Retrofitting RABS to existing aseptic filling lines

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The challenge

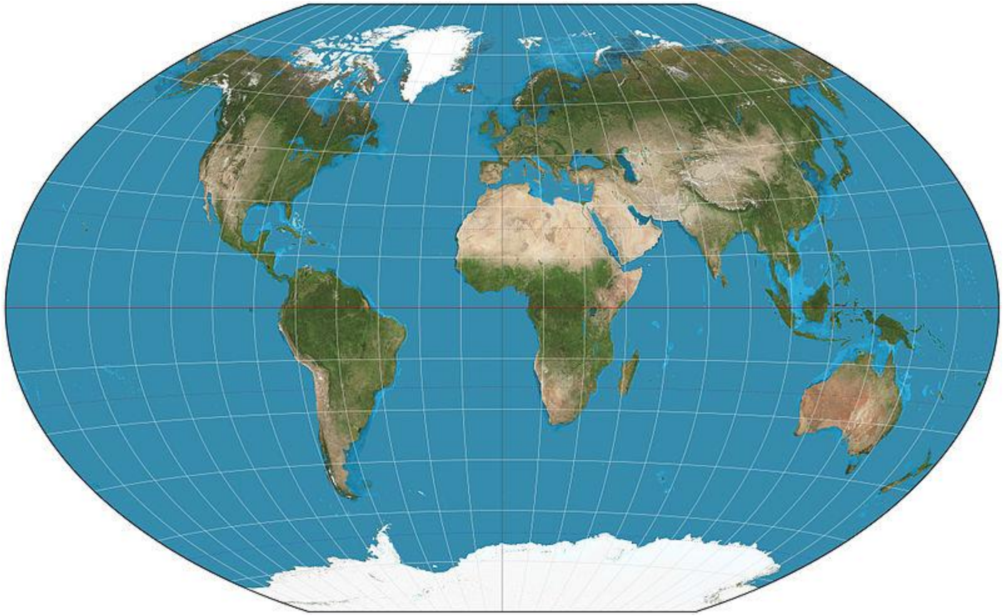
- How can the industry adapt existing equipment to include effective barrier systems without going to full isolator technology?

Why not go straight to isolators?

- Line design
- Line capacity
- Cost
- Time

Sanofi aseptic filling capability

- More than 100 conventional aseptic filling lines globally
- Need for more capacity to meet growing product demand

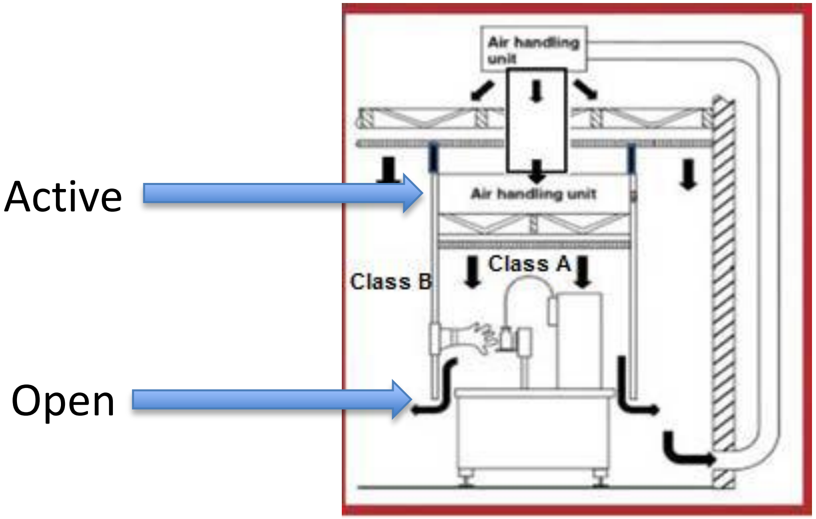


Sanofi strategy

- New lines
  - Full isolation technology
- Existing lines
  - Open active RABS system
    - Rigid barrier enclosure with glove ports
    - Doors kept closed in routine operation / sanitization & line clearance if opened / automatic recording of door opening
    - Introduction of components through a system to protect them from exposure to surrounding Class B outside the barriers

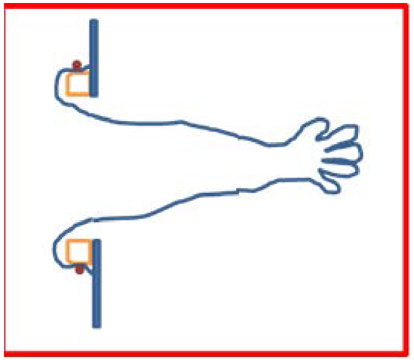
"Open" & "Active" RABS

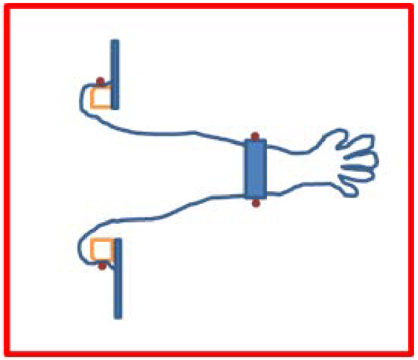
- Sanofi definition
  - "Open": class A air exits to class B zone through space on the bottom part of filling line
  - "Active": dedicated AHU for RABS enclosure



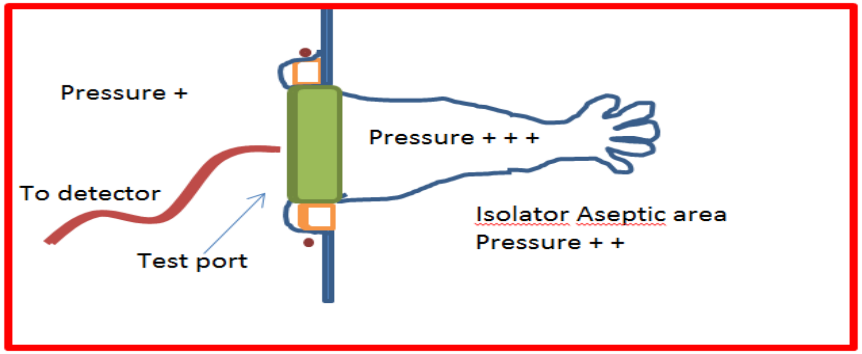
Gloves

- Could be "long" or "short" sleeve





- Preferred integrity test in place from outside



Sanofi RABS retrofit approach

- Key criteria before starting
  - Satisfactory history of operation
  - Good environmental monitoring results and trends
  - Routine Media fills successful
  - Limited number of technical issues

Sanofi RABS retrofit approach

- Step 1: Technical evaluation of filling line
  - Check feasibility of any operation that has to be performed with doors kept closed (use 3D CAD)
    - Machine set-up or change-over
    - Routine production
    - Interventions during production
    - Environmental monitoring (sampling etc…)
  - "Tight connection" of all access hatches to all mechanical parts located on the main frame of equipment,
  - Review of age and maintenance history of equipment

Sanofi RABS retrofit approach

- Step 2: Review surrounding Class B area
  - Ensure full access around filling equipment for manufacturing and maintenance operation
    - Notably easy access to the rear side of filling machine which is necessary for set-up and troubleshooting
  - Sufficient space to install a dedicated air handling unit (AHU) to achieve Active RABS design
  - Material and equipment flow and handling
  - Decontamination

Sanofi RABS retrofit approach

- Step 3: Mock up
  - Need to check feasibility of any operation that has to be performed with the doors kept closed
  - Must account for a range of operators
  - Dummy machine base with dummy key components
    - A frame with guards and ports
    - Built in cheap and easy to modify materials
    - Full scale to model future equipment and layout

