Regulations and guidelines governing stem cell based products: Clinical considerations

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Abstract

The use of stem cells as medicines is a promising and upcoming area of research as they may be able to help the body to regenerate damaged or lost tissue in a host of diseases like Parkinson's, multiple sclerosis, heart disease, liver disease, spinal cord damage, cancer and many more. Translating basic stem cell research into routine therapies is a complex multi-step process which entails the challenge related to managing the expected therapeutic benefits with the potential risks while complying with the existing regulations and guidelines. While in the United States (US) and European Union (EU) regulations are in place, in India, we do not have a well-defined regulatory framework for "stem cell based products (SCBP)". There are several areas that need to be addressed as it is quite different from that of pharmaceuticals. These range from establishing batch consistency, product stability to product safety and efficacy through pre-clinical, clinical studies and marketing authorization. This review summarizes the existing regulations/guidelines in US, EU, India, and the associated challenges in developing SCBP with emphasis on clinical aspects.

Key words: Regulations, stem cell products, clinical considerations

INTRODUCTION

Stem cells have a unique ability to differentiate into the specific cells required for repairing damaged or defective tissues or cells. Stem cell based therapies, encompassing collection, purification, manipulation, characterization delivery of cells for therapeutic purposes, have existed since the first successful bone marrow transplantation in 1968.[1] Presently, human embryonic stem cells (hESCs) are used in 13% of cell therapy procedures, while fetal stem cells are used in 2%, umbilical cord stem cells in 10%, and adult stem cells in majority (75%) of treatments.[2]

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The term "stem cell based products (SCBP)" is used to refer to products intended to be administered to a patient and that contain or are derived from stem cells.[3] Commercial clinics worldwide are currently advertising so-called stem cell "therapies" for a host of diseases. Most of the clinics providing stem cell based interventions do not operate within the context of a formal clinical trial (CT). Whether the motive is outright profiteering or an attempt to help needy patients, the risks to patients of physical harm and financial exploitation remain extremely high. Globally, many pharmaceutical companies, including the big ones, are reluctant to enter this segment because of the great investment required and the uncertainties associated with it which include the regulatory framework. While some have regulations in place, others do not even

have their own national guidelines to follow. Appropriate regulation of SCBP is essential to ensure public safety and trust while minimizing unnecessary barriers to product development, but presents numerous regulatory challenges.

REGULATORY CHALLENGES

There are several regulatory issues that relate to the safety, efficacy, and quality of SCBPs to be considered while preparing a cell- and tissue-based therapy for clinical and commercial use. Initially, safety testing is critical, including assays for potential microbial, fungal, endotoxin, mycoplasma, and viral contamination; karyotype testing; and enrichment for the required cell population. Once safety has been established, the product must pass *in vitro* functional assays designed to act as surrogate measures for clinical effectiveness.[4,5] These potency assays must be fully validated to meet regulatory requirements, including appropriate standards and controls. The product has to be made to a certain set of specifications, ensuring high quality. Another aspect is the scarce availability of classical toxicology studies from the pre-clinical development. All animal models have inherent limitations, like, for example, the application of human cells in a xenogenic milieu.[6] This requires the use of severely immuno-compromised small animals. Furthermore, for a variety of diseases, for example, in orthopedics, small animals are not capable of modeling the disease. Selection of the most appropriate and sensitive model for conducting tumorigenicity studies should take into account the biological characteristics, conditions of *in vitro* manipulation, persistence of cells, route of administration and the intended clinical use of the SCBP. In the presence of reduced pre-clinical data, it is required that the CTs should be performed, with the highest attention being paid to the safety and ethical issue involved.[7]

The following paragraphs focus on the existing clinical considerations from regulations and guidelines governing stem cell based therapies/products within EU, US and India.

REGULATORY FRAMEWORK IN EU

Legislation on cell therapy in Europe is based on three directives:[8]

- Directive 2003/63/EC (amending Directive 2001/83/EC), which defines cell therapy products as clinical products and includes their specific requirements.
- Directive 2001/20/EC, which emphasizes that CTs are mandatory for such cell therapy products and describes the special requirements for approval of such trials.
- Directive 2004/23/EC, which establishes the standard quality, donation safety, harvesting, tests, processing, preservation, storage, and distribution of human tissues and cells.

The EU directives recognize that conventional nonclinical pharmacology and toxicological studies may be different for cell-based drugs, but should be strictly necessary for predicting response in humans. The EU regulation (1394/2007) on Advanced Therapy Medicinal Products (ATMPs) became effective from December 2008 and is binding in its entirety and directly applicable in all Member States of the European Parliament and of the council. ATMPs include gene therapy medicinal products, somatic cell therapy products (as defined in Directive 2001/83/EC), and tissue engineered products.[9] Cells fall under this regulation, in case they have been subjected to substantial manipulation, resulting in a change of their biological characteristics, physiological functions or structural properties relevant for the intended therapeutic application. The Committee for Advanced Therapies (CAT) within European Medicines Agency (EMA) is responsible, among other tasks, for preparing a draft opinion on the quality, safety, and efficacy of ATMPs that follow the centralized marketing authorization (MA) procedure. Yet, no MA has been granted for any stem cell based medical product (SCBPM) in the EU.[10]

EMA has very recently released a **"**Reflection Paper"[11] which covers specific aspects related to SCBPs with an intention for MA application. This reflection paper is relevant to all medicinal products using stem cells as starting material regardless of their differentiation status at the time of administration. SCBPs intended for clinical use should be produced via a robust manufacturing process governed by quality control sufficient to ensure consistent and reproducible final product. EMA suggests a risk-based approach according to Annex I, part IV of Dir 2001/83/EC for SCBPs.

Generally, the clinical development plan should follow corresponding EU guidance on medicinal products and specific relevant guidance for the diseases to be treated. CTs should be designed to demonstrate safety and efficacy as well as provide evidence to substantiate the mode of action identified during the CT. For first-in-man studies, the principles of the guideline on strategies to identify and mitigate risks for first-in-human CTs with investigational medicinal products (EMEA/CHMP/SWP/28367/07) should be considered. In first-in-man studies, specific safety endpoints may need to be defined based on theoretical considerations and in order to detect early any toxicity arising from potential contaminants in the final product. In those cases where sufficient proof-of-concept and safety cannot be established in the nonclinical studies, for example, due to justified difficulties in finding

an appropriate animal model, the evidence should be generated in CTs by including additional endpoints for efficacy and safety, respectively. Clinically meaningful endpoints related to the pharmacodynamic effect of the product should be used for efficacy assessment in the target indication. The effective range of stem cells and/or stem-cell derived cells administered should be defined during dose finding studies, unless justified. A safe and effective treatment dose should be identified, and where possible, the minimally effective dose should be determined. The selected biomarkers should permit delineation of the differentiation status of the SCBP at time of patient administration as well as facilitate *in vivo* monitoring once administered. The presence of the administered stem cells in places other than those intended should be investigated. It is important to evaluate the time to achieve the clinical outcome and, where relevant, the time to engraftment in order to correctly define the cell population required for such an *in vivo* effect. The need for and duration of post-authorization long-term efficacy follow-up should be identified during the CTs, taking into consideration results from nonclinical studies and the intended therapeutic effect.

REGULATORY FRAMEWORK IN THE US

In the US, use of cell therapy products is codified within the Code of Federal Regulations in the following sections: IND regulations (21 CFR 312), biologics regulations (21 CFR 600) and cGMP (21 CFR 211). In particular, US federal regulation on cellular therapy is divided into two sections of the Public Health Service Act (PHSA), referred as "361 products" and "351 products". Traditional blood and bone marrow progenitor cells as well as other tissues for transplantation fall into 361 products definition. The Food and Drug Administration (FDA) has established that cells or tissues used for therapeutic purposes and the regulation that pertains to processing of 361 products are codified under the Good Tissue Practice (GTP).[7] CFR, Part 1271 provides US regulations on Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps).[12] This became effective in 2005 as rules for HCT/Ps. The FDA has also issued guidance documents about how the drug, biologic, and device regulations apply to cellular and genetic therapies.[13]

Classification of stem cell based therapies is based on indication to be treated. Restrictions are limited to research with federal funds. No limitations exist for research with hESCs, provided the funds come from private investors or specific states. The FDA has developed a regulatory framework that controls both cell- and tissue-based products, based on three general areas:[8]

- Prevention of use of contaminated tissues or cells (e.g. AIDS or hepatitis);
- Prevention of inadequate handling or processing that may damage or contaminate those tissues or cells; and
- Clinical safety of all tissues or cells that may be processed, used for functions other than normal functions, combined with components other than tissues, or used for metabolic purposes.

