Containment Solutions
Equipment Design and Applications

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FOOD PHARMA SYSTEMS

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FPS Food and Pharma Systems Organization

Head Quarter (Como - Italy)

- Administration
- Marketing
- Sales

Engineering Plant - Italy

- Activities:
  - Project and Design
  - Manufacturing and Assembly
  - R&D Centre and QA Dept.
- 5000m^2 surface
- 30 people

Worldwide agent network

- In Korea: Sanitary Equipment Korea

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FPS Food and Pharma Systems
Working “style”

Each situation has its own solution

We do not propose pre-defined solutions but solutions which correspond to end user needs

We always try to understand and know the needs, the history and the experience of our customers

The starting point of a project is not our machine but our customer need around which we build our systems

We are 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

FPS Food and Pharma Systems Product Range

Containment systems

- Isolators
  - Glove-boxes
  - Half-Suit isolators
- RABS
- LAF
- Down-Flow booths
- Pack-off systems
- Local Suction Arms

Micronisation systems

- Jetmills
  - R&D units
  - Pilot units
  - Production units
- QMills
  - R&D QMill
  - Pilot QMill
  - Production Qmill
- PinMills

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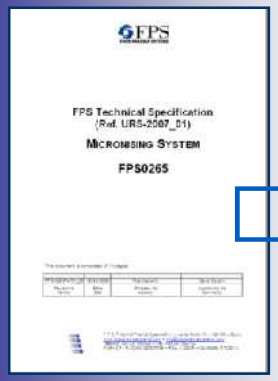
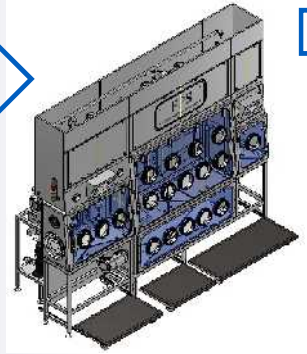
FPS Food and Pharma Systems
Project Activities

- On-site preliminary discussion
- Front-end design
- Detail engineering
- Manufacturing
- Document review
- FAT

- Transport & installation
- SAT
- Validation (IQ/OQ)
- Maintenance and operator training
- Lifetime assistance





Containment Systems
Equipment Design and Applications

Containment Introduction

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Containment Systems Definitions

What is containment system?

Containment system ensures the separation between a specified work volume (internal environment) and surrounding space (external environment).

Why do we need containment system?

Containment system is needed to prevent any negative impacts from work volume and surrounding space (toxic application) and vice-versa (sterile application)

How do we define the containment system?

The most common value used in in the pharmaceutical industry is the Occupational Exposure Level (OEL).

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Containment Systems
Occupational Exposure Level

The Occupational Exposure Level is the limit on the acceptable concentration of a hazardous substance in a workplace air for a particular material or class of materials.

$$OEL = \frac{NOEL\ (mg/Kg/day) * BW\ (Kg)}{V\ (m^3/day) * S(days) * SF * \alpha *} = [mg/m^3]$$

- NOEL=No Observable Effect Level = LD_{50} * 0.00005 [mg/Kg/day]
- BW = Body weight [Kg]
- V = volume of air breathed in an 8 hour work day [m^3] = (10 m^3)
- S = time in days to achieve a plasma steady state = we will set 1
- SF = safety factor:
  - 10 x = using subchronic in lieu of chronic tox studies
  - 10 x =using animal data in lieu of human data
  - 10 x = intraspecies variation
  - 10 x = using estimation of the NOEL
  - 10 x = if the substance is carcinogen and or teratogenic or sensitising
- α = percent of compound absorbed from inhalation = 100

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Containment Chart

Level	Range of OEL (µg/m³)	Containment strategy	Equipment
OEB1	> 1.000	LEV – Local Exhaust Ventilation	
OEB 2	100 – 1.000	LEV – Laminar Flow Booths	
OEB 3	10 - 100	Down cross containment booths	
OEB 4	1 - 10	Closed systems – RABS, barrier isolators	
OEB 5	< 1	Closed handling within isolator, high containment devices	

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Factors affecting Exposure Potential

Wet	Physical Form	Dry
Large	Particle Size	Small
Dense	Density	Light
Closed	Operation	Open
No Energy / Velocity	Process	High Energy/ Velocity
None Required	Operator Skill	Highly Dependent
Low Δ p	Pressure	High Δp
None	Transfers	Multiple
Well	Training	Poorly
Well	Maintenance	Poorly
Routine	Task Type	Non Routine
One Operation	Frequency	Multiple Operation

Exposure Potential is also dependant on operator: in general up to 50% of containment performance is connected to isolator use.

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Containment Systems
The performance

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.

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

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Containment Systems
SMEPAC test

Containment performance verification following ISPE guideline during FAT and at end user site from approved third party

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Leak tightness

Isolator tightness defined and assessed according ISO10648 and ISO14644-7

Table 1 — Classification of containment enclosures according to their hourly leak rate

Class	Hourly leak rate, T_f h^{-1}	Example
1 *)	$\leq 5 \times 10^{-4}$	Containment enclosure with controlled atmosphere under inert gas conditions
2 *)	$< 2{,}5 \times 10^{-3}$	Containment enclosure with controlled atmosphere under inert gas conditions or with permanently hazardous atmosphere
3	$< 10^{-2}$	Containment enclosure with permanently hazardous atmosphere
4	$< 10^{-1}$	Containment enclosure with atmosphere which could be hazardous

*) The classification of leak tightness required for a particular application under classes 1 and 2 shall be decided by the designer and user and licensing authorities. Normally, class 1 will be applied for technical reasons when higher gas purity is required.

When leak test is performed:

- FAT
- SAT
- After any maintenence, repair activity or operator need

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Leak measurement

Different methods:

- Oxygen method (class 1)
- Pressure change method (class 2 and 3)
- Constant pressure method (class 3 and 4)

Pressure change method:

- Easy to perform
- Not need specialized equipment
- Not need highly trained presonnel
- The test can be performed by itself

$$T_f = \frac{60}{t} \times \left(\frac{p_n T_1}{p_1 T_n} - 1 \right)$$

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Containment Solutions
Leak detection

If the isolator leaks, we have to detect the sources

Leak detection methods

- Soap solution

The test is exactly the same as applied to pneumatic tyres. Overpressurise and monitor all welds, gaskets, connections, …
The method is cheap, but messy

- Helium

Isolator is pressurized to 100-200Pa with helium.
An helium detector (sniffer) is used to search the leakage points
We can detect 10ppm

- Smoke test

Overpressurise and monitor all welds, gaskets, joint filter housing, ….

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Glove testing

Glove testing assure glove integrity. Automatic / Manual Glove tester:

- Available for different flange size/shape
- Sterile / Toxic application
- Fast response
- Easy to use
- Efficient

Glove breach test:

In the event of «worst case» (glove removal) isolator has to be able to guarantee a correct air flow. Guidancer value: 0,5m/s

Containment Systems
Equipment Design and Applications

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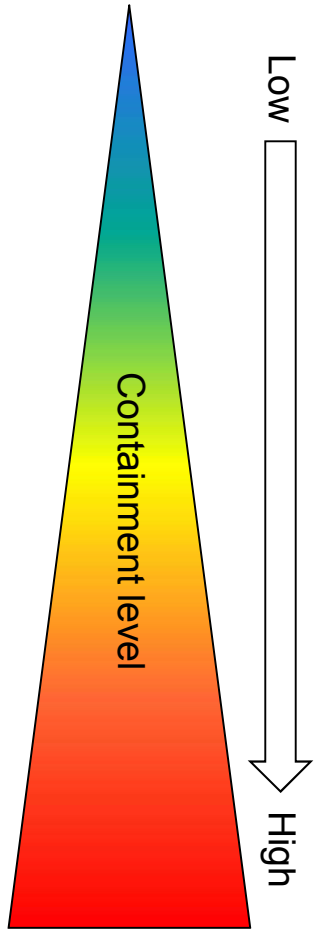
Containment Solutions
Strategy Selection Chart

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 FOOD PHARMA SYSTEMS	

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



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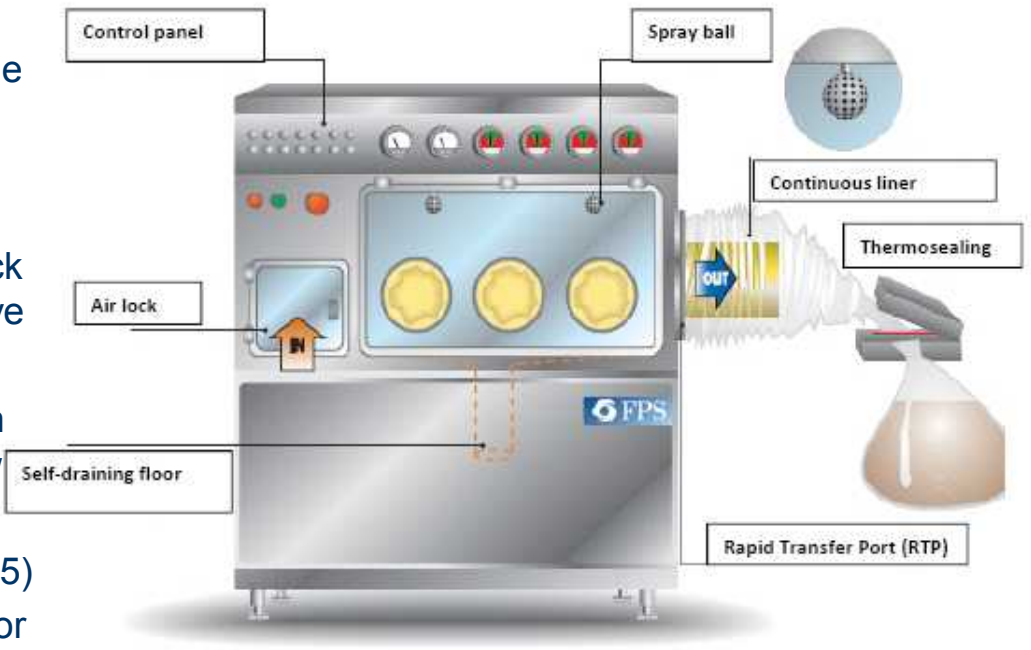
Containment Solutions
Design Features

- Stainless Steel 316L construction following cGMP requirements
- FDA approved materials for not Stainless Steel parts
- Configuration for HPAPI or Sterile products activities
- Constant negative (positive) pressure working condition
- Transfer system available: Airlock / RTP / Endless Liner / Split Valve
- Full WIP / CIP / SIP available
- Electrical classified configuration
- Internal class to ISO5 / Class A / Class 100 / Class M3.5
- OEL < 0.05µg/m^3 8h TWA (OEB5)
- Leak test following ISO10648-2 or AGS-2007 with 0.5% of Volume leak rate
- Sterility level below to 6log by VHP



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Containment Solutions
Project Development

Sterile dispensing and
vessel charge

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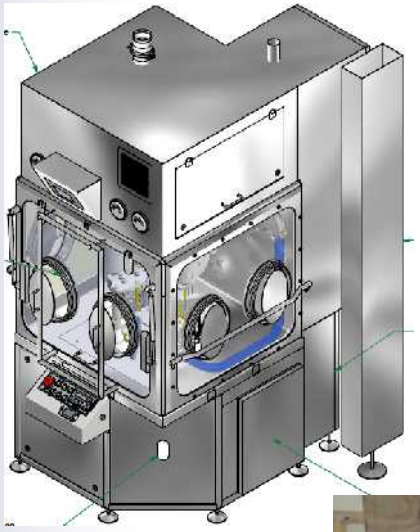
Containment Solutions
Project Development



Tablet press and capsule filling machine integration

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Contained Transfer Systems
Pass-box

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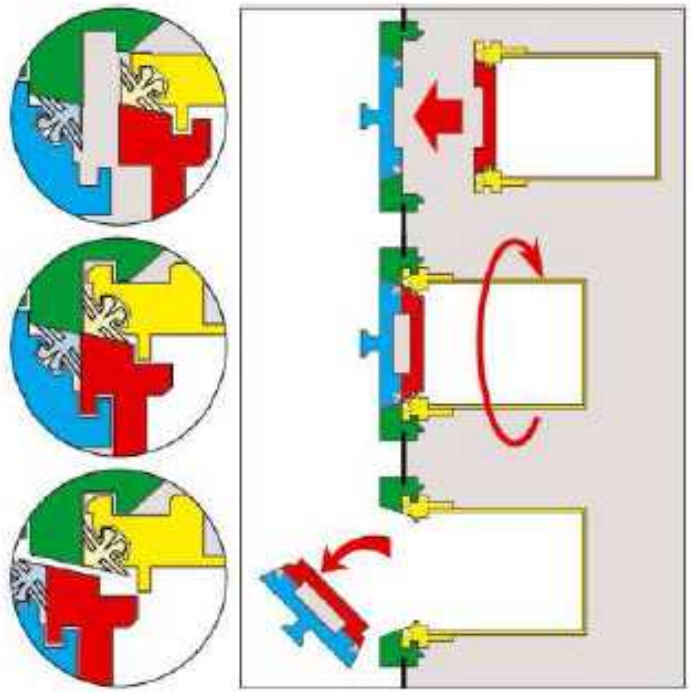
Contained Transfer Systems
Rapid Transfer Ports (RTPs)



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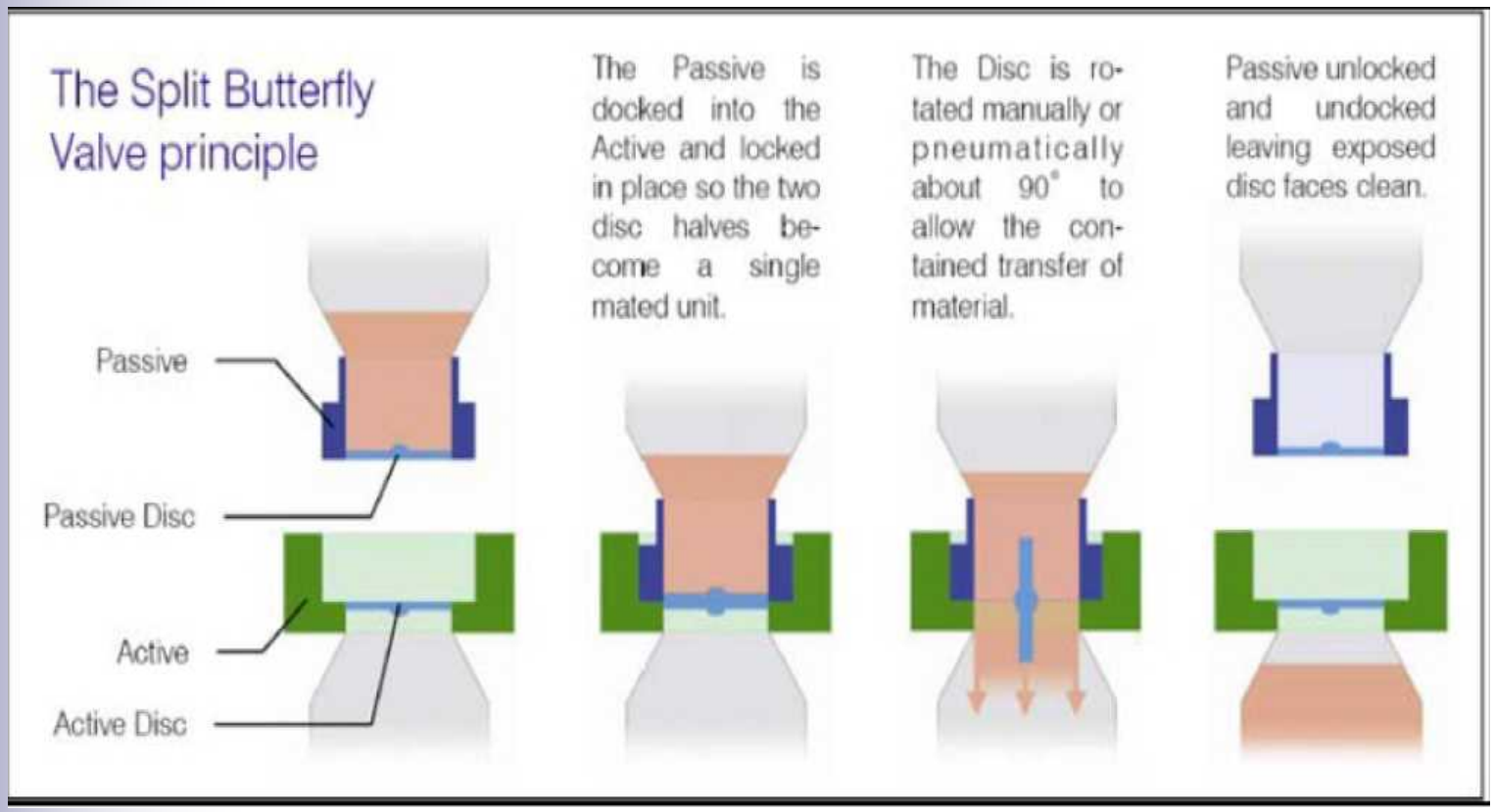
Contained Transfer Systems
Split Butterfly Valve



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Contained Transfer Systems
Continuous liner

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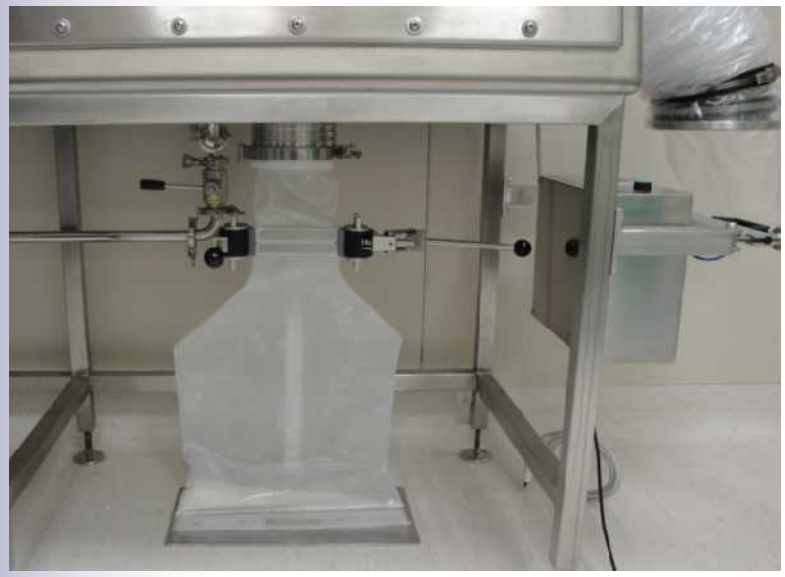
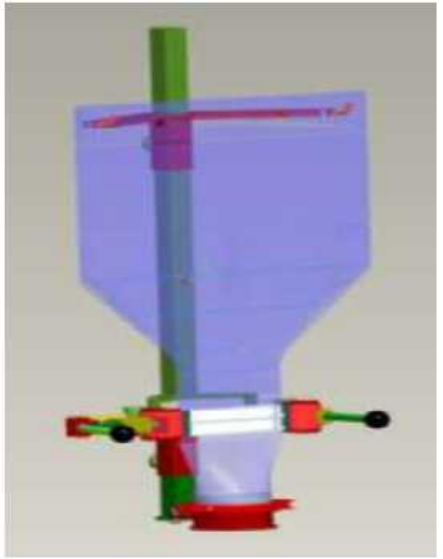
Contained Transfer Systems
Hicoflex®





