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Evolution of China's stem cell regulatory framework and review considerations for cell–biomaterial combination products

Yibei Chen,[1,*] Jinju Ding,[1] and Bin Liu[1]

[1]Greater Bay Area Center for Medical Device Evaluation and Inspection, National Medical Products Administration (NMPA), Shenzhen 518045, China

*Correspondence: chenyb@mdei.org.cn

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Stem cell therapy has emerged as a transformative frontier in regenerative medicine, offering immense potential to address unmet clinical needs in tissue regeneration, immunological disorders, and degenerative diseases. Globally, the regulation of stem cell–based therapeutic products is not yet fully harmonized across different regions, being primarily determined by their intended application, risk profile, and the applicable legal frameworks. Within the purview of major international regulatory bodies, such products typically fall into the categories of biological products, medical technologies, or advanced therapy medicinal products (ATMPs).[1] Figure 1 compares the regulatory frameworks for stem cell products across the FDA, EMA, Japan, and China, with emphasis on classification and lead authority. This regulatory framework, centered on approval by drug regulatory authorities, ensures rigorous evaluation of product safety, efficacy, and quality and facilitates innovative development while safeguarding public health.

EVOLUTION OF STEM CELL REGULATION IN CHINA AND RECENT DEVELOPMENTS

China's regulation of cell therapy products dates to 1993, when they were first brought under pharmaceutical oversight. A turning point came in 2015, when the NHFPC and CFDA jointly issued the Measures for Stem Cell Clinical Research and accompanying guidelines, establishing a non-registered clinical research system with stem cells as a pilot and designating medical institutions as responsible parties. In 2017, authorities clarified application requirements for new therapies. Since 2020, a series of regulatory policies and guidance documents have been issued in rapid succession.

The Regulations on the Administration of Clinical Study and Clinical Translation and Application of New Biomedical Technologies (Order No. 818), effective May 1, 2026, mark a law-based, standardized phase for stem cell-related innovative technologies.[2] The Order builds upon and systematizes the parallel drug registration and medical technology filing framework under administrative regulations:

(1) The technology track, supervised by the National Health Commission (NHC), applies to individualized, not fully commercialized stem cell therapies limited to tertiary hospitals. After institutional academic/ethical review and preclinical studies, projects are filed with the National Health Commission for clinical trials. Approval from national authorities is required for routine clinical use under ongoing health authority oversight.

(2) The drug track, overseen by the National Medical Products Administration (NMPA), applies to standardized stem cell products developed for commercial-scale use. Consistent with international practice, standalone stem cell therapeutic products are regulated as pharmaceutical drugs under this track, specifically falling into the category of advanced therapy medicinal products (cell therapy products).

On January 2, 2025, the NMPA approved China's first stem cell drug, Amimestrocel Injection, through priority review—a milestone demonstrating the maturity of the drug regulatory pathway. Recently, the NMPA has accepted multiple IND applications for stem cell products, with indications expanding from immune disorders to tissue regeneration and degenerative diseases.

CONSIDERATIONS FOR THE REVIEW OF INNOVATIVE STEM CELL–BIOMATERIAL COMBINATION PRODUCTS

The aforementioned stem cell drugs are predominantly administered via local or systemic injection, with their therapeutic mechanisms relying on immunomodulation, paracrine signaling, and tissue regeneration. These products already have relatively clear regulatory boundaries. Concurrently, stem cell–biomaterial combination products are experiencing unprecedented developmental opportunities. By utilizing the biomaterial to provide spatial scaffolding and physical guidance, these combination products leverage the synergy between the materials and cellular components to facilitate tissue regeneration, thereby achieving both structural restoration and biological activity while adapting to complex tissue-repair scenarios. Numerous studies have demonstrated their distinct advantages in bone, skin, and other tissue regeneration applications, with several products already transitioning to the clinical phase. Local governments have also introduced explicit supportive policies, such as the Shenzhen Work Plan for Promoting High-Quality Development of the Cell and Gene Field issued on April 3, 2026.[3]

From a regulatory standpoint, stem cell–medical device combination products designed for tissue regeneration exhibit distinct regulatory characteristics compared with either standalone stem cell drugs or conventional medical devices. The primary challenge lies in clarifying the product's primary mode of action (PMOA) and ensuring the safety, efficacy, and quality of both the stem cell and the device components. Consequently, the primary regulatory focus should encompass the following dimensions:

Regulatory classification and PMOA determination

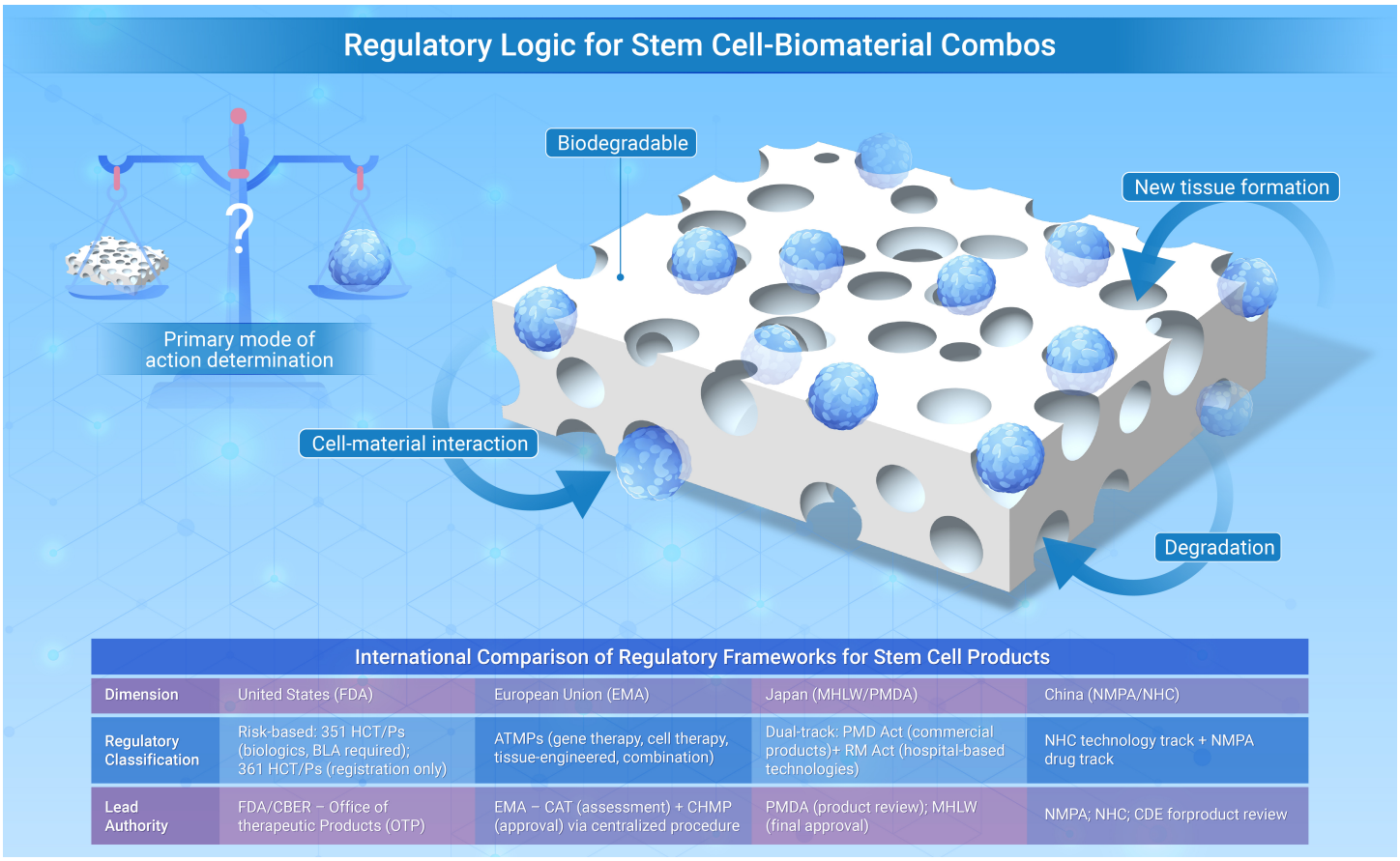
Currently, a standardized framework for distinguishing a standalone stem cell drug from a genuine stem cell–medical device combination product remains to be fully established. For products containing both cellular and biomaterial components, the regulatory pathway and review standards are not clearly defined. PMOA determination is key in resolving this classification challenge. Under the regulatory framework,[4] the following decision-making path may be considered: Step 1, identify all modes of action—pharmacological effects of stem cells (immunomodulation, paracrine signaling, tissue regeneration, etc.) and physical/structural functions of the biomaterial (scaffolding, guidance, barrier, etc.). Step 2, assess the relative contribution of each mode to the overall therapeutic effect. Step 3, determine the PMOA—if stem cell effects are indispensable and the biomaterial is primarily a delivery vehicle, the product may be drug-led; if the biomaterial's structural/physical function is the principal mechanism, it may be device-led. Step 4, when the PMOA is not readily discernible and no similar product is marketed, applicants should apply for formal combination product classification.

