Manufacturing of CAR-T cells using in-house vectors and the CliniMACS Prodigy

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ABSTRACT

Objectives: This article provides a practical, regulatory-focused guide for the clinical-grade manufacturing of autologous CAR-T cells using in-house lentiviral vectors and the CliniMACS Prodigy system. **Methods:** A narrative review and technical synthesis of the scientific literature, institutional manufacturing workflows, platform-specific protocols, and Brazilian and international regulatory documents were performed. **Results:** The detailed process includes leukapheresis, receipt of the material, chain-of-identity and chain-of-custody controls, and initial testing of the starting material, including total nucleated cell count, CD3+ cell content, viability, and microbiological screening. The Prodigy system utilizes automated modules for magnetic T-cell enrichment, CD3/CD28 activation, lentiviral transduction, cell expansion, harvesting, formulation, and cryopreservation. Operational conduct can affect reproducibility, starting material quality, transduction efficiency, and the cell culture process. Final product release is conditional on comprehensive quality control, and coordination among the laboratories is essential. Accordingly, quality assurance procedures, deviation and corrective and preventive action management, process validation, and traceability constitute essential components in a manufacturing center. **Conclusion**: Integrating manufacturing and quality procedures within a structured workflow facilitates platform standardization and automation, hence promoting consistent CAR-T-cell production.

Keywords: CAR-T; In-house vectors; CliniMACS Prodigy; Quality control.

INTRODUCTION

Chimeric antigen receptor T cells (CAR-T cells) therapy has become a central innovation in modern immuno-oncology, with expanding indications in hematological malignancies and the establishment of manufacturing centers worldwide.[1,2] Manufacturing CAR-T cells requires a series of complex, carefully coordinated, and time-sensitive steps involving apheresis, cell processing, quality control (QC) laboratories, and clinical teams.[3] While the manufacturing of CAR-T cells differs from traditional hematopoietic stem cell transplantation processing, it naturally corresponds to centers experienced in cellular therapies, cryopreservation, traceability, and product-release procedures.

Manufacturing centers have faced challenges in integrating CAR-T-cell manufacturing into reliable clinical processes, particularly when using in-house lentiviral vectors.[4,5] This process requires integrated design, rigorous quality testing, and extensive documentation to achieve regulatory approval. Automated closed systems such as the CliniMACS Prodigy can mitigate these challenges by reducing manual handling, standardizing procedures, and enhancing traceability.

Viral vectors are addressed in this chapter strictly as input materials, not as a description of the vector manufacturing process itself. In-house vectors may vary in design but are commonly based on second- or third-generation lentiviral systems, which have been used for clinical-grade gene transfer because of their safety features, reduced risk, and suitability for stable transgene expression.[3,6] Regardless of the supplier, lentiviral vectors must undergo predefined QC testing, including assessments of functional titer, sterility, endotoxin, mycoplasma, and other quality parameters.[6] The supplier may provide these results to ensure traceability throughout the process and to obtain approvals from regulatory agencies during clinical trials and product registration.[7]

Regulatory rules relevant to CAR-T manufacturing in Brazil include Agência Nacional de Vigilância Sanitária (Anvisa) Resolution No. 505/2021 and No. 506/2021 for advanced therapy products, Resolution No. 836/2021 for good manufacturing practices (GMP), and institutional biosafety requirements.[8-11] International guidelines, such as the U.S. Food and Drug Administration Chemistry, Manufacturing, and Control guidance for gene-modified cellular therapies, and the Foundation for the Accreditation of Cellular Therapy–Joint Accreditation Committee International Society for Cell & Gene Therapy–Europe & European Society for Blood and Marrow Transplantation Standards further support the harmonization of best practices.

Therefore, this article is intended to provide a practical technical workflow for the clinical-grade manufacturing of autologous CAR-T cells using in-house lentiviral vectors and the CliniMACS Prodigy platform. Emphasis was placed on every detail of manufacturing, QC, and real-world implementation challenges in academic or resource-diverse cellular therapy centers.

Starting materials and acceptance criteria

Leukapheresis collection

The manufacturing of CAR-T cells begins with the collection of peripheral blood mononuclear cells via leukapheresis. This process requires meticulous coordination between the clinical team and laboratories to confirm adequate lymphocyte counts, patient stability, and sufficient clearance from prior exposure to cytotoxic, lymphotoxic, or immunosuppressive agents.[12] In parallel, the quality of the leukapheresis product is a critical determinant of manufacturing outcomes, as factors such as lymphopenia, elevated tumor burden, recent chemotherapy, ongoing infections, corticosteroid exposure, and other factors can affect CAR-T cell manufacturing.

