Isolator Integration in Cell and Gene Therapy Manufacturing

A Framework for Equipment and Process Decision-Making

Cell and gene therapy (CGT) manufacturing has expanded rapidly in recent years, with the global CGT market valued at approximately USD 13.9 billion in 2024 and projected to exceed USD 100 billion by the early 2030s at compound annual growth rates exceeding 20% across multiple market analyses [1, 2]. This growth trajectory, combined with the commercial approval of more than eleven CAR-T cell therapy products globally as of early 2026 [3], has brought into sharp focus a facility design decision that planners, process engineers, and quality teams must address early and rigorously: which process steps and equipment should be integrated into an isolator, and which are better suited to a biological safety cabinet (BSC)?

This decision sits at the intersection of sterility assurance, operator safety, regulatory compliance, ergonomics, equipment compatibility, and economics. Made well, it underpins a robust Contamination Control Strategy (CCS) that can withstand regulatory expectation and support commercial-scale manufacturing. Made poorly, it creates costly remediation, scheduling bottlenecks, and potential patient safety risks.

This white paper provides a structured, multi-dimension decision framework for navigating this choice, grounded in current regulatory expectations, the unique biological characteristics of CGT processes, and practical operational considerations.

Scope and limitations: *This document addresses process and equipment decision-making for aseptic CGT manufacturing. It is not a substitute for facility-specific regulatory consultation, risk assessment, or engineering design. Regulatory expectations for ATMPs continue to evolve, and manufacturers should engage in qualified regulatory, quality, and engineering advisors for program-specific guidance.*

Introduction: Why CGT Demands a Different Approach

Traditional aseptic pharmaceutical manufacturing such as small molecules, monoclonal antibodies, and recombinant proteins has well-established norms for environmental control, accumulated over decades of regulatory precedent and industrial practice. Cell and gene therapies challenge these norms in fundamental ways that demand a distinctly different analytical framework.

The central challenge is biological complexity. Unlike conventional drug substances, CGT products are living or biologically active entities that cannot be terminally sterilized. Their quality attributes like viability, potency, phenotype, and genomic integrity can be irreversibly altered by thermal and mechanical stress, exogenous microbial contamination, or inappropriate environmental conditions at any stage of manufacture. Several characteristics distinguish CGT manufacturing from conventional aseptic processing:

- As living biological is used as starting materials, patient-derived cells (autologous) or donor-derived cells (allogeneic) are sensitive to environmental perturbation, temperature fluctuation, and handling stress throughout the manufacturing process.
- Autologous manufacturing eliminates the ability to pool, reprocess, or hold products while awaiting release testing. Each batch represents a single patient (patient-specific); a contamination event or process failure is, in principle, irreplaceable.

- Lentiviral and adeno-associated virus (AAV) vectors as the most widely used gene delivery systems in current clinical and commercial programs require simultaneous product protection (to maintain vector viability and titer) and operator/environmental containment (to prevent inadvertent occupational exposure or environmental release).
- Involves complex, multi-step processes. A representative autologous CAR-T manufacturing process encompasses leukapheresis material receipt, mononuclear cell selection, T-cell activation, viral transduction, cell expansion, harvest, washing, formulation, fill, and cryopreservation, each step with a distinct contamination risk profile and environmental control requirement.
- Autologous manufacturing creates scheduling and turnaround pressure that limits flexibility in environmental setup and decontamination cycle time with small batch size and high batch frequency.

These characteristics mean that a one-size-fits-all approach to environmental control is inappropriate. A nuanced, step-by-step assessment is required, one that begins from process characterization and works outward to facility design, rather than starting from facility convention and working inward.

Six Dimension Decision Framework

The decision of whether to integrate a process step or piece of equipment into an isolator versus operate it under a BSC should be systematically evaluated across the following six dimensions. Each dimension contributes to the overall risk profile; no single dimension is sufficient to determine the optimal approach in isolation.

Sterility Criticality

The primary question in any environmental control decision is: what is the consequence of a contamination event at this step, and is there a subsequent step capable of detecting or removing the contaminant?

Steps involving open manipulation of the final drug product, or open aseptic processing of intermediates that will not undergo subsequent bioburden reduction, carry the highest sterility risk and most strongly benefit from isolator-level control. Steps that are inherently closed or that involve non-sterile intermediates that will be subjected to further processing, such as viral transduction or cell expansion prior to washing, carry lower risk and may be appropriately conducted in a Grade B BSC environment with suitable procedural controls.

