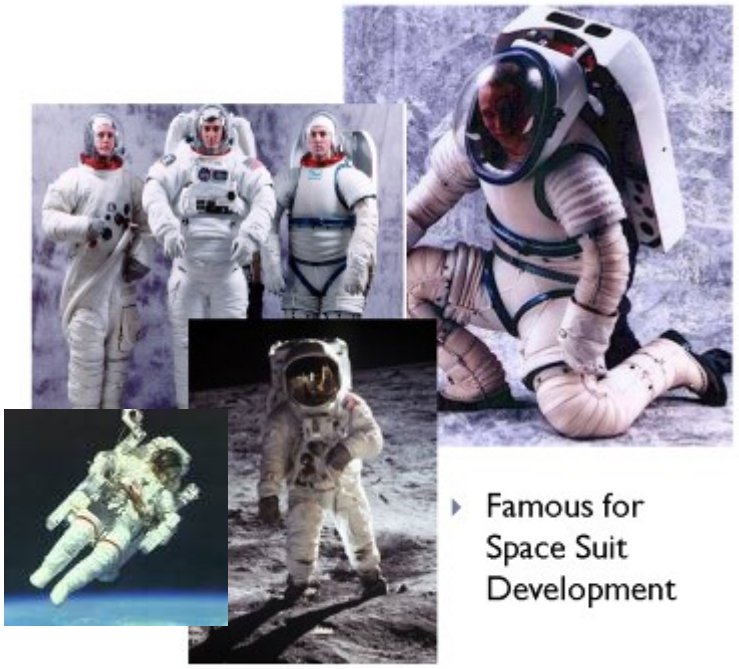
Using Flexible Technology for Process Containment and GMP, Weigh & Dispense, and Product Protection (RiskMaPP*)

Malcolm Cunningham - ILC Dover

* RiskMaPP is a published ISPE guide

DoverPac Containment Systems

ILC Dover LP – Pioneers of Flexible Technology



- Famous for Space Suit Development

- LTA (Lighter than Air) Products

Flexible designs for life critical applications and Solving Pharmaceutical Containment Process Requirements

- PPE Products

DoverPac Containment Systems

1997 - Flexible High Containment launch

- Eli Lilly recognizes drug compounds are becoming more potent and high containment is necessary
- Installation of isolators, laminar flow booths, split valves and other devices are costly and cannot retrofit to existing process easily
- Lilly seeks out partners to develop high containment IBC technology and the Continuous Liner System

2012 – Over 200,000 Flexible Systems used Globally

DoverPac® Containment Systems

Progress of Containment Philosophy

Circa 1960 – The boundaries of the plant site

Circa 1980 – The boundaries within a building

Circa 2000 – The boundaries within a suite

Current **– Contain at the Source which is more practical**

Contain at the Source

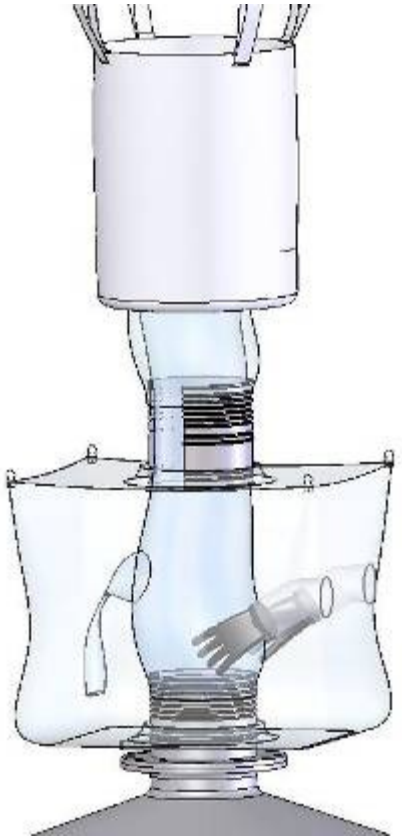
Flexible Containment technology has made this possible on a greater range of processes

- Easy to retrofit on an existing process
- Takes less space, utilities, and is portable
- Installation / Removal time and labor minimized
- Ergonomics designed into the systems to enhance user friendly systems
- Cost of ownership including capital cost and long term use is proven to be dramatically less than hard wall type systems

Flexibles are Globally Accepted

Not a new technology – Validated installations

- Case Studies in Chemical Synthesis and OSD processes report containment levels typically achieve OEB 5 Levels
- HAPI processes requiring nanogram level containment applications can use primary and secondary flexible containment to achieve the required OEL



DoverPac Containment Systems

Defining High Containment w/ Flexibles

Typical Containment Levels Achieved

- Majority of applications have been evaluated and achieved less than ***1.0 ug/m3*** on 8.0 hour time weighted average
- FIBC Data = ***0.7 to 0.05 ug/m3***
- Flexible Isolator data = ***1.0 to***

Product Testing to establish Baseline Data

SMEPAC Established Test Guidelines are the accepted standard for Containment Testing

ILC Dover Installed Controlled Test Facility to obtain Data using a Surrogate

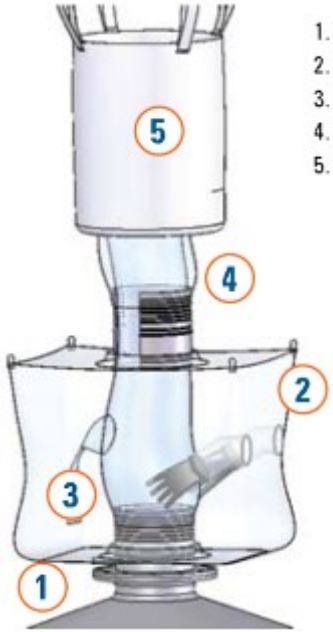
Correct Test Procedures

Baseline Testing* – Data example

* Source IES Engineers Containment Verification Feb 08

Sample Description	Baseline	Run 01 (µg/m³)	Run 02 (µg/m³)	Run 03 (µg/m³)	Arithmetic Mean (µg/m³)
DISCHARGE FROM DOVERPAC TO MOCK VESSEL AND CRIMP AFTER DISCHARGE					
PSBZ – Operator #1 (Gary Handy) during the discharge of 75 L from the DoverPac to the mock vessel and the crimping and cutting of the liner following the discharge		0.014	<0.014	0.024	**<0.0173**
PSBZ – Operator #2 (Adam Sadkowski) during the discharge of 75 L from the DoverPac to the mock vessel and the crimping and cutting of the liner following the discharge		0.015	<0.024	0.047	**<0.0287**
SS – Approximately 200 mm from the bottom connection of the glovebag to the mock vessel at the right side of the operator platform		<0.0088	<0.0083	<0.0092	**<0.0088**
AS-OBH – Approximately 2 m from the transfer point at the discharge of the vessel on the ground floor of the testing facility		<0.01	<0.0081	<0.0074	**<0.0085**
AS-OBH – Center of airlock		<0.0088	<0.0097	<0.0088	**<0.0091**

Notes:
- All airborne contaminant concentrations are expressed in micrograms of the surrogate test compound per cubic meter of air (µg/m³).
- "<X" indicates that the contaminant was not detected in the sample. If present, the contaminant concentration is less than X, the lower limit of quantification for the sampling and analytical method used.