Sanofi RABS retrofit approach

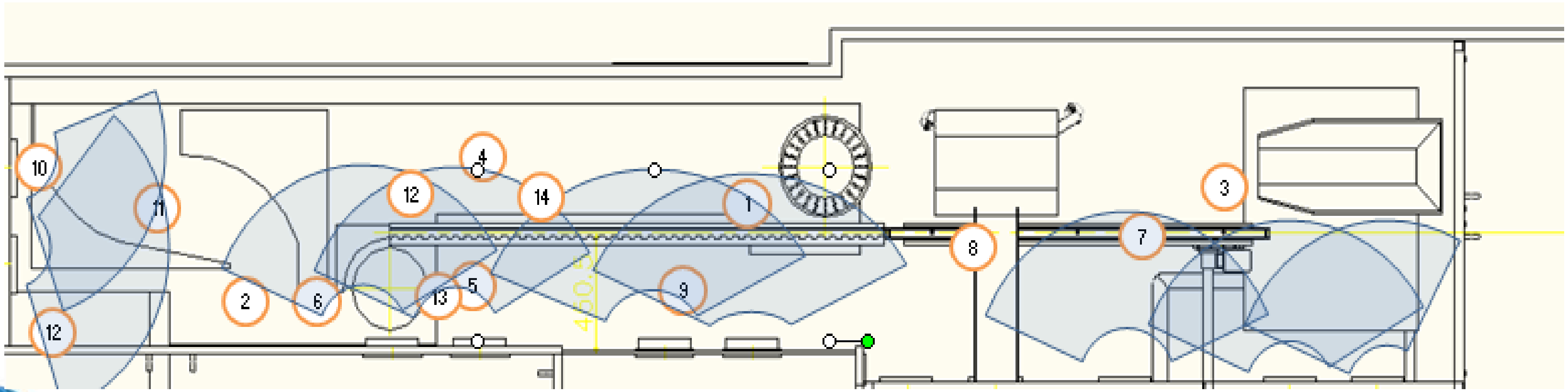
- Step 3: Mock up (continued)
  - Feasibility criteria
    - Operation to be performed in a 100% reliable manner by any qualified operator or technician
    - Number and position of gloves port must be optimized without causing damage to any machine part (e.g. gloves)
    - Interventions can be made in a timeframe that is acceptable for line operational performance

Practical Examples

- Case study 1: Aseptic filling operation in Italy
  - Multiple conventional filling lines
  - Manufacture of life saving / medically necessary products
  - Running at close to full capacity

Case study 1 – Solution

- Technical solution developed
  - Install barriers with glove ports around existing filling line
  - Rapid implementation
    - Possible to do the work in planned shutdowns
    - Work could be phased
  - Significantly lower cost than a full new line with RABS or isolator



