ILC DOVER

WHITEPAPER

Modern Containment Solutions in OSD Processes

BEYOND BOUNDARIES®

Introduction

In this Whitepaper, ILC Dover focuses on modern containment solutions in small molecule Oral Solid Dosage (OSD) handling processes, walking you through the as-is paradigm of past containment philosophies and into to-be concepts when applying state-of-the-art flexible film single-use isolators.

Consider this analogy of Coca-Cola as the to-be concept.

In 1886, John Pemberton invented the syrup for Coca-Cola. Do you think he ever anticipated that 135 years later, a bottle of water would be more valuable than his syrup mixed in with the water? In most stores today, individual bottles of water are the same or higher priced than Coca-Cola!

The same concept can be applied to ILC Dover's containment philosophy when making water for injection for cleaning and the labor for cleaning, plus disposal costs.

Let's Dive In...

The Changing Containment Landscape

There's a changing landscape in the containment world for OSD processing. Here, we break down how past drivers for OSD containment have shifted to accommodate modern needs.

While previously there was master site planning for an extended period, we now have very short-range production planning, and we follow a lot of the CMO model for multiple-use products in a facility. We've seen this model use up to sixty molecules in a facility in one year.

Going back about ten years, the high bar for containment was 1 µg/m³ and determined on a time-weighted average (TWA). Today, this is no longer the case when looking at HPAPIs that often have ten times stricter tolerances at .1 micrograms per cubic meter and not a TWA.

Past Drivers for OSD Containment		The Current Situation
Master site planning for 10 years or longer	→	Shorter production planning / CMO model
Containment for < 1.0 µg/m3 (on a TWA)	→	Containment for HPAPI to <0.10 µg/m3 (not TWA)
Containment strategy focused on operator exposure	→	Containment strategy includes cross contamination
Central manufacturing in metric tons	→	Global manufacturing of smaller batch sizes

Original containment strategy was focused on operator exposure, and while we still focus on operator exposure today, we also concentrate on mitigating risk for cross contamination.

Finally, there used to be central manufacturing and tonnage, but now with global manufacturing sites, we see smaller batch sizes and more changeover, which require greater levels of efficacy, efficiency, and speed.

Containment Designs Need to Be Adaptable

The changing containment landscape is further demonstrated in an analysis of two exact isolators that were tested for the same performance. The image on the left shows a past hard wall isolator concept, and the image on the right shows the future flexible isolator concept.

Past Hard Wall Isolator Concept

Future Flexible Film Isolator Concept

The analysis showed that stainless-steel facilities compared to flexible film isolator facilities are capital intensive and require long build times of up to five years. Interestingly, facilities often do not make the intended design due to shifting business models within that five-year planning phase and ever-changing sales forecasts in the pharmaceutical industry.

The Modern Mock-Up Experience: Nimble & Iterative

Traditional isolator designs risked significant costs and delays, requiring an unchanging mock-up of the isolator. Layout and dimensions needed to be precise, SOPs needed to be worked out and documented in advance for all functions, and the sizes and weight of the materials and tools needed to be laid out perfectly. This not only created ergonomic challenges, complaints, and injuries for operators of varying heights, but any process changes would render the original workflow dysfunctional with incorrect glove positions and transfer technology.

The modern design process is nimble and iterative.

In this example design process for a portable and configurable tablet press, we start with a basic tablet press and then create the containment zone. After that, we position the operator gloves to do the work and then add a transfer isolator for analytical evaluation. You can see the final result of this iterative process in the image on the right, supplemented by an adapted retrofit-type process with minimal changes to the SOPs for operators.

Typical Iterative Design Process for a Flexible Film Isolator System

This design easily allows for post-installation changes to the isolator and hardware, such as adding or moving glove locations and sample sleeves, without incurring a high cost or delay.

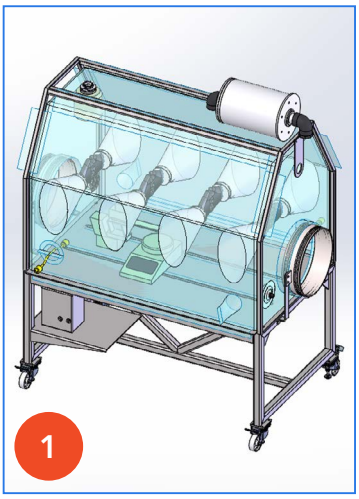
More on Modern Flexible Containment Designs

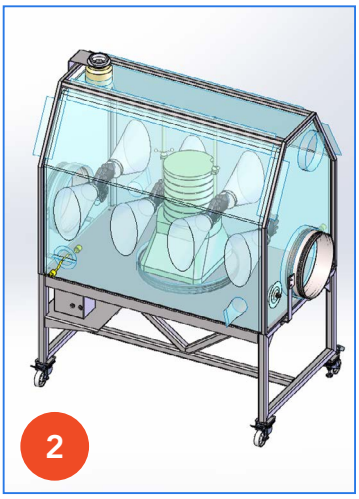
The images shown on this page include one frame and two isolators. The exact same frame is used for two different processes by simply changing the flexible film isolator. The frame design is developed for multiple uses, and the transfer systems allow processes to be unidirectional, enhancing containment. Products can pass in from one side and out the other.

