Cleaning out of Place – Concepts and case study

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Pharma Cleaning Forum
Israel Edition

CLEANING EXCELLENCE

Background

…prevent cross contamination…

…The data should support a conclusion that residues have been reduced to an acceptable level…

…Particular attention should be accorded to the validation of the … cleaning procedures…

… Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure…

For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators….

Background

Guidelines:

- FDA's cleaning validation guideline
- Volume 4 EU Guidelines
  - Chapter 3: Premises and equipment
  - Chapter 5: Production
  - Annex 15 to EU GMPs - Qualification and Validation
- PDA Tech. Report N°29 (TR 29) - Points to Consider for CV
- others ….

Background

Why Cleaning Validation

"It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process"

Source: Eudralex Vol. 4 Annex 15: Qualification and Validation

Background

When Cleaning (validation)

- between manufacturing of different products
- between batches of the same product
- after product changeover

Background

Where Cleaning validation

Normally only cleaning procedures for product contact surfaces of the equipment need to be validated.

Consideration should be given to non contact parts into which product may migrate.

Source: CLEANING VALIDATION JANUARY 2013
HEALTH SCIENCES AUTHORITY -GUIDE -MQA-008-008

Background

Targets for the cleaning validation

"To confirm the effectiveness of a cleaning procedure for all product contact equipment".

Source: Eudralex Vol. 4 Annex 15: Qualification and Validation

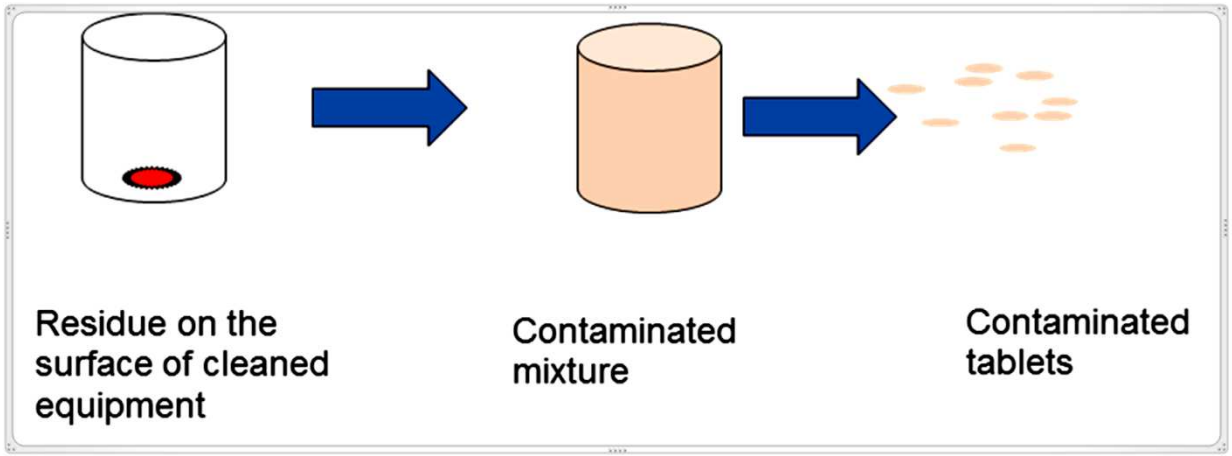
Background

Targets for the cleaning validation

"Prevention of cross-contamination"

"Cross-contamination should be prevented by attention to design of the premises and equipment..."

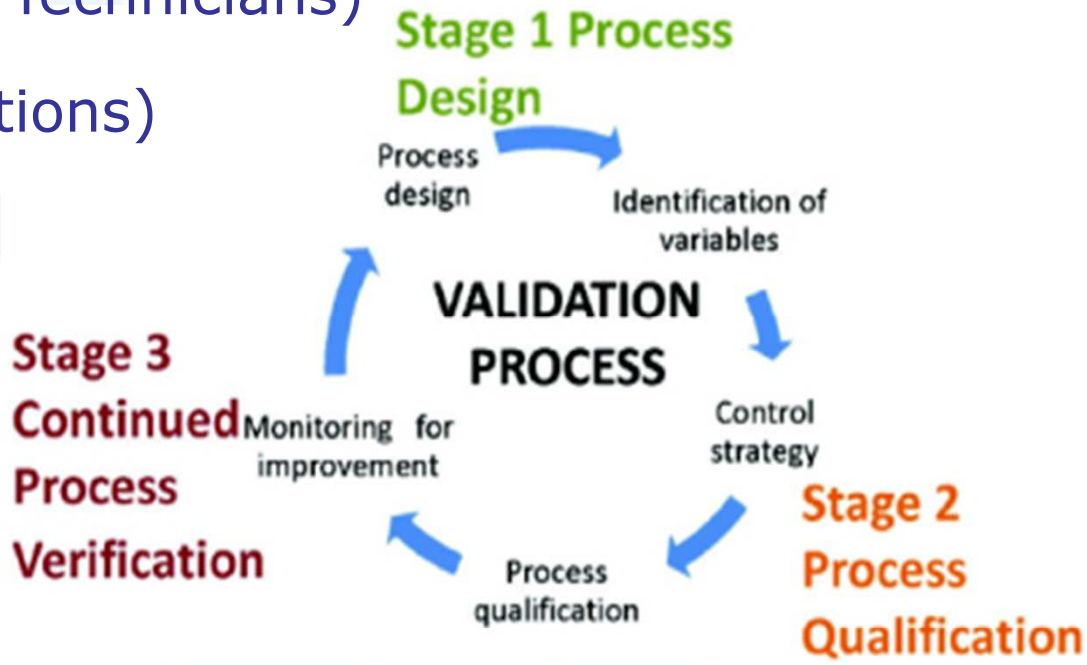
Source: Volume 4 EU Guidelines Chapter 3 Premises and equipment and Chapter 5: Production



Background

Steps of the cleaning validation process:

- Development of the procedures (QC)
- Validation of the procedures (QC/Technicians)
- Application of procedures (Operations)
- Verification of the process (QC)



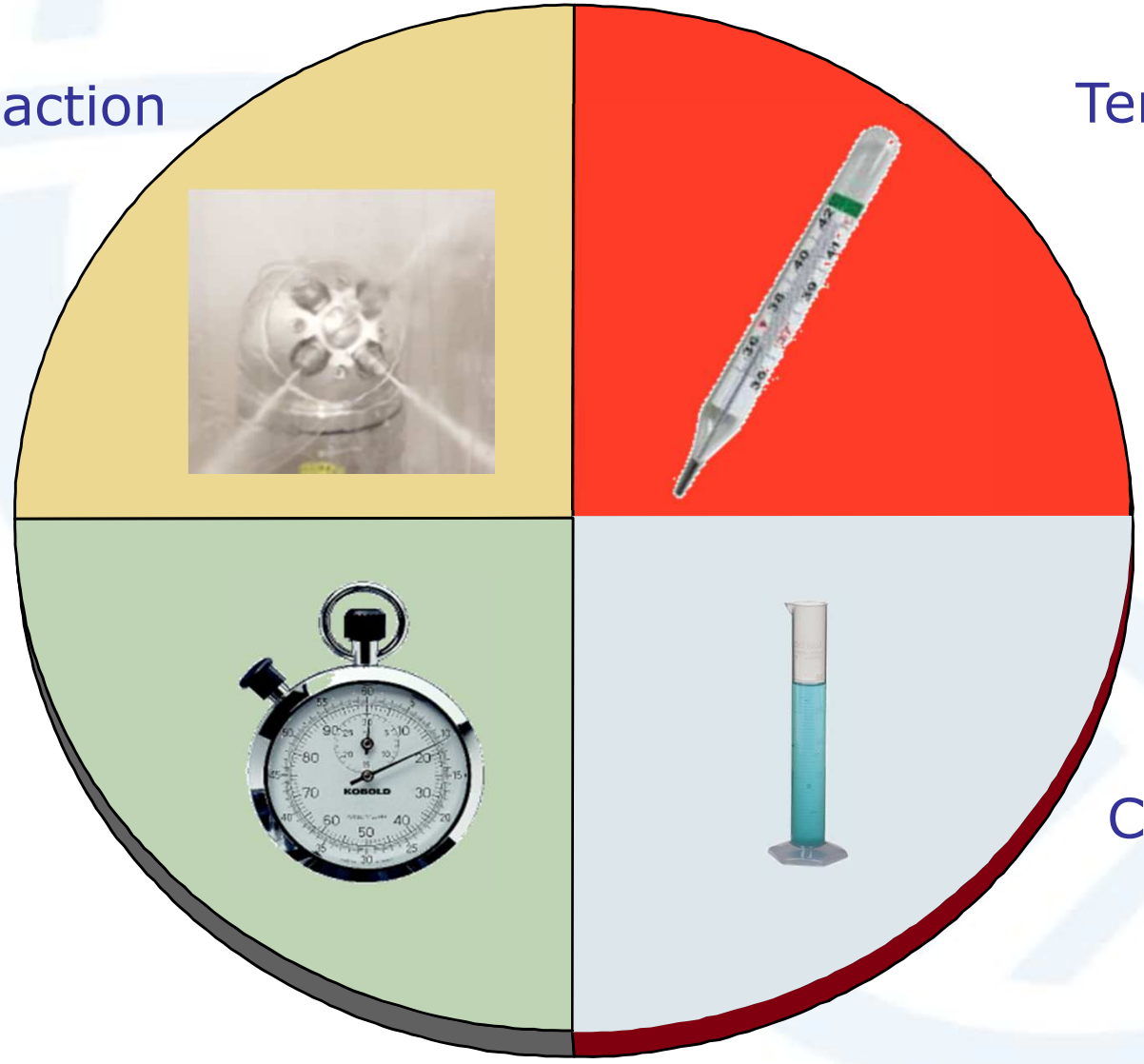
Source: FDA Guidance for Industry. Process Validation: General Principles and Practices. January 2011.

