ILC DOVER

WHITEPAPER

The Future of ADC Manufacturing:

Benefits of Single-Use Isolators for Cytotoxic Payload Handling

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Introduction

Recent advancements in Antibody-Drug Conjugates (ADCs) have significantly expanded the landscape of potential payloads, offering promising prospects for precision cancer therapy. Concurrently, 15 ADCs are approved globally, with about 140 organizations advancing over 300 ADC candidates[1]. Simultaneously, the growth in ADC production, especially concerning ADC payloads, introduces new complexities in ensuring occupational health and safety standards are met.

High-potency cytotoxic payloads are vital for anti-cancer ADCs due to low tumor antibody uptake and they possess picomolar cytotoxicity, far exceeding conventional high-potency active pharmaceutical ingredients (HPAPIs)[2]. They generally fall into Occupational Exposure Limits (OELs) of less than 30 ng/m^3[3]. In addition, many new payload molecules with unknown toxicities are under early development. Therefore, it is important for drug research and development parties such as Contract Research Organizations (CROs) and Contract Development and Manufacturing Organizations (CDMOs) to prioritize containment controls for regulatory compliance, mitigating the potential exposure risks and reducing cross-contamination risk.

Let's Dive In...

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Single-use Containment for ADC Handling

Currently, more than 70% of ADCs production is outsourced to CDMOs[2] due to distinct reasons:

Complexity
ADCs involve intricate processes with multiple components (antibodies, payloads, and linkers), necessitating specialized expertise and facilities.

Coordination Challenges
ADC components may be manufactured at various sites, requiring careful coordination. Several CDMOs are integrating all ADC components production for efficiency.

Toxic Compound Handling
ADC production involves handling highly toxic substances and complex waste disposal, areas where CDMOs with HPAPI experience excel.

High Failure Rate
ADCs face a high failure rate in clinical trials due to design complexity, payload toxicity, and other factors. Outsourcing to CDMOs enables testing clinical and commercial viability before major manufacturing investments.

Considering the forementioned realities of outsourced ADCs research, development and production, CROs and CDMOs are facing big challenges of using limited numbers of high-containment facilities such as isolators under current capacities to handle multiple products from various customers. Regulatory authorities have imposed stringent compulsory requirements on using shared facilities to produce multiple products including developing standardized operation protocols (SOPs) for cleaning and cleaning validation between product change-over[3-4], and this has further led to a broad adaption of single-use systems (SUS) throughout the biotherapeutic production. The complexity of ADCs amplifies the difficulty of cleaning traditional rigid isolators for payload-related operations due to stringent cleaning limits of residual

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cytotoxin. The time-consuming cleaning and its validation procedure also mean "production time lost", plus the cost of proper waste disposal. Alternatively, incorporating additional rigid isolators for capacity expansion necessitates extensive facility design/modifications and validation, leading to prolonged timelines and elevated risks for revenue and sustainability, especially given the high failure rate of ADCs.

Single-use isolators (aka. flexible isolator or flexible containment) have gained more attraction in ADCs manufacturing, with broad recognition of their performances and inherent benefits

1. High-Containment Performance

One of the key concerns for single-use isolator has been containment performance vs. traditional rigid isolators. With the advancement of materials and manufacturing process and incorporating pressure-decay integrity release test, single-use isolator has shown containment of 10 ng/m^3 airborne concentration during entire lifecycle of ADC-payload handling from sample weighing, dispensing, dissolving into solution, material transferring in/out, solution transferring, till contaminated enclosure disposal. Single-use isolators equipped with sensors and PLC-based control system are able to detect pressure change and adjust the internal isolator pressure back to the setpoint to maintain necessary negative pressure, thus ensuring containment and mitigate risks in upset conditions, such as power failure and induced breach. Product and equipment removal using continuous liner welding (Bag in Bag out, BIBO) has also provided a simple and cost-effective process for material removal, while still meeting 10 ng/m^3 containment performance. Together with pre-welded hose line port with single-use tube assembly for payload solution transferring in contained manner, a fully integrated total single-use solution has been demonstrated, achieving proper containment of high-potency ADC payloads during operation and transfer of materials and eliminating the risk of particle migration at the transfer points by integral connections.
(*See Figure 1 & Table 1*)

