干细胞产品质量研究与检测专栏

[编者按]

干细胞是一类原始且未分化，具有自我更新，自动归巢，免疫原性低，多向分化潜能以及再生各种组织器官潜在功能的细胞，对多种难治性的人类重大疾病具有潜在治疗意义。多年来，各国对干细胞研究和临床转化非常重视，出台了一系列干细胞产品的相关指南，用于指导干细胞临床应用。2008 年国际干细胞研究协会（ISSCR）制定了《干细胞临床转化指南》，2009 年国际干细胞组织（ISCF）制定了《人胚胎干细胞建库和供应指南》，为干细胞临床转化研究奠定了基础。此后，美国食品药品监督管理局（FDA）、欧洲药品管理局（EMA）、世界卫生组织（WHO）、药品注册的国际协调组织（ICH）、ISSCR 和 ISCF 等机构对干细胞从起始原材料到最终产品的质量控制、临床前和临床研究等进一步制定技术规范并更新了指南。截止到 2024 年 10 月 23 日，以“stem cell”作为关键词，搜索全球在 clinicaltrials.gov 注册的干细胞治疗临床试验方案有 13 021 项，统计有研究结果的项目 1 942 项，目前国际上已有 20 余种干细胞药物批准上市，干细胞治疗已成为各国研究的热点。

我国于 2015 年 7 月 20 日由原国家卫生和计划生育委员会和原国家食品药品监督管理总局联合发布了《干细胞临床研究管理办法（试行）》，同年 7 月 31 日，两部委又共同组织制定了《干细胞制剂质量控制及临床前研究指导原则（试行）》，以确保干细胞治疗的安全性和有效性。近年来，国家药品监督管理局药品审评中心出台了一系列相关指导原则，包括《细胞治疗产品研究与评价技术指导原则（试行）》（2017.12），《人源干细胞产品药学研究与评价技术指导原则（试行）》（2023.04），《人源干细胞产品非临床研究技术指导原则》（2024.01）。截止到 2024 年 12 月底，我国共有 159 项干细胞药物向 NMPA 提交了 IND 申请，其中 117 项获临床默许，适应症包括：肺纤维化、膝骨关节炎、骨折、肝硬化、慢加急性肝衰竭、脑卒中、类风湿关节炎、糖尿病足溃疡、克罗恩病等。2025 年 1 月 2 日，我国首款干细胞治疗药品 – 艾米迈托赛注射液（商品名：睿铂生）批准上市，标志着我国在干细胞治疗领域迈入了新阶段。

与其他药品相比较，干细胞具备自我更新和多向分化潜能，因此，干细胞产品的细胞类型多样，产品细胞本身具备体内生存、增殖、分化、细胞间相互作用等能力。干细胞产品作为一种活的无菌注射药物，生产过程中其干细胞来源、类型、扩增、基因修饰、诱导分化等存在较大差异，因此干细胞产品的均一性和稳定性相对较差，使用的时间窗口较短，其质量控制过程更加复杂，需要建立相应的快速有效的检验新方法新技术。为此申请并承担了北京市科委 CGT 课题研究任务“基因修饰免疫细胞和基因治疗药物质量控制关键技术与服务平台建设”部分项目，建立了相应的包括干细胞产品检验检测的新方法，为企业申报干细胞产品临床研究或新药审批进行检验奠定了基础。

为迎接即将到来的干细胞产品的研究热潮，我们组织干细胞产品质量分析专业人员撰写相关论文数篇，特设 3 期“干细胞产品质量研究与检测专栏”，内容涉及干细胞产品质量控制检测新技术新方法以及干细胞检测实验室质量体系的构建。本期 4 篇文章，包括“干细胞产品质量控制分析方法研究进展”“间充质干细胞产品生物学活性检验方法建立”“间充质干细胞端粒酶催化亚基 RT-qPCR 方法的建立”“AAV 载体 -HPV16-HPV18-HPyV 假病毒的构建及其在干细胞人源病毒检查中的应用”。希望借助专栏的内容，为相关企业及研究机构提供参考，促进干细胞产品的临床研究和产业化进程。

[特邀栏目主编：饶春明、庞琳]

Special Column for Quality Research and Evaluation of Stem Cell Products

[Editor's Note]

