ILC DOVER

solocontainment
Now part of ILC Dover

WHITEPAPER

Highly Potent Active Pharmaceutical Ingredients Containment

A FULL LIFECYCLE SAFETY INNOVATION

BEYOND BOUNDARIES®

Executive Summary

As leaders in the field of powder containment, ILC Dover has vast experience in the delivery and testing of flexible film isolator technology for hazardous API containment applications. Now, with the acquisition of Solo Containment into the ILC Dover family, we can bring in extensive front-end application risk and hazard assessment skills with a methodology for SOP development. This provides an enhanced Full Lifecycle Safety structure that ensures our customers can enjoy the highest standards of operator protection from single-use flexible film containment systems.

A Brief History

As early as 1989, Solo Containment's Martyn Ryder was looking at environmental monitoring systems to deliver concise information about exposure potential of various pharmaceutical operations and the performance of containment systems.

In the first investigation, it was realized that the recognized dust-in-air monitoring practice of Gravimetric sampling (as used in 1989) was not sufficiently accurate for "containment" applications. Gravimetric was sufficiently accurate for industrial dust mitigation but no more.

An assay method was developed using acetaminophen as a surrogate API using HPLC to analyze the complete filter head in solution the LOQ was 0.090 +/- 0.002 µg/M³ with 95% confidence. This test method was applied to a powder dispensing booth over a five-day period along with real-time aerosol monitoring. The data over the five days of testing revealed significant variations in exposure levels between operator groups, and the real-time monitoring revealed that instantaneous exposure dramatically increased as the operator reached into the powder drum.

These problems are now well understood but the application of the real-time monitoring in these 1989 tests made it clear that segregation between operator and API powder was a key driver in reducing occupational exposure. These tests were followed up with further evaluation to examine the beneficial effects of positioning barriers, drum lifters, and barriers screens in airflow containment systems.

Throughout the 1989 and 1991 testing programs, the real-time data whilst not strictly qualitative did focus on the importance of workplace setup and SOPs to reduce exposure. By 1997, the author was working with the UK Institute of Chemical Engineers (IchemE) to produce a design guide for containment technology, and from this developed the understanding of the hardware/software reliance in attaining long-term and repeatable safety standards in occupational exposure levels within the pharmaceutical sector.

Full Lifecycle Safety Structure

The ILC Dover method looks at all aspects of a given pharmaceutical containment application and appraises these in several stages.

STAGE 1. Process Score

STAGE 2. Quality By Design

STAGE 3. Manufacturing Integrity

STAGE 4. Factory Acceptance Testing

STAGE 5. Containment Performance Testing

STAGE 6. Automatic Pressure Decay Test – Each Run Cycle

STAGE 7. Elimination of Cleaning

STAGE 8. Contaminated Enclosure Disposal

Read on for a closer look at how we implement safety assurance at each stage.

STAGE 1. Process Score

In Stage 1, we take the client-generated data for containment performance targets and product toxicity data to set a HAZARD benchmark. Here we run the information relating to powder transfer quantities, dustiness, or otherwise of the materials and the energy implied by the transfer sampling being low energy and milling our bulk sack transfer being high energy.

This data provides the RISK benchmark for the specific operation. Both ILC Dover and Solo Containment have extensive test data for variations in flexible film isolator design that allow the isolator technology to be matched against the Process Score. Let us put this into context for you.

An application with a low potency material with a CPT (containment performance target) of <10µ/M³, that even though dusty when handled at 10Kg mass transfer volumes creates a Process Score of 25. This is suitable for a simple ambient pressure flexible film isolator. Now replace the material with a more hazardous API having a CPT of <1.0µ/M³ same quantity – same operation and the Process Score rises to 40. Now the containment device should be upgraded to negative pressure operation, H14 HEPA inlet and exhaust, and a pressure loss alarm system. Now, replace the API with an ultra-high potency material, like a cytotoxin. The volume transfer will most likely reduce as the dispensing will involve small quantities. With a CPT of <0.01µ/M³ x < 0.5Kg transfer size – dusty material, the Process Score rises to 60. To match the 60 Process Score, we need negative pressure operation + 2 x stage H14 exhaust filters + pressure loss alarm, and we add the ability to run an automatic enclosure leak test (pressure decay test) on each start cycle. Also, reflecting the high potency (0.01µ/M³ CPT) of this material, we design an isolator that is fully disposable. No stainless-steel parts in touch with the HPAPI and a design that can be "vacuum-packed" flat with all HEPA filters in place at the end of the campaign.

Put simply, the higher the Process Score the more mitigation we add for poor SOP's or upset conditions. The driver is high standards of operator protection even in adverse situations.