Cleaning variables

Cleaning variables

Mechanical action
Exposure
Coverage

Temperature

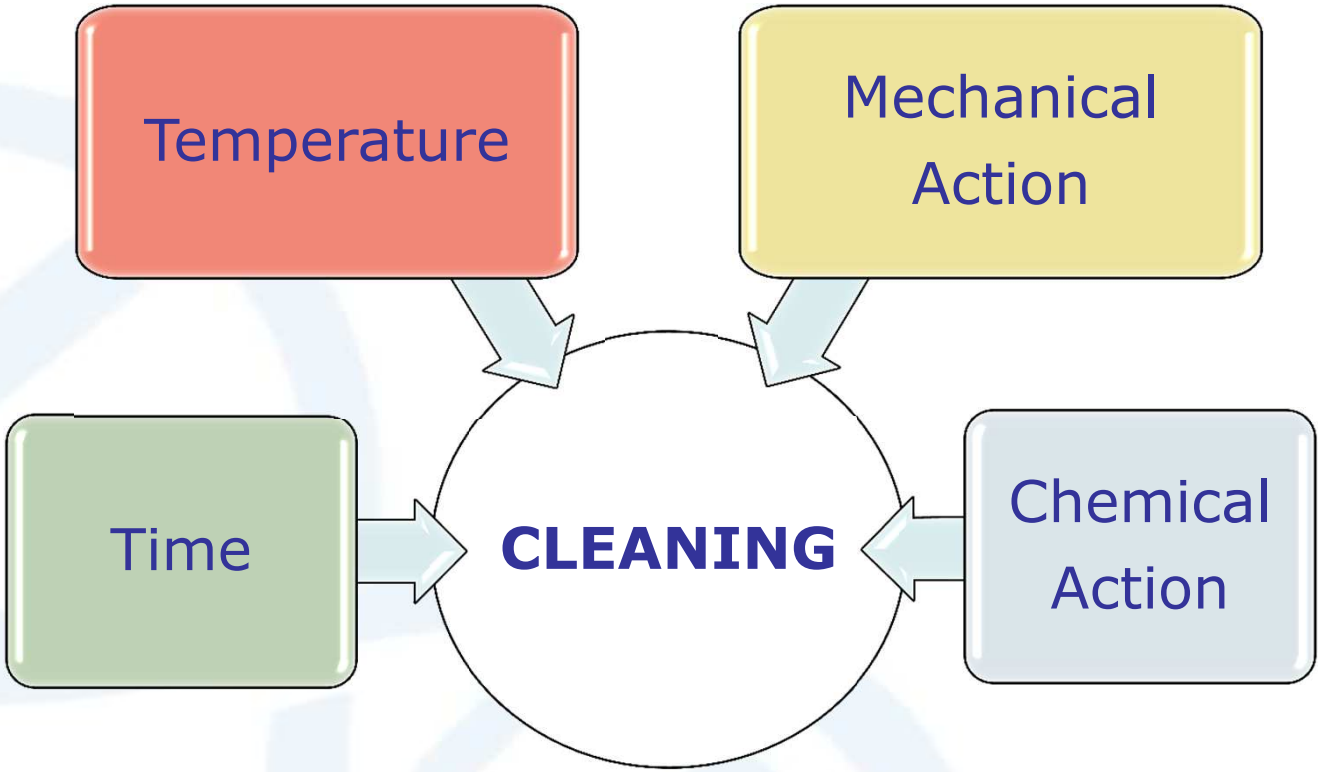


Time

Chemical action

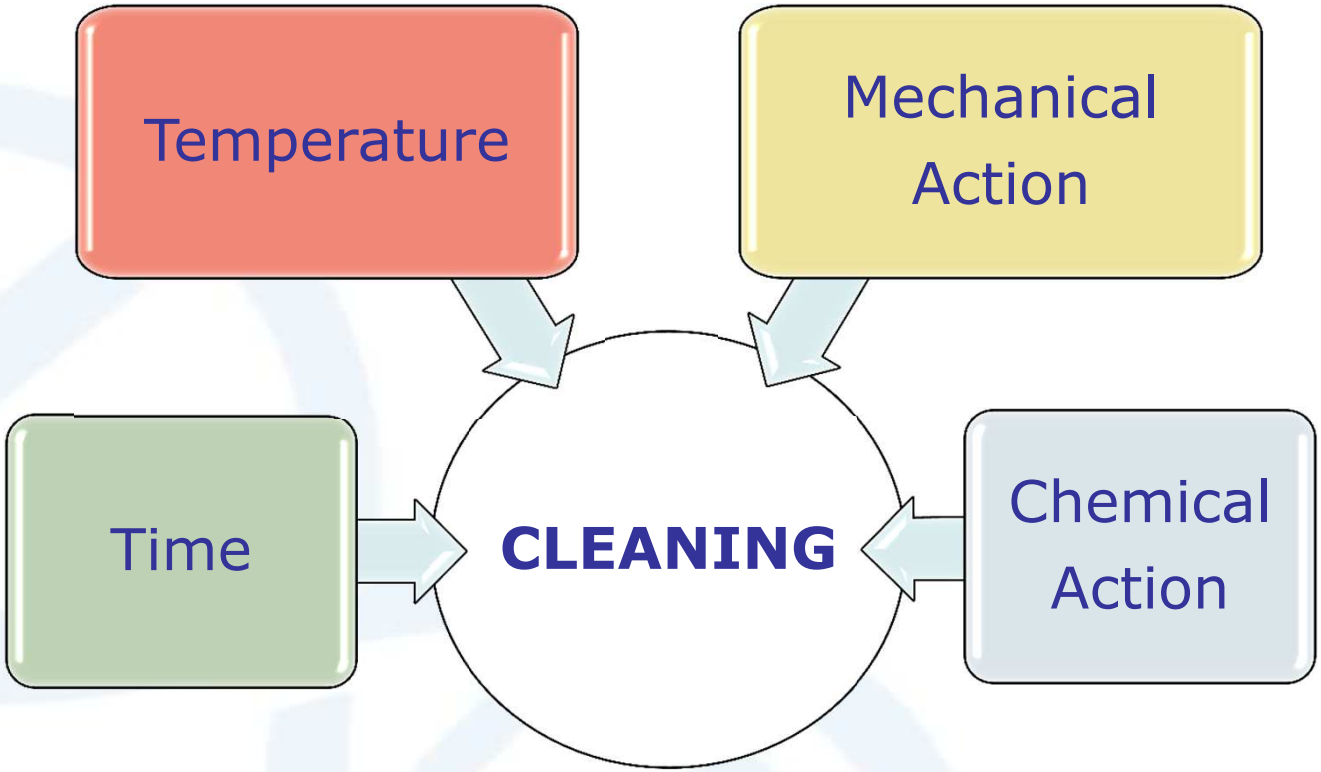
Cleaning variables

1. Time
2. Temperature
3. Mechanical action
4. Chemical action



Cleaning variables

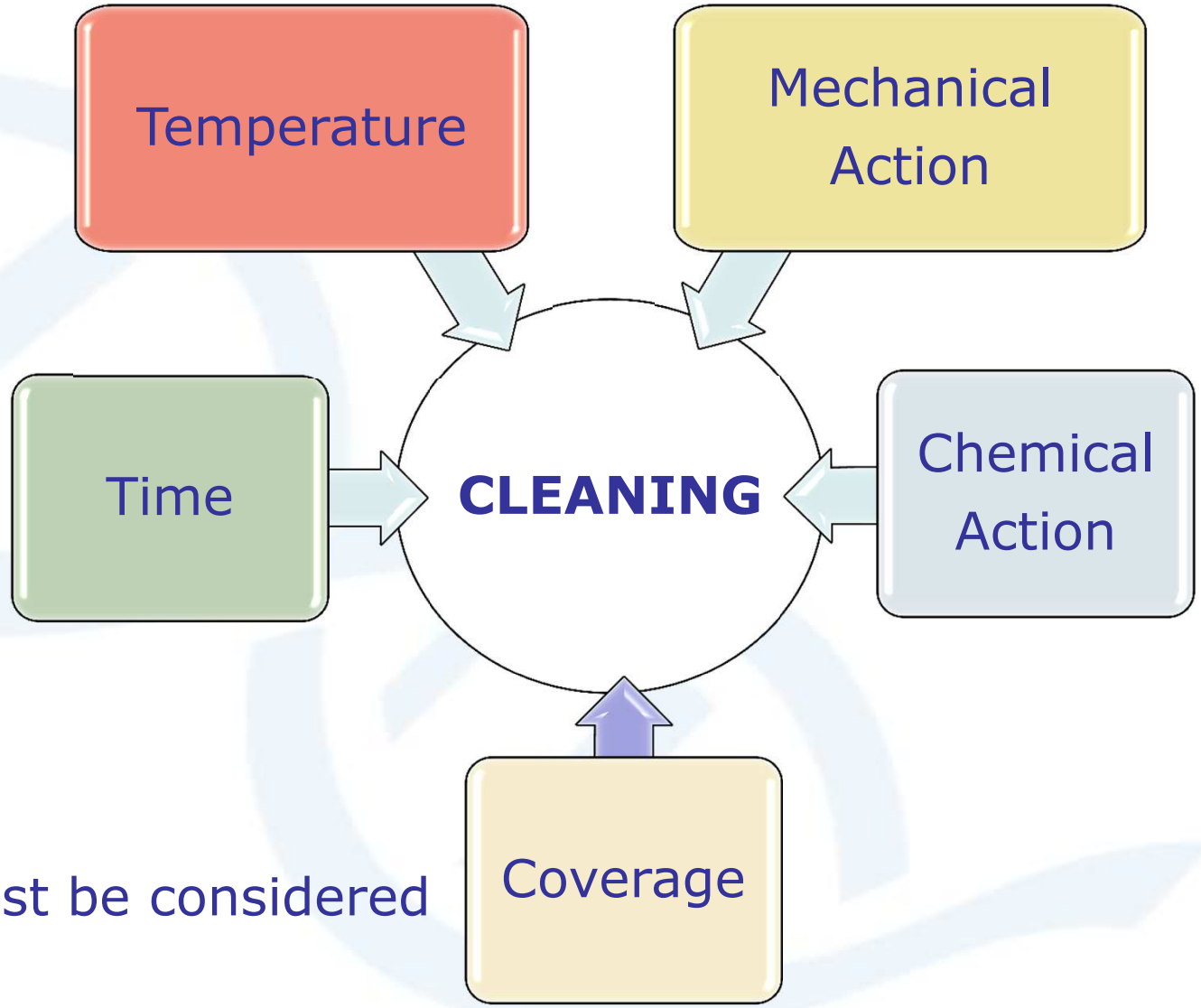
1. Time
2. Temperature
3. Mechanical action
4. Chemical action



Are these variables sufficient for a perfect cleaning?

Cleaning variables

1. Time
2. Temperature
3. Mechanical action
4. Chemical action



Exposure & coverage must be considered

Understanding the cleaning variables

Cleaning variables

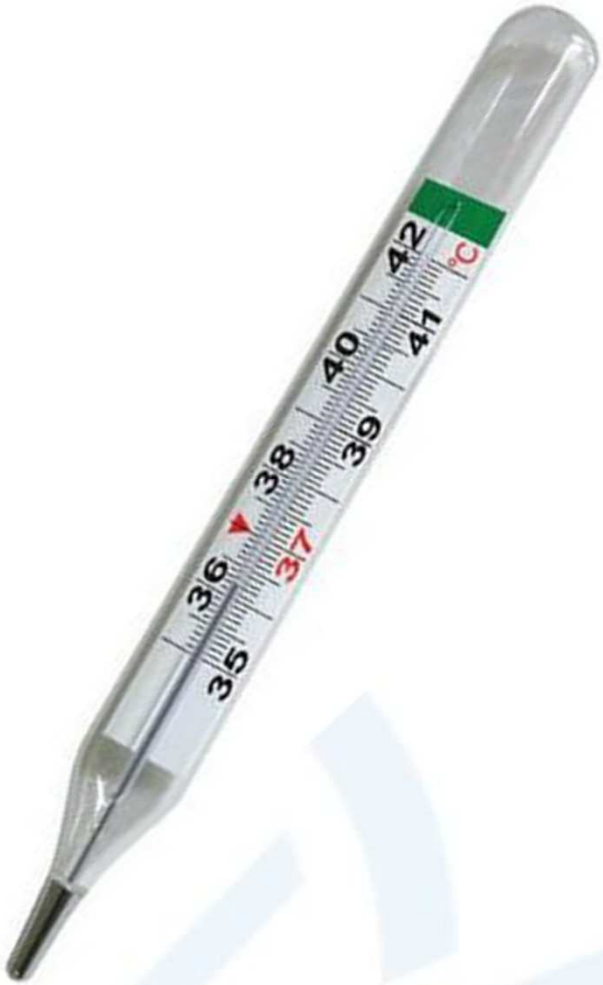
Time:

- Guarantee proper coverage
- Allow effective chemical action
- Allow efficient mechanical action

Cleaning variables

Temperature:

- Allow melting of the soil (e.g. wax)
- Prevent detergent from foaming
- Facilitate detergents solubility
- Increase detergents performance
- Boost water rinsing capacity
- Reduce the drying time



NOTE: in some cases high temperature can be an issue

Cleaning variables

Mechanical action:

- Is the impact force of the water on the soil to remove
- Generates a scraping effect

velocity

Kinetic energy $E_k = \frac{1}{2}mv^2$ (kJ)

mass "or weight"

Cleaning variables

Coverage & exposure:

- Total “wetting” of the load
- Load duly exposed to water and chemical
- All the surfaces are duly invested by washing solutions and rinsing water

Cleaning variables

Different types of water are used for washing:

- Softened water (<150PPM CaCO3)
  generally used, only for pre-wash – wash - pre-rinse
- PW
  generally used for rinse and final rinse
- WFI
  generally used for final rinse in aseptic mftg plant

PW and WFI are typical pharmaceutical waters produced according to EP, USP, JP

Cleaning variables

Chemical action:

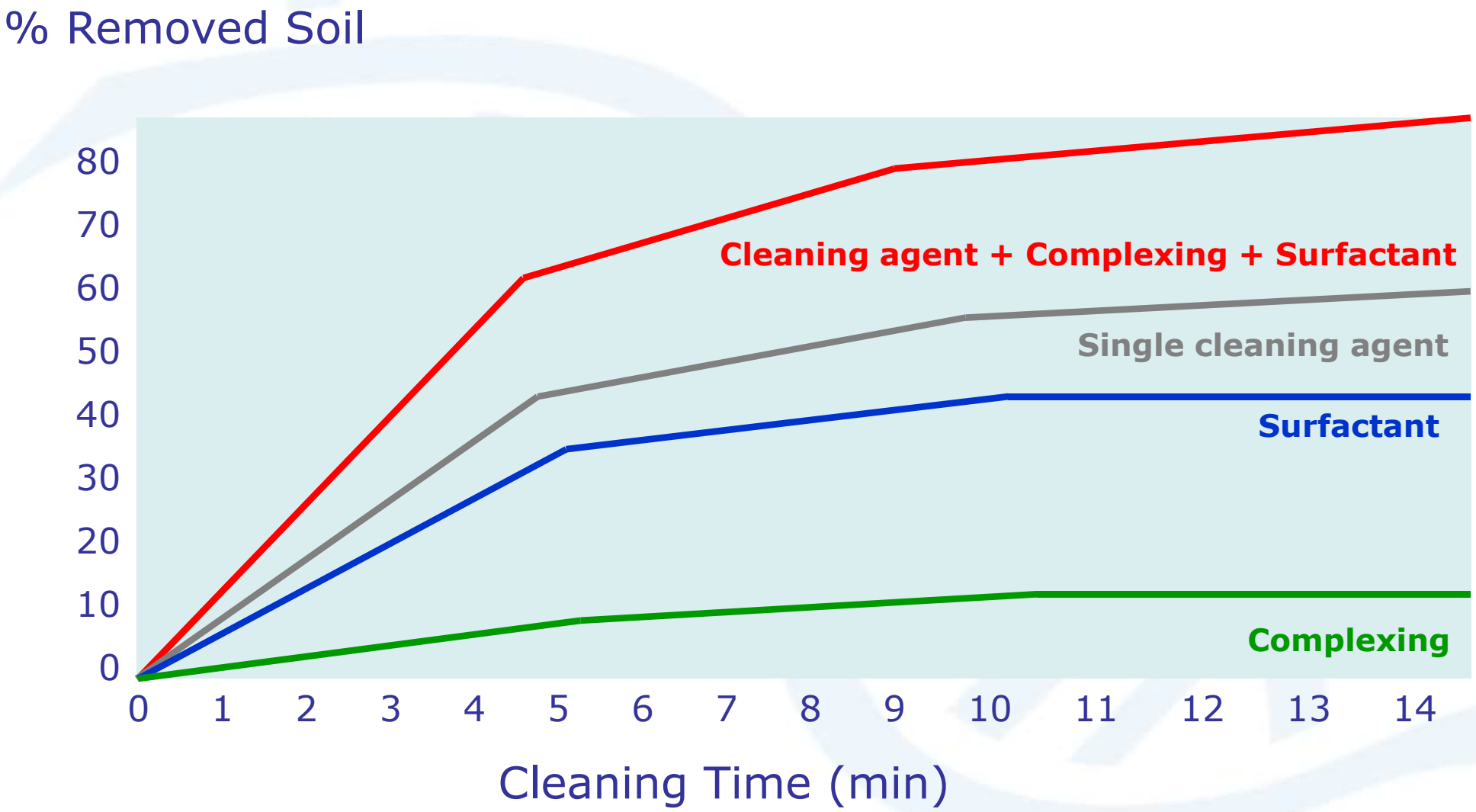
- Obtained by adding chemicals
- Chemically breaks molecule bonds
- Facilitate soil removal by chemical decomposition
- Which chemical are we supposed to use?
  Depends on the type of soils

Cleaning variables

Type of chemicals:

- Alkalis for organic contaminant
- Acids for inorganic contaminant
- Surfactants surface tension + capillary action + wetting and emulsion former
- Complexing agents with minerals and inorganic components
- Sequestering agent prevention of scale formation
- Oxidizing agents
- Deformers
- Corrosion inhibitors - Silicates

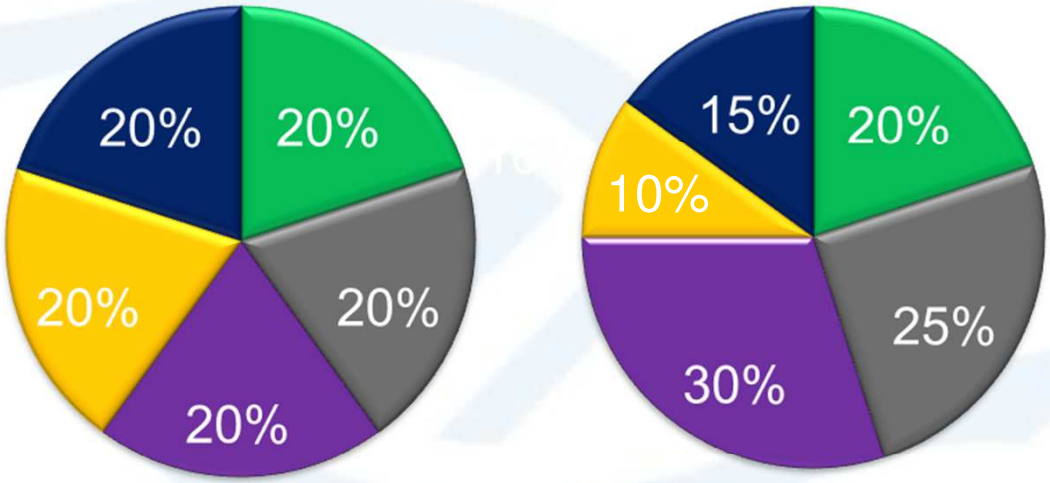
Cleaning variables



Cleaning variables

The correlation between the different cleaning variables is according to the CONTAMINATION to remove.

1. Time
2. Temperature
3. Mechanical action
4. Chemical action
5. Coverage/exposure



Cleaning variables

Possible contaminants to deal with:

- Product residues
- Cleaning agent residues
- Airborne matters
- Lubricants, ancillary material
- Decomposition residues
- Microbiological load

How do we clean?

How do we clean?

How to set-up a cleaning strategy:

Manual cleaning or automated cleaning

How do we clean?

Manual cleaning:

- according to validated SOPs
- process monitored by the operator (accuracy issues)
- relies on human performances and attention (repeatability)
- Appropriate training and supervision are a must
- Cannot validate people; can measure proficiency

How do we clean?

Automatic:

- according to validated SOPs
- process fully monitored by the machine
- fully repeatable and traced
- fully validated

How do we clean?

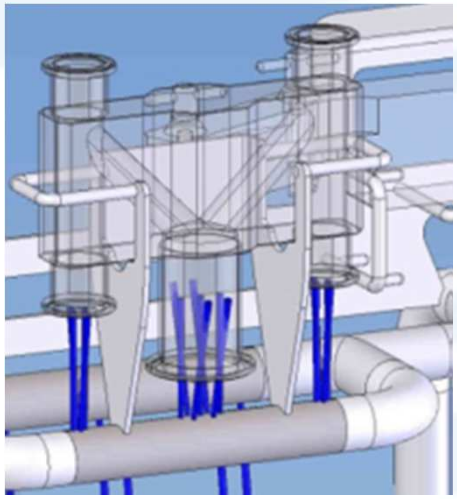
How to set-up a cleaning strategy:

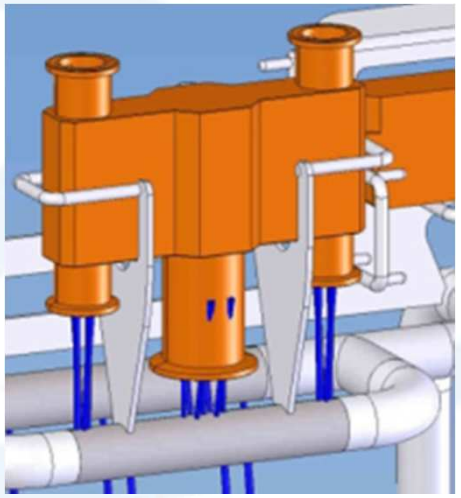
- Focus on the result of the process
- Identify the proper solution to meet the acceptance criteria
- Flexible enough to process multiple parts from different equipment and actives (worst case?)
- "Punctual" cleaning approach for automated cleaning
- Validateable, repeatable and traced and cost effective (use of water, chemical and time)

How do we clean?