The Center for Biologics Evaluation and Research (CBER), the division of US FDA that regulates stem cell based therapies, has so far approved ApliGraf®, Carticel® and Epicel®. Those cell-based therapeutics "that are, minimally manipulated, labeled or advertised for homologous use only, and not combined with a drug or device" do not require FDA approval.[14] In contrast, manipulated autologous cells for structural use meet the definition of somatic cell therapy products and require an "investigational new drug" (IND) exemption or the FDA license approval. In 2007, the "Guidance for Industry: Regulation of HCT/Ps – Small Entity Compliance Guide" and in 2009, the "Guidance for Industry on Current Good Tissue Practice (cGTP) and Additional Requirements for Manufacturers of HCT/Ps" (http://www.fda.gov) had been released.[15] Clinical studies employing mescenchymal stem cells (MSCs) underlie the IND mechanism. Accordingly, the investigators have to make an IND application, which necessitates detailed study protocols describing the clinical plan as well as the preparation and testing of the therapeutic cell product.[16]

Under the current FDA policies, there are at least two ways in which physicians may administer more than minimally manipulated stem cell products to patients. The first is under the FDA's program for expanded access to investigational drugs and biological products for treatment use (what is sometimes referred to as "compassionate use") as long as these products are currently being tested elsewhere in a CT and only if expanded access will not interfere with the conduct of clinical investigations. FDA allows clinicians to charge for direct cost recovery and administrative costs associated with expanded access use.[17] The second is the off-label prescribing of FDA-approved stem cell products. Off-label prescribing is premised on the position that the FDA does not have the authority to regulate medical practice and the assumption that physicians can be trusted to use their professional judgment in deciding how to treat their patients.[18]

SCENARIO IN INDIA

The "Ethical Guidelines for Biomedical Research on Human subjects" released by Indian Council of Medical Research (ICMR) in 2006[19] has provided under Section

V, the requirements for carrying out "stem cell research and therapy". These guidelines have categorized research on stem cells into mainly three areas, namely, permissible, restrictive and prohibited areas. Under permissible category, CT with clinical grade stem cells, following ICMR Guidelines for Biomedical Research and GCP guidelines of the Government of India (GOI), may be carried out with prior approval of Institutional Committee for Stem Cell Research and Therapy (IC-SCRT), Institutional Ethics Committee (IEC) and Drug Controller General of India (DCGI). Clinical grade stem cells are required to be produced under international GMP/GTP conditions. The headings under which the CT protocols should be written need to be as per Annexure III of the guideline. All CTs on stem cells shall be registered with National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) through IC-SCRT. Restricted category includes CTs sponsored by multinationals, involving stem cell products imported from abroad. Such collaboration shall require prior approval of the NAC-SCRT through IC-SCRT, IEC, DCGI and respective funding agency as per its procedure/Health Ministry's Screening Committee (HMSC). Each institution shall constitute an IC-SCRT as provided in these guidelines and provide adequate support for its functioning.

ICMR and the Department of Biotechnology (DBT) have together laid down "Guidelines for Stem Cell Research and Therapy" in Nov 2007.[20] The guideline has many commonalities with the ICMR, 2006 guidelines. The guideline has emphasized on mechanism for review and monitoring research and therapy in the field of human stem cells, one at the National level (the NAC-SCRT) and the other at the institutional level (the IC-SCRT). All established human stem cell lines from any source, imported or created in India, should be registered with IC-SCRT and NAC-SCRT. The investigators should ensure that the cell lines have been established in accordance with the existing guidelines of the country. An appropriate Material Transfer agreement (MTA) should be adopted for the purpose. The investigators and the institutions where the stem cell research is being conducted need to bear the ultimate responsibility of ensuring that research activities are in accordance with laid down standards and integrity. CTs with cells processed as per National GTP/GMP guidelines (minimally manipulated or manipulated with alteration in functionality or genetic characteristics) may be carried out with prior approval of IC-SCRT/IEC/DCGI, as applicable. The informed consent process for participation in CTs for SCBP encompasses many more details and conditions than those for other type of products. All records pertaining to adult stem cell research must be maintained for at least 5 years and those related to hES cell research must be maintained for 10 years.