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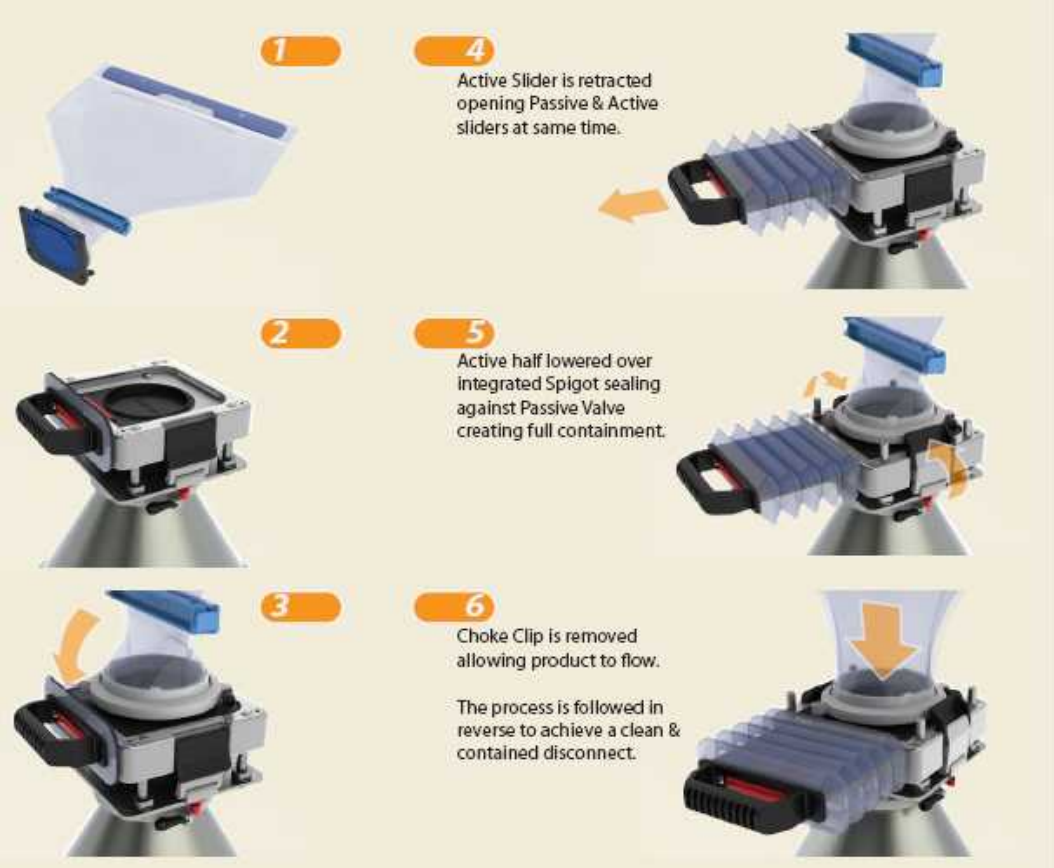
Contained Transfer Systems
Ezi-Dock™



Chargebags available in sizes: 2/5/10/15/25/40 litre

Phamaceutical Chargebottles available in sizes: 15/25/30/40 litre

Optional Hicoflex style adapter mount

Containment Systems
Equipment Design and Applications

Some Examples

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Isolator Systems

Laboratory Isolators

Stainless Steel isolators for:

- Weighting
- In Process Control
- Sampling
- Charging
- Discharging
- Sieving…

Pharmaceutical Processing

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Isolator Systems
Complete API lines

Isolator System for API Production Plants

- Synthesis
- Filtration
- Milling
- Dispensing
- Packing

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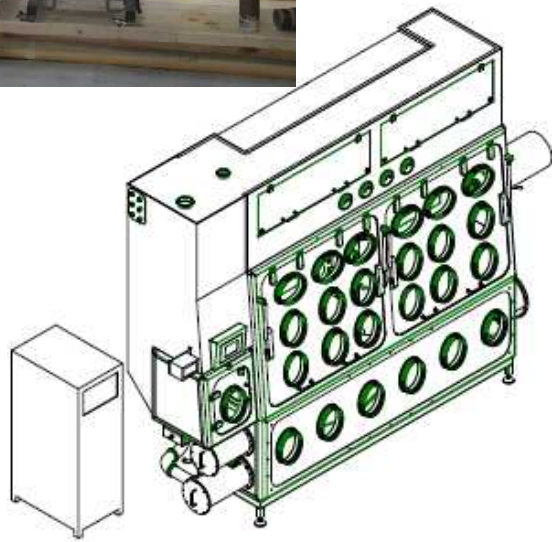
Isolator Systems

