Standardization of Stem Cell and Regenerative Medicine in China

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1 Introduction

With the continuous progress in the clinical practice of cell therapy and the gradual integration of regulatory policies, there has been a rapid surge in the development of cellular therapy products. Increasing cell therapy products for different indications have entered the phase of confirmatory/pivotal trial or NDA (New Drug Application). However, unlike traditional small molecule or biomacromolecule drugs, cell therapy products represent a fundamentally new class of "living" medicine. Their preparation involves complex operations unique to living cells, such as donor screening, cell collection and isolation, proliferation, passaging, cell line/bank establishment and characterization, production, genetic editing, induced differentiation, purification, harvesting, cryopreservation, and transportation, among others. These unique operations are difficult to fully apply to the regulatory framework for traditional drugs and may require frequent updates as relevant technologies advance. Therefore, to facilitate the clinical translation of stem cells and adapt to scientific and technological progress, it is important to formulate and update the regulatory policies and standards that are specifically appropriate for cell therapy.

2 Regulatory Oversight of Stem Cell-Based Therapeutic Products in China

In China, the government continuously makes efforts to formulate regulations encouraging new technologies and new products for drugs. The former National Health and Family Planning

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Commission (NHFPC) and the former China Food and Drug Administration (CFDA) released *Management Methods for Clinical Research of Stem Cells (Trial)* [1] and *Guidelines for Quality Control of Stem Cell Preparation and Preclinical Research (Trial)* in 2015 [2], setting out the basic principles for the preparation and preclinical research of clinically used stem cells. In 2017, the former CFDA issued the *Guideline for Research and Evaluation of Cell Therapy Products (Trial)* [3], which clarified the drug properties of cell therapy products and provided a general description of the technical requirements for cell therapy products according to relevant laws and regulations on drug administration.

Currently, the National Medical Products Administration (NMPA) is responsible for new drug registration, organizing the formulation and publication of the Chinese Pharmacopoeia and other drug standards, and formulating policies to facilitate new technologies and new products for drugs. Based on updated technology and accumulated experience, NMPA has issued a series of guidelines and policies to support the further development of therapeutic stem cell products. Representative documents are listed as follows.

Manufacturing Quality Management Guidelines for Cell Therapy Products (Trial) [4] issued in October 2022. This document can be considered as an appendix to *GMP,* specifying the management requirements for stem cell medicine preparation, covering transportation and receiving of donor materials, production, inspection, release, storage, and transportation. It provides guidance for cell medicine manufacturers and can also be used as an important reference for regulatory agencies to carry out on-site inspections.

Guidelines for Pharmaceutical Research and Evaluation of Human Stem Cell Products (Trial) [5] issued in April 2023. This document is an updated version of the *Guidelines for Quality Control of Stem Cell Preparation and Preclinical Research (Trial)* [2] in 2015, providing more systematic recommendations on technical issues of stem cell medicine pharmaceutical research. It covers general considerations on common problems of stem cell medicine (such as biological activity, directed differentiation

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and unexpected biological effects, tumorigenicity, pluripotent stem cell residue, genetic and epigenetic stability, genetic editing, heterogeneity, risk control), materials used in production, production process, quality research and standard, stability, packaging and sealing container systems.

Guidelines for Clinical Trials of Human Stem Cells and Their Derived Cell Therapeutic Products (Trial) [6] in June 2023. This document provides suggestions on technical issues of stem cell therapy clinic trial design, including general considerations on ethics, participants, risk control, individualized treatment, feasibility assessment, preclinical research data, exploratory clinical trials, and confirmatory clinical trials. It also includes recommendations on long-term follow-up of clinical trial participants and post-marketing research/monitoring.

Guidelines for Clinically Relevant Communication of Cell and Gene Therapy Products [7] issued in December 2023. This document provides suggestions for communication between the new cell medicine applicants and the drug regulatory agency during the development of cell and gene therapy products, addressing the key points and general considerations at different stages of communication.

Guidelines for Nonclinical Research of Human Stem Cell Products [8] in January 2024. This document is formulated to put forward special considerations and requirements for nonclinical research and evaluation during stem cell medicine development, including the key concerns on nonclinical research strategy, the general guidance on the basic principles and content of nonclinical research, such as pharmacology studies, pharmacokinetics research, safety studies (safety pharmacology, general toxicity, tumorigenicity, genetic toxicity, reproductive toxicity, formulation safety, etc.).

