

The Impact of Process Closure on Biomanufacturing Risk

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Introduction

“Closed system.” The term itself appears deceptively simple. However, the definition of a closed system, its implementation, and its impact on biomanufacturing has been anything but straightforward.

The journey toward implementing closed systems spans over 20 years. The concept of closed systems was introduced in January 2000 with the draft issue of ICH Q7.^[1] Since then, other industry guidance documents emerged, defining and supporting process/system closure as a primary means of risk mitigation to meet the baseline requirement of protecting the product, as defined in cGMP.^[2]

Presently, global regulatory agencies recognize three distinct definitions of a closed system. These definitions, found in EU Annex 1^[3], EU Annex 2^[4], and the PIC Annex 2A^[5], all focus on product protection where the product is not exposed to the immediate room environment during manufacturing. This is where the journey begins.

Protecting the Product

Product protection is paramount. But what exactly is a closed system? According to Annex 1, it's defined as “a system in which the product is not exposed to the surrounding environment.”

Regulatory agencies across the globe focus on three aspects of manufacturing: safety, efficacy, and quality. Safety consistently takes precedence as it concerns the patient's well-being.

Regulatory agencies also recognize that industry guidance cannot be overly prescriptive in defining expectations and requirements. Recent guidance documents put an increased focus on the principles of risk management. Formal risk assessments (RAs) with associated risk mitigation practices are considered a mandatory basis for cGMP compliance. A contamination control strategy (CCS) has become an essential design-basis document, ensuring the appropriate design of the facility, equipment, systems, and associated processes to mitigate and control the risks of contamination and cross-contamination. The RA and CCS help define what

is appropriate and required to meet regulatory expectations, including but not limited to open/closed processes. Again, with the primary goal of protecting the product.

It's widely known that biopharmaceutical manufacturing unit operations are carried out in either an open or closed process. Process closure is critical for all biopharmaceutical products that are potentially adulterated via outside incursions of contamination. That said, the simple intent of a closed process is to manage outside access to contaminants and preserve product quality, thus supporting patient safety.

To achieve effective product protection during manufacturing operations, it's essential to understand the potential sources of contamination that could contribute to the breach of integrity of the API. Potential sources of contamination in a typical bioprocessing environment include:

- Raw materials used as manufacturing process components
- In-process materials such as buffers
- Consumables, single-use bags, tubing, and filters
- Utility services, air, water-for injection (WFI), O₂, CO₂, and N₂

The actual manufacturing environment can also be a contributor:

- Personnel within the manufacturing suite
- PPE such as gowns that are shedding, shoes, or other items
- Equipment such as motors, fans, and compressors as all generate particulates and aerosols
- Process equipment that is inappropriately cleaned and sanitized between operations

The fundamental premise of biomanufacturing is this— a system is either open or closed. While there may be varying conditions during process operations, equipment is one or the other. If it is closed, the product is at a much lower risk of being contaminated from any contaminants present in the manufacturing environment.

The layers of protection needed to safeguard products,

processes, and ultimately patients from contaminants present in the production environment are a key element of process and facility design (Figure 1).^[6]

Defining Closure Boundaries

Process closure requires the identification of boundaries that describe the biomanufacturing unit operations and facility attributes that protect the product (Figure 2).

In a closed system, the primary system barrier (process zone), is controlled and plays a pivotal role by enabling leak detection and contaminant control within the system. Product protection within the process zone requires control of the introduction of components such as unfiltered air, gases, liquids, and operator contamination. The primary barrier acts as a protective layer in immediate proximity to the product, encompassing and controlling the process.