CPT	< 10
Dust	High
Quantity	Medium <10kg
Process	Open Powder Handling
Score	**25**

CPT	< 1
Dust	High
Quantity	Medium <10kg
Process	Open Powder Handling
Score	**40**

Simple ambient pressure flex isolators

Negative pressure flex isolators

CPT	< 10
Dust	High
Quantity	Small <0.5kg
Process	Sampling
Score	**19**

CPT	< 1
Dust	High
Quantity	Small <0.5kg
Process	Sampling
Score	**28**

Negative pressure flex isolators + dual stage HEPA exhaust filtration + Low Pressure sensing alarm + Automatic pressure decay test

CPT	< 0.1
Dust	High
Quantity	Medium <10kg
Process	Dispensing
Score	**50**

CPT	< 0.01
Dust	High
Quantity	Small <0.5kg
Process	Dispensing
Score	**60**

ILC Dover's Process Score algorithm matches the containment isolator performance to the risk and hazard profile information generated by the clients EHS group.

STAGE 2. Quality By Design

In Stage 2, setting clear expectations and understanding all the application requirements is vital to developing a quality solution that delivers right first-time performance (QbD). These requirements include facility layout, gowning and material access, scale of operation, equipment interface, container sizes, and waste removal.

Depending on the project complexity, ILC Dover's lifecycle safety structure ensures customers enjoy the highest standards of operator protection through single-use flexible containment systems. We can elect to conduct an Engineering Study in which preliminary designs are generated for client review often with a full-scale ergonomic mock-up. For more straightforward applications, we can use the in-house Containment Application Questionnaire or run this alongside a customer-generated URS. The result in both cases is that all parties must be in alignment with regards to the isolator design, its operation, and any limits of use, so that operational procedures, technical specifications, and performance characteristics are all fully recognized. The QbD validation is the customer sign-off on these critical parameters prior to any detailed design.

STAGE 3. Manufacturing Integrity

In Stage 3, we look at manufacturing integrity calling on ILC Dover's experience designing and manufacturing a multitude of products from highly engineered flexible materials since 1937. In many cases, these are life critical products, including the spacesuit used for the first mission to the moon and an updated design that is used for space walks in the International Space Station. This knowledge of flexible materials, manufacturing practices, and product testing made ILC Dover a perfect fit to supply flexible single-use solutions for processing of pharmaceuticals. From the start it was understood that operator safety and limiting the exposure to pharmaceutical active ingredients is critical.

To achieve products that could be used to handle potent pharmaceutical drug powders and to assure no risk of failure, a range of problems had to be solved. The first was the selection of the flexible film that needed significant physical properties but also would comply with global regulatory standards for product contact. The ArmorFlex® Family of Films was developed, and over the years new films are developed to meet the ever-changing regulatory landscape as well as to leverage new polymers that provide improved performance.

Having developed the right film for pharmaceutical powder handling, the next challenge was to develop manufacturing processes that achieved the quality and assured repeatability. Automated manufacturing processes including computer controlled cutting of the film stock were developed. This automatic cutting guarantees that the components to be welded together are always cut exactly the same leading to a final product that is always the same. Having the piece parts prepared, the fabrication or welding is also computer controlled to control the time and temperature used for each weld. This also leads to manufacturing efficiencies utilizing a single operator for multiple work stations.

The manufacturing processes described are developed to "build quality in" leveraging highly automated processes and skilled operators. With that, integrity testing of the products confirms the containment system will perform as required. Integrity testing is a precise process using a positive pressure and sensing pressure change. Again, ILC Dover developed a fully automated test protocol and test area which tests the product at 10-to-20 times the typical operating pressure. Using a PLC-based test fixture thousands of containment systems are tested each year that results in an extremely low rate of failure but regardless, integrity testing is critical to the Full Lifecycle Safety commitment.

STAGE 4. Factory Acceptance Testing

In Stage 4, Factor Acceptance Testing (FAT) forms the continuation of the specification trail from the engineering study or URS and site survey questionnaire, including the manufacturing approval drawing and the technical specification.

The FAT allows the customer to prove that all dimensions, components, operations, and filter integrity are as ordered and fully compliant with the design brief. It provides the ideal "off-site" location for any last-minute adjustment to ergonomics and other adjustment before the system is taken into manufacturing operation.

For very high-potency materials (Process Score of 50+), there is evidence that using the FAT to develop detailed operating procedures can de-risk some of the activities, especially the non-routine such as contaminated enclosure removal and correct setup and testing of an all-new enclosure.