Case study 1 – Ergonomic study

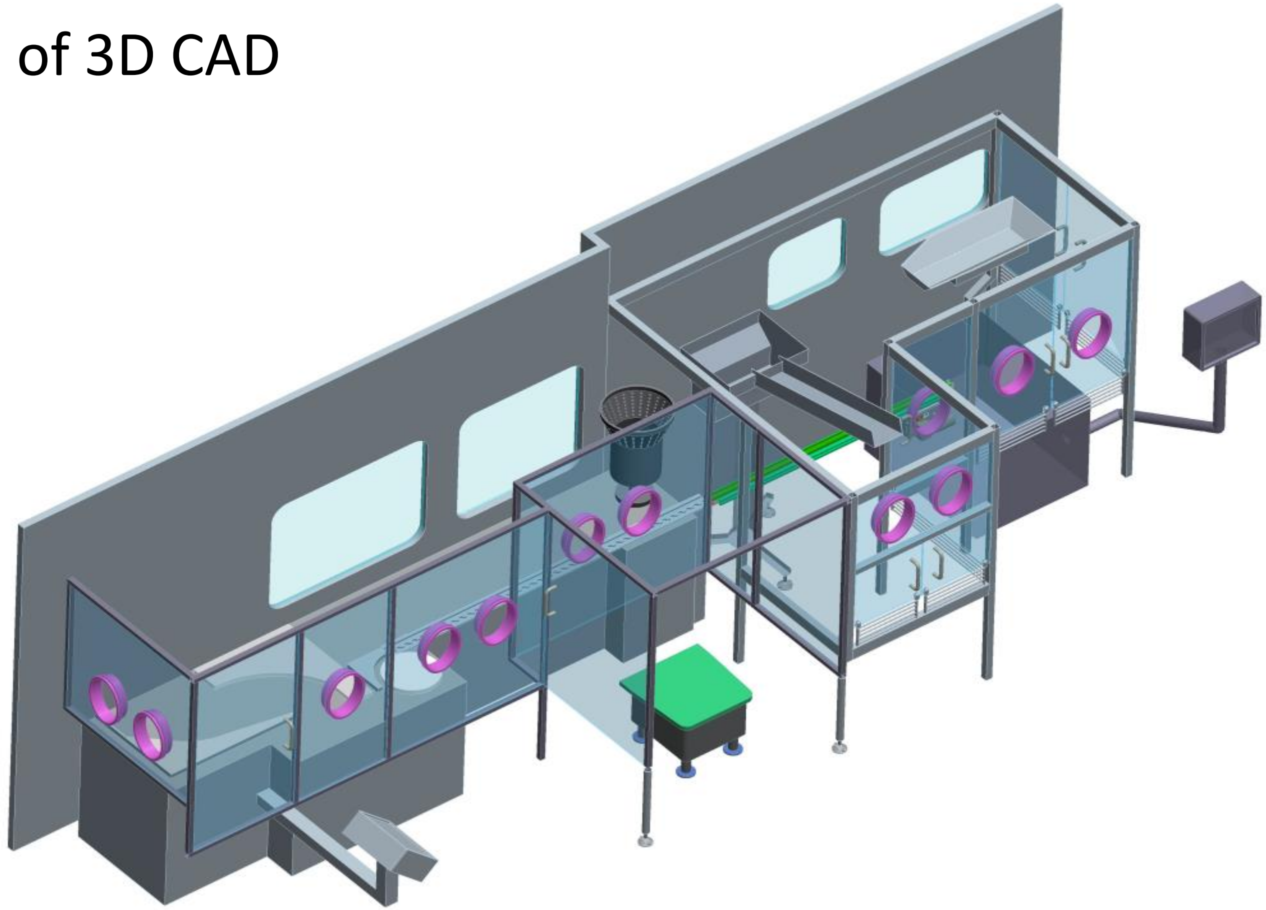
- Intervention review
  - Reviewed all the type, location and frequencies of interventions

Attività	Frequenza (1 ogni sei mesi; 2 ogni mese; 3 ogni settimana)	ID punto	facilità accesso (1:buona con 2 guanti; 2:scarsa con un guanto; 3:non raggiungibile)	fattore rischio	Azioni
Regolazione scivolo combiseals	1	1	2	2	
Regolazione coclea ingresso flaconi	1	2	3	3	
Regolazione testine ghieratrice	2	3	1	2	
Sbloccaggio ghiera su scivolo	2	1	2	4	
sostituzione siringa	1	4	3	3	
sostituzione acquasant	1	4	3	3	
sostituzione filtrini	3	4	3	9	gestione del livello acquasant con un allarme in caso di eccessiva aprtura valvola.
centratura aghi	3	5	1	3	
sostituzione aghi	3	5	1	3	
sistemazione perno siringa	1	4	3	3	
regolazione fotocellula presenza flaconi	2	6	2	4	
regolazione fotocellula minimo accumulo nastro	2	7	2	4	
regolazione fotocellula massimo accumulo nastro	2	8	3	6	
regolazione contrasto inferiore stellare ingresso flaconi	1	6	3	3	
regolazione cuscinetti guida	1	5,9	3	3	
rimozione flacone caduto nastrino	2	7	2	4	
rimozione flacone caduto nastrino	2	8	3	6	valutare se il flacone caduto può essere raccolto nel punto 7
rimozione flacone caduto coclea	3	2	3	9	spostare drenaggio ed inserire un guanto supplementare di fronte alla coclea
rimozione flacone caduto polmone ingresso	3	10->11	2	6	
Controllo dosaggio	3	8	3	9	inserire un dispensatore di ghiere sulla stazione combiseal
monitoraggio microbiologico esposizione	3	12	2	6	
monitoraggio microbiologico aspirazione	3	13	1	3	
monitoraggio microbiologico contatto	3	5	1	3	