Reactors for Synthesis

Different size and type of pilot reactors in glass or SS can be integrated in different way depending on reaction process steps



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Isolator Systems

Reactors for Synthesis

25-50litres reactors in glass or SS

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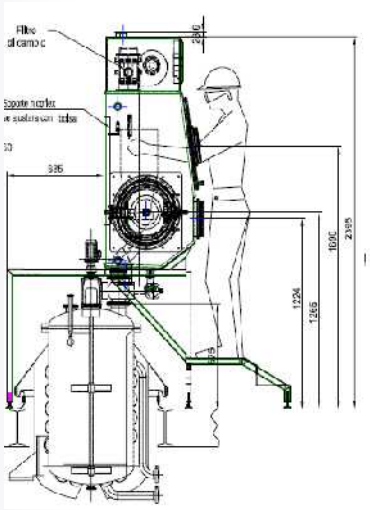
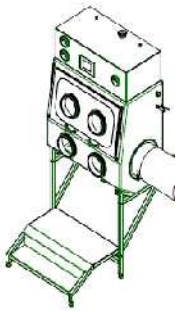
Isolator Systems

Reactors Charging

Small and large production reactors can be interfaced with isolator for safe charging by gravity or by VTS





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Isolator Systems

Tray Dryer

Tray dryer for pilot plant integrated with complete automation control

Tray dryer door open

Tray dryer door closed

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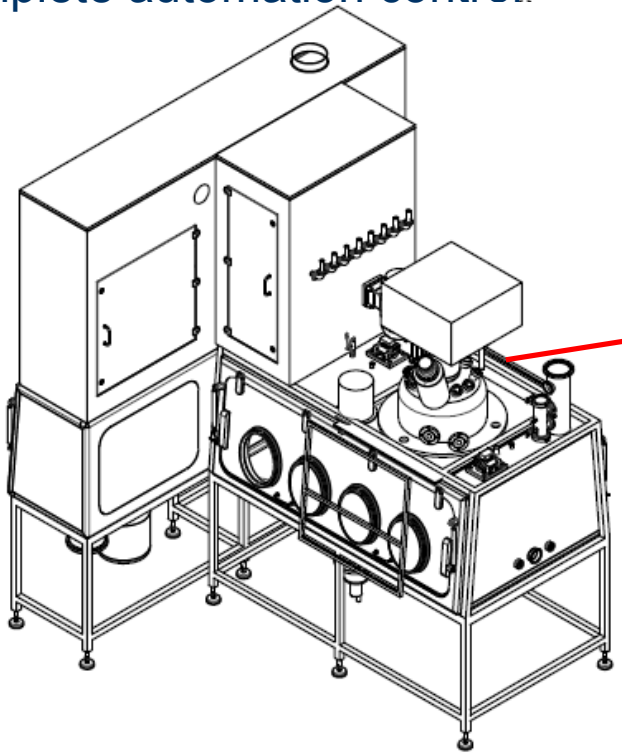
Isolator Systems

Filter Dryers (pilot plant)

Agited Nutsche Filter Dryer for pilot plant fully integrated with complete automation control.



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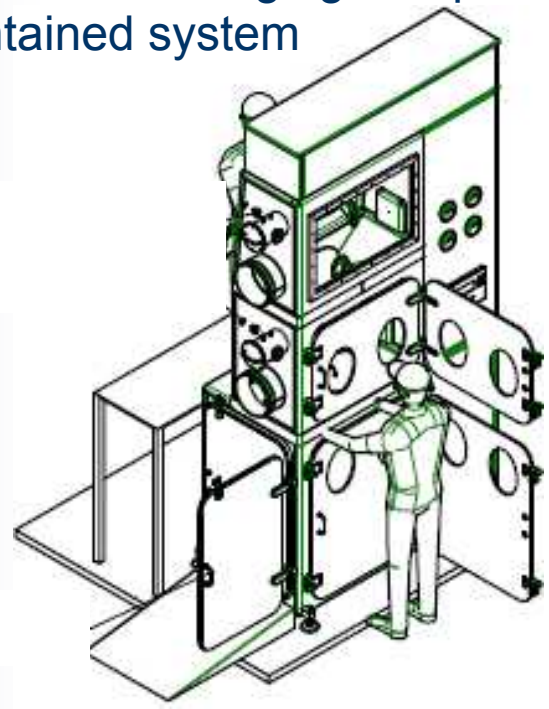
Isolator Systems