Guidelines for Clinical Trials of Mesenchymal Stem Cells Against Graft-Versus-*Host Disease (Trial)* [9] issued in January 2024. This document applies to mesenchymal stem/stromal cell products isolated from tissues (such as bone marrow, umbilical cord, umbilical cord blood, or fat) or derived from pluripotent stem cells (embryonic stem cells (ESCs)) or (induced pluripotent stem cells (iPSCs)), providing research recommendations for clinical trials of mesenchymal stem cell against GVHD, including considerations on clinical trial (clinical history and best available treatment, study population, study endpoint, trial design, subject follow-up) and communication with the Center for Drug Evaluation (CDE), NMPA.

3 Regulation of Drug Standards in China

"Drug standards" refer to technical requirements formulated based on the physical, chemical, and biological characteristics of the drug, for testing whether its quality is stable and uniform, and meets the requirements for medicinal use.

In order to standardize the management of drug standards, NMPA promulgated "*Management Methods for of Drug Standards*" [10] in July 2023. According to this regulatory document, the Chinese drug standard system includes national drug standards, drug registration standards, and provincial traditional Chinese medicine standards. This regulation has clarified the formulation and revision procedures of the three types of standards. Also, the responsibilities of medical product administrations and pharmaceutical enterprises have been clarified.

National drug standards refer to Chinese Pharmacopoeia and drug standards promulgated by the drug regulatory authority. The formulation and management of national drug standards are organized by the Chinese Pharmacopoeia Commission. Social organizations, enterprises and institutions, and citizens are encouraged to participate. The formulation procedure of national drug standards is clearly stated in the regulation.

Drug registration standards refer to the quality standards for specific drugs proposed by the drug registration applicant, checked and ratified by the Center for Drug Evaluation (CDE), and approved by the NMPA, and issued to the drug marketing authorization holder (hereinafter referred to as "holder") when the drugs are approved for marketing. The registration standard is a quality stan-

dard for a specific drug, which can control the drug quality in a more targeted manner. During the formulation and revision of drug registration standards, the responsibilities of the "holder" are strengthened.

The national drug standards reflect the overall level of drug quality in China and shall be regarded as the most basic requirement for a drug. The requirements in the registration standard shall not be lower than those in the national drug standard.

The Chinese Pharmacopoeia is updated every 5 years, during this period, the supplementary version of the Chinese Pharmacopoeia can be formulated in a timely manner according to actual situations. The supplementary version holds the same legal status as its corresponding current version of the Chinese Pharmacopoeia. In two recent years, the Chinese Pharmacopoeia Commission has announced a set of exposure drafts of cell therapy-related standards on its official website for widely soliciting opinions from society, including *Cellular Species Authentication Methods, Guidelines for Microbiological Examination of Cellular Products, Guidelines for Bioassay Methods of Genetically Modified Cell Lines, Preparation and Quality Control of Animal Cell materials for Biological Product Control, Preparation and Quality Control of Animal Cell materials for Biological Product Manufacture.* Therein, *Guidelines for Microbiological Examination of Cellular Products* [11] and *Guidelines for Bioassay of Genetically Modified Cell Lines* [12] are approved and published in the 1st supplementary version to *Chinese Pharmacopoeia (2020)* in October 2023. The representative guidelines and standards related to cell therapy are listed in Table 1.

Table 1 Representative cell therapy-related standards in *Chinese Pharmacopoeia*

Title	Status
Cellular Species Authentication Methods [13]	Under development
Guidelines for Microbiological Examination of Cellular Products [11]	Published (1st supplementary version 2020 Chinese Pharmacopoeia)
Guidelines for Bioassay Methods of Genetically Modified Cell Lines [12]	Published (1st supplementary version 2020 Chinese Pharmacopoeia)
Preparation and Quality Control of Animal Cell materials for Biological Product Control [14]	Under development
Preparation and Quality Control of Animal Cell materials for Biological Product Manufacture [15]	Under development
9012 Guidelines for Quantitative Analysis Methods of Biological Samples [16]	Published (2020 Chinese Pharmacopoeia)
9099 Guidelines for validation of analytical methods [17]	Published (2020 Chinese Pharmacopoeia)
9101 Guidelines for verification of analytical methods [18]	Published (2020 Chinese Pharmacopoeia)
9201 Guidelines for validation of alternative methods for microbiological testing of pharmaceuticals [19]	Published (2020 Chinese Pharmacopoeia)
9401 Guidelines for validation of biological activity/potency assays for biological products [20]	Published (2020 Chinese Pharmacopoeia)
9402 Guidelines for stability assays for biological products [21]	Published (2020 Chinese Pharmacopoeia)
Management and Quality Control of Raw Materials and Auxiliary Materials for Biological Product Manufacture [22]	Published (2020 Chinese Pharmacopoeia)
Management and Quality Control of Microorganism Strain for Biological Product Manufacture and Control [23]	Published (2020 Chinese Pharmacopoeia)
Preparation and Quality Control of Animal Cell materials for Biological Product Manufacture and Control [24]	Published (2020 Chinese Pharmacopoeia)
Management and Calibration of Standard Substance for Biological Product [25]	Published (2020 Chinese Pharmacopoeia)
Viral Safety Control of Biological Products [26]	Published (2020 Chinese Pharmacopoeia)
Management of Packaging, Storage and Transportation for Biological Product [27]	Published (2020 Chinese Pharmacopoeia)

