Following Up on Stem Cell Guidelines in India

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The National Guidelines for Stem Cell Research, 2013 jointly developed by the Indian Council of Medical Research and the Department of Biotechnology (The National Guidelines)[1] and the draft Guidance Document for Regulatory Approvals of Stem Cell and Cell Based Products (SCCPs), December 2013 by the Central Drugs Standard Control Organization (CDSCO Guidance)[2] were recently released to regulate stem cell research and approvals procedure for release of Stem Cells and Cell Based Products. Emphasis is made to stop unapproved therapies, while ensuring that scientifically designed and responsible research on stem cells is not hindered.

These guidelines received wide attention from the press and various stakeholders[3-5]. We also made certain observations on regulatory issues associated with therapeutic aspects of regenerative medicine and tissue engineering highlighting the challenges, limitations, funding aspects, role of the local bodies, role of the investigators, differentiating fraudulent and genuine therapies, rights of the patients etc.[6], Unregulated Stem Cell Therapy[7] and Policy Considerations for Stem Cell Therapy.8 We made a detailed analysis of the new guidelines: the National Guidelines and CDSCO Guidance and highlighted the gap areas missed out for the therapeutic applications of the cells.

The ICMR guidelines published in 2007 were progressive and promoted clinical research using adult stem cells (ASCs). However, there was no clear mechanism put in place to bring the use of ASCs into routine clinical practice. The revised 2013 guidelines still do not provide a framework for clinical use of ASCs. In addition, the draft regulation proposed by the DCGI does not sync with the ICMR guidelines, which has unfortunately left the Stem Cell Industry widely, confused[9].

There have been number of observations made by other authors also for consideration by the regulatory agencies. Expectations are wide open as to how the agencies involved with developing these guidelines would react to various suggestions made from all quarters of society. The stem cell industry is also eagerly waiting to the release of final guidelines with amendments based on invited suggestions.

It is clear that adult stem cells (ASCs) have a major role in the future of medicine. Over the past few years, evidence demonstrating the usefulness of ASCs in numerous disease conditions has been mounting. Many countries have been proactive and have modified regulations so as to promote the use of stem cells in clinical practice. For instance, Japan has recently passed a bill that allows the use of all types of stem cells as far as safety has been demonstrated.

The new guidelines are a sincere effort by the regulatory bodies to address issues related to therapeutic use of stem cells keeping in view as foremost priority the safeguard and protection of the subjects receiving stem cells. The regulatory authorities may like to consider various concerns that rose from different quarters of society.

India is one of the biggest markets for stem cell therapy. With the new guidelines in place, it is difficult to judge how many of the new leads / findings in stem cell would end up for publications in the journals and how many of them would lead to translational use for Indian public and when that would happen. Ultimately, the role of regulation should be to promote a clear, time-bound mechanism to bring stem cells into clinical practice in the shortest possible time. This will help the scores of patients waiting for treatment. Given the present understanding, the strict compliance of the Guidelines would hold back the commercial application of stem cells in India for unlimited period and would deny the beneficiaries the genuine treatment using the cell types prepared by standardised technologies. Under the circumstances, more number of SCCP therapeutic products expected to be eligible in the country would be either through import of the product and technology or through international collaborations with MNCs by larger companies resulting in monopolised use of stem cell

therapies. This would also mean slow death to small and medium companies unless new mechanism of generating funding for stem cell research and therapy including liberal funding by the funding agencies is considered.

Stringent requirements under the guidelines has raised an imminent threat to the therapeutic use of the stem cells as only very few of clinical entities and the industry involved in regenerative medicine have facilities for research and clinical trials. It is a set back to the established industry already providing cellular therapy to re-establish to meet the stringent requirement under the guidelines to generate pre-clinical information and clinical trial data before seeking the necessary licenses from the regulators. Under the guidelines the therapeutic use of stem cells in India can only be done in the context of a clinical trial.