The FAT is an opportunity to get to know the containment system, all the operational functions and enclosure change overs, as well as develop actions for alarm or upset conditions and plan ahead for worst-case scenarios.

STAGE 5. Containment Performance Testing

In Stage 5, ILC Dover follows the ISPE Good Practice Guide as a containment evaluation format with all tests run on a realistic representation of the true operational cycle. This means the containment test needs to mirror the actual customer operations in terms of material volumes transfer methods—even to the extent of the surrogate reflecting the dustiness of the customers materials where possible.

Test run duration should be fully representative of the real-time operations with the data presented as "task specific" and not diluted down as a TWL (time weighted average). Unlike a hard-shell stainless-steel isolator, the flexible film containment system will operate on a single-use or at least a replaceable basis, bringing the need for a whole lifecycle approach to running a containment test as outlined here.

Test	Locations	Stainless Steel Isolator	Flexible Film Isolator
Operator Breathing Zone	Each Operator	✓	✓
Load Port	Static at Connection Points	✓	✓
Drum Interface	Static at Connection Points	✓	✓
Waste Exit	Static Around Crimping Location	✓	✓
Product Exit	Static at Connection Points	✓	✓
Glove Change	Static at Shoulder Ring	✓	✓
Power Failure			✓
Simulated Breech		✓	✓
Removal of Contaminated Equipment		✓	✓
Enclosure Disposal	Personnel & Static		✓

Put simply, ILC Dover will agree on all parameters with the user group in good time to allow robust containment test protocols to be developed ahead of the actual test period. This allows for setup and rehearsal of the SOP's developed during the FAT.

STAGE 6.
Automatic Pressure Decay Test – Each Run Cycle

In Stage 6, we subject the isolator to a pressure decay test.

WHY IS THIS IMPORTANT?

When we are targeting low ng/M^3 containment targets and the Process Score is driving up the level of technology in the containment system, we need to be sure that every time a new enclosure is installed, safe conditions are guaranteed. An easy and quick method to prove this is to subject the isolator to a pressure decay test.

WILL A PRESSURE DECAY TEST IDENTIFY TINY PIN HOLES IN THE FILM?

Providing that the pressure loss in the flexible enclosure does not exceed a 25pa loss over a 90-second timespan, we are confident that we have a secure and safe system.

The 90-second timeframe is roughly 3x what it will take ILC Dover's ACM to sense that the negative pressure level in the flexible isolator is falling and respond by increasing fan RPM to compensate.

For customer staff using the flexible film isolator with highly hazardous APIs or HPAPIs, the push-button simplicity of running a pressure decay test cycle gives great peace-of-mind. Pass and continue into production. Fail and investigate reasoning and/or replace the flexible enclosure if needed and re-test. No pass means no operation.

STAGE 7. Elimination of Cleaning

With increasing drug potency rises the problems of decontamination.

In Stage 7, we eliminate cleaning for CDMO's who process differing customer batches with a range of drug potencies. This serves as a safety benefit (elimination of accidental exposure during cleaning activities) and reduces enclosure changeover time and eliminates cleaning validation costs.

There are several drivers under consideration here. Eliminating occupational exposure is king but QA and regulatory compliance will also drive the elimination of cleaning activities. As with many activities in the pharm and biopharma sector, the trend to adopt single-use technologies has many benefits.

Note: When the same materials are handled batch after batch and the Process Score is a low number (reflecting a low-hazard material), cleaning the isolator parts may not be a concern.

STAGE 8. Contaminated Enclosure Disposal

In Stage 8, we safely dispose of the contaminated enclosure. When the Process Score is high, reflecting a very low CPT, it becomes obvious that disposal of a highly contaminated flexible film enclosure is a major critical step in the Full Lifecycle Safety process.

At the start of the full lifecycle process, we looked at QbD and identified that planning for all operational activities pays off. Where the isolator designer is aware of the occupational exposure risk that disposal of a contaminated enclosure may release, we can design out some, if not all, of the risk. But how?

By creating a six-sided enclosure that is fully sealed and by designing the inlet and exhaust HEPA filters, so they stay in place, always sealed to the flexible enclosure, and most importantly, using fan vacuum to collapse the contaminated enclosure so it ends as a flat air free-assembly on the stainless-steel worktable.

No dismantling. No double-tie and cut sleeves. Using QbD we can provide most, if not all, interface ports and connections as disposable single-use items to vastly reduce enclosure setup and disposal timelines and eliminate activities that could generate accidental occupational exposure.