It is worth noting that, the quality standards for critical quality attributes of cell medicine remain blank in the drug standard system. Stem cell technology is rapidly developing and constantly innovating, in order to keep the balance between standard formulation and technological development, it is necessary to update the management of cell preparations in a timely manner according to technological innovation.

The drug standards of stem cell medicine would be directly related to the health of people and will develop along with the application of stem cell medicine. The formulation of drug standards usually undergoes a strict process of verification and validation. Other types of standard documents, such as the Social Community Standard issued by stem cell therapy-related societies, the Chinese National Standard on Relevant Technologies issued by SAC (Standardization Administration of the People's Republic of China), and International consensus and standards issued by influential international organizations (for example, ISO standards issued by the International Organization of Standards), could provide important supporting references for stem cell medicine standardization.

4 Development of Stem Cell Standards in China

In an emerging field, technology development is often "one step faster" than standard setting. To increase the effective supplement of standards, the Chinese government encourages social organizations and industrial technology alliances to coordinate with relevant market entities to jointly formulate standards that meet the needs of the market and technology innovation. Therefore, "Social community standards, first trial" becomes the starting point of stem cell standardization.

The Standard Committee of Chinese Society for Cell Biology (the former Stem Cell Standardization Working Group founded by the Chinese Society for Stem Cell Research and the Chinese Society for Cell Biology in 2016) published the first Chinese stem cell standard, *T/CSSCR 001 General Requirements for Stem Cell* [28], in 2017 and the first specific standard for quality control of human ESCs, *T/CSSCR 002 Human Embryonic Stem Cell* [29], in 2019 respectively (revised in 2020, renamed *T/CSCB 0001—2020 General requirements for stem cells* [30] and *T/CSCB 0002—2020 Human embryonic stem cell* [31] respectively). The two standards have attracted much attention in the field and are widely referred to during the formulation of subsequent guidelines and standards by NMPA and other social organizations. The committee continuously convenes proposals, and so far has issued a total of 15 group standards related to cell preparations, including stem cell general requirements, technical specification for ethics review, and specific standards for various cell types, organoids, and extracellular vesicles [28, 29, 32–44]. The English version of these standards has also been published in international journals substantially [45–59]. Increasing standards related to analytical methods, data processing, quality, and process control are currently under development in the committee.

Encouragingly, the Social Community Standards on cell preparation have gained rapid progress in recent years. More societies have joined the formulation of cell group standards. According to the website of the National Public Service Platform for Standards Information (https://std.samr.gov.cn/), from 2020 to 2024, there were nearly 20 societies and industry associations that published more than 80 cell-related group standards. Representative standards are listed in Table 2.

In addition to Social Community Standards, Chinese National Standards on relevant technologies issued by SAC and local standards issued by provincial standardization administrative agencies could also serve as supporting references. The first Chinese National Standard on the human pluripotent stem cell, *GB/T 42466–2023 Technical specification for pluripotent stem cell management in biobank* [89], was released on September 2023. This document specifies the requirements for the collection and reception of biological source material, PSC line establishment, thawing and culture, cryopreservation and storage, quality control, distribution, and trans-