Operator Breathing Zone – < 0.0287 µg/m³

Process: Contained Powder Transfer from DoverPac Co-Axial to Vessel with Secondary Containment

Dual Purpose for Containment

Containment Systems - Protect the workers and facility from the effects of the drug compound

The same Containment Systems provide protection for the product from contamination entering the process

RiskMaPP

The start – Guidance from regulating bodies (FDA, EMA, ANVISA) recognizing the concerns of processing highly potent drug compounds recommend these products be treated like penicillin and hormone products and be ***processed in dedicated facilities***

The concern – ISPE recognizes the impact this will have on facility costs and launches an initiative for an alternate control

RiskMaPP - Current

RiskMaPP has been published and provides a methodology for mitigating the risk of cross contamination in a multi use facility.

The regulating bodies are recognizing, ***based on real data,*** that following the RiskMaPP method successful

RiskMaPP – Data indicates Retention is a Key Issue

- Retention of product on surfaces poses the greatest risk.
- There are limits to cleaning and cleaning validation. More cleaning, more risk.

Reducing / eliminating cleaning reduces the KEY RISK of contamination

RiskMaPP – Data indicates Retention is a Key Issue

Stainless Steel Systems

<u>Clean after every use</u> Washing, Drying, Inspection, Validation

Flexible Film Systems

Safe Disposal after <u>Single use</u>

Rigid IBC

<u>Clean after every use</u> Washing, Drying, Inspection, Validation

Flexible IBC

Safe Disposal after <u>Single use</u>

Two Categories for Flex Containment

Powder / Product Transfers

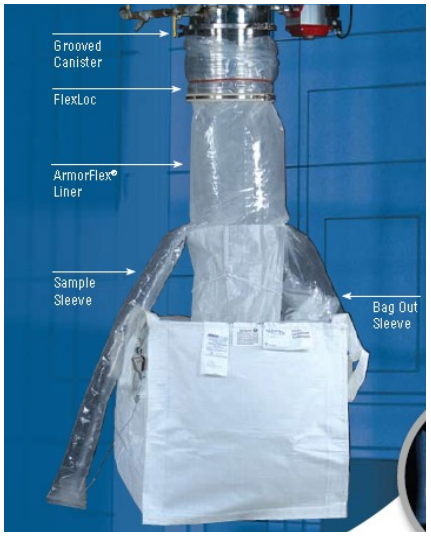
- Transfers from one process step to the next
- Product transportation i.e. Bulk Chemical shipping for OSD finishing

Process Containment

- Isolator (flexible) type solution to contain a process at the

Flexible Powder / Process Transfers

Powder Transfer Bag



FIBC Filling

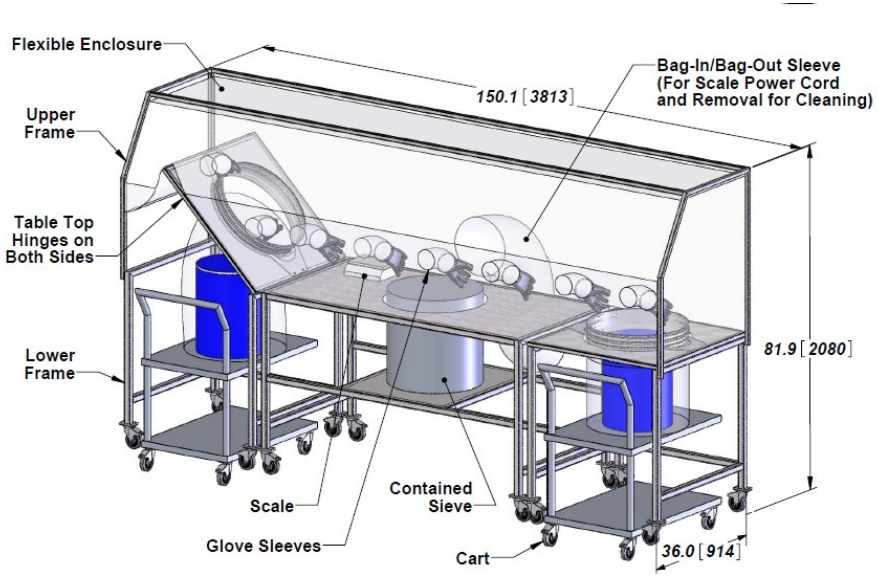
FIBC Discharging

Flexible Powder / Process Transfers

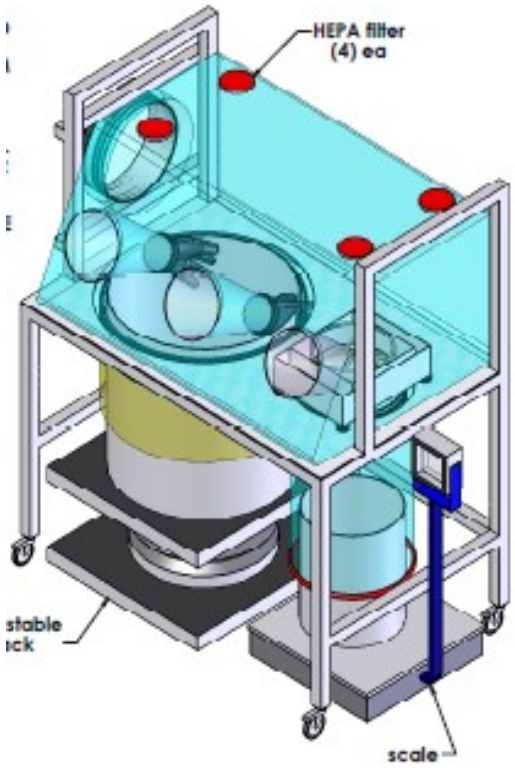
Continuous Liner Systems

Transfer Chutes

Flexible Isolator for Weigh and Dispense



Sub Division



Dispense Weigh
and Sieve

Flexible Isolators for Weigh & Dispense

Versatile systems meet specific process demands

- Improved Ergonomics using Flexible wall
- Low Capital Cost to Purchase and Install
- Disposable System for reduced Cleaning and Operating costs
- Accurate Weighing System designed for the application and process
- Proven Containment using the Static or Dynamic Flexible Isolator System

Weigh & Dispense – Options

- N2 Inerting of the System
- Low humidity control
- Alternate transfer options
- Wash-In-Place Cleaning
- Adjustable height base
- Collapsible Frame for storage
- Passive or Pressure Controlled
- Scale Options

