A Decentralized and Integrated Manufacturing System for the Rapid and Cost-Effective Production of Cell Therapy Drug Products

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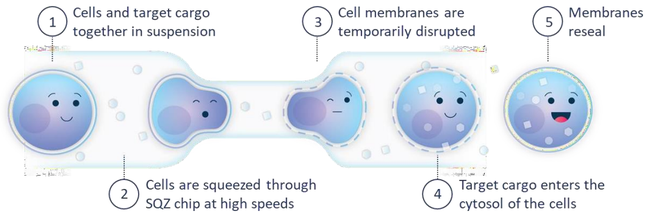
Background

The cell and gene therapy space continues to expand as new technologies and advancements promote the development of a widening array of novel therapies. Despite the growth in this industry, the manufacturing processes and unit operations used to produce clinical batch sizes have remained fairly unchanged. Cell therapies are manufactured in clean rooms with multiple open manipulations, require significant number of trained operators, and are performed at a centralized manufacturing site. SQZ Biotechnologies has developed a fully closed automated system for manufacturing cell therapies that integrates cell isolation, cell washing, cell delivery and bag filling. This system processes subject material within a fully closed, single use sterile disposable tubing set. The customized tubing set has been optimized specifically for aseptic processing and product yield. This totally enclosed manufacturing system is portable and has the potential to be operated outside of a clean room. This could allow the manufacturing to be decentralized and located at or near the point of care which could boost production capacity and reduce chain of custody and logistics issues. The automation of the system is designed to be fully 21 CFR Part 11 compliant which aids in eliminating failure modes, further removing operator introduced variability, and capturing more processing data to aid in process development. The first-generation prototype is completing comparability testing. The results of these studies and the conduct of numerous user studies and risk analyses have been incorporated into the design of a second-generation prototype. The final implementation of this system for cell therapy manufacturing is expected to yield a reduction in manufacturing cost and processing times while improving process reproducibility and final product yield.

Proprietary Cell Squeeze® Technology Enables Rapid Development of Various Cell Therapy Drugs



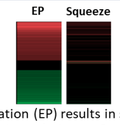
Applicable to diverse cell types

Immune Cells
RBCs
HSC/iPSCs

Robust across material classes

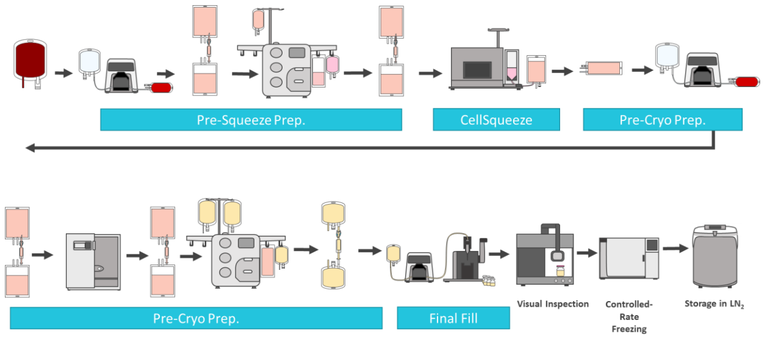
Proteins and peptides
Gene editing complexes
Nanomaterials
Nucleic Acids
Small molecules

Preservation of cell function



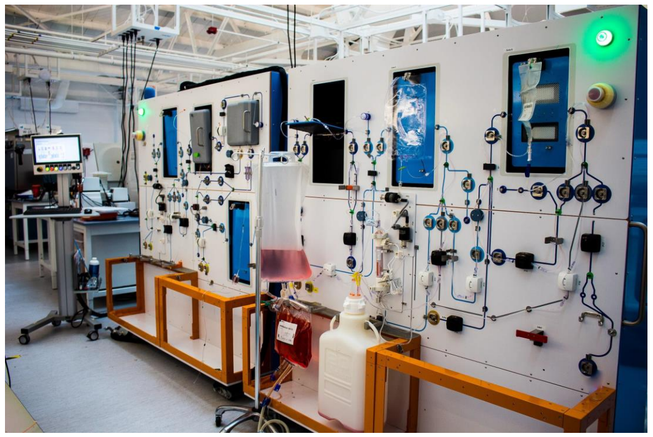
Electroporation (EP) results in substantial gene misregulation vs. Squeezing

Current SQZ® Manufacturing Workflow for Red Blood Cell Based Activating Antigen Carriers (AAC)



Patient whole blood is drawn in a hospital setting and shipped under controlled conditions to an ISO-7 clean room suite located at a centralized manufacturing facility. The manufacturing process requires multiple manual interventions for in-process checks, cell counts, sterile connections, and sterile disconnections. The entirety of the manufacturing process, minus the vial filling, is performed inside the closed, sterile tubing set. Throughout the manufacturing process, a paper batch record accompanies the in-process material where all manipulations are tracked, signed, and witnessed by trained operators inside the clean room suite.

