

The regulatory sciences for stem cell-based medicinal products

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Abstract Over the past few years, several new achievements have been made from stem cell studies, many of which have moved up from preclinical stages to early, or from early to middle or late, stages thanks to relatively safe profile and preliminary evidence of effectiveness. Moreover, some stem cell-based products have been approved for marketing by different national regulatory authorities. However, many critical issues associated mainly with incomplete understanding of stem cell biology and the relevant risk factors, and lack of effective regulations still exist and need to be urgently addressed, especially in countries where establishment of appropriate regulatory system just commenced. More relevantly, the stem cell regulatory sciences need to be established or improved to more effectively evaluate quality, safety and efficacy of stem cell products, and for building up the appropriate regulatory framework. In this review, we summarize some new achievements in stem cell studies, especially the preclinical and clinical studies, the existing regulations, and the associated challenges, and we then propose some considerations for improving stem cell regulatory sciences with a goal of promoting the steadfast growth of the well-regulated stem cell therapies abreast of evolvement of stem cell sciences and technologies.

Keywords stem cell-based medicinal products (SCMPs); stem cell therapy (SCT); safety; effectiveness; standards; guidelines; regulatory science

Introduction

Stem cell research holds a tremendous promise for the development of novel therapies for treating many serious diseases and injuries. While hematopoietic stem cell transplantation has become a standard health care for treating leukemia, non-hematopoietic stem cells have significantly expanded in recent years as major cell types in potential novel therapies [1].

Stem cells are defined as the cells possessing various differentiation potentials and capacity of cell renewal. The resultant stem cell-based therapy (SCT) has emerged as a potential therapeutic modality in which the stem cells isolated from autologous or allogeneic human donors are *ex vivo* processed, expanded, and then administered to patients for treating diseases. Stem cells used in therapies can be categorized as somatic or adult stem cells (SSCs or ASCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSs). The SSCs include hematopoietic stem cells, mesenchymal stem cells (MSCs) and various types of

progenitor or precursor cells existing in fetal, adult or birth-associated tissue, such as the Wharton's Jelly of umbilical cord and the placenta. MSCs of various origins are among the most frequently used cell type in clinical studies largely due to the ease of derivation, relatively safe profile and unique immunomodulatory functions of the cells [2].

However, stem cell-based medicinal products (SCMPs) may represent the most complicated therapeutics in human history of health care due to their extreme complex nature. In many perspectives, they share characteristics with drugs, biological products, cell and tissue products, and even medical devices [1,3,4]. Therefore, development of SCMPs must follow a clinical trial pathway including preclinical and clinical studies (phases I, II, and III) with rigorous regulatory oversights to ensure product's quality, safety and effectiveness during the entire cycle of product development [1,3,4].

While SCTs hold a big promise for improving health care of many serious diseases, they also presents new challenges to both research and regulatory scientists. Stem cells are not a homogeneous population of cells; "SCTs" are not one-fits-all cures. Unrealistic expectation to SCTs by both patients and media can lead to unproven use of stem cells or their derivatives. It is believed that the current challenges are associated with an incomplete understanding of stem cell

biology, limited capability of product evaluation, and, consequently, insufficient regulations [1].

In this review, we summarize some new achievements in stem cell studies, current regulation systems as well as the challenges in order to show the urgency of establishing or promoting stem cell regulatory sciences, which can guide development of new capabilities of product evaluation and effectively link all parts together for advancing development of SCMPs and quality of SCTs [5].

New achievements of SCTs in the world

Over past few years, a large number of clinical studies on non-hematopoietic stem cells have been conducted for treating various diseases in the world. Among top diseases registered in ClinicalTrials.gov are cardiovascular diseases, graft versus host diseases (GVHD), ophthalmological disorders, spinal cord injury, diabetes, neurodegenerative diseases, osteoarthritis, cirrhosis, etc. A vast majority of them use MSCs with only few using hESCs or neural stem cells (Table 1) [6]. Meanwhile, the stem cell industry has also been growing very fast with the activities like sponsoring various types of stem cell clinical trials to develop new stem cell products through the associated regulatory authorities.

New progresses from SCT studies

New progresses from MSCs-based studies

Various preclinical or clinical studies, especially cardiology studies, have used MSCs as single cell type, in combination with other cells, or with scaffold materials.

In a recent pioneering surgery, a new type of vasculature tissue engineered by the mixture of autologous bone marrow MSCs and endothelial progenitor cells with an acellular vein scaffold was successfully used to treat a patient with incurable blood clot to avoid a likely very serious complication, thus

demonstrating a big promise in replacing severely damaged vasculatures using MSC-based tissue engineering [7].

In a TOPCARE-AMI trial (phase II study), autologous bone marrow mononuclear cells (BMMNCs, including MSCs and endothelial progenitor cells) infused into coronary arteries of acute myocardial infarct (AMI) patients demonstrated a notable five-year safety and significant improvement of functionalities. This study together with a recent meta-analysis of 50 studies (2626 patients) has supported the BAMI trial (NCT01569178), a multinational randomized phase III study investigating whether intracoronary infusion of autologous BMMNCs is safe in reducing all-cause mortality in patients of AMI [8].