Filter Dryers (production plant)

ANFD for production plants are fully integrated with sampling, heel push, product discharging and packing-off contained system



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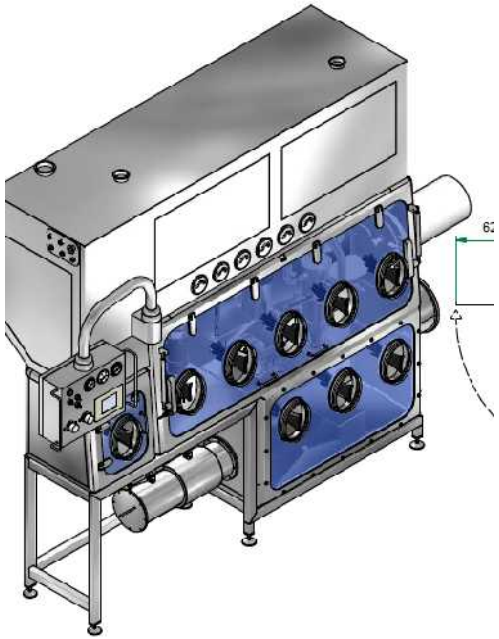
Isolator Systems
Milling and Micronization

FPS Multi-milling platform for R&D and Pilot Plants

- Cone-mill
- Pin-mill
- Spiral jet mill
- Cryogenic milling



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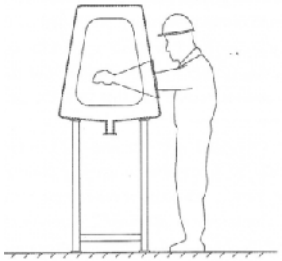
Isolator Systems

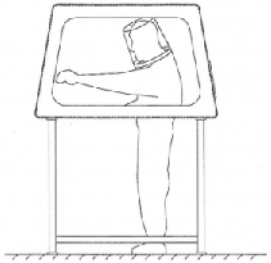
Milling and Micronization

FPS Half Suit or glove Isolator Systems for Production Plants

- ProMill-8
- ProMill-12



Glove-box isolator



Half-suit isolator

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Isolator Systems

R&D Oral Forms line

Weighting

Semi-automatic capping machine

Sieving and blending

Capsule-filling and capsule-orienting

Semi-automatic counting machine

Pharmaceutical Processing

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Isolator Systems

Oral Solid Forms processing

Pan Coating machine

Dispensing

In Process Control

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Oral Solid Forms processing

Capsule filling machine Overview

Tablet press machine

Capsule filling machine – Internal View

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Isolator Systems

Oral Solid Forms processing

OEB5 Blistering machine

OEB4 Blistering machine

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Isolator Systems

RABS for Sterile Lines

A Restricted Access Barrier System (RABS) is defined as:

"An aseptic processing system that provide and enclosed, but not closed, environment meeting Grade 5 conditions utilizing a rigid wall-enclosure and air overspill to separate its interior from the surrounding environment"

Vials filling line

Powder dosing unit

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Isolator Systems

Sterile Isolators

Isolators integrated for sterile operations:

- Dispensing and vessel charging
- Caps washer and sterilizers

Sterile tank charging

Sterile caps discharging

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Isolator Systems

Glove tester

Automatic / Manual Glove tester:

- Efficient
- Fast response
- Easy to use
- Available for different flange size/shape
- Sterile / Toxic application

Final Notes and References

FPS has set up a small library collecting articles and documents specific on containment.

In the preceding pages we made reference to:

- Assessing the Particulate Containment Performance of Pharmaceutical Equipment - ISPE
- Containment Systems – a Dseign Guide – IChemE Guide 2002

If you are interested, we can share our bibliography as regards specific subjects: let's stay in contact.

Thank you for your attention!

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