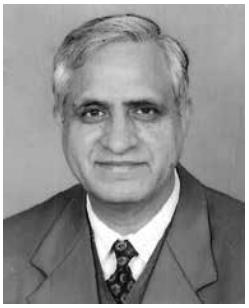
New Guidelines Casts a Shadow of Gloom of Slow Death to Efforts on Stem Cell Therapy in India



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Abstