintenance only possible during shut-downs
- Small airlock to access the technical room (to prevent contamination of the clean room)
- Access to the technical room via the space above the false ceiling of the clean room (if feasible)

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Ease of Maintenance

What about this situation? Ok or not? Problems?

Supply air outlet in the clean room ceiling, with HEPA filter

Fan-filter-unit (FFU), ceiling mounted

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Ease of Maintenance

Problem with the situation shown before: The HEPA filter is not accessible anymore

- Exchange of the HEPA filter (if necessary) is difficult
- The regular integrity test for the HEPA filter by scanning with a particle counter (DOP or DEHS test, etc.) cannot be performed
- The supplied air volumes cannot be measured anymore (required to calculate air change rates)
- The homogeneity of the air speed in the UAF area might be affected negatively

=> Such construction practices should not be accepted

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Floor Drains

Is this floor drain suitable for a grade C clean room? Risks?

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Floor Drains

Potential risks related to floor drains are:

- Microbial growth in stagnant water (e.g. in the syphon)
- Carry-over of microbial contamination from the floor drain into the clean room
- Backflow of contaminated waste water into the clean room
- Release of odors
- Potential obstacle in the room which could lead to accidents, etc.

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Floor Drains

Quality by design risk assessment:

- Risk: Microbial growth in stagnant water (e.g. in the syphon). Measures?
- Cleaning and disinfection of the drain must be possible, syphon could be filled with disinfectant after use

- Risk: Carry-over of microbial contamination from the floor drain into the clean room. Measures?
- Cover with gasket for tight closing and sealing of the floor drain

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Floor Drains

Quality by design risk assessment:

- Risk: Backflow of contaminated waste water into the clean room. Measures?
- Tight cover with gasket, syphon, drain piping connected to vent line

- Risk: Release of odors. Measures?
- Tight cover with gasket

- Risk: Potential obstacle in the room which could lead to accidents, etc. Measures?
- Installation flush with the flooring, no handle on the cover

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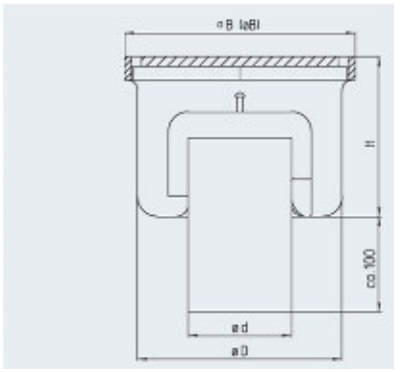
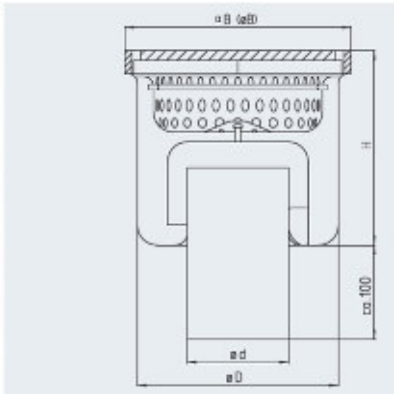
Floor Drains