"Punctual" cleaning approach:

- Identify all the critical points
- Water addressed to all the critical points
- Drying air delivered through the same piping
- Rotating arms used to perfect the overall cleaning

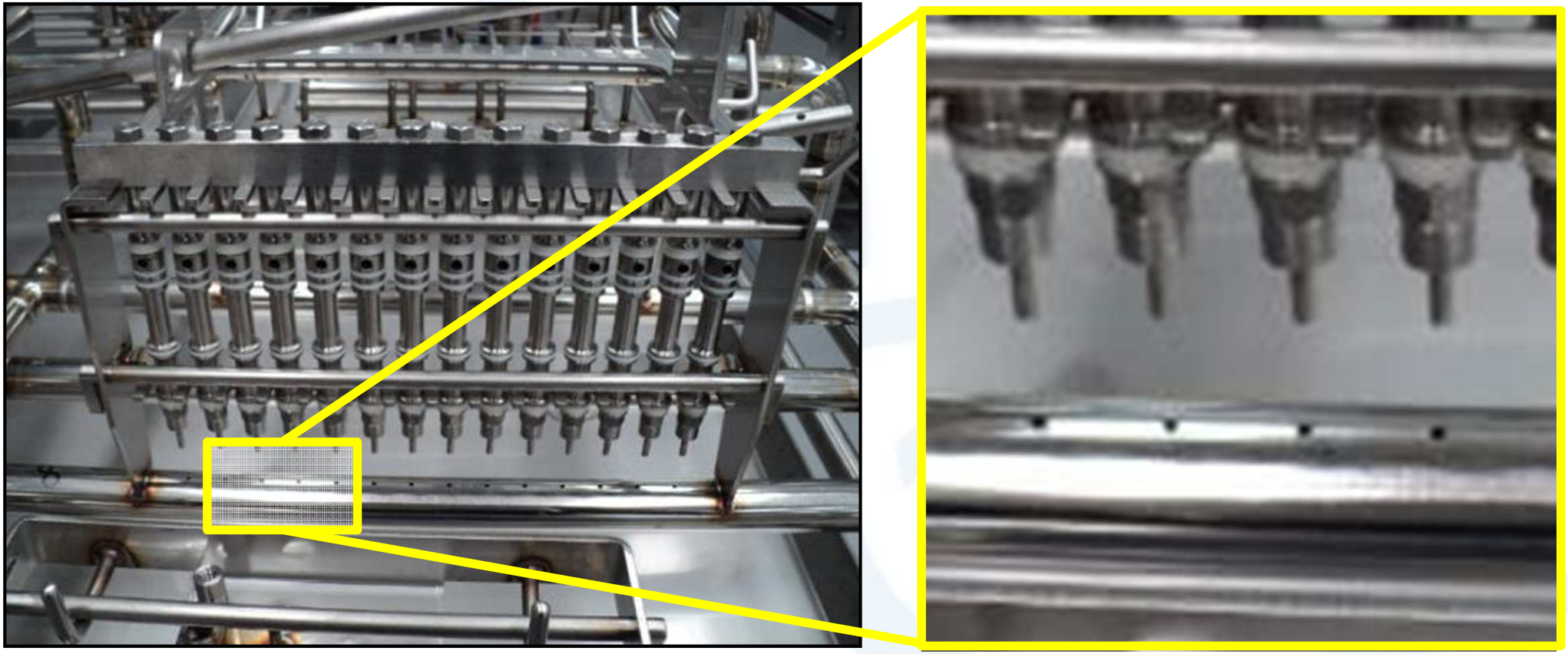




How do we clean?

Injectors from a suppository dosing pump

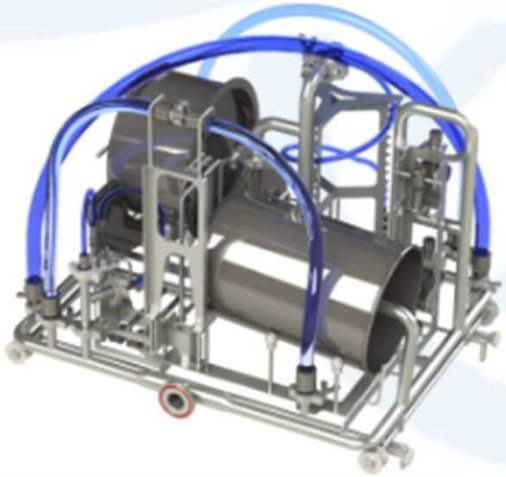
Punctual cleaning approach



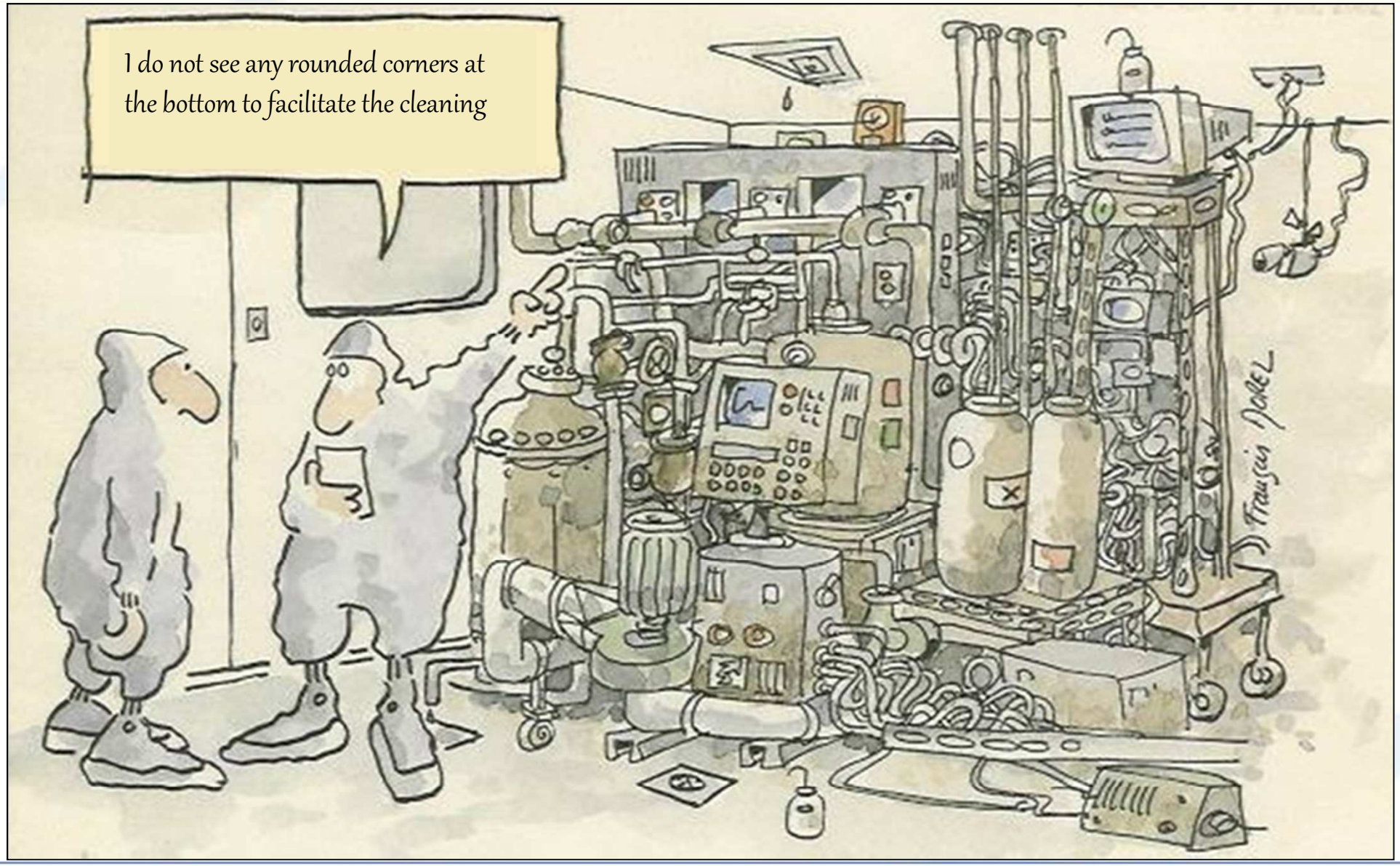
How do we clean?