Leukapheresis is typically performed with continuous-flow cell separators under closed-system conditions, with anticoagulants such as acid citrate dextrose solution A. The processed volume usually ranges from 1 to 3 total blood volumes, with adjustments based on patient weight, peripheral blood counts, vascular access, and institutional protocols.[13]

In clinical practice, apheresis collection may need to be individualized, particularly for heavily pretreated patients, pediatric patients, or those with cytopenias. A risk-based assessment of the suitability of the collected material for manufacturing should supplement predefined acceptance criteria.[14]

Transport and receipt

Leukapheresis material must be transported directly to the manufacturing center or stored under appropriate temperature conditions. This process must be regulated by Anvisa's resolutions and by well-structured, documented temperature conditions to maintain cell viability and product quality. According to Brazilian resolutions,[8,15] the collected material should be stored at 2–8 °C, with transport maintained at 2–24 °C.

Temperature monitoring during transport is essential, and the manufacturing center must verify container integrity, labeling, transport duration, temperature records, and documentation. Also, apheresis units could be cryopreserved at or below -150 °C for long-term storage before CAR-T cell manufacturing or even for transport to other manufacturing centers.

Upon arrival, the apheresis product is checked for identity, integrity, and label consistency. Deviations should be documented and evaluated by quality assurance (QA) before acceptance for manufacturing.

Acceptance testing

The starting material is quickly evaluated before manufacturing.[16] Standard testing commonly involves measuring total nucleated cell count, CD3+ T-cell count, other lymphocyte markers, cell viability, and sterility. Additional characterization may include differential cell counts to detect other contaminating cell types (granulocytes or monocytes). Infectious disease tests must be performed in compliance with local regulations, institutional policies, and clinical trial requirements. It is evident from many publications that serology or nucleic acid tests for infectious diseases are primarily based on institutional clinical protocols.

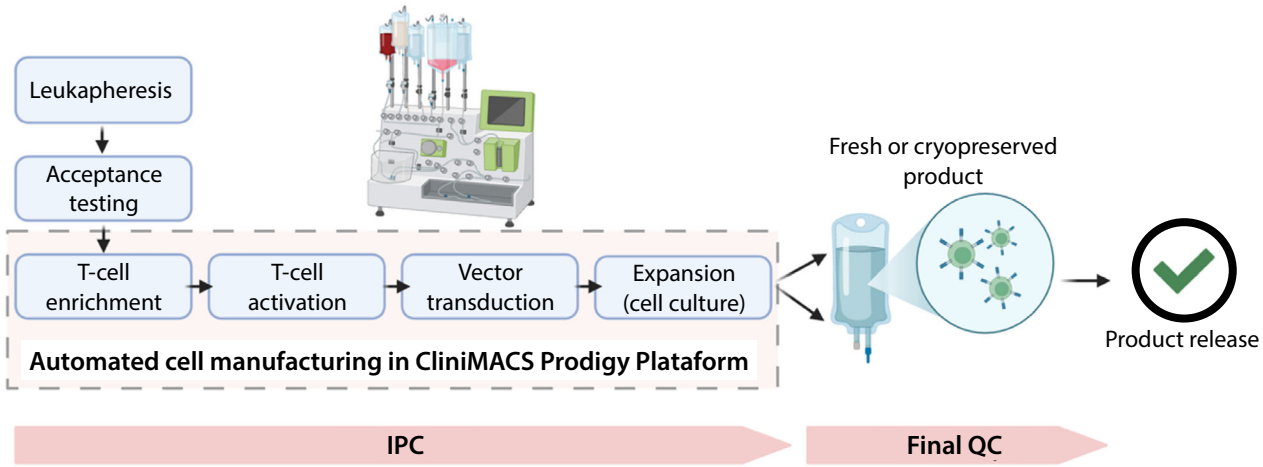
Acceptance criteria for starting materials should be well established to define minimum requirements and ensure a successful manufacturing process. Since CAR-T-cell products are autologous and frequently derived from heavily pretreated patients, borderline starting material may still be processed if a documented risk assessment is available. In these instances, any potential effects of deviations on expansion kinetics, final cell dose, transduction efficiency, release testing, and clinical scheduling must be communicated among the manufacturing, quality, and clinical teams.