Good solution for clean room facilities

Cover with gasket



Tool to remove the cover



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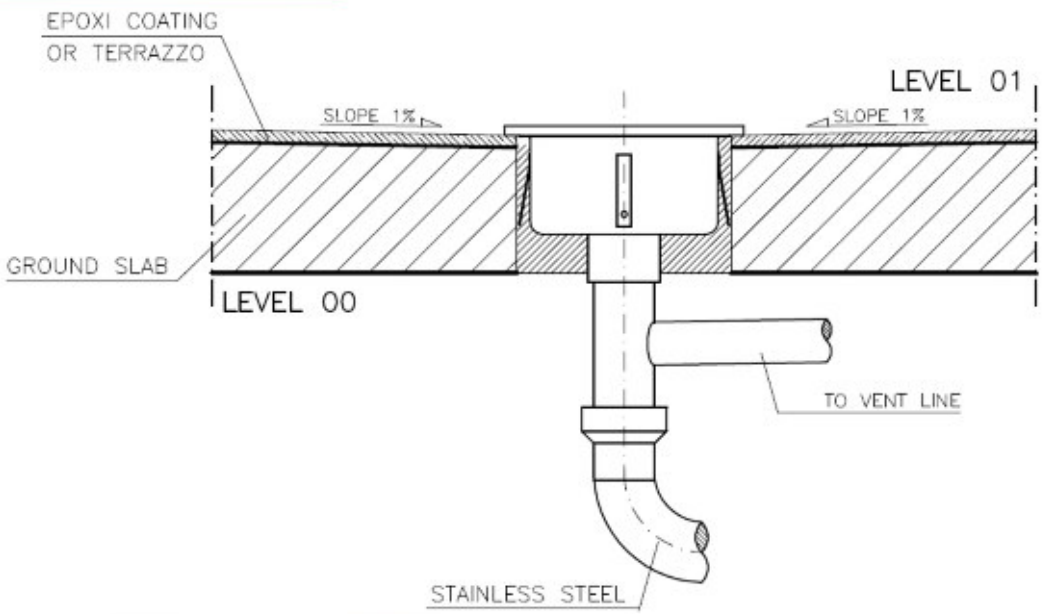
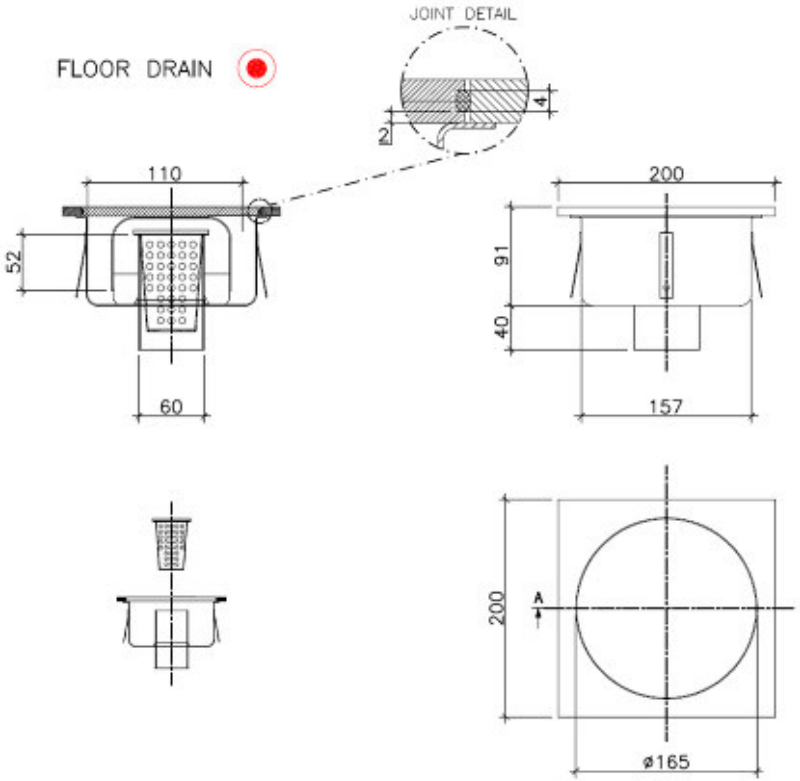
Floor Drains

Good solution for clean room facilities





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ATEX Clean Room

Is this power socket suitable for an ATEX clean room? Why or why not?

No, because:

1) The design is not suitable for clean rooms (difficult to clean, etc.)

2) The design is not suitable for ATEX (sparks could cause fires / explosions)

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ATEX Clean Room

Improvements:

- Use components which are suitable for clean rooms (installation flush with the wall panels, easy to clean design, etc.)
- Use suitable ATEX solutions, e.g. ATEX switch boxes to which the equipment to be powered is connected permanently

