



WHITEPAPER

Retrofit Pharmaceutical Equipment for High Containment and Reduced Risk of Cross Contamination

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Introduction

With the growth of highly potent active pharmaceutical ingredients (HPAPIs) and multiple-use facilities that must protect against product cross contamination, the need for engineering controls to achieve high containment has become more critical. Technology has evolved over the past 20 years to meet reduced exposure levels while also making high-containment systems financially reasonable. Not so long ago there was a mindset in pharmaceutical processing that containment systems came at a significant capital cost, and handling HPAPIs resulted in an even higher CapEx for the proper controls. This does not need to be the case with the implementation of single-use or flexible containment technology.

Let's Dive In...

The start of a disruptive technology... for the better

Eli Lilly began to understand the future of potent pharmaceuticals as early as 1996 and that state-of-the-art containment systems based on durable stainless-steel construction would lead to significant capital expenses for new equipment to achieve the Occupational Exposure Limits (OELs) that were being set for new potent compounds. The Containment Committee at Eli Lilly had the foresight to understand more than just the high capital expenses they would incur; they would face increased operating expenses for cleaning and maintaining stainless-steel containment devices as well. Even with using the stainless-steel systems, like bulk containers with split butterfly valves or steel and glass isolators, achieving an OEL of less than 1.0 microgram/m³ airborne concentration of the drug particulate was not always possible. This exposure limit was the gold standard at the time to protect operators when handling HPAPIs. The Containment Committee pursued the idea of developing single-use technology to charge and discharge powders from the processes. Fast forward to current time and the single-use, high-containment systems have become the standard and often preferred technology in pharmaceutical processing both for drug substance and drug product workflows.

So how does single-use containment technology impact capital spending and operating expenses in these workflows? First let's deal with the thinking that containment is a cost and high containment for potent compounds comes at a higher cost. The view presented at the HPAPI Summit by David Eherts, PhD CIH uses the ROHSEI¹ method, which believes that containment systems can deliver Return-on-Invest to companies while mitigating many risks. The ROHSEI analysis takes into consideration a range of cost savings that can be won including reduced lost product, reduced use of PPE, and labor savings, as well as intangibles such as reduced worker injuries, including ergonomic issues. The innovation of flexible-film isolators has the potential to create better ergonomics for the tasks operators perform inside the isolator. Anyone who has worked with stainless and glass isolators has experienced some of the challenges in performing tasks leading to possible injury.

Flexible-film isolators have significantly reduced the ergonomic stresses that can occur. The ROHSEI method is a tool to evaluate financial returns and it was created well before the emphasis to eliminate cross contamination, which is now of equal importance with regulatory requirements driven by Health Based Exposure Limits.

Examining CapEx and OpEx using a common example

Let's explore some examples of the CapEx and OpEx savings that can be won by implementing single-use, high-containment systems as a retrofit into an existing facility. A good example is to use a "hard to contain" step in the pharmaceutical workflow of a Vacuum Tray Dryer (VTD). We label the VTD as "hard to contain" not only for the equipment but for the functions required to load and unload it. A brief description of the functions is wet powders are manually loaded onto large trays and placed on racks inside the VTD. The door of the VTD is like a refrigerator door that swings open and closes once the trays are loaded. As with all pharmaceutical processes, the size of the VTD is based on the use in development or formulations activity or full-scale production. The full-scale production units always create the most challenges for containment. Two examples are shown below in Figure 1 to illustrate the VTD process and the challenge with the equipment size.

Figure 1



Pilot Plant, Vacuum Tray Dryer

*Production Scale, Vacuum Tray Dryer,
Isolator support frame not shown*

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For the Pilot Plant VTD, there is a possibility to use a hard-wall isolator but even this small-scale solution creates many retrofit problems. The Production Scale is nearly impossible to contain with any other control than a flexible-film isolator. Case in point is simply just opening the VTD door. A hard-wall isolator design will be limited to roughly an 800mm reach making the door a challenge. The flexible isolator is often designed with a “moving wall” that collapses and opens as needed while maintaining containment integrity, even on a VTD door that is 2.0 meters high and wide. Another aspect to consider is the best practices design referred to as “contain at the source.” This “contain at the source” practice may consider the need for atmospheric control of the isolator to maintain a negative pressure for containment and breach control. It might also include the need for a low oxygen environment or that the isolator operates with a low particulate count similar to a cleanroom meeting Grade C or Grade B levels. The flexible isolator utilizes local safe change HEPA filters whereas many hard-wall systems require connection to the facility’s dust collection system. Particularly when retrofitting a process, this portable stand-alone design is much more effective.