Chain-of-identity and chain-of-custody (COI/COC)

Since CAR-T cells are autologous, maintaining the COI and the COC is essential at every step.[17,18] Many procedures can be implemented to reduce human error, such as electronic documents, barcodes, and double-checking systems. COI/COC procedures should include collection, labeling, transport, receipt, processing, sampling, cryopreservation, storage, release, shipment, and infusion. Any differences in patient ID, labels, documentation, or records are critical deviations and must be investigated before proceeding.

Overview of CAR-T product manufacturing steps using the CliniMACS Prodigy

The workflow underlying CAR-T cell manufacturing is fundamentally consistent across systems and laboratories in general terms (Fig. 1), including the use of the CliniMACS Prodigy system.[19] The procedure begins with T-cell enrichment, which generally relies on magnetic bead-based isolation of CD4+ and/or CD8+ T-cell subpopulations. The degree of enrichment directly influences subsequent steps in CAR-T cell manufacturing, including transduction efficiency.[20]



Source: Elaborated by the authors.

Figure 1. Schematic workflow of autologous CAR-T-cell manufacturing using in-house lentiviral vectors and the CliniMACS Prodigy platform.

After enrichment, cells are activated using anti-CD3/CD28 magnetic beads or polymeric nanomatrices, which provide the stimulatory signals required to induce cell-cycle progression and enhance cell proliferation and vector transduction. Then, activated cells are cultured in GMP-grade medium supplemented with cytokines such as interleukin (IL)-2, IL-7, IL-15, or combinations thereof, depending on the desired expansion profile and institutional protocol.[6]

Transduction efficiency can vary considerably between patients and across manufacturing runs. This difference frequently results from differences in starting-material composition, T-cell fitness and activation status, vector architecture, multiplicity of infection, culture density, or timing of vector addition.[21] In-house lentiviral vectors require careful monitoring of lot-to-lot consistency, vector genome titer, infectious titer, storage conditions, thawing procedures, and hold times before use. Any modification to the vector lot, transduction enhancer, cytokine strategy, or culture conditions should be assessed within the site's change-control and comparability framework.

Following gene transfer (transduction), T cells are placed in an expansion phase for approximately 7 to 10 days in a gas-permeable culture chamber. Cell culture expansion depends on different factors, including nutrient availability, cytokine supplementation, stable pH and gas exchange, control of cell density, and the proliferative capacity of the patient-derived T-cell population.[13] Centers with high experience in cell culture are usually well prepared to identify all aspects of cell culture expansion. Nevertheless, expansion failure or poor growth may occur, for example, because of heavily pretreated patients (inefficient washout), low CD3+ input, reduced cell viability, or high monocyte or granulocyte contamination in the starting material. These events may affect the final product.

When the desired CAR-T cell number and phenotype are achieved, the culture proceeds to harvesting, during which cells are washed and formulated for either immediate infusion or cryopreservation for later administration.[22] These formulation solutions generally consist of isotonic media or cryoprotectant-containing solutions (supplemented with 5–10% DMSO or other validated cryoprotectants) and depend on the validated protocol in each institution. As mentioned, cryopreservation may be an option and should be performed using controlled-rate freezing and storage at temperatures below –150 °C in vapor-phase liquid nitrogen tanks with continuous temperature monitoring. Cryopreservation is ideal for products that need to be transported to distant institutions as well as for those awaiting the patient's preparation.

Critical process parameters are present at every step of the manufacturing process. Each step could represent a potential factor that could influence whether it becomes a problem.[13] Among them are cell concentration input, CD4/CD8 composition, activation reagent/medium ratio, multiplicity of infection, vector quality, cytokine supplementation, culture volume modifications, feeding and washing strategy, and many other factors. These parameters should be defined in the manufacturing protocol and monitored through in-process controls (IPC) and electronic batch records (EBRs). System-generated alerts and decision logs support deviation detection, root-cause analysis, and batch review.

Troubleshooting is a systematic process for identifying and resolving malfunctions within a system. In the context of the CliniMACS Prodigy system, successful troubleshooting requires trained staff to identify and resolve errors or malfunctions, such as flow occlusions, sensor misreadings, or partial failures of magnetic selection cartridges. The Prodigy system provides a considerable operational advantage by generating comprehensive EBRs that document every aspect of equipment function.