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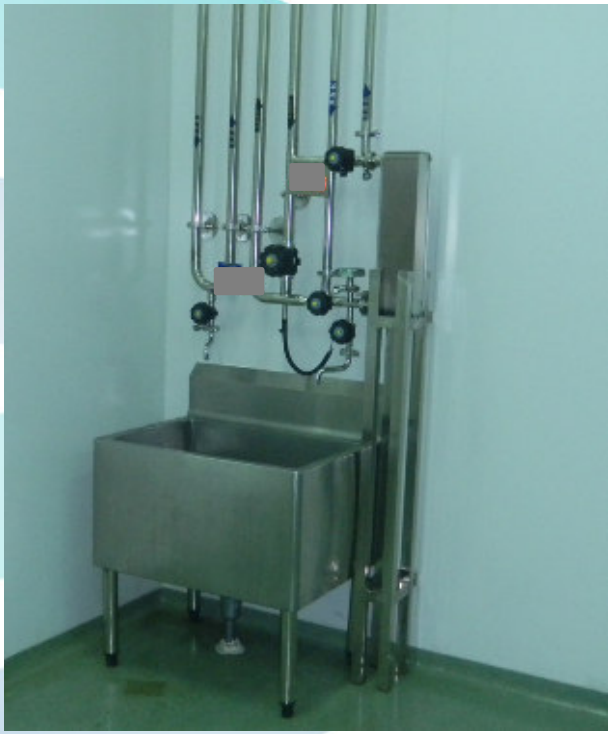
WFI Point of Use Cooler

Is this heat exchanger suitable for WFI cooling?
Why or why not?



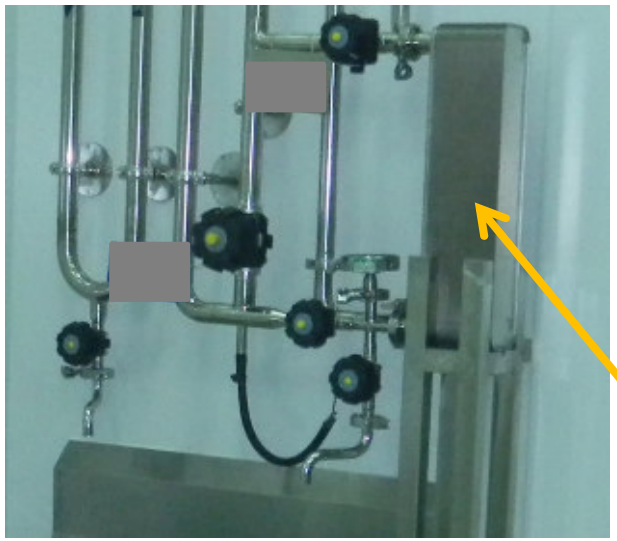


Plate heat exchanger

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WFI Point of Use Cooler

Problems with plate heat exchangers:

- Plate heat exchangers cannot be drained completely
- Therefore, such heat exchangers are difficult to dry, clean and / or sanitize
- If permanently flushed by WFI in a loop / subloop, it cannot be guaranteed that turbulent flow prevails in this type of heat exchanger (areas similar to dead-legs may occur)

=> Plate heat exchangers might be susceptible to biofilm growth and are not considered sanitary therefore

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WFI Point of Use Cooler

Better solution: Sanitary double-tube-sheet heat exchangers:

- WFI passes through a long folded tube or a bundle of tubes for cooling
- With this design, the heat exchanger can be better drained and dried (and cleaned / sanitized if required)
- The flow through all individual tubes can be kept at turbulent conditions