1st Generation Point-of-Care Manufacturing System



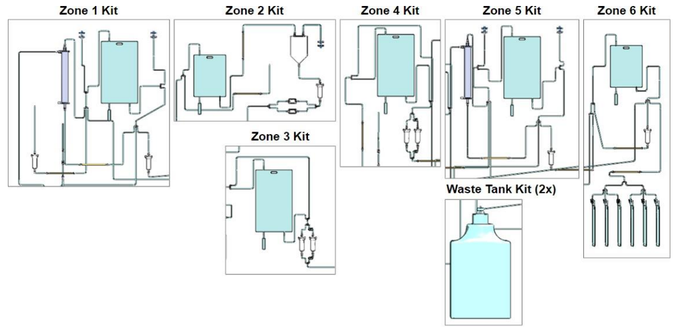
The 1st Generation Point-of-Care Manufacturing System (POC) has been designed to reduce operator involvement from the current manufacturing process while also providing improvements in various processing metrics. The manufacturing processes developed at SQZ Biotechnologies for PBMCs and RBCs share many similarities and thus, the POC system is designed to accommodate a wide range of potential processes spanning different cell types, delivery materials, and drug product profiles. Several key design improvements and additions to the system are listed below:

Point-of-Care Manufacturing System Has Been Designed to Improve Upon the Current Manufacturing Process

- **Operator Training → Automation:** Sensors and monitors in addition to automated fluid movement ensure processes are controlled and reproducible. Pre-defined process recipes reduce operator involvement.
- **Manual Manipulations → Automation:** Automated fluid movement inside a single fully disposable tubing set eliminates many processing steps. Multiple unit operations implemented on a single system.
- **Processing Time → System Customization and Automation:** A fully closed tubing set that can be pre-installed on the system eliminates many setup steps downstream in the process. Tubing sets designed for the needs of specific processes and batch sizes allows for enhanced processing time control. Pre-set process recipes can be launched, reducing turnover time between batches.
- **Paper Batch Record → Electronic Data Capture:** Data printout can be supplemented with a paper batch record to facilitate efficient execution of data transfer and sign-off
- **Manufacturing Overhead → Fully Closed Processing:** Fully closed tubing set reduces burden on environmental monitoring and controls. Automated recipes reduce the number of operators required to complete a clinical batch. System can be split into two segments and are installed with locking casters to reduce equipment turnover time and allow for simpler transport
- **Multiple Disposable SKU's → Single Disposable:** Gamma sterilized family of single use disposables are installed onto the system and sterile-welded. Disposable layout has been designed to allow customization for multiple manufacturing processes

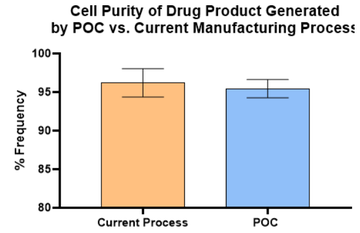
Singe-Use Disposable Tubing Set

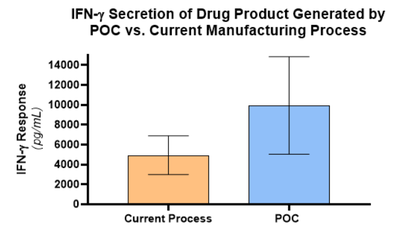
The single-use disposable tubing set is comprised of six unique gamma sterilized tubing subsets that are sterile-welded together at system setup. The POC system is marked with a routing diagram and contains visual cues to guide users during kit installation. The system performs a pressure integrity test on each tubing set individually and the fully welded tubing set. Following the pressure integrity test, a buffer prime is conducted through each zone of the fully assembled kit.

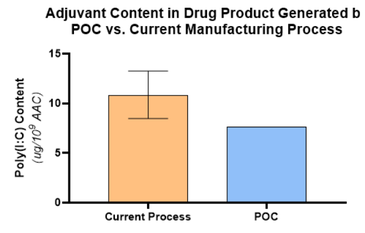


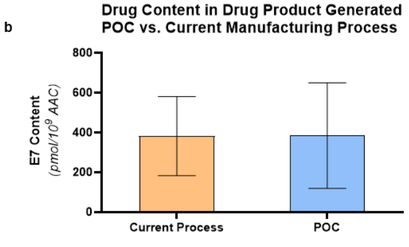
1st Generation POC System Produces Comparable Drug Product with Improved Process Efficiency

To evaluate the suitability of the first-generation manufacturing system that captures the full end-to-end drug product manufacturing process, the red blood cell based AAC-HPV drug product was produced on the POC system. Several drug product critical quality attributes, as well as key process performance indicators, were compared to historical clinical batches produced on the standard manufacturing process.









Resource	Current Process	POC System
# Operators	12	2
Required Person-Hours	150 hours	15 hours
Unique SKUs	>25	6
Dose Yield	9	10
Average Processing Time	12 hours 45 minutes	5 hours 45 minutes

2nd Generation Point-of-Care Manufacturing System Vision

The 1st Generation POC system was intended to be a learning tool to evaluate whether an integrated manufacturing system can generate quality drug product while alleviating some manufacturing overhead. After documented system evaluations and design improvements, the 2nd Generation Point-of-Care is being developed for use in a clinical manufacturing setting to produce SQZ Biotechnologies' cell therapy products. The first implementation is anticipated for the red blood cell derived celiac disease product candidate.

- Reduced number of functional zones
- Able to install additional functions
- Improved portability
- Electronic batch records
- Virtual monitoring of live processes
- Additional automated controls
- Reduced number of disposables
- Electronics signatures
- Full 21 CFR Part 11 compliant software
- Improved safety features
- Simplified disposables
- Built-in calibration functions

The vision of this manufacturing system is to enable reliable, cost-effective, and rapid production of novel cell therapies. The POC system is designed to reduce in-house development time and improve process efficiency. Building additional manufacturing systems could allow for efficient ramp up at multiple manufacturing sites, and possibly enable drug production to occur at the point of care (i.e., hospital). SQZ Biotechnologies intends to implement this manufacturing system in early 2023 for the development and production of an RBC based therapy targeting Celiac Disease (Raposo CJ et al. (2022) Engineered RBCs Encapsulating Antigen Induce Multi-Modal Antigen-Specific Tolerance and Protect Against Type 1 Diabetes. Front. Immunol. 13:869669).