Table 2 Representative cell therapy-related Chinese social community standards

Published Time	Title	Formulated by
2017/11/22	*T/CSSCR 001—2017 General requirements for stem cells* [28] (revised in 2020, renamed *T/CSCB 0001—2020 General requirements for stem cells* [30])	Chinese Society for Cell Biology
2019/2/26	*T/CSSCR 002—2019 Human embryonic stem cell* [29] (revised in 2020, renamed *T/CSCB 0002—2020 Human embryonic stem cell* [31])	Chinese Society for Cell Biology
2020/10/23	*T/SRA 003—2020 Preparation and quality control of embryonic stem cell-derived marrow mesenchymal stem cell* [60]	Guangdong Stem Cell and Regenerative Medicine Association
2021/1/26	*T/CSCB 0003—2021 Human mesenchymal stem cell* [40]	Chinese Society for Cell Biology
2021/1/26	*T/CSCB 0004—2021 Human hematopoietic stem/progenitor cell* [41]	Chinese Society for Cell Biology
2021/1/26	*T/CSCB 0005—2021 Human induced pluripotent stem cell* [42]	Chinese Society for Cell Biology
2021/1/26	*T/CSCB 0006—2021 Human retinal pigment epithelial cell* [43]	Chinese Society for Cell Biology
2021/1/26	*T/CSCB 0007—2021 Human cardiomyocyte* [44]	Chinese Society for Cell Biology
2021/1/26	*T/CSCB 0008—2021 Primary human hepatocyte* [32]	Chinese Society for Cell Biology
2021/3/4	*T/SRA 005—2021 Clinical Cell Preparation and Quality Control of Bone Marrow Mesenchymal Stem Cell* [61]	Guangdong Stem Cell and Regenerative Medicine Association
2021/12/30	*T/JPMA 008—2020 The technical specification practices of medicinal nano-sized iron oxide tracers labeling clinical grade human umbilical cord mesenchymal stem cells* [62]	Jiangsu Preventive Medicine Association
2022/4/28	*T/SBX 055—2022 Test methods for tumorigenicity of stem cell therapy products* [63]	Shijiazhuang Standardization Association
2022/6/28	*T/SHPPA 012—2022 Validation technical requirements for rapid sterility testing method of cellular and gene therapy products* [64]	Shanghai Pharmaceutical Profession Association
2022/8/15	*T/QMHIPA 004—2022 Specification of Release Testing for Stem Cell-based Medicinal Products of Cell Preparation Center* [65]	Qingdao Medical Care and Health Industry Promotion Association
2022/9/23	*T/CSCB 0009—2022 Technical Specification for Ethics Review of Human Stem Cell Research* [33]	Chinese Society for Cell Biology
2022/9/23	*T/CSCB 0010—2022 Human Natural Killer Cells* [34]	Chinese Society for Cell Biology
2022/9/23	*T/CSCB 0011—2022 Human Midbrain Dopaminergic Progenitor* [35]	Chinese Society for Cell Biology
2022/9/23	*T/CSCB 0012—2022 Human neural stem cell* [36]	Chinese Society for Cell Biology
2022/9/23	*T/CSCB 0013—2022 Human intestinal organoid* [37]	Chinese Society for Cell Biology
2022/9/23	*T/CSCB 0014—2022 Human intestinal cancer organoid* [38]	Chinese Society for Cell Biology
2022/9/23	*T/CSCB 0015—2022 General requirements for production of extracellular vesicles derived from human stem cells* [38]	Chinese Society for Cell Biology
2022/10/26	*T/XSMIA 0005—2022 Digitization Consultant for Cell Bank* [66]	Xinjiang Social Medical Institutions Association

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Table 2 (continued)

Published Time	Title	Formulated by
2022/11/29	*T/CMBA 018—2022 Biosafety—Guideline of description for pathogen safety data sheets* [67]	China Medicinal Biotechnology Association
2022/11/29	*T/CMBA 019—2022 Specification for informed consent for donors of stem cells* [68]	China Medicinal Biotechnology Association
2022/11/29	*T/CMBA 019—2022 Specification for informed consent for donors of stem cells* [68]	China Medicinal Biotechnology Association
2023/2/22	*T/CMBA 020—2023 Guideline for preparation, cryopreservation, recovery and identification of organoids of human normal breast and breast cancer tissue* [69]	China Medicinal Biotechnology Association
2023/8/22	*T/CMBA 015—2021 Guideline for Ethical Assessment of Stem Cell Sources* [70]	China Medicinal Biotechnology Association
2023/8/22	*T/CMBA 015—2021 Guideline for Ethical Assessment of Stem Cell Sources* [70]	China Medicinal Biotechnology Association
2023/8/22	*T/CMBA 017—2022 Guideline of construction and preservation of organoids of gastrointestinal epithelial tissues* [71]	China Medicinal Biotechnology Association
2023/8/23	*T/CMBA 013—2021 Specification for hospital in management of clinical application of chimeric antigen receptor T cell marketed products* [72]	China Medicinal Biotechnology Association
2023/9/14	*T/CMBA 021–2023 Specification of quality management for ancillary materials present during the production of cellular therapeutic products* [73]	China Medicinal Biotechnology Association
2024/10/29	T/CSCB 0016—2024 Determination of cell viability—AO/PI staining method [74]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0017—2024 Determination of cell viability—Tropan blue staining [75]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0018—2024 Determination of ATP content in cell [76]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0019—2024 Detection method of stem cell marker proteins—Flow cytometry method [77]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0020—2024 Human gallbladder cancer organoids [78]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0021—2024 Human pancreatic cancer organoids [79]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0022—2024 Human gastric cancer organoids [80]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0023—2024 Human gastric organoids [81]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0024–2024 Human spinal cord GABAergic neural progenitor cell [82]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0025—2024 Human cortical neural progenitor cells [83]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0026—2024 Technical specification for hemocompatibility assessment of human mesenchymal stem cells [84]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0027—2024 Human islet [85]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0028—2024 Testing for bacteria and fungi in cell preparation and ancillary materials present during the production—TaqMan quantitative PCR assay [86]	Chinese Society for Cell Biology

