How to Make the Best Use of Open RABS

- A Case Study on Overcoming Design Limitation with Supplementary Tool and Enhanced Control Strategy

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Critical points to consider in design

FDA's Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing

- Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment.
- The layout of equipment should provide for ergonomics that optimize comfort and movement of operators.
- The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from an aseptic processing room and, most significant, its **critical area**. Regarding the latter, the number of transfers into the **critical area** of a traditional cleanroom, or an isolator, should be minimized. To prevent changes in air currents that introduce lower quality air, movement adjacent to the **critical area** should be appropriately restricted.

Critical points to consider in design

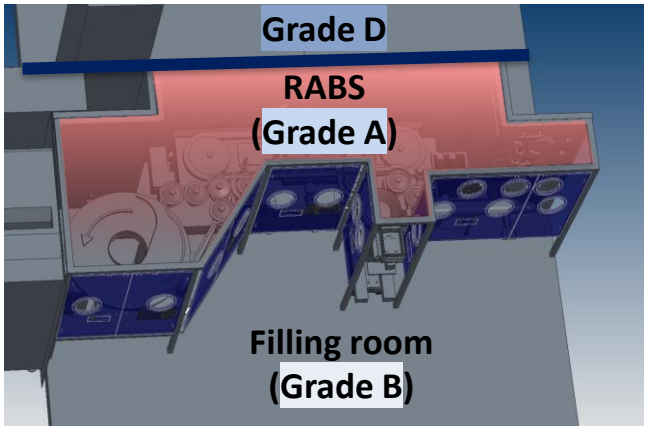
EU GMP Annex 1: Manufacture of Sterile Medicinal Products

- 4.19 The design of RABS should ensure grade A conditions with unidirectional airflow and **first air protection** in the **critical zone**. A positive airflow from the critical zone to the supporting background environment should be maintained.
- 4.4 Direct intervention (e.g. without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.
- 8.16 The process of designing interventions should include the consideration of any impact on air-flows and **critical surfaces** and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention.

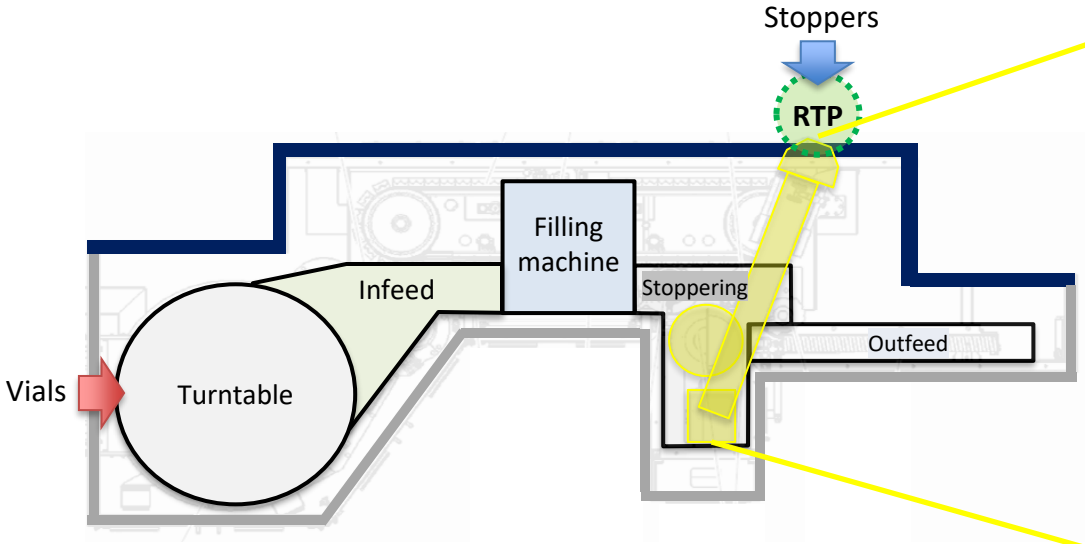
- ***Critical surfaces****: Surfaces that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.*
- ***Critical zone****: A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.*

