CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

# Closed-system process optimization for CGT manufacturing and storage

Erik Woods, Jon Pileggi, and Sean Werner

The manufacture of cell and gene therapies (CGTs) faces persistent cost, quality, and contamination challenges from open, manual processing and uncontrolled storage. Transitioning to closed-system manufacturing and cryostorage has been shown to reduce batch failures threefold and manufacturing costs by up to 45%, while tripling throughput and maintaining cell viability. This article summarizes comparative data and case studies demonstrating how process closure supports scalable, contamination-resistant, and economically viable CGT production.

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## EVOLVING NEEDS IN CGT MANUFACTURING

Cell and gene therapies have transformed oncology and regenerative medicine but remain limited by manufacturing complexity and cost. Typical batch costs, ranging from approximately US $36,000 to over $100,000 per patient, reflect the manual manipulations required under high-grade cleanroom conditions and the infrastructure needed to maintain asepsis at small scale. These operational constraints drive high cost of goods sold (COGS) and limit scalability, highlighting the need for automated, closed systems that deliver reproducible quality at lower cost.

As the field matures, industrial scale initiatives have demonstrated that standardized donor recovery networks and bone marrow–derived manufacturing platforms can enable reproducible sourcing and large-scale processing of cellular materials. The next step is to extend this level of process control and contamination resistance across manufacturing and storage.

## TRANSITION FROM OPEN TO CLOSED PROCESSING: OPERATIONAL & ECONOMIC OUTCOMES

In traditional open processing, manual operations performed under Grade A unidirectional airflow within a Grade B background expose products to contamination risk and limit throughput. Closed systems maintain sealed fluid paths using sterile welds and aseptic connectors, enabling production in Grade C or D environments while achieving equivalent sterility assurance.

Closed processing reduces labor intensity and cleanroom requirements, supporting automated, reproducible operations

with minimal operator exposure. When modeled for identical 1,000 m² facilities, closed systems reduce total facility costs by ~50% and expand throughput capacity up to 15-fold. Downgrading from Grade B to C environments alone yields savings of roughly US $45,000 per suite, while lower HVAC and filtration demand further decrease capital expenditure.

Labor, which represents about 50% of total COGS in open systems, falls to 18–26% in automated closed configurations. Fixed labor distributed across higher batch volumes produces an overall 45% reduction in COGS, with batch-failure rates dropping from ~10% to ~3%. Collectively, these changes deliver simultaneous gains in cost efficiency, throughput, and reproducibility while reducing contamination-related deviation or batch loss (Figure 1).

## CASE STUDY: VALIDATION OF A FULLY ENCLOSED CAR-T MANUFACTURING PROCESS

A proof-of-concept study conducted at CTMC in collaboration with BioLife Solutions evaluated a fully closed CAR-T process using CellSeal® Connect vials for starting material containment and CellSeal CryoCases for final product storage. The workflow was benchmarked against a conventional biosafety cabinet process using cryovials under identical expansion and transduction conditions.

Across three donors, T-cell growth kinetics, transduction efficiency, and post-thaw viability were comparable between open and closed configurations. Viable cell counts expanded 33–40× from seed to day 7, maintaining >90% viability (Figure 2A). Transduction efficiencies ranged from 43 to 59% CAR⁺ (GFP⁺) viable cells, with total CAR⁺ cell yield equivalent between container types (Figure 2B). Post-thaw recovery exceeded 94% for all donors (Figure 2C).

The weldable PVC tubing of the CellSeal Connect vials remained intact under cryogenic conditions, although long-term liquid nitrogen stability requires further verification. Eliminating biosafety cabinet transfers simplified facility layout, reduced operator exposure, and maintained reproducibility across donors and runs.

These findings confirm that a fully enclosed manufacturing and storage workflow can maintain product comparability while significantly reducing manual handling and contamination risk.

## CONTAMINATION PREVENTION IN CRYOGENIC STORAGE

While open manufacturing steps often attract the most attention for contamination control, cryogenic storage presents an under-recognized risk. A documented hepatitis B virus transmission event demonstrated that liquid nitrogen can act as a contamination vector, transferring microbial and viral material between stored vials. Six patients were infected, and subsequent investigations identified microbial growth

### FIGURE 1

Comparative impact of open versus closed manufacturing on cost of goods, labor contribution, and batch-failure rate, based on identical facility and production assumptions.