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Table 2 (continued)

Published Time	Title	Formulated by
2024/10/29	T/CSCB 0029—2024 Detection of residual pluripotent stem cells in differentiated cells—General requirements on TaqMan quantitative PCR assay [87]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0030—2024 Human cerebral organoids [88]	Chinese Society for Cell Biology
2024/10/29	T/CSCB 0031—2024 Human microglia cell	Chinese Society for Cell Biology

port on biobanking of PSCs. There are also sets of Chinese National Standards on testing methods and data analysis that have been issued or underdeveloped, *such as GB/T 40365 General guide for cell sterility testing* [90]*, GB/T 40172 General guidance on detection methods of mammalian cell cross-contamination* [91]*; GB/T 39730 General requirements for cell counting—Flow cytometry* [92]*, GB/T 39729 General requirements for measurement of cell purity—Flow cytometry* [93]*, GB/T 42076.1 Biotechnology—Cell counting—Part 1: General guidance on cell counting methods* [94], providing technical supports for stem cell standardization. The representative relevant national and local standards are listed in Table 3.

5 International Consensus and Standards Supporting Stem Cell Research and Development

The International Society for Stem Cell Research (ISSCR), one of the most influential professional international organizations in stem cell research, issued *Guidelines for Stem Cell Research and Clinical Translation* [107], which is widely adopted worldwide. In partnership with global stakeholders, ISSCR released *Standards for human stem cell use in research* [108] in June 2023, aiming to improve the reproducibility of research from lab to lab and from cell line to cell line. This standard is formulated based on previous recommendations for the characterization of cell lines and recommend standard, addressing the standards for basic stem cell characterization, undifferentiated stem cell identification, pluripotency analysis, genomic characterization, and stem cell-based model systems. According to the schedule of the standard initiative of ISSCR, the development of clinical standards follow in 2023–2024, which will provide precise recommendations to streamline and facilitate regulatory review, manufacturing, and scale-up or -out-of-cellular therapies.

International Organization for Standardization (ISO) is an independent, nongovernmental organization with a membership of over 170 national standard bodies. So far, ISO has developed more than 25, 000 international standards covering almost all aspects of technology and manufacturing. ISO/TC276, the technical committee of biotechnology, works on the standardization of biotechnology processes including terms and definitions, biobanks and bioresources; analytical methods; processioning, data processing, and metrology. There are a number of cell application standards published or under development in TC276, covering various types of cell resources, interoperability of stem cell data, risk management, manufacturing, packaging, transportation, and analytical methods (Table 4). Therein, some of the published ISO standards have already been adopted in an identical or modified manner for formulating Chinese national standards [109, 110, 121, 128].