Stem cells are a class of primitive, undifferentiated cells characterized by their capacity for self-renewal, intrinsic homing capability, low immunogenicity, multipotent differentiation potential, and the ability to regenerate various tissues and organs. These unique biological properties make them a promising therapeutic tool for numerous intractable and severe human diseases. Over the years, the significant global attention has been directed toward advancing stem cells research and clinical translation, with the publication of a series of guidelines to facilitate their clinical application. In 2008, the International Society for Stem Cell Research (ISSCR) published the Guidelines for the Clinical Translation of Stem Cells. In 2009, the International Stem Cell Forum (ISCF) released the Guidelines for the Derivation and Distribution of Human Embryonic Stem Cell Lines, which provided foundational standards for the translational development of stem cell-based therapies. Subsequently, regulatory agencies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the World Health Organization (WHO), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ISSCR, and ISCF, have developed technical specification and updated technical guidelines. These guidelines encompass quality control from the procurement of raw materials to the final product, as well as preclinical and clinical studies. As of October 23, 2024, a keyword search for "stem cell" on ClinicalTrials.gov identified 13 021 globally registered clinical trials focused on stem cell-based therapies, including 1 942 studies with published results. To date, over 20 stem cell-based pharmaceutical products have been approved for market worldwide. Stem cell therapy has thus emerged as a critical focus in international biomedical research, driving innovation and advancing the frontiers of regenerative medicine.

In our country, the National Health and Family Planning Commission and the China Food and Drug Administration jointly issued the Administrative Measures for Stem Cell Clinical Research (Trial) on July 20, 2015. Shortly thereafter, on July 31, 2015, the two agencies collaboratively formulated the Guidelines for Quality Control of Stem Cell Preparations and Preclinical Research (Trial) to ensure the safety and efficacy of stem cell therapies. In recent years, the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) has released a series of relevant technical guidelines, including: Technical Guidelines for Research and Evaluation of Cell Therapy Products (Trial) (December 2017), Technical Guidelines for Pharmaceutical Research and Evaluation of Human Stem Cell Products (Trial) (April 2023), and Technical Guidelines for Nonclinical Research of Human Stem Cell Products (Trial) (January 2024). As of the end of December 2024, a total of 159 stem cell pharmaceutical products have submitted IND applications to the NMPA. Among these, 72 products have been granted clinical trial approval by default. The indications for these therapies include pulmonary fibrosis, knee osteoarthritis, bone fractures, liver cirrhosis, acute-on-chronic liver failure, stroke, rheumatoid arthritis, diabetic foot ulcers, Crohn's disease, and others. Crohn´s disease, and others. On January 2nd, 2025, China´s first stem cell therapy drug, Amy Metotrexate Injection (trade name: Ruibo Sheng), was approved for marketing, marking a new stage in China´s stem cell therapy field.

Compared with other pharmaceuticals, stem cells possess self-renewal and multipotent differentiation capabilities. As a result, stem cell products exhibit diverse cell types, with the cells themselves capable of *in vivo* survival, proliferation, differentiation, and intercellular interactions. As living, sterile injectable medicines, stem cell products are exposed to significant variability in aspects such as cell source, type, expansion, genetic modification, and induced differentiation during production. This inherent heterogeneity and instability result in relatively short usage windows and present challenges in ensuring consistent quality. Consequently, quality control for stem cell products is

more complicated, necessitating the development of novel, rapid, and effective testing methodologies and technologies. To tackle these challenges, we applied for and undertook part of the CGT (Cell and Gene Therapy) research project funded by the Beijing Municipal Science and Technology Commission. The project, titled Key Technologies for Quality Control and Service Platform Construction for Genetically Modified Immune Cells and Gene Therapy Drugs, includes the development of innovative testing methods for stem cell products. These advancements lay a foundation for enterprises to conduct testing required for clinical research applications or new drug approvals for stem cell products.

To embrace the forthcoming boom in stem cell product research, we have organized a team of stem cell product quality analysis experts to author several specialized articles. These contributions form a three-part series titled Special Column on Quality Research and Evaluation of Stem Cell Products. The series covers novel techniques and methods for quality control and testing of stem cell products, as well as the establishment of quality systems for stem cell testing laboratories. This issue features four articles, including: "Research Progress on Quality Control Analysis Methods for Stem Cell Products" "Biological Activity Methods Development of Mesenchymal Stem Cell Products" "Establishment of RT-qPCR Method for Telomerase Catalytic Subunits of Mesenchymal Stem Cells" and "The Construction of AAV Vector-HPV16-HPV18-HPyV Pseudoviruses and Application in the Examination of Human-derived Viruses in Stem Cells". We hope the insights shared in this column will serve valuable opinions for relevant enterprises and research institutions, accelerating the clinical research and industrialization of stem cell products.

[Invited Column Editor-in-chief: RAO Chun-ming, PANG Lin]