The facts:

- Dedicated loading solutions
- The basket is built around the parts
- Dedicated loading position for each part (repeatability)
- Safe loading, minimizing the possibility of human mistakes



Case study


I do not see any rounded corners at the bottom to facilitate the cleaning
Francois Dakel

Case study

Customer asked us to clean and dry parts coming from the dosing line of suppositories.

- Suppository dosing pumps
- Accessories
- Injectors
- Ancillary parts

Case study

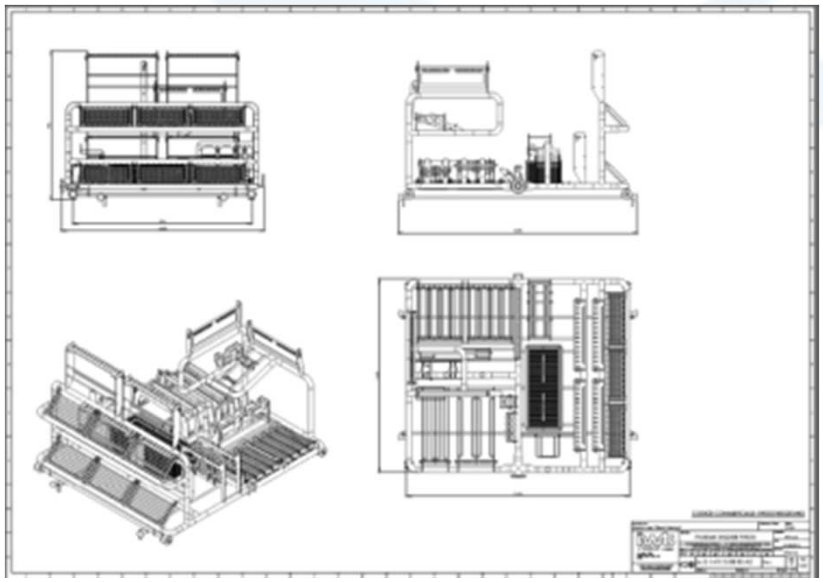
Always consider:

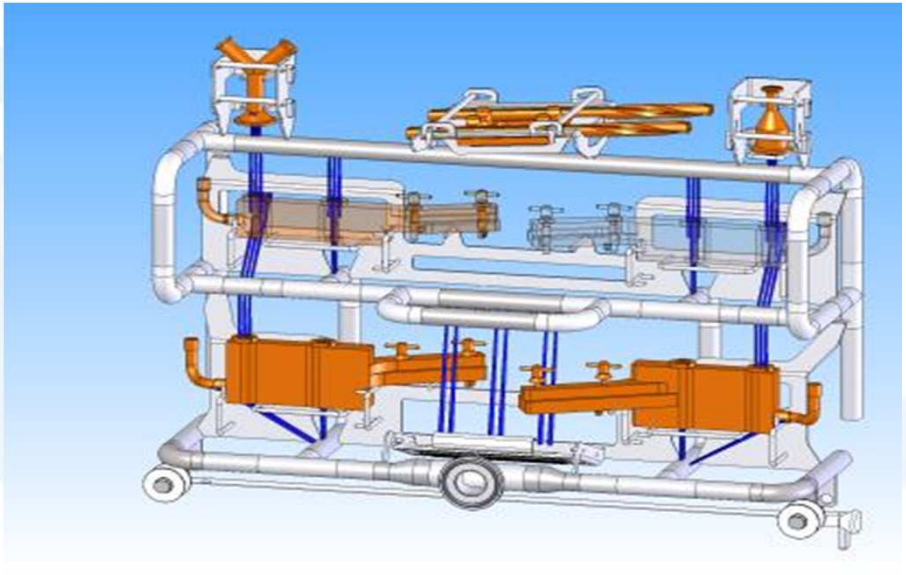
- Quantity of parts to process
- Workload / throughput
- Identification of the batches and variety of the load
- Morphology of the parts
- Critical points (hollows, cavities, material of construction)
- Nature of the contamination to remove (API – excipients)

Case study

Deployment of the loading systems:

- Positioning of all the parts to be cleaned
- Optimization of the loads per each basket
- Designation of cycles required to process all the parts

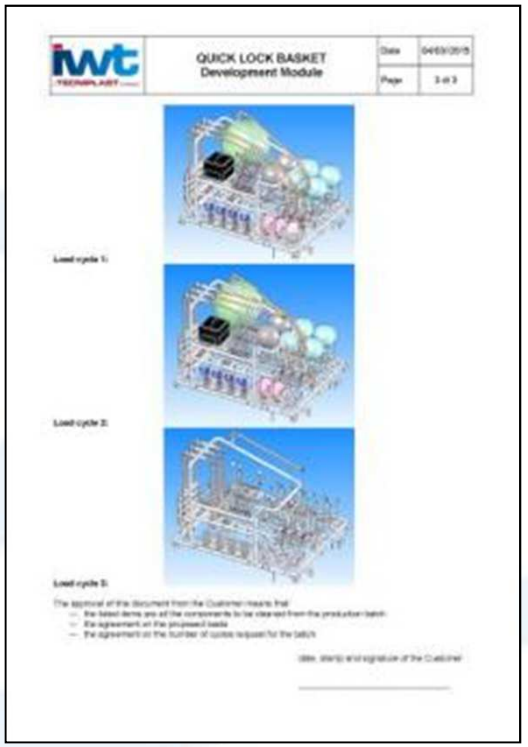




Case study

Definition of the loads:

- Developed in a team
- Specific module provides comprehensive overview for approval



Case study

Analysis of the water flow (exposure & coverage)
and water pressure (mechanical action)

Delta P [bar]	Velocity[m/s]	Flow rate (hole 2mm)[m³/h]	Flow rate (hole 2.5mm)[m³/h]	Total flow rate[m³/h]
1,9	13,78404875	0,155893919	0,243584248	46,65125516
2,25	15	0,169646003	0,26507188	50,76656649
2,42	15,55634919	0,175938164	0,274903382	52,64949568
2,65	16,2788206	0,184109123	0,287670505	55,09465521
2,72	16,4924225	0,186524904	0,291445163	55,81757757

Hp flow rate (Bernoulli)

$$\rho \frac{v^2}{2} = \Delta p - \beta\rho \frac{v^2}{2}$$

PRESSURE-FLOW INLET BASKET RANGE[50Hz]	
Flow rate [m^3/h]	Pressure [bar]
0	2,72
10	2,8
20	2,8
30	2,72
40	2,65
50	2,42
60	2,25
70	1,9

Case study

Calculation of the water distribution (exposure & coverage)

Basket Inlet(A) (Flow simulation calculate pump working point)

Local parameters

Parameter	Average
Relative Pressure [bar]	2,41451056
Total Pressure [bar]	4,49556656
Dynamic Pressure [bar]	1,08780601

Integral parameters

Parameter	Value
Volume Flow Rate [m^3/h]	50,0650609

Nozzle1(B)

Local parameters

Parameter	Average
Relative Pressure [bar]	0,03309264
Total Pressure [bar]	2,38191156
Dynamic Pressure [bar]	1,36556892

Integral parameters

Parameter	Value
Volume Flow Rate [m^3/h]	-0,140826541

Nozzle2(C)

Local parameters

Parameter	Average
Relative Pressure [bar]	2,2953E-12
Total Pressure [bar]	2,2654477
Dynamic Pressure [bar]	1,2521977

Integral parameters

Parameter	Value
Volume Flow Rate [m^3/h]	-0,17471357

Nozzle3(D)