Concurrently, the Chinese team is providing a great contribution to developing stem cell standards in ISO, leading the drafting of a set of stan-

Table 3 Representative biotechnology Chinese national standards and local standards

Title	Hierarchy	Issued By	Status	Published Time
GB/T 42466–2023 Biobanking technical requirement for management of pluripotent stem cells [89]	National standard	SAC	Published	2023/9/7
GB/T 42398–2023 Technical specifications of cleanroom design for cell culture [95]	National standard	SAC	Published	2023/3/17
20230708-T-469 Biomaterial——General requirements for transportation of cells [96]	National standard	SAC	Underdevelopment	/
GB/T 42076.1–2022 Biotechnology—Cell counting—Part 1: General guidance on cell counting methods [94]	National standard	SAC	Published	2022/12/30
GB/T 41895–2022 Determination for DNA viruses of cell—MNP marker method [97]	National standard	SAC	Published	2022/10/12
GB/T 40365–2021 General guide for cell sterility testing [90]	National standard	SAC	Published	2021/08/20
GB/T 40172–2021 General guidance on detection methods of mammalian cell cross-contamination [91]	National standard	SAC	Published	2021/05/21
20211026-T-469 Determination of styrene monomer and 2-chloroethanol residues in cell culture—GC-MS [98]	National standard	SAC	Underdevelopment	/
20211115-T-306 Specification on general descriptors for cell-line resources [99]	National standard	SAC	Underdevelopment	/
GB/T 39730–2020 General requirements for cell counting—Flow cytometry [92]	National standard	SAC	Published	2020/12/14
GB/T 39729–2020 General requirements for measurement of cell purity—Flow cytometry [93]	National standard	SAC	Published	2020/12/14
DB61/T 1497–2021 Specification for the construction and management of human mesenchymal stem cell banks [100]	Local standard	Shaanxi Administration for Market Regulation	Published	2021/12/17
DB22/T 3203–2020 Specification for stem cell quality management [101]	Local standard	Jilin Administration for Market Regulation	Published	2020/11/23
DB4403/T 121–2020 Specifications for transportation technology and management of human cell products [102]	Local standard	Shenzhen Administration for Market Regulation	Published	2020/11/23
DB13/T 5162–2020 Specifications for the construction and management of cell preparation centers [103]	Local standard	Hebei Administration for Market Regulation	Published	2020/3/25
DB32/T 3544–2019 Specification for quality control and management of clinical grade human tissue-derived Mesenchymal Stem Cells [104]	Local standard	Jiangshu Administration for Market Regulation	Published	2019/2/28
DB33/T 2030–2017 Specification for the construction and management of human mesenchymal stem cell banks [105]	Local standard	Zhejiang Administration for Market Regulation	Published	2017/5/10
DB31/T 687–2013 Basic requirements for clinical cell therapy platform setting [106]	Local standard	Shanghai Administration for Market Regulation	Published	2013/03/11

Table 4 Representative biotechnology ISO standards

Standards	Category	Status
ISO 20391-1:2018 Biotechnology—Cell counting—Part 1: General guidance on cell counting methods [109]	Analytical methods	Published
ISO 20395:2019 Biotechnology—Requirements for evaluating the performance of quantification methods for nucleic acid target sequences—qPCR and dPCR [110]	Analytical methods	Published
ISO 21899:2020 Biotechnology—Biobanking—General requirements for the validation and verification of processing methods for biological material in biobanks [111]	Analytical methods	Published
ISO 24190:2023 Biotechnology—Analytical methods—Risk-based approach for method selection and validation for rapid microbial detection in bioprocesses [112]	Analytical methods	Published
ISO 20391-2:2019 Biotechnology—Cell counting—Part 2: Experimental design and statistical analysis to quantify counting method performance [113]	Analytical methods	Published
ISO 20397-2:2021 Biotechnology—Massively parallel sequencing—Part 2: Quality evaluation of sequencing data [114]	Analytical methods	Published
ISO 23033:2021 Biotechnology—Analytical methods—General requirements and considerations for the testing and characterization of cellular therapeutic products [115]	Analytical methods	Published
ISO 24421:2023 Biotechnology—Minimum requirements for optical signal measurements in photometric methods for biological samples [116]	Analytical methods	Published
ISO/TS 23511:2023 Biotechnology—General requirements and considerations for cell line authentication [117]	Analytical methods	Published
ISO/DTR 4752 Biotechnology—Inventory of methods for detection of microbiological contamination in mammalian cell culture [118]	Analytical methods	Underdevelopment
ISO 24479:2024 Biotechnology—Cellular morphological analysis—General requirements and considerations for cell morphometry to quantify cell morphological features [119]	Analytical methods	Published
ISO/DIS 8934 Biotechnology—General considerations and requirements for cell viability analytical methods—Part 1: Mammalian cells [120]	Analytical methods	Underdevelopment
ISO 24603:2022 Biotechnology—Biobanking—Requirements for human and mouse pluripotent stem cells [121]	Biobanking	Published
ISO/TS 22859:2022 Biotechnology—Biobanking—Requirements for human mesenchymal stromal cells derived from umbilical cord tissue [122]	Biobanking	Published
ISO 21709:2020 Biotechnology—Biobanking—Process and quality requirements for establishment, maintenance and characterization of mammalian cell lines [123]	Biobanking	Published
ISO 24651:2022 Biotechnology—Biobanking—Requirements for human mesenchymal stromal cells derived from bone marrow [124]	Biobanking	Published
ISO/CD 20012.2 Biotechnology—Biobanking—Requirements for human natural killer cells derived from pluripotent stem cells [125]	Biobanking	Underdevelopment
ISO 18162:2024 Biotechnology—Biobanking—Requirements for human neural stem cells derived from pluripotent stem cells [126]	Biobanking	Published
ISO/TS 23565:2021 Biotechnology—Bioprocessing—General requirements and considerations for equipment systems used in the manufacturing of cells for therapeutic use [127]	Bioprocess	Published
ISO 20399:2022 Biotechnology—Ancillary materials present during the production of cellular therapeutic products and gene therapy products [128]	Bioprocess	Published
ISO 20404:2023 Biotechnology—Bioprocessing—General requirements for the design of packaging to contain cells for therapeutic use [129]	Bioprocess	Published

