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# Studying the Global Progress and Regulatory Landscape of Stem Cell Therapy Research

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## Abstract

**Objective:** Stem cell therapy has emerged as a pioneering front in the biomedical domain, characterized by its rapid strides in innovation and progress. Such advancements hold profound implications for public health. Notably, Europe, the United States, Japan, and China have all crafted comprehensive regulatory frameworks to expedite the fruition of stem cell therapy. This article meticulously scrutinizes and evaluates the progression of clinical trials in cell therapy across major global jurisdictions. It delineates the trajectory of regulatory evolution in Europe, the United States, Japan, and China, and systematically collates the pivotal normative guidelines. This article is crafted with the intent to serve as a reference for regulatory agents, enterprises, and professionals in the field.

**Methods:** Stem cell therapy, a paragon of innovative medical technology, heralds a new era of treatment possibilities for hitherto intractable diseases. It is more than just a benchmark of technological advancement; it represents a revolutionary shift in the pharmaceutical landscape. Since Dr.Thomas was awarded the Nobel Prize for his research on bone marrow transplantation in 1990, he has gradually moved from the laboratory to the clinical application stage, bringing new hope for treatment to patients. Stem cell therapy is a type of cell therapy. There are various types of cell therapy, which can be classified into stem cell

therapy and immune cell therapy based on their cell sources. They can also be classified into autologous, allogeneic, and heterologous cells based on their donor sources. As a cutting-edge application technology in life science research, cell therapy has shown great therapeutic potential in various disease fields such as malignant tumors, genetic diseases, and chronic degenerative diseases. Multiple cell therapy products have been successfully launched and demonstrated excellent efficacy, among which stem cell therapy stands out due to its long application history and active research trend. Bone marrow/hematopoietic stem cell therapy is the earliest stem cell therapy, mainly used for bone marrow/hematopoietic stem cell transplantation to treat hematological malignancies such as leukemia. Human derived stem cells and their derived therapeutic products, as important regenerative medicine products, have great potential in cell replacement, tissue repair, disease treatment, and other fields. Nearly 70% of the stem cells used in clinical studies are hematopoietic stem cells and mesenchymal stem cells derived from bone marrow, peripheral blood, and umbilical cord. Technical methods include purification, in vitro culture and amplification, drug treatment, or gene modification. Immune cell therapy is a method of treating diseases using immune cells, which was originally mainly used to treat malignant tumors. According to the specificity of immune cell therapy, it can usually be divided into specific immune cell therapy and non-specific immune cell therapy. Specific immune cell therapy includes chimeric antigen receptor T-cell (CAR-T) therapy, T-cell receptor engineered T cell therapy, chimeric antigen receptor natural killer cell therapy (CAR-NK), and DC-CIK immunotherapy. Nonspecific immune cell therapy mainly includes lymphokine activated killer cell therapy and cytokine induced killer cell therapy. In addition, extracellular vesicles, as cell derivatives, have the advantage of non-living properties that are easier to characterize, store, package, and transport than living cells, and their research has shown explosive growth. Extracellular vesicle is a general term for lipid bilayer membrane-bound vesicles released by cells into the extracellular space, with a diameter range of 50-2,000 nanometers. Exosomes are extracellular vesicles with a diameter of 30-150 nanometers. At present, the Food and Drug Administration (FDA) has approved at least 8 extracellular vesicle products to enter phase II/III clinical trials. In recent years, the development of organoid technology, cell lineage tracing technology, single-cell spatial omics-sequencing technology, single-molecule technology, micro proteomics and proximity labeling technology has greatly promoted the progress of stem cell research and laid a good technical reserve for achieving functional organ reconstruction.

**Results:** In the realm of emerging technologies, industry development often precedes regulatory frameworks. The swift progression of innovative stem cell therapy products not only propels medical innovation but also challenges existing regulatory technologies and institutions. Regulatory agencies must, therefore, continually innovate their strategies and technologies.

**Conclusion:** Countries worldwide have crafted regulatory policies and technical evaluation systems tailored to their specific contexts. The variety of stem cell therapy types and applications defined by national regulations reflects this diversity. This article delves into the clinical research status of stem cell therapy through statistical analysis and dissects the regulatory frameworks governing it across nations, offering a valuable resource for stakeholders in this dynamic field.