In studies on chronic ischemic cardiomyopathy and heart failure, a strategy combining stem cell therapy with novel *in vivo* differentiation and imaging approaches was employed. A FOCUS-CCTRN trial (phase II) in patients with chronic ischemic cardiomyopathy for investigating a 6-month efficacy of trans-endocardial delivery of BMMNCs on myocardial function and perfusion revealed a significant improvement in some heart functions. The studies support a notion that the combinatorial therapy using MSCs and other cell types may provide a greater regenerative benefit than MSCs alone [8].

In addition to cardiology problems, MSCs have been trialed for treating vision disorders. In a phase I clinical trial (NCT00458575), a patented umbilical cord MSC line, CNTO 2476, was evaluated with satisfactory safety and efficacy outcomes in patients of retinopathies (RP). Following this study, a phase I/II clinical trial (NCT01226628) transplanting CNTO 2476 into subretinal space of patients with age-related macular degeneration (AMD) has been proposed to further determine its ability to slow degeneration and preserve vision for patients. Interestingly, bone marrow-derived MSCs (hBM-MSCs) also showed an ability to rescue retinal degeneration in mouse models. Based on this promising work, clinical trials have been initiated to determine the safety

Table 1 The representative stem cell clinical trials at different phases

| Cell type | Indication | Phase | Sponsor and location(s) for clinical trials | Clinical trial number |
|---------------------------|--|-------|---|----------------------------|
| hBM-MSCs | Degenerative disc disease | II | Mesoblast, Ltd., USA, Australia | NCT01290367 |
| hBM-MNCs (MSCS + EPCs) | Acute myocardial infarction | III | Barts & The London NHS Trust, UK, Belgium, Denmark, France, Finland, Italy | NCT01569178 |
| hBM-MSCs | Type I diabetes | II | Osiris Therapeutics, Inc., USA, Canada, New Zealand | NCT00690066 |
| hAC-MSCs | Acute myocardial infarction | II | Cytori Therapeutics, USA | NCT01216995 |
| hUC-MSCs | Age-related macular degeneration | I/II | Janssen Biotech, Inc, USA | NCT01226628 |
| hESCs | Advanced dry age-related macular degeneration (Dry AMD) | I/II | Advanced Cell Technology, USA | NCT01344993 |
| Adult hNSCs | Amyotrophic lateral sclerosis (ALS); Chronic spinal cord injury | I/II | NeuralStem, Inc., USA | NCT01348451 NCT01772810 |
| Fetal hNSCs | Spinal cord trauma; age-related macular degeneration (AMD) | I/II | StemCell, Inc., USA | NCT01725880 NCT01632527 |

and efficacy of these cells in patients with various eye diseases (NCT01560715, NCT01531348, NCT01518127 and NCT01518842 trials) [9].

Prochymal, a hBM-MSC product approved already by the regulatory authorities of both Canada and New Zealand for treating acute pediatric steroid-resistant GVHDs, is currently being evaluated in phase III clinical trials to treat moderate-to-severe Crohn's disease (NCT00482092) and the newly diagnosed acute GVHD (NCT00562497), and in phase II trials to treat recently diagnosed type 1 diabetes mellitus (NCT00690066) and acute myocardial infarction (NCT00877903). All these trials are ongoing in multiple centers in the US, Canada, Europe, and Australia [10,11].

New progresses from the hESC-based studies

Advanced Cell Technology have used hESCs to make retinal pigment epithelial cells to treat two forms of blindness (Stargardt's macular dystrophy and dry AMD, NCT01344993), and the trials have shown significant vision improvement. Sahlgrenska Academy was known for using hESCs to repair damaged corneas. When transplanting hESCs onto the damaged human corneas *in vitro*, they found that the hESCs proliferated and differentiated into corneal epithelial-like cells [9].

A novel approach from Lorenz Studer's laboratory showed that dopaminergic neurons derived from hESCs can have robust effects across a range of animal models of Parkinson's diseases (PD), thus encouraging an early clinical trial in patients with PD in next 5 years [12].

New progresses from iPSC-based studies

The granting of 2012 Nobel Prize of Physiology and Medicine to John Gurdon (UK) and Shinya Yamanaka (Japan), who discovered reprogramming of mature cells into pluripotent stem cells, encouraged studies of iPSCs in treating human diseases. However, due to substantial safety concerns, up to date, only one iPSC clinical trial was approved in the world to treat AMD [13]. Currently, a vast majority of iPSC studies with clinical implications are focusing on disease modeling, for either improving the understanding of pathogenesis of, or screening for effective new therapeutic agents for treating, the modeled diseases, like PD [14].

New progresses from neural stem cell (NSC)-based studies

NSCs have been used in treating spinal cord injury, vision diseases, and chronic degenerative disorders. A neural stem cell line (HuCNS-SCs) developed by StemCells Inc. from the fetal brain of the second trimester has been used in a spinal cord injury trial (NCT01725880). To date, a satisfactory safety profile and preliminary efficacy have been observed in patients receiving HuCNS-SCs. In a preclinical study, transplantation of HuCNS-SCs was conducted in rats with RPE defect and significantly improved photoreceptor survival and vision of the animals. Based on this study, the StemCells

Inc. recently launched a clinical trial for treating AMD using HuCNS-SCs (NCT01632527) [9,11,12].