Background

Current RABS design for aseptic manufacturing at Incheon



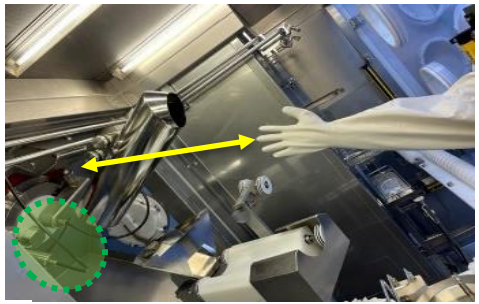
Case study



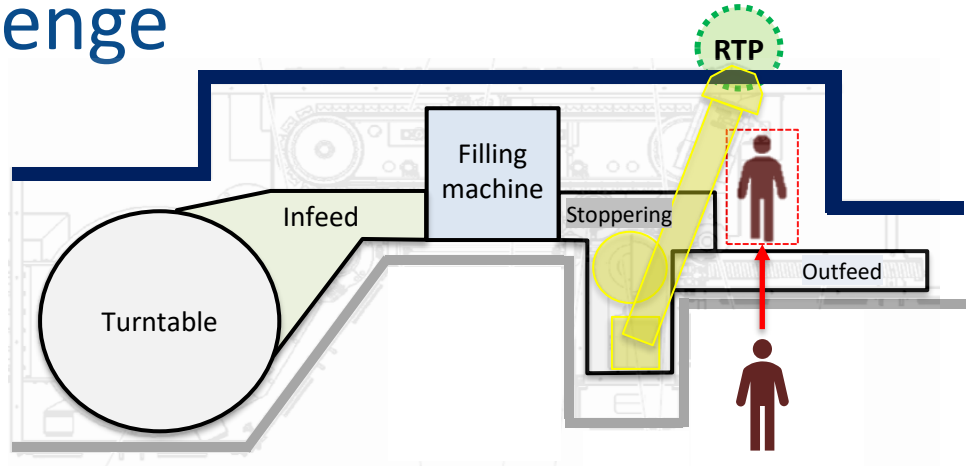
Top-Down View of RABS

Parts	Picture
Chute	
Bunker	
Vibrating plate	
Transfer pipe	
Stopper hopper	

Key Challenge



Limited Reach of RABS Glove



Top-Down View of RABS

RTP port from the outside

"…the operator must **squat and enter** the RABS through the open RABS door **under the vial transporting belt** that may that potentially contaminate the operator's gown during the process and may lead to **subsequent contamination of then filling area** when the operator is inside the RABS."

Additional Improvement Opportunities

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established or are deficient.

Critical zone protection

- ✓ Operator blocked first air over the exposed indirect product contact surfaces with the RABS glove during intervention
- ✓ Operator blocked first air over the exposed tubing outlet and ferrule by placing a gloved hand (RABS glove) over the clamp while connecting the sterile filtration tubing (downstream of sterilizing filters)

Material transfer

- ✓ Operator handed partially open sterile bag, from under the RABS wall, during the aseptic connection of the sterile filtration tubing

Disinfection

- ✓ RABS gloves were not disinfected by operators during the startup, setup, and intervention.

Process Risk Assessment

- Preparation of materials/parts
- Material transfer/storage
- RABS set-up
- Environmental monitoring
- Filling/Intervention
- Stoppering

Step	Number of evaluated steps	
	Initial Assessment	Re-assessment
Preparation/General	10	10
Material transfer/storage	9	12
RABS Setup	17	75
Environmental Monitoring	2	17
Filling/Intervention	24	34
Stoppering	2	2
Grand Total	**64**	**150**