Local parameters

Parameter	Average
Relative Pressure [bar]	2,2953E-12
Total Pressure [bar]	2,41573836
Dynamic Pressure [bar]	1,40248836

Integral parameters

Parameter	Value
Volume Flow Rate [m^3/h]	-0,184358397

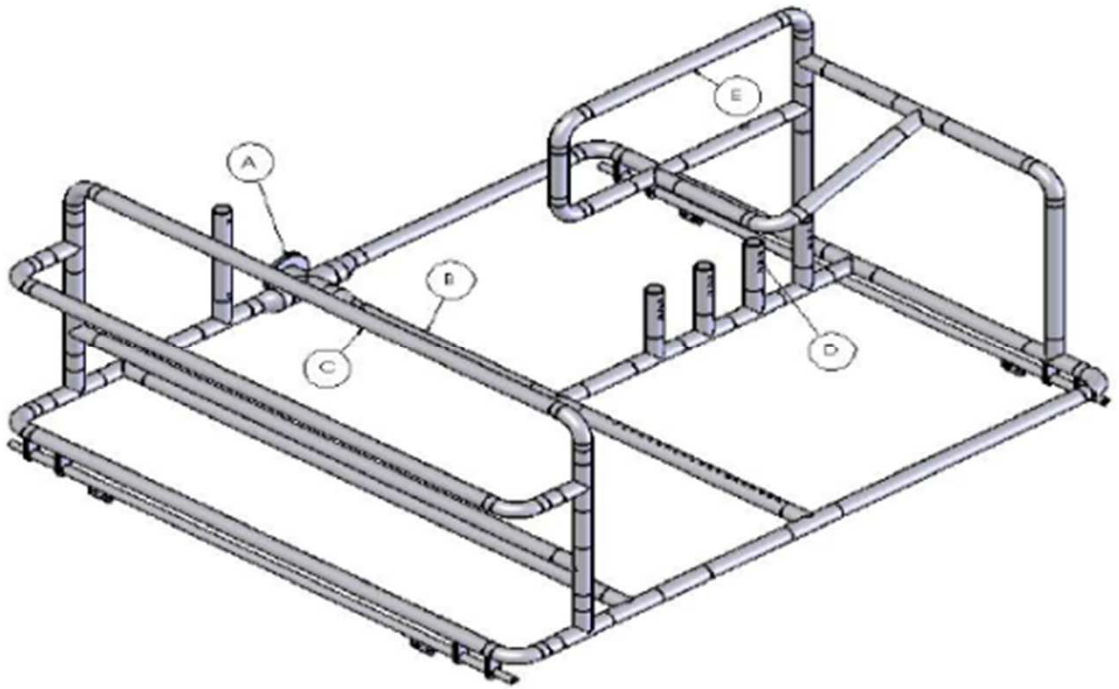
Nozzle4(E)

Local parameters

Parameter	Average
Relative Pressure [bar]	7,79E-07
Total Pressure [bar]	2,5792216
Dynamic Pressure [bar]	1,56597082

