Isolator Aseptic handling and processing of toxic material

Presented by:
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Presentation Summary

1. Containment target and containment system definition
2. HPAPI process equipment integration
3. Sterile/HPAPI process equipment integration
4. Conclusions and new challenges

1- Containment Performance Target definition

The analysis to specify the design of the containment systems is based on Containment Performance Target (CPT).
CPT is based on the OEL of the material handled.

The containment performance is defined as the airborne particulate concentration measured around the contaminated device and the operator (µg/m3 on 8 h TWA).

The methodology for the evaluation is detailed in the ISPE guide "Good Practise – Assessing the particulate containment performance of pharmaceutical equipment", Second Edition, developed by the SMEPAC (Standardised Measurement of Equipment Particulate Airborne Concentration) Committee.

1- Containment Target definition

Process to be contained? YES

Aseptic Environment? NO

1- Containment Target definition

Process to be contained? YES

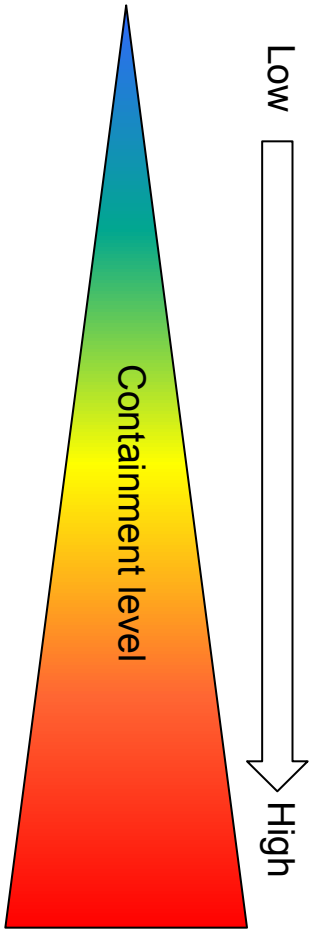
Aseptic Environment? YES

1- Containment Strategy Selection chart

Exposure potential: solids

Quantity handled \ Dustiness Potential	Low	Medium	High
Micro (<10 g)	EP0 / EP0	EP0 / EP1	EP1 / EP2
Small (<10'000 g)	EP1 / EP1	EP1 / EP2	EP2 / EP3
Medium (<100 kg)	EP1 / EP2	EP2 / EP3	EP3 / EP4
Large (>100 kg)	EP2 / EP3	EP3 / EP4	EP3 / EP4
Task duration	Short / Long	FPS	

Hazard group	Exposure limit	OEB (solids)	EP0	EP1	EP2	EP3	EP4
A	1'000-10'000 µg/m³ dust	OEB 1	1	1	1	1	2
B	100-1'000 µg/m³ dust	OEB2	1	1	2	2	3
C	10-100 µg/m³ dust	OEB3	2	2	3	3	4
D	1-10 µg/m³ dust	OEB4	2	3	3	4	4
E	0,01-1 µg/m³ dust	OEB5	3	4	4	4	4
F	<0,01 µg/m³ dust	N/A	4	5	5	5	5



1- Containment system definition

Each situation has its own solution

There are no universal pre-defined solutions but solutions which correspond to end user and process specific needs

Always try to understand and know the needs, the history and the experience of end user

The starting point of a project is not the machine but end user needs around which we build our systems

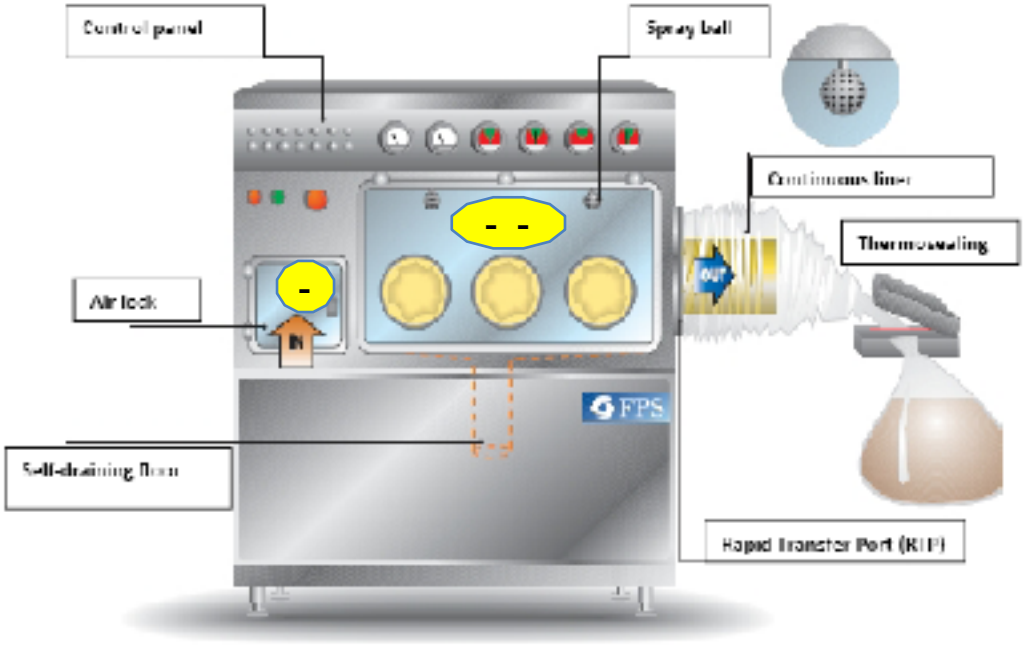
To be always open to new ideas and challenges

We have a wide experience but we are learning something every day to improve our knowledge and face new challenges

1- Containment system definition (Toxic case)

Technical Features

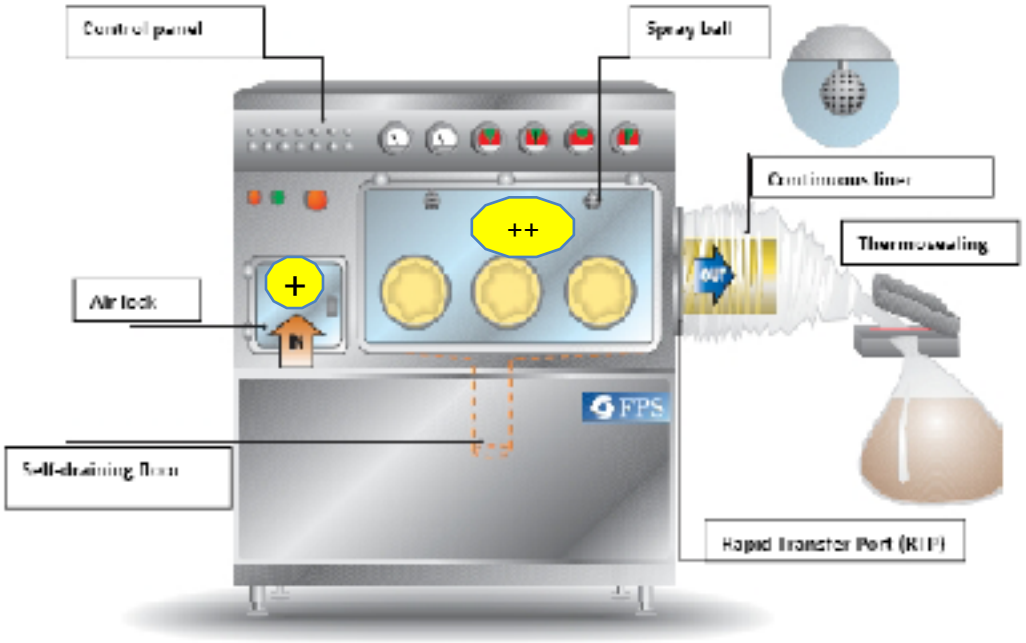
- *Full Stainless Steel construction following cGMP requirements*
- *FDA approved materials for not Stainless Steel parts*
- *Configuration for HPAPI products handling*
- *Constant negative pressure working condition*
- *Transfer system available : Airlock / RTP / Endless Liner / Split Valve*
- *Full CIP*
- *ATEX configuration*
- *Internal class below to ISO5*
- *OEL < 0.01µg/m3 8h TWA*
- *Leak test following ISO10648-2 below to class 1 or AGS-2007 with 0.5% of Volume leak-rate*



1- Containment system definition (Sterile case)

Technical Features

- *Full Stainless Steel construction following cGMP requirements*
- *FDA approved materials for not Stainless Steel parts*
- *Configuration for Sterile products activities*
- *Constant positive pressure working condition*
- *Transfer system available : Airlock / RTP / Endless Liner / Split Valve*
- *Full CIP / SIP available*
- *ATEX configuration*
- *Internal class below to ISO5 / Class A / Class 100 / Class M3.5*
- *Leak test following ISO10648-2 below to class 1 or AGS-2007 with 0.5% of Volume leak-rate*
- *Sterility level below to 6log (SAL 10^{-6}) by VPHP generator*



1- Containment system definition (Toxic/ Sterile case)

Technical Features

- *Full Stainless Steel construction following cGMP requirements*
- *FDA approved materials for not Stainless Steel parts*
- *Configuration for HPAPI and Sterile products activities*
- *Constant positive/negative pressure working condition*
- *Transfer system available : Airlock / RTP / Endless Liner / Split Valve*
- *Full CIP / SIP available*
- *ATEX configuration*
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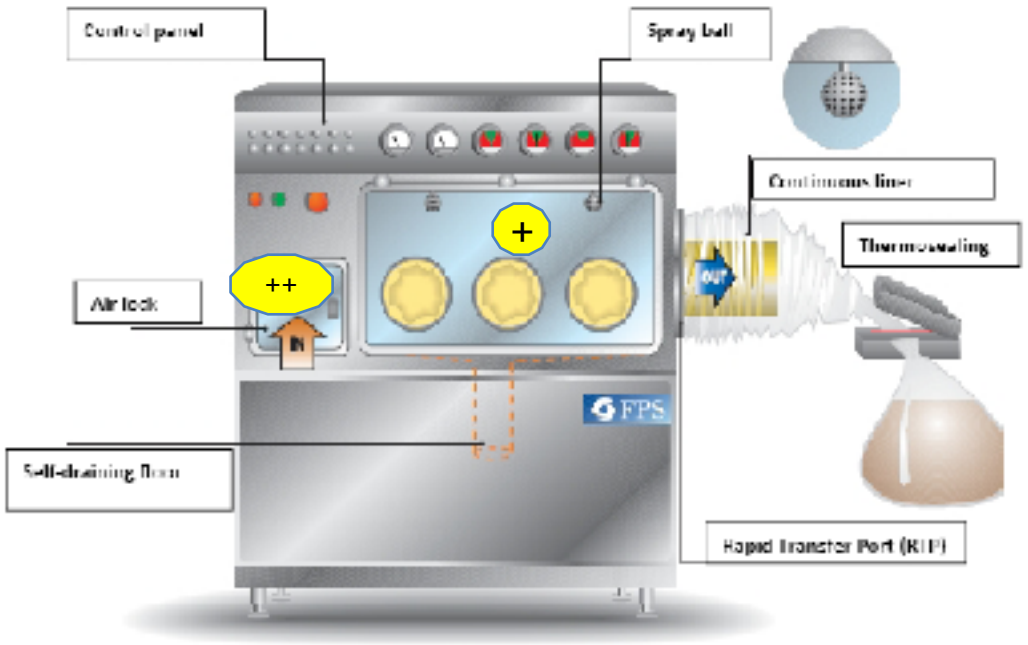

Typical approach

1- Containment system definition (Toxic/ Sterile case)

Technical Features

- *Full Stainless Steel construction following cGMP requirements*
- *FDA approved materials for not Stainless Steel parts*
- *Configuration for HPAPI and Sterile products activities*
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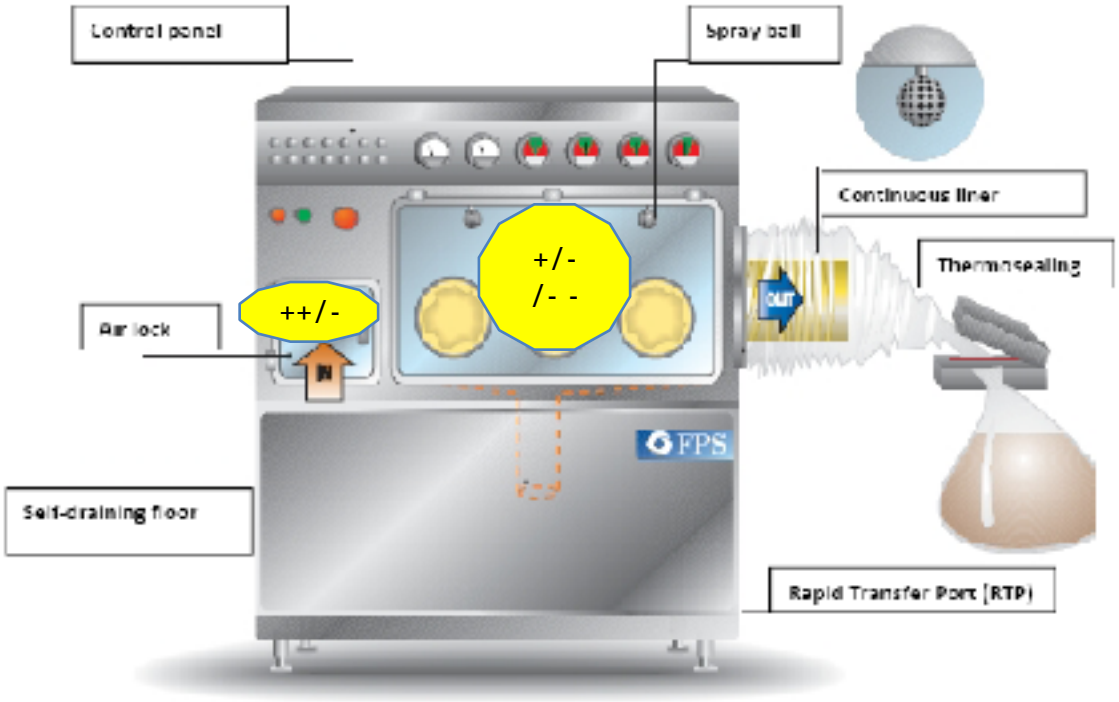


Clever system!!!! = Risk Reduction!!!!

1- Final combination of available containment solution (T[illegible] case)

R&D Unit (CPT 10 ng/m³)

Pilot Unit (CPT 10 ng/m³)

Production Unit (CPT 50 ng/ m³)

1- Final combination of available containment solution (Toxic/Sterile case)

Dispensing Unit (Sterile/CPT down to 100 ng/m³)

Dispensing and process vessel charging (Sterile/CPT down to 100 ng/m³)

ANFD with discharge, milling and pack-off station (Sterile/CPT down to 1μg/m³)

Milling, Micronisation and final dispensing station (Sterile/CPT down to 1μg/m³)

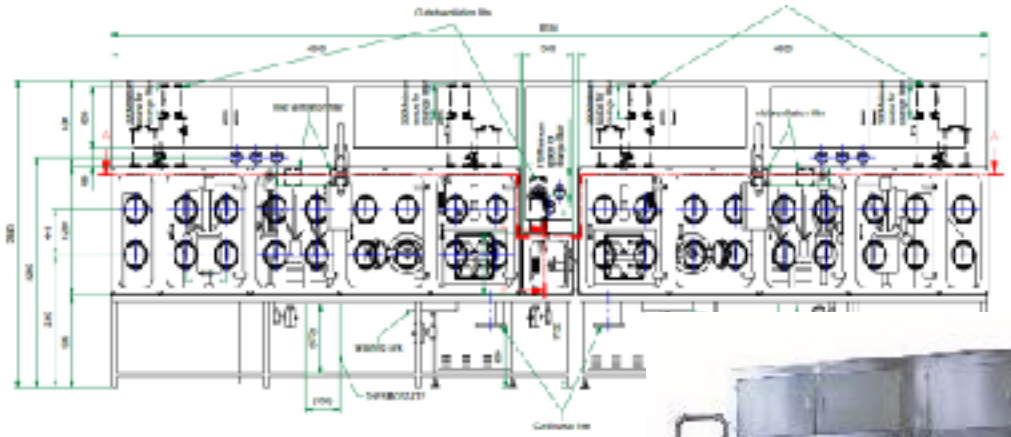
HPAPI containment system

2. Case Studies

2-Ergonomic study -Mock up Execution -

Internal process equipment integration

- Preliminary model
- Ergonomic study by Mock-up Execution
- Ergonomic study final report



2-HPAPI integrated system

R&D Isolator with integrated process equipment

Technical solution and layout configuration to achieve CPT of 10 ng/m^3 on 8 h TWA

2-HPAPI integrated system

R&D Isolator with integrated process equipment

Technical solution and layout configuration
to achieve CPT of 10 ng/m^3 on 8 h TWA

2-HPAPI integrated system

Pilot Plant Isolator with integrated process equipment

Technical solution and layout configuration to achieve CPT of 10 ng/m^3 on 8 h TWA

2-HPAPI integrated system

Pilot Plant Isolator with integrated process equipment

Technical solution and layout configuration to achieve CPT of 10 ng/m^3 on 8 h TWA