The CDSCO Guidance considers all forms of stem cells as INDs and makes it mandatory to go through the IND process for any therapeutic use of stem cells. Securing of licenses for collection, processing and storage of stem cells and cell-based products (SCCP) require GMP facility, dedicated clean area in the hospitals/ clinics; technically competent and trained personnel; uniformity in manufacturing and process controls; safety testing etc. There are very few facilities in the country which have required contained facilities meeting the regulatory requirements of clinical grade cells under strict GMP conditions. It virtually means barring few, none of the existing facilities would qualify to legally obtain approvals of the regulators.

Hardly there are GMP facilities in institutional set up and the big pharmaceutical industries have very little or left with no interest in stem cells. Most of the research in India is through public funding and restricted to major institutions doing basic research. Most of institutions have no facility or qualified to run clinical trials. Under the proposed mechanism the funding would be difficult to come for small and medium industry. Thus the implementation of the new Guidelines may pose an imminent threat to commercial use of such products and technologies.

Challenges

Successful therapy of stem cells involves challenge of evaluation, length of time and capital resources, gestation period, sustained public funding, limited funding by big companies and capacity of early-stage start-up companies/ small cell therapy developers. Only limited number of regenerative medical companies has achieved commercial status. Regulatory uncertainties, lack of universal agreement and restrictive policies by different governments impede international collaborations practices for stem cell therapy. Patient's acceptance / awareness / medical insurance and coverage are the other challenges. In India one of the major challenges is to regulate clinics offering stem cells for therapy outside a regulated processing facility.

The Drugs and Cosmetics (Amendment) Act, 2013 to regulate clinical trials and related issues including exports submitted by the Ministry of Health and Family Welfare, Government of India, in August 2013 is yet to be discussed by the Rajya Sabha. At present there is no clear legal policy or restriction on therapeutic use of stem cells. There is nothing in the Guidelines to outlaw, prohibit or punish those carrying out stem cell treatments. The guidelines are not binding. Taking advantage, a large number of laboratories, private clinics and hospitals are boldly jumping the laws and administering unproven therapy to unsuspecting thousands of patients in the country, raising several ethical, legal and social issues and putting desperate patients at health and financial risks. In terms of Guidelines of Indian Council of Medical Research, all those entities providing stem cells therapy in patients outside an approved clinical trial are into malpractice and should be penalized. All efforts should be made to get the Act 2013, which envisages penal actions for violation and non-compliance in terms of fine and imprisonment, approved by the Parliament at the earliest and notification issued before it becomes difficult to manage unethical use of stem cell therapies.

Role of Funding Agencies

Guidelines provide for emphasis on research and development and pre-clinical studies. Given the circumstances, the government funding in regenerative medicine would be limited more to academic institutions. However, because of the wide potential of stem cell therapy for treatment of incurable tissue degenerative diseases, development of the industry is equally important. Sustained funding need to be committed both from Government as well as private resources. There has to be separate funding mechanism for supporting stem cell research for proof of concept, upscale and manufacture of therapeutic products. The agencies may consider developing centralized infrastructure facilities like GMP facilities for testing, standards and characterization of stem cells; low-temperature bank of stem cells and tissues; development of animal models based on the requirements; and centres of excellence in states . Innovative mechanisms may be considered to support and nurture early stage researches

and small cell therapy developers and evolve Public–Private Partnerships models for joint development of products between academicians and industry; and generating the necessary skills.

Role of Local Bodies

Harmonization in cellular therapy regulations between the centre and state should clearly delineate the role of local bodies in promoting the implementation and understanding the widening imbalance between the research and application. The patients are provided sufficient information to increase their level of knowledge and understanding about the approved/standard therapies and other cellular therapies approved for marketing; controlled clinical trials; treatments not subject to independent scientific and ethical review; legal measures; and compassionate use of unapproved therapies.

Role of the Investigators

National Guidelines has outlined the role of investigators in providing cellular therapy to ensure that their activities are in com¬pliance with all relevant regulatory authorities and ethics committee requirements to ensure safety of the patients. The onus is on the investigators that no hype or unrealistic expectations are created in the minds of subjects or public at large regarding stem cell therapy. The guidelines must ensure that researchers follow the code of ethics and does not infringe on biosafety.