A practical risk stratification for environmental classification, consistent with Annex 1 CCS principles, is shown in Table 1.

Table 1. Risk-based environmental classification for CGT process steps.

Risk Level	Characteristics	Preferred Environment
Critical	Open aseptic manipulation of final drug product; no subsequent bioburden-reduction step	Isolator (strongly preferred)
High	Open manipulation of sterile intermediates; aseptic connections; semi-closed steps upstream of fill	Isolator or Grade B BSC with documented CCS justification
Medium	Closed system steps; reagent preparation; media addition to closed vessels	Grade B BSC or Grade C closed system
Low	Non-sterile upstream steps; non-aseptic material preparation	Grade C/D as appropriate

Adapted from EU GMP Annex 1 (2022)

Containment Direction

CGT manufacturing presents a dual-protection challenge that does not exist in conventional pharmaceutical manufacturing: the same unit operation may simultaneously require inward product protection (to maintain sterility) and outward containment (to protect operators and the environment from biohazardous material).

This challenge is most acute during viral vector handling. Replication-incompetent lentiviral and AAV vectors used in current CAR-T and gene therapy manufacturing are not classified as human pathogens, but occupational exposure risk assessments, informed by the vector's tropism, the intended dose, and the potential for recombination events, should be conducted by a biosafety officer on a program-specific basis. Where both inward and outward protection are required simultaneously, options include:

- Negative-pressure containment isolator which provides inward product protection (Grade A environment within the isolator) combined with outward operator protection (negative pressure relative to the surrounding room, with validated double-HEPA exhaust and cascade pressure zoning). This approach is technically complex to design and validate, as maintaining negative pressure while achieving Grade A aseptic conditions requires careful engineering of airflow and pressure differentials.
- Closed system processing within a BSC that relies on closed fluid paths (sterile-welded tubing, aseptic connectors, closed culture vessels) to provide product protection, while the BSC provides operator protection by directional airflow. The degree of process closure achievable, specifically the management of all potential open connection and disconnection events, must be rigorously assessed.

The choice between these approaches depends on the specific vector, its regulatory biosafety classification, the degree of process closure achievable with available technology, and the facility's overall biosafety framework. Neither approach is universally superior as both require documented risk assessment and validation.

Physical Integration Feasibility

Not all equipment can be practically or economically integrated into an isolator. A structured feasibility assessment should evaluate each candidate's instrument across three sub-dimensions:

Ergonomic and Operational Feasibility in Isolator-Based Processing

Glove port-based operation introduces both physical and cognitive constraints compared to open bench work. These constraints can affect operator performance, increase fatigue, and elevate the risk of procedural error, particularly during prolonged or complex manipulations. As such, ergonomic feasibility is a critical consideration in isolator integration decisions, alongside contamination control.

Key factors include:

Manipulation duration

- Extended glove port work typically beyond 30–45 minutes of continuous operation leads to arm and shoulder fatigue, reduced dexterity, and increased likelihood of error. Process steps requiring prolonged or complex operator handling may be better suited to a biological safety cabinet (BSC) from an operator's performance and consistency perspective.

Fine motor requirements

- Precision tasks such as recovering small cell pellets, performing secure aseptic connections in confined spaces, or reading instrument displays at indirect angles are inherently more difficult through gloves. These challenges should be evaluated early through process-specific simulation studies to identify high-risk manual steps.

Adaptive process flexibility

- Many CGT workflows, particularly in early clinical phases, require real-time adjustments (e.g., modifying media volumes based on interim cell counts). Such flexibility is more easily accommodated in open systems, whereas isolator-based processes typically rely on fixed, validated workflows.

Equipment fit and accessibility

- All instruments must fit within the isolator's working volume while maintaining sufficient clearance for operator access via glove ports. Controls, displays, and access points must be positioned on the operator-facing side to ensure usability. Poor accessibility can significantly impact both efficiency and error rates.

Isolator Geometry and Glove Port Design

- The number, positioning, diameter, and reach of glove ports as well as overall chamber height and depth directly influence ergonomic performance. Suboptimal geometry amplifies fatigue, reduces precision, and should be treated as a primary evaluation criterion during equipment selection.

Figure 1. Ergonomic trials

Best practice

Mock-up studies and simulated use trials with representative operators are strongly recommended to assess ergonomic feasibility prior to equipment procurement. These studies help identify operational constraints early and inform both process design and equipment configuration.

Mitigation measures

Even with optimal design, isolator-based processing requires robust operator training, routine simulated-use exercises, and ongoing glove integrity monitoring to maintain performance and reduce risk over time.