The primary goal for retrofitting all process equipment should be minimal modifications to the equipment and maintaining operator procedures. Avoiding revalidation work is key and minimizing changes to SOPs is also important. This is the start to the benefits of using single-use containment systems for lower costs and shorter times for the equipment to be ready to handle HPAPIs. The retrofit of a VTD has two main components. The first is a flange that is mounted around the door of the VTD and can be installed without welding or drilling on the equipment. The second component is the portable support frame for the single-use flexible-film isolator. The flange will create the contained seal of the flexible-film isolator around the VTD using a manually applied trim to lock the flexible-film to the flange. Note, the flange does not change the use of the VTD in any way and if a compound is to be processed that does not require high containment, the flange will not disrupt the process.

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The portable frame is the structure to facilitate all the VTD functions. It will support the flexible-film isolator as well as the devices that allow for the product to enter the containment zone and to be discharged from the containment zone. This is a unique part of the containment design that has little limitations. Because the frame is portable and basically a skeleton, it can also be a robust design for multiple functions, including the ability to allow stability for weighing accurately inside the flexible isolator. But the design can also be a collapsible type in case the room footprint or the door dimensions will not allow for a rigid structure. Often, an existing facility that is upgrading to handle potent compounds could have limitations in the width of the hallway or turning corners. These restrictions make it difficult for a rigid isolator to be moved while the flexible isolator frame is adaptable. When the frame is in position, the flexible-film isolator system is easily mounted to the VTD and ready for use in approximately 1.0 hour or less.

Workflow Assessments that are critical to success

Whenever evaluating a containment system for a process, we must consider the workflow that occurs before and after that process. In the case of the VTD, often the process before was a centrifuge in a chemical synthesis workflow or perhaps a wet granulation step in an oral solid dosage workflow. An example of the process after the VTD can be a milling process, whether it be a conical mill or a hammermill. It is important to plan for containment at these unit operations as well since the hazard of the compound is the same. There are other factors to be considered including the batch size or sampling that is required. Containing these unit operations in the workflow will lead to achieving the highest level of containment and improved ergonomics. This was outlined in a case study shown below in Figure 2 and 3 by a CMO.²

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Workflow example case study

This was a manufacturer of clinical supplies that often-handled compounds in Clinical I or Clinical II phases before any toxicology was done on the compound. They defaulted to retrofit the granulator and the tray dryer with flexible-film isolator systems. In the case study, the solutions are demonstrated along with data from a containment assessment that was performed to the ISPE SMEPAC protocol. In this case study, the steps in the workflow were contained as well as the transfers between steps. This minimizes operator and cross-contamination risks.



Figure 2: Wet Granulation



Figure 3: Tray Dryer

The report summarized the containment performance well for the process steps and cleaning. As seen in Figure 4, the CMO implemented multiple controls starting with the flexible-film isolators and then PPE. In some cases, with the containment assessment reporting less than $0.300 \mu\text{g}/\text{m}^3$, the PPE could be reduced. But since the compounds processed are typically in early clinical stages and lacking toxicology data, the Sentinel Clear XT™ Powered Air Purifying Respirator (PAPR) has been adopted which offers a 1,000 APF for additional operator protection.

| Process | Function | Operator Breathing Exposure |
|------------|---|--------------------------------------|
| Granulator | Processing, Discharging, and Transfer Using Bag Out | $0.112 \mu\text{g}/\text{m}^3$ (max) |
| Granulator | Cleaning and Removal | $0.300 \mu\text{g}/\text{m}^3$ (max) |
| Tray Dryer | Transfer Using Bag In, Processing, and Transfer Bag Out | $0.042 \mu\text{g}/\text{m}^3$ (max) |
| Tray Dryer | Cleaning and Removal | $0.063 \mu\text{g}/\text{m}^3$ (max) |