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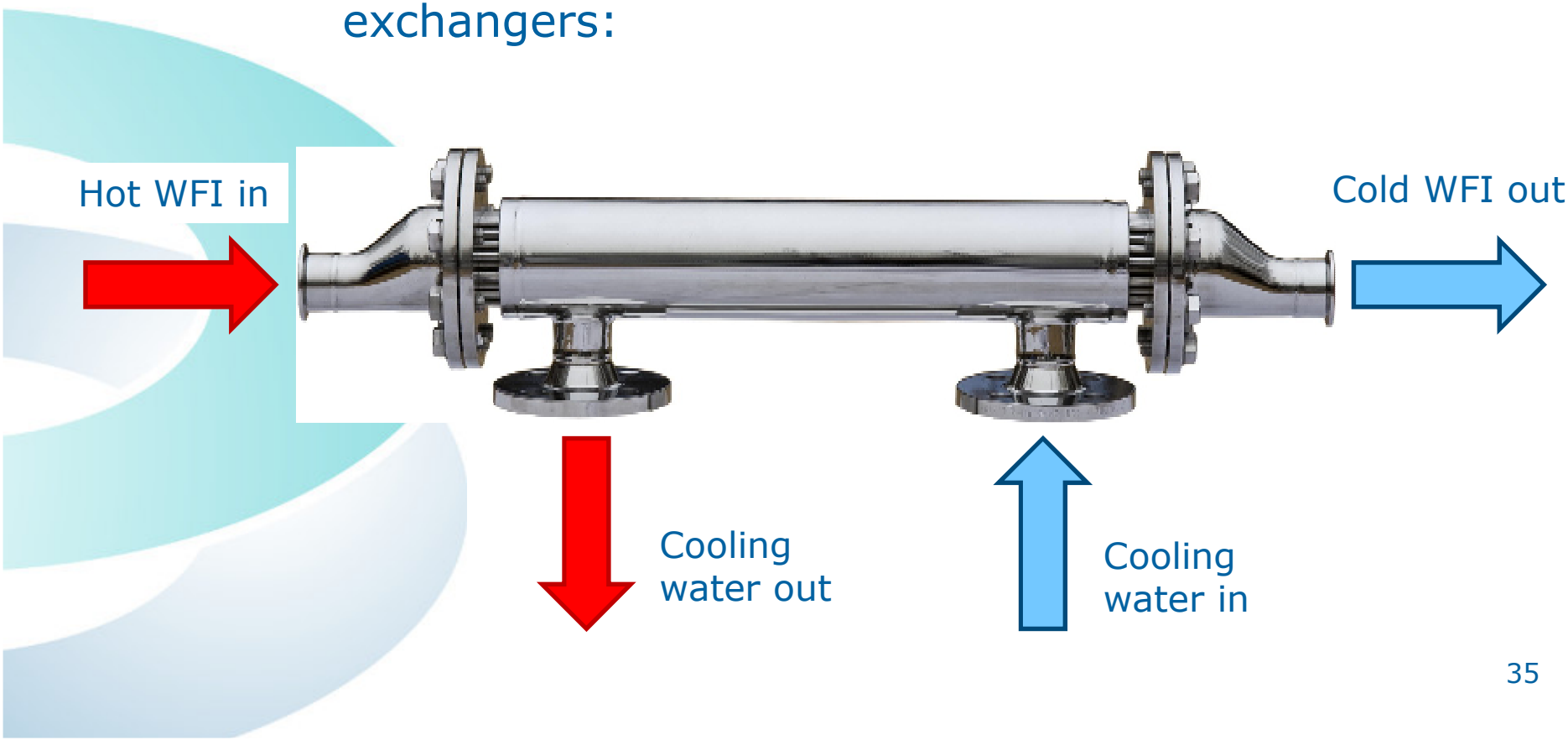
WFI Point of Use Cooler

Better solution: Sanitary double-tube-sheet heat exchangers:



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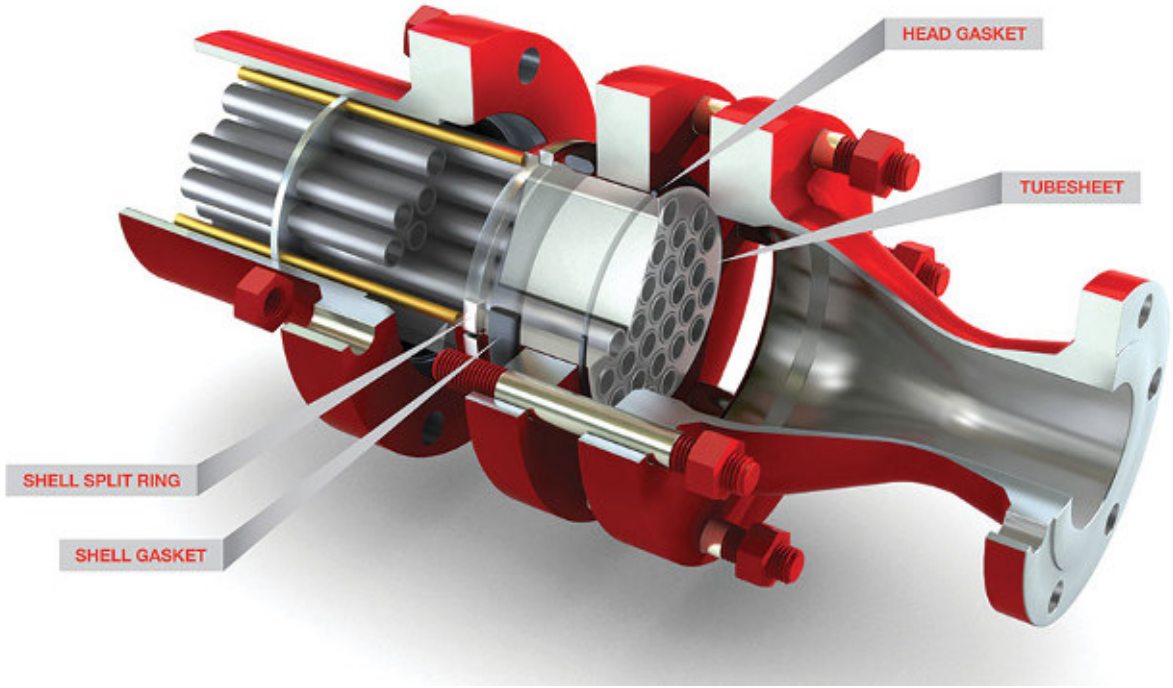
WFI Point of Use Cooler