Observation of manufacturing operations used in risk analysis
1)Frequency of interventions
2)Area of interventions

Case study 1 – Ergonomic study

- Use of 3D CAD



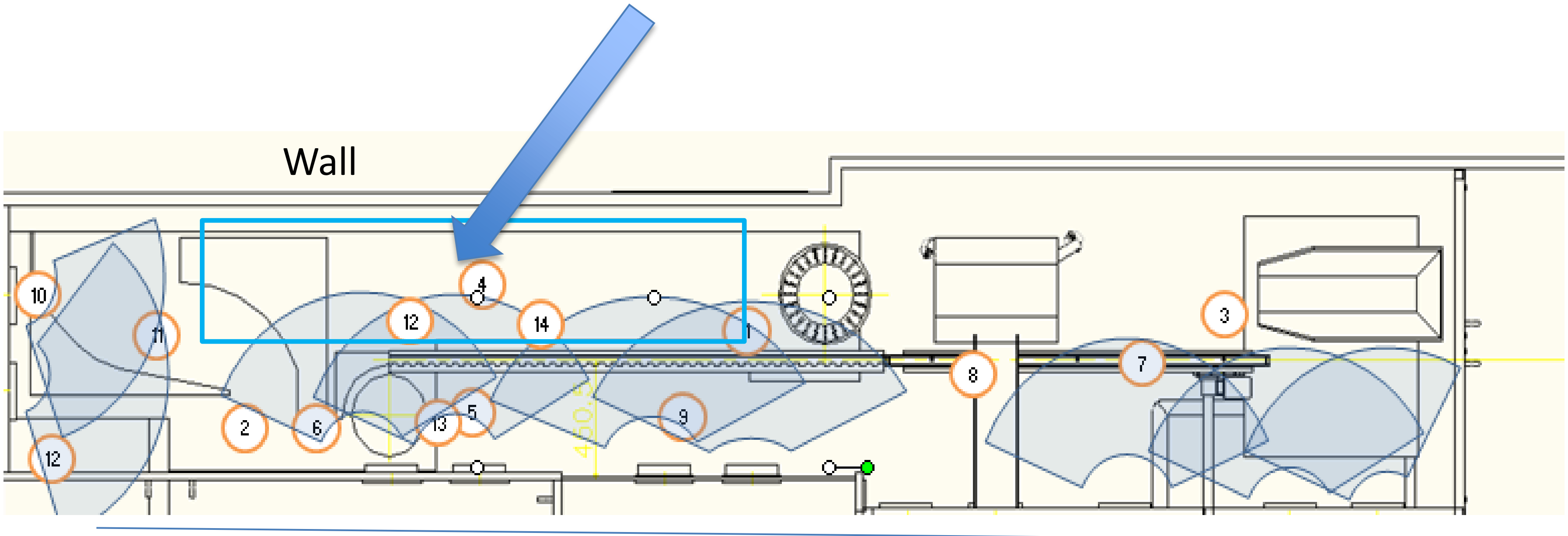
Case study 1 – Solutions implemented

- Installation of double gloves
  - Used near critical points that need most frequent intervention (e.g. filling needles)