Key review points

Building upon existing guidance for drug-device combination products, specific evaluation requirements must be meticulously tailored to the biological characteristics of stem cells. Core safety considerations encompass the traceability and ethical sourcing of stem cells, tumorigenicity, immunogenicity, and the biocompatibility and overall safety profile of the biomaterial, among others. Quality control systematically covers the biological activity, directed differentiation capacity, and batch-to-batch consistency of the cells, alongside the physicochemical properties and degradation kinetics of the biomaterial, etc. Furthermore, given the inherent complexity of these combination products, particular attention must be paid to the reciprocal interactions between the biomaterial and cellular components, as well as their safety and efficacy during the dynamic phases of degradation, stem cell differentiation, and tissue regeneration—representing critical obstacles that must be resolved to facilitate successful translation and market entry.

Regulatory logic and risk stratification

The regulatory logic for these combination products should center on product classification and PMOA identification. When the PMOA is characterized by structural support, barrier functions, or physical guidance—rather than primary pharmacological effects—the evaluation should focus on the mechanical strength, biocompatibility, and degradation characteristics of the scaffold, while concurrently assessing the viability, differentiation potential, and therapeutic contribution of the seeded stem cells. Clinical evaluation



International Comparison of Regulatory Frameworks for Stem Cell Products

Dimension	United States (FDA)	European Union (EMA)	Japan (MHLW/PMDA)	China (NMPA/NHC)
Regulatory Classification	Risk-based: 351 HCT/Ps (biologics, BLA required); 361 HCT/Ps (registration only)	ATMPs (gene therapy, cell therapy, tissue-engineered, combination)	Dual-track: PMD Act (commercial products)+ RM Act (hospital-based technologies)	NHC technology track + NMPA drug track
Lead Authority	FDA/CBER – Office of therapeutic Products (OTP)	EMA – CAT (assessment) + CHMP (approval) via centralized procedure	PMDA (product review); MHLW (final approval)	NMPA; NHC; CDE forproduct review

Figure 1. International comparison of regulatory frameworks for stem cell products

should be oriented toward tissue-regeneration-specific endpoints, such as tissue integration and functional recovery, while carefully monitoring long-term safety outcomes.

Within this framework, a risk stratification assessment based on three dimensions is recommended: stem cell risk, such as whether the cell type is pluripotent/genetically modified, adult/allogeneic, or autologous/minimally manipulated; biomaterial risk, such as whether the material is novel/non-degradable, an established biodegradable polymer, or an inert material; and combination-specific risk, such as strong cell–material interactions, physical interactions, or relatively independent functions. Overall, the scope and intensity of preclinical and clinical studies should be informed by the risk profile across these dimensions. This framework aligns with the "specific analysis for specific products" principle, ensuring regulatory intensity is proportionate to the actual risk profile of each product.

OUTLOOK

Order No. 818 refined China's stem cell framework, yet implementation for combination products is still nascent. A clear regulatory pathway is urgently needed to facilitate clinical translation.

We offer three recommendations here. First, the PMOA-based classification logic should serve as the foundational principle for regulatory determinations. Second, our risk stratification framework offers a practical tool for calibrating study requirements, and we recommend its refinement through regulatory practice. Third, we consider it essential that the NMPA strengthen internal coordination with the NHC; we recommend a joint expert working group to develop classification guidelines and review standards within the next few years, providing regulatory certainty for innovation. This proposal is feasible: China already has an established joint review mechanism for drug–device combination products , which can be extended to stem cell–biomaterial combinations. Internationally, the FDA's Office of Combination Products (OCP) offers a proven model for PMOA-based classification and cross-center coordination.

We acknowledge that no mature regulatory pathway for stem cell–medical device combination products has yet been established in China. This should not be viewed as regulatory lag, but rather as an opportunity to build a fit-for-purpose evaluation framework from the outset—one that is scientifically sound, risk-proportionate, and internationally aligned. Proactive pre-regulatory research is not merely advisable; it is essential for evidence-based policymaking. We call upon all stakeholders to work together in establishing a clear translational pathway, enabling China to build a robust regulatory environment that ultimately benefits patients and advances the field of regenerative medicine and related disciplines.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.