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# DESIGNING SCALABLE CELL THERAPY PROCESSES: A FRAMEWORK FOR SIMULATION, BOTTLENECK ANALYSIS, AND SCALE-UP EVALUATION

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## ABSTRACT

Cell therapy manufacturing presents unique challenges due to its high complexity, stringent regulatory requirements, and patient-specific variability. To enhance production efficiency and ensure robust scalability, simulation modeling emerges as an effective strategy to evaluate and refine manufacturing processes without disrupting ongoing operations. This study introduces a comprehensive framework that integrates discrete-event simulation (DES) to model critical cell therapy manufacturing stages—including inbound receipt and verification, QC sampling, material and kit-building, media fill process, manufacturing, cryopreservation, and outbound logistics. The framework not only captures resource constraints, batch scheduling, equipment utilization, and potential failure modes but also identifies the root causes of process bottlenecks. Further, it provides a roadmap for scenario design and scale-up analysis, enabling systematic sensitivity evaluations to quantify impacts on throughput, cost, and lead time. The findings underscore the framework's potential to support capacity planning, workforce allocation, and quality risk management, thereby accelerating commercial readiness and improving patient access.

## 1 BACKGROUND AND MOTIVATION

Cell and gene therapies hold transformative clinical promise, yet their production pipelines remain among the most intricate in biomanufacturing. Each autologous lot is effectively a custom product, produced under Good Manufacturing Practice (GMP) constraints, where any deviation can jeopardize patient safety and market approval. Traditional "trial-and-error" optimization in live suites is risky, slow, and expensive. Consequently, DES has emerged as a non-intrusive, data-driven way to reproduce time-dependent shop-floor dynamics, quantify uncertainty, and test "what-if" changes before implementation. However, published DES models usually focus on single unit operations (e.g., expansion or cryopreservation) or narrow tactical questions (e.g., one-off equipment sizing). A unified, end-to-end framework that (i) stitches together all critical stages, (ii) links GMP resources to patient-specific demand, and (iii) is explicitly built for scenario design and scale-up is still missing. This work fills that gap.

## 2 OBJECTIVE

We propose and illustrate a conceptual framework that guides practitioners through building and exploiting an integrated DES of an autologous cell-therapy facility. The framework is intended to: 1. Encode the full manufacturing value stream – inbound receipt and verification, material and kit-building, media fill process, manufacturing, QC sampling, cryopreservation, and outbound logistics. 2. Capture resource calendars (operators, biosafety cabinets, incubators, clean-room slots), batch-release logic, and failure/hold events. 3. Provide a structured "roadmap" for scenario generation (e.g., staggered schedules, overnight staffing, parallel bioreactors, multi-lot campaigns). 4. Deliver sensitivity analyses that translate model inputs into throughput, lead-time, and risk metrics, thereby informing capacity planning and investment decisions.

## 3 FRAMEWORK ARCHITECTURE

The proposed framework is organized into four concentric layers:

- Process definition layer: Standardized templates specify each unit operation's precedence relations, duration distributions, material requirements, and quality gates.
- Resource layer: Captures capacity units, shift patterns and breaks, cross-coverage rules, gowning time, as well as maintenance and cleaning cycles.
- Control-policy layer: Defines batch arrival timing and weekly distribution, batch-start and preparation triggers, and queue disciplines.
- Scenario and analytics layer: Provides scenario modeling with embedded dashboards that compute key performance indicators (KPIs) such as equipment utilization, queue times, and cumulative work-in-process.

The framework is software-agnostic: while the pilot study is implemented in FlexSim®, the meta-structure can be ported to SIMIO®, AnyLogic®, or open-source SimPy.

## 4 RESULTS AND DISCUSSION

This study presents a two-phase framework for evaluating and improving throughput in cell-therapy facilities. Phase 1 establishes a validated baseline by integrating SME workshop inputs and SOPs into a discrete-event simulation. The model captures interactions across warehouses, gowning, cleanrooms, QC/QA, manufacturing, and logistics, identifying bottlenecks and time-coupled delays linked to task allocation, shift boundaries, and shared assets. Phase 2 scales resources through a design-of-experiments layer and global sensitivity analysis, testing equipment capacity, staffing strategies (shifts, contingencies), and layout adjustments. Scenario stress-tests assess robustness to demand surges, staff outages, and planned shutdowns, while optional simulation-optimization highlights high-leverage operating rules. Results show that maintaining balanced ratios of resources and staffing during scale-up—and accounting for interdependencies such as coordinated scheduling, warehouse, and gowning logistics—often delivers larger, more reliable gains than resource additions alone. Cross-training and modest shift refinements further smooth peak loads without compromising compliance. Although designed for both autologous and allogeneic modalities, the framework generalizes to patient-tailored manufacturing where variability and shared resources dominate.