Better solution: Sanitary double-tube-sheet heat exchangers:



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Process Equipment Design, Centrifuge

Situation:

- Discontinuous centrifugation, the process step is also biosafety-relevant

- Product is removed manually in a grade C room

- Open processing, system is not tight, not vented via a sterile filter

- Liquid is drained openly

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Process Equipment Design, Centrifuge

Problems with this design?

- No UAF / biosafety cabinet protection for the product

- System is not tight (GMP and biosafety issue => generation of aerosols)

- No sanitary design, difficult to clean, CIP / SIP impossible

- Open draining of liquids is unacceptable (biosafety)

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Process Equipment Design, Centrifuge

Better solution, separator for continuous centrifugation:

- Closed system, suitable for GMP and biosafety

- Sanitary design with CIP / SIP

- No UAF / biosafety cabinet needed

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Environment for Media / Buffer Preparation

We sometimes encountered the situation that the following solutions are prepared in a grade D environment before sterilization:

- Media for cell culture or fermentation processes
- Buffers for purification or even formulation of the sterile final product

=> Is a grade D environment acceptable for these purposes? Why or why not?

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Environment for Media / Buffer Preparation

Current regulatory requirements covering this issue (e.g. WHO TRS 961, Annex 6, 4.17):

"The preparation of solutions which are to be sterile-filtered during the process should be undertaken in a Grade C environment (unless a closed system is used, in which case a Class D environment may be justifiable)"

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Environment for Media / Buffer Preparation

WHO Guideline "environmental monitoring of clean rooms in vaccine manufacturing facilities", November 2012:

	Open Systems	Closed Systems
Preparation of media to be sterilized by heat	▪ Component weighing, mixing: D	▪ N/A
Preparation of media to be sterilized by filtration	▪ Component weighing, mixing: C	▪ Media final filtration: UDAF in D (a closed system is normally required)

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Environment for Media / Buffer Preparation

Conclusions: a grade D environment is ok for:

- Buffer / media preparation in **open systems** before **heat** sterilization
- Buffer / media preparation in **closed systems** before **sterile filtration**

=> For preparation in **open systems** before **sterile filtration**, a grade C environment is needed (normally with additional protection by an UAF unit)

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Environment for Media / Buffer Preparation

Consequences for the facility design:

- For most processes, a lot of different media / buffer are required
- In most cases, both methods, heat and filtration, are used for sterilization of these media / buffers
- Weighing is part of the preparation procedure as well
- Closed systems may be a theoretical option to justify a grade D environment for preparation of solutions to be sterile filtered, but in fact, their use is not appropriate in most cases (weighing glove boxes, isolators, alpha / beta port systems, etc. would be needed)

=> Thus, in most cases, it makes sense to design the media / buffer preparation area as a **grade C area**

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Laundry Design (for clean room clothes)

Grade D laundry found during an inspection:

Good or bad design?

What can be improved?

Suggestions please…

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Laundry Design (for clean room clothes)

Regulatory requirements for the laundry design (e.g. WHO TRS 961, Annex 6, 10.9):

"Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable."

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Laundry Design (for clean room clothes)

What are potential sources / risks for recontamination of clothes?