Utility and Connectivity Requirements

Instruments to be integrated into an isolator require electrical power, gas (CO_2, N_2, compressed air), data connectivity, and potentially fluid connections, all of which must be safely penetrated through the isolator wall with appropriate sealing and leak-testing provisions. Vibration-generating instruments may affect adjacent processes or analytical measurements. These interactions must be characterized and managed during design.

Maintenance and Consumable Access

The frequency and nature of maintenance, calibration, and consumable-change events must be assessed against the constraints of glove port access. Instruments requiring regular filter changes, sensor replacements, or mechanical adjustments that cannot be performed through gloves will require planned isolator integrity interruptions, each of which triggers a requalification event. Minimizing the frequency and burden of such events is an important design criterion.

Hydrogen Peroxide Compatibility

All equipment integrated into an isolator must withstand repeated hydrogen peroxide-based decontamination cycles. Hydrogen peroxide as the dominant decontamination agent for pharmaceutical isolators, capable of achieving 6-log reduction of biological indicators (Geobacillus stearothermophilus spores) is a powerful oxidizing agent with broad material reactivity.

The complete decon cycle, depending on the mechanism (nebulized, atomized or vaporized), encompassing preconditioning or priming, conditioning (injection and distribution), decontamination (dwell or hold), and aeration (purge to ≤1 ppm residual), creates a chemically harsh environment that must be characterized for each integrated instrument and material [17]. Key compatibility considerations include:

- Enclosures and structural materials like stainless steel 316, PTFE, borosilicate glass, and HDPE. Certain aluminum alloys, copper, zinc, and uncoated carbon steel are susceptible to corrosion and should not be used for isolator-interior components.
- Standard EPDM and neoprene degrade under repeated hydrogen peroxide exposure. PTFE and specifically formulated silicone elastomers are preferred for isolator seals.
- Standard LCD screens, capacitive touchscreens, and unprotected printed circuit boards are vulnerable to hydrogen peroxide oxidation. Instruments intended for isolator integration should have externalized or isolated electronics, shielded control connections, and VHP-resistant display technologies.

- Camera lenses, microscope objectives, fiber-optic probes, and sensor windows must be assessed for hydrogen peroxide compatibility; anti-reflection coatings on optical surfaces are frequently incompatible.

Instrument manufacturers should be required to provide documented hydrogen peroxide compatibility data before integration is finalized. The absence of such data is a disqualifying factor and is not remediable after procurement.