Clinical use of stem cells is not permitted until the

- Efficacy and safety of the procedure is established;
- Origin, safety and composition of the product is adequately defined and labeled; and
- Conditions for storage and use are given in detail.

Our Central Drugs Standards Control Organization (CDSCO) has released guidance document on submission requirements for new drug approvals for Biotechnological/Biological products in Dec 2008[21] along the lines of the CTD format. However, the same format cannot be directly applied for SCBP due to inherent differences. Again, under the Drugs and Cosmetics Act and Rules,[22] there is no specific "Form" applicable either to apply for grant or renewal of manufacturing licence for SCBPs. While there has been a subtle growth in the number of private hospitals and clinics providing stem cell therapies across India, the Indian industry is at crossroads in deciding how to take their SCBPs, for which they have gone through the CTs (after taking due approvals from DCGI, IEC and ISCRT), to a commercially licensed product within India! In the absence of laws/regulations specifying the requirements, it is difficult to enforce the existing guidelines in India. Also, NAC-SCRT is yet to become functional. Once regulations are laid down, one can be either in compliance or out of compliance, and automatically an enforcement mechanism would get built-in against non-compliance. Indian government has taken steps in this direction. A new central committee, viz. Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) has been set up, under the chairmanship of DG ICMR, with the mandate to advice on regulatory pathway for CT marketing approval for therapeutic products derived from stem cells, human gene manipulation and xenotransplant technology. CBBTDEC had its first meeting to discuss various proposals put up to DCGI by the sponsors/CROs on March 9, 2011. Formal recommendations have been communicated in May 2011.

EFFORTS TOWARD HARMONIZATION

Though the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has not yet formulated any guidelines specific to SCBPs, some of its guidelines on biotechnology products are relevant to this area.[23] Various non-binding codes of practice and guidelines to cover stem cell research have also been published by international bodies such as the International Society for Stem Cell Research (ISSCR)[24] and the Hinxton Group.[25] "The Guidelines for the Clinical Translation of Stem Cells" drafted by ISSCR emphasize the CTs approach in the majority of translational stem cell

studies. Fundamental principles in the responsible clinical application of stem cells are the following:

- Only quality-controlled cells with known biological characteristics are used;
- Efficacy and safety after delivery of the cells have been demonstrated in appropriate animal models;
- Stem cell specific expertise is involved in the peer review of the clinical protocols and the underlying pre-clinical research; and
- Voluntary informed consent is obtained prior to a CT to ensure that recipients are aware of the risks of tumor formation and lack of proof of clinical benefits.[17]

But, as guidelines, the ISSCR's recommendations are essentially an unenforced code of professional conduct! Both the regulatory frameworks in the EU and USA are structured to assure safety and thus they require a thorough analysis of all critical steps and aspects in advance. Although there are still differences, the authorities are in contact to further harmonize them.[9,14,16,26]

WAY FORWARD

There is still a significant gap between promising laboratory-based research and approved SCBPs in this fast emerging field. Legislation in this field must seek to both regulate and enable scientific progress without being confusing, difficult to interpret or unnecessarily onerous. In addition, the public must have confidence that its interests are protected.[27] Few of the measures which could help to speed up the translation of SCBP from bench to bedside while still ensuring patient safety include the following.

- Compliance with the existing regulations and guidelines to ensure that the product is safe, pure, and potent meeting GTP, GMP and GCP requirements.
- Nonclinical evidence on the proof-of-principle and safety in a relevant animal model should be tried before administration to humans.
- Encourage companies to develop and validate new non-invasive methods for biodistribution studies in humans to follow the cells during the CTs. Possible markers/tracers should be evaluated and justified.
- A risk-based approach to be applied while giving regulatory approvals. Conditional marketing authorization could be a possible approach without compromising on patient safety.