- Water used for rinsing
- Storage of the clothes in wet conditions (microbial growth)
- Exposure to the air in the laundry (may contain particles)
- Workers shedding particles

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Laundry Design (for clean room clothes)

Quality by design risk assessment:

- Risk: Water used for rinsing. Measures?
- Use water treated with a controlled purification process / with a controlled quality (purified water)

- Risk: Storage of the clothes in wet conditions (microbial growth). Measures?
- Dry clothes immediately after washing

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Laundry Design (for clean room clothes)

Quality by design risk assessment:

- Risk: Exposure to the air in the laundry (may contain particles). Measures?
- Laundry designed as grade D clean room (basic protection), washed and dried clothes shall continuously be handled under an UAF unit until sealing in bags has been completed (improved protection)

- Risk: Workers shedding particles. Measures?
- Grade D hygiene and gowning for personnel. Personnel should not enter the UAF area where cleaned / dried clothes are handled

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Laundry Design (for clean room clothes)

Things to improve:

Loading / unloading of the washing / drying machines should be UAF-covered as well (continuous protection of clean garments)

Machines could be installed into recesses, flush with the wall (optional)

UAF area requires curtains to guide the air flow, the worker should sit outside of the UAF area defined by the curtains

Clothes should be UAF-protected until they are sealed in bags

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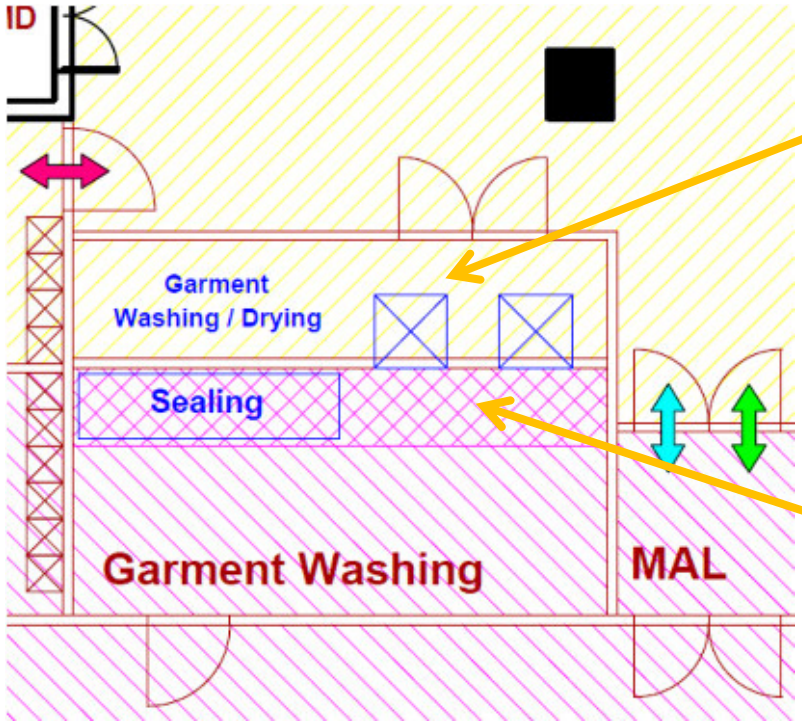
Laundry Design (for clean room clothes)

Layout example for an optimally designed grade D laundry:



CNC installation space for the washing / drying machines

Grade D laundry, the cross-hatching marks the UAF area

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Biosafety Concept

During an inspection, we found the following situation for an OPV facility (BSL 2):

- Waste water from the bio-positive area is decontaminated (heat)
- Solid waste and reusable goods are decontaminated in autoclaves during the transfer out of the bio+ area
- Open virus handling does **not** take place in biosafety cabinets (but in UAF units with outward air flow)
- Bio-positive rooms are operated with a **positive** differential pressure compared to the environment
- There are **no** HEPA filters for the exhaust air
- Other vaccine bulk facilities are located in the same building