The secondary system barrier acts as a supplemental boundary that supports closure of the process zone. It surrounds the primary barrier and is also subject to control measures aimed at mitigating contamination risk from the external environment (Figure 3).^[7]

Closing the System

Closing a biomanufacturing system should focus on treating each process unit operation as a unique closed system. Each unit operation should “run” as a closed system. Breaking down each unit operation into sub-closed systems is recommended (Figure 4).^[8]

In this situation, a closed system can be broken down into three basic parts:

- The **equipment assembly**. Examples: bioreactor, vessel, filtration system, chromatography systems, etc.
- The **streams** in and out from the system. Examples: compressed air, exhaust, media, and buffers, etc.
- The **connections and disconnections** to the system. Examples: valve, double-block, valve ring, single-use connectors and disconnectors, etc.

The goal is to demonstrate risk mitigation for each component/part to ensure that the system operates in a closed manner. A typical schematic of a closed system is shown in Figure 5.^[9] Proof of closure can be achieved via a closure analysis risk assessment (CLARA).

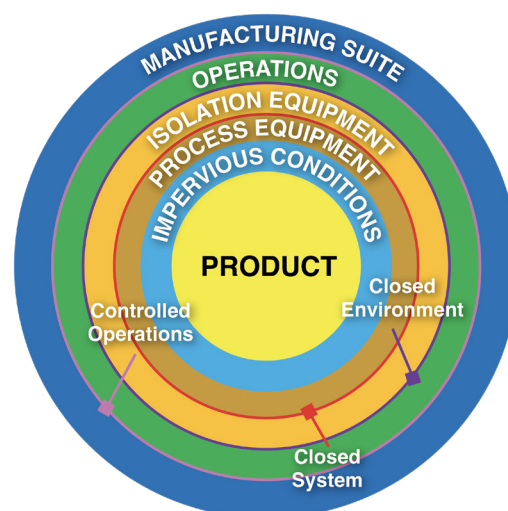


FIGURE 1. The layers of protection and analysis (LOPA).^[6]

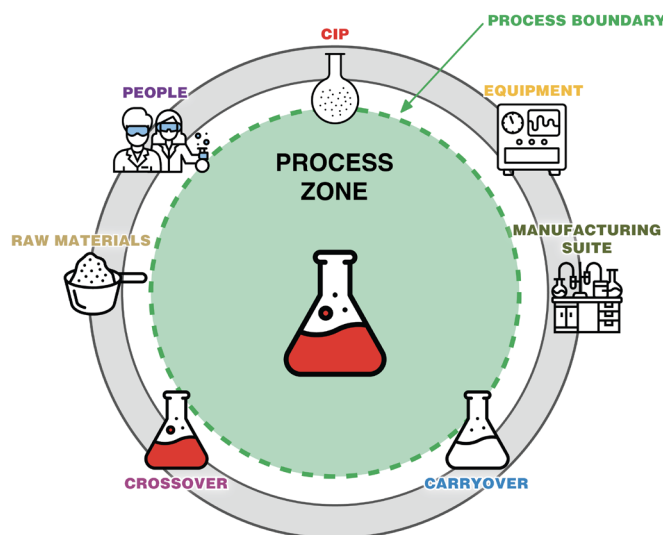


FIGURE 2. Closure boundaries.