NeuralStem Inc., who already has an ongoing trial for treating ALS (NCT01348451), moved a step closer to clinical trials in chronic spinal cord injury (NCT01772810). The company published a preclinical study data in September 2012 showing that rats with spinal cord injury injected with the company's proprietary spinal cord stem cells (NSI-566) regained movement in previously paralyzed limbs [9,11].

Stem cell industries and the approved products in the world

Stem cell industries

The SCT is an emerging branch of the regenerative medicine (RM). Currently, there are about 700 RM companies in the world: 65% of them are in the US, 20% in Europe, and 15% in other countries.

From 2007 to 2012, the industry-sponsored clinical trials for cell therapy showed a significant uptrend from 198 to 241 with many trials having moved from early to late stages: trials on phase I — down from 77 to 52, phase II — up from 89 to 148, and phase II/III — up from 32 to 41 [11,15,16]. Among the companies moving from early stage are Advanced Cell Technology, NeuralStem and StemCells Inc. There are about 50 late stage (II/III, III or pivotal) ongoing trials, sponsored by approximately 40 companies. No major setbacks or significant numbers of failures in industry-sponsored clinical trials were seen in 2012. Potential market approvals in 2013–2014 have been expected for some companies with certain products, such as Sanofi with MACI and TiGenix with Chondrocelect in Europe and Pharmicell with product Livercellgram in Korea. Overall, it is expected to see a greater success rate for the progression and approval of cell therapy trials compared to conventional drugs [11,15,16].

The approved SCMPs

To date, four SCMPs, all derived from MSCs, have been approved by the regulatory authorities in different countries. They are Prochymal, HeartiCellgram, Cartistem (Medipost), and Cupistem (Anterogen).

Prochymal is an allogeneic hBM-MSC product, manufactured by Osiris Therapeutics, Inc. and approved by the Health Canada and the New Zealand Therapeutic Products Agency for treating acute pediatric GVHD. Osiris claimed that nearly 10 000 doses can be manufactured from a single donor using its proprietary isolation and proliferation procedures, therefore making Prochymal a true "out of shelf" stem cell drug in human history of health care [10,11,16].

The other three SCMPs were approved by Korea FDA (KFDA), which has a relatively relaxing efficacy requirement for approval of SCMPs comparing with the US and the EU. HeartiCellgram, approved in 2011 and derived from autologous BM-MSC, represents the world's first stem cells for

non-homologous use, i.e., for treating heart failure. Cartistem was an allogeneic umbilical cord-derived MSC product approved in 2012 for treating degenerative arthritis. It represents the world’s first allogeneic “stem cell product” and the first commercial “stem cell product” derived from umbilical cord. Cupistem is an autologous adipose tissue-derived MSC product approved in 2012 for treating anal fistula (Crohn’s disease). It became the world’s first commercially approved “stem cell product” derived from adipose tissue. Taking into account these three stem cell products, South Korea has become the world’s leader with 3 products available on the market [13,15,16].

SCTs in China

Stem cell research and clinical uses in China

Over the last decade, the Chinese government has strongly supported stem cell research through a “four-pronged approach” [17]. While the support has led to a substantial success in basic research, it ignored in some extent establishment of effective regulatory oversight, consequently unleashing unproved SCTs in China.

A recent survey showed that over 300 clinical studies across the country were undertaken with 140 of them using HSCs, 250 using MSCs, part of which were combined with HSCs, and less than 10 using other types of stem cells, like NSCs [18]. Among top indications using non-HSC SCTs were GVHD, autoimmune diseases, diabetes, liver cirrhosis, osteoarthritis, spinal cord injuries, inflammatory bowel diseases, and degenerative disorders. About 50 of these studies, all using MSCs, were also registered in the NIH clinical trial website with some of them claiming that the studies have moved up to phase III stage (Table 2) [6]. However, by the time of the survey, less than a handful of these studies were approved by SFDA (currently known as CFDA). No cell product has been approved to date for marketing. However, there were over 700 “stem cell clinics” practicing unproved SCTs, which have now become the

major problem faced by the Chinese regulatory authority [18].

The situation of unproved clinical studies and SCTs were largely attributed to the confusion of product categorization. Before 2010, non-hematopoietic SCTs, especially the autologous SCTs, were categorized more as innovative medical technologies. Till very recently, stem cell products, either autologous or allogeneic, were generally considered more as medicine, and a consensus has been generally reached that development of stem cell products for clinical use should follow the route of new drug development under rigorous regulations by the national regulatory authority [4,19,20].

Stem cell companies/developers in China

As seen in Table 3, vast majority of the SCMPs developed in China were MSC-based products with only few ESCs or NSCs products. Stem cell companies in China were involved mainly in manufacturing and distributing cell products to hospitals or clinics across the country. Currently, there are approximately 20 stem cell companies or developers in China. However, only few of them plan or are undergoing a comprehensive quality testing following the interim quality requirements [4,13,17,21].