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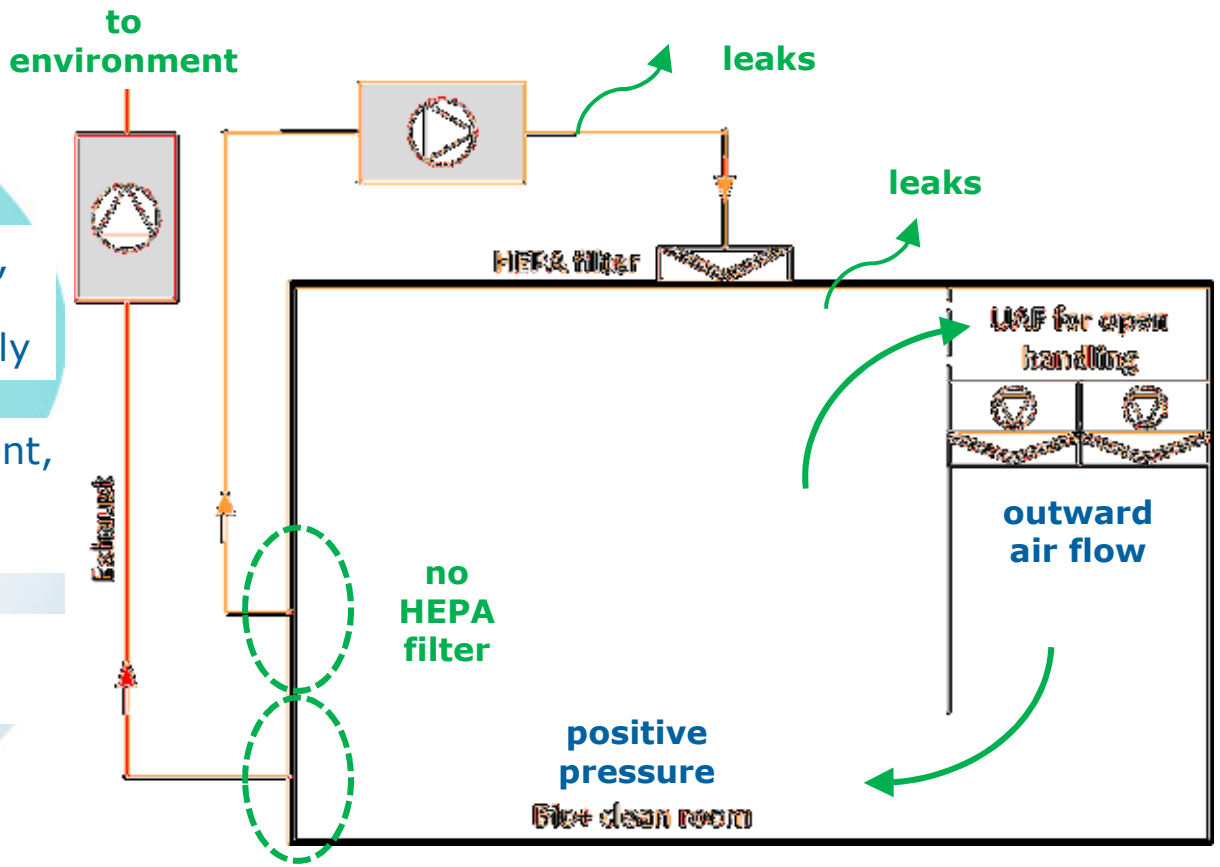
Biosafety Concept

Problems with the situation described before?

No primary containment, clean room will be contaminated significantly

No secondary containment, contamination of the technical area / building

Contamination of the environment



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Biosafety Concept

WHO requirements for BSL 2:

Neither inward air flow, nor exhaust HEPA filters, nor biosafety cabinets are strictly required for BSL 2, but…

The omission of all 3 features together may lead to significant risks as shown in the example before

Table 3. ***Summary of biosafety level requirements***

	BIOSAFETY LEVEL			
	1	2	3	4
Isolation[a] of laboratory	No	No	Yes	Yes
Room sealable for decontamination	No	No	Yes	Yes
Ventilation:				
— inward airflow	No	Desirable	Yes	Yes
— controlled ventilating system	No	Desirable	Yes	Yes
— HEPA-filtered air exhaust	No	No	Yes/No[b]	Yes
Double-door entry	No	No	Yes	Yes
Airlock	No	No	No	Yes
Airlock with shower	No	No	No	Yes
Anteroom	No	No	Yes	—
Anteroom with shower	No	No	Yes/No[c]	No
Effluent treatment	No	No	Yes/No[c]	Yes
Autoclave:				
— on site	No	Desirable	Yes	Yes
— in laboratory room	No	No	Desirable	Yes
— double-ended	No	No	Desirable	Yes
Biological safety cabinets	No	Desirable	Yes	Yes
Personnel safety monitoring capability[d]	No	No	Desirable	Yes