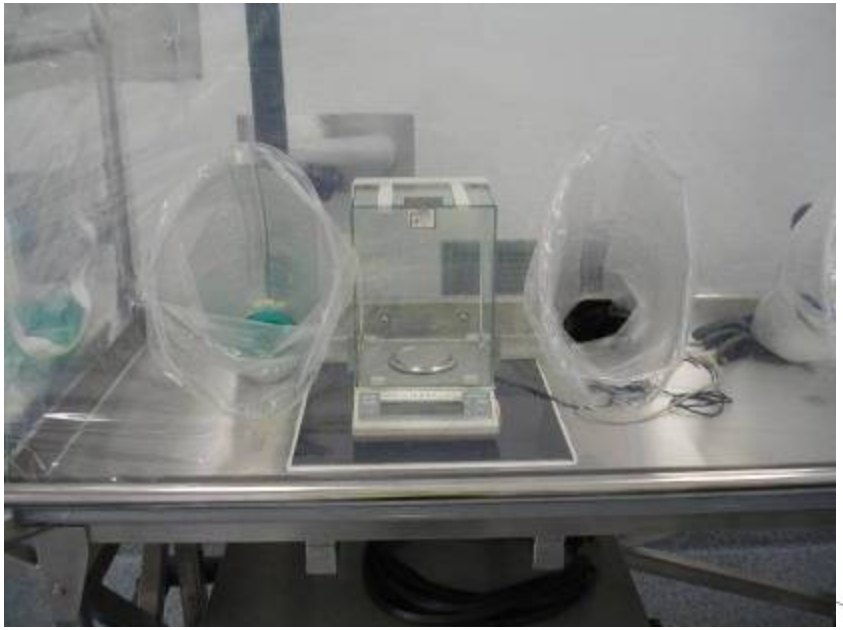
Weigh & Dispense – Scale Capability

Versatile Designs to use

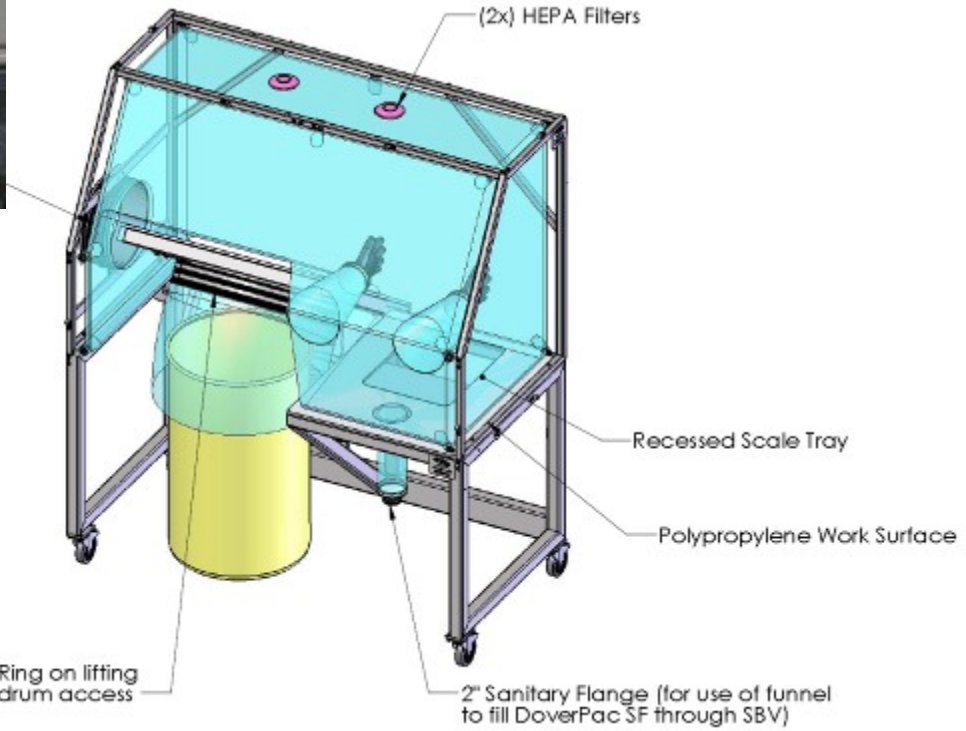
- Standard Balances- Internal or External
- Load Cell Systems
- Floor Scales