- Loading of components
  - Sealed bag of stopper is put on a perforated surface under Laminar Air Flow
  - By the use of the gloves the bag is cut and emptied into the hopper through the chute

Case study 1 – Limitations

- Limitations of RABS approach
  - Difficulty to access the filling pumps / reservoir
  - Means having open doors at least in the set up phase



Operator side

Practical Examples

- Case study 2: Aseptic filling operation in France
  - Manufacture of lyophilised vaccines
  - Good example of use of a full size mock up

Practical Examples

- Case study 3: Aseptic filling operation in Germany
  - Older design filling line
  - Involved a "ground up" rebuild

Case study 3 – Challenges

Uncovered neon lights in class A

Sliding doors: very large + move into unclassified area

Huge opening beneath doors

Stopper hopper very close to class B

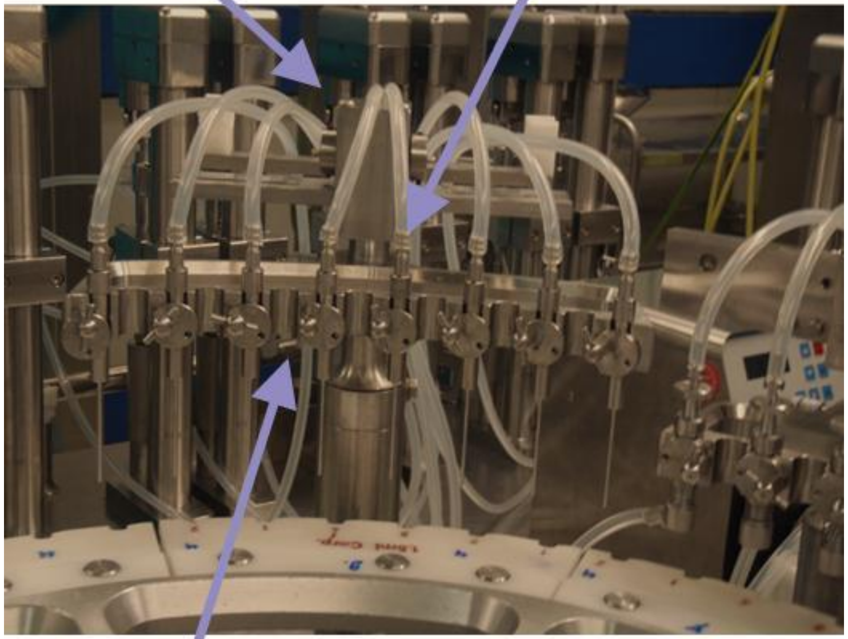
No stopper container → Operator leans over hopper during re-fill

Sorting wheel for single-hole plungers in place

Case study 3 – Challenges

Tubes disorderly

Difficult aseptic
connections



filling needles
Screwed fixture
Hard to reach
poor visibility
difficult hand position

Case study 3 – Solutions

Turnable needle fixture → improved visibility and reachability

Optimized position of filling pipes
→ behind pumps

clamps for filling tubes

MPC-couplings → safe aseptic connections

fewer parts in class A
(no peristaltic pump, filling tubes, output for empties)

Simplified safer set up

Case study 3 – Solutions

Contained neon lights in class A

13 gloves at critical positions

Upgrade monitoring systems

Segmented class A area (Cap + stopper hopper)

LF ceiling lower then room

→ easier to clean, optimized air flow

movable vessel protected by vertical LF

Additional Class A outside filling machine
→ Sufficient room for sterile containers during set up

When is a RABS retrofit maybe not the best solution?

- If the line does not perform well currently
- If the ergonomic layout of the line limits glove access
- If the line concept and design cannot be easily adapted
- If the line is becoming obsolete

Conclusions

- Retrofitting an existing aseptic filling line is possible and can:
  - Save time
  - Reduce cost
  - Improve line aseptic performance

- Success only comes from careful planning and study of the existing line and the proposed solution

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Thank you!

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