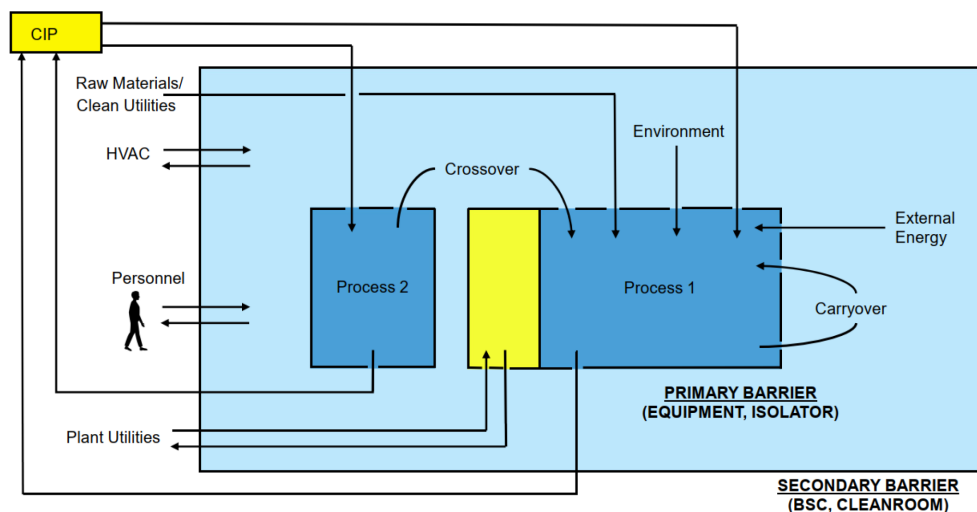


FIGURE 3. Secondary barrier system.^[7]

The Impact of Process Closure on Biomanufacturing Risk

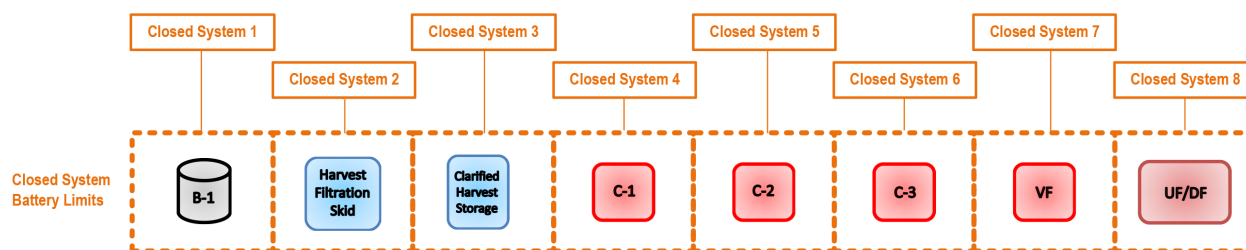


FIGURE 4. Closed biomanufacturing system.^[8]