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2. Flexibility & Process Simplification

Single-use isolators can be easily adapted to existing facilities and various scales of ADC production due to their flexible customization and less production time, allowing for fast and efficient scale-up, scale-down and scale-out as needed, which is crucial for pharmaceutical companies and CDMOs to advance these molecules more quickly. In addition, single-use isolators eliminate the needs for complex cleaning and cleaning validation, therefore mitigating the risk of cross-contamination and simplifying the process with much less down-time. Furthermore, single-use isolator has recently adapted with automatic control system for flexibility GMP chambers where airflow, temperature, humidity and pressure differentials exist from room to room. For example, ILC Dover's single-use isolators are equipped with the Atmospheric Control Module (ACM) to precisely regulate fan speed and process gas to facilitate automatic negative pressure control as of set point for high-potency payloads handling. It also can be used with fresh or recirculated nitrogen gas for materials that are oxygen sensitive or explosive. These requirements are part of the evolving ADC process which is another benefit offered by single-use isolators. As new ADC molecules are developed and processes are defined, the single-use isolator is easily changed to meet process needs and support operator ergonomics. The ability to change and adapt the isolator design is unique to the single-use technology. Finally, single-use isolators are engineered to collapse through fan exhaust airflow after use without risk of exposure to the operators or the process suite. The entire folded enclosure easily fits into an incineration bin, streamlining the disposal process and reducing risks and costs significantly versus handling liquid waste containing toxic chemicals after cleaning rigid isolators.

3. Economic Benefits

An in-depth cost analysis is conducted, simulating cumulative cost of a CDMO using single-use isolators and one rigid isolator for multi-product ADCs cytotoxic payload operation, respectively. As presented in Figure 2, there is a minor initial capital investment on single-use isolators, the main cost is linearly associated

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with quantity of multiple products that CDMO is handling per year with small portion of maintenance and operator training cost. In the case of rigid isolator, a large capital investment is spent at the very beginning. With projects for multi-product development coming in every year, validated cleaning processes must be developed and followed for individual products for compliance with stringent regulatory requirement to mitigate cross-contamination risk on a shared isolator. A higher accumulative cost vs. that of single-use isolator over years is observed, which is mainly contributed to residual toxins QC assay development, QC release test and collateral project down-time due to isolator cleaning between change-over. More importantly, these costs are in proportion to the quantity of multiple products that CDMOs are handling annually. Thus, the more payloads that one CDMO handles annually, the higher accumulative cost of using rigid isolators. Furthermore, the high cytotoxicity of ADCs payload will impose ultra-low cleaning limits (ppb ~ppt level) for decontamination between product switching and this will potentially introduce additional cost of multiple cleaning and QC release tests. Later on, when capacity expansion is required, it will also be much easier using single-use isolators instead of rigid isolators considering the flexibility and ease of adaption.

4. Sustainability

Single-use isolators optimize resource usage by eliminating the need for extensive water, inactivation and cleaning reagents, and energy consumption associated with traditional cleaning processes of rigid isolators. This leads to reduced demand on natural resources, making the production process more sustainable. For example, about 100-200L water will be used for cleaning a contaminated rigid isolator to ensure the effectiveness of decontamination and incinerated within a waste collection plastic bag afterwards, which is completely avoided when a single-use isolator is employed. An in-depth study by the Bio-Process Systems Alliance (BPSA) found that single-use products used in biotherapeutics processing is overwhelmingly more sustainable than like products made from stainless steel[5].

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Summary

Incorporating single-use isolators into ADC manufacturing processes leverages the established benefits of single-use technologies while addressing the unique challenges posed by cytotoxic payloads and allowing pharmaceutical companies to concentrate on their core competencies, thus, will ultimately improve safety, efficiency, and cost-effectiveness in ADC production.