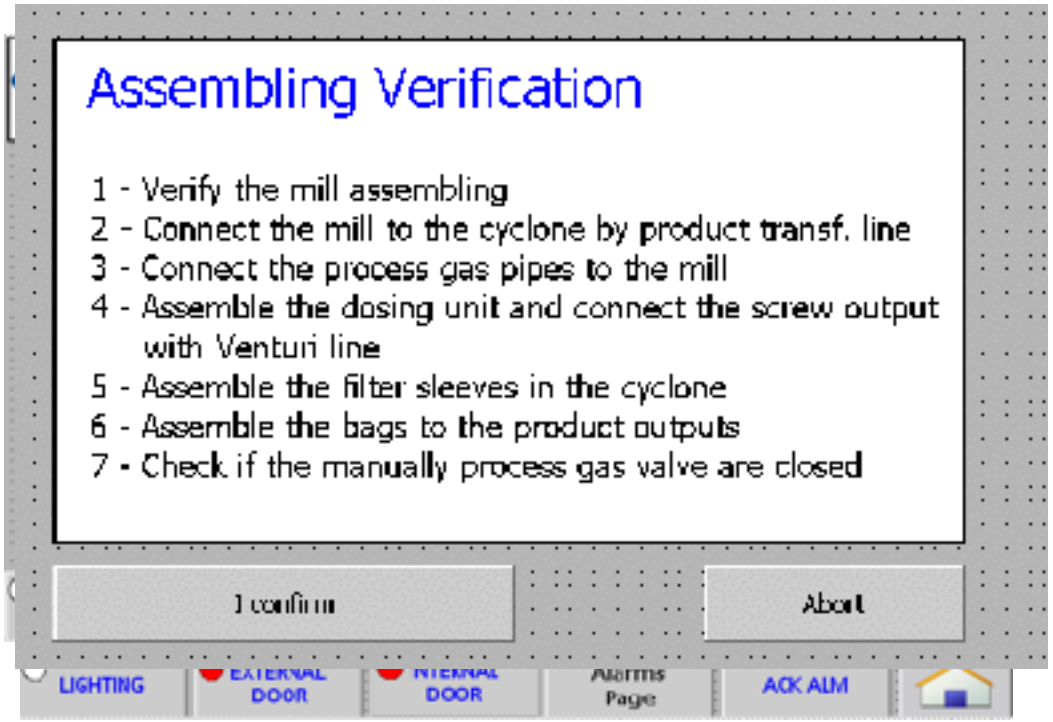
2-Case Studies HPAPI integrated system

Special features to achieve ng level of containment:

- Taylor made engineered material inlet airlock with proper interlock management and integrated bag-in port
- Taylor made engineered material outlet airlock with integrated double continuous liner system and thermal welding machine
- Proper design of ventilation and filtration system and special design of exhaust piping
- Proper definition of safety level of selected critical instruments
- Proper design of washing line and waste washing liquid discharge
- Proper design of control system

2-Case Studies HPAPI integrated system

R&D and Pilot Plant Isolator control system:



- Automatic leak test
- Selection of ventilation mode
- Selection of process equipment
- Process parameter setting
- WIP mode selection
- Safety managements
- Data Record system

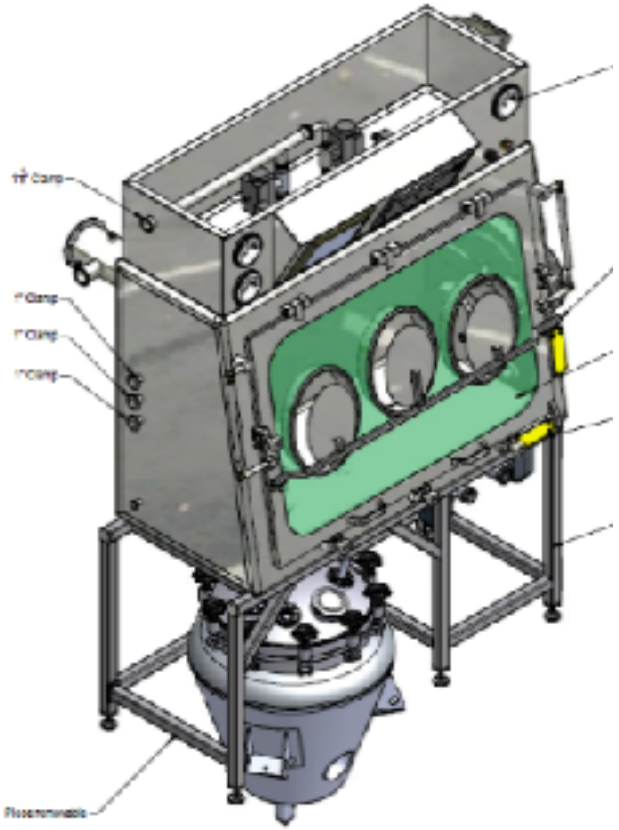
Sterile/HPAPI containment system

3. Case Studies

3- Sterile/HPAPI integrated system

Process Vessel Toxic/Sterile charging isolator:

- OEB 5 process vessel charging isolator
- Internal class A under turbulent airflow
- ATEX installation area
- Integrated VPHP decontamination system
- Integrated SIP system
- Integrated weighting system
- Process vessel internal CIP control by integrated ATEX video camera



3- Sterile/HPAPI integrated system

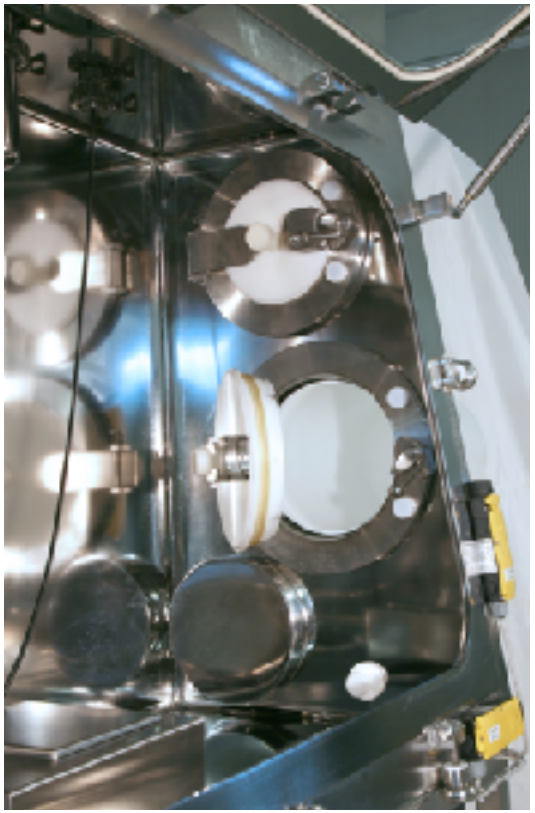
Preparation Functional sequence:

1. Automatic Glove leak test
2. Automatic Isolator integrity test
3. Internal component preparation for decontamination phase
4. VPHP decontamination cycle
5. Ventilation cycle start (positive pressure)
6. Introduction of autoclave sterilized components
7. SIP of connected process vessels

3- Sterile/HPAPI integrated system

Vessel charging activities:

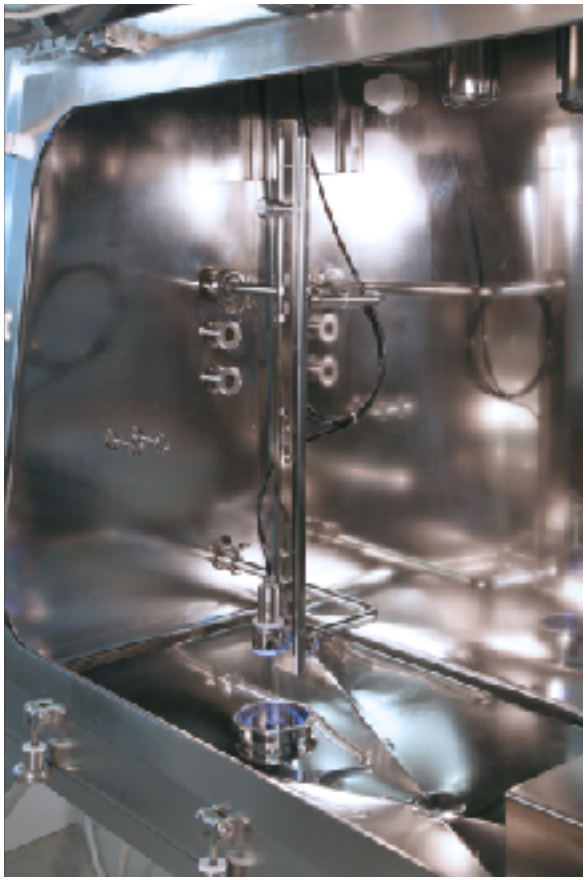
1. Material introduction (RTP)
2. Weight check
3. Material loading into process vessel
4. Waste material removal (RTP)
5. Closing of connection to process vessel

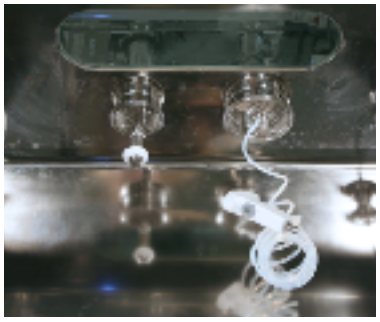


3- Sterile/HPAPI integrated system

Isolator Washing sequence:

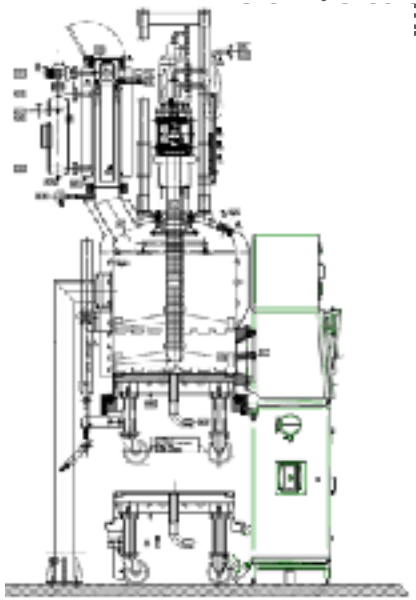
1. Ventilation switch to negative mode (sterility break)
2. Preparation of washing tools
3. Preliminary automatic wash/wet by spray nozzle
4. Final manual washing
5. Final drying
6. Check of vessel cleaning by installed video camera

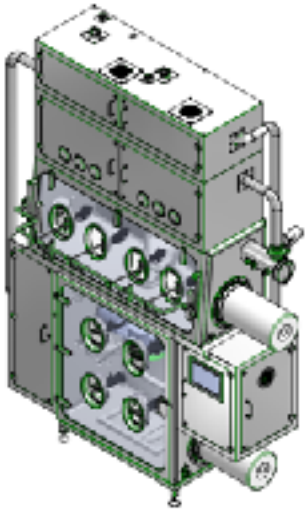




3-Sterile/HPAPI integrated system

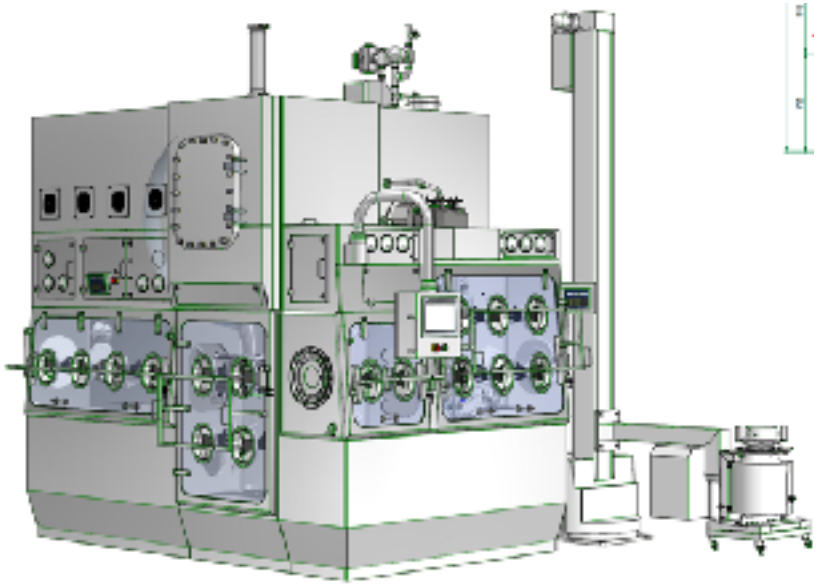
Production plant Isolators with integrated process





STEP 1

ANFD Discharge system with integrated milling station



STEP 2

Micronisation station with final discharge and dispensing station

3-Sterile/HPAPI integrated system

Overall equipment features:

- CPT=1 $\mu g/m^3$
- Internal class A under turbulent airflow
- ATEX installation area
- Integrated VPHP decontamination system management
- Integrated SIP system management
- Integrated Particle Monitoring System
- Integrated process vessel internal SIP/CIP
- 21 CFR Part 11

3-Sterile/HPAPI integrated system

ANFD Isolator discharge (Activities):

- Product sampling (manual)
- Product discharge (automatic)
- Heel recover (manual)
- Product Milling (Cone Mill SIP version)
- Product discharge:
  - Continuous liner system
  - Split butterfly valve

3-Sterile/HPAPI integrated system

ANFD Isolator system (environmental sequences):

1. Automatic Glove leak test
2. Automatic Isolator integrity test
3. Automatic ANFD leak test
4. Internal component preparation for decontamination phase
5. VPHP decontamination cycle
6. Ventilation cycle start (positive pressure)
7. Introduction of autoclave sterilized components
8. SIP of process vessels and of discharging line

3-Sterile/HPAPI integrated system

ANFD Isolator discharge:

- Product sampling (manual)
- Product discharge (automatic)
- Heel recover (manual)
- Product Milling (Cone Mill SIP version)
- Product discharge:
  - Continuous liner system
  - Split butterfly valve
- Product handling by taylor made trolley

3-Sterile/HPAPI integrated system

ANFD Isolator Cleaning:

- Sterility break and Isolator switch to negative pressure mode
- CIP on automatic CIP provided equipment (ANFD, ConeMill and SBV)
- Manual cleaning of isolator internal surfaces
- Drying of internal process equipment parts
- Drying of internal isolator surfaces

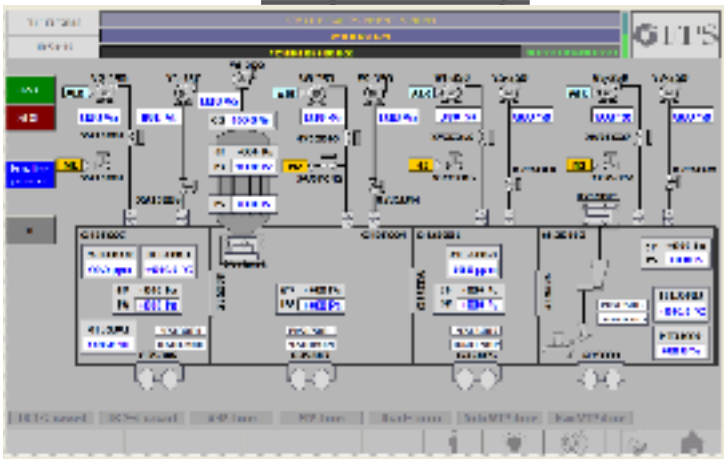
3-Sterile/HPAPI integrated system

Micronisation, discharge and dispensing isolator (Activities):

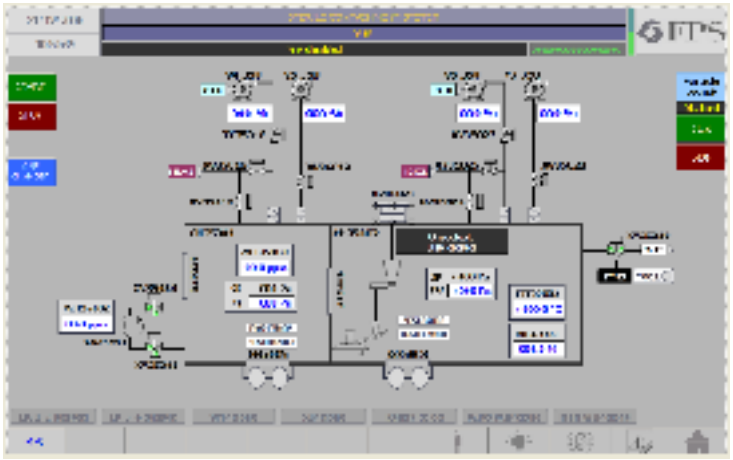
- Product Loading (automatic)
- Product Feeding and micronizing (automatic)
- Product Discharge (automatic)
- Product packing off (manual/automatic)
- Product Dispensing (manual)

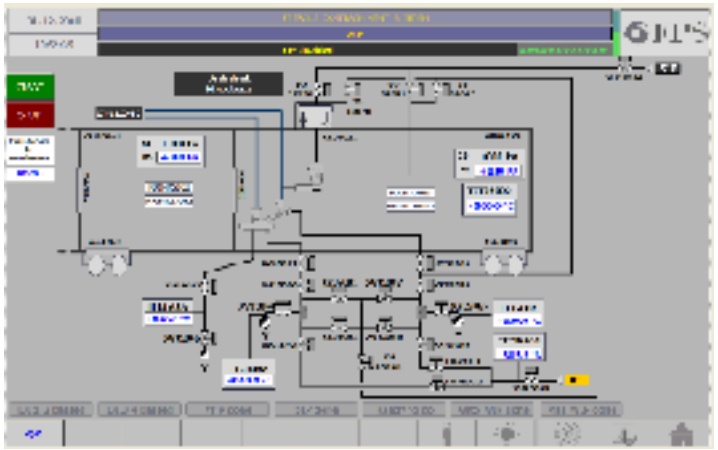
3-Sterile/HPAPI integrated system

Micronising/dispensing Isolator system (environmental sequences):