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REFERENCES

1. Gatti RA, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 1968;2:1366-9.
2. Ahrlund RL, De Luca M, Marshak DR, Munsie M, Veiga A, Rao M. Isolation and production of cells suitable for human therapy: Challenges ahead. Cell Stem Cell 2009;4:20-6.
3. Halme DG, Kessler DA. FDA regulation of stem-cell based therapies. N Engl J Med 2006;355:1730-5.
4. Collins NH. Product review, release, and administration. In: Gee A, editor. Cell Therapy: cGMP Facilities and Manufacturing. New York: Springer; 2009. p. 215-28.
5. Rayment EA, Williams DJ. Concise Review: Mind the gap: Challenges in characterizing and quantifying cell- and tissue-based therapies for clinical translation. Stem Cells 2010;28:996-1004.
6. Bianco PG, Robey, Simmons PJ. Mesenchymal stem cells: Revisiting history, concepts, and assays. Cell Stem Cell 2008;2:313-9.
7. Giuseppe A, Sabrina S, Viviana Lo C, Francesco S, Daniel S, Lucia T, *et al*. Am J Transl Res 2010;2:285-95.
8. Antonio L. Future research and therapeutic applications of human stem cells: General, regulatory, and bioethical aspects. J Transl Med 2010;8:131.
9. Schneider CK, Salmikangas P, Jilma B, Flamion B, Todorova LR, Paphitou A, *et al*. Challenges with advanced therapy medicinal products and how to meet them. Nat Rev Drug Discov 2010; 9:195-201.
10. Committee for Advanced Therapies and CAT Scientific Secretariat. Use of unregulated stem-cell based medicinal products. Lancet 2010;376:514.
11. Reflection paper on stem cell-based medicinal products. Committee for Advanced Therapies. EMA/CAT/571134/2009. 2011; 1-14.
12. Human Cells, Tissues, and Cellular and Tissue-Based Products Regulations, 21 C.F.R., Part 1271.
13. US Food and Drug Administration. Guidance for human somatic cell therapy and gene therapy, FDA Center for Biologics Evaluation and Research, 1998.
14. Parson A. The long journey from stem cells to medical product. Cell 2006;125:9-11.
15. Bieback K, Kinzebach S, Karagianni M. Translating research into clinical scale manufacturing of mesenchymal stromal cells. Stem Cells Int 2010;1-11.
16. Gee A. Mesenchymal stem-cell therapy in a regulated environment. Cytotherapy 2001;3:397-8.
17. Hyun I. Allowing innovative stem cell-based therapies outside of clinical trials: Ethical and policy challenges. 2010;38:277-85.
18. Dresser R, Frader J. Off-Label Prescribing: A Call for heightened professional and government oversight. J Law Med Ethics 2009;37:476-86.
19. Indian Council of Medical Research. Ethical guidelines for biomedical research on human subjects, 2006.
20. Indian Council of Medical Research. National guidelines on stem cell research and therapy, 2007.
21. Guidance for Industry on submission of clinical trial application for evaluating safety and efficacy. CDSCO Doc No. CT/71108, Version 1.1, 2008. Available from: http://www.cdsco.nic.in.
22. Malik V. Laws relating to Drugs and Cosmetics. 19th ed. Lucknow: Eastern Book Company; 2008.
23. Catalano J. The International Conference on Harmonization (ICH) and its Relevance to Cell Therapy. ISCT 6th Annual Somatic Cell Therapy Symposium 2006. Available from: http://www.fda.gov/cber/genetherapy/isct092506jc.htm.
24. ISSCR Guidelines for the Clinical Translation of Stem Cells. Available from: http://www.isscr.org/clinical_trans/index.cfm.
25. The Hinxton Group. An International Consortium on Stem Cells, Ethics and Law. Law Hum Genome Rev 2006;24:251-5.

26. Martell K, Trounson A, Baum E. Stem cell therapies in clinical trials: Workshop on best practices and the need for harmonization. Cell Stem Cell 2010;7:451-4.
27. Leanne B, Sarah D. Gaps and overlaps: Improving the current regulation of stem cells in the UK. J Med Ethics 2007;33:621-2.

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