**KeyWords:** stem cell therapy, drug regulatory policy, clinical study

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## 1 INTRODUCTION

The clinical research landscape has witnessed a remarkable uptick in the exploration of stem cell therapy[1,2], spurred by the burgeoning incidence of chronic diseases, the aging population, and the quantum leap in technological innovation. Nations such as the United States, China, Japan, and Europe are banking on the cell therapy industry as a cornerstone of their future scientific and technological growth, channeling substantial funds into the foundational research and clinical application of stem cell therapy. The global cell therapy market is poised for exponential growth, with a projected increase of USD 31.04 billion at a

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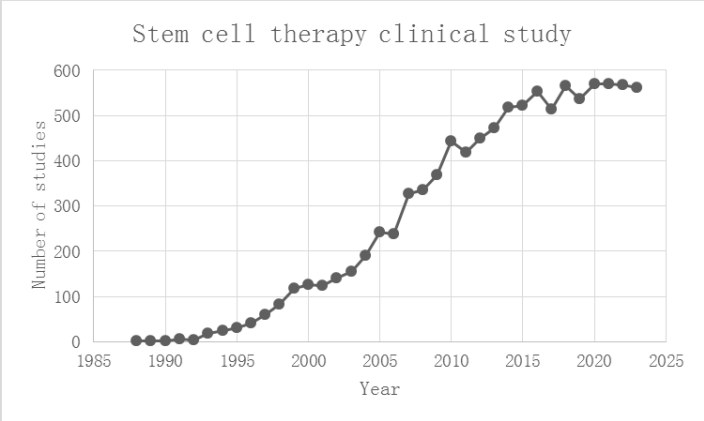


**Figure 1. Global Statistics of the Number of Clinical Studies on Stem Cell Therapy.**

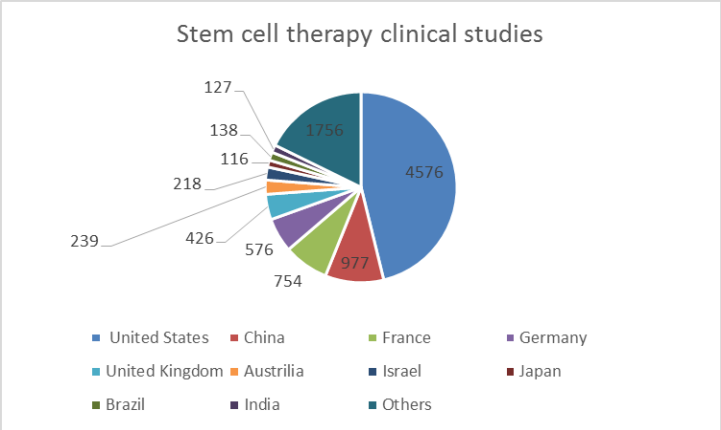


**Figure 2. The Number of Clinical Studies on Stem Cell Therapy Conducted in Major Countries.**

staggering CAGR of 57.06% from 2022 to 2027[3].

This scholarly inquiry delves into the trajectory of clinical research on stem cell therapy, charting its ascendancy over the past two decades. As of the end of 2023, the US clinical trial registry, clinicaltrials.gov, lists over 2,300 clinical studies on stem cell therapy worldwide, reflecting a consistent upswing in the initiation of new cell clinical studies annually. Since 2018, the aggregate count of new studies has consistently exceeded 560 each year. Despite a moderation in growth post-2022, due in part to the pandemic's repercussions, the annual tally of studies has persisted above the 560 projects, as shown in Figure 1. This sustained activity underscores the resilience and potential of stem cell therapy research amidst challenges and the ongoing quest for therapeutic breakthroughs.

In recent years, with the increasing emphasis on cell and gene therapy technology and industry, the number of clinical studies worldwide is continued rising. The main regions for global stem cell therapy research and development are North America, East Asia, and Western Europe. This paper makes statistics on the clinical research of stem cell therapy carried out in the United States, China (mainland), France, Germany, Britain, Australia, Israel, Japan, Brazil, India and other countries or regions. The United States holds a leading position in global stem cell therapy research and development, conducting approximately half of the world's clinical studies on cell therapy, with over 4,500 projects. Chinese Mainland accounts for about 1/5 of the world, ranking second in the world, as shown in Figure 2.