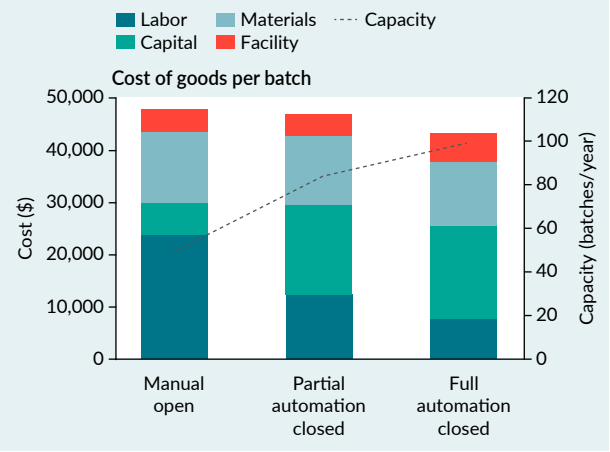
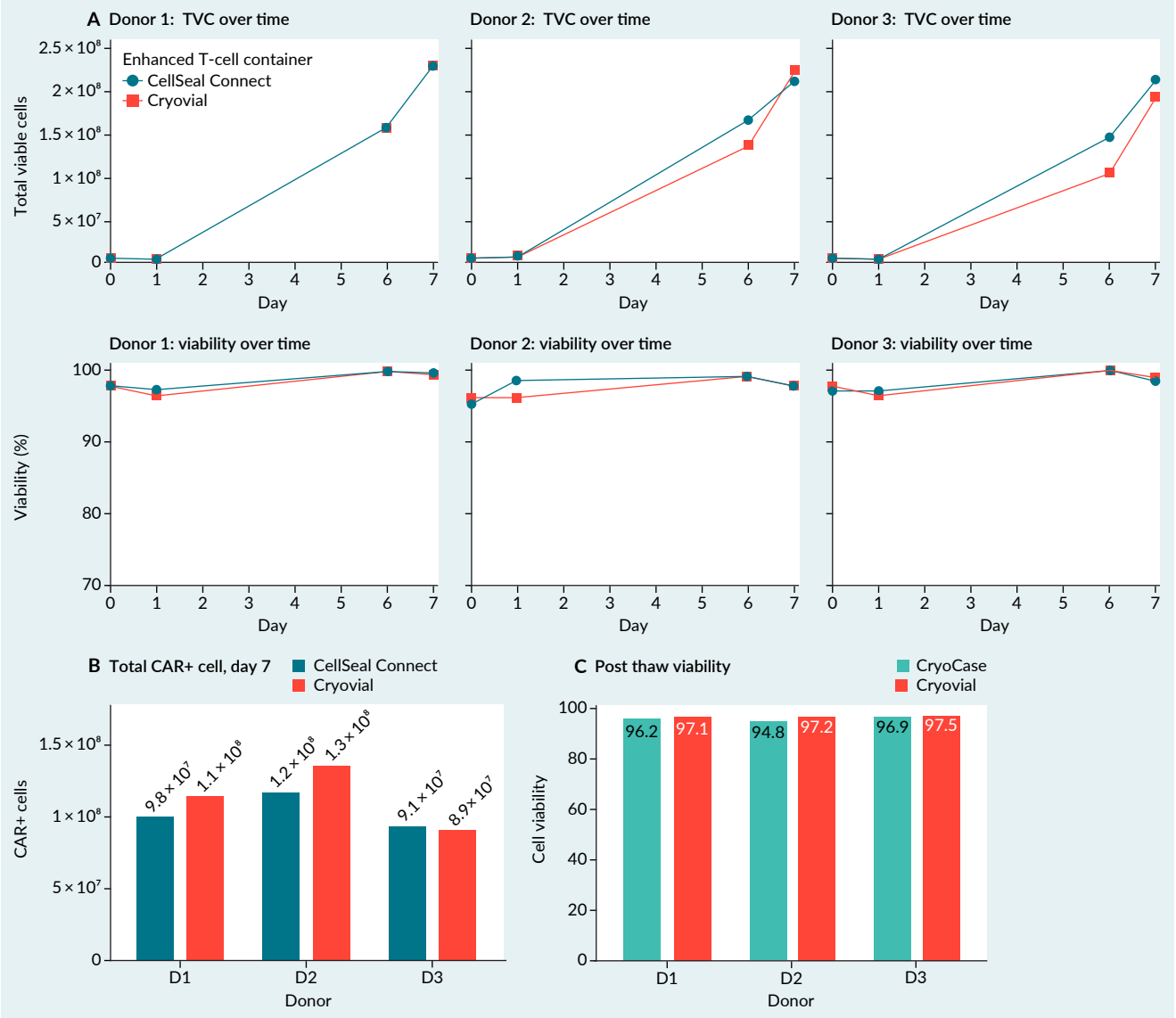



Figure from [1].