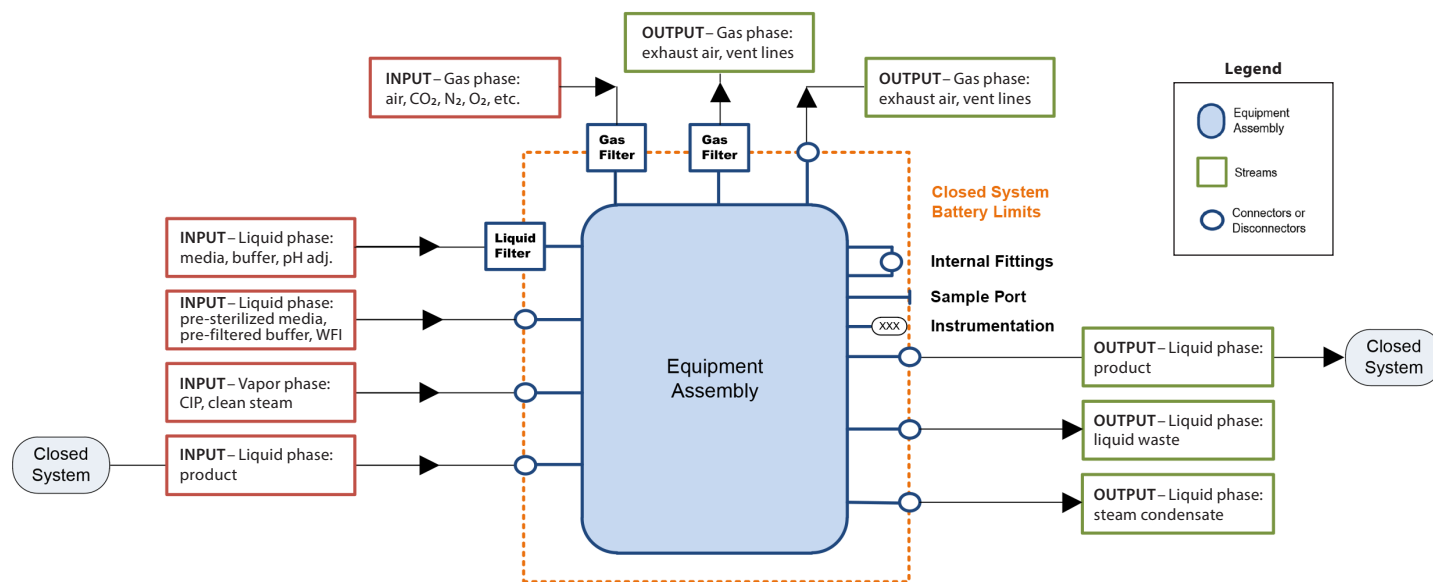


FIGURE 5. Closed system schematic.^[9]

Knowing When to Close

The closure process should prioritize open aseptic operations. These operations include cell bank preparation, inoculum preparation, some weigh-and-dispense operations, and sampling. The analysis must also include all connections that pose a risk for contamination, as defined in the executed CLARA.

With the current industry focus on cell therapy (CT) manufacturing as an example, when to focus on closure for autologous and allogeneic manufacturing processes is represented in Figure 6.

Impacting Facility Design: Case Study Example

To illustrate the significant impact that process closure can have on biomanufacturing design, we have provided the following case study.

Challenge

A biotech manufacturer sought an aseptically controlled environment to produce its autologous and allogeneic

therapeutics with a high level of sterility assurance. Their target goals were:

- Expedited transfers of biological materials in various containers (cell culture flasks, conical tubes, cryovials, bags, etc.)
- Gene manipulation by viral transduction/electroporation
- Rapid and ultra-rapid decontamination cycles
- Operator and patient safety
- Acceptance from cGMP regulatory authorities, US FDA and EU EMA, and other global agencies in the future
- Preference for Grade C cleanroom facility with Grade A closed system to reduce gowning and operational costs from planned Grade B/biosafety cabinet (BSC) approach

The original production suite employed traditional manual-focused manufacturing operations within a designated Grade A BSC, operational within a Grade B background