- Accurate Weighing along with Tare removal of packaging for Net Weight accuracy

Weigh & Dispense – Scale Capability

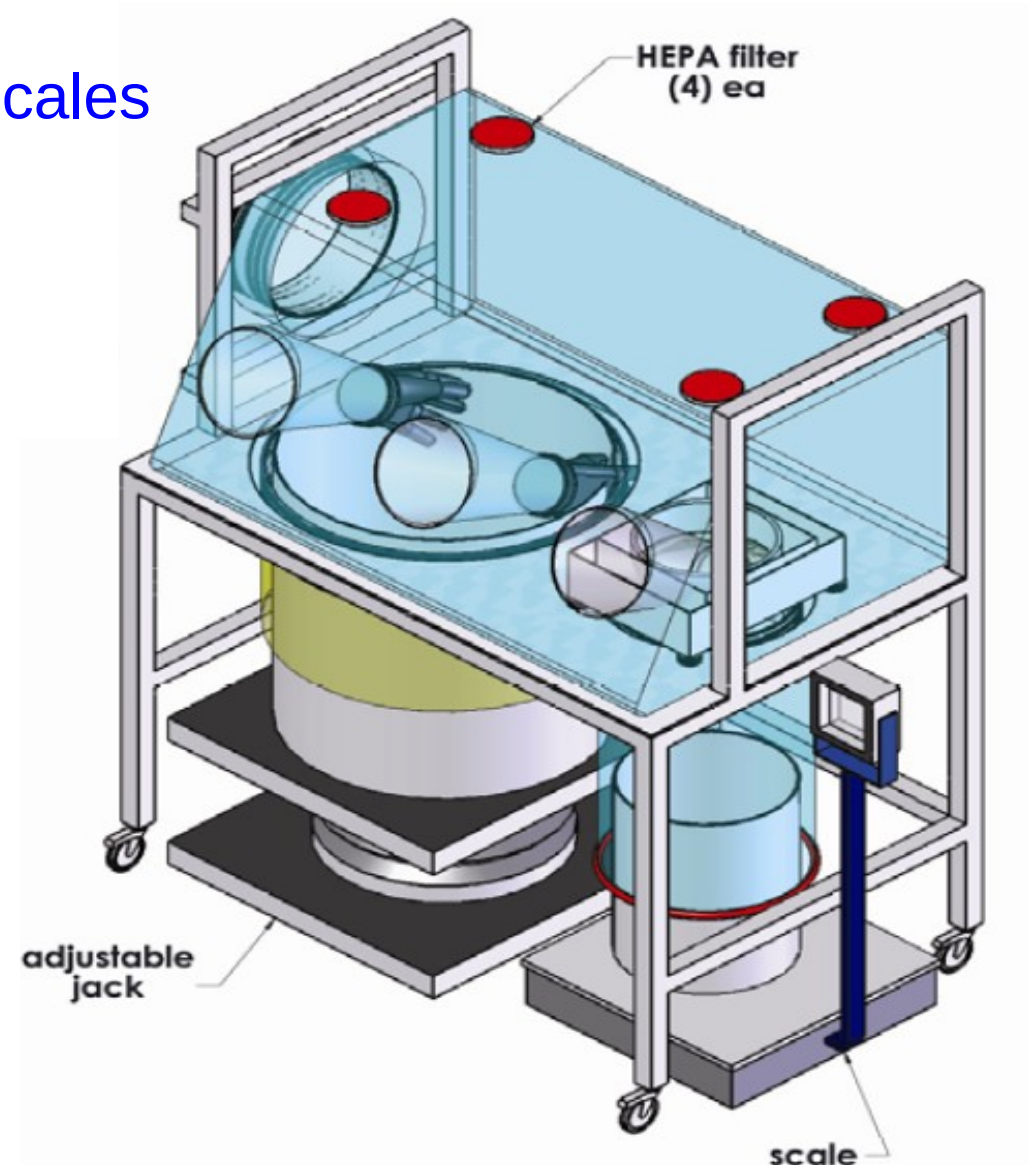


- Standard Balances- Internal or External

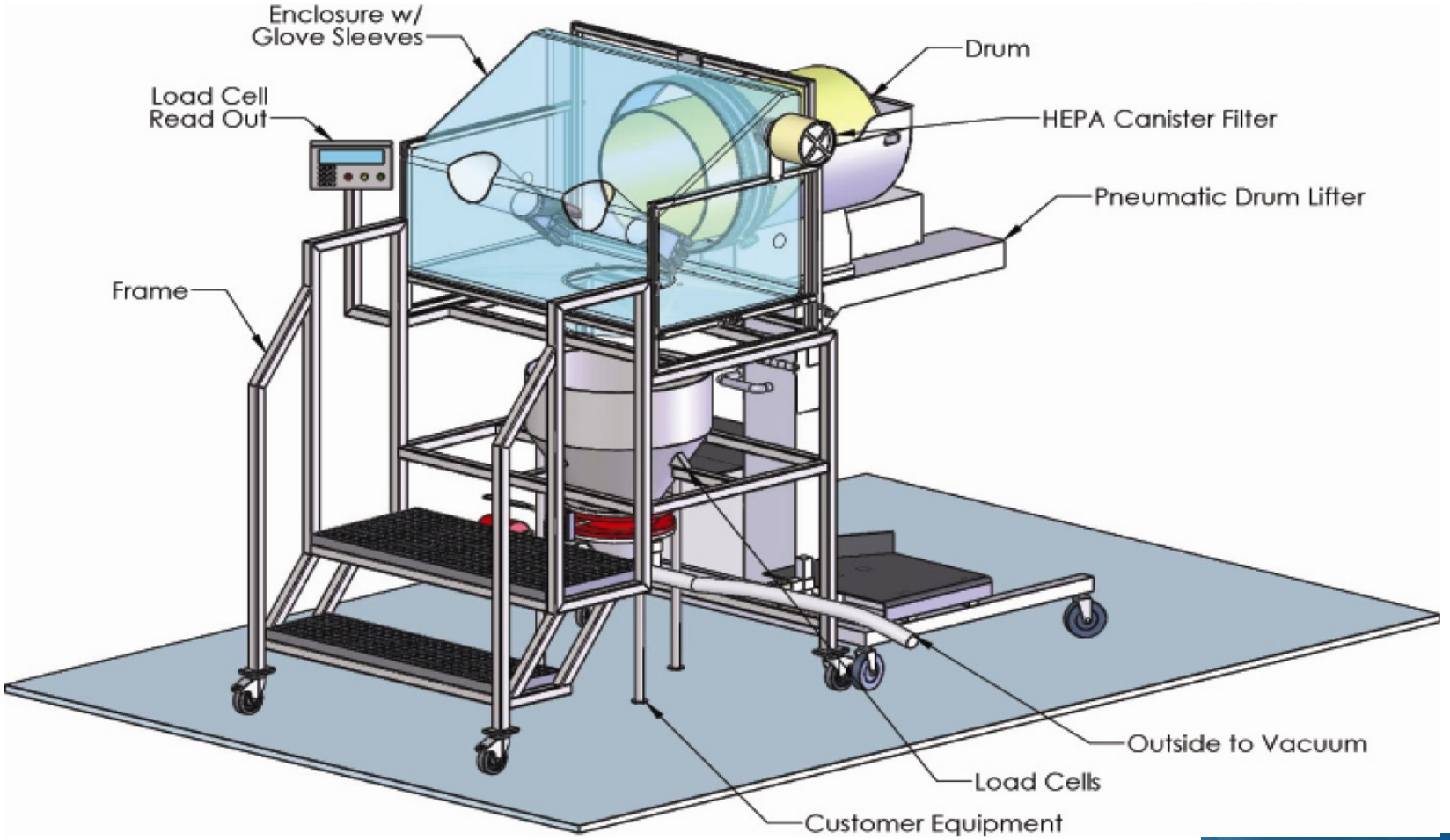


Weigh & Dispense – Scale Capability

- Floor Scales

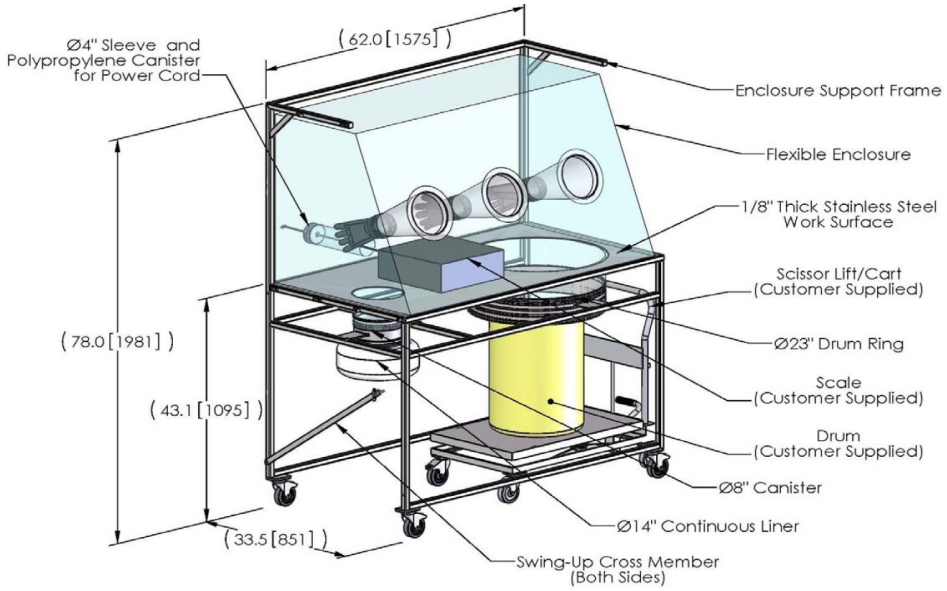


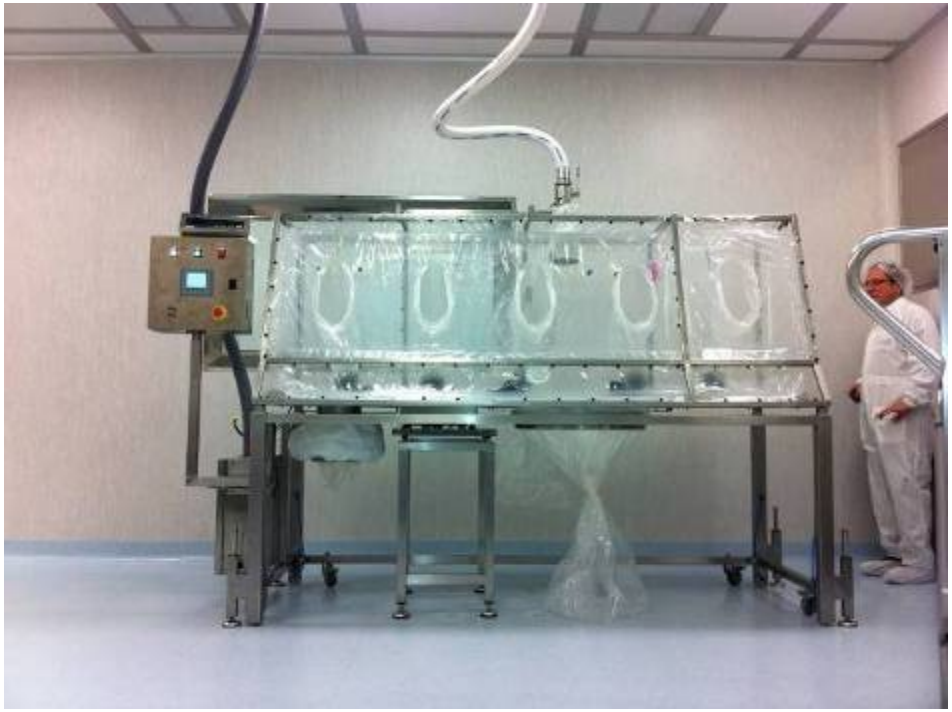
Weigh & Dispense – Scale Capability



Load Cell Systems

Negative Pressure vs. Static Pressure



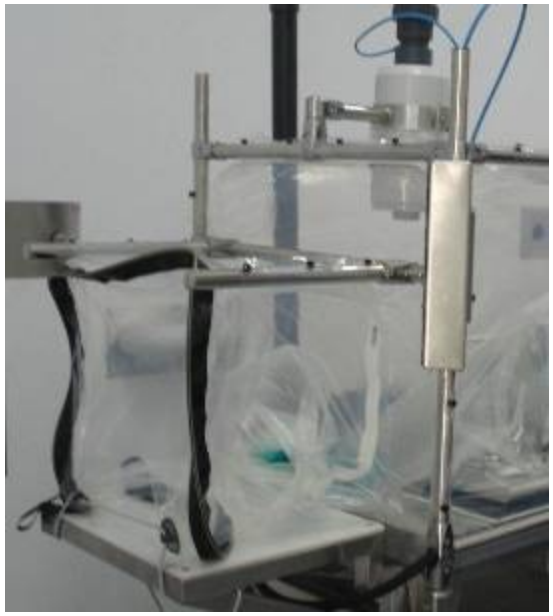


Negative Pressure vs. Static Pressure

- Both designs are closed systems that can maintain total containment
- The areas of concern are common for the designs and exist at the transfer points where product and materials go and out of the system
- Well designed transfer systems operated correctly minimize the potential for a breach

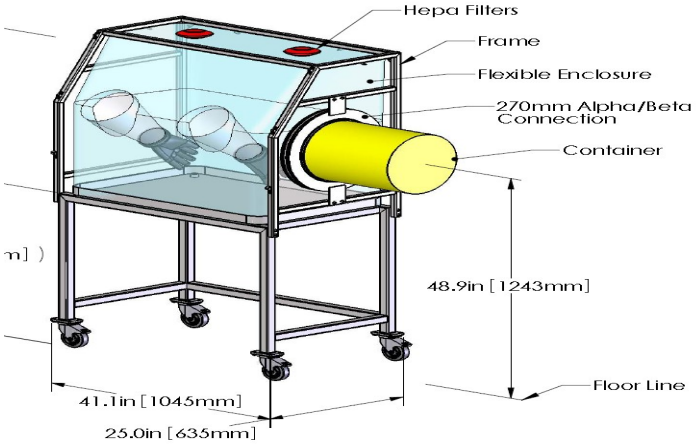
The benefit of a negative pressure is for secondary or protection in case of failure and data indicates that containment levels are not improved