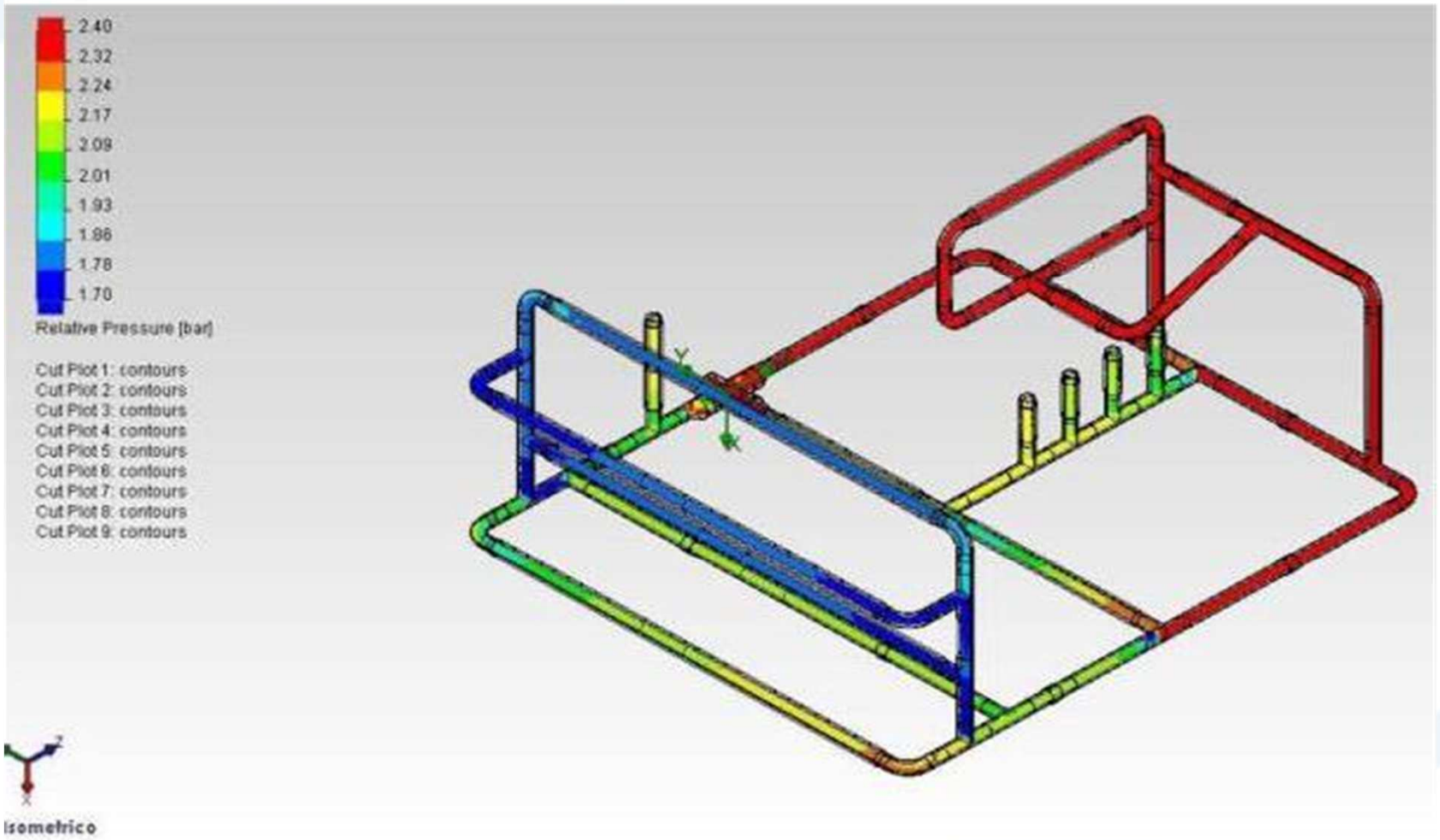
Integral parameters

Parameter	Value
Volume Flow Rate [m^3/h]	-0,193365787



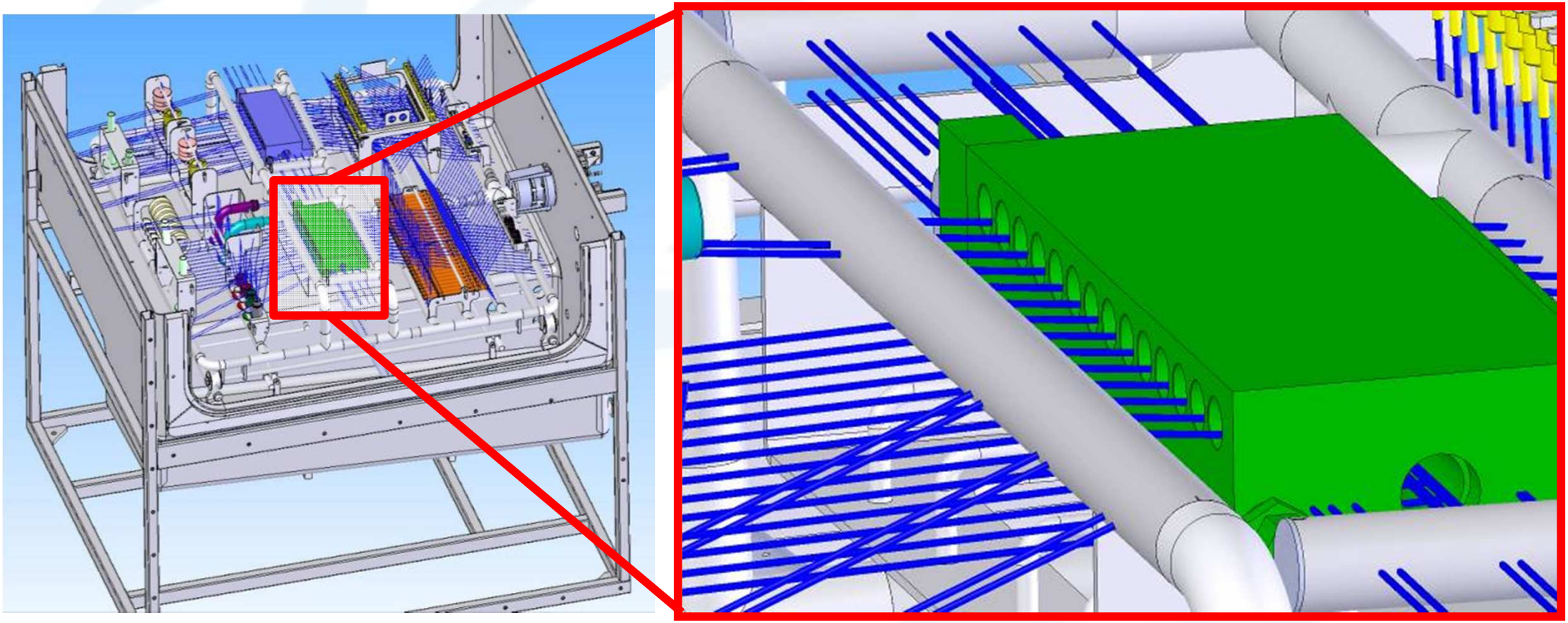
Case study

Simulation of the water pressure (mechanical action)

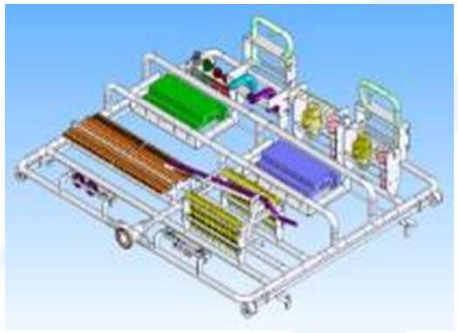


Case study

Simulation of the exposure and coverage



Case Study



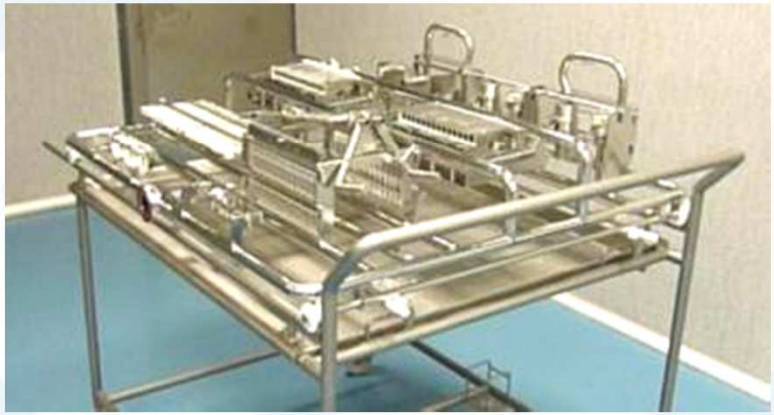
Concept

Customer approval

Production

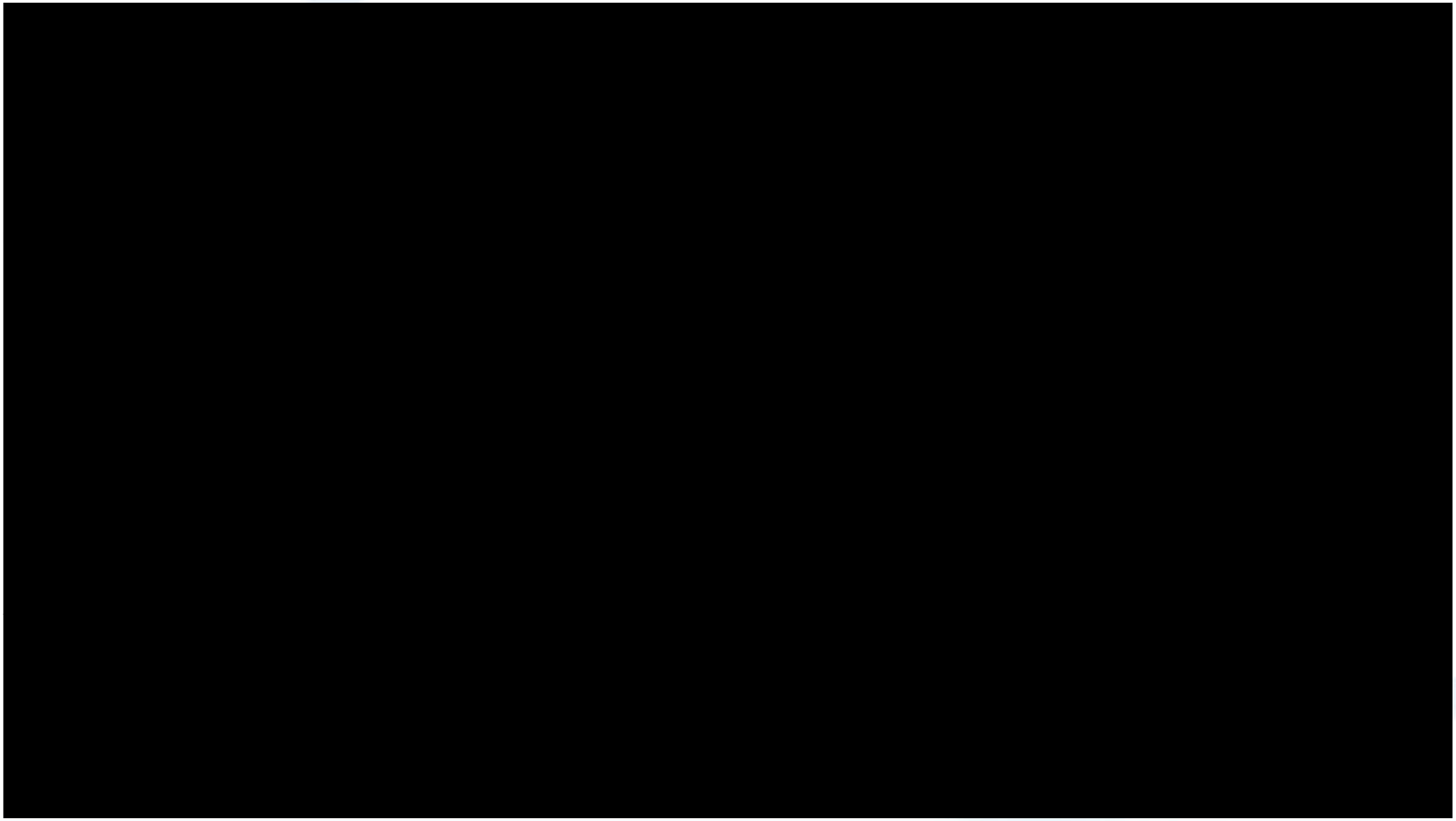
Qualification

Delivery to site



Routine operation

Case Study - Video



Manufacturing

Glassware

Plastic ware

Filling line batch

Dosing pump

Miscellaneous

Hoses

Conclusion

Conclusion:

- An appropriate cleaning validation strategy is needed
- Each single situation must be assessed in detail
- Scientific rationale must be developed:
  - Selection of the “modus operandi”
  - Definition of the cleaning approach
  - Cleaning validation verification techniques
- Regulatory compliance