Process Openness and Contamination Risk

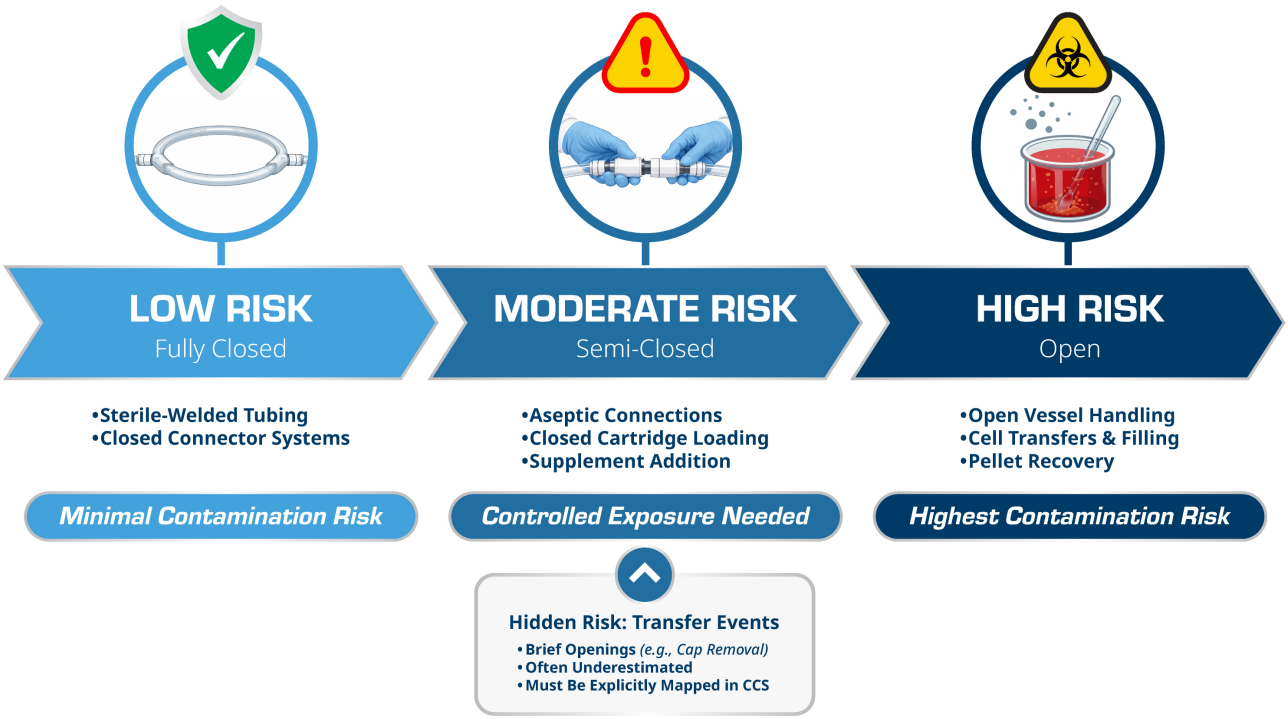


Figure 2. Process openness and its link to contamination risk

The degree to which a process involves open fluid handling is a critical driver of environmental control requirements and, by extension, isolator integration decisions. A systematic process-mapping exercise by characterizing each fluid handling event as fully closed, semi-closed (involving aseptic connection or disconnection), or open (involving exposure of fluid to the environment) is essential input to the CCS and integration decision.

Fully Closed Steps

Fluid transfers via sterile-welded tubing or closed connector systems that have been validated for the specific process conditions, fluid types, and operational parameters carry significantly reduced contamination risk when implemented and maintained under validated conditions. The case for isolator integration of fully closed steps is driven by regulatory defense-in-depth, failure mode mitigation, and CCS documentation requirements. Isolator integration provides a secondary containment barrier in the event of an unexpected connection failure and should not be dismissed solely on the basis that contamination risk is low under nominal operating conditions.

Semi-closed Steps

Connection and disconnection of aseptic connectors, loading of cartridge-based automated cell processing systems, and addition of supplements to culture vessels via aseptic transfer carry moderate contamination risk and benefit from enhanced environmental control. The classification of a given step as semi-closed rather than fully closed is contingent on the specific connector system, the validated procedure, and the way the connection or disconnection is performed. Steps that appear closed by virtue of the device used may revert to semi-closed or open classification if performed outside validated parameters or in a manner not covered by the connector's validation package.

Open Steps

Opening of culture vessels, transfer of cells between open containers, recovery of cell pellets, and open fill operations carry the highest contamination risk and strongly favor isolator integration. Transfer events including brief, apparently minor open steps such as removing a cap to add a reagent are frequently under characterized in early process mapping and must be explicitly assessed. Failure to capture all open events during process mapping represents a significant gap in CCS development and may introduce unmitigated contamination risk that is difficult to defend during regulatory review.

Economics: Total Cost of Ownership

Economic comparison between isolator and BSC-based approaches should be conducted at the total cost of ownership (TCO) level, not on capital cost alone. The cost structure of each approach is materially different, with the dominant differentiator at commercial scale being the background cleanroom grade required, Grade C/D for closed isolators versus Grade B for BSC-based aseptic processing.

Table 2. Comparative total cost of ownership: isolator versus Grade B BSC.

Cost Element	Isolator Approach	Grade B BSC Approach
Capital equipment	USD 100K–USD 1M+ per isolator (process complexity, scale and integration dependent)	USD 5K–USD 30K per BSC
IQ/OQ/PQ qualification	Higher (isolator qualification + integrated equipment validation)	Moderate
Background cleanroom grade required	Grade C or D (lower cost of gowning and facility cost)	Grade B (significantly higher HVAC and facility cost)
Decontamination cycle overhead	1–4 hours per cycle (scheduling constraint, load-dependent)	15–30 minutes per use preparation with manual disinfection
Ongoing monitoring & validation	Decontamination cycle requalification, chamber and glove integrity testing, particle/viable monitoring, airflow	Annual BSC certification, particle and viable monitoring
Consumables	H_2O_2, gloves, HEPA filters, seals	Disinfectants, HEPA filters
Maintenance complexity	Higher (integrated systems, pressure hold testing)	Lower

Cost ranges are directional estimates for planning purposes. Actual costs are highly site- and program-specific.

At commercial scale, facility capital and operating cost savings from a lower-grade background cleanroom can offset a substantial portion of the isolator capital premium, particularly where multiple isolators share a Grade C/D suite. On the early clinical scale, where facility investment is more modest and batch frequency is lower, BSC-based Grade B approaches may be more economical and operationally flexible.