Transfers to/from Flexible Isolators



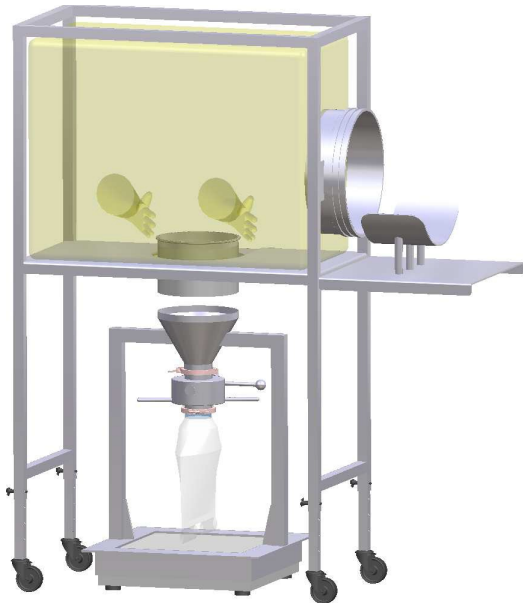
Transfer Hatch with Airtight Zips

Transfer BIBO with Transfer Sleeves and Crimping

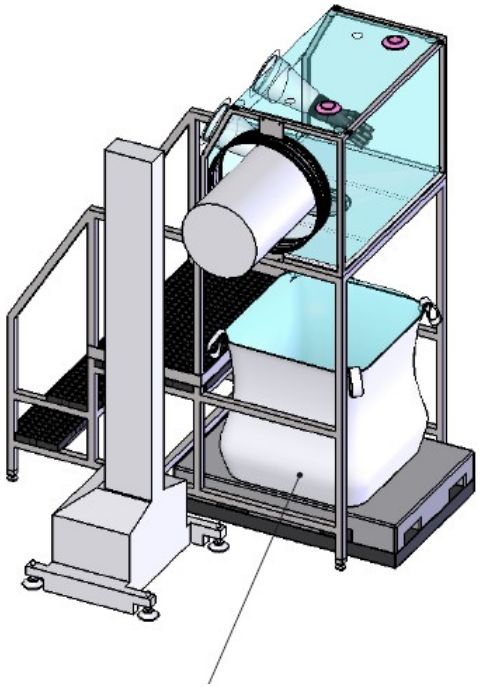


RTP Ports

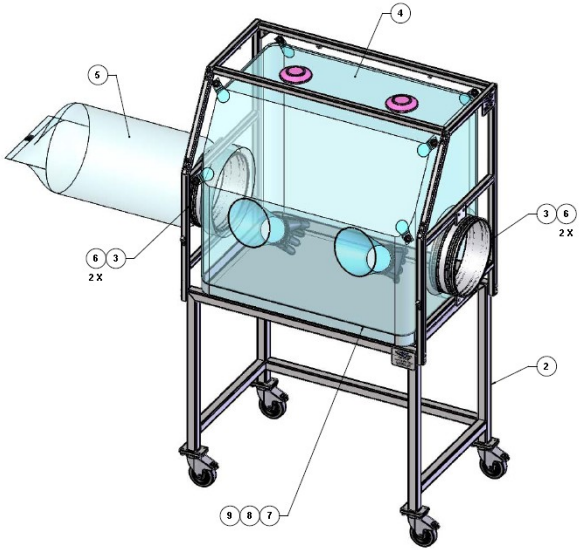
Transfers to/from Flexible Isolators



Transfer to SBV Valved Containers

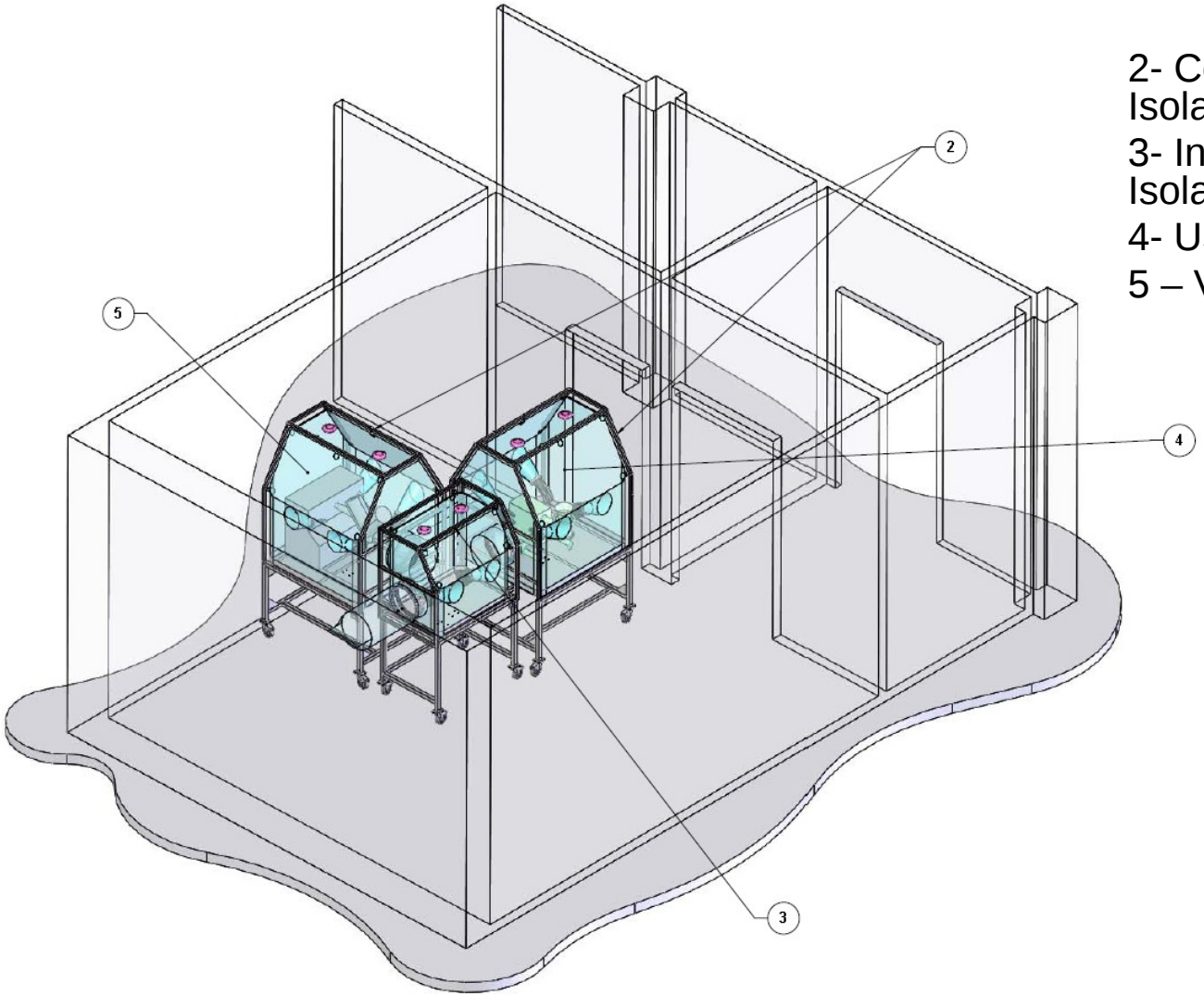


Transfer High Containment DoverPac FIBCs



In Process Isolator

Process Train between Flexible Isolators



2- Contained Universal Isolator System with

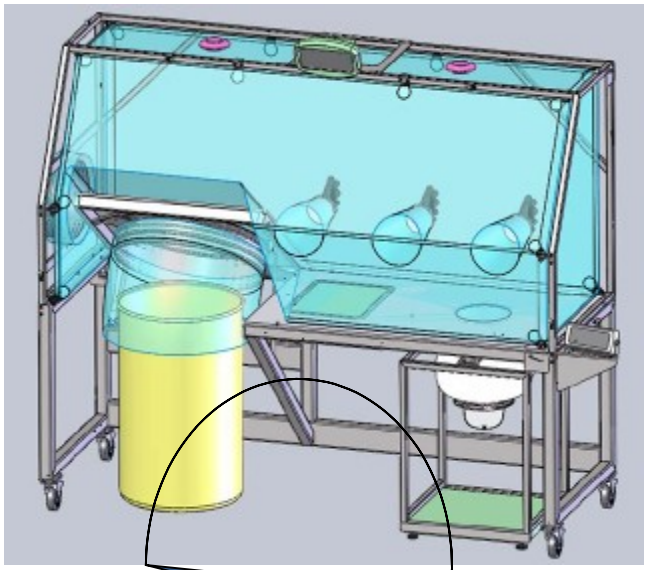
3- In Process Transfer Isolator

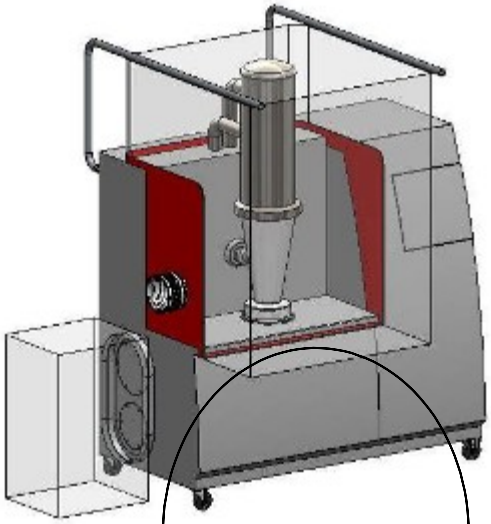
4- U5 Cone Mill Isolator

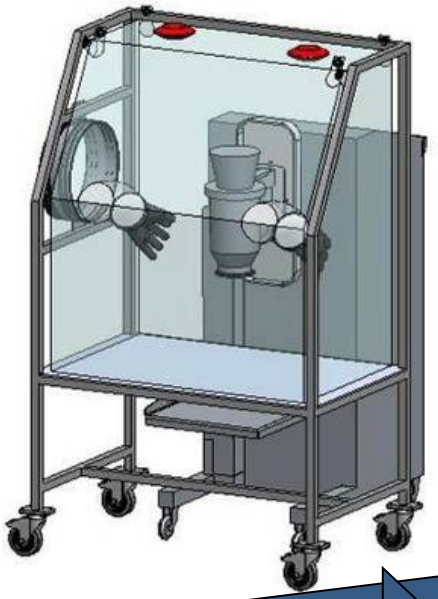
5 – V Blender Isolator

Process Train Containment

Containment is maintained during each process
and transfers between the processes







