




# Regulatory and operational framework for chimeric antigen receptor T cell therapy in Brazil

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## ABSTRACT

**Objective:** Provides an overview of Brazil's CAR-T regulatory structure, emphasizing post-authorization surveillance, clinical approval, manufacturing, and product release. **Methods:** Good Manufacturing Practice, ethics, biosafety, quality control, traceability, pharmacovigilance, and international harmonization are among the national and ANVISA laws governing advanced therapeutic products reviewed in this work. **Results:** Brazilian CAR-T manufacturing requires GMP-certified facilities, trained workers, and proven processes in addition to quality control and environmental monitoring. ANVISA and CONEP approval, as well as CTNBio authorization for GMOs, are necessary for clinical investigations. Sterility, endotoxin levels, mycoplasma presence, viability, potency, vector copy number, transduction efficiency, identification, and traceability are some of the variables that affect the product release process. Pharmacovigilance, safety reporting, inspections, and manufacturing management are among the duties that follow approval. **Conclusion:** Brazil has established a comprehensive regulatory framework for CAR-T therapy that accounts for both regional operational requirements and international norms. Expanding safe, long-term access to cell and gene therapies would require bolstering national manufacturing capacity and the development of flexible regulatory frameworks.

Keywords: CAR-T; Advanced therapy medicinal products; Regulatory framework; Good manufacturing practices.

## INTRODUCTION

The rapid development of chimeric antigen receptor T (CAR-T) cell therapy in Brazil has demanded the establishment of clear regulatory and operational guidelines to ensure product quality, patient safety, and compliance with international standards.<sup>1</sup> The Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária [ANVISA]) plays a central role in defining the requirements for laboratories operating under Good Manufacturing Practice (GMP), clinical research authorization, and product release. These guidelines are harmonized with the principles of the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and the World Health Organization (WHO), but tailored to Brazil's institutional and healthcare context.

## GMP laboratory requirements

GMP certification is mandatory for any facility involved in the manufacturing, processing, or storage of CAR-T cells and other advanced therapy medicinal products. ANVISA's regulatory framework, anchored in standards described in Table 1, defines the essential structural, operational, and quality management criteria required for GMP compliance. Laboratories must demonstrate environmental control, personnel qualification, and validated production processes to ensure product consistency and sterility.<sup>2</sup>

**Table 1.** Table detailing the regulatory instruments for CAR-T therapy.

Regulatory instrument	Object
Resolution No. 836/2023 <sup>3</sup>	It establishes guidelines for good practices in human cells for therapeutic use and clinical research, and provides other related measures.
Resolution No. 505/2021 <sup>4</sup>	It provides for the registration of advanced therapy products.
Resolution No. 506/2021 <sup>5</sup>	This law establishes the rules for conducting clinical trials with investigational advanced therapy products in Brazil and provides other related measures.
Normative Instruction No. 270/2023 <sup>6</sup>	It establishes guidelines for GMPs for advanced therapy products.
Resolution No. 412/2020 <sup>7</sup>	This document establishes the requirements and conditions for conducting stability studies for registration and post-registration changes of biological products, and provides other related measures.

Source: Elaborated by the authors.

Physical facilities must be designed with controlled cleanroom classifications (International Organization for Standardization 5-8), pressure differentials to prevent contamination, and high-efficiency particulate air filtration systems with validated heating, ventilation, and air conditioning performance.<sup>8</sup> Areas must be segregated for cell manipulation, vector transduction, cryostorage, and product release. Continuous environmental monitoring for particulate matter, microbiological load, temperature, and humidity is required. The laboratory must also establish gowning procedures, material flow controls, and dedicated waste-disposal systems.

Personnel involved in GMP manufacturing must undergo continuous training in biosafety, aseptic technique, and documentation practices. Each process is recorded under the quality management system (QMS), which includes deviation management, corrective and preventive actions, and change control. Process validation and product traceability are fundamental pillars of compliance, supported by robust documentation and electronic data integrity systems.

## Clinical study requirements

Any clinical investigation involving CAR-T therapy in Brazil must be authorized by ANVISA and approved by the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa [CONEP]). The sponsor or institution must submit a Dossier for Advanced Therapy Products or Clinical Development Dossier through ANVISA's electronic petitioning system. This submission must include preclinical data, product characterization, GMP certification of the manufacturing facility, and a detailed clinical protocol with risk mitigation strategies.<sup>4</sup>

In parallel, because CAR-T cells are legally defined as genetically modified organisms (GMOs) under Brazilian Law 11.105/2005,<sup>9</sup> all institutions involved in their production, storage, manipulation, or clinical use must obtain prior authorization from the National Technical Biosafety Commission (Comissão Técnica Nacional de Biossegurança [CTNBio]). This requires holding a Biosafety Quality Certificate (Certificado de Qualidade em Biossegurança) for risk-class determination of the CAR-T product, generally classified as Risk Class 2 due to the use of replication-deficient viral vectors. No clinical activities involving GMOs may begin without CTNBio's approval of the containment level, risk class, and operational biosafety measures.