Scoring Matrix

Consequence	Severity	Likelihood	Detectability	Score
Contamination of final **drug product**	Contamination of **critical surfaces**	Inevitably occurs due to inadequate procedure.	Only observed through non-routine system/process review (infrequent).	**10**
Carry over contamination to **critical surfaces**	Contamination of **non-critical surfaces** (that may directly / indirectly contaminate critical surface)	Procedure exists but the risk is high as the action is not aligned with the procedure.	Failure may be evident to a technical expert. Logbook/batch record-controlled activities with review after execution.	**8**
Increase of bioburden in Grade A	Contamination of **non-product contact parts / RABS environment**	Risk of contamination due to existing procedure where **insufficient subsequent controls** are in place.	Only covered by **general microbial data** (general EM data, simulation in routine APS)	**5**
Carry over contamination to Grade A	Contamination of Grade B environment	Risk of contamination exists but **sufficient contamination controls** are in place.	Covered by general microbial data (EM & APS), **along with double witness / visual alarms, controls**	**2**
		Has never occurred and is highly unlikely to occur unless intended	Failure and effect of failure evident. Combination of multiple documented controls and testing before use	**1**

High risks identified from Risk Assessment

RPN = Severity * Likelihood * Detectability

Process Step	Potential Causes of Failure Mode	Severity	Likelihood	Detectability	RPN	Impact Level
Operator entry into RABS	Exposure of Grade A operator gown below working level when **squatting** below the screw to enter RABS	8	5	5	200	**High Impact**
Operator entry into RABS	Contact of Grade A operator gown on surface below working level when **squatting** below the screw to enter RABS	8	5	5	200	**High Impact**

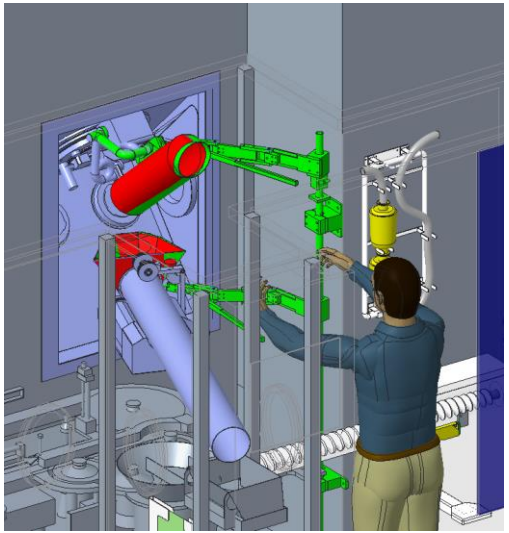
Engineering Solutions

Options	Solutions	Considerations	Selected?
Eliminate squatting	▪ Modification of conveyor	▪ Remaining contamination risk of filling area when the operator is inside the RABS	✗
Eliminate entry into RABS	▪ Modification of filling line components and RABS set-up process	▪ Impact on qualification/validation	✓
	▪ Modification of RABS – UDAF extension	▪ Impact on qualification/validation ▪ Extensive construction ▪ Time required for implementation	✗
	▪ Modification of stopper transfer system	▪ Impact on qualification/validation ▪ Extensive construction ▪ Time required for implementation ▪ Technical complexity	✗

Engineering Solutions

Modify product contact parts and revise setup activities

[Installation of chute] (Past)



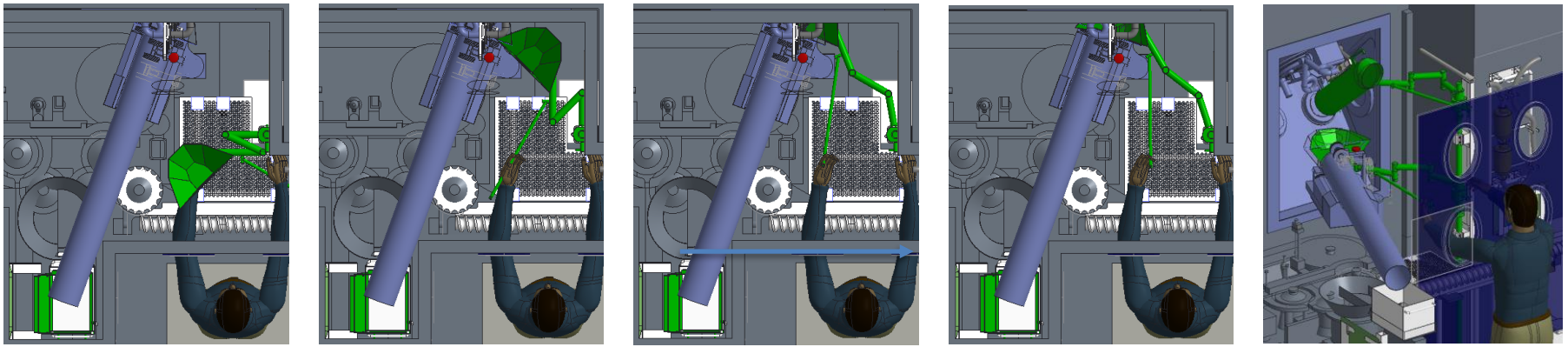
[Installation with mechanical arms]

