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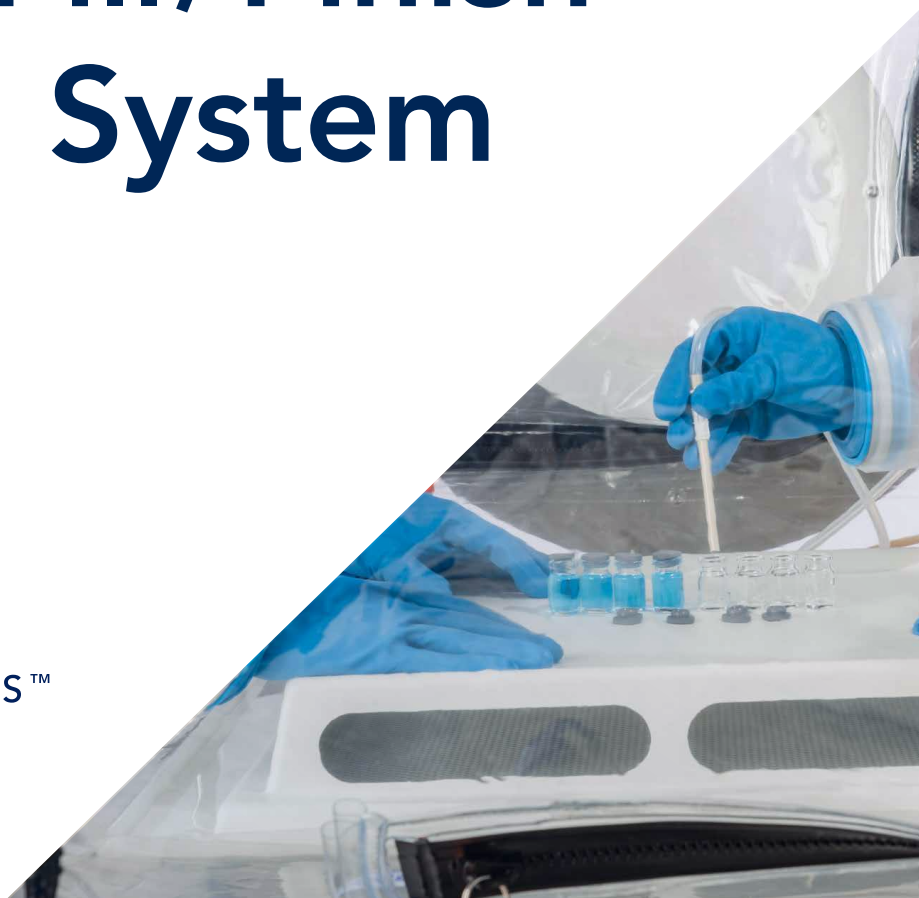
WHITEPAPER

Development of a Disposable Grade-A Aseptic Fill/Finish Isolation System



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Introduction

Isolation of aseptic processes is not a new technology. Rigid stainless-steel isolators have been available for decades and have been a very successful application within the industry. Flexible Film isolation has been used in aseptic processing since the 1970's but these systems tended to be a composite of stainless-steel chambers and airflow modules with a flexible film user interface. (Hybrid: rigid/flexible). In this paper we are going to investigate how Solo Containment (Solo) developed a fully disposable aseptic isolation system.

The starting point for building this system stemmed from a request of a French CDMO to develop a low-cost single use aseptic fill/finish isolator for small batch (500-1000) hand filling of vials, syringes, or cartridges.

The system URS itemized the following user needs:

- Two work chambers – vial preparation and vial filling/stoppering
- Heat sealable exit via continuous liner to maintain sterility on product exit
- ISO 5 particle count attainable in 30 minutes from start up
- ISO Kinetic particle and pressure monitoring in each work chamber
- Entire system must be delivered as a gamma irradiated entity
- System must be customizable, so it is delivered with batch dictated fill and filtration utilities

No RTP / DPTE technology was requested by the CDMO in order to drive down the cost of the disposable isolator.

Initial Prototyping

Early development attempts were focused on a low airflow system with compressed air feed via aseptic filtration capsules. ISO 5 particle count could be attained with some difficulty after several days purge, but any movement of the glove sleeves soon created a particle concentration spike. Clearly a higher airflow rate would be needed and in January 2017 the Solo team modelled and mocked up a much higher airflow system. This created a prototype with panel HEPA filters in the roof and base panels of the flexible enclosures with a mean 0.45 m/s vertical flow velocity. With this arrangement the particle purge from room background to ISO5 standards was almost instantaneous.