Concerns and needs for improving regulations

The fast growth of SCTs has brought up concerns over product safety and effectiveness. The big promise inspired by some exciting stem cell studies has inflated expectations of the society, thus resulting in the rise of unproved SCTs, as frequently seen in unauthorized “stem cell clinics”.

Concerns about quality and safety

It is generally agreed that before applying SCTs to patients, comprehensive studies are needed to understand stem cell behaviors upon transplantation as well as mechanisms of stem cell interaction with the diseased or injured microenvironment. Stem cells following *ex vivo* processes could introduce risks, some of which are known and some are still not known.

Table 2 The representative Chinese stem cell companies/developers and products

| Company | Product (tissue origin) | Years |
|---|---------------------------|-----------|
| Beijing Keyu United Stem Cell Center | MSC (?) | 2005 |
| Shanghai GuoRui Life Tech., Inc. | MSC (?) | 2009–2013 |
| Tianjing Angsai Biotherapeutics | MSC (umbilical cord) | 2009 |
| HeZe Biotherapeutics | MSC (umbilical cord) | 2011–2013 |
| ZheJiang New Moon | MSC (adipose tissue) | 2011 |
| Jilin Tuo Hua | MSC (umbilical cord) | 2012 |
| 307 Military Hospital Stem Cell Center | MSC (umbilical cord) | 2013 |
| Basic Research Institute of the CAMS | MSC (adipose tissue) | 2013 |
| Beike Stem Cell | MSC (umbilical cord) | 2013 |
| Genetics and Development Institute of the CAS | MSC (umbilical cord); ESC | 2013 |
| Shanghai AnJiXieKang Biotechnology | NSC (fetal forbrain) | 2013 |

Table 3 The representative clinical trials of MSCs in China registered in www.clinicaltrials.gov

| Indication | MSC type | Phase | Sponsor and location | Clinical trial number |
|------------------------------|--------------------|--------|--|-----------------------|
| Graft-versus-host disease | Autologous BM-MSCs | II/III | Chinese Academy of Medical Sciences | NCT01526850 |
| Ulcerative colitis | Allogeneic UC-MSCs | I/II | Qingdao University | NCT01221428 |
| Multiple sclerosis | Allogeneic UC-MSCs | I/II | Shenzhen Beike Bio-Technology | NCT01364246 |
| Systemic lupus erythematosus | Allogeneic BM-MSCs | I/II | Nanjing Medical University | NCT00698191 |
| Type I diabetes | Autologous BM-MSCs | III | Third Military Medical University | NCT01157403 |
| | Allogeneic UC-MSCs | II | Fuzhou General Hospital | NCT01374854 |
| Type II diabetes | Allogeneic UC-MSCs | II | Shandong University | NCT01413035 |
| Spinal cord injury | Autologous BM-MSCs | II | Guangzhou General Hospital of Guangzhou Military Command | NCT01446640 |
| Liver cirrhosis | Allogeneic UC-MSCs | III | General Hospital of Chinese Armed Police Forces | NCT01491165 |
| | Allogeneic UC-MSCs | II | Alliancells Bioscience Corporation Limited | NCT01573923 |
| | Autologous BM-MSCs | II | Wenzhou Medical University | NCT01560845 |
| | Allogeneic UC-MSCs | II | Chinese Academy of Sciences | NCT01233102 |
| | Autologous BM-MSCs | II | Sun Yat-sen University | NCT00993941 |

Therefore, stem cell products must be subjected to strict regulations [1,22].

The *ex vivo* process should be considered as manufacturing process and the processed “stem cells” should be defined as “medicine,” which need to be manufactured in clean environments in compliance with requirements of current Good Manufacturing Practice (cGMP) [1,4,23–26].

Potential transmission of infectious or genetic diseases from donors, process-related cell damage, product purity and potency are directly related to *in vivo* safety and effectiveness. The level of concerns about quality, safety and effectiveness depends on the ways and extent of cell processing and manipulation. Products that are banked, transported, or intensely processed through the more complicated procedures will have higher risk of contamination of adventitious agents or affecting other biological characteristics of the cells. Growth in culture may also involve the use of xenogeneic feeder cells, which most often are mouse embryonic feeder cells and may bring up risks of introducing adventitious agents of animal origin [1,3,4,26–29].

Potential genetic and/or epigenetic alterations acquired during long *ex vivo* expansion or complicated manipulation represent another big concern, particularly in those derived from human embryonic stem cells. Aberrations in copy number, mitochondrial DNA sequence, and DNA methylation during long-term passage of human embryonic stem-cell lines have been commonly reported [30–33].

Differences in fate and behavior of the transplanted stem cells are associated with different risk levels. For the therapies, such as restoring insulin level in blood, the site-specific integration of stem cell products is not required for efficacy. However, for others, like transplanting stem cells for treating Parkinson’s disease, cell integration on specific sites is essential. In either case, integrating the cells into a non-

target location could raise questions about safety [1,4,22, 32, 34,35].

Increased needs for improving regulations

Current regulations for stem cell products are based in general on the existing regulation systems for drugs, biological products, and cell and tissue products. However, the vast majority of stem cell products and their derivatives represent novel products, with which scientists, clinicians, and regulators have only limited experience. All parts involved in regulation of SCMPs need an increased awareness of critical questions more specific for stem cell products before establishing effective regulations [1,3,4,24,25,29,36,37].