In 2023, there were over 420 clinical studies on stem cell therapy worldwide. Among them, in 2023, the United States will conduct approximately 30% of global clinical research on cell therapy, with 160 projects. Chinese Mainland, France and Germany have 135, 40 and 30 projects respectively, as shown in Figure 3.

## 2 REGULATORY SYSTEM FOR STEM CELL THERAPY APPROVAL

Stem cell therapy products, like other cell therapy products, are usually regarded as advanced therapy medicinal product (ATMPs), with different definitions and regulatory mechanisms in different countries and regions. Overall regulation and approval of stem cell therapy can be divided into two categories. The first type is to strictly follow the process of drug product approval, with drugs or medical device products being regulated and approved by drug regulatory agents for clinical admission and application. In the US, the Food and Drug Administration (FDA) classifies and human cells, tissues, or cellular or tissue-based (HCT/Ps), while the he European Medicines Agency (EMA) classifies and regulates medical products

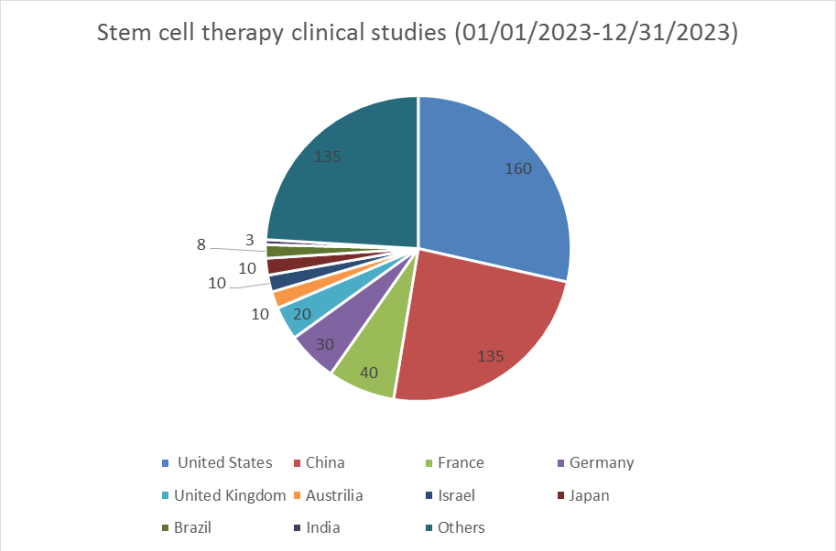


**Figure 3. The Number of Clinical Studies on Stem Cell Therapy Conducted in Major Countries in 2023.**

based on advanced technology. The second type is registered according to the classification of new drugs and medical technologies, and is supervised separately by the drug regulatory agents and the relative department of Health Ministry, such as Japan and China.

### 2.1 Introduction to the Regulatory System for Stem Cell Therapy in The USA

Recently, FDA has launched new measures to enhance the efficiency and safety of cell and gene therapy regulation with revise regulatory mechanisms and improving professionalism and precision. The FDA regulates cell and gene therapy as biologics, initially approved and managed by the Office of Cellular, Tissue and Gene Therapy under the FDA Center for Biologics Evaluation and Research (CBER). In 2016, the specific management department for cell therapy products was reorganized into the Office of Tissues and Advanced Therapies (OTAT). The Office of Therapeutic Products (OTP) established by the FDA CBER in 2023 replaced OTAT. With hierarchical management model based on risk levels and categories, OTP ensure the safety and effectiveness of cellular products, while simplifying the review process and improving work efficiency.