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Figure 1

Photo of **(A)** a single-use isolator (soloADC from ILC Dover) for high-potency ADC payloads handling; **(B & C)** single-use isolator operation wearing powered air purification respirator (PAPR); **(D)** BIBO process using continuous liner welding; **(E)** pre-welded peristaltic pump hose line ports on single-use isolator

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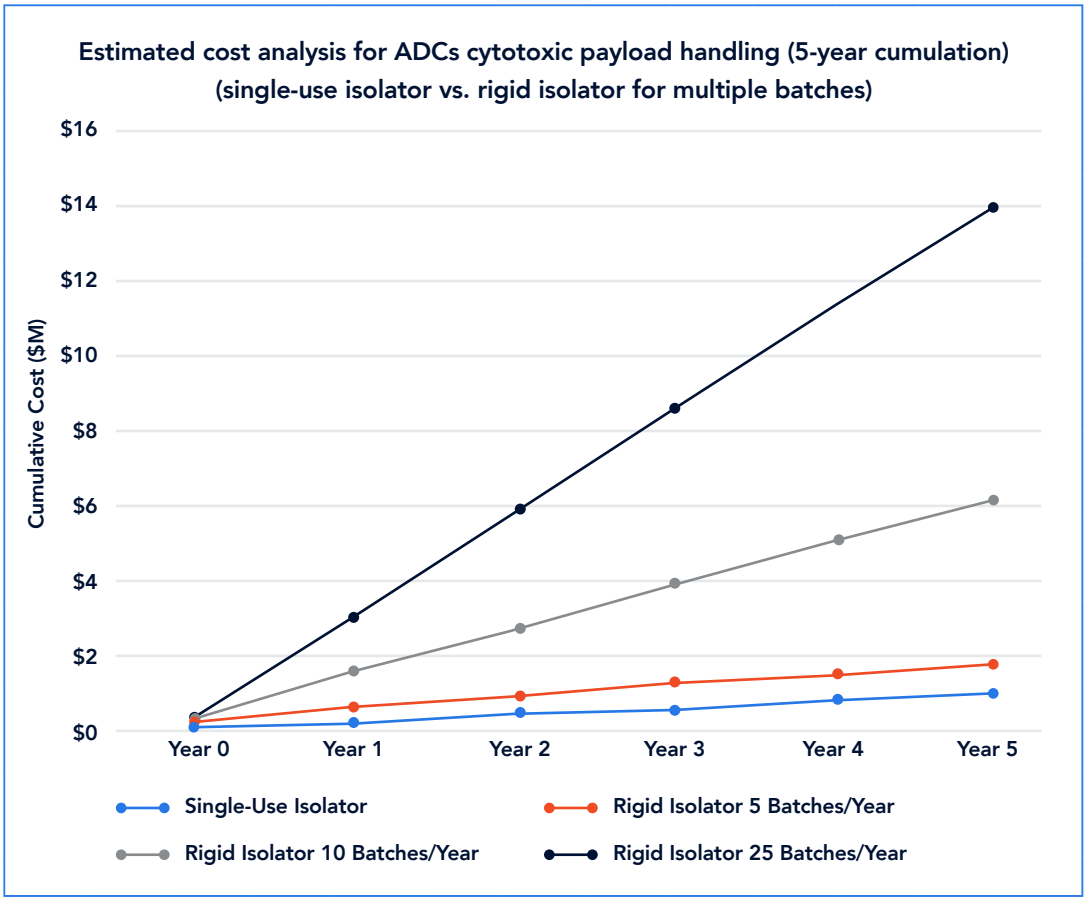
Figure 2



Simulated cumulative cost between single-use isolators and one rigid isolator for multiple payload products (5, 10 and 25) handling annually.

(Assumption: full-time employee labor rate = $ 50/hour; 8 working hours/day; one cleaning assay development time = 40 hours; cleaning QC release test time =8 hours; rigid isolator down-time cost = $ 5000/hour; routine maintenance & training cost included. Consumables & reagents for cleaning QC assay not included due to variation. single-use isolator and rigid isolator costs are based on average market selling price with specification of HPAPIs (OEL 1-0.1 μg/m^3) containment.

