Aseptic Isolated Filling Line, QRM approach and case study

The Comecer and IBI Project

PDA Italy Chapter

Aseptic Filling: Innovazioni tecnologice e trend regolatori

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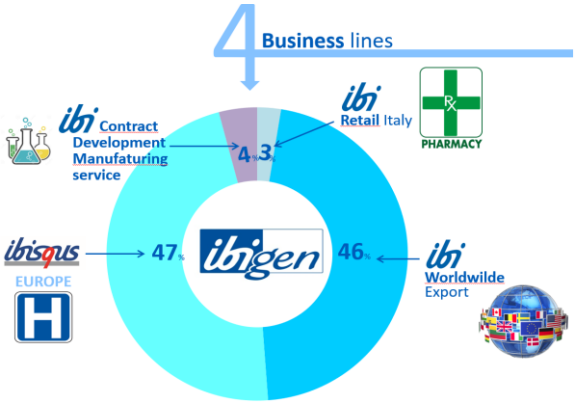
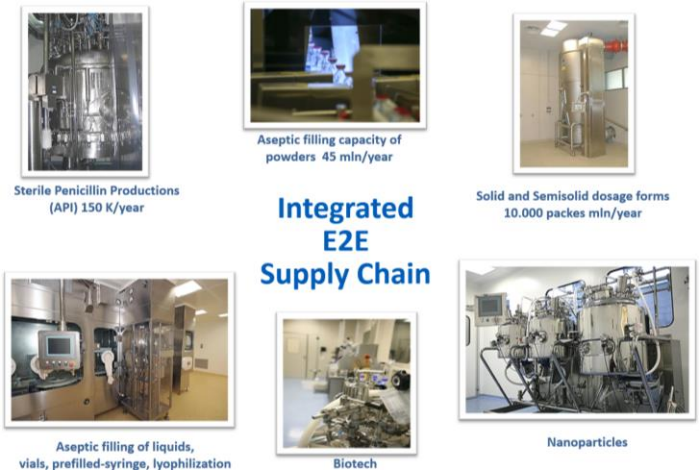
Summary

- IBI Company Profile
- Project Background: Espresso Concept
- Collaboration: The importance to share competences
- Process Analysis
- Process Splitting
- Process Risk Analysis
- Lesson Learned

IBI Company Profile

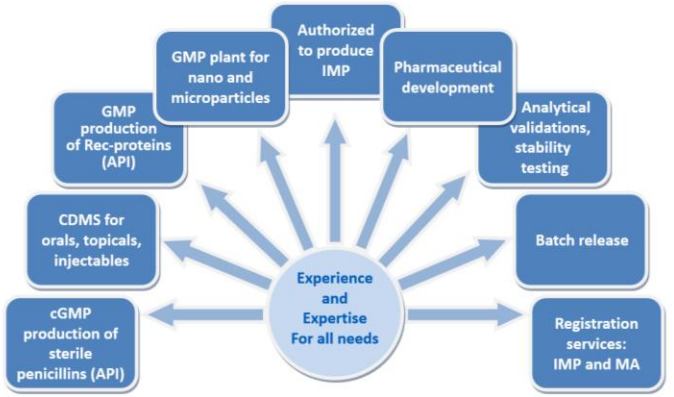
Founded in 1918 by Prof. Giovanni Lorenzini, IBI exports worldwide its drug products manufactured according to cGMP standards.





1918 - 2018 Fare per Dare

One partner, from product development to market



Project Background: Espresso Concept

Espresso® is ready to mix solution, consisting of a standard vial and a diluent bag assembled under sterile conditions. The Espresso® bag is equipped with a patented connector and each connector with a spike, able to penetrate from the bag to the vial, allowing to activate communication between the two containers under sterile condition.

Any standard vial may be plugged in to the bag's Espresso® connector.

CUSTOM SOLUTION

EXPERTISE

COMECER an ATS company

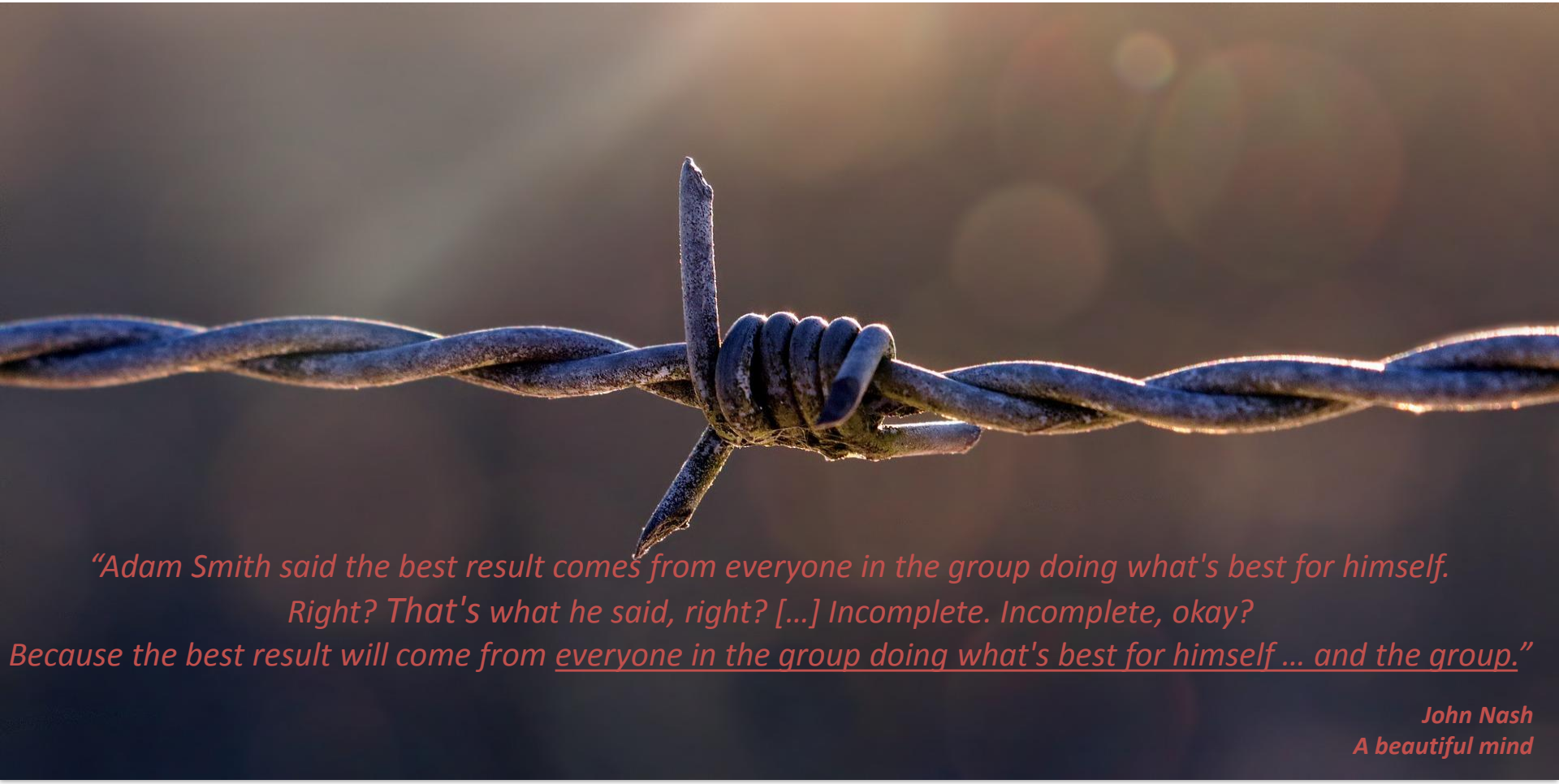
HELP

KNOW HOW

ESPRESSO® BAG + STD VIAL = ESPRESSO®

https://www.youtube.com/watch?v=8bQDbMX9sGE&feature=youtu.be

Collaboration: The importance to share competences

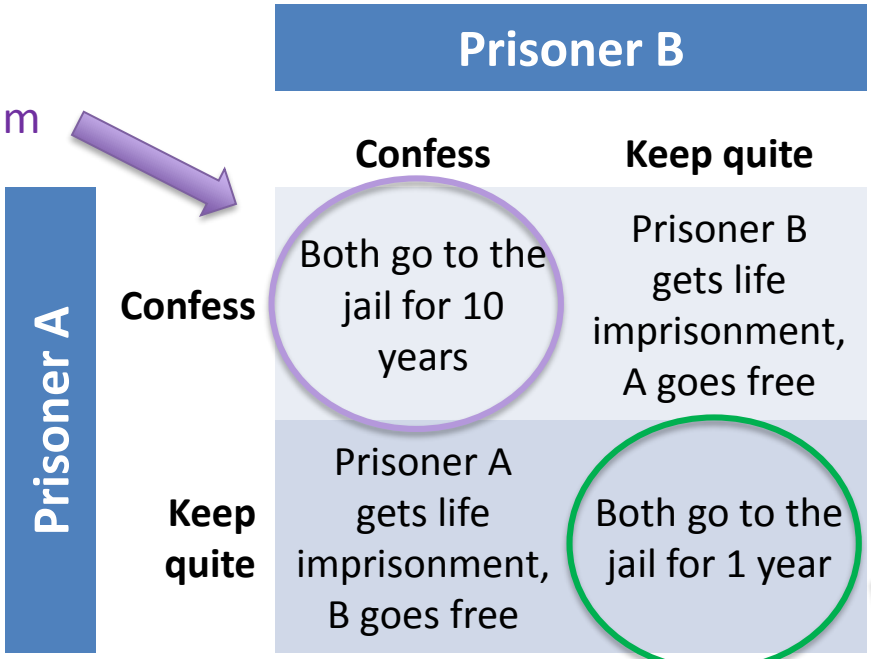


"Adam Smith said the best result comes from everyone in the group doing what's best for himself.
Right? That's what he said, right? […] Incomplete. Incomplete, okay?
Because the best result will come from everyone in the group doing what's best for himself … and the group."