The United States has established a legal and regulatory framework in the field of cell therapy, consisting of three layers: laws, regulations, and guidance. At the law level, it mainly includes two congressional Act related to cell therapy, including the FD&C Act and the PHS Act. At the regulations level, it mainly includes the United States Federal Regulations (CFR), which provides the basis for cell therapy regulations. The 21 CFR part 312 provides requirements for investigational new drug applications, the 21 CFR part 210&211 provides requirements for drug production quality management standards, the 21 CFR part 610 contains general biological product standards for final product characterization, and the 21 CFR part 1,271 provides the main basis for cell therapy approval[4,5]. At the level of guidelines, the FDA has developed a series of guidelines and standards related to the manufacturing, clinical trials, registration and approval of cell therapy products. The FDA has been issuing a series of guidelines and regulations since 1998, including cell therapy guidelines for specific diseases and industry common guidelines. This not only standardizes and improves the cell therapy review and approval system, but also further stimulates innovative research on key technologies by industry stakeholders, as shown in Table 1.

### 2.2 Introduction to the European Regulatory System for Stem Cell Therapy

EMA classifies cell therapy products as ATMPs for regulation, including somatic cell therapy drugs, gene therapy drugs, tissue engineering products, and combination ATMPs. According to EU requirements, ATMPs are subject to graded regulation. The clinical trial application of ATMPs is approved by relevant institutions in each country, but the product marketing authorization is reviewed and verified by the Committee on Medicinal Products for Human Use (CHMP) and the Committee on Advanced Therapeutics (CAT) under EMA. Finally, the European Commission (EC) conducts research to determine whether the product is approved for marketing[6,7]. The CAT is a multi-disciplinary committee established by EMA based on the progressiveness and particularity of ATMPs and the relevant (EC) 1394/2007 regulations of ATMPs, convened by European senior experts proficient in ATMPs, which is mainly responsible for evaluating the quality, safety and effectiveness of ATMPs and continuously tracking the scientific development in this field[8]. The evaluation opinion is submitted to the CHMP, which makes a recommendation for approval of the marketing authorization; then the EC makes the final decision that is binding on all member states.

In addition, given the unique nature and rapid

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**Table 1. FDA Key Regulatory Guidelines for Cell Therapy**

| No. | Guidance | Year |
|---|---|---|
| 1 | Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy | 1998 |
| 2 | Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry | 2007 |
| 3 | Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs) | 2008 |
| 4 | Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products | 2009 |
| 5 | Guidance for Industry: Cellular Therapy for Cardiac Disease | 2010 |
| 6 | Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage | 2011 |
| 7 | Current Good Tissue Practice and Additional Requirements for Manufacturers of HCT/Ps | 2011 |
| 9 | Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products | 2011 |
| 10 | Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products | 2013 |
| 11 | BLA Guidance for Industry: BLA for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System | 2014 |
| 12 | IND Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System - Guidance for Industry and FDA Staff | 2014 |
| 13 | Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products; Guidance for Industry | 2015 |
| 14 | Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry | 2015 |
| 15 | Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry | 2015 |
| 16 | Recommendations for Microbial Vectors Used for Gene Therapy, Guidance for Industry | 2016 |
| 17 | Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff Updated | 2017 |
| 18 | Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry | 2017 |
| 19 | Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271; Guidance for Industry | 2017 |
| 20 | Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Guidance for Industry | 2019 |
| 21 | Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry | 2019 |
| 22 | Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency; Guidance for Industry | 2021 |
| 23 | Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial; Guidance for Industry | 2022 |
| 24 | Human Gene Therapy for Neurodegenerative Diseases; Guidance for Industry | 2022 |
| 25 | Potency Assurance for Cellular and Gene Therapy Products; Draft Guidance for Industry | 2023 |
| 26 | Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products; Draft Guidance for Industry | 2023 |
| 27 | Considerations for the Development of CAR-T Cell Products; Guidance for Industry | 2024 |

technological development of ATMPs, in order to benefit special needs patients who do not meet medical needs but urgently need treatment with ATMPs from clinical research, the European Union has passed the Hospital Exemption scheme, which stipulates that some ATMPs can be used in hospital and research entities without obtaining marketing authorization[9]. However, EMA emphasizes from a cautious perspective that EMA strongly does not recommend "hospital exemptions" as the preferred way to supply the ATMP market. The EU has established a systematic regulation of ATMPs. At the law level, European Union legislation in the pharmaceutical sector and medical devices sector provide a legal regulatory framework for the entire industry chain, including preclinical research, clinical research, manufacturing, and sales. At the regulation level, the European Union issued Regulation (EC) No.1397/2007 on Advanced Therapy Medical Products in 2007.At the level of guidelines, the EMA has developed a relatively complete set of full chain regulatory norms and guidelines based on ATMP research and regulatory requirements, as shown in Table 2.