## FIGURE 2

Comparative outcomes of open and closed CAR-T manufacturing configurations.




**(A)** T-cell expansion and viability over 7 days for three donors using CellSeal Connect vials versus cryovials. **(B)** Total CAR⁺ cell yield at day 7 showing equivalent outcomes across container types. **(C)** Post-thaw viability of final drug product cells stored in CellSeal CryoCases compared with cryovials.

and human or viral DNA in multiple nitrogen tanks.

Hermetically sealed containers and vapor-phase storage eliminate direct contact between liquid nitrogen and stored products, reducing cross-contamination risk and protecting upstream manufacturing investments. Effective prevention also requires end-to-end validation of shipment and storage conditions to maintain container integrity and sterility. Closed thawing technologies, such as automated, water-free systems for dry thawing, further minimize operator exposure and post-thaw variability.

## CLOSED-SYSTEM SINGLE USE TECHNOLOGIES

Single use closed systems have become foundational to compliant CGT

manufacturing, providing validated sterile barriers that minimize environmental control requirements and contamination risk. In upstream workflows, closed bioreactors and bag systems maintain sterility through aseptic welds and verified container integrity. Downstream, disposable chromatography and filtration modules with sterile tube sets support closed transfer during formulation and fill operations.

These configurations sustain sterility without reliance on classified cleanroom environments and align with regulatory frameworks from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for Advanced Therapy Medicinal Product (ATMP) manufacturing, as well as inspection standards under the Pharmaceutical Inspection Co-operation Scheme and International Organization for Standardization. Collectively, these standards define expectations for sterility assurance, material qualification, and system validation within CGT manufacturing.

## SUMMARY

According to the case studies presented, closed-system integration delivered measurable operational and economic advantages. When applied to equivalent facility footprints, overall manufacturing costs decreased by up to 45%, labor requirements fell from roughly half of total COGS to ~20%, and batch-failure rates declined threefold. Throughput increased up to fifteenfold, reflecting improved utilization and automation.

Empirical data from the closed CAR-T workflow further demonstrates that process closure maintains cell quality and viability while enabling scalable, contamination-resistant manufacturing. Incorporating closed cryostorage completes an end-to-end containment strategy that reduces product loss and safeguards manufacturing investments. Together, these results define a practical, data-driven framework for compliant, scalable, and contamination-resistant CGT production.

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## AFFILIATIONS

**Erik Woods**, Executive Vice President and Chief Science Officer, Ossium Health, Indianapolis, IN, USA

**Jon Pileggi**, Associate Director of Process Development, Cell Therapy Manufacturing Center (CTMC), Houston, TX, USA

**Sean Werner**, Chief Technology Officer, BioLife Solutions, Bothell, WA, USA

## AUTHORSHIP & CONFLICT OF INTEREST

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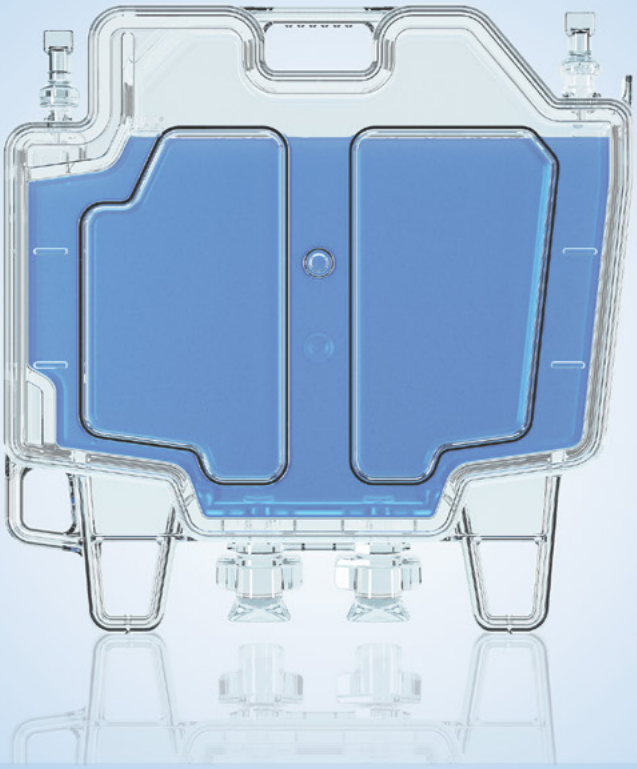

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