Application to CAR-T Manufacturing: A Representative Process Map

Chimeric antigen receptor T-cell (CAR-T) therapy represents one of the most complex manufacturing challenges in modern biologics. Unlike conventional pharmaceutical products, CAR-T therapies are derived from a patient's own immune cells, requiring a manufacturing process that begins with leukapheresis (the collection and isolation of T-cells from peripheral blood) and ends with a cryopreserved, patient-specific dose returned for infusion. Between those two endpoints lies a sequence of highly sensitive biological manipulations: T-cell activation, viral vector-

mediated genetic transduction, expansion, harvest, formulation, and fill. Each step introduces distinct contamination risks, viral biosafety considerations, and sterility assurance challenges that must be addressed through a robust contamination control strategy (CCS) as defined under current Good Manufacturing Practice (cGMP) frameworks.

The complexity of CAR-T manufacturing is further compounded by the autologous nature of the product and the clinical urgency driving turnaround timelines. Because each batch is traceable to a single patient, a contamination event is not merely a product loss, it may represent an irreplaceable therapeutic opportunity. This reality places exceptional demands on environmental control decisions, including the selection and integration of isolator technology. The framework presented in Table 3 applies a structured, risk-based approach to categorizing representative CAR-T unit operations by process openness, sterility criticality, and viral vector exposure, translating these parameters into recommended environmental control strategies. All classifications are illustrative and must be confirmed through program-specific risk assessment and CCS documentation.

Figure 3. Framework application to representative autologous CAR-T manufacturing unit operations.

This figure is illustrative and process specific. Regulatory classifications and risk levels should be confirmed through program-specific risk assessment and CCS documentation.

Emerging Considerations

Fully Automated Closed Processing Platforms

A growing category of automated, closed-system cell processing platforms including systems designed to integrate selection, activation, transduction, expansion, harvest, and formulation within a single closed cartridge is fundamentally reshaping the isolator integration question. For these platforms, the decision shifts from "which individual steps require isolator integration" to "how to interface the closed platform with the isolator or cleanroom environment, and how to manage aseptic material transfer into and out of the platform."

The isolator remains relevant in this context as an environment for managing the connection and disconnection events at the platform's boundary, and for fill/finish operations on the platform's output. Manufacturers evaluating closed-platform technologies should assess the degree of process closure actually achieved (including all connection events and any open steps within the platform's workflow) and the regulatory acceptance basis for the environmental classification applied to platform operation.

CCS Documentation as a Living System

The Annex 1 CCS requirement is to create a documentation standard that CGT manufacturers must develop and maintain as processes evolve. Best practice is to develop the CCS as a living document, one that is explicitly linked to the process risk assessment, the facility design qualification, the monitoring program, and the change control system. Changes to the process (new step, new equipment, new supplier), the facility (HVAC modification, cleanroom reclassification), or the regulatory landscape (new guidance, inspection findings) should trigger a defined CCS review and update cycle.

Digital Integration and Data Integrity

As CGT manufacturing becomes more data-intensive with real-time cell count, metabolite, phenotype, and viability data informing adaptive process decisions, the challenge of integrating analytical instruments into isolators while maintaining 21 CFR Part 11 / Annex 11 data integrity compliance is growing in practical significance. Instrument selection and isolator design must explicitly address data connectivity (wired or wireless penetration through the isolator wall), audit trail integrity, electronic record management, and the physical routing and labelling of data cables. These requirements should be incorporated into the user requirement specification (URS) for both the isolator and any analytical instruments intended for integration.

Point-of-Care and Decentralized Manufacturing

Emerging point-of-care (POC) manufacturing models where CGT products are manufactured at or near the clinical site rather than in a centralized commercial facility, place new demands on isolator technology. POC isolators must be operable by clinical staff and must be maintained under hospital environment constraints, and must be compatible with small-scale, infrequent batch schedules. Modular, compact, and operationally simplified isolator designs are increasingly relevant to this segment. Regulatory frameworks for POC manufacturing, including hospital exemption pathways, remain in development and should be monitored closely.

Case Study Insight: Isolator-Based Point-of-Care Manufacturing as an Emerging CGT Model

A recent perspective on isolator-based point-of-care (POC) manufacturing highlights a fundamental shift in how cell and gene therapies may be produced and delivered [4]. The primary driver for this shift is the inherent limitation of centralized manufacturing for CGT products. Transportation between manufacturing sites and clinics introduces risks such as temperature excursions, delays, and handling variability, all of which can compromise the viability and biological activity of sensitive cell-based products. These challenges are particularly critical for autologous and short shelf-life therapies, where timely administration is essential for clinical efficacy.