The Impact of Process Closure on Biomanufacturing Risk

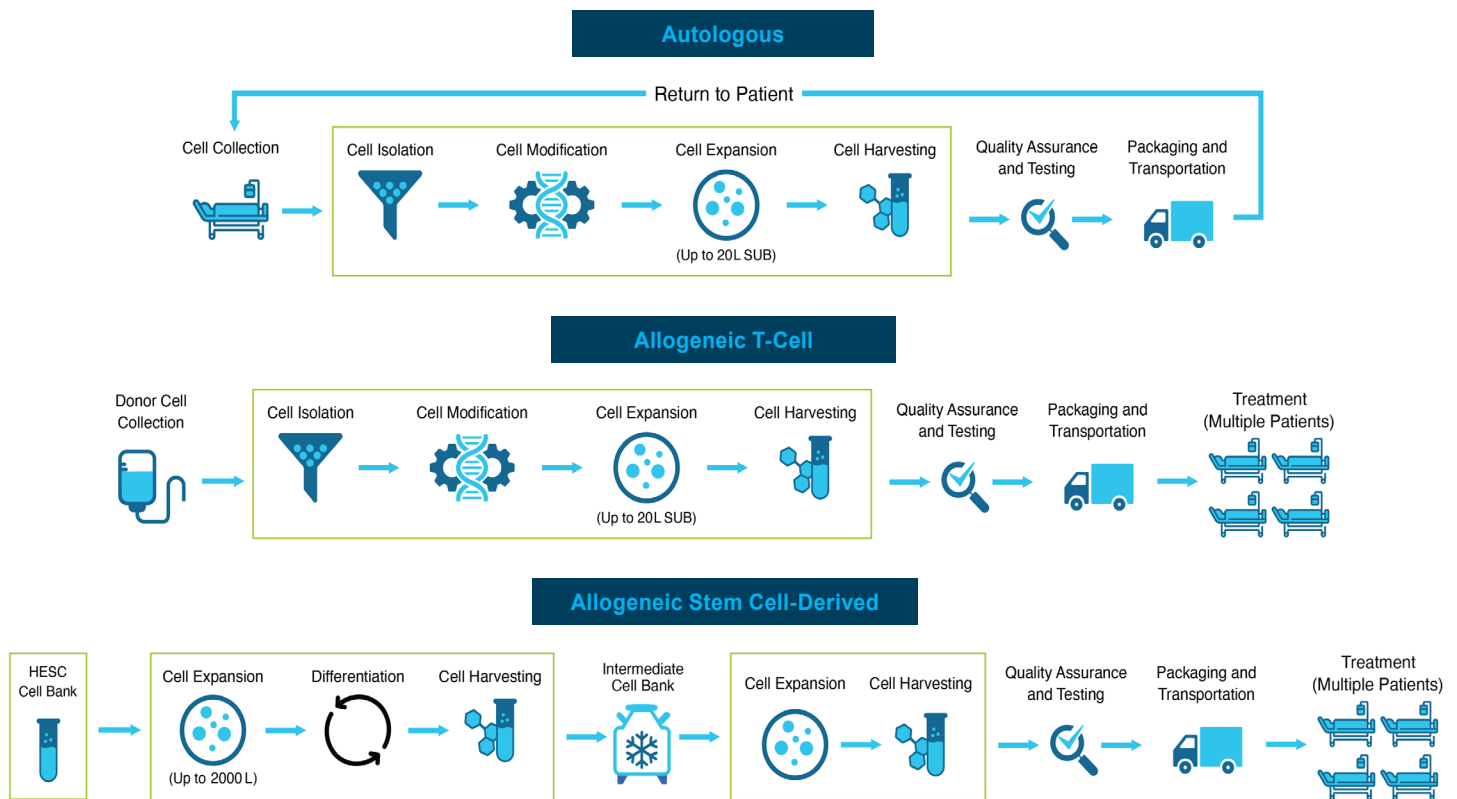


FIGURE 6. Closure for autologous and allogeneic CT manufacturing processes.