[Installation of chute]

Engineering Solutions

Modify product contact parts and revise setup activities

Initial → Final



Critical zone protection (Multiple sterile layers)

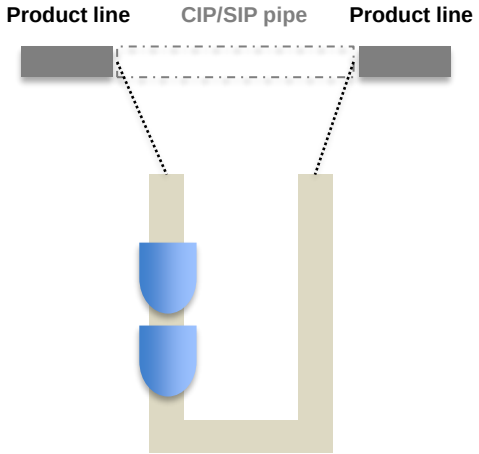
To protect the critical zone of filling component from exposure of Grade B area during the material transfer

[Material Transfer] (Past)

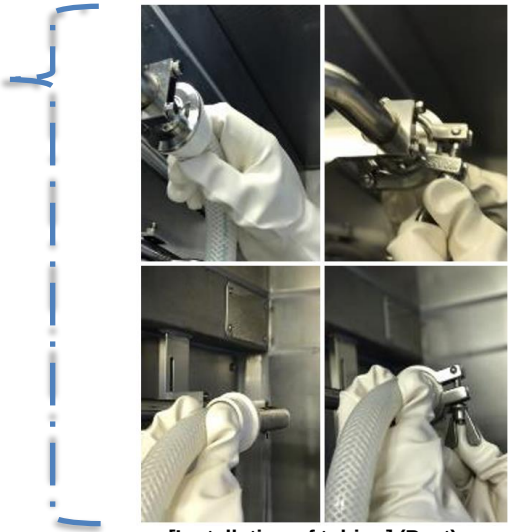
[Material Transfer] (Current)

Critical zone protection

To protect the critical zone by unidirectional airflow and first air



Sterile filtration line



[Installation of tubing] (Past)

[Installation of tubing] (Current)

Critical zone protection

To protect the critical zone by unidirectional airflow and first air

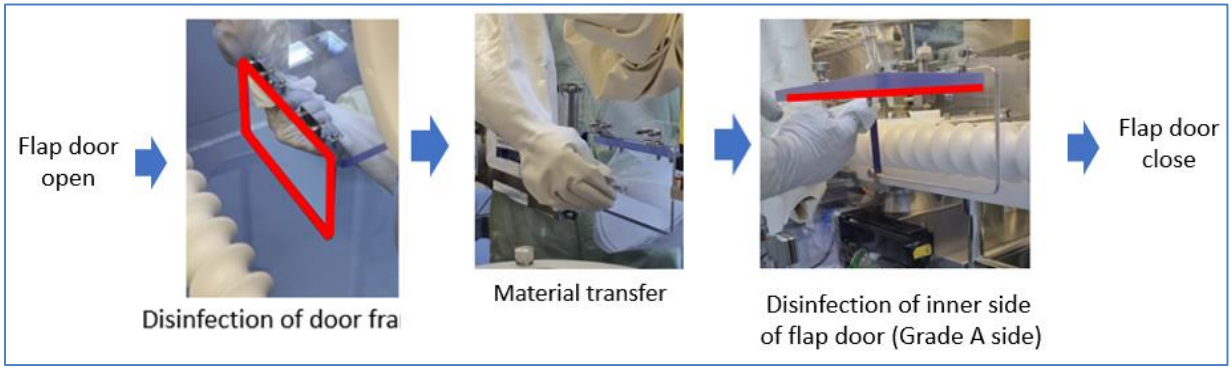
[During intervention] (Past)