These isolators can be connected to achieve a Daisy Chain configuration, providing the ability to work in a single-unit flexible film isolator or combine single units for a continuous workflow. Connecting two or more isolators eliminates risk and labor time to transfer material from one unit to the next, leading to greater containment and process efficiency.

Isolator #1
Features eight gloves for a weigh and dispense application.

Isolator #2
Designed with seven gloves and a Rotap system inside for containment during the Rotap process.





The ability to have one frame with two completely different designs is entirely possible with flexible film isolator technology. Modern containment design, including collapsible frames and Gerteis compactor designs, allows operators to deploy the system only when needed, saving valuable space in the processing suite.

OSD Case Study:
Containment Strategy for Multi-Step Processes

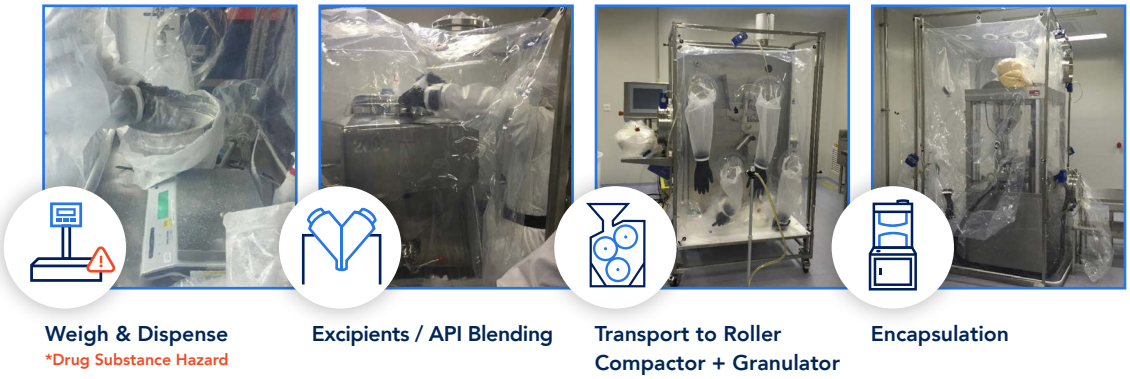
Situation

A CDMO Formulation Lab, with complete capabilities for multiple forms of OSD manufacturing, lacked the ability to handle HPAPIs. With the opportunity to increase sales and revenue by expanding into HPAPI formulation, the Lab wanted to quickly implement containment systems across its workflow in less than twenty weeks. The Lab needed to prove containment performance of the isolation systems to a client, assuring no cross-contamination risks.

Strategy

The Lab applied a retrofit design strategy to its existing equipment and leveraged flexible film isolator technology to quickly deploy the solutions. The Lab performed robust surrogate testing using the ISPE SMEPAC protocol to measure: 125.0 nanogram/m3 target with statistical confidence factored into the results; Naproxen Sodium surrogate; drug substance with no excipient; and drug product testing with an excipient.

The containment strategy would be used during four steps of the OSD dry granulation workflow.



Weigh & Dispense
*Drug Substance Hazard

Excipients / API Blending

Transport to Roller Compactor + Granulator

Encapsulation

With multiple steps, it was critical that the containment strategy focused on containing at the source to minimize cleaning requirements in the suite, and containing Bag In / Bag Out transfers with secure crimping for high containment assurance.

CONTINUED

OSD Case Study:
Containment Strategy for Multi-Step Processes

Results

Containment Performance <125 ng/m3 was Achieved	One system failed and traced to an open connection; Retested and PASS.	The PASS / FAIL was based on EN689 **PASS <31 ng/m3**
Containment Design Completed Without Mock-Ups	Flexible isolators design updates from operator input. Did not delay production.	One stainless frame required modification. Completed in 48 hours – no impact
Average Isolator System Cost Less Than $65,000	Minimal equipment modifications. Typical flange addition using silicone adhesive.	Cost avoidance over alternative solutions was greater than **$1.4 M USD**

Benefits of Flexible Single-Use Containment Systems

- Streamlined production efficiency and greater capacity
- Eliminated large CapEx and OpEx compared to stainless-steel solutions
- Protected operators from exposure to HPAPIs and facility from contamination
- Created opportunities for business growth in the HPAPI market segment
- Offered superior sustainability benefits by reducing waste when cleaning
- Allowed modifications and improvements to be made based on operator feedback
- Expedited the delivery and installation experience by having the project execution be supported by complete engineering drawings and documentation

Conclusion: **Hard-Wall Vs. Flexible Wall System**

When weighing your options between a hard-wall system and a flexible-wall system, consider the pros and cons demonstrated in this Whitepaper.

Execution Excellence

While both isolators provide the same performance, hard-wall isolator delivery can have major delays that impact the engineering batch schedule for a new product launch. In contrast, a flexible wall system can be designed, manufactured, and delivered in eight weeks, keeping the product launch on schedule with associated market capture.