### 2.3 Introduction to the Regulatory System for Cell Therapy in Japan

In Japan, according to the aim of whether they are marketed, regulation of cell therapy and gene therapy separated from drugs, medical devices and cosmetics, and divides them into technologies and products. Clinical Research can be conducted in qualified medical institutions, but cannot be approved for marketing as a product. The

**Table 2. EMA Guidelines for Stem Cell Therapy**

| No. | Guideline | Year |
|---|---|---|
| 1 | Quality and Safety Standards for Donated Human Tissues and Cells (Directive2004/23/EC) | 2004 |
| 2 | Guideline on clinical trials in small populations (CHMP/EWP/83,561/2005) | 2005 |
| 3 | Guideline on Human Cell-based Medicinal Products (EMEA/ CHMP/410,869/2006) | 2006 |
| 4 | Guideline on Environmental Risk Assessments For Medicinal Products Consisting of, or Containing, Genetically Modified Organisms(GMOs) (EMEA/CHMP/BWP/473,191/2006-Corr) | 2006 |
| 5 | implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells (Directive 2006/17/EC) Directive 2006/86/EC | 2006 |
| 6 | Guideline on xenogeneic cell-based medicinal products (EMEA/ CHMP/CPWP/83,508/2009) | 2009 |
| 7 | Reflection paper on stem cell-based medicinal products (EMA/CAT/571,134/2009) | 2009 |
| 8 | Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products | 2010 |
| 9 | Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014) of gene therapy medicinal products (EMA/CAT/80183/2014) | 2014 |
| 10 | New Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products | 2017 |
| 11 | Draft guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials - First version (EMA/CAT/852,602/2018) | 2018 |
| 12 | Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials | 2019 |
| 13 | Guidelines on good clinical practice specific to advanced therapy medicinal Products | 2019 |
| 14 | Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) | 2019 |
| 15 | Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells | 2020 |
| 16 | Questions and answers on the principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs (EMA/246,400/2021) | 2021 |
| 17 | Draft guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials - Second version | 2023 |

product is a registration trial for the purpose of applying for product marketing authorization, and after being launched, it becomes a regenerative medicine product. Clinical research is the scientific and ethical study of new technologies or therapies aimed at medical institutions conducting medical research on patients[10-13].

In 2014, based on the Pharmaceutical Affairs Act and Order for Enforcement of the Pharmaceutical Affairs Act, the Ministry of Health, Labour and Welfare (MHLW) issued the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act. In the same year, the Act on the Safety of Regenerative Medicine (ASRM) was issued, promulgated to reform the regulatory system of regenerative medicine. The relevant Act on quality, efficacy, and safety assurance of pharmaceuticals, medical devices regulate the supervision of multiple links such as market application, production, circulation, use, and post market monitoring. The Act on the Safety of Regenerative Medicine puts forward requirements for hospital and medical entities to conduct clinical research. Both registration trials and clinical studies have clear regulatory processes. Among them, the applicants for registration trials are generally pharmaceutical companies. According to the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act, the Medical Device Integrated Agency (PMDA) is responsible for supervising the clinical trial applications submitted by applicants.

The specific approval is handled by the Cellular and Tissue-based Products Subcommittee under the Center for Product Evaluation of PMDA. Clinical research is the scientific and ethical study of new technologies or therapies aimed at medical institutions conducting medical research on patients. It requires an application to the clinical trial institution review committee and is regulated by the MHLW in accordance with the ASRM[11-13]. The promulgation of the ASRM has conducted a specific impact on the status of cell-based intervention measures in Japan. Cellular intervention measures are divided into three risk categories: Level I, Level II, and Level III. Level I intervention measures involve high-risk cells, including embryonic stem cells, induced pluripotent stem cells, or allogeneic stem cells. Level II intervention measures involve low-risk cells, including adult stem cells, cultured adult cells, or non-homologous cells. The Level III intervention measures involve minimal handling; do not involve cell culture or use of non-homologous cells. In addition, Japan has introduced a series of research guidelines and standards, including related guidelines and notifications for regenerative medical products, which were compiled and opened on the PMDA official website (https://www.pmda.go.jp/english/review-services/reviews/0003.html).