Figure 4: Preventing Cross-Contamination Within a Multi-Product Facility:
A Case Study Of Granulation, Pharmatek

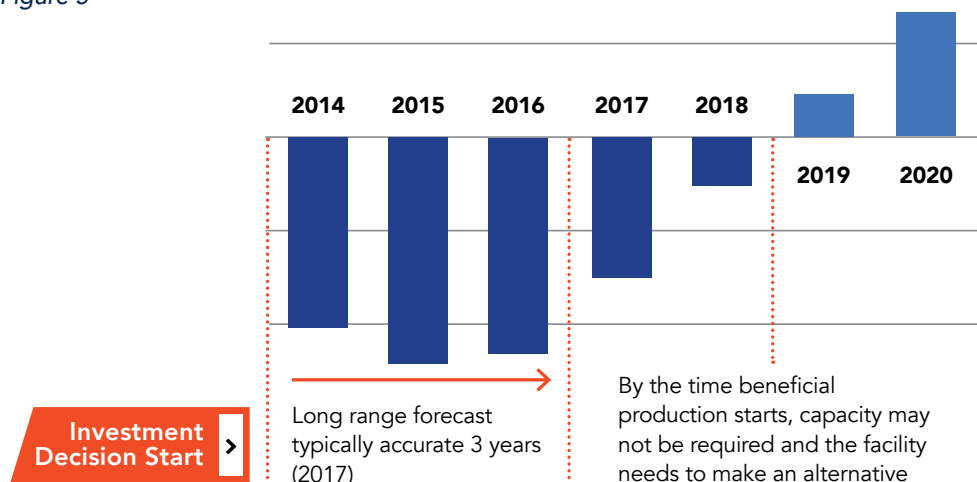
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This case study captured an interesting action that can be seen in Figure 3 above of the Tray Dryer. See how the operator is comfortably working with the flexible isolator at almost a 90-degree angle. This is just not possible in a hard-wall isolator system. As previously mentioned, ergonomic benefits allow operators to perform the tasks while mitigating the risk of personal injury.

There are always challenges to make sure that the containment design meets the full range of performance requirements knowing that design changes and rework can be costly and delay production. Flexible containment systems have really changed this dynamic. There have been a lot of lessons learned from the manufacture of biopharmaceuticals and the adoption of single-use technologies (SUT). Figure 5 below is from a report commissioned by ILC Dover³ that describes the capital-intensive costs for new facilities and outlines the risks when following the past paradigm of using stainless-steel process equipment.

Cash Flow Forecast for New Large Scale SS Facility

Figure 5



- Capital intensive
- Long build times - in excess of 5 years
- Facilities generally don't make what they designed to do
- Product forecasts are inaccurate beyond 3 years

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There are many similar examples in API manufacturing that recognize the same cost profile of high CapEx when building a new facility or expanding a facility and requiring stainless-steel systems. The example in Figure 6 combines the CapEx profile of the stainless-steel isolator to the same flexible-film isolator. The starting point at Year 1 demonstrates the delta in CapEx between the solutions, which is dramatic. This application was for a Drum Dispensing Isolator to dispense and weigh powders meeting a containment level of $< 1.0 \mu\text{g}/\text{m}^3$.