(continued)

Table 4 (continued)

Standards	Category	Status
ISO 21973:2020 Biotechnology—General requirements for transportation of cells for therapeutic use [130]	Bioprocess	Published
ISO/TS 23494–1:2023 Biotechnology—Provenance information model for biological material and data—Part 1: Design concepts and general requirements [131]	Bioprocess	Published
ISO 20691:2022 Biotechnology—Requirements for data formatting and description in the life sciences [132]	Data processing	Published
ISO 21710:2020 Biotechnology—Specification on data management and publication in microbial resource centers [133]	Data processing	Published
ISO/TR 3985:2021 Biotechnology—Data publication—Preliminary considerations and concepts [134]	Data processing	Published
ISO/CD 8472–2 Biotechnology—Data interoperability for stem cell data—Part 2: Key characteristics of stem cell data [135]	Data processing	Underdevelopment
ISO 8472-1:2024 Biotechnology—Data interoperability for stem cell data—Part 1: Framework [136]	Data processing	Published

dards relevant to stem cell resources. For example, the first stem cell standard in the ISO system *ISO 24603 Biotechnology—Biobanking—Requirements for human and mouse pluripotent stem cells* [121], utilized the Chinese group standard *T/CSCB 0001 General Requirements for Stem Cell* [28] and *T/CSCB 0002 Human Embryonic Stem Cell* [29] at the beginning of drafting. The technology requirements from the Chinese social community standards *T/CSCB 00010 Human natural killer cells* and *T/CSCB 00012 Human neural stem cell* are also referenced during the formulation of the corresponding ISO standards [137, 138], among which the neural stem cell standard *ISO 18162:2024 Biotechnology—Biobanking—Requirements for human neural stem cells derived from pluripotent stem cells has been released at December 2024.* The Chinese national standard *GB/T 40365–2021 General guide for cell sterility testing has been derived into an* ISO technical report *ISO/DTR 4752 Biotechnology—Analytical methods—Considerations for development of approach and selection of methods for detection of microbiological contamination in mammalian cell cultures.* The two-way transformation and adoption of good international and domestic standards would effectively promote the development of stem cell standardization.

6 Establishing a Standard System for Stem Cell Medicine in the Future

Mature standard systems are often established based on mature practices. However, most of the stem cell therapy products are in such an early development, and the application and management of cell preparation products still have a long way to go. In facing these challenges, the stem cell standard system should be established step by step according to the existing good practices and field consensus from scientific research to clinical application. In addition, it is important to collect available clinical trial data, which is the basic reference to set the acceptable criteria for stem cell drug standards.

According to the regulations and requirements of stem cell therapy, the standard system for stem cell therapy should include standards that cover process management, quality control, analytical method, and data interoperability [139].

Process Standardization Before being applied in the clinic, the stem cell preparations will go through a rigorous preparation and evaluation process. As summarized in the above section, NMPA has launched a series of guidelines for the process control of stem cell products. Generally

speaking, during the development of stem cell-based drugs, the production process shall comply with Good Manufacturing Practice (GMP), the nonclinical research should comply with Good Laboratory Practice (GLP) requirements, and the clinical trial shall be in accordance with the requirements of Good Clinical Practice (GCP). However, some particular characteristics of stem cell-based medicines cannot be completely applicable to these current documents and the cell-based medicines are exquisitely responsive to changing environmental conditions, it is recommended to develop the process standards with the requirements directed at the specific process of stem cell medicine production and application. These should include but are not limited to, ethical review, collection, and reception of biological raw materials, cell line establishment, expansion, characterization, cell bank management, quality control, product release, information management, traceability, storage, transportation, the assessment on pharmacokinetics, efficacy pharmacology, and safety pharmacology, etc.