ANVISA evaluates each study based on safety, manufacturing consistency, and ethical compliance. Pharmacovigilance plans must be established to monitor adverse events and long-term follow-up. Any modification to the production process, vector design, or storage conditions during the study requires prior approval by ANVISA. Importation of materials, such as viral vectors or cell banks, is permitted only from certified international suppliers with specific regulatory authorization.

### **Product release and quality control**

The release of CAR-T cell products is contingent on meeting rigorous quality control criteria. Each batch must be tested for sterility, endotoxin levels, mycoplasma, viability, and potency. Vector copy number, transduction efficiency, and phenotypic characterization of the final product must be documented before release. The responsible technical person, qualified under Brazilian regulation, is legally accountable for product conformity and batch release decisions.

Product release must be supported by complete documentation within the QMS, including batch records, deviation reports, and validation data. Stability studies must define the storage conditions and expiry for cryopreserved CAR-T cells. Cold-chain validation and continuous temperature monitoring are essential for maintaining product integrity during transport to clinical sites. ANVISA requires full traceability from donor collection to patient administration, with documentation retention for at least 15 years.

### **Post-authorization monitoring and pharmacovigilance**

Once a CAR-T product is authorized for clinical or commercial use, continuous post-market surveillance is mandatory (Imprensa Nacional). The manufacturer or sponsor must maintain a pharmacovigilance system to collect, analyze, and report adverse events. Periodic safety update reports must be submitted to ANVISA in accordance with the agency's defined intervals. Signal detection and corrective actions must be documented within the QMS and communicated transparently to regulatory authorities and investigators.

ANVISA also conducts periodic inspections to verify compliance with GMP and pharmacovigilance standards. Any change in the production process, equipment, or facility layout requires prior submission and approval through a variation process. The agency emphasizes continuous improvement and data-driven evaluation to ensure product safety and efficacy throughout its lifecycle.

### **Harmonization with international standards**

Brazil's regulatory framework for CAR-T cell therapies is designed to align with international best practices while accounting for local realities. ANVISA's participation in the Pharmaceutical Inspection Co-operation Scheme ensures that GMP inspections are recognized internationally and harmonized with EMA and FDA guidelines. This mutual recognition facilitates technology transfer, importation of qualified materials, and international collaboration in multicenter clinical trials.

The main challenge remains the dependence on imported reagents, viral vectors, and single-use materials. Strengthening domestic production capabilities, such as those led by the Instituto Butantan, Universidade de São Paulo, and Fundação Oswaldo Cruz, will be critical to reducing costs and ensuring supply continuity. Harmonization also extends to establishing national standards for potency assays, cell identity testing, and long-term patient registries.

### **Future perspectives**

The Brazilian CAR-T landscape is rapidly evolving. Academic and public institutions, supported by ANVISA's evolving regulatory vision, are establishing national centers of excellence for cellular manufacturing. Future regulatory updates are expected to streamline approval timelines for investigator-initiated trials and compassionate use programs while maintaining rigorous safety standards.

Greater integration between ANVISA, academic centers, and industry partners will be essential to accelerate innovation. Implementing electronic GMP systems, enhancing inspector training, and developing adaptive regulatory pathways for advanced therapies are key priorities. As Brazil consolidates its capacity in cell and gene therapy, the ANVISA framework stands as a model of balanced regulation, promoting innovation without compromising patient protection.

### Key points summary

- ANVISA requires GMP certification for all CAR-T manufacturing facilities, with strict environmental, personnel, and quality system controls.
- Clinical trials must obtain both ANVISA and CONEP approval, supported by GMP-compliant production and risk management plans.
- Product release depends on validated sterility, potency, and traceability tests under the supervision of a responsible technical person.
- Post-market pharmacovigilance and periodic inspections ensure continuous product safety.
- National harmonization with international GMP standards and the expansion of public manufacturing hubs are central to Brazil's CAR-T development strategy.

### CONFLICTS OF INTEREST

Nothing to declare.

### DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that no artificial intelligence tools were used in the preparation, writing, data analysis, or review of this manuscript.

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### DATA AVAILABILITY STATEMENT

Data will be provided upon request.

### AUTHOR CONTRIBUTIONS

**Conceptualization:** Hamerschlak N; **Investigation:** Kondo A, Mesquita F, Sekine L, Maia M, Hamerschlak N; **Methodology:** Kondo A, Mesquita F, Sekine L, Maia M, Hamerschlak N; **Writing:** Kondo A, Mesquita F, Sekine L, Maia M, Hamerschlak N; **Supervision:** Hamerschlak N; **Final approval:** Mesquita F.

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