Manufacturing, GMP, and OEM Integration

Title: *Integrated System and Method for Feedback-Controlled Cytokine Delivery in GMP-Compliant Immune Cell Manufacturing and OEM-Compatible Bioreactor Environments*

Claim 1 (Independent – Method of Manufacture)

1. A method of manufacturing an immune cell therapy product in a GMP-compliant bioreactor system, comprising:

(a) introducing immune cells into a closed, sterile, single-use culture chamber;

(b) supplying a cytokine-conditioned medium comprising at least one cytokine selected from IL-2, IL-7, IL-15, IL-21, IL-12, IFN-γ, and GM-CSF;

(c) sampling the culture supernatant continuously or at defined intervals using an integrated cytokine sensor module;

(d) detecting immune phenotype markers including CD25, PD-1, CD127, CD45RA, CD45RO, or CCR7 via inline or sampled analysis;

(e) adjusting the concentration, timing, or identity of cytokines delivered based on predefined immune condition logic executed by a software control unit; and

(f) releasing the batch only upon confirmation of an immune profile consistent with clinical-grade infusion criteria, including:

- viability consistent with accepted therapeutic standards,
- predominance of central or stem-like memory markers including CD45RO+ and CCR7+, and
- expression levels of exhaustion-associated markers including PD-1, TIM-3, or LAG-3 below thresholds defined in validated GMP protocols.

Claim 2 (Independent – Bioreactor Automation System)

2. A feedback-controlled bioreactor automation system for immune cell expansion, comprising:

(a) a culture vessel with single-use tubing sets and sterile weld ports;

(b) microfluidic or inline sensors configured to detect cytokine concentrations including IL-2 and IL-15;

(c) phenotype analysis modules for detecting CD25, CD127, PD-1, or CD45RA;

(d) a programmable logic controller configured to: – receive and analyze sensor and phenotype data,
– determine optimal cytokine dosing based on predefined rules or adaptive models, and
– actuate dosing pumps accordingly;

(e) a batch execution module configured to log cytokine dosing events, phenotype profiles, and viability metrics in accordance with 21 CFR Part 11 compliance.

Dependent Claims

3. The method of claim 1, wherein the cytokine dosing logic transitions from IL-2 to IL-15 or IL-21 when memory phenotypes are detected in >25% of the population.
4. The method of claim 1, wherein the release criteria are validated via pre-established flow cytometry gating strategies.
5. The system of claim 2, wherein phenotype detection is integrated with a sterile side channel connected to an automated cytometer.
6. The system of claim 2, wherein the programmable logic includes override rules based on pH, lactate, or oxygen consumption thresholds.
7. The system of claim 2, wherein the dosing system includes a safety lockout if cytokine accumulation exceeds a defined threshold or exhaustion markers persist beyond three consecutive sampling intervals.

Claim 3 (Independent – Sterile Tubing System Integration)

1. A sterile fluidics architecture for immune cell expansion in a GMP-compliant bioreactor, comprising:

(a) a single-use tubing system comprising: at least one cytokine infusion line, a supernatant sampling loop, an inline sterile filter, and sterile weldable ports;

(b) a plurality of cytokine reservoirs coupled to the tubing system via programmable peristaltic or syringe pumps;

(c) at least one sampling port configured for inline flow cytometry or biosensor interfacing;

(d) a fluid routing control module configured to direct flow based on sensor input or pre-programmed cytokine schedules;

(e) a disposable cassette housing the entire fluidic loop, configured for barcode validation and automated QC lockout.

Claim 4 (Independent – Batch Execution and GMP Compliance Engine)

2. A batch execution and compliance system for adaptive immune cell therapy manufacturing, comprising:

(a) a digital batch record platform configured to receive cytokine infusion logs, phenotype profiles, and metabolic sensor data;

(b) logic-based event tracking rules that generate deviation alerts upon exceeding predefined immune or metabolic thresholds;

(c) a batch lockout feature that prevents product release unless viability, exhaustion marker expression, and memory phenotype consistency meet validated clinical SOP parameters;

(d) 21 CFR Part 11–compliant signature and logging interface for release authorization;

(e) an audit-ready export feature for FDA or EMA regulatory submission.

Claim 5 (Independent – Sensor Integration Protocol)

3. A method for integrating cytokine concentration sensors into an immune cell bioreactor system, comprising:

(a) positioning one or more cytokine sensors inline with the culture medium recirculation pathway;

(b) calibrating each sensor using cytokine-specific validation curves prior to infusion initiation;

(c) capturing and transmitting sensor data to a programmable logic controller configured for real-time cytokine modulation;

(d) maintaining cytokine concentrations within predefined therapeutic windows using feedback-controlled infusion;

(e) triggering infusion pauses or dilution events if noise thresholds, drift rates, or biological consumption variances exceed system tolerance margins.