Eliminate Large CapEx and OpEx

	Flexible System	Hard Wall System
Acquisition Cost	$55,000	$725,000
Delivery Time	8 weeks	26 weeks
OEL Achieved	< 1.0 µg/m3 TWA	< 1.0 µg/m3 TWA ‹ Same Performance
Consumables	Flex Isolator = $1800 per batch and BIBO sleeves est. at $250 per batch. Total = $2050 per batch	Filters and cleaning materials
Air Flow / Utilities	Static / No Utilities	Negative air, WFI, Electric
Cleaning	The Isolator surface to be cleaned is the flat work surface est 2,200 in2	The Isolator has greater than 18,000 in2 of surface to be cleaned ‹ 800% less surface area
Acquisition Cost Δ	$670,000	

Summary

The $670k CapEx savings will have OpEx savings added with the reduced cleaning. The reduced cleaning will make the equipment ready for production much quicker resulting in the potential of more campaigns.

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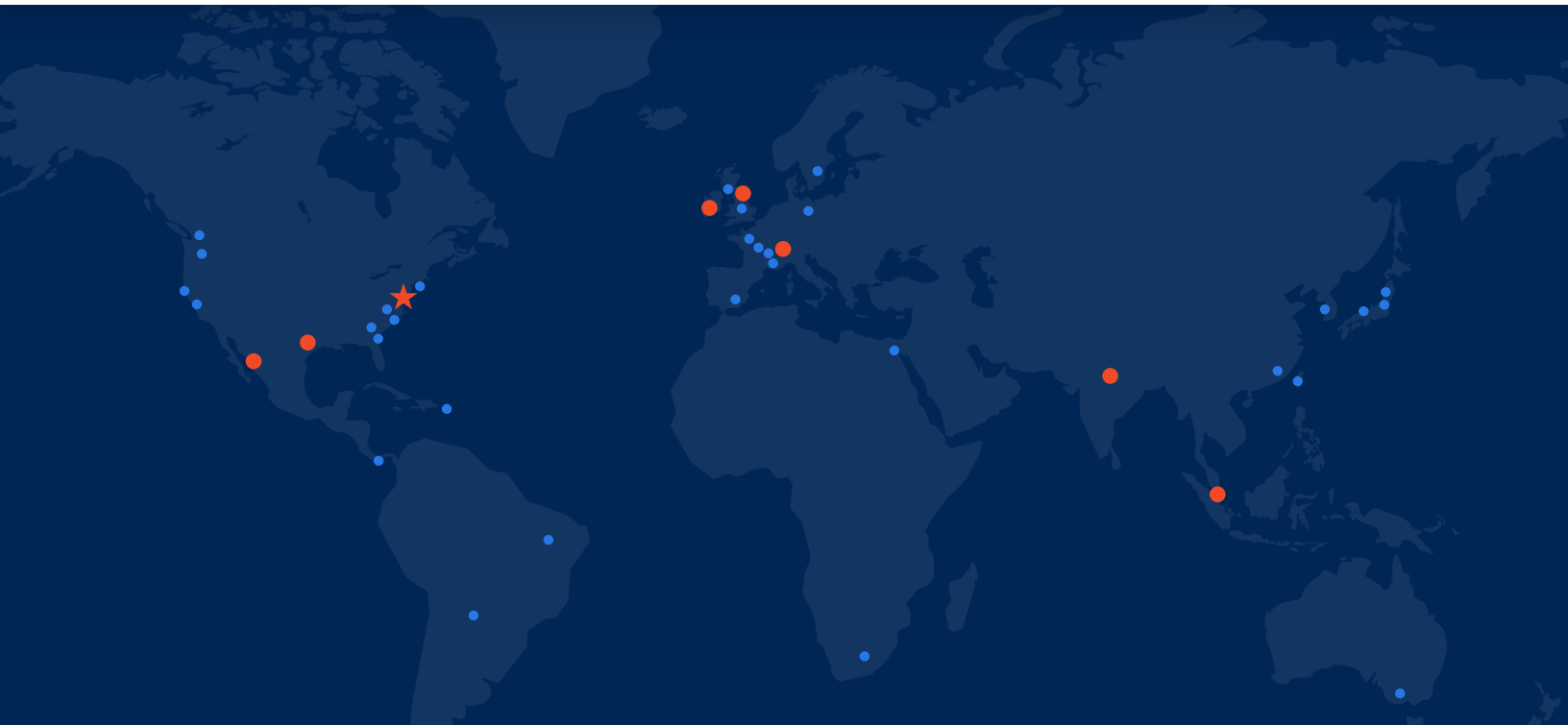
ILC Dover is a world-leader in the innovative design and production of engineered flexible protective solutions for pharmaceutical and biopharmaceutical, flood protection, personal protection, bulk packaging, and aerospace industries. Our customers will attest to our relentless dedication to high value products, advanced technology, and responsive service, as our visionary flexible protective solutions have improved efficiency while safeguarding people, product, and infrastructure in hazardous conditions since 1947.



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