### 2.4 Introduction to China's Cell Therapy Regulatory System

In China, cell therapy including stem cell therapy is

**Table 3. Guidelines for Cell Therapy in China**

| No. | Guidance | Year |
|---|---|---|
| 1 | Guidance for Research on Human Cell Therapy and Quality Control of Preparations 2003 | 2003 |
| 2 | Guidance for quality control technology of 27 person gene therapy research and formulation 2003 | 2003 |
| 3 | Management Regulations for Hematopoietic Stem Cell Therapy Technology of Umbilical Cord Blood (Trial) 2009 | 2009 |
| 4 | Management Measures for Clinical Research of Stem Cells (Trial) 2015 | 2015 |
| 5 | Guidance for Quality Control and Preclinical Research of 25 Stem Cell Preparations (Trial) | 2015 |
| 6 | Guidance for Research and Evaluation of 23 Cell Therapy Products (Trial) | 2017 |
| 7 | Management Regulations for Hematopoietic Stem Cell Transplantation Technology (2017 Edition) | 2017 |
| 8 | Key considerations for quality control testing and non clinical research of 22 CAR-T cell therapy products | 2018 |
| 9 | Management Measures for Clinical Research and Translational Application of 28 Somatic Cell Therapy (Exposure Draft) | 2019 |
| 10 | Guidance for Pharmaceutical Research and Evaluation of Gene Therapy Products (Exposure Draft) | 2020 |
| 11 | Guidance for Pharmaceutical Research and Evaluation of Immune Cell Therapy Products (Exposure Draft) | 2020 |
| 12 | Guidance for Pharmaceutical Research and Evaluation of Gene Transduction and Modification Systems (Exposure Draft) | 2020 |
| 13 | Chinese Pharmacopoeia Part III - General Introduction to Human Gene Therapy Products | 2020 |
| 14 | Technical Guidance for Clinical Risk Management Plan of CAR-T Product Application for Market Listing (Exposure Draft) | 2021 |
| 15 | Guidance for Clinical Trial Technology of Immune Cell Therapy Products (Trial) | 2021 |
| 16 | Technical Guidance for Pharmaceutical Research and Evaluation of Human Derived Stem Cell Products (Exposure Draft) | 2021 |
| 17 | Draft General Rules for Microbial Inspection of Cellular Products | 2021 |
| 18 | Guidance for Non Clinical Research Techniques of Gene Modified Cell Therapy Products (Trial) | 2021 |
| 19 | Technical Guidance for Non Clinical Research and Evaluation of Gene Therapy Products (Trial) | 2021 |
| 20 | Technical Guidance for Long term Follow up Clinical Research of Gene Therapy Products (Trial) | 2021 |
| 21 | Draft Guidance for Biological Assay Based on Gene Modified Cell Lines | 2021 |
| 22 | Guidance for Pharmaceutical Research and Evaluation of Immune Cell Therapy Products (Trial) | 2022 |
| 23 | Good Manufacturing Practice for Drugs-Appendix to Cell Therapy Products (Exposure Draft) | 2022 |
| 24 | Technical Guidance for Clinical Communication and Exchange of Cell and Gene Therapy Products in 2023 | 2023 |
| 25 | Guidance for Clinical Trial Technology of 5 Human Derived Stem Cell and Its Derivative Cell Therapy Products (Trial) | 2023 |
| 26 | Guidance for Pharmaceutical Research and Evaluation of Human Stem Cell Products (Trial) | 2023 |
| 27 | Guidance for Clinical Pharmacology Research Techniques of Cell Therapy Products (Exposure Draft) | 2024 |
| 28 | Technical Guidance for Clinical Trials of Mesenchymal Stem Cells in the Prevention and Treatment of graft-versus-host Disease (Trial) | 2024 |
| 29 | Guidance for Non Clinical Research Techniques of Three Source Stem Cell Products | 2024 |