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Table 1

Test		No. Test Runs	Outcome (Task-Based)		
Ref:	Device/Activity		Personal	Static	Overall
02	Sample removal through contunous liner	3	3 of 3 results <10% CPT	15 of 15 results <10% CPT	**PASS**
03	Toxin linker dispensing and transfer	3	3 of 3 results <10% CPT	15 of 15 results <10% CPT	**PASS**
04	Power failure	3	3 of 3 results <10% CPT	15 of 15 results <10% CPT	**PASS**
05	Induced containment breach	3	3 of 3 results <10% CPT	15 of 15 results <10% CPT	**PASS**
06	Flexible isolator contaminated enclosure disposal	1	2 of 2 results <10% CPT	3 of 3 results <10% CPT	**PASS (indicative)**

Single-use isolator containment performance for ADCs operation

(5 Day containment test: 3 x Operator sizes –following Standardized Measurement of Equipment Particulate Airborne Concentration (SMEPAC) test protocol and Containment Performance Target (CPT) = 10 ng/m^3)

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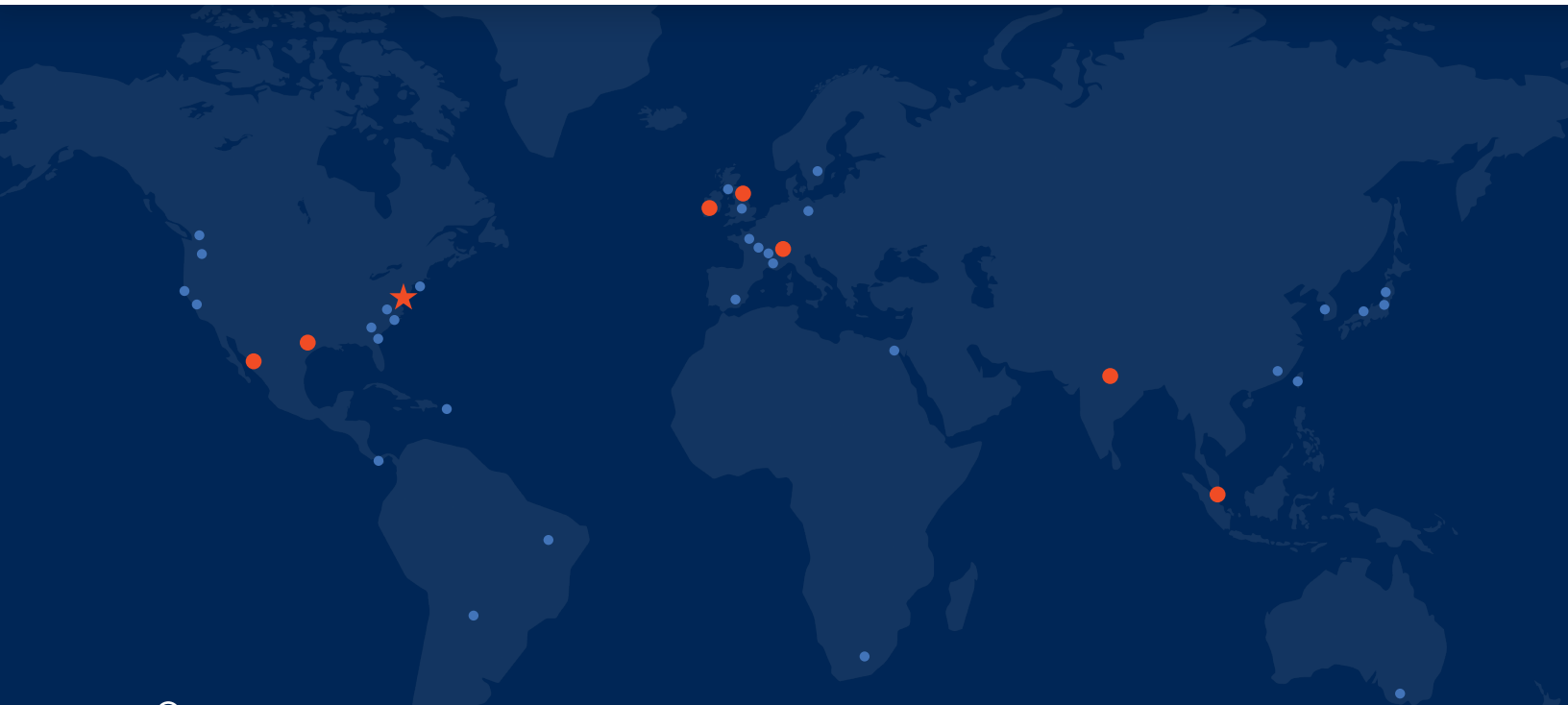

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