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Biosafety Concept

Problems with the situation described before:

- There is a significant risk that the technical area and the building will be contaminated with polio viruses
- This contamination might be transferred to other bulk vaccine facilities, e.g. by maintenance personnel moving through the different areas of the building (also a GMP risk, not only biosafety)

=> In particular for an OPV facility, this situation may not be acceptable since the WHO strives for the eradication of polio

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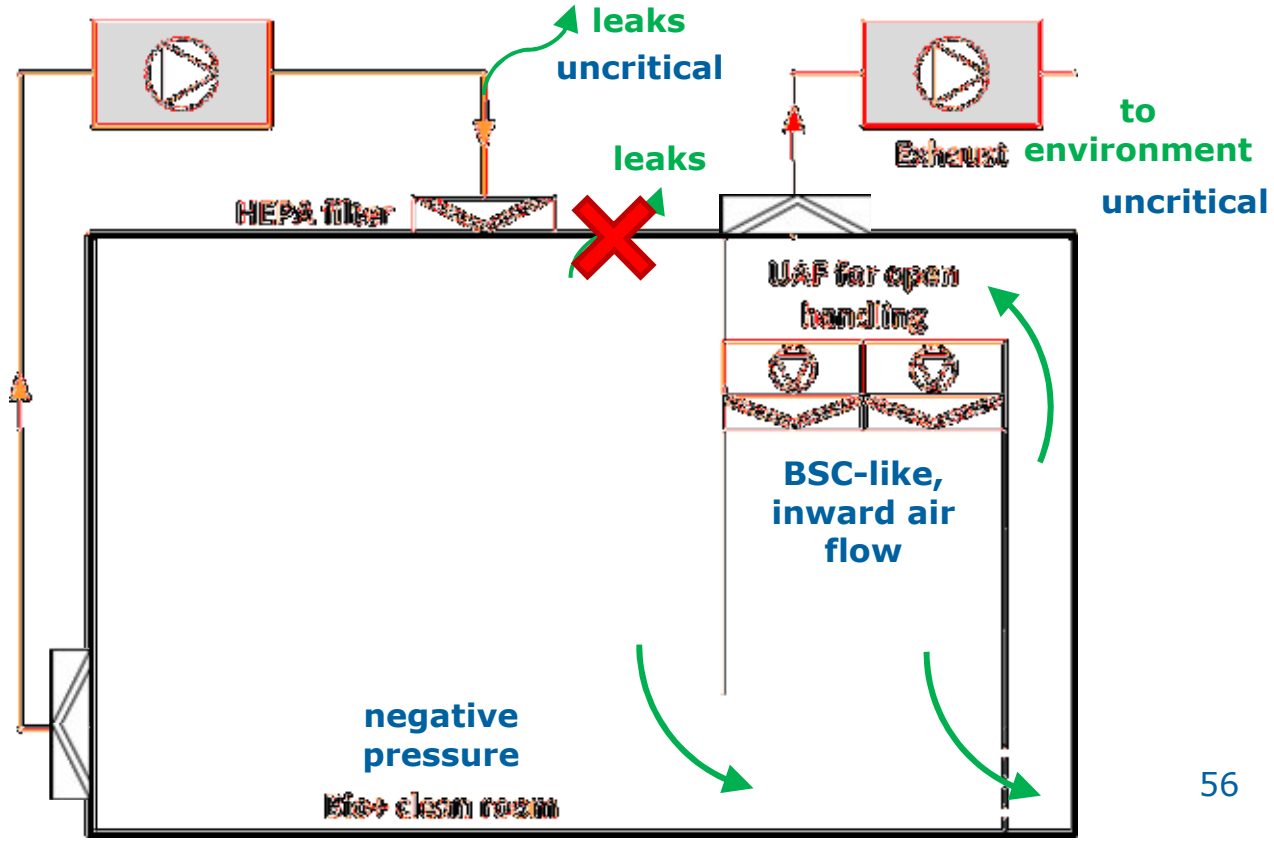
Biosafety Concept

Optimized BSL 2 concept for the OPV facility

Primary containment, contamination of the clean room is minimized

Secondary containment, no transfer of contaminated air to the technical area / building

HEPA filters prevent the release of virus via the exhaust air, or on the pressurized side of the recirculation AHU



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Further Questions?