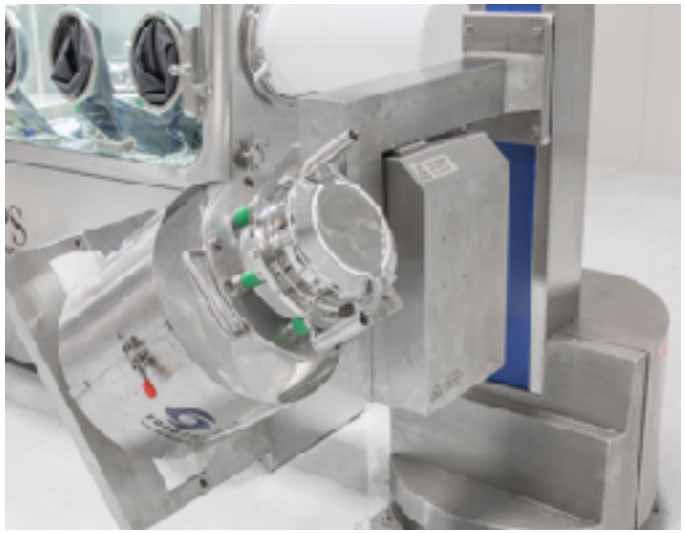
1. Automatic Glove leak test
2. Automatic Isolators integrity test
3. Automatic micronisation system leak test (charge SBV, dosi system, mill, piping cyclone filter, discharge SBV)
4. Internal component preparation for decontamination phase
5. VPHP decontamination cycle
6. Ventilation cycle start (positive pressure)
7. Introduction of autoclave sterilized components
8. SIP of micronisation in place





3-Sterile/HPAPI integrated system

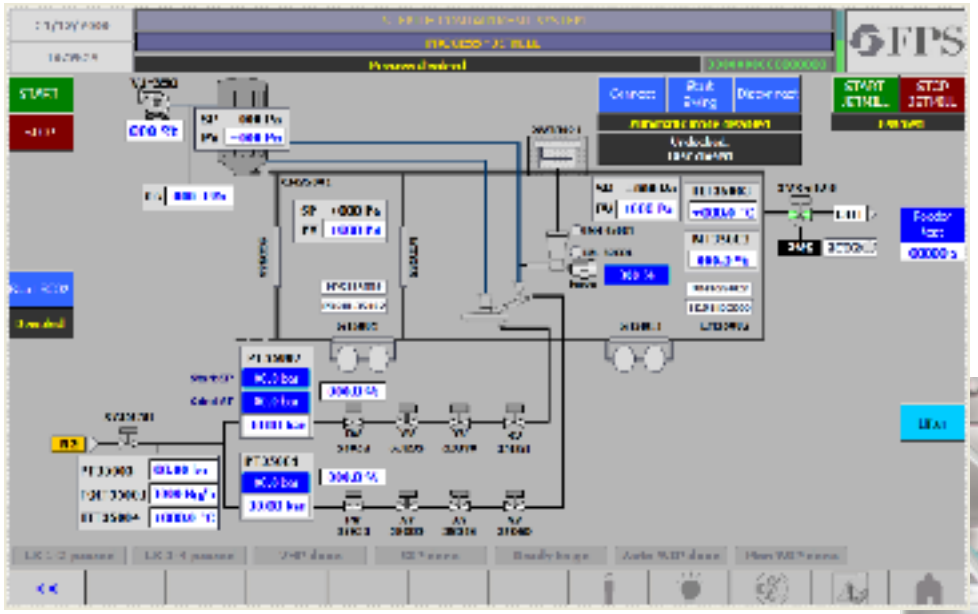
Micronisation loading Activities:



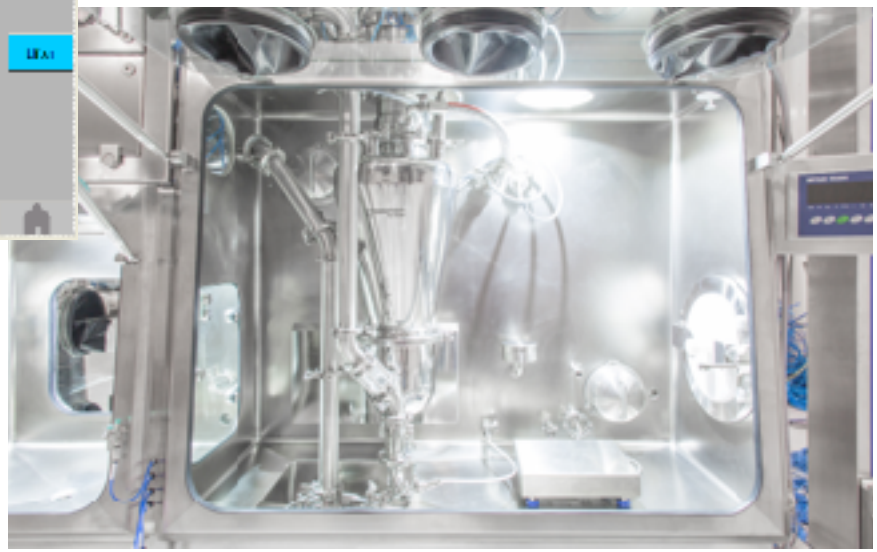
- Product Loading by integrated lifter
- SBV VPHP decontamination cycle
- Final docking
- Product automatic loading into dosing unit

3-Sterile/HPAPI integrated system

Micronisation Activities:

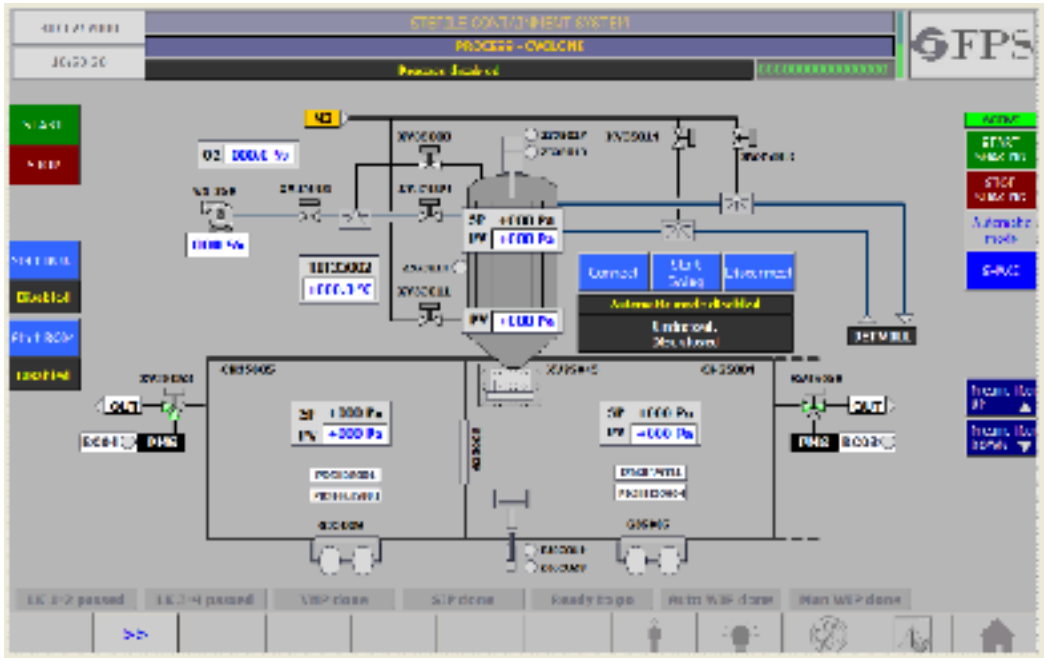


- Process recipe loading
- Automatic process start
- Process parameters control (P, T, Feed Rate)



3-Sterile/HPAPI integrated system

Micronisation discharge:



- Automatic product discharge
- Final product removal (SBV)
- Final product weighting or dispensing

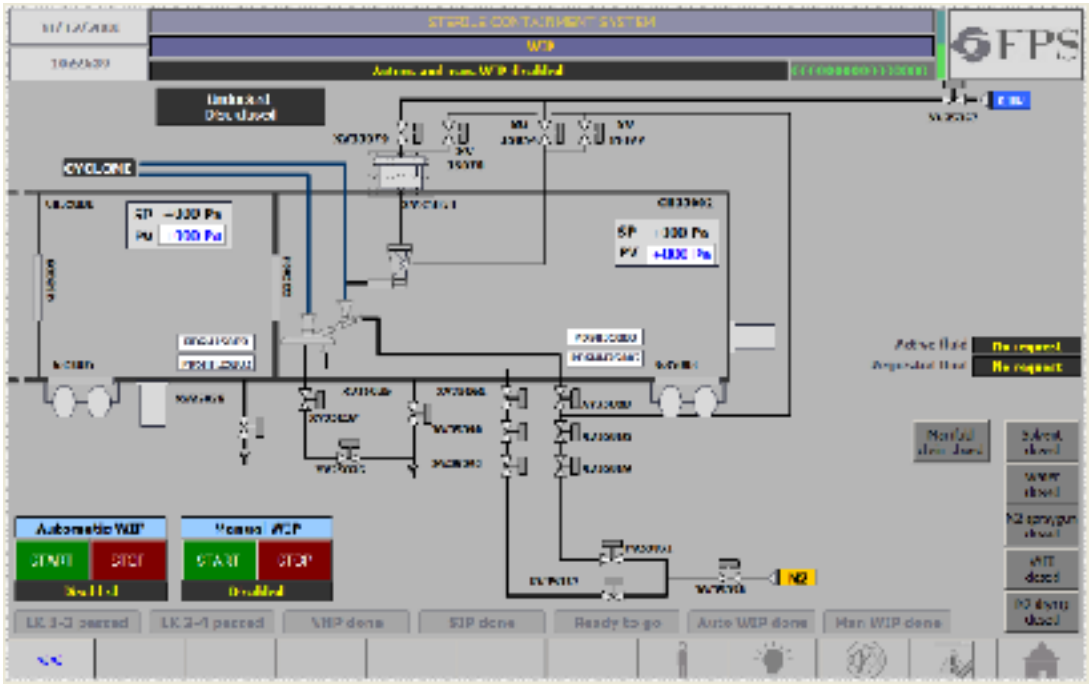
3-Sterile/HPAPI integrated system

Dispensing chamber:

- Final product weighting
- Final product re-packing
- Assembling of SBV under sterile environment
- Removal by RTP continuous liner system with thermal welding machine

3-Sterile/HPAPI integrated system

Overall Isolator Cleaning:



- Sterility break and Isolator switch to negative pressure mode
- CIP on automatic CIP provided equipment (charge SBV, Dosing unit, Product piping, Cyclone filter ,discharge SBV Cone-Mill)
- Manual cleaning of isolator internal surfaces
- Manual cleaning of isolator internally installed equipment (Spiral-Jetmill and dosing unit screws)
- Drying of internal process equipment parts
- Drying of internal isolator surfaces

4. Conclusions and new challenges

4-Conclusions

Following conclusion could be indicated as general key points to evaluate when defining new containment system:

- Great attention to boundary limits definition
- Detailed analysis of process from safety, from containment and from Sterility point of view by dedicated and combined risk assessment
- Evaluate all containment aspects from operators to maintenance people
- Detailed operator and maintenance people training
- Proper equipment maintenance plan
- Proper equipment containment/sterility performance evaluation:
  - As part of validation
  - As part of normal maintenance/verification plan

4-Conclusions

Great attention **MUST** be paid to flexible part of containment system like gloves or half suit by dedicated procedure and instruments!

4-New Challenges

Every day there are new challenges we are discussing and evaluating in order to bring the target of containment to an highest level :

- Higher containment of sterile processes
- Reduction of manual intervention inside isolators
- Improvement of existing interfaces from outside/ inside
- Improve overall clean-ability of internal parts
- Accurate and fast response real time check of isolator tightness
- ……

Biography

1. *EN 14175 Biosafety cabinet (Part 1,2,3 and 6)*
2. *ISO 14644-7 Separative devices (clean air hoods, glove boxes, isolators, and minienvironments)*
3. *ISO 10648-1 Containment enclosure - Part 1 Design principles*
4. *ISO 10648-2 Containment enclosure - Part 2 Classification according to leak tightness and associated checking method*
5. *AGS-G001-2007*
6. *Containment Systems a design guide (IchemE editor)*
7. *SMEPAC guideline (second edition)*
8. *All images and drawings taken from FPS project reference archive*

Final Notes – Any question?

- Process aspects?
- Design details?
- Operations?

Your comments are the starting point for possible future improvement.

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Thank you for your attention!