John Nash
A beautiful mind

Nash equilibrium

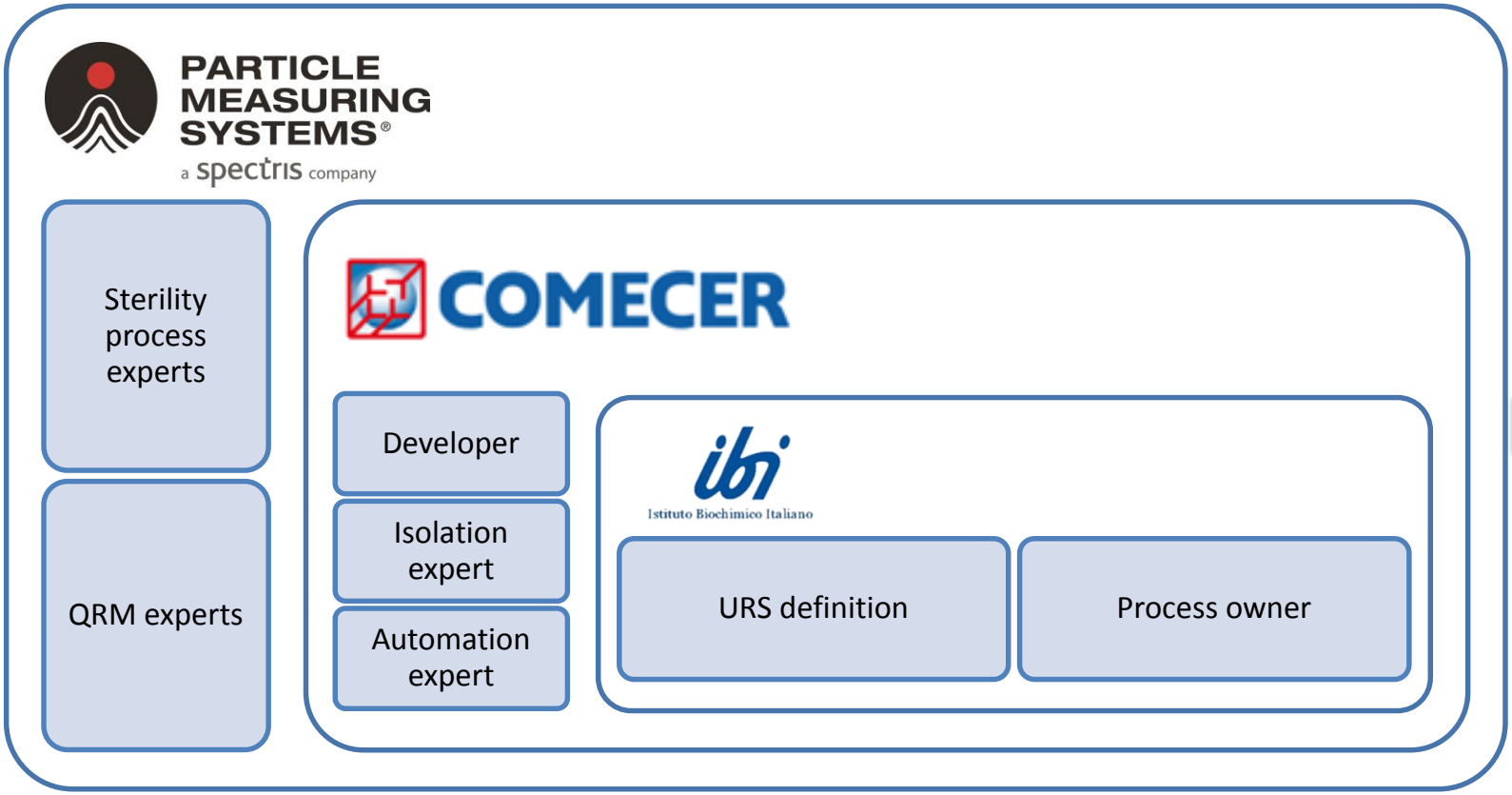
Decisions good for individual can be terrible for the group