Unethical Advertisements

Mushrooming of the laboratories, private clinics and hospitals providing unapproved therapies goes unabated and they openly solicit unsuspecting patients through electronic and print media, for treatment of plethora of diseases. Only very few of them have the required expertise and facility for separation of required cells and clinical therapy and are dependent on established laboratories subjecting the clinical samples to varied conditions and shocking treatment. Such advertisements definitely raise expectations in the minds of general public. The cost of treatment is exorbitant with varied results. This also infringes on consumers right. Efforts made so far to curtail the mushrooming of such clinical healthcare entities have been very scanty. CDSCO Guidance to great extent would curtail unapproved therapies but no action plan seems to be in place and the fate of ongoing therapies by a number of clinics / hospitals including some of the prestigious hospitals. The Medical Council of India supposed to regulate clinicians involved in unethical acts but so far it has failed to achieve its goals to a larger extent. The regulatory authorities till such time, an act is notified, can send notices and seek information from such entities.

Legal Issues

All stem cell research in India for therapeutic purposes is considered experimental, with the exception of use of hematopoietic stem cell transplantation (HSCT) for haematological disorders. The draft Guidelines are totally silent on how to prohibit or punish those carrying out unethical stem cell treatments beyond the permitted therapies. The unsuspecting clinics are taking advantage of the limited permissions and developing their facilities to expand also on prohibitive therapies for which stringent safety aspects are yet to be established. Doctors/ clinics are treating a wide range of diseases making the patients believe that the use of adult stem cells is safe. In cases of a consumer having a complaint against cellular therapy provider, the government has no power to act on the complaint. The laws and regulations must differentiate clearly between the standard therapies and other cellular therapies which are approved for marketing and clinical trials.

Patients Advisory for Stem Cell Therapy

In view of false promises by the unauthorised providers of the therapy for treatment for incurable, potentially untreatable diseases, patient's awareness on specific treatment including all costs, potential risks and benefits and expected outcomes would help the patients and their families to decide the preferred therapies. It should be made mandatory for all such therapy providers to provide information to patients the treatment being offered in terms of informed consent in local language, treatment procedure and reporting procedures, their results and outcomes.

Patients Rights: Since all stem cell therapies are considered experimental, the laws should protect the fundamental rights of the patients seeking stem cell treatment for their diseases regarding the right to informed consent in language of their understanding of the risks, benefits, costs, safety, compensation against complications and insurances, if any for injury, investigator conflicts of interest and alternative therapies.

Growth of Industry

The restrictions imposed on stem cell therapy in India have already started showing its impact on the growth potential of the stem cell industry. Funding has become difficult to come in this area. The requirement of IND process and phase 1-3 trials as well as RCT before being allowed is a major barrier in promotion of the field. There is hesitation on the part of the international companies to partner with Indian companies and at the same time Indian

companies are restricting themselves to banking only. Allowing import of stem cells is also detrimental to indigenous business especially when the Indian regulatory policies have been unclear, unhelpful, and largely restrictive to therapeutic developments. Clinical trials are limited to few companies that would monopolise the therapy in the country. Restrictive regulations have limited the scope of industries in producing patentable consumables, procedures and devices required to carry out stem cell research in new molecules and media used for in vitro cell or tissue culture protocols thus increase the dependency on the foreign treatments. Indirectly there would be spurt in number of unsuspecting clinics providing unapproved therapies.