Within this context, isolator-based systems are positioned as a key enabling technology for decentralized manufacturing. The study describes isolators as fully enclosed, GMP-compliant environments capable of supporting end-to-end processing, from cell isolation and expansion to formulation and administration, within a single controlled system. This closed configuration minimizes environmental exposure, reduces contamination risk, and enables consistent aseptic conditions independent of the surrounding facility classification.

A critical advantage highlighted is the ability of isolator systems to operate in lower-grade background environments (e.g., Grade C or D) while still maintaining ISO Class 5 conditions internally. This significantly reduces infrastructure requirements compared to traditional cleanroom-based manufacturing and makes deployment in hospital settings more feasible. At the same time, integration with automated decontamination (e.g., atomized/vaporized/nebulized hydrogen peroxide), real-time monitoring, and in-process quality control supports GMP compliance in decentralized settings.

Importantly, the paper reinforces that in CGT manufacturing, "the process is the product," meaning that consistency, sterility, and control must be embedded directly into the processing environment. In this regard, isolator-based POC platforms not only improve contamination control but also enable tighter integration of processing steps and quality control within a single system, reducing variability across batches.

However, the study also acknowledges key challenges associated with this model, including regulatory ambiguity across regions, the need for highly trained operators in clinical settings, and the complexity of maintaining consistent quality assurance across decentralized sites. Addressing these challenges will require standardized workflows, digitalized quality systems, and closer coordination between regulators, manufacturers, and healthcare institutions.

Overall, this case study illustrates that isolator integration is not only a tool for improving contamination control within a facility, but also a foundational enabler of new manufacturing paradigms in CGT. It reinforces the need to evaluate environmental control strategies not only at the unit operation level, but also in the broader context of manufacturing architecture, logistics, and patient-specific delivery models.

Recommendation

Based on the framework and analysis presented, the following recommendations are offered for CGT manufacturers evaluating isolator and BSC integration strategies:

- Develop a step-by-step contamination risk assessment that characterizes each unit operation across all decision dimensions before making integration decisions. Do not default to BSC-based approaches because they are familiar, or to isolator-based approaches because they appear to be regulatorily preferred, without completing this analysis.
- Every environmental classification choice should be documented, justified, and defensible to regulators before facility construction begins. The CCS should be developed in parallel with process development, not retrospectively.
- Engage equipment and instrument vendors early and require documented hydrogen peroxide compatibility data as a qualification criterion before procurement. Do not assume compatibility based on material type alone; test conditions (concentration, cycle count, temperature, relative humidity) must be specified and validated.
- Build a quantitative scheduling model that accounts for decontamination cycle time, instrument maintenance downtime, and isolator availability constraints before committing to an isolator-heavy design for autologous manufacturing. Isolator capacity may be the throughput-limiting factor at commercial scale.
- A BSC-based Grade B approach may be appropriate for early clinical phases, with a planned transition to isolator-based commercial manufacturing as the process matures. Build this transition into the development plan rather than treating clinical and commercial manufacturing as separate design exercises.
- Glove port ergonomics, operator training, simulated use studies, and glove integrity monitoring are significantly underinvested in many CGT facility designs. The human factors dimension of isolator operation is a material source of contamination and process variability risk.
- The isolator integration question will continue to evolve as automated closed CGT manufacturing platforms mature, gain regulatory acceptance, and potentially reduce or redefine the role of traditional isolator technology in certain process steps.