Claim 6 (Independent – Preloaded Cytokine Cartridge System)

4. A single-use cytokine delivery cartridge for adaptive immune expansion, comprising:

(a) a sterile-sealed housing containing at least three cytokine reservoirs selected from IL-2, IL-7, IL-15, IL-21, IL-12, or IFN-γ;

(b) a luer-lock or quick-connect outlet port compatible with GMP tubing sets;

(c) a machine-readable label encoding dosing schedules, cytokine concentrations, and lot numbers;

(d) a tamper-evident closure and integrated RFID tag for real-time authentication by the infusion controller;

(e) an internal safety baffle preventing backflow or air intrusion into the cytokine loop.

Claim 7 (Dependent – Batch Release Logic with Redundant Safety)

5. The system of claim 2, wherein the batch execution module includes a dual-layer safety system comprising: (i) a software-based viability and phenotype check, and (ii) a manual operator confirmation, both required to release product.

Claim 8 (Dependent – Sensor Redundancy Protocol)

6. The system of claim 3, further comprising a backup sensor switching protocol that enables alternate data acquisition when a primary cytokine sensor fails validation or calibration.

Claim 9 (Dependent – AI-Assisted Dosing Logic)

7. The batch execution system of claim 2, wherein cytokine modulation is governed by a machine learning algorithm trained on historical donor response data, phenotype transition dynamics, and cytokine consumption kinetics.

Claim 10 (Dependent – OEM Bioreactor Interface Specification)

8. The system of claim 1, further comprising an OEM interface module configured to integrate with third-party bioreactor platforms via USB, CAN bus, or cloud API for coordinated batch processing.

Claim 11 (Dependent – ML-Guided Cytokine Modulation)

11. The system of claim 2, wherein cytokine modulation is governed by a machine learning algorithm trained on historical donor response data, phenotype transition dynamics, and cytokine consumption kinetics.

Claim 12 (Dependent – Batch Learning Retraining Engine)

12. The system of claim 11, further comprising a retraining module that continuously updates cytokine dosing logic based on batch-level phenotypic outcomes, immune exhaustion markers, and cytokine consumption profiles.

Claim 13 (Independent – Cloud-Connected GMP Execution Platform)

13. A cloud-connected execution control system comprising: (a) remote access to batch execution logs; (b) real-time deviation alert streaming; (c) synchronized GMP protocol deployment across multiple manufacturing sites; and (d) supervisor override and review logging via encrypted interface.

Claim 14 (Independent – Transcriptomic-Driven Cytokine Scheduling)

14. A method for configuring cytokine dosing based on pre-infusion biomarkers, comprising: (a) obtaining transcriptomic, proteomic, or surface marker data from the patient or donor; (b) computing expected cytokine requirements using an immune activation prediction model; (c) configuring initial cytokine concentrations within the bioreactor software interface; and (d) updating cytokine delivery based on real-time immune phenotype tracking.

Claim 15 (Independent – Lyophilized Cytokine Cartridge System)

15. A single-use, lyophilized cytokine cartridge system comprising: (a) dry-state cytokine reservoirs containing IL-2, IL-7, IL-15, IL-21, IL-12, or IFN-γ; (b) an RFID-enabled housing containing lot metadata, dosing profile, and expiration date; (c) a sterile weld interface compatible with GMP bioreactor tubing; (d) a self-reconstitution buffer chamber for immediate hydration upon activation.

Claim 16 (Independent – Lysate Composition Personalization Method)

16. A method for customizing tumor lysate compositions used in ex vivo immune education, comprising: (a) profiling tumor cells using proteomics or transcriptomics to identify high-yield neoantigens; (b) preparing lysate using protocols that preserve intracellular and membrane-associated antigen profiles; (c) incubating immune cells with lysate in a cytokine-conditioned medium; (d) measuring CD69, CD25, and granzyme B as indicators of successful immune education; and (e) adjusting lysate composition and dosing based on immune response outputs.

Claim 17 (Dependent – Lysate Extraction Techniques)

17. The method of claim 16, wherein lysate is generated via techniques selected from heat lysis, detergent extraction, freeze-thaw cycles, or autophagic vesicle harvesting to optimize antigen exposure.