Advantage India for Stem Cell Trials

India is considered as hub for clinical trials because of its large, diverse, and treatment-naive population provides a valuable resource for clinical trials, especially for rare diseases where the Indian population could provide sufficient patients for trial groups. Pharmaceutical and biotechnology sectors are well developed and regulated and have attained expertise in conducting clinical trials. Stem Cell Entrepreneurship in India will be of great advantage as therapies generated in India would cost less than treatments developed in industrialized countries due to its low R&D cost and process engineering advantages. The cost of reagents, cheap services, cost-efficient cell and tissue culturing and storage techniques help reduce the cost. Based on these strengths, India could become a potential for clinical trials of choice for stem cell therapies for a variety of diseases. The new Indian guidelines regulating the stem cell though may encourage the researchers to start working in complex areas of stem cell research but the absence of a pro-active policy towards therapeutic applications of clinical trials is becoming a significant hindrance to the development of this field. Due to lackadaisical approach towards framing clear and progressive regulation, India is losing its advantage of being a dominating destination for development of stem cell therapies particularly related to international collaborations

New MTA Policy

India is following a liberal policy of termination of pregnancy. There is almost no public or religious debate on abortion, which is legal across India up to 12 weeks of pregnancy under the Medical Termination of Pregnancy Act, 1971. This policy is further being liberalised and only few days earlier, the Ministry of Health and Family Welfare has proposed to introduce an amendment to the act known as the Medical Termination of Pregnancy (Amendment) Bill, 2014, to allow abortion until the 24th week of pregnancy. The draft bill also says that abortions can be performed not only by allopathic doctors but by ayurveds, homeopaths and midwives as well. That is raising concerns that stem cell researchers providing stem cells therapy with embryonic stem cells may have no limitations of collecting cells from the foetus till 24 weeks of pregnancy and India may emerge as a major source of embryonic stem cells even for international companies. The weak Indian law may become a victim of further exploitation of foreign companies. The regulations would have to be redrafted for research on human embryonic stem cells within the country as well as possible international projects sourcing embryonic material from India.

Regulation for ART

The investigators and institutions conducting stem cell research has the ultimate responsibility of ensuring that research activities are in accordance with the national regulations and guidelines including public concerns about research that involves human embryos. The spare embryos created during infertility treatment being the most valuable source for stem cells needs an effective legislation with penal provisions for regulating artificial reproductive technologies (ART) clearly delineating the rights of the donor of embryos, number and quality of spare embryos, preservation and disposal of frozen embryos etc. and financial compensations. Registration of the clinics providing ART services should have mandatory registration to regulate use, disposal and preservation of embryos.

Sensitive Areas of Research

While the National Guidelines have identified the potential areas of research, it must also identify the areas for research, which may pose potential risks of human health and biosecurity. Those working with human iPS cells shall be particularly careful with the vectors and genes used for induction of stemness against malignant transformation. Sponsors must also ensure that the researchers apply the most current standards and follows the codes of ethics and biosafety.

Social Issues

Costs of most stem cell treatments are very high while many Indians cannot afford even basic health care. The high cost of the stem cell therapy is affordable to only wealthy few and some

of the stem cell treatments such as bone marrow transplants are beyond the budget of an average Indian. Poor patients with incurable disabling diseases are desperate and most vulnerable of being exploited. Limited therapeutic options; weak laws and lack of monitoring have led to the clinics charging exorbitant costs anything between 0.5 to 1.5 million rupees for a single course of treatment. Limitations of scarce stem cell therapy options may create social injustice and inequality in violation of basic principles of clinical research.

Complementing The Guidelines

National Guidelines requires approval of IEC and IC-SCR for pre-clinical experimental studies, both for basic and clinical research and on all types of human stem cells and their derivatives. Permission is also required from NAC-SCERT for clinical studies. The CDSCO Guidance at the same time also require clearance of the regulatory bodies for grant of Category I and II licenses for test, analysis, approval of clinical trial protocols for generation of safety and efficacy data. These are overlapping areas and a reason for confusion for the cellular therapy developers. The regulatory agencies incorporate necessary amendments to make the guidelines complementing both research and therapy favouring the end-users.

