



## High Containment and Cost Savings with Single-Use Isolator Technology

The current trend of increased potency of drug substances is driving the need for better cleaning methods to reduce cross contamination. The Level of Detection (LOD) methods are improving so that cleaning limits can be reduced to further mitigate risk of cross contamination due to retention on the process equipment and containment devices. Cleaning protocols are becoming more complicated to achieve the cleaning limit. In the case of isolator technology, the isolator surfaces add to the overall cleaning requirements while often making the cleaning ergonomically challenging. This is where a single use isolator will provide significant economic advantages, lower costs, and reduce the risks of cross- contamination over traditional hard wall isolators.

# CONTAINMENT PERFORMANCE MUST BE ACHIEVED

The pharmaceutical market has been adopting single use or disposable solutions for over 20 years and the rate of installations continues to grow. The key issue has been containment performance and meeting the exposure limits of the HPAPI market. ILC Dover has been collecting data from dozens of installations using multiple industrial hygiene groups to demonstrate the ability of single use containment. This technology was once thought to be only for short-term use while permanent containment solutions were put in place. Now single use technology is used by most pharmaceutical companies as the primary engineering control for containment. Data for single use isolators has shown containment of less than 50.0 nanograms/m<sup>3</sup> airborne concentration. Referencing one study of a wet granulation and tray drying process, the containment of each system and the transfer from the granulator to the dryer was less than 5.0 nanograms/m<sup>3</sup>. This level of containment testing is critical as the industry guidance and regulatory demands tighten. In 2018 the EN689 statistical methodology in the SMEPAC standard changed the sample size requirement. Previously, 3 samples taken during a containment assessment allowed an acceptable level at 25% of the CPT. The revised EN689:2018 changes the acceptable level to 10% of the CPT. This directly recognizes the risk of handling HPAPI's and that small samples cannot be in this risk-based analysis.

These studies compare favorably to down flow booth systems and negative pressure hard wall systems. As with all isolator systems, the transfer of products and tools in and out are the points with the most risk of exposure and selection of the transfer method is critical to a successful design. Below in Chart 1 is data from SMEPAC tests conducted on different processes:

Chart 1 - Data Summary for Flexible Containment Solutions

With containment performance proven, the real economic benefits of a single-use isolator can be realized. Using the example of weighing and dispensing a drug substance, the single-use isolator capital cost and operational costs are significantly less than hard wall type systems. See the example of a standard single-use isolator by ILC Dover in Picture 1. The capital cost of the single-use isolator will be one quarter the cost (or less) of the same hard-wall system.

Picture 1. Typical Single-Use Isolator for Weigh and Dispense



This example is for a static pressure isolator, but many companies have created containment policies or conducted a risk analysis that requires a negative pressure system when dealing with HPAPI to further reduce exposure risks. In this case, the ILC Dover isolator is adapted with the JetVent™ system from their Modular Process Control (MPC) line of equipment. The JetVent™ provides a steady negative pressure inside the single-use isolator while monitoring and adjusting for pressure fluctuations. The fan and filter system can react even in a breach condition to maintain a negative pressure and safety for operators. Once the pressure control system realizes an upset condition the fan automatically creates higher air flow and alerts the operator with an alarm.

# COST ADVANTAGE OF SINGLE-USE VS. CLEANING AND VALIDATION

So where is the economy and the cross-contamination reduction with the single-use isolator? It starts with an easy calculation of the isolator surface area. A typical dispensing isolator can be 60" wide x 30" deep x 40" high. The total surface area of the "box" is 10,800 square inches. That entire surface must be cleaned and meet the validation cleaning limit or risk cross-contamination. This simple surface calculation does not consider some of the most critical areas from cleaning which include the gloves. Employing a single-use isolator solution, the cleaning is nearly eliminated. The entire "box" will be disposed of instead of the rigorous cleaning and validation of a hard wall system. The gloves will have direct contact with the product and requires diligent cleaning and testing. The gloves of a single-use isolator are connected with a film gauntlet and plastic cuff. The assembly is part of the single-use concept and are disposed with the isolator. The entire design for single-use is to eliminate the cleaning and potential residual product that can adulterate a compound.

The "balloon" design (6-sided isolator) by ILC Dover as shown in Picture 1, eliminates 100% of the surface area except where transfer points might be located. In any case, this is a dramatic reduction in cleaning time and risk. The transfer points are sealed and separated using CrimpLoc™ technology and the gas inside the isolator is used with a stainless-steel working surface. A unique trim sealing surface locks the flexible isolator to the stainless-steel surface. For safe disposal of this style, a wet in place spray wand is integrated into the isolator. The isolator surfaces are wetted, and it is now safe for removal. A study in Japan of this system included Operator Breathing

Zone (OBZ) monitoring of the operators doing the removal and swab testing for residue on the floor. That resulted in meeting the containment performance target from set-up, operation, and disposal. It also dramatically reduced cleaning time.

The clean-up after processing of many pharmaceutical molecules is not as easy as a water rinse and wash. Solvents and detergents are used regularly for cleaning which creates more problems and costs. The first issue is the water stream of the cleaning materials that is created. Particularly during initial cleaning, the liquids will now have some level of the API requiring special treatment and disposal. Some solvents used take a toll on stainless steel surfaces ranging from chemical attack to surface roughness changes. The roughness of product contact parts is strictly controlled when making pharmaceutical grade stainless steel processing equipment. Soon after use and multiple cleanings the surfaces will become rough and more difficult to clean. Particles can remain in the roughness, particularly scratches, requiring even more attention to cleaning while posing the risk of contamination again. The ILC Dover single-use isolator is made of ArmorFlex® film. This film was developed specifically for the pharmaceutical market using voice of the customer to include design attributes that would be key to successful use. ArmorFlex® is a special blend of polyethylene polymers to deliver a high strength film. ArmorFlex® 113 used for single-use isolators allows for more than 500% elongation before failure. The risk of any failure of the flexible wall is all but eliminated. Another attribute is solvent resistance. Knowing the ArmorFlex could be exposed to solvents the compound was chosen

over less resistant materials like polyurethane. ArmorFlex® was tested to the most critical ASTM standard for submersion in typical solvents used in pharmaceutical manufacturing to assure resistance and that physical properties would be maintained.

## **SUMMARY**

The need for better cleaning and reducing risk of cross contamination is covered in many directives and guidance documents. FDA GMP Guidelines, EU GMP Annex I, ICH Q9, and ISPE RiskMaPP all are used to provide guidance on risk-based controls for cross-contamination. It's clear that data driven studies understand that a surface is never perfectly clean no matter how much time is spent cleaning. A cleaning hierarchy can be developed to mimic the well-known containment hierarchy. In containment, elimination of the hazard is considered. Adapting the hierarchy for cleaning, eliminating cleaning or a significant reduction when it comes to the containment system will reduce the hazard. Single-Use isolator technology performs to the current containment targets of HPAPI drug substances and reduce costs and risks associated with cleaning.

## TURNKEY SYSTEMS TO SOLVE POWDER-HANDLING CHALLENGES

For powders that tend to clump or aggregate, we offer rotating comb systems for fluidization (Fig. 6) or our JetBreaker™ delumping system (Fig. 7). And for particles in suspension, we can provide homogenizers that can be calibrated to produce specific final particle sizes. In fact, we have demonstrated complete delumping and mixing of media and buffers, even at a charging rate of 1,250 kg per hour, when used in conjunction with our drum tipper and JetBreaker delumper. This allows for rapid, efficient mixing of large quantities of buffer to speed time-to-manufacture.

In addition, we can provide our novel EZ BioPac® single-use, closed system for powder handling. This is a proven system that reduces fill time and cross-contamination. The EZ BioPac bags facilitate rapid filling and final-weight adjustment of powders, and offer a separate discharge outlet combined with a unique antistatic polymer that allows for faster, cleaner discharge.

## TESTING TO PROVE PERFORMANCE AND PRODUCT PROTECTION

To prove operational efficacy and assess mixing efficiency, ILC Dover cooperated with a major biopharmaceuticals manufacturer to conduct a series of tests mixing three different powders with water. The powders were dextrose, HEPES and sodium chloride (NaCl).

For the glucose test, the temperature of the water was held at approximately 70° C, while the water temperature for the other two powders was approximately 25° C. Powder was added to the hopper manually for all three.

## TEST PROTOCOL

Testing followed a clearly established protocol agreed to by ILC Dover and the manufacturer, and was run on equipment provided by ILC Dover, in a facility operated by the manufacturer.

The primary purpose of the testing was to establish whether or not powder fed freely into the JetMixer system or if bridging occurred. For the glucose powder, testing was also used to establish whether or not clogging of the injector occurred due to vapor from the hot water reacting with the powder.

The test protocol specified procedures and parameters for charging the reactor vessel, monitoring and controlling process water temperature to ensure operation at target temperature, recirculation to stabilize temperature, complete injection of one drum of powder, and system cleaning (duration = 30–60 min.).

Individual trials for dextrose powder included operation with no vibration, with vibration, with bag dumped into the hopper and with bag poured into the hopper. Because of agglomeration of the feedstock, both the sodium chloride and HEPES were processed through an ILC Dover JetBreaker system before feeding to the JetMixer system. Some trials were conducted with vibration and some without, for both powder types.



FIGURE 6



FIGURE 7

## TEST RESULTS

1

For **dextrose**, the system successfully mixed 25 kg of powder into water at 65° C, in times ranging from 1 minute, 9 seconds to 2 minutes, 14 seconds, depending on method of loading hopper and whether or not vibration was used.

2

For **sodium chloride**, times to mix approximately 20 kg of powder ranged from 58 minutes at a water temperature of 33° C (no vibration) to 52 minutes at a water temperature of 28° C (with vibration).

3

Testing for the **HEPES powder** demonstrated that, even with significant delumping using the JetBreaker, time to mix 11.5 kg of powder into water at 21° C was just 35 minutes.

## CONCLUSIONS

According to an assessment by the manufacturer, the combined results for all trials for all three powder types showed:

1 Performance of the JetMixer system surpassed expectations of the manufacturer's team.

2 The manufacturer affirmed that, based on test results, the system would fulfill its needs, not just for the three powders tested, but also for other powders used in its production processes.



## BEYOND BOUNDARIES™

Innovators at our core, we develop engineered solutions for our customers' complex problems. Recognized globally for our flexible containment solutions, ILC Dover serves customers in a diverse range of industries, including pharmaceutical and biopharmaceutical manufacturing, personal care, food and beverage, chemical, aerospace, healthcare and government agencies. At ILC Dover, quality is a culture, not a measurement. Our customers will tell you that we cater to their every need and that we're highly innovative, responsive, dedicated and competitive. We have been innovating since 1947. ILC Dover's visionary solutions improve efficiency, safeguard workers and product, and prevent disasters — proof that we are on the front line of business excellence.

**Engineering evolution beyond boundaries.**



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