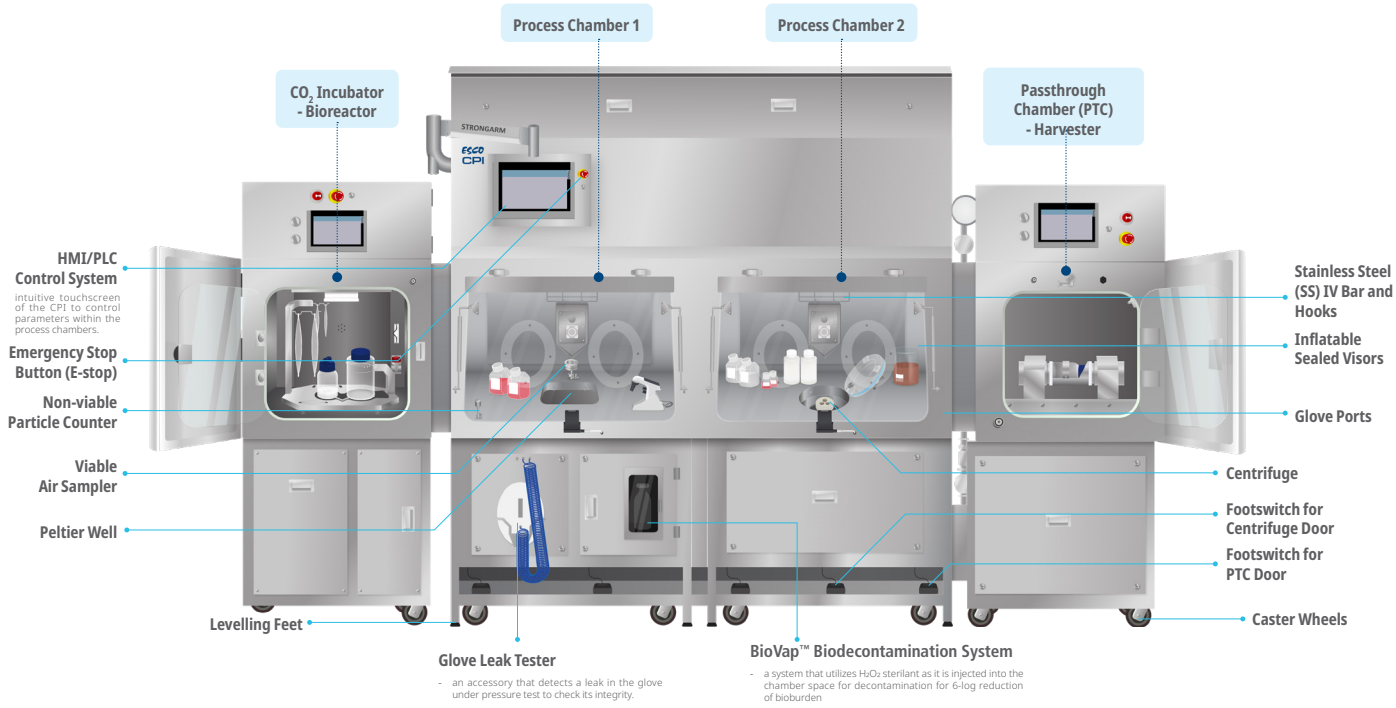
Case Example: Customizable Isolator Platforms for Integrated CGT Processing

While the preceding framework outlines how to evaluate integration strategies from a process and risk perspective, its practical value ultimately depends on how effectively these principles can be translated into real equipment configurations. In cell and gene therapy (CGT) manufacturing, this requires not only design thinking but also engineering platforms capable of accommodating diverse process needs without compromising environmental control.

Modern isolator systems have therefore evolved beyond static enclosures into configurable processing environments, where multiple unit operations and monitoring functions can be consolidated within a single, closed system. This approach supports a more coherent contamination control strategy by reducing the number of open handling steps and minimizing operator intervention.

One example of this implementation is the Esco Cell Processing Isolator (CPI), a platform designed to support both standardized and fully customized configurations for CGT manufacturing. The CPI enables integration of process-critical equipment and environmental monitoring tools within a unified isolator enclosure, supporting a continuous workflow from cell receipt through downstream processing and final handling.

Take A Closer Look!



Optional Equipment Integration:

- Benchtop Freeze Dryer
- Benchtop Shaker
- Biobank
- Bioreactor
- Biosafety Cabinet
- Centrifuge
- CO_2 Incubator (with Docking/Undocking Capability)
- Cooling/Heating Well
- Laminar Airflow Cabinet
- Microscope
- Sieve
- Rapid Transfer Port (RTP)
- Rapid Decontamination System
- Refrigerator/Freezer
- Sterile Liquid Transfer Port

Note: Customizations may apply based on end user's requirement. This pre-set is for general culture process only. Contact Esco Sales Representative for more information

A key design principle of the CPI platform is the ability to integrate multiple categories of process-critical and monitoring equipment within a single isolator enclosure. This reduces the number of material transfers between unit operations and supports a consistent Grade A environment across the process workflow. Integration can be achieved using equipment from Esco's own portfolio or from qualified third-party manufacturers, depending on process requirements.

