Regulatory Framework and Clinical Translation of Automated Cell Production in China

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Abstract

The clinical translation of cell therapies in the People's Republic of China has experienced unprecedented growth, transitioning from early experimental stages to the industrialization of automated cell production. This review comprehensively analyzes the evolving regulatory framework governing cell and gene therapies in China, with a specific focus on the dual-track regulatory system managed by the National Medical Products Administration (NMPA) and the National Health Commission (NHC). We evaluate key legal clauses, including the Good Manufacturing Practice (GMP) guidelines for cell therapy products and the Biosafety Law, which collectively mandate the shift toward closed, automated manufacturing systems. Furthermore, this article reviews recent clinical findings from 20 to 30 scholarly studies, highlighting the clinical outcomes of NMPA-approved chimeric antigen receptor T-cell (CAR-T) therapies and the automated expansion of mesenchymal stem cells (MSCs). The synthesis of regulatory policy and clinical evidence demonstrates that automated production is not only a compliance requirement but a critical determinant of therapeutic efficacy and patient safety in China's rapidly advancing regenerative medicine sector.

Key words

automated cell production, clinical translation, regulatory framework, GMP compliance, dual-track system, China NMPA

1. Introduction: The Evolution of Cell Therapy in China

The landscape of cell and gene therapy (CGT) in the People's Republic of China has undergone a dramatic transformation over the past decade. Driven by substantial national investment, a vast patient population with unmet medical needs, and a rapidly maturing biotechnology sector, China has emerged as a global leader in

clinical research for advanced therapy medicinal products (ATMPs). Historically, the sector was characterized by fragmented oversight, leading to the proliferation of unproven stem cell treatments. However, recent sweeping regulatory reforms have fundamentally restructured the industry, prioritizing patient safety, scientific rigor, and industrial scalability [1, 2].

A central pillar of this transformation is the transition from manual, open-system cell culture techniques to automated, closed-system manufacturing. The inherent biological complexity of living cell products necessitates stringent control over the manufacturing microenvironment to ensure product consistency, sterility, and therapeutic potency [3]. In China, this technological shift is not merely an industry preference but is increasingly mandated by evolving regulatory policies and Good Manufacturing Practice (GMP) guidelines. This review aims to dissect the intersection of these regulatory mandates and clinical outcomes, demonstrating how the legal requirement for automated cell production is directly shaping the clinical success of stem cell and immune cell therapies in China.

2. The Dual-Track Regulatory System and Key Legal Clauses

The governance of cell therapies in China operates under a unique "dual-track" regulatory system, distinguishing between early-stage clinical research and commercial drug registration. This system was designed to balance the need for rapid scientific innovation with stringent safety oversight for commercialized products [4, 5].

2.1 The Investigator-Initiated Trial (IIT) Track

The first track is governed primarily by the National Health Commission (NHC) in conjunction with the NMPA. It oversees Investigator-Initiated Trials (IITs) conducted within certified medical institutions. The foundational policy for this track is the *Administrative Measures for Clinical Trials of Stem Cells (Interim)*, issued in 2015. This regulation explicitly prohibits the commercialization of stem cell therapies during the IIT phase and mandates that institutions must possess robust ethical review boards and adequate facilities to handle complex biological materials [6]. The flexibility of the IIT track has fueled a massive surge in clinical research; recent analyses indicate that approximately 50% of CAR-T trials and 75% of stem cell trials in China are initiated as IITs [7]. This pathway allows clinicians to rapidly translate novel automated production techniques from the bench to early-phase human trials, generating critical safety and preliminary efficacy data.

2.2 The Investigational New Drug (IND) Track

The second track is the formal drug registration pathway overseen by the NMPA, guided by the *Drug Administration Law of the PRC* (DAL, revised in 2019). Under this framework, ATMPs are classified and regulated as "innovative biological products" [1]. To transition a cell therapy from an IIT to a commercial product, developers must submit an Investigational New Drug (IND) application to the Center for Drug Evaluation (CDE). The NMPA has issued numerous technical guidelines to standardize this process, most notably the *Technical Guideline for Research and Evaluation of Cellular Therapy Products (Interim)* (2017) and the *Technical Guideline for Pharmaceutical Study and Evaluation of Cell-based Immunotherapy Products* (2022) [8]. These guidelines explicitly demand comprehensive pharmaceutical research, including rigorous validation of the manufacturing process, quality control, and stability testing, which heavily favors the adoption of automated manufacturing platforms to meet the required reproducibility standards.

2.3 GMP Compliance and the Mandate for Automation

The legal imperative for automated cell production is most clearly articulated in China's evolving GMP frameworks. The *Good Manufacturing Practice for Cellular Therapy Products (Interim)* and the specific *GMP Appendix for Cellular Therapy Drugs* emphasize the critical need to minimize human intervention and environmental exposure during cell processing [9]. Furthermore, the *Biosafety Law of the PRC* (2021) enforces strict biological safety protocols, requiring that the production of therapies involving genetic modification

(such as CAR-T cells) or extensive ex vivo expansion (such as MSCs) be conducted in highly controlled, closed systems to prevent cross-contamination and protect operators [10]. Consequently, automated bioreactors and closed fluidic systems have transitioned from being optional technological upgrades to essential compliance tools for any entity seeking NMPA approval.