In addition, new concerns may emerge as SCT evolves. For example, the systemic administration of MSCs has been established as a route of administration for treating diseases, like GVHD. In this way, large amount of MSCs are introduced into the bloodstream, which is not natural environment of MSCs. They are infused on expectation that the cells will reach target organs that do not normally contain MSCs. There is a wealth of knowledge about MSC functions in their natural sites, like bone marrow, and properties they exhibit in a tissue culture dish, but it is not clear how exogenous MSCs will behave in the brain, kidney, or lung. With inherently osteogenic and adipogenic properties, MSCs could generate bone or fat in non-target organs if transplanted in extra large amount [38]. MSCs can also embolize in the lungs and damage local microcirculation. Allogeneic MSCs may trigger an adverse reaction—instant blood mediated inflammatory reaction (IBMIR) [39], which leads to activation of coagulation and complement cascades, resulting in damage or even death of the infused cells. IBMIR can also result occasionally in thromboembolism. It was unknown until recently that IBMIR could be triggered by MSCs. This

exemplifies why infusion of MSCs must necessarily be studied in rigorously controlled and monitored clinical trials before such therapies can be considered safe in patients and regulations based on the updated understandings should be set up accordingly [22,31,32,34].

Stem cell regulations in the world

With the more specific regulations for SCMPs still largely unavailable, the relevance from the existing regulation systems for drugs, biological products, cell substrates and cell and tissue products can help build up or promote effective regulations for SCMPs. Also helpful are clearly defined product categorization and jurisdiction of the regulatory authorities.

The existing regulations in the US and EU

In both the US and the EU, the regulatory systems in forms of “law/legislation-regulation-guidance” have been generally established for regulating biological products, which include therapeutic cell products.

In the US, the SCMPs are clearly defined as medicine and the FDA takes full jurisdiction over regulations of production and marketing of all types of SCMPs for use in humans. The US regulations were framed in levels of federal laws, regulations and guidance. The relevant sections in Public Health Service (PHS) Acts, i.e., PHS Acts 351, PHS Acts 361, govern regulations on stem cell products. The regulations, especially Title 21 of Codes of Federal Regulations (21 CFR), set up the detailed requirements, such as the requirements regarding manufacturing and Investigational New Drug (IND) application in 21CFR211 (Part 211 of 21 CFR) and 21CFR312, general safety for biological products in 21CFR610, and manufacturing, registration/listing, biological safety, and Good Tissue Practice (GTP) of cell products in 21CFR1271, which address the more specific concerns for stem cell products than other sections of 21 CFR [40–43]. The FDA Guidance for Industries further interprets the regulatory codes into the more practical guidelines, including the guidelines related to SCMPs for CMC information and IND application [3], potency assay [36], preclinical assessment [44], and the design of early-phase clinical trials [45] established or drafted in 2008, 2011, 2012 and 2013, respectively. Given that the FDA is actively establishing new guidelines associated more with biological effectiveness of the stem cell products, it is clear that, in addition to the strict safety requirements, the FDA also emphasizes the importance of efficacy requirement of the SCMPs.

Similarly, the EU also regulates stem cell products based on the existing “legislations/directives-regulations-guidelines” system. The legislations/directives include the Directives 2001/20/EC, 2003/65/EC, and 2004/23/EC, which

define cell therapy products as clinical products and mandate clinical trials for development of SCMPs. The regulations include EU regulation (1394/2007) on Advanced Therapy Medicinal Products (ATMPs), which is binding in its entirety and directly applicable in all member states of the European Parliament and Council. The ATMPs include gene therapy and somatic cell therapy products, and tissue engineered products. The Committee for Advanced Therapies (CAT) within European Medicines Agency (EMA) is responsible among all tasks for preparing a draft opinion on quality, safety, and efficacy of ATMPs that follow the centralized marketing authorization (MA) procedure. Yet, except for some somatic cell products, like Chondrocelect which is the derivative of autologous chondrocytes, no MA has been granted for any SCMPs in the EU [23–25,36,46].

Stem cell regulations in China

Currently, there is no regulation system in China similar to that in the US or the EU. To safeguard a steadfast and healthy growth of stem cell studies and to tackle the problems caused by the unproved SCTs, the Ministry of Health (currently known as the Ministry of Health and Family Planning, MHFP) and SFDA (currently known as CFDA) worked together and mandated a complete stop of all types of unproved SCTs including all stem cell clinical studies at the end of 2011. One of the joint efforts resulted in the formation of an interim regulation committee with top research scientists as well as regulatory scientists in China for proposing new regulations. Consequently, three new regulatory documents have been drafted out and are undergoing public critics or comments.

The three interim regulatory documents are: (1) general requirements for conducting clinical studies of SCMPs, which highlights principles of the informed consent from donors and recipients, free of charges from patients, and prohibiting unlawful marketing or advertising activities during clinical studies; (2) qualification of institutions for conducting clinical studies of the SCMPs, which states that only the “Triple-A” grade hospitals in China recognized by the CFDA with experiences in stem cell studies can be qualified for conducting clinical trials of the SCMPs; (3) guidelines for quality control and preclinical studies of the SCMPs, which covers general quality requirements, quality control and validation testing, and the general considerations regarding the issues of safety and effectiveness to be addressed in preclinical studies for SCMPs [4,19,20].