With the unidirectional airflow proving our predictions, Solo's project team needed to develop the methodology to incorporate large panel HEPA filters into the disposable flexible film enclosure. The final design which was subsequently patented provided for fixed multiple fan arrays above and below the HEPA filters with a gasket seal to the disposable HEPA panel assembly. This design simply separated the permanent stainless-steel frame parts, fan units, speed controls and worktable from the flexible film disposable enclosure. Furthermore, even with the prototype modules the actual enclosure changeover was both fast and tool free.

By June 2017, a fully operational stainless frame and several gamma irradiated aseptic processing enclosures were delivered to the French CDMO. Here the operational protocols and batch validation methods were refined to a degree allowing the production of the world's first clinical batch in a disposable flexible film isolator.

Development of the MKI

The MKI single use system was created from concept to working prototype in a remarkably short timeline. Whilst the system delivered the key URS points needed, there were still some elements that needed further refinement, including:

1. Fully bonded HEPA filter housings did not permit any HEPA panel failing integrity test as part of PDI to be replaced. Meaning in the event of a DOP test failure the entire enclosure was rejected.
2. Transit damage both to the GI contractor and to the final job site could be an issue as the completed 2 chamber (4 x HEPA panel) enclosure could weigh up to 40kg.
3. No facility to run daily pressure decay testing prior to start up.

In addition to the above, it was decided to run a further development program to meet the requirements of EU Annex 1.

Development of the MKII (soloPURE)

The first area to receive attention was the method for sealing the HEPA panel filters into the flexible enclosure. A new innovative system that restrained and sealed the HEPA panels was tested and this demonstrated that at any time prior to the GI treatment a damaged HEPA filter could be exchanged within minutes.

The new HEPA mount system incorporates a 4-bolt flange system (external to the flexible enclosure) and this was foreseen as the way to overcome transit damage and site handling issues. Solo then developed a robust transit jig plate method that is used to clamp all four HEPA filters at a secure spacing in a vertical pattern. The final height of the complete assembly is within the height restriction of all EU gamma irradiation contractors allowing the triple packed sterile enclosure to be transported directly to the end users' site. Here once decoupled

from the transit pallet, the transit jig is used to transfer the delicate enclosure through any airlocks to the aseptic processing suite.

The revised HEPA filter panel system permitted a simple seal plate to be added that permits the enclosure to be pressure decay tested on a regular basis in accordance with EU Annex 1.

At this moment the controls and pressure monitoring packages available for the soloPURE system are all manual but a GAMP 5 compatible upgrade will be available in the future.

Clearly, the development of single use soloPURE is perfectly suited to the requirements of small batch and hand fill finish operations and is perfect for orphan drugs and ATMP's. However, some early customers required automated vial filling and stoppering or even a lyophiliser interface.

With these applications a significantly larger processing footprint is needed and the soloPURE system of captive panel HEPA filters was passed over in favor of a conventional gel seal ceiling grid. Solo's design would be similar in some ways to the classic aseptic processing flexible isolators in that a composite part stainless steel, part flexible film solution would be needed. Many of the design nuances from the soloPURE design have been carried over allowing the same modular design to be applied to the larger soloUNI product platform. Some of these features include wall-to-wall unidirectional airflow, perforated stainless steel work deck capable of supporting up to 200kg and with sanitization provided by the clients VHP cycle.

soloUNI can be applied to small scale syringe fill lines, lyophilizer interfaces and solids processing such as dispensing, extruding and powder fill activities.

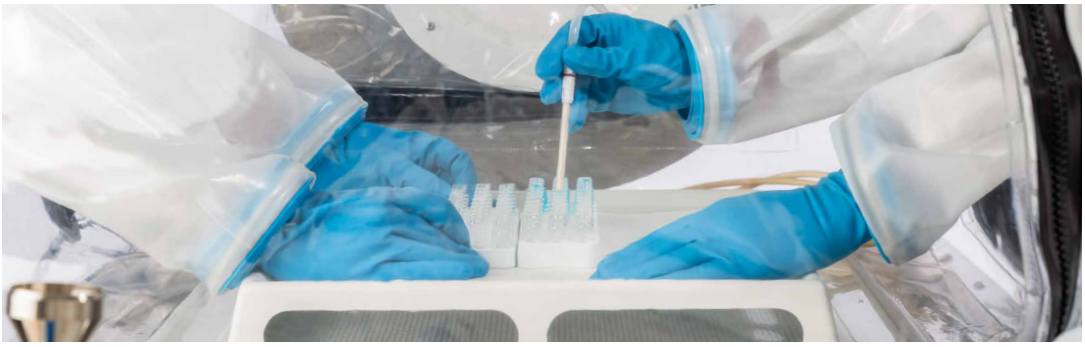
Advantages of Flexible Film Aseptic Containment

It will come as no surprise to hear that Solo has had interest from high speed automated filling line companies and a variation of the soloUNI is available with stainless steel exhaust low level return air exhaust plenums allowing the high flow unidirectional airflow system to be dropped completely over a modern robotized automated vial fill/vial seal machine.