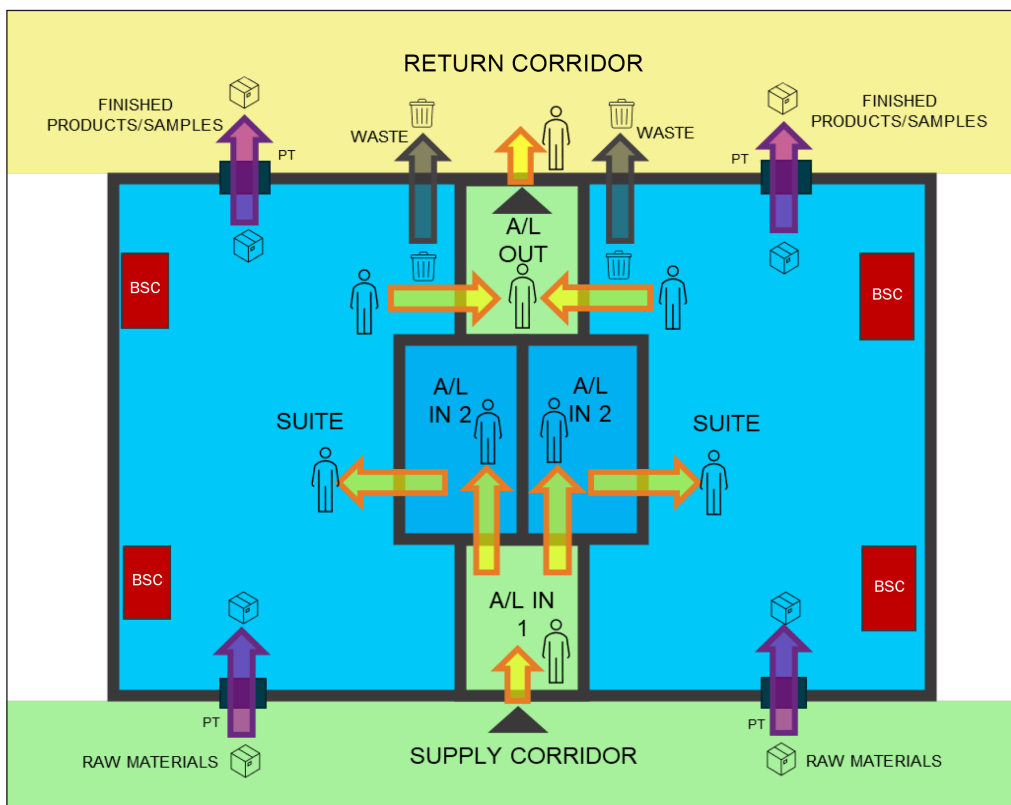


FIGURE 7. Original bioproduction suite schematic.

environment (**Figure 7**). The unit operations consisted of initial apheresis processing, thaw/wash/incubation operations, sorting/sampling, expansion/harvest, and cryopreservation.

Approach

After conducting an analysis of the unit operations mentioned above, the key risk mitigation strategies were to:

- Close the primary operations by moving operations out of the BSC and into a closed isolator system
- Reduce the environmental classifications
- Optimize the air handling unit design based on lower HVAC design criteria
- Reduce gowning requirements to correspond with new manufacturing approach

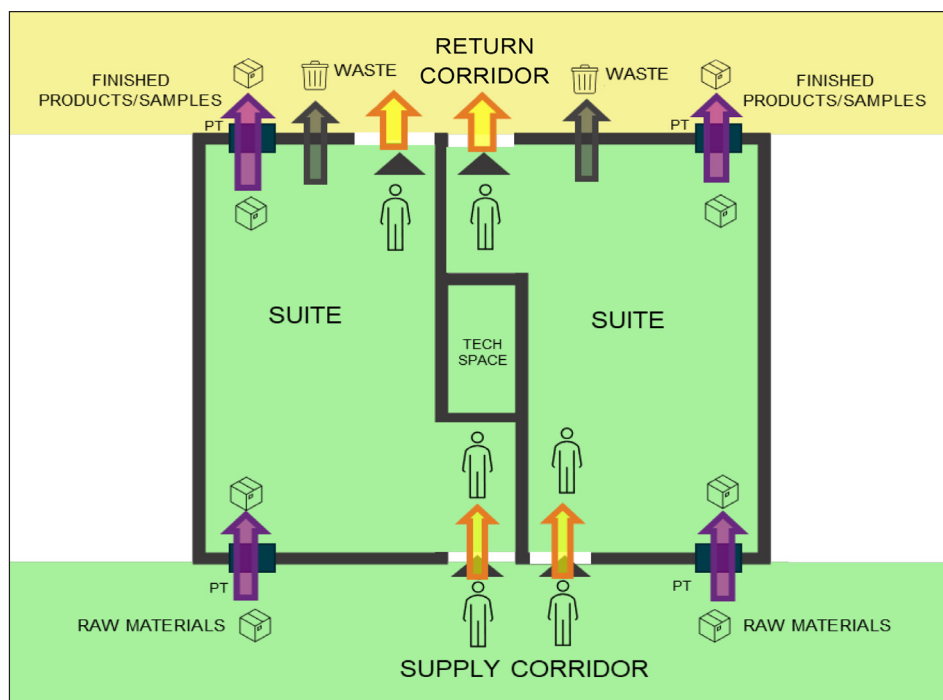


FIGURE 8. New bioproduction suite schematic.