The third document was drafted based on the principles described in the relevant parts pertaining to quality control of biological products, cell substrates, and therapeutic cell products in Chinese Pharmacopeia (Volume III, 2010), Chinese guideline for therapeutic somatic cell products, and the relevant regulations or guidelines of the WHO, FDA, ISSCR, USP or EP [1,3,23–29,36,47,48].

Regulatory sciences for SCMPs

Principles of the regulatory sciences for SCMPs

Regulatory science is a type of applied science associated with multidisciplinary areas of sciences. It helps translate discovery and innovation into products through developing new technical procedures, standards, and models to evaluate product's safety, quality, efficacy and performance. It also contributes to the acceleration of regulatory processes, such as reviewing, approval, and ongoing oversight of the regulated products throughout their life-span [49].

The regulatory sciences for SCMPs should consist of the areas of sciences for improving assessment of quality, safety and efficacy of the SCMPs throughout their life-span, as well as the scientific areas in regulatory decision-making. They should include basic and applied biomedical sciences, such as cell biology, immunology, biostatistics, and clinical trial specialties, and social sciences, such as decision-making sciences, risk assessment and communication sciences. All of them together should lead to the development of standards and tools to be used in the regulation of the SCMPs [5].

Needs of promoting stem cell regulatory sciences

Effective regulation for SCMPs depends on continuous improvement of all perspectives of the regulatory sciences, which include benefit-risk analysis, research on regulatory processes, and incentives to support regulatory science and regulatory expertise.

Benefit-risk assessment needs to be properly performed for each product before its clinical use. Given that behaviors or consequences of the transplanted stem cells inside the body of recipients, such as tumor formation, abnormal immune responses, and uncontrolled (or ectopic) differentiation, still remain largely unknown, it is extremely difficult to determine appropriate risk level over benefit of each SCMPs [1,4,22].

To ensure quality of research on regulatory sciences, researchers need to be sufficiently funded to finish the tasks and to have guaranteed access to raw data, which include results of preclinical and clinical studies, and results from market surveillance, and so on. In addition, links between regulatory sciences and the communities of the stem cell science and technology should be established to nurture regulatory innovations and increase recognition of investment in regulatory sciences [5].

It is extremely critical to understand that effective regulation of the SCMPs is very important to all stakeholders, which include basic scientists, clinicians, communities, finance providers and manufacturers/developers. Uncontrolled/unproved stem cell therapy cannot only cause bad outcomes to patients, but also reduce fund support for basic research, and may cause delay or stop of some promising studies and even severely adverse impact on the health of the stem cell industry. However, it is still difficult to quantify and

communicate about the value of stem cell regulatory sciences among all stakeholders because the focus of perspective of each stakeholder can be so different, thus difficult to reach consensus on many regulatory principles, resulting in eventually the lack of incentives for supporting regulatory sciences [1,5,49].

Challenges from establishing stem cell regulatory sciences

Given the unique biological nature of stem cells and their progeny, and uncertainties inherent in their clinical use, SCTs present to regulatory authorities with unique challenges that may not have been anticipated within the existing regulatory systems, especially in development of standards and tools for both quality control and relevant regulations [1].

Challenges from developing the tools of conducting effective quality control

Challenges from the limited capability of product characterization and lack of quick testing technologies

One of the critical quality control tools is the product characterization, which should be designed to address concerns regarding risks of transmitting infectious or genetic diseases, cross-cell contamination, cell damage in the final product, and safety and effectiveness in patients. However, since stem cell science is still in its infancy and many critical issues still remain unsolved, standard operating procedures guiding all details of product characterization during cell derivation and processing, and the distinct principles limiting the extent of cell manipulation prior to their use in patients are thus far from establishment [1].

Quick testing methods for assessing safety and efficacy are extremely needed for stem cell products because all cell products have short shelf life and cannot go through terminal filtration or sterilization. Among the most urgent needs is the development of quick sterility test because likely very short shelf time of the product makes the conventional sterility tests described in the existing regulations/guidance not feasible to meet the clinical needs for SCMPs [1,4].

Challenges from safety assessment through preclinical and clinical studies

Although it has been acknowledged that preclinical assays from animal studies may help predict behaviors of the transplanted cells in humans, given the dissimilarities in physiology between animals and human, preclinical models may not faithfully anticipate all potential deleterious events [1].

Many safety issues can only be addressed through clinical studies. However, it is very difficult to run large well-designed clinical trials, i.e., the randomized, multi-centered, double-blind and placebo-controlled studies. The difficulties are associated with both technical and ethical problems. For examples, the extremely strict or sometimes less flexible

requirements of product qualities may make the clinical trial application process extremely lengthy; narrow clinical indications may limit the number of participants; the study design with sole placebo as control can help determine efficacy of treatment, but is generally considered not ethical for many clinical indications. In addition, the existing evaluation systems for clinical studies, which are based on the principles for testing small chemical drugs or biopharmaceuticals, may not be directly applicable to SCMPs, especially in the countries, like China, where the establishment of effective regulation system for SCMPs just commenced [19,20].