Hematopoietic Stem Cell Transplantation

Blanket permission on use of hematopoietic stem cell transplantation (HSCT) for haematological disorders has created doubts and confusion in the minds of the law abiding therapy providers and the consumers. While others hospitals and clinics are exploiting this blanket approval and providing stem cell therapy to the patients at the facilities which do not have necessary expertise, infrastructure and facility for separation and purification of cells and are dependent on other laboratories for separation of stem cells. They are not following the guidelines on the collection, storage, transportation, processing and transplantation of cells. Most of these therapies involve substantial manipulation and must be subjected to regular monitoring and regulatory clearances. The regulatory authorities need to develop guidelines clearly indicating the therapies which are exempted for necessary approvals; minimum requirements in terms of expertise and infrastructure for the facility; accreditation of each facility separately, providing specific therapy for specific disease, for which approvals are given; and monitoring mechanism for existing facilities. There need to be a clear policy on granting permission to the existing facilities or to re-establish the existing industry providing cellular therapies and have invested huge money on their facilities and are involved in banking and use of stem cells.

Related issues for consideration; Discussions with various stake holders also raised the following issues:

- All the processing centres in the country should be registered with the Central Agency. The Centre should be licensed as an accredited cell processing centre for which a clear and transparent rule should be framed. The GSR 899 (E) rules on umbilical cord blood stem cells can be applied and facilities should be allowed to apply through the same. Facilities with existing license based on GSR899 (E) can be automatically approved. Facilities in the process of application through GSR899 (E) should be granted Category 1 license based on the same application.
- The treatment centres need to be registered with CDSCO exclusively for the treatment for which permission has been granted. Any violation is considered unapproved therapy and shall be made punishable offence. There should be separate rule for accreditation of processing facilities and the treatment facility. The rule should also define the definite time-line and guaranteed turn-around times for accreditation and issue of licence to the centre;
- Unregistered treatment centres may not be allowed to offer unapproved treatment or advertise and create unnecessary hype regarding the benefits of the stem cells especially for anti-ageing, health and beauty benefits. The regulators must ensure a ban on advertising / publicity in electronic / print media or otherwise of unsubstantiated claims with stem cell therapy and make it punishable offence;
- The regulatory bodies may consider allowing treatment centres to do patient-funded research or trials under oversight of the institutional committees and it may not follow the IND route. Proposals with clear objective end-points, well defined protocols for treatments, approvals of IC-SCRT and EC, patient's informed consent and ascertained safety process and cells may be categorised under this group. It may be an option for patients on compassionate ground.
- CDSCO must ensure that it follows a fast, fair, transparent application and review process with definite time-lines. A dedicated group of officers having necessary knowledge

about research and therapy in stem cell and regenerative medicine would ensure a friendly and progressive atmosphere for development of regenerative medicine. The High Powered Committees defining rules and regulations for the stem cell research and clinical trials must have adequate representation from the clinicians and industry having demonstrated experience in the multifaceted areas of stem cells.

- Define proactive role for officers of CDSCO in monitoring, evaluation and issue of license while granting permissions in time bound manner, inspecting the facilities provided in the clinic for manufacture stem cells for therapeutic use and related follow ups and reporting on regular basis. Enact laws to fix responsibilities in cases of gross violation of the Act if takes place by the doctor/clinic/institution situated in their jurisdiction.
- The requirement of IND process and completion of required clinical trials before being allowed for use is a major barrier in promotion of the field. To overcome situation, multiple clinical research by various organizations may be encouraged to ensure a rapid and reliable progress in this field. Use of adult stem cells has already entered into the generic space and companies are hesitant to spend the vast amount of money needed to take them through the several years required for the IND and NDA route.
- The exclusion of bone marrow transplantation as medical procedure from the purview of the guidelines is difficult to understand and defies the logic that the active part of bone marrow is the stem cells component: in effect it is also stem cell transplantation.

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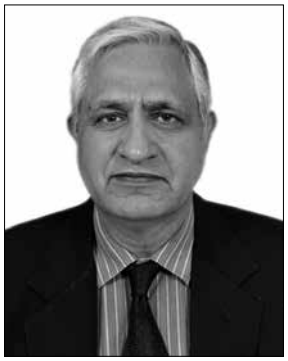

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