Within this platform, integration extends beyond physical placement to include functional alignment of process steps, environmental monitoring, and data continuity. The following categories illustrate how key unit operations and monitoring tools can be embedded within a unified isolator system:

Equipment Category	Integration Capability and Process Role
CO_2 incubator / bioreactor docking	Direct docking and undocking of CO_2 incubator units (including Esco CelCulture®) or bioreactor systems. Maintains temperature, CO_2, and humidity control throughout cell expansion without external transfer.
Refrigerated centrifuge	Integrated refrigerated centrifuge for in-isolator cell pelleting, washing, and density gradient separation, eliminating the cell transfer step between centrifuge and isolator that represents a primary contamination risk in BSC-based processes.
Freezer / cold storage unit	Integrated cold case or Peltier-cooled storage compartment for reagent, media, and intermediate product temperature management within the isolator environment, reducing the number of material transfer events through the isolator wall.
Peltier temperature-controlled well	Precision temperature-controlled wells for sample holding at defined temperatures (4°C, 37°C) during in-process operations, supporting, for example, timed incubation steps without requiring removal from the isolator.

Equipment Category	Integration Capability and Process Role
Non-viable particle counters	Continuous environmental monitoring within the isolator process chamber, supporting Annex 1 requirements for real-time Grade A monitoring and providing immediate feedback. Integrated counters eliminate the need for operator intervention for routine sampling.
Active air sampler	Integrated active air sampling for viable monitoring within the Grade A zone, supporting Annex 1 CCS monitoring requirements with reduced operator interference and improved data integrity.
Automated cell counter	Integration of image-based or impedance-based automated cell counting instruments for in-process cell viability and density assessment without removing samples from the controlled environment. Supports data-driven process decisions within the isolator workflow.

Aseptic ATMP Processing Isolators

This integrated equipment ecosystem supports a continuous, closed processing strategy from cell receipt through formulation and fill, minimizing cumulative contamination risk associated with repeated boundary crossings.

Third-party equipment integration is supported as a customized configuration option. Engineering considerations include dimensional compatibility, utility requirements, and hydrogen peroxide resistance. Appropriate system design incorporates necessary penetrations, connections, and qualification strategies to ensure seamless integration. All configurations undergo Factory Acceptance Testing (FAT) and are supported by Installation Qualification (IQ) and Operational Qualification (OQ) documentation.

The final configuration including isolator type, level of equipment integration, glove port positioning, and pressure strategy should be defined based on specific process requirements, regulatory expectations, and facility constraints.

This example highlights that isolator integration is not a binary decision, but a spectrum of configurable design choices. The optimal approach should be guided by a structured evaluation of process risks, operational complexity, and contamination control objectives, as outlined in the earlier framework.

Conclusion

The decision of which process steps and equipment to integrate into an isolator, and which to operate under a BSC, is among the most consequential facility design choices a CGT manufacturer will make. It cannot be resolved by regulatory precedent alone, by analogy from conventional pharmaceutical manufacturing, or by a single-dimensional focus on sterility assurance. It requires a multidimensional assessment that considers contamination control, containment direction, physical integration feasibility and ergonomics, hydrogen peroxide compatibility, process openness, and economics, all anchored in a documented and defensible CCS.

Manufacturers who conduct this assessment rigorously at the beginning from process characterization and working outward to facility and equipment design will build manufacturing operations that are not only GMP-compliant but operationally robust, scalable, and suited to the unique demands of delivering living medicines to patients.

Reference

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Disclaimer

This white paper is intended for informational purposes and represents a general review and understanding of comparisons in aseptic barrier systems from different regulatory framework. It does not constitute regulatory guidance, engineering advice, or a product specification. Specific regulatory requirements, process characteristics, and facility constraints will influence the application of this framework to individual program. Manufacturers should engage qualified regulatory, engineering, and quality consultants in developing facility-specific contamination control strategies.

ESCO LIFESCIENCES

Esco Micro Pte. Ltd.
19 Changi South Street 1,
Singapore 486779
Tel: +65 65420833
Email: mail@vaccixcell.com

Esco Technologies, Inc.
2512 Metropolitan Drive, Suite 120 B
Feasterville- Trevose, PA 19053-6738
Tel: +1 215 322 2155
Email: eti.pharma@escolifesciences.com

Esco GB Ltd
Unit 2 R-evolution @ Gateway 36, Kestrel Way, Barnsley, S70 5SZ
Tel: +44 (0) 1226 360 799
Email: egb.info@escolifesciences.co

Esco Lifesciences Offices: Bangladesh | China | Denmark | Germany | Hong Kong | Indonesia | Italy | Lithuania | Malaysia | Myanmar | Philippines | Russia | Singapore | South Africa | South Korea | Taiwan | Thailand | UAE | UK | USA | Vietnam