Challenges from developing regulatory tools—the standards/guidance, standard materials, and criteria for product release

Development of applicable standards, including standard testing methods and specifications, relies on in-depth understanding of the risks associated with specific cell derivation, processing and/or clinical procedures. For example, development of new routes of administration may bring up new concerns about safety and efficacy of products. Systemic administration of the MSC-based products has proved to be effective in treating diseases with major contribution of abnormal immunology to their pathogenesis. However, the potential of cells to persist or expand in the body, additional toxicity, selection against cancer patients-concerns from possible tumor-promoting effects of MSCs, and the likelihood of long-term consequences of fusion of delivered cells to host cells become new issues associated with systemic use of the products, thus necessitating development of new standards or guidance to properly address the issues regarding this type of route of administration [2,22,31].

With acknowledgment of limitations in current assays, it is urgent to develop common reference standards for assessing minimally acceptable changes during cell culture and for facilitating comparisons among different studies [1]. Should also be developed uniform standards relating to eligibility of donors, consent, procurement, manufacturing, delivery, and selection of recipients for novel SCTs. Currently, following a previous publication [1] and continuously increased understanding of MSCs, it is now more feasible to set up a roadmap for establishing a minimum set of standards for the MSC-based products regarding cell collection, characterization, and potency tests in association with cell origins and clinical indications. Other standardization efforts should include development of recommendations for storage, deposit, and analysis of different types of stem cells [1].

Lack of effective criteria for product release also represents a big challenge. Unlike chemicals or proteins that can be manufactured to high degrees of homogeneity, manufactured cells or those harvested and processed from different anatomic sites or unrelated individuals are of significant biological variability. In the case of allogeneic therapies,

establishment of a single master cell source may mitigate variability [22,31].

New studies for improving stem cell regulations

For improving stem cell regulations, new studies involving basic research, clinical studies, regulatory sciences and studies of other disciplines are needed for establishing sound regulation system for governing development of new testing methods, appropriate quality control specifications, standards and reference substances [1,5].

Studies for building up the effective “law-regulation-guidance” regulation system

Effective regulation of medical products depends on the regulation system that conveys legislative requirements through NRAs to manufacturers, developers or clinical institutions, where medical products are used for treating patients. The law-regulation-guidance system, as exemplified by the US “Acts-CFR-Guidance” system, provides an administratively effective pathway, through which, new technical guidelines can be effectively developed for meeting any emerging needs [29,36,46].

Currently, no technical guidelines specific for stem cell products have been developed from all NRAs in the world. Although China is moving faster in promoting this effort, its regulation system addressing both safety and efficacy issues of wide-range biological products need to be established or improved in order to be more competent to face any new challenges from any emerging biological products [4].

Studies for enhancing quality control capability

The overall quality requirements for SCMPs are identity, quality, purity, safety, biological effectiveness and stability, and should be assessed in each critical step of the manufacturing process, including the steps of cell collection, purification, expansion, targeted cell differentiation, before and after cryopreservation, residual removal, and packaging [1,4,36,50]. The extensive in-process testing and final product testing plus the validation testing should be conducted using the appropriate testing strategies with different combinations of testing methods and specifications [1,4,36].

Quality control technologies should be constantly improved to meet the continuously updated requirements of product qualities. After appropriate correlation studies, the newly developed technologies should then be employed in various quality control tests [1,4,30].

Among the top priorities are the technologies for testing cell identity, quality, purity, safety, and potency. For example, quality testing can be improved by employing early apoptosis

detection-based method(s) to more accurately measure cell viability comparing with the much less sensitive MTT exclusion-based method, or by using telomerase activity assay or measurement of telomere length to determine the senescence of stem cells comparing to the general growth curve description.

As the study of each SCMP proceeds, new potency assay(s) for each product should be developed according to each clinical indication [1,4,36]. Specifically, for the MSC-based products, new potency assays based on current understanding of MSC immunology, such as the assays revealing effects of MSCs on subpopulations of the CD4⁺ lymphocytes, should be developed [2].

Various “omics” studies, like genomics, proteomics and even metabolomics studies for developing effective new surrogate biomarkers for identity, quality, purity, safety and potency through basic research and validation studies are extremely encouraged [1,4]. In particular, based on up-to-date knowledge of tumor molecular biology, the studies for developing surrogate biomarkers to properly assess tumorigenicity should be among top priorities of developing new safety assessment technologies because tumorigenicity of most stem cell products cannot be effectively evaluated in current model systems.

Stability studies for each SCMP during cryopreservation, transportation or temporary storage prior to clinical use should be conducted. Following stability studies, the optimum conditions for establishing appropriate cell preservation, formulation of preparation, storage and transportation, as well as “the shelf time” of the product should then be determined.

Studies for improving preclinical assessment

Two objectives of the preclinical studies are provision of supporting evidence of product safety and effectiveness, or proof-of-principle, and provision of information helpful for initiating clinical studies. Before initiating clinical studies, persuasive evidence from appropriate *in vitro* and/or animal models should support the likelihood of a positive clinical outcome. Preclinical testing in animal models is especially important because stem cells can act through multiple mechanisms and *in vitro* model alone is very difficult to predict behaviors of stem cells in humans.