Weigh and Dispense

Fluid Bed Processor

Conical Mill

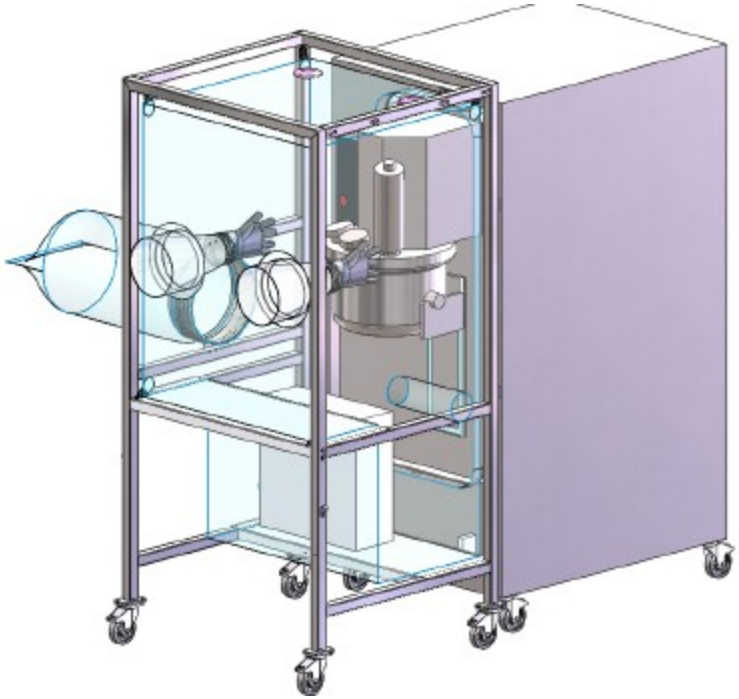
Flexible Isolator for Process Containmen

Fluid Bed Processor

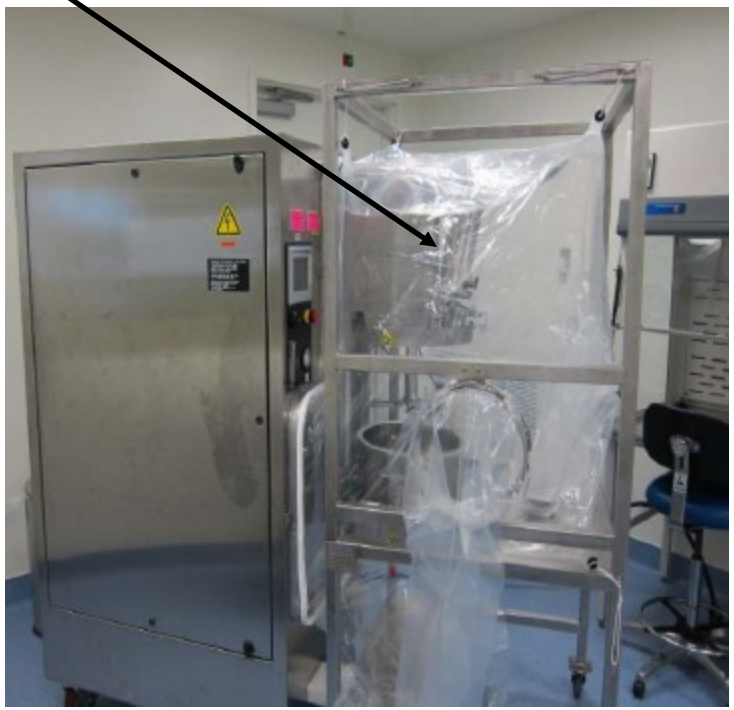
Tablet Press with In Process Isolator

Mill with negative pressure

Containment Data - Granulator



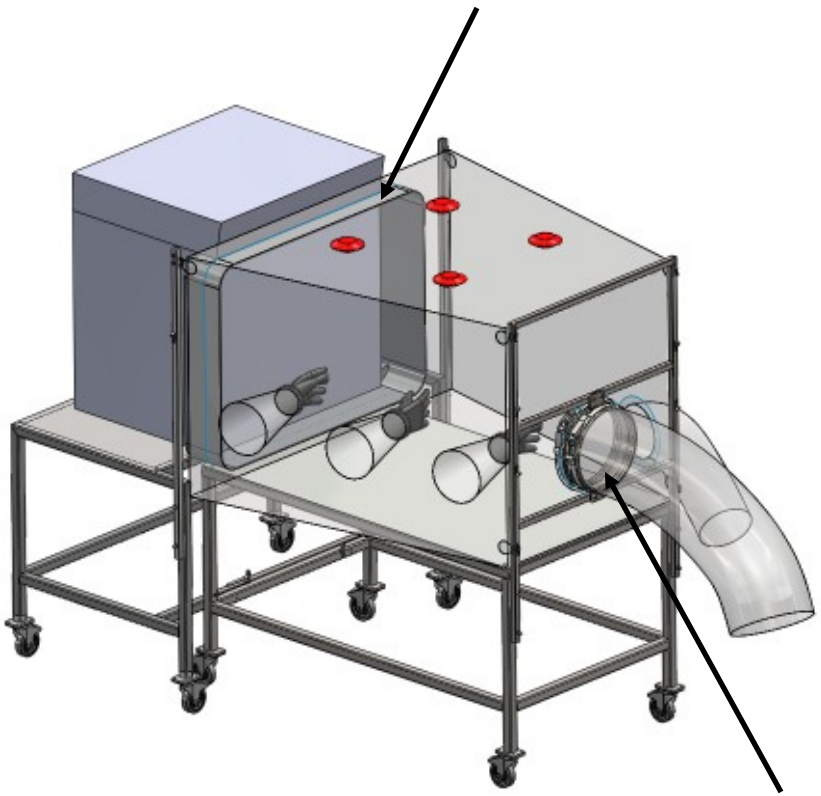
Flexible Isolator System



Data and examples for Granulator and Dryer from ISPE presentation courtesy of PharmaTek