In Summary

The Full Lifecycle Safety Innovation system available through ILC Dover is a major step forward in assurance of long-term operator safety. ILC Dover will always be guided by the professional EHS stakeholder's toxicology dataand MSDS information. What we deliver in Full Lifecycle Safety is a "cradle to grave" attention to how we deliver the best possible containment solutions for a given application.

REFERENCES

Peter H Gough: 1991 April: Performance Testing of 3 configurations of dispensing booth with reference to operator protection and dust containment.

N. Hirst: 2002: IchemE Containment Systems - A Design Guide.

NG Cocker: 1999: Evaluation of the level of containment performance achieve by Extract technology Barrier Isolator.

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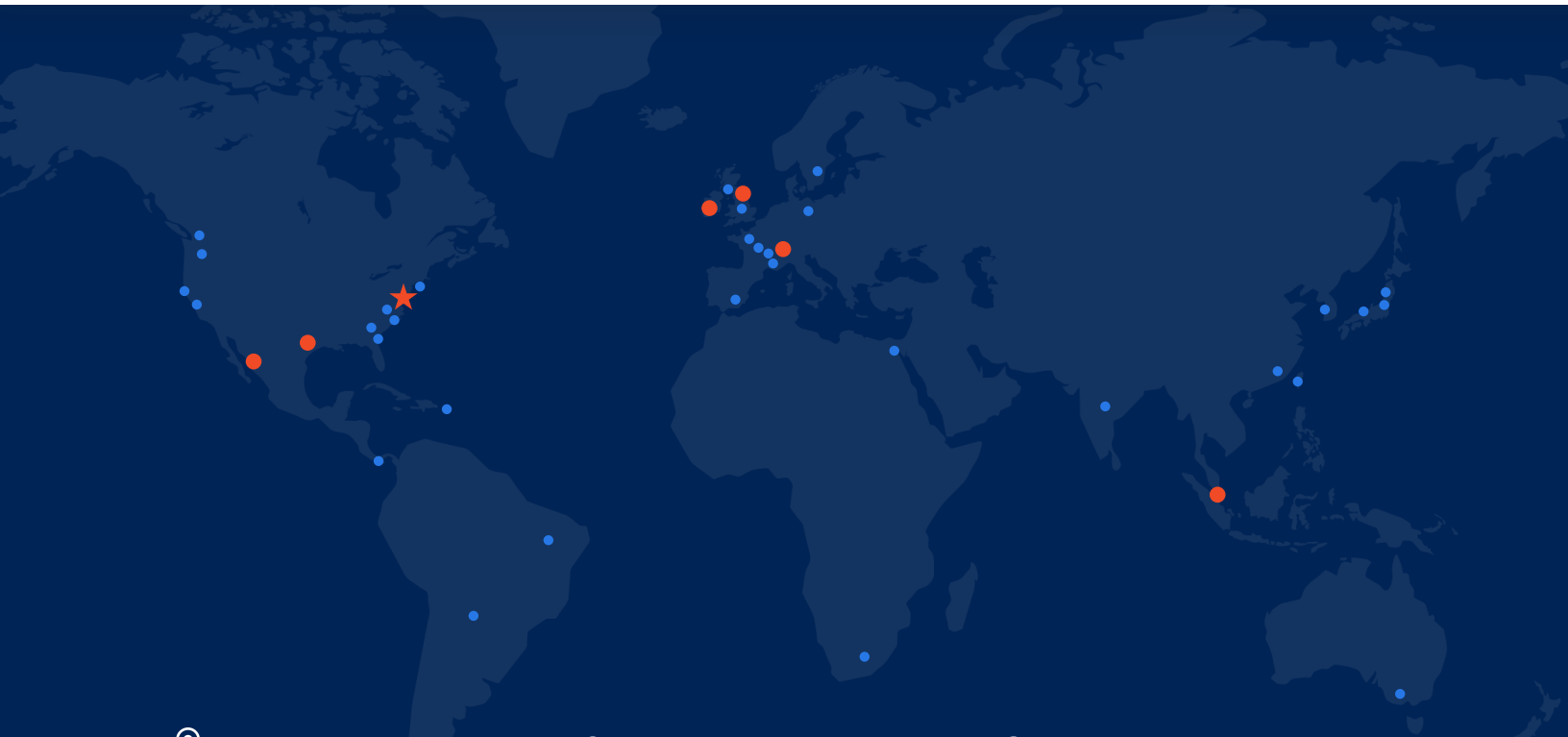
ILC Dover is a world-leader in the innovative design and production of engineered flexible protective solutions, for pharmaceutical and biopharmaceutical, flood protection, personal protection, bulk packaging, and aerospace industries. Our customers will attest to our relentless dedication to high value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



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MKT-0288 Rev A