The indication-specific animal models should be developed and used to determine tissue/organ distribution and “homing”, preferably moving to the diseased/injured or inflamed sites, as well as to assess possible adverse effects, like abnormal or ectopic differentiation, or even tumorigenicity of the infused or implanted stem cells [4,36,51,52].

Enhancing quality of clinical trials with appropriate regulatory oversight

All clinical trials for SCMPs should be in compliance with the

internationally accepted requirements, such as the Good Clinical Practices (GCP) requirements, in terms of ethical conduct and protection of human subjects. The key requirements include regulatory oversight, peer review by expert panel(s) independent of the investigators and sponsors, fair subject selection, informed consent, and patient monitoring for ensuring safety of SCMPs in clinical trials with scientific merit [1].

The regulatory competence should be developed not only at the national level, but regional, or local level as well to monitor clinical interventions with SCMPs. In the regulatory approval process, the information outlining well-defined goals of the clinical trial, detailed research protocols, outlined manufacturing process, and toxicology information should be required from investigators [1].

A number of important studies merit special attention: (1) monitoring research subjects for long-term health effects using the newly developed monitoring technologies, such as the predictive biomarkers; (2) offering a clinical plan to deal with adverse events, such as eliminating tumor cells transformed from the transplanted stem cells by, for example, triggering expression of “suicide gene” introduced into the cells during early product development [1].

New strategies and actions needed for promoting stem cell regulatory sciences.

For promoting the stem cell regulatory sciences, appropriate strategies and actions should be taken including the increase of funding for developing new quality control technologies, generating repositories of samples to validate new methods or standards, encouraging studies in regulatory sciences, and global exchanges on regulatory sciences and coordination of regulatory efforts. They are also needed to enhance efforts in national and international convergence of regulatory standards, such as written standards, measurement standards, standardization of assays, and consensus on setting specifications. Given that large amount of various MSC-based products have been extensively studied for different clinical applications, the efforts for developing standards are urgently needed to guide cell derivation, banking, *ex vivo* expansion/manipulation, and quality assessment testing, the testing for immunomodulatory functions in particular, of the clinical grade MSCs, and to promote global or regional exchanges in data, methods and regulatory philosophies for MSC-based products [1,5,52].

Conclusions

Although over the past decade several new achievements were made in stem cell studies and significant growth was seen in stem cell industries, many critical issues still need to be carefully addressed. However, as summarized in Fig. 1, all actions should be taken in the context of establishing and

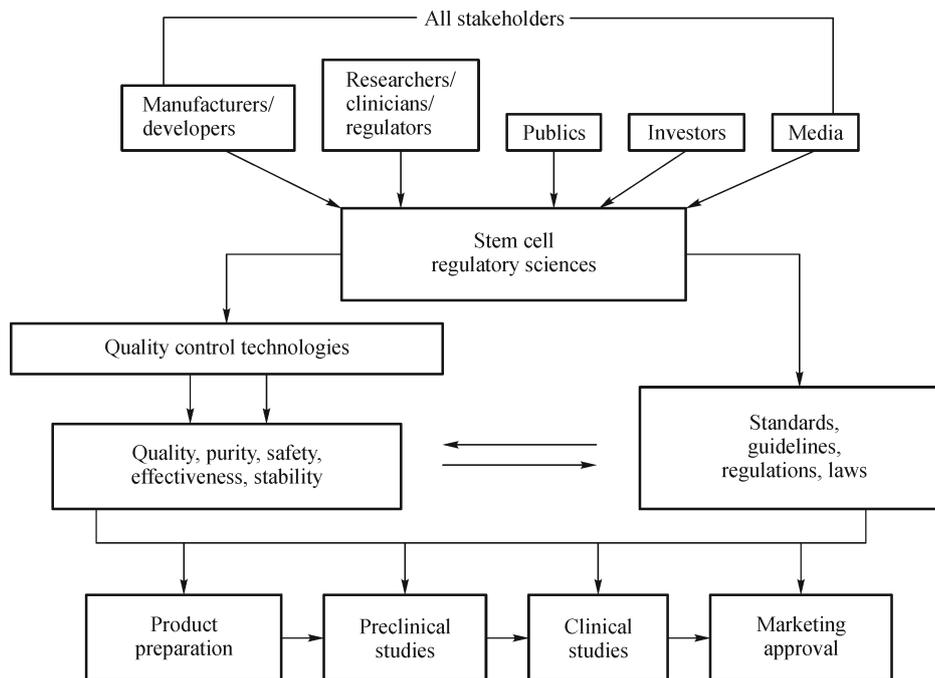


Fig. 1 Promoting stem cell regulatory sciences.

promoting regulatory sciences, which make awareness of the importance of effective regulations in stem cell studies and clinical uses to all stakeholders, help translate new discovery and innovation from stem cell sciences into the promising products, and keep the growth of SCTs steadfast and well-regulated.

Compliance with ethics guidelines

Bao-Zhu Yuan and Junzhi Wang declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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