Also, one of the advantages of closed systems, compared with conventional open systems, is reduced operator-skill dependence and lower contamination risks, which lead to more consistent manufacturing outcomes.[23] For centers initiating CAR-T manufacturing programs, primarily in hematopoietic cell transplantation settings, the platform delivers a reproducible, standardized approach suitable for resource-constrained settings.

QC of the final product

QC tests for CAR-T cell products must be rapid and reliable.[17] Final release testing should evaluate not only the presence of the intended cell population but also its functional activity, safety, and suitability for patient administration.

Identity determination is primarily performed by flow cytometry to confirm the expected T-cell phenotype (CD3, CD4, CD8, etc.), CAR expression, and cell viability. Purity assessments evaluate the presence of unwanted cell populations, residual activation beads, and cellular doublets. It is already well established that identity and purity can interfere with CAR-T cell manufacturing. Another feature is cell viability, assessed at the time of product release, and typically requires values of at least 70%, determined by flow cytometry using viability dyes such as 7-AAD or equivalent reagents.

Potency testing remains one of the most challenging aspects of CAR-T-cell product release.[24] Ideally, potency assays should reflect the mechanism of action and demonstrate antigen-specific function. Common methods include cytotoxicity assays, luciferase-based killing assays, and cytokine release after antigen stimulation (e.g., interferon [IFN]-γ or IL-2). However, these assays vary substantially across institutions in target cell lines (NALM6, NAMALWA, etc.), effector-to-target ratios, incubation periods, and other aspects. This variation limits interlaboratory comparability and highlights the need for assay validation and harmonized reporting strategies.

The interpretation of results should also consider the variability of the starting material. Products manufactured from heavily pretreated patients may present reduced cell proliferation, altered CD4/CD8 ratios, lower transduction efficiency, or increased expression of exhaustion markers. Therefore, final QC results should be interpreted alongside in-process data to ensure the product's efficacy and safety.

Safety product evaluation is considered the most relevant aspect of CAR-T cell manufacturing, and Anvisa is explicit in its resolutions.[8] Among the evaluations are the determination of sterility, endotoxin, mycoplasma, and replication-competent lentivirus (RCL).

Overall, QC for CAR-T-cell products should be designed as an integrated release strategy rather than a set of isolated assays (Table 1). Release criteria may vary according to the manufacturing platform, clinical protocol, regulatory pathway, and whether the product is fresh or cryopreserved. Therefore, each institution needs to establish its own criteria based on local regulatory and institutional rules, as well as the methods used.[25]

In this sense, in academic or low-resource institutions, implementing robust QC can be very difficult, as it requires validated assays, trained personnel, qualified equipment, documented controls, and clear decision-making procedures for out-of-specification or atypical results.

Table 1. QC parameters for CAR-T product release.

Parameter	Purpose	Typical methods	Minimum release requirements	Critical considerations
Identity	Confirms product phenotype and CAR expression	Flow cytometry: CD3, CD4, CD8, CAR markers, viability dyes	CAR expression detected; T-cell phenotype consistent with specification	The CAR detection strategy should be validated for the specific construct
Purity	Detects unwanted cell types or residual reagents	Flow cytometry; residual bead quantification	Undesired populations below threshold; minimal residual beads	Contaminating cells may reflect starting-material quality or incomplete enrichment
Potency	Demonstrates functional CAR-T-cell activity	Cytotoxicity assays; cytokine release; CD107a degranulation	Functional response within validated potency range	High assay variability requires validated controls and predefined readouts
Safety	Ensures absence of microbial and vector-related contaminants	Sterility, endotoxin, mycoplasma, RCL testing	Sterility passed; endotoxin within limit; mycoplasma negative; RCL negative	Rapid or automated methods may be required to meet release timelines
Viability	Confirms adequate live cell proportion	7-AAD or equivalent viability dyes	≥ 70% viable cells at release	Should be interpreted with cell dose, cryopreservation status, and infusion timing

Source: Elaborated by the authors.

QA and IPC

QA and IPC provide the consistency, safety, traceability, and regulatory conformance throughout cell manufacturing. Consequently, QA should not be restricted to final batch review but should be integrated into the entire manufacturing lifecycle.[18]

Standard operating procedures (documents) are the foundation of this system. They should describe all critical process parameters, acceptance criteria, testing requirements, cleaning and environmental monitoring procedures, deviation management, and responsibilities of each team involved in the process.[25,26] These documents must be regularly reviewed, updated, version-controlled, and in line with current regulatory requirements and institutional policies. At academic or newly established centers, particular attention should be given to staff training, competency assessment, document control, and harmonization of procedures between clinical, manufacturing, QC, and QA teams.