regulated with a dual track regulatory system. Firstly, according to the Drug Registration Management Measures, cell therapy products are regulated by the National Medical Products Administration, and enterprises are the responsible parties. They submit registration to the national drug regulatory department and are applicable to somatic cell therapy products developed by enterprises. Secondly, according to the "Regulations on the Clinical Application Management of Biomedical New Technologies (Draft for Comments) issued by the National Health Commission in 2019, it is managed by the National Health Commission, and medical institutions are the responsible parties. It is applicable to the clinical research and translational application of somatic cell therapy developed, prepared, and carried out by medical institutions within their own medical institutions. Among them, clinical research on low-risk biomedical new technologies is managed by provincial health authorities, while clinical research on high-risk biomedical new technologies is managed by the National Health Commission[14,15]. Especially since 2017, the Center for Drug Evaluation of the National Medical Products Administration has successively released more than 30 technical guidelines related to cell and gene therapy, forming a preliminary regulatory system for the entire life cycle from research and development, registration, production to market launch, as shown in Table 3.

## 3 CONCLUSIONS

The global progress in stem cell therapy research is characterized by a patchwork of regulatory policies, each designed to balance the potential of this cutting-edge technology with the need for patient safety and ethical considerations. As the field continues to mature, it is crucial for stakeholders to stay abreast of the evolving regulatory frameworks and clinical research trends.

In the United States, the FDA regulates stem cell therapies through scientific and rigorous approval

processes, as well as specific guidelines for cellular and gene therapies. The FDA's approach emphasizes the need for robust preclinical data and clinical trials to ensure the safety and effectiveness of stem cell products. In Europe, EMA plays a pivotal role in regulating ATMPs, including stem cell therapies. The EU has implemented regulations that require comprehensive data on safety, efficacy, and quality for the approval of stem cell therapies. The Clinical Trials Directive and the Medical Devices Directive provide additional guidance for researchers and developers. In Japan, the PMDA oversees the regulation of regenerative medicine products. Japan has been proactive in developing a regulatory environment that supports the rapid approval of promising stem cell therapies while maintaining appropriate standards of safety and efficacy. In China, the National Medical Products Administration regulates stem cell therapies within a framework that encourages domestic innovation and harmonization with international standards. China has implemented guidelines that address the quality control, safety, and efficacy of stem cell-based products.

As the international community grapples with the potential and pitfalls of stem cell therapy, regulatory policies continue to evolve. Key normative guidelines are being updated to reflect new scientific knowledge and to address emerging challenges such as the long-term effects of stem cell therapies, the ethical use of stem cells, and the potential for immune reactions.

This study on the international development of clinical research and regulatory policies on stem cell therapy provides a critical reference for understanding the current landscape and future direction of this field. By providing a clear and comprehensive overview of the regulatory systems in place and the challenges ahead, this article enables stakeholders to make informed decisions and collaborate more effectively in the pursuit of safe and effective stem cell therapies. As the promise of stem cell therapy continues to unfold, a shared understanding of global regulatory trends and best practices will be crucial in translating scientific breakthroughs into meaningful healthcare solutions.

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Not applicable.

**Conflicts of Interest**
The authors declared no conflict of interest.

**Data Availability**
All data generated or analyzed during this study are included in this published article and its supplementary information files.



**Author Contribution**
The author contributed to the manuscript and approved the final version.

**Abbreviation List**
ASRM, Act on the Safety of Regenerative Medicine
ATMPs, advanced therapy medicinal product
CAR-T, chimeric antigen receptor T-cell
CAT, Committee on Advanced Therapeutics
CBER, Center for Biologics Evaluation and Research
CFR, United States Federal Regulations
CHMP, Committee on Medicinal Products
EC, European Commission
EMA, European Medicines Agency
FDA, Food and Drug Administration
HCT/Ps, human cells, tissue, and cellular and tissue-based products
INDs, Investigational New Drug Applications
MHLW, Ministry of Health Labour and Welfare
OTAT, Office of Tissues and Advanced Therapies
OTP, Office of Therapeutic Products
PMDA, Pharmaceuticals and Medical Devices Agency

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