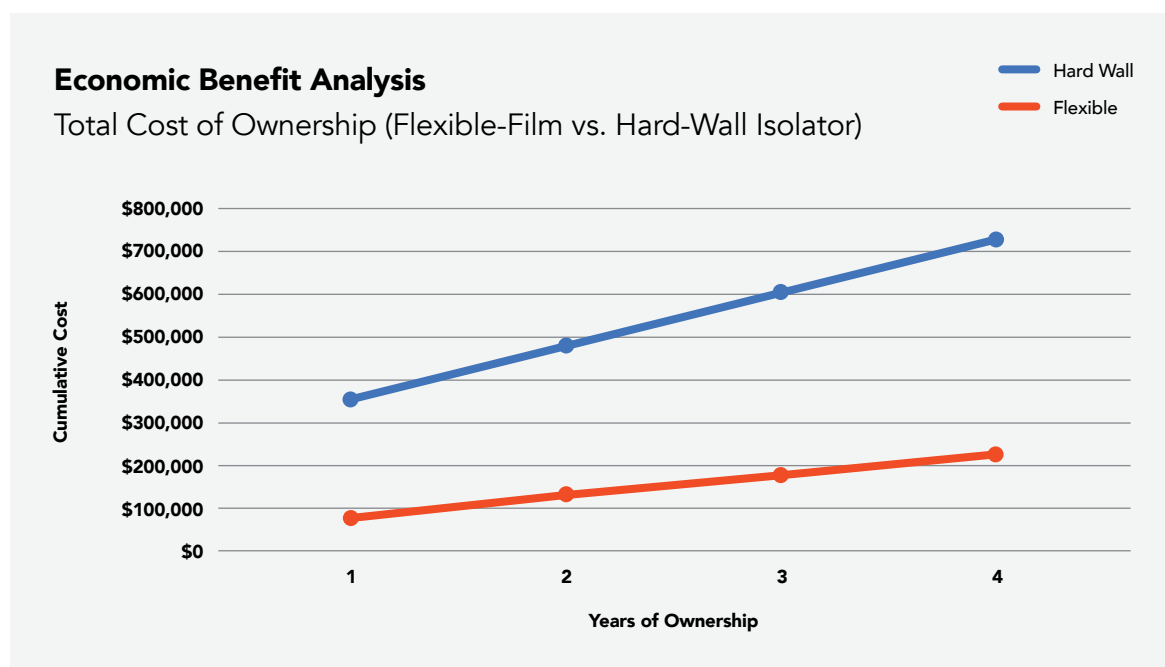


Figure 6

The example was expanded to consider the Total Cost of Ownership (TCO). The main cost driver for the durable solution is the cleaning required. There are other costs for consumables such as filters as well as maintenance on seals and gaskets. Ultimately, it is the cost of cleaning materials and labor for cleaning that drives the difference shown in the slope of the cost lines through Year 4. The perception that a flexible-film isolator will save CapEx but then OpEx costs will offset the savings is not correct.

Evaluating the impact on production efficiency

One consideration that was not made in the TCO analysis was hold times. A hard-wall isolator will be unavailable for production while cleaning is done, and validation is being processed. The hold time is extended if the cleaning validation reports that the cleaning limits were not met, requiring the process to start over and keeping the isolator on hold. Overtime achieving the validated cleaning limits can be more challenging with stainless-steel equipment due to deterioration of the surface finish. The smooth polish that is required when the equipment is new will change with surface scratches and marks from general use. Solid particles can be retained in the rougher surface causing more aggressive cleaning which will perpetuate the problem. The flexible-film isolator is disposed of after use leaving minimal surfaces for cleaning and potentially ready for production in hours. The value of gaining additional production time by minimizing downtime for cleaning can be in the millions of dollars over a year. This can be the single most important reason to choose single-use technology for high containment.

The original published *Retrofitting Process Equipment*⁴ paper in 2009 established the perceived benefits that were reported by many pharmaceutical processors who were early adopters to flexible-film, single-use containment systems. Since that time there have been hundreds of process trains or workflows that have deployed flexible containment succeeding in high containment, reduction in safety risks, and reduced Total Cost of Ownership. This proven technology has a strong legacy of performance that continues to adapt to meet the stricter containment requirements for highly potent compounds that require OELs well under 50.0 nanograms/m³. The retrofit capability has minimized the reliance on PPE for operator protection even on hard-to-contain processes as described with the Vacuum Tray Dryer. There is also a “lessons learned” detail from the early adopters with the risks associated with flexible-film isolators. The perceived risks of a failure due to operator errors or some upset condition has been minimized with good design practice that makes the flexible isolators robust as well as intuitive for operators to assemble and maintain. Knowing the facts about flexible-film isolators can allow processes to achieve containment that protects the operators, the products, and the facilities.



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