Lot records should report every critical action, including deviations, during CAR-T cell manufacturing. Electronic records are useful and can be used in order to reduce transcription errors and enable real-time review, but they require validated systems, controlled access, and data integrity procedures.[27] When paper records are used, further verification steps are needed to minimize incomplete entries, illegible records, or other inconsistencies.[28]

IPCs are important for the early detection of manufacturing risks. These controls are performed during the manufacturing process and may include laboratory evaluations such as cell counts, viability, metabolic indicators, and transduction-related parameters.[17] Results should be compared with predefined alert and action limits, and any deviations from expected trends should trigger a documented investigation and risk assessment.

Common deviations include temperature excursions during transport or storage, delayed processing, labeling inconsistencies, incomplete documentation, reagent preparation errors, unexpected equipment alarms, flow occlusions, partial failures of automated steps, out-of-range cell densities, low transduction efficiencies, and microbial contamination.[29] Each deviation should be classified according to severity, potential product impact, and patient risk.

In that sense, corrective and preventive actions (CAPA) should be based on root cause analysis and aim not only to correct the immediate event but also to prevent recurrence.[30] Examples of CAPA include retraining operators after documentation errors, revising technical documents, adding additional checkpoint steps, or revising acceptance criteria.

Process validation verifies that the manufacturing process consistently produces a product that meets predefined quality attributes.[31,32] This includes several aspects of the entire productive chain, such as equipment qualification and calibration, supplier qualification, validation of all analytical methods, cryopreservation procedures, and shipping conditions. Periodic requalification or revalidation should be performed after relevant changes, such as the introduction of a new vector lot, modifications to cytokine supplementation, changes in culture medium, equipment replacement, software updates, or the transfer of the process to another manufacturing site.

Future perspectives

Future perspectives in CAR-T cell manufacturing point toward greater automation, decentralization, and the implementation of alternative gene-delivery technologies. Fully automated systems are being developed to enable consistent production. These platforms may facilitate implementation in centers with prior experience in hematopoietic cell transplantation and other cellular therapies, especially when combined with robust quality-assurance management and trained personnel.[20]

Point-of-care manufacturing models are also gaining attention because they may shorten manufacturing time, reduce logistical complexity, and improve access for patients treated outside large industrial manufacturing networks.[33] This approach is especially relevant for middle-income countries, where centralized manufacturing, international shipment, and high production costs can limit access to advanced therapy products.

In parallel, non-viral gene delivery approaches, including transposon systems such as Sleeping Beauty, mRNA electroporation, and CRISPR-based engineering, are gaining attention as strategies to lower dependence on viral vectors, optimize regulatory pathways, and reduce manufacturing costs.[34-36] However, these technologies introduce new analytical and supervisory challenges. Non-viral and genome-editing methods need to be well validated and studied for gene transfer efficiency, off-target effects, genomic integrity, and safety.

Despite the promise of automation and non-viral engineering, implementation remains limited by infrastructure requirements, validation costs, supply chain stability, and staff training. Academic and resource-limited centers may encounter additional challenges related to cleanroom capacity and regulatory expertise.[37] For these reasons, a risk-based implementation model may be more realistic than the immediate adoption of fully decentralized production.

Therefore, emerging manufacturing technologies are likely to improve reproducibility, reduce costs, and expand access to CAR-T-cell therapy in many countries. However, wider implementation will depend not only on technological innovation but also on harmonized regulatory criteria, validated quality-control strategies, training programs, and financial support from public and private sponsors.

Key points

Viral vectors are among the main reagents in CAR-T manufacturing.

Platform standardization is vital for safety, reproducibility, and compliance with regulatory standards.

The quality of the apheresis product strongly determines the final yield.

COI/COC must be applied consistently across all procedures.

Viability, lymphocyte markers, and sterility are key acceptance parameters.

QA confirms that CAR-T manufacturing is controlled, consistent, and auditable.

CAPA systems prevent recurrence of deviations.

Traceability is essential due to the autologous nature of CAR-T products.

CONFLICTS OF INTEREST

Nothing to declare.

AUTHOR CONTRIBUTIONS

Conceptualization: Kerbauy LN, Mesquita FP; **Investigation:** Kerbauy LN, Mesquita FP; **Methodology:** Kerbauy LN, Mesquita FP; **Writing:** Kerbauy LN, Mesquita FP; **Final approval:** Mesquita FP.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

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