Within a 3-year period the Solo Containment engineering group have delivered several innovative and successful aseptic isolation systems to customers across Europe and even into the USA. In all cases the advantages of flexible film aseptic containment can be seen as:

- Significantly lower cost than rigid stainless-steel isolators
- Faster delivery
- Simple addition or changes to glove sleeve / operator access interface as processes change
- Eliminated (soloPURE) or vastly reduced cleaning validation as flexible element can be disposed of every campaign change

With identical design characteristics as the classic hard-shell stainless-steel isolators flexible film aseptic isolators offer several advantages that should be given careful consideration.



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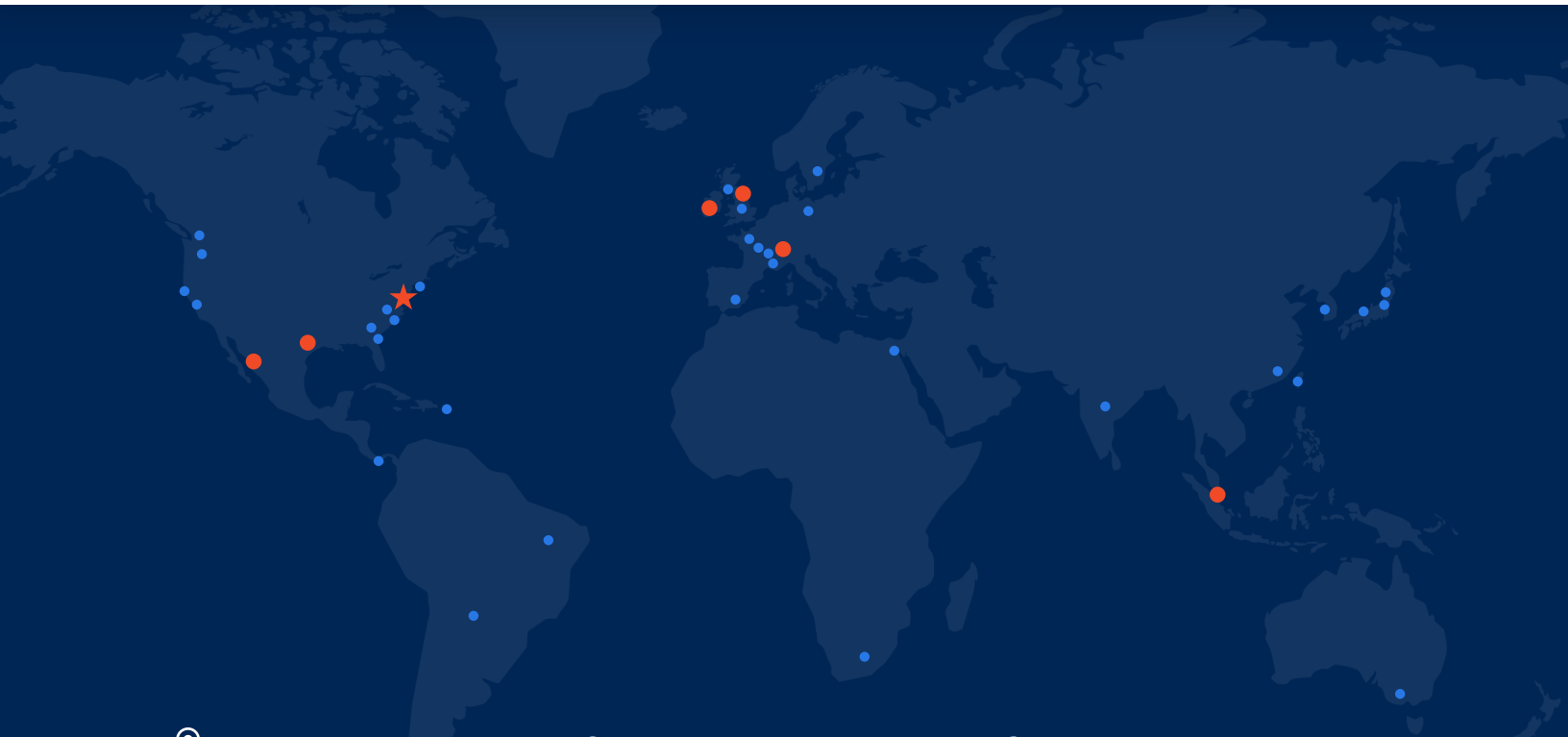

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