Quality Control Standardization The quality standards are directly relevant to stem cell product eligibility, which are established to specify requirements for the critical quality attributes of products that affect the safety, efficacy, and stability of clinical treatments. These critical quality attributes include but are not limited to, cell viability, purity, genomic stability, sterility, absence of infectious pathogens, expression of specific genes, tumorigenicity, unexpected differentiation, pluripotent stem cell residue, and functional potency. Establishing criteria that distinguish between acceptability and unacceptability is at the heart of quality standard formulation. During the establishment of acceptance criteria, a series of decisions need to be made, including the selection of the most informative parameter for each quality attribute, the establishment of appropriate methods to give reliable and reproducible measurands; setting realistic tolerances that avoid unnecessary waste of batches with acceptable functionality [140]. Furthermore, it should be noticed that the evaluation of potency is typically based on a functional assay, which should be a readout of a specific biological activity relevant to the product's proposed mode of action. The "identity" markers of a particular cell type in the native tissue may not relate to the potency of a particular PSC-based product which is an in vitro artifact [141]. A deeper understanding of the relationship been the cell quality attributes and sustained efficacy and safety of the final product will support the quality standardization of stem cell products.

Analytical Methods Analytical methods applicable to cell medicine manufacture should be developed, including new methods for cell function evaluation, specific pretreatment for cell samples of existing traditional measurements that cannot be directly used in cell biology research, release testing methods for technical acceptance of crucial material used in production, and the methods for testing intermediates for process control. When developing new methods, the following considerations should be addressed: (1) compliance to the relative regulations and policies; (2) specificity of the target quality attribute; (3) proper parameters for readout and judgement of result; (4) control design; (5) accuracy and reducible results; (6) standard substance for quantitative analysis; (7) limit of detection and the criteria; (8) difficulty of operation, which may induce excessive systematic error; (9) accessibility of facilities and instruments; (10) detection of duration. A newly developed method must be verified and validated before its application, and the process of verification and validation can reference *ICH Q14 Analytical Procedure Development* [142], *ICH Q2 (R2) Validation of Analytical Procedures* [143] and the relevant guide principles in Pharmacopoeia, such as *9012 Guidelines for Quantitative Analysis Methods of Biological Samples* [16], *9099 Guidelines for validation of analytical methods* [17], *9101 Guidelines for verification of analytical methods* [18], *9201 Guidelines for validation of alternative methods for microbiological testing of pharmaceuticals* [19], *9401 Guidelines for validation of biological activity/potency assays for biologi-*

cal products [20]*, 9402 Guidelines for stability assays for biological products* [21].

Data Interoperability Collection and analysis of the valuable data are crucial for both technical improvement and standard establishment. Along with the progress in, and development of stem cell medicine, cross-sector collaborations between academic research institutes, enterprises, hospitals, and governments have been initiated, and the data associated with stem cell biobanking and clinical research/trial is continuously accumulated. It is recommended for standardizing common approaches to working with data (data sharing, storage, analysis, etc.), There are a series of projects on data interoperability standards under development in ISO, and the first stem cell data interoperability standard *ISO 8472-1:2024 Biotechnology—Data interoperability for stem cell data—Part 1: Framework* has been published in July 2024. It is believed that these standards will be helpful to improve the efficiency of data sharing and interoperability, develop a deeper understanding of the relationship between cell medicine characteristic parameters and its therapeutic efficiency, and facilitate recourse sharing from national or international cooperative organizations such as China alliance of stem cell and regenerative medicine (CASCRM), human pluripotent stem cell registry (www.hPSCreg.eu), and International stem cell banking initiative (ISCBI, www.iscbi.org), etc.

7 Perspectives

Standards are essentially a combination of quality and conscience, helping to ensure that the products are safe, reliable, and of high quality. As stem cell medicines are entering mainstream drug development, coming with new opportunities and challenges arise, standardization would set stem cell therapy for success. It is expected that early developers of stem cell medicine will create an open environment for information sharing and consensus establishment.

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