3. Automated Manufacturing Platforms: Technological Paradigms

The translation of regulatory guidelines into practical manufacturing has spurred the development and adoption of various automated cell production platforms in China. The primary objective of these systems is to achieve a completely closed, aseptic "donor-to-patient" biomanufacturing process [11].

For immune cell therapies, particularly CAR-T cells, automated systems must integrate multiple complex steps: cell isolation, activation, viral transduction, expansion, and final formulation. Platforms that consolidate these steps into a single, enclosed device are increasingly favored by Chinese biopharmaceutical companies, as they significantly reduce the footprint of high-grade cleanrooms required under Chinese GMP [12, 13].

For stem cell therapies, particularly the large-scale expansion of MSCs, the technological paradigm centers on 3D automated bioreactors. Traditional 2D planar cultures are insufficient to meet the massive cell numbers required for clinical dosing. Recent studies have highlighted the successful deployment of the Automated Closed Industrial Scale Cell Production (ACISCP) platform in China. This system utilizes GMP-grade 3D microcarriers suspended in dynamic bioreactors, enabling the scalable, automated expansion of umbilical cord-derived MSCs while maintaining their multipotency and genetic stability, perfectly aligning with NMPA quality control mandates [14, 15].

4. Clinical Findings and Outcomes of Automated Cell Therapies

The rigorous implementation of automated production under the dual-track regulatory system has yielded significant and highly encouraging clinical outcomes in China, particularly in the fields of hematological oncology and regenerative medicine.

4.1 CAR-T Cell Therapies: NMPA Approvals and Efficacy

The most visible success of China's regulatory and manufacturing evolution is the approval and clinical deployment of CAR-T cell therapies. In 2021, the NMPA approved China's first independently developed CAR-T therapy, relmacabtagene autoloader (Relma-cel), for the treatment of relapsed or refractory large B-cell lymphoma [16]. The clinical data supporting this approval, generated from rigorously controlled, GMP-compliant automated manufacturing processes, demonstrated profound efficacy. In pivotal trials, the best overall response rate (ORR) reached 75.9%, with a complete response (CR) rate of 51.7% [17].

Subsequent long-term follow-up studies of Relma-cel in Chinese patients confirmed the durability of these responses, reporting a 3-month ORR of 60.3% and a median progression-free survival (PFS) of 7.0 months [18]. Furthermore, the automated, closed-system manufacturing of these CAR-T products has been crucial in managing safety profiles. By ensuring consistent cell viability and precise CAR expression levels, clinicians have been better equipped to predict and manage severe adverse events, such as cytokine release syndrome (CRS) and neurotoxicity, which remain critical concerns in the clinical application of genetically modified cells [19, 20]. Recently, Relma-cel received supplementary NMPA approval for mantle cell lymphoma, achieving an outstanding ORR of 81.36%, further validating the robustness of the underlying automated manufacturing platform [21].

4.2 MSC Therapies: Scaling Up for Regenerative Medicine

In the realm of regenerative medicine, China has become a global epicenter for MSC clinical trials, particularly those utilizing umbilical cord-derived MSCs (UC-MSCs). It is estimated that a significant majority of worldwide UC-MSC trials are currently conducted in China [22]. The clinical success of these trials is heav-

ily dependent on the automated, large-scale expansion of cells to meet the required therapeutic doses without inducing replicative senescence or loss of immunomodulatory function [23].

Clinical translational research utilizing automated 3D bioreactor systems has demonstrated that expanded UC-MSCs retain high therapeutic potency. In early 2025, this culminated in a landmark regulatory milestone: the NMPA granted conditional approval to China's first MSC therapy, amimestrocel injection (hUC-MSC PLEB-001), for clinical use [24]. Clinical studies supporting this and similar MSC products have shown promising results in treating severe inflammatory and autoimmune conditions, including acute graft-versus-host disease (GvHD) and acute respiratory distress syndrome (ARDS) [25, 26]. The ability to consistently produce billions of high-quality MSCs via automated platforms has been the decisive factor in moving these therapies from small-scale IITs to formal NMPA drug registration and commercial availability [27].

5. Conclusion

Despite the remarkable progress in regulatory frameworks and clinical outcomes, several challenges remain in the widespread implementation of automated cell production in China. First, the high capital cost of automated biomanufacturing equipment and the requisite GMP-compliant cleanroom infrastructure present a significant barrier to entry for smaller academic institutions and biotech startups [28]. While the dual-track system allows for early-phase research via IITs, the financial leap required to meet NMPA IND standards for automated production is substantial. Second, the regulatory landscape, while comprehensive, is still evolving. The CDE frequently issues new draft guidelines, requiring manufacturers to remain highly agile and continuously adapt their automated processes to maintain compliance [29].

Looking forward, the integration of artificial intelligence (AI) and machine learning into automated cell production systems represents the next frontier for China's CGT industry. By utilizing AI to monitor real-time bioprocess data from closed bioreactors, manufacturers can implement predictive quality control, dynamically adjusting culture parameters to optimize cell yield and therapeutic potency [30]. As the NMPA continues to refine its regulatory standards to accommodate these advanced technologies, the synergy between strict legal compliance and cutting-edge automated manufacturing will undoubtedly accelerate the delivery of safe, curative cell therapies to patients across China and globally.

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