[During intervention] (Current)

Enhanced material transfer process

To protect the material by unidirectional airflow and first air

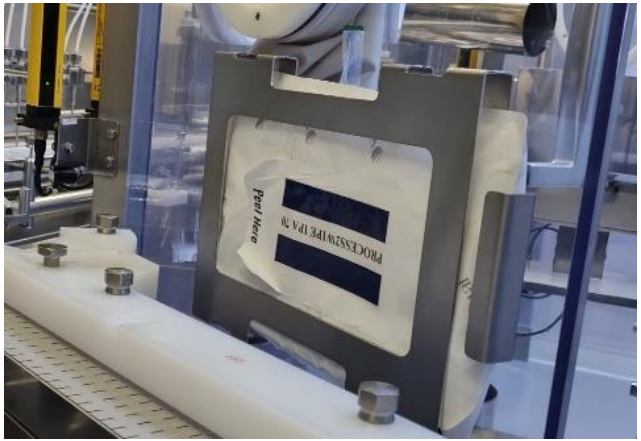
[Material transfer] (Past)



[Material transfer] (Current)

Enhanced disinfection during Filling

To disinfect the RABS gloves during RABS set-up/filling/intervention



Process step	When to sanitize
Startup	After glove installation
Setup	After door open/close during set-up
	After each use during set-up
Intervention	After Intervention
EM Activity	After EM

- The RABS gloves are also always disinfected using the pre-soaked wipe (70% IPA)

Enhance Aseptic Operator Training Program

Effort to increase/maintain high quality standard of aseptic operating/behavior

Continuous improvement in Aseptic performance

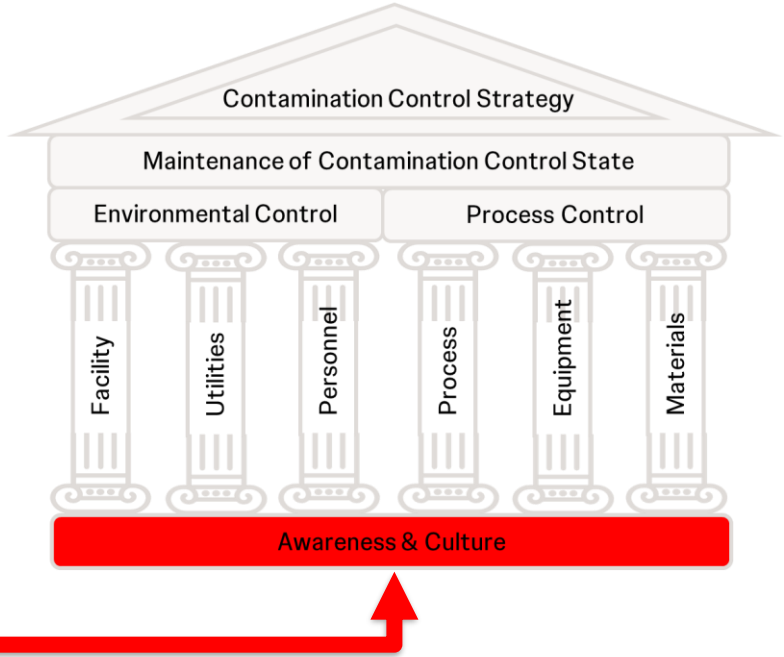
Personnel Training

- Operator training
- QA oversight personnel training
- Training experts in Site Sterility Assurance Team

Proactive monitoring of potential risks

- QA oversight / Ops supervision
- Internal audit
- Site quality risk register
- Gap assessment of regulatory guidelines / external site observations

Enhancing quality mindset



Thank You

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