- Provide comprehensive operator training on new equipment, and when applicable, procedures
- Optimize the facility layout design in accordance with new area classification requirements

Based on these recommendations, the new manufacturing suite schematic layout is shown in **Figure 8**.

Results

The optimized design features:

- Grade C or Grade D Suites with Grade A closed systems to reduce gowning and operational costs from planned Grade B/BSC approach
- Improved operator and patient safety
- Increased probability of acceptance from cGMP regulatory authorities, US FDA and EU EMA, and other global agencies in the future
- Lower HVAC and operational costs
- Fewer classified spaces—easier to operate, maintain,

and validate

- Reduced maintenance shutdowns
- Decreased solid waste handling

In summary, the risk mitigation effort resulted in the following outcomes:

- Overall reduction of 995 sq. ft. in the classified environment space of the facility
- Elimination of 4,475 sq. ft. of Grade B-classified space
- Removal of multiple Grade B airlocks
- 35% reduction of air handling unit sizing
- Increase of \$800,000 in equipment qualification/validation costs
- Decrease in overall facility qualification costs by \$250,000
- Projected reduction of environmental monitoring costs by \$1.5 million

This risk mitigation effort was also analyzed over a five-year projected ROI. The results are shown below in **Table 1**.

TABLE 1. Cost Analysis: Five-Year Outlook			
BASELINE OPTION: Open Aseptic		IMPROVED OPTION: Closed Aseptic	
Direct Costs	\$4,679,000 (TIC)	Direct Costs	\$6,640,000 (TIC)
Annual Operating Costs	\$6,077,000	Annual Operating Costs	\$3,202,000
Five-Year Projected Ops	\$30,387,000	Five-Year Projected Ops	\$16,000,000
TOTAL	\$35,066,000	TOTAL	\$22,640,000
Estimated Savings: ~35%			

A pros/cons review of the risk mitigation effort yielded the following analysis:

Baseline Open Manufacturing Controls:

- Significantly higher costs for Grade B space due to:
 - Environmental monitoring
 - Gowning
 - Unidirectional airflow to create Grade A aseptic environment ONLY possible when used with FULL GOWNING in a Grade B environment
 - Multi-step airlocks required
 - HEPA certification
 - Construction
- Lower BSC costs due to:
 - Equipment
 - Qualification
- Allows for current operational baseline functionality and continuity:
 - Protocols
 - SoPs
 - Simple controls
- Higher lifecycle costs

New Closed Process-Driven Layout Design:

- Initial capital total installed cost (TIC) was 142% higher:
 - Equipment costs were 215% higher

- Facility costs were 45% lower
- Validation costs were 220% higher due to:
 - Isolator decontamination cycle validation
- Annual operating costs were 47% lower due to elimination of Grade B space
- Simplification of operations:
 - Facility flows
 - Gowning
 - Operator training
- Higher sterility assurance levels:
 - 10E6 vs. 10E3
- Lower risk of microbial contamination

Key Takeaways

This risk-driven exercise demonstrates that implementing a closed system can lead to lower facility costs by reducing area environmental classifications, annual operations costs, overall space footprints, and simplifying day-to-day operations. However, it also comes with challenges such as moving away from the traditional operational philosophy, adopting a new paradigm approach for certain manufacturing unit operations, enhancing employee skillsets, and changing risk mitigation approaches.

Nevertheless, the numbers make a strong case for using process closure as a manufacturing risk mitigation strategy.

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Jeff is a globally recognized SME in biomanufacturing facilities with over 30 years of experience in consulting and operational roles. He has authored more than 70 technical articles, published four industry reference books, and presented at more than 200 industry forums globally. A Certified Pharmaceutical Industry Professional, his projects have resulted in \$3B+ in total installed costs for biomanufacturing operations while leading the development of numerous industry guidance documents throughout his career.