Containment Data – Tray Dryer

Sealed Flange Connection



System in Use

Bag In / Bag Out System for transfers

Process Monitoring Data

Example of Results using SMEPAC protocol

ILC Dover Enclosure System	Test Material	OBZ	*OBZ-TWA ($\mu g/m^3$)	Comment (No. of operators)
Granulator	Lactose	0.1120-0.0108	0.0026-0.0027	Operation (2)
Granulator	Lactose	0.0247-0.3000	0.0027-0.0331	Cleaning (2)
Drying Oven	Lactose	0.0395-0.0416	0.0026-0.0028	Operation (2)
Drying Oven	Lactose	0.0142-0.0630	0.0026-0.0037	Cleaning (3)

Operator Sample – 8hour TWA exposure < 0.0026 µg/m³

DoverPac Containment Systems

Containment Data - CoMil

U5 CoMil in a negative pressure flexible isolator

Containment Data - CoMil

iii) Run 2 (10/03/2010)

Sample Details	Sampling Time (minutes)	Mean Flow Rate ($l.min^{-1}$)	Total Volume (m^3)	Mass of API Detected (µg)	Airborne Concentration of API ($\mu g.m^{-3}$)	8-hour TWA Exposure ($\mu g.m^{-3}$)
Personal sample *9948*	57	2.0	0.114	<0.015	<0.13	<0.015
Background (position 1) *9949*	57	2.0	0.114	<0.015	<0.13	-
Background (position 2) *9950*	57	2.0	0.114	<0.015	<0.13	-
Background (position 3) *9951*	57	2.0	0.114	<0.015	<0.13	-
Background (position 4) *9952*	57	2.0	0.114	<0.015	<0.13	-

Operator Sample – 8hour TWA exposure < 0.015 µg/m³

DoverPac Containment Systems

Economic Benefits of Flexible System over hard wall type

Flexible containment offers a significantly lower capital cost for installation and continues to have an operational cost benefit

- Lower capital investment
- Minimal cleaning or maintenance costs

Critical Manufacturing Quality for Flexibles

Final Inspection – Critical checks to assure the designed system will perform to the requirements

- Inflation dwell testing – Guarantees integrity
- Visual inspection *while inflated* to check contamination
- Controlled welding procedures. Lap seams best design
- Automatic cutting of film – No hand cutting

Product should have a Certificate of Conformance

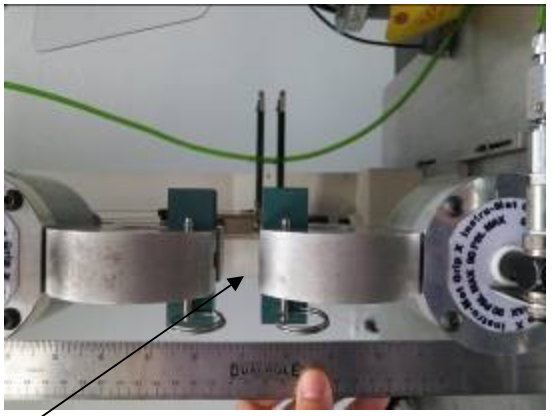
Physical Requirements of Flexible Materials

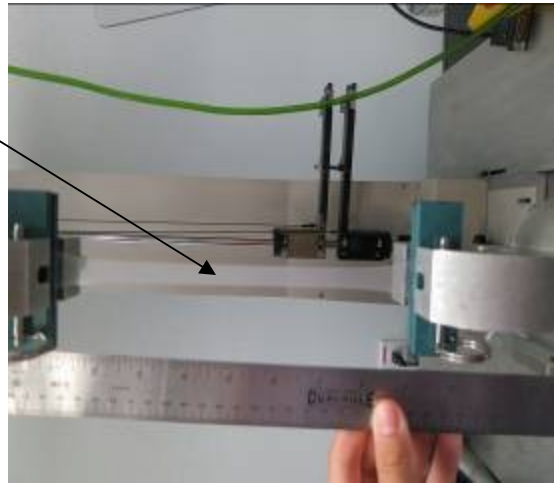
- **Solvent Resistant**
- **Static Dissipating to eliminate the risk of static build up and potential discharge**
- **The material should serve the process to attach easily and remove easily**
- **High strength to resist tears, puncture, and other damage**
- **Long Shelf Life for Storage**

Flexible materials are reliable

A flexible material designed with LLDPE will provide a reliable strong structure

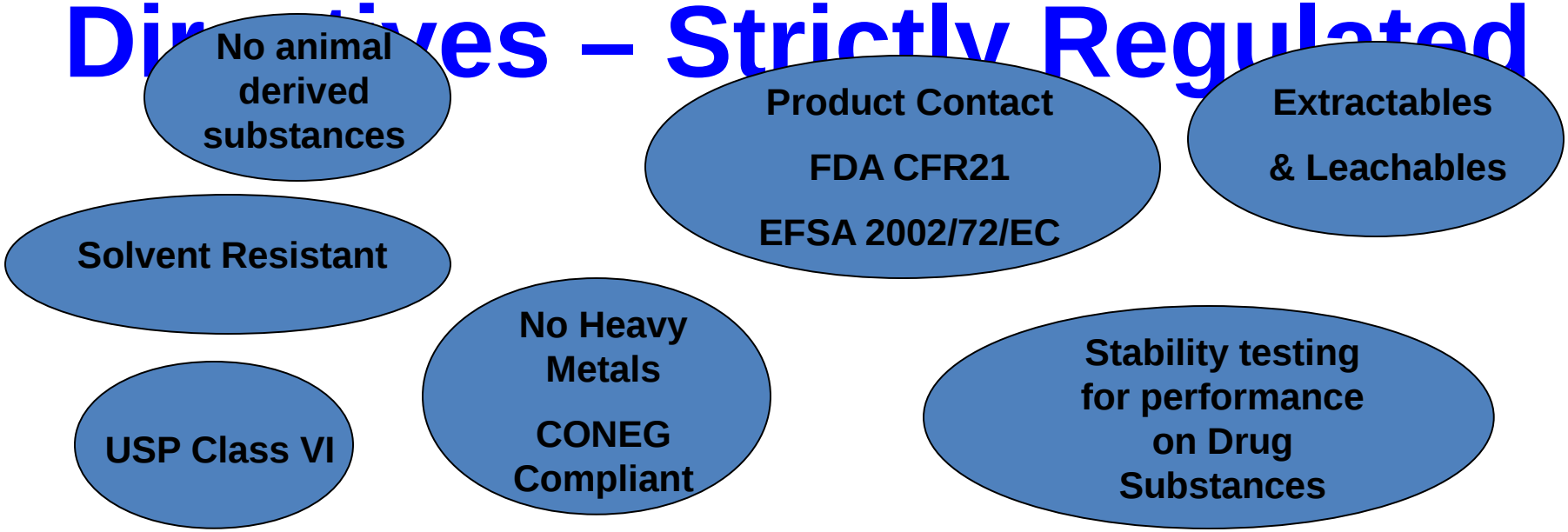
Film Tensile Test showing 500% elongation before failure





Regulatory Compliance of Flexible Materials

Global compliance standards follow FDA, USP, and EP Directives – Strictly Regulated



DoverPac Containment Systems

THANK YOU

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