Reachable by collaborating not with individualistic strategies

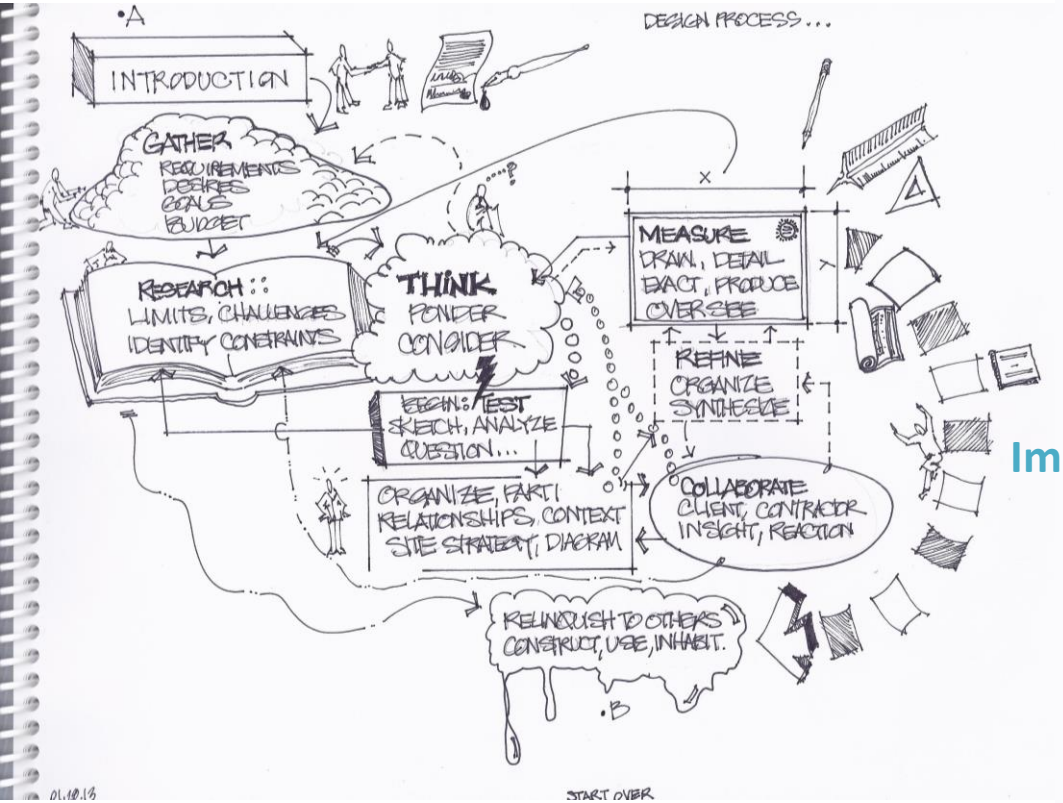
Pareto efficiency

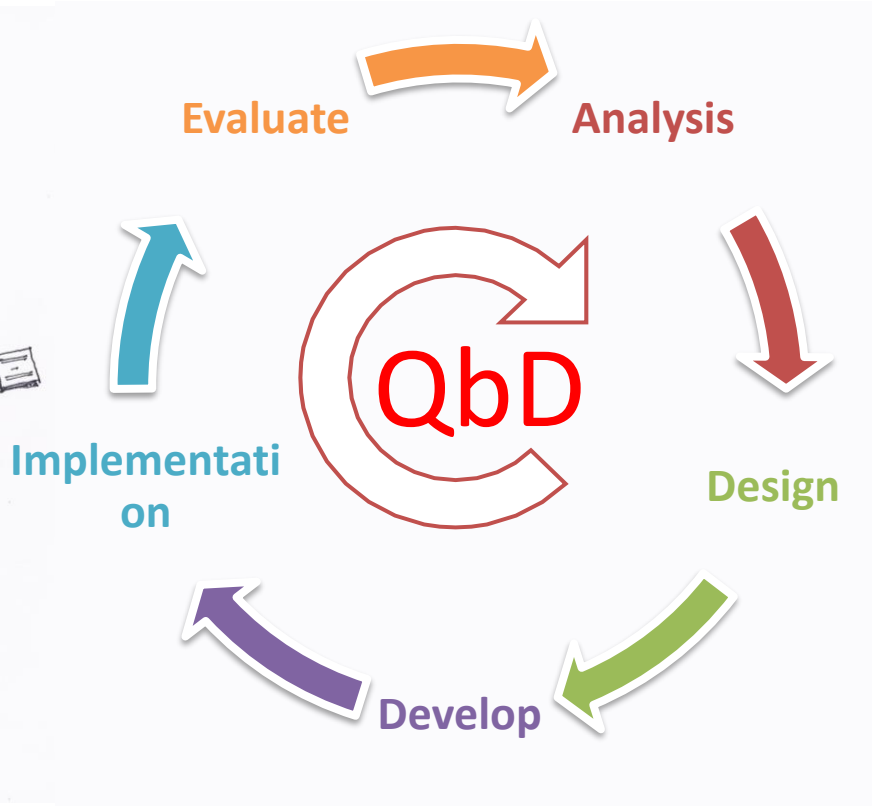
Team structure and responsibilities



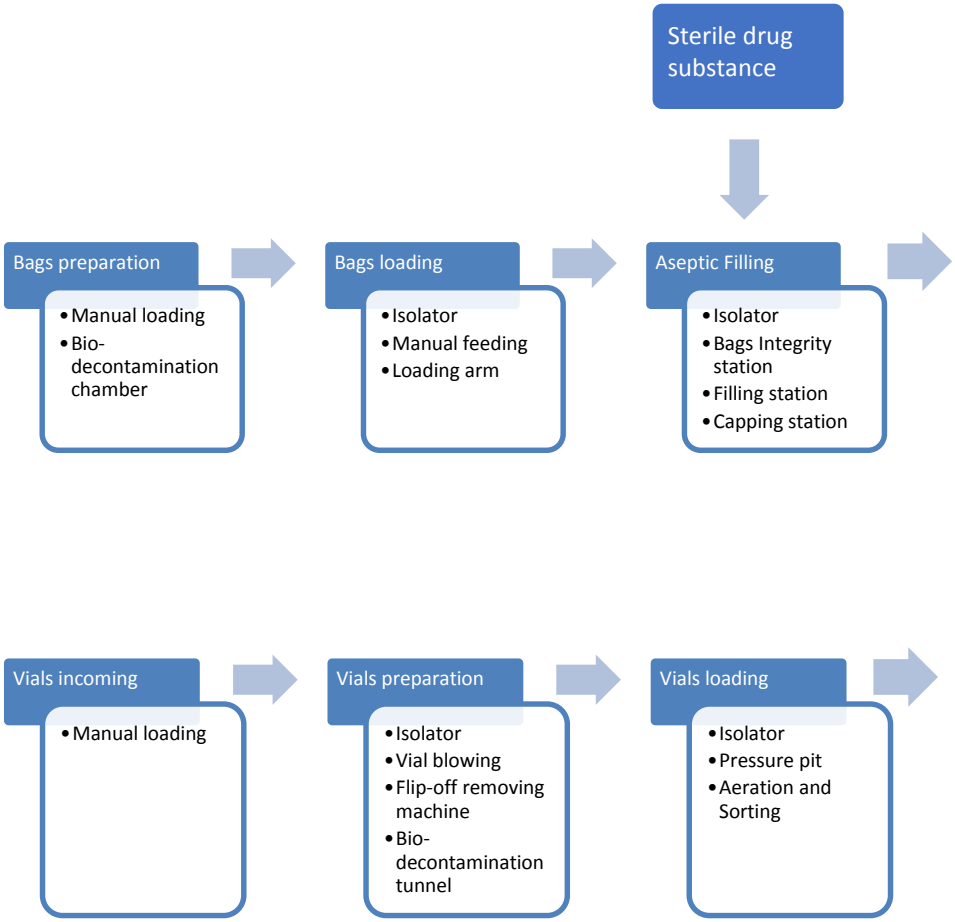
Pareto efficiency

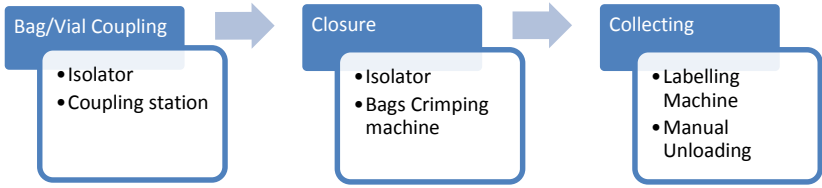
Pareto efficiency: the ADDIE Model





Process Analysis: The Starting Point



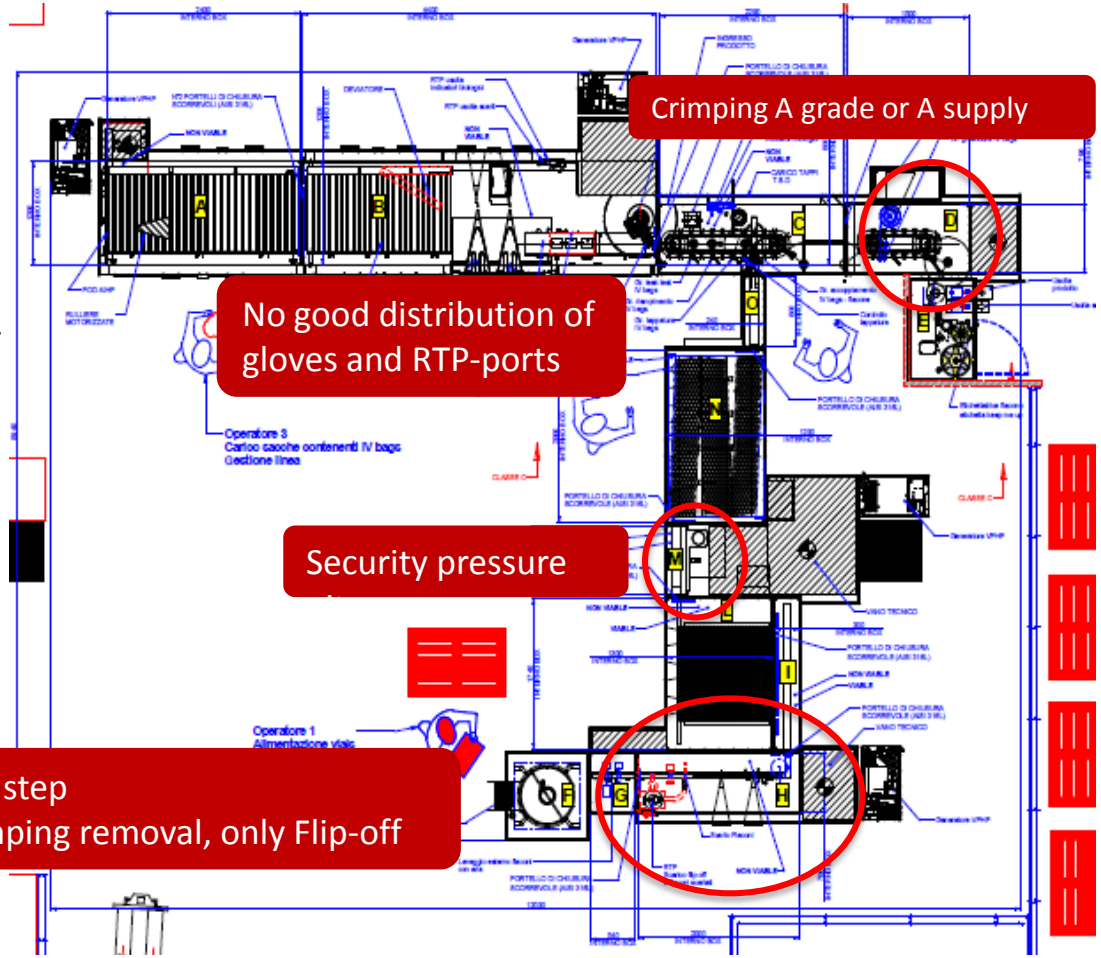


- Bags ready to use
- Manual feeding
- Filling & capping
- Coupling bag-vial
- Bag crimping

- Sterile Penicillin Aseptic Filled Vial drug product
- Flip-off removing

Process Analysis: Preliminary Drawing

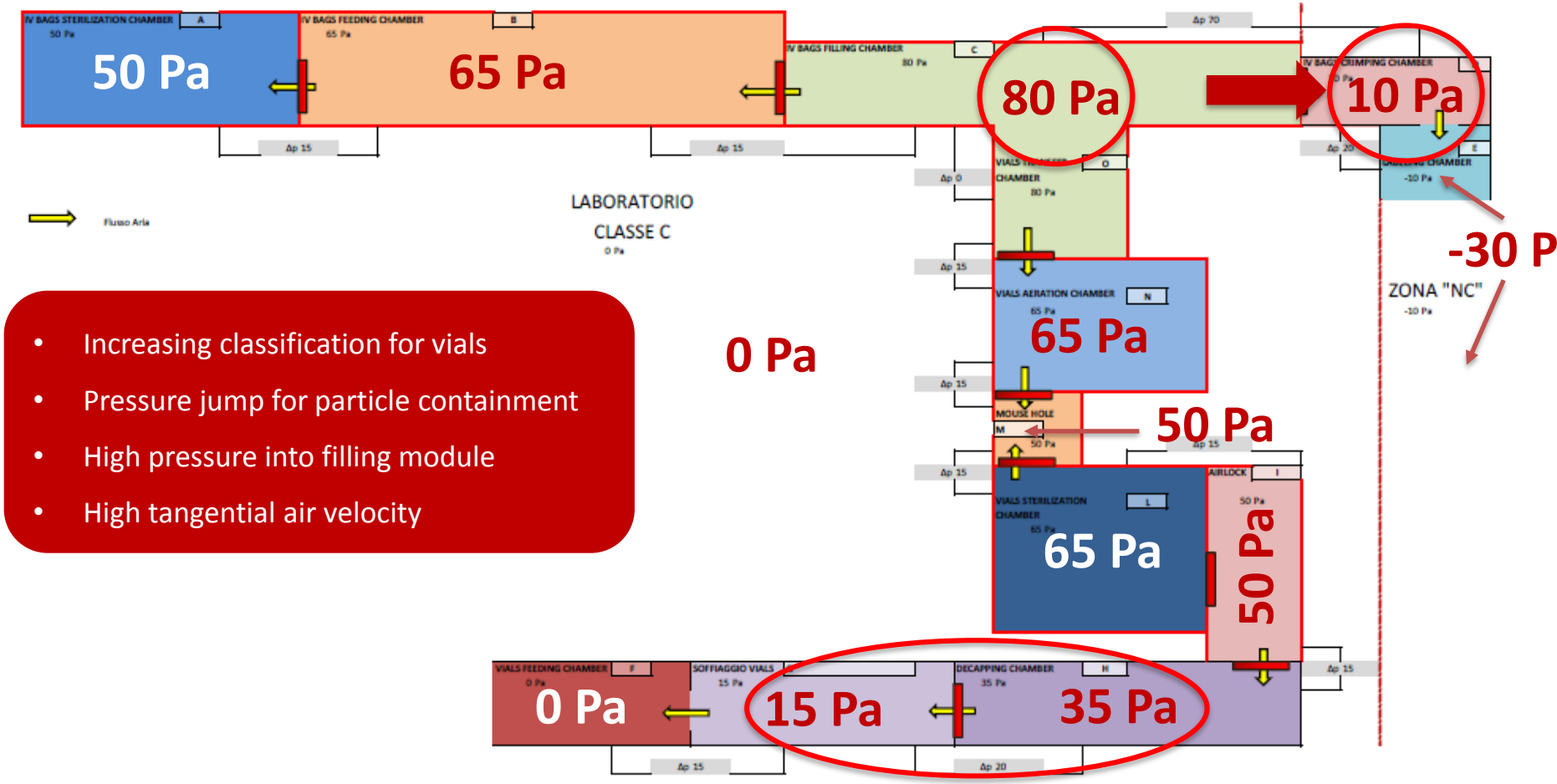
- A: Bags decontamination
- B: Bags feeding
- C: Filling, capping & Coupling
- D: Bags Crimping
- E: Labeling



- Blowing step
- Not crimping removal, only Flip-off

- F: Vials feeding
- G: Vials blowing
- H: Flip-off removal
- I: Airlock
- L: Decontamination tunnel
- M: Mouse hole
- N: Vials aeration
- O: Vial transfer

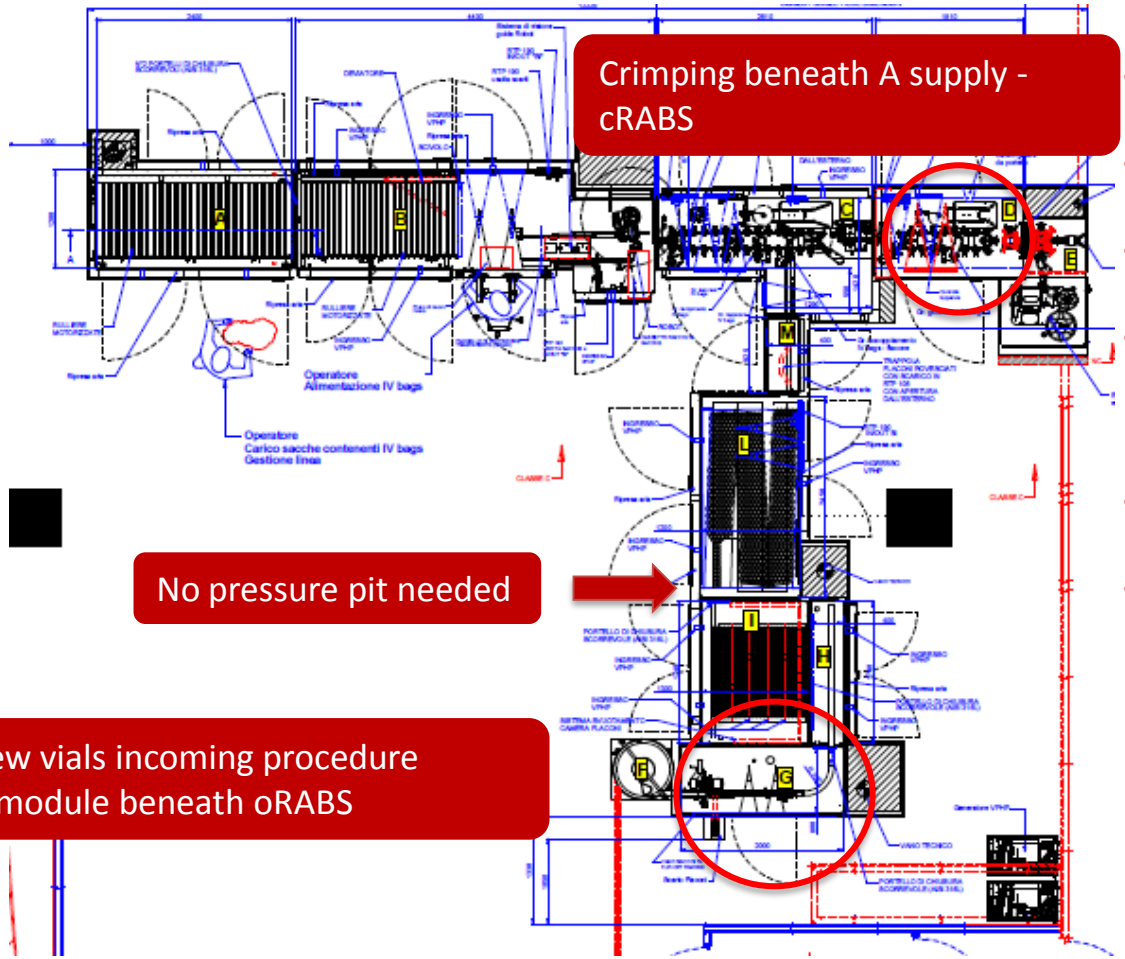
Preliminary drawing: Pressure cascade analysis



- Increasing classification for vials
- Pressure jump for particle containment
- High pressure into filling module
- High tangential air velocity

Process Analysis: Actual Drawing

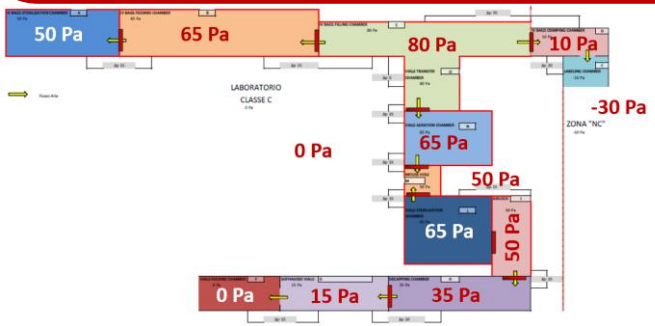
- A: Bags decontamination
- B: Bags feeding
- C: Filling, Capping & Coupling
- D: Bags Crimping
- E: Labeling

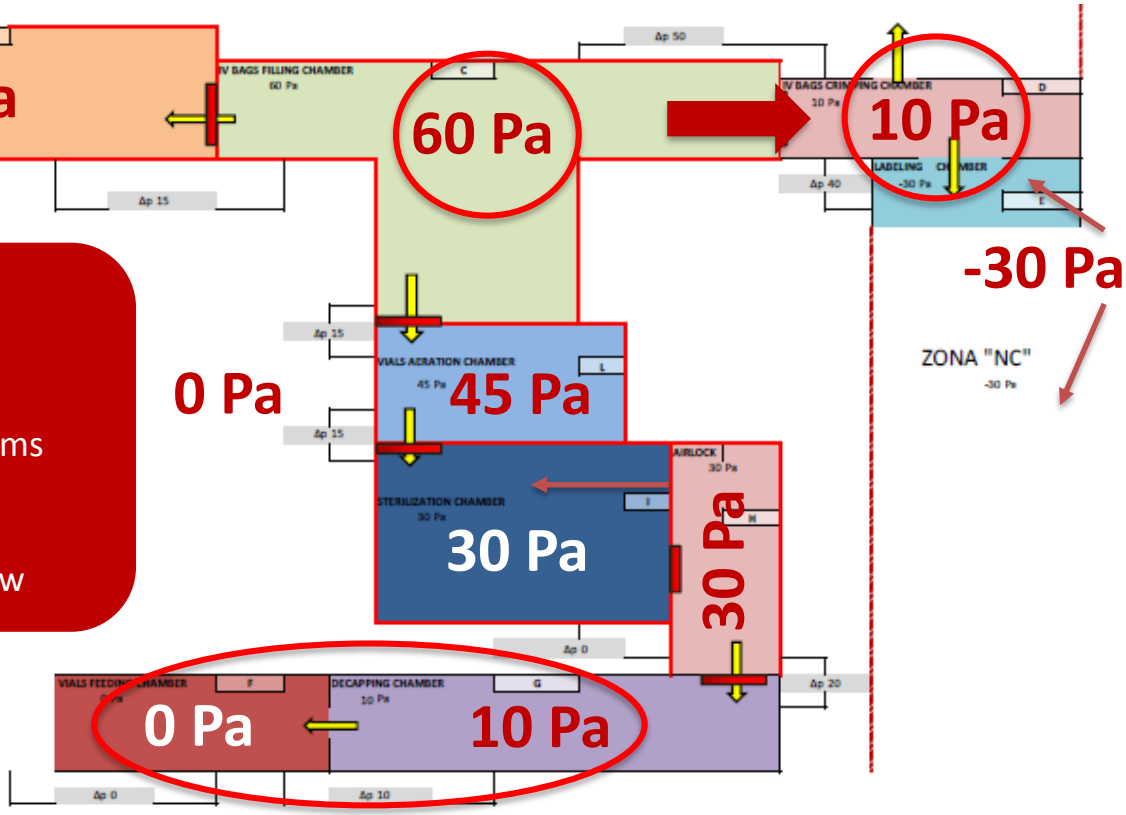


- F: Vials feeding
- G: Flip-off removal
- H: Airlock
- I: Decontamination tunnel
- L: Vials aeration
- M: Overturned Vials trap

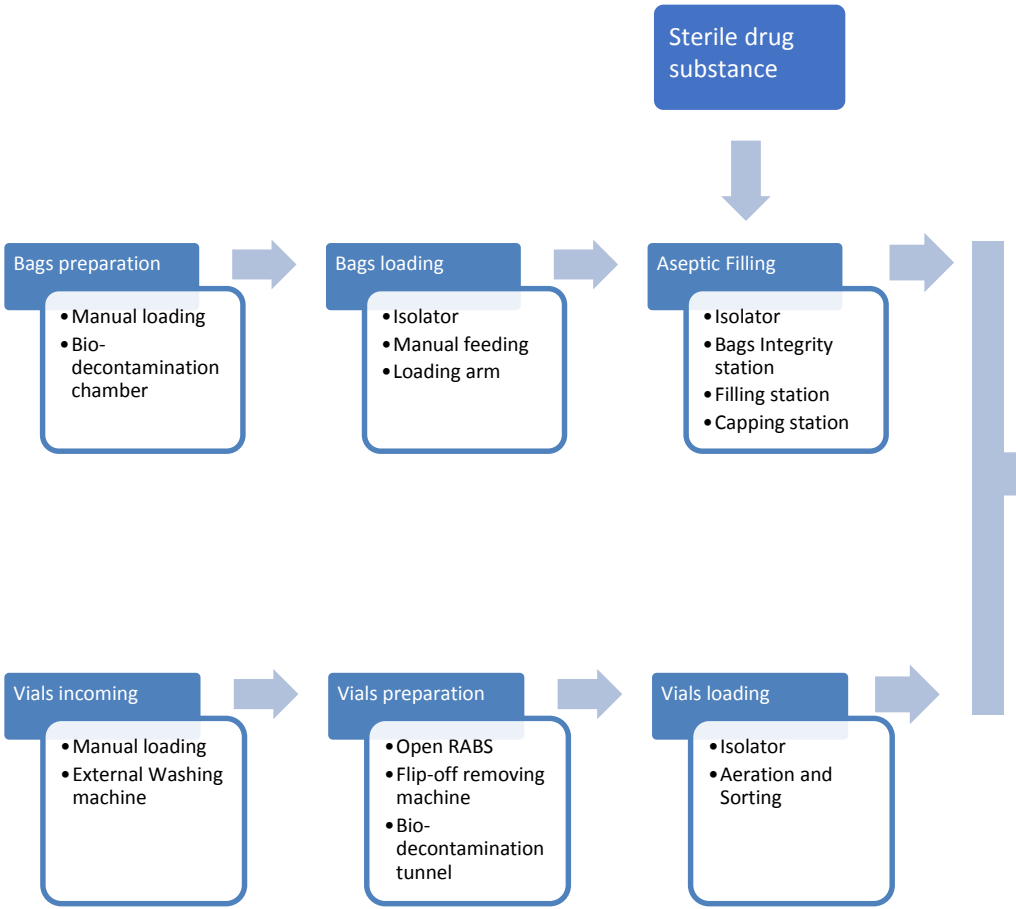
Process Analysis: Final Pressure Cascade

- Greater balance between the phases
- oRabs with light over pressure
- Filling with 15 Pa more than surrounding rooms
- Reduced tangential air velocity
- Exhaust grid needed to cut the tangential flow

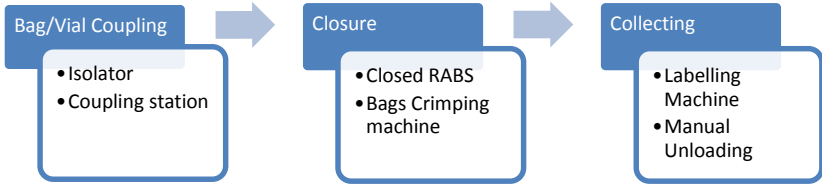




Process Analysis: The Optimized Process



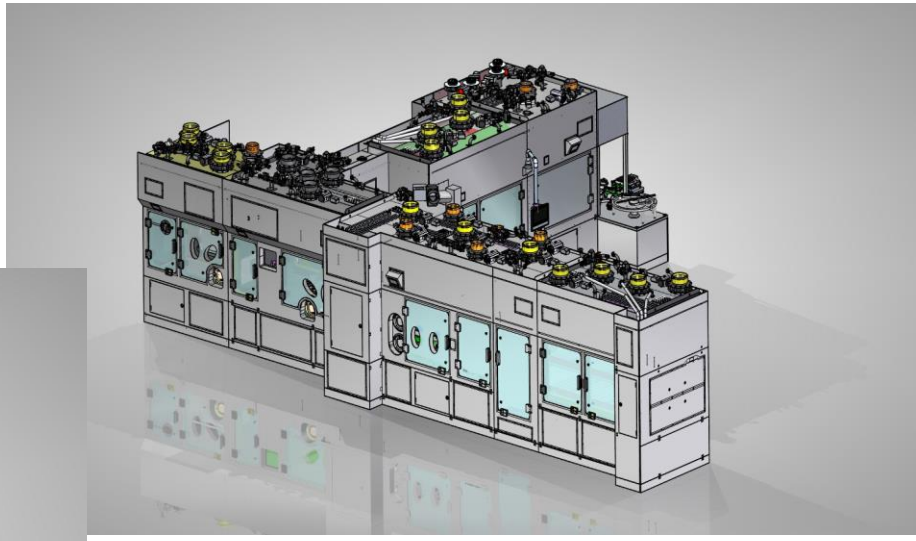
- More flexible distribution of gloves and RTP-port
- Better solution for coupling station
- Better solution for crimping process

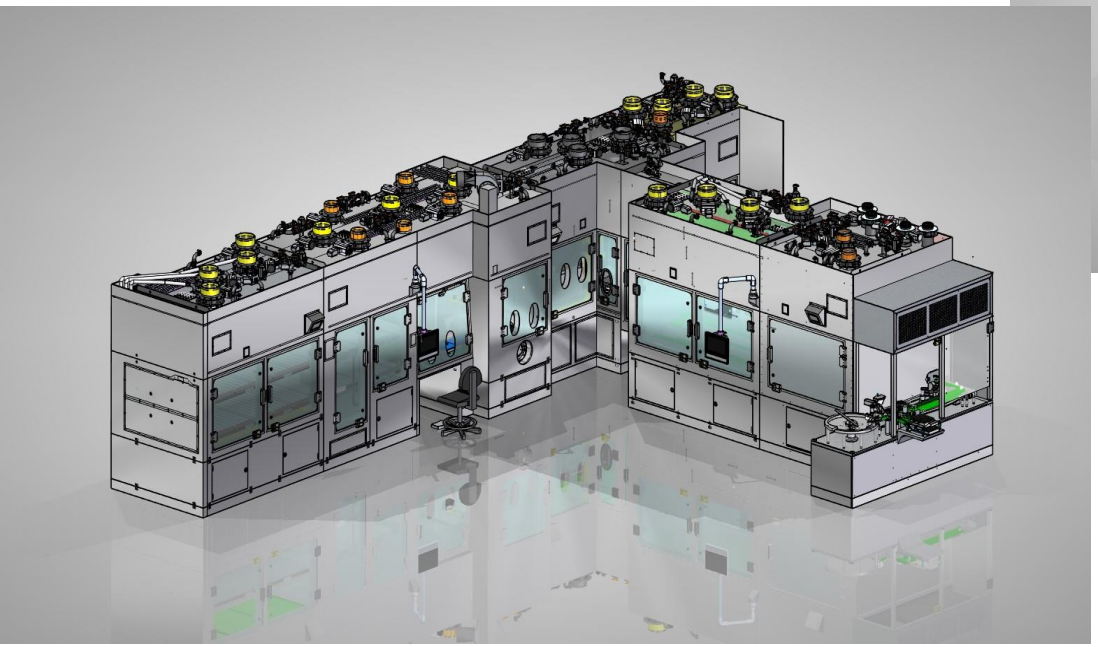


- Better quality of the incoming vials
- Better pressure distribution

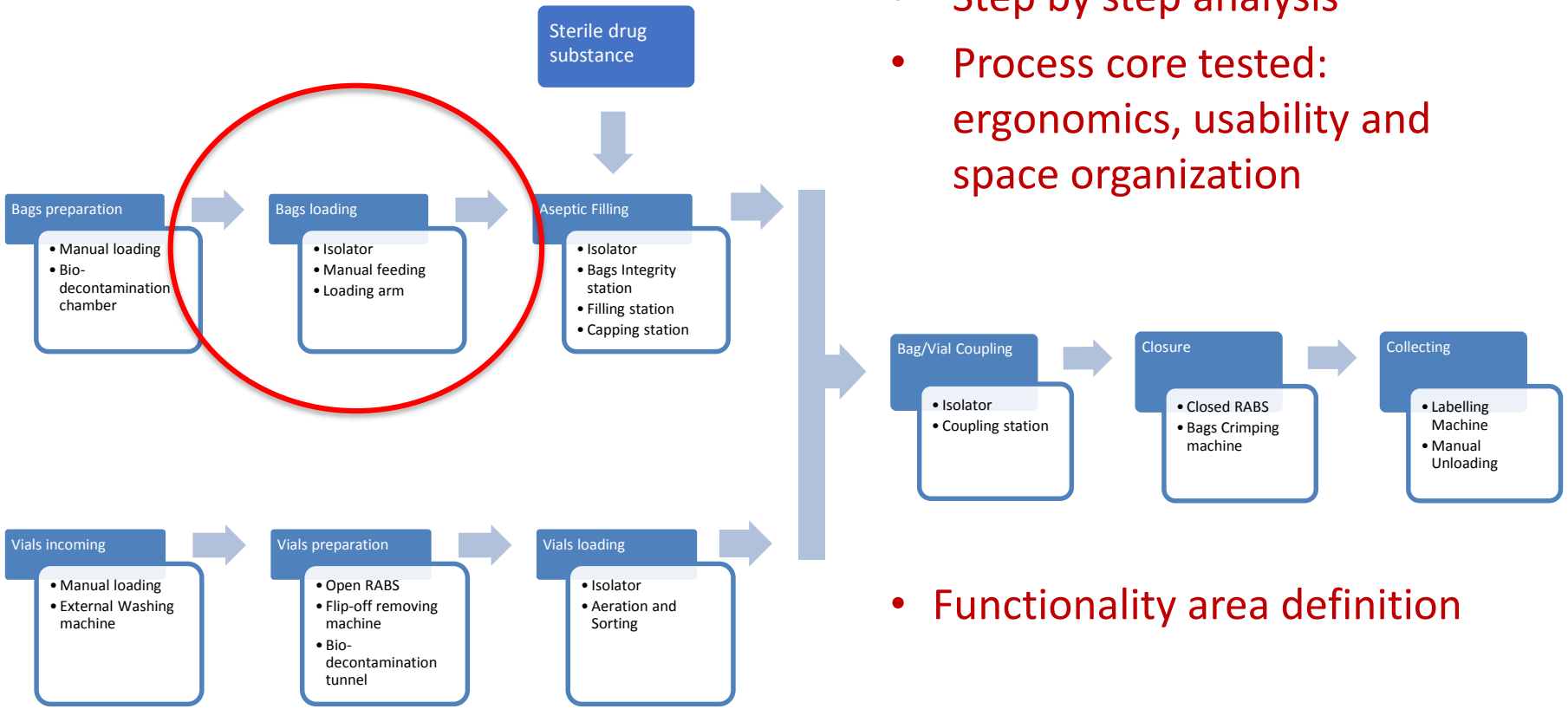
3D Rendering

COMECER an ATS company



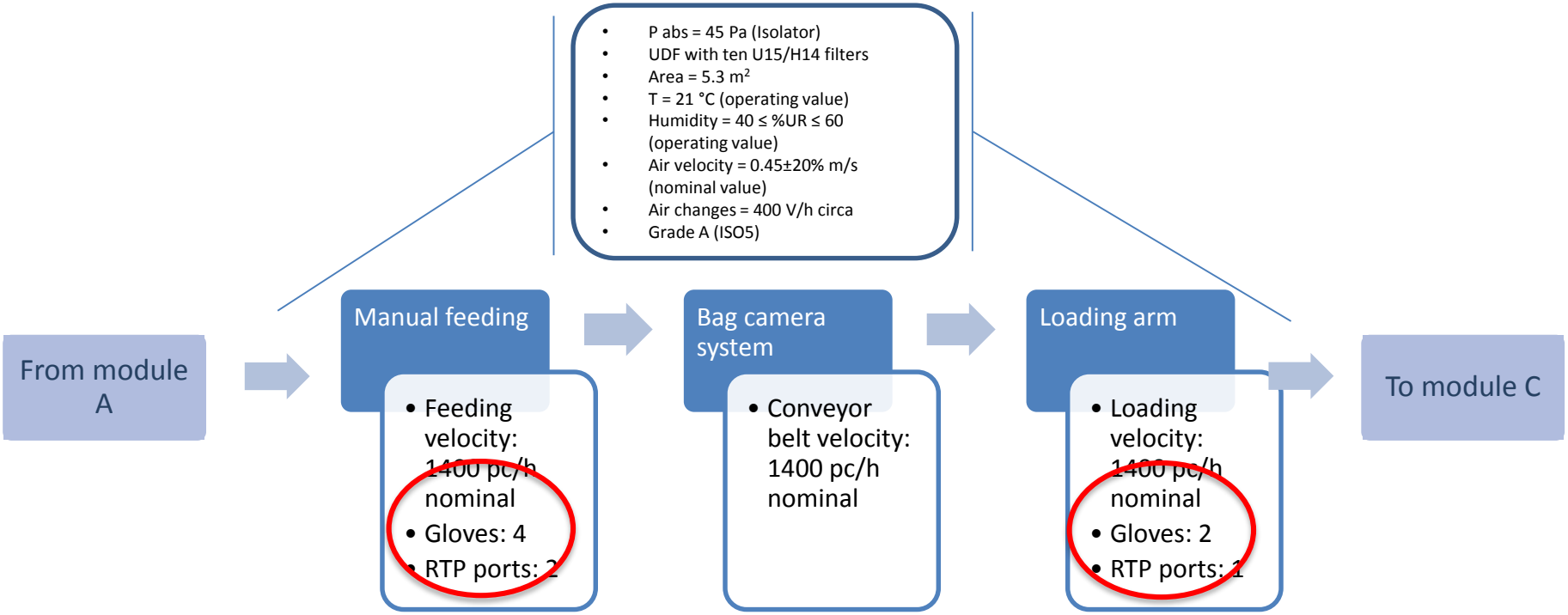


Process Splitting: The Mock-up



- Step by step analysis
- Process core tested: ergonomics, usability and space organization
- Functionality area definition

Splitting step: Bags loading (module B)



Risk Assessment for air monitoring points

Step 1
- Audit
- Process Analysis
- Functional area
- HACCP Analysis

Step 2
- Definition of all the possible sampling location
- FMEA analysis
- Sampling point definition

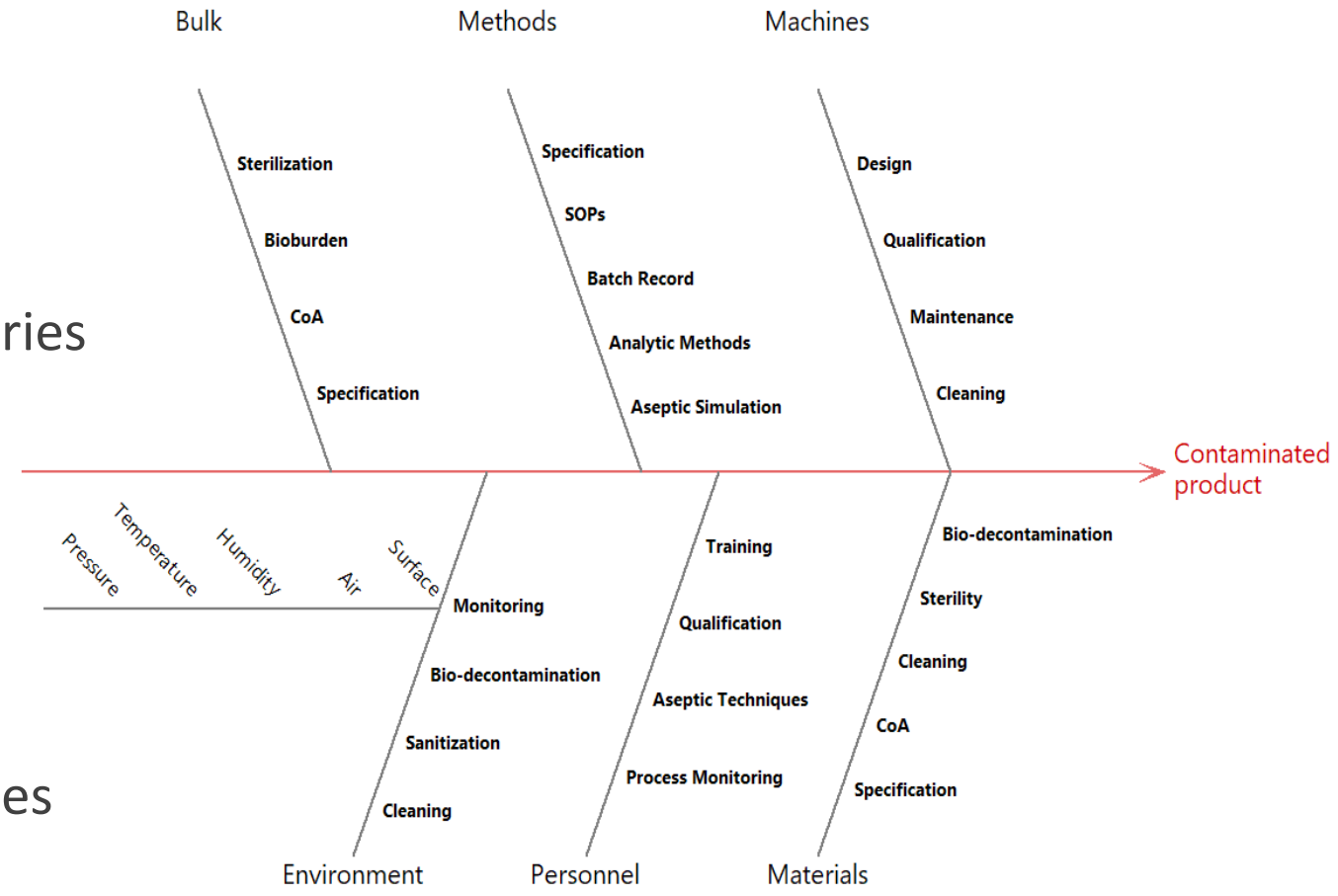
Step 3
- Frequency definition
- Monitoring Plan definition

Step 4
- Monitoring methodologies:
  - Total particles
  - Passive air sampling
  - Active air sampling

Recommendation & Action

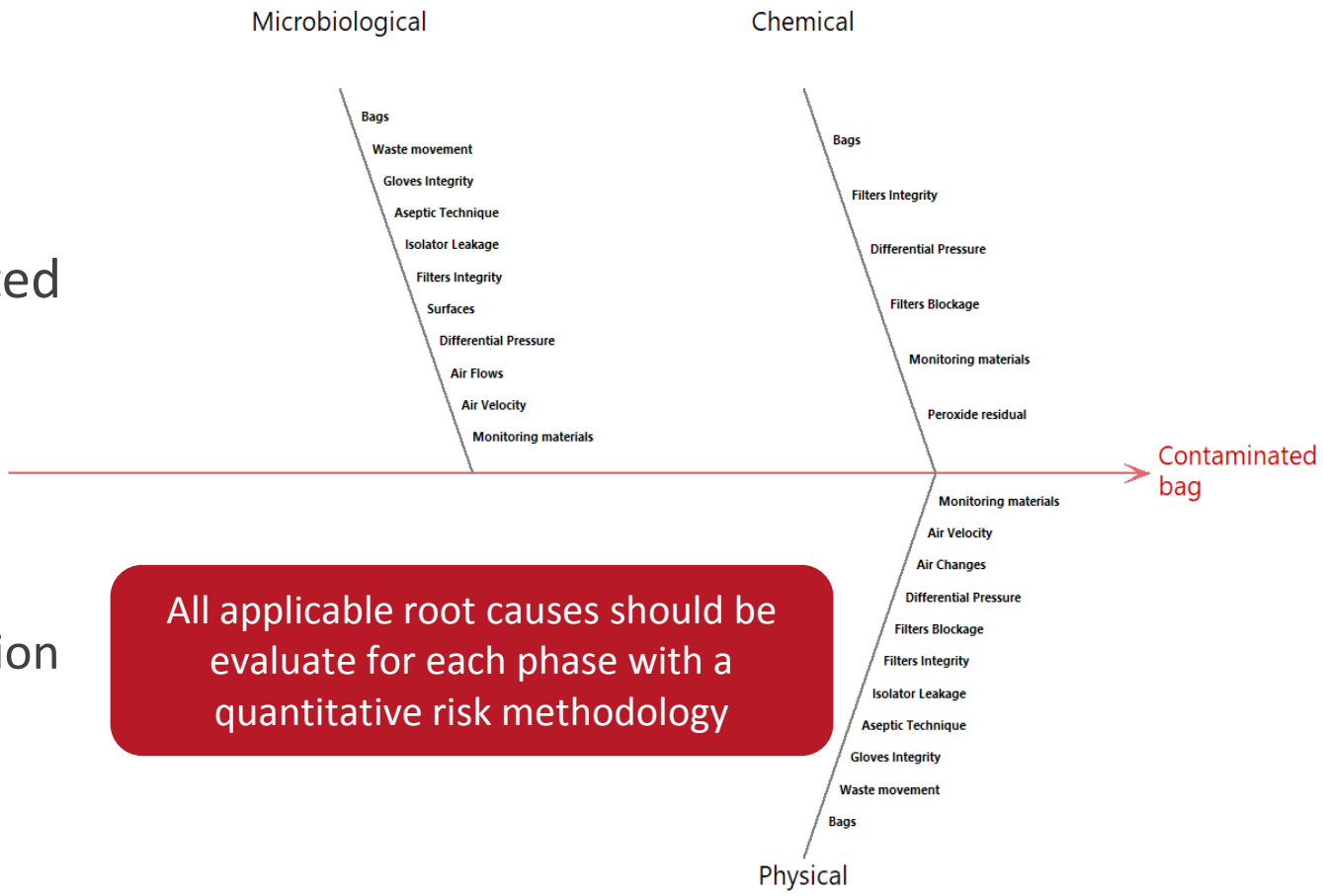
Process Risk Analysis: Structured Approach

- Visual analysis (fishbone)
- Fish head = defect
- Ribs = Major categories
  - Men
  - Material
  - Machine
  - Methods
  - Mother Nature
- Sub-ribs = root causes



Process Risk Analysis: Structured Approach

- Fishbone for finding the root causes
- Defect = Contaminated liquid drug product
- Major categories
  - Chemical contamination
  - Physical contamination
  - Microbiological contamination



All applicable root causes should be evaluate for each phase with a quantitative risk methodology

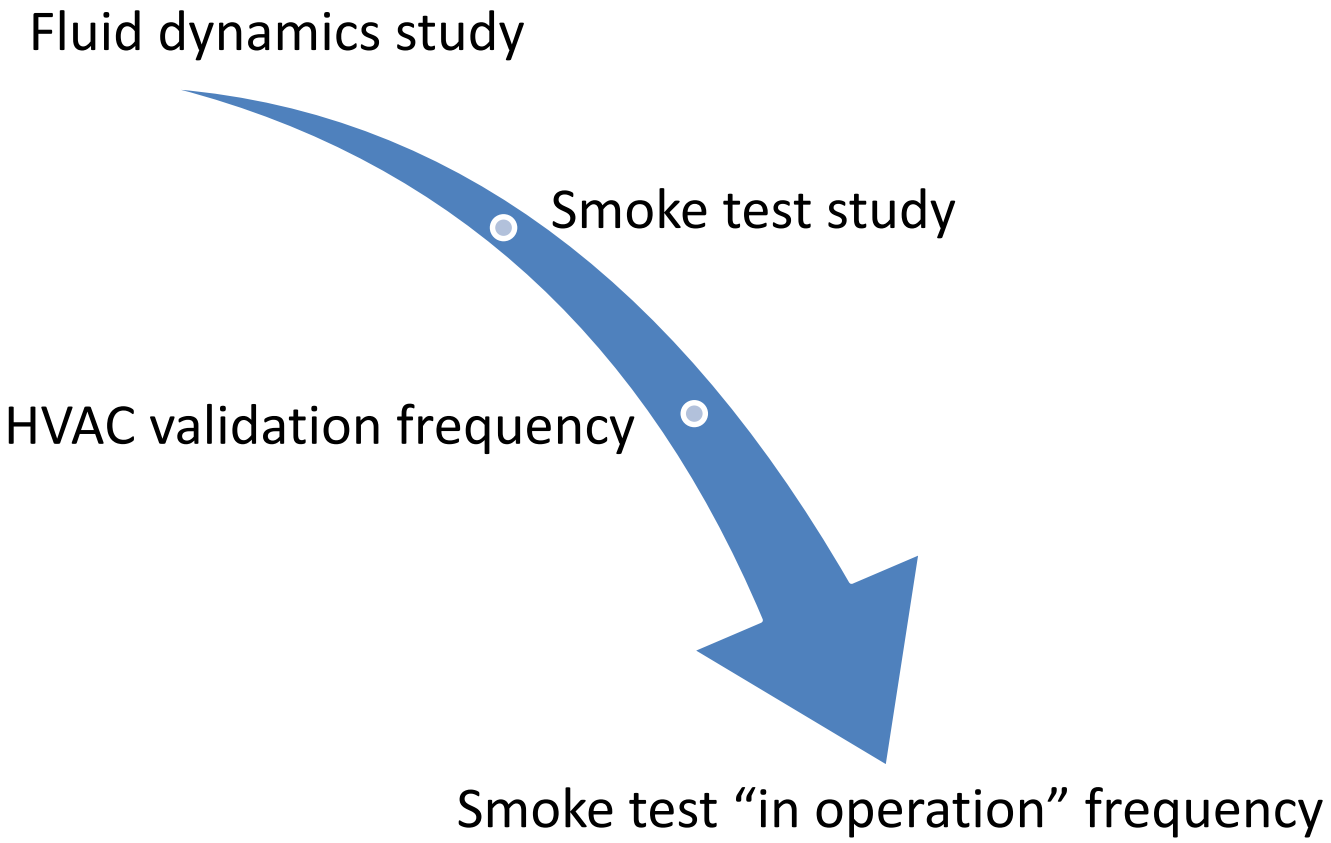
FMEA Method

The selection of "critical" action to perform was based on the calculation of a number that reflects the "risk" the product will be contaminated by a major category. This "risk" was expressed via the Risk Priority Number (RPN):

- Evaluation of the knowledge of the process;
- Evaluation of the probability to contaminate with the operation;
- Evaluation of the severity of the contamination;
- The evaluation of the detectability methods in place.

Risk Matrix

Risk Category	Risk Category Description
UNACCEPTABLE	High Risks that are above the acceptability threshold must be reduced through risk control measures: It's necessary to modify the design or perform a study/validation
ACCEPTABLE when justified	Medium Risk is acceptable when justified: It's necessary improve the knowledge during the validation phase.
ACCEPTABLE	Low Risk is acceptable. It's not necessary to take actions

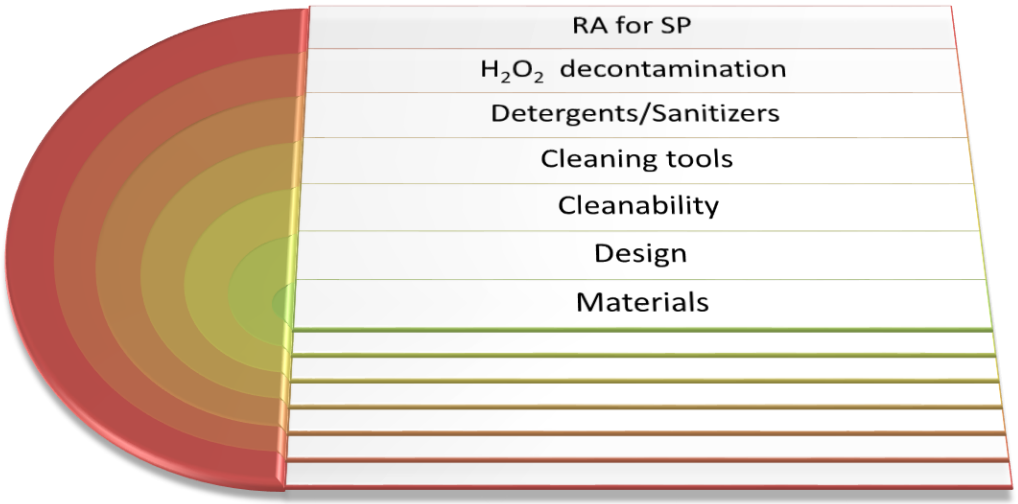


UNACCEPTABLE

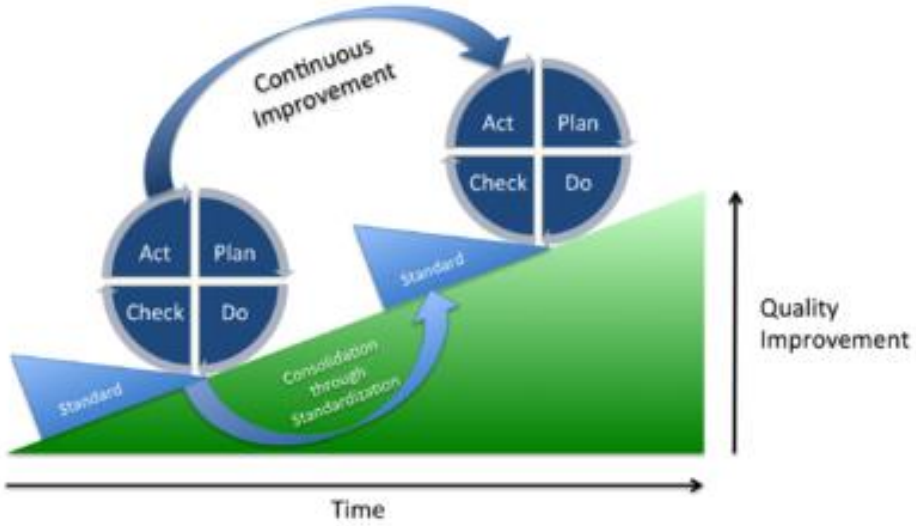
RPN

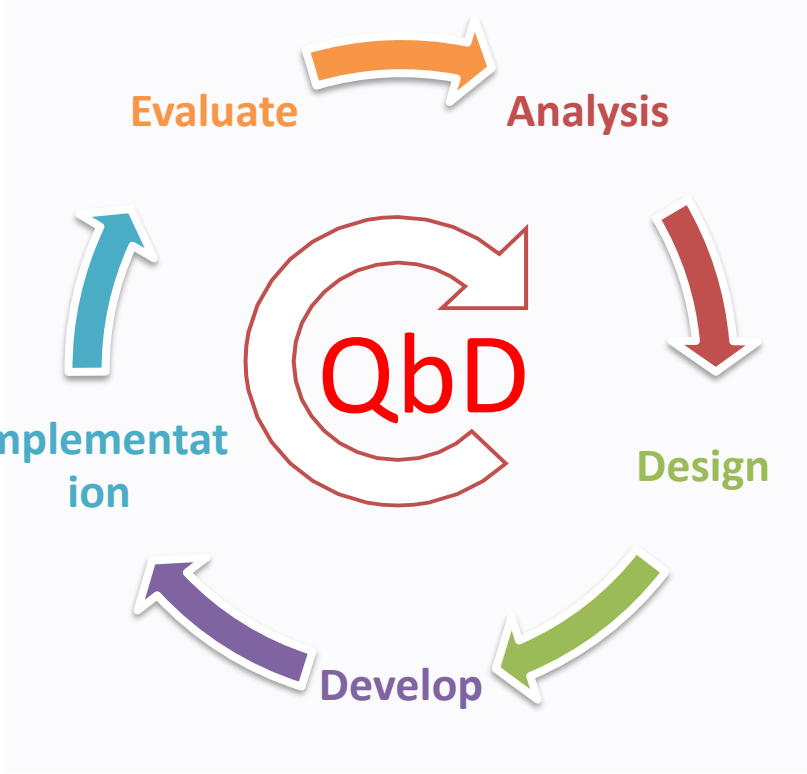
ACCEPTABLE

Process Risk Analysis: Structured Approach



- Materials:
  - Stainless steel typology
  - Plastic typologies
- Design:
  - Worktop
  - Machine top
  - Conveyor belts and roundabouts
- Cleanability
  - Exhaust grids
  - Conveyor belts and roundabouts
  - Moving parts
- Hydrogen Peroxide decontamination
  - Definition of the cycle
  - Coverage study





Applying 360° QRM and Team Work Approach your mind is so open that once you arrive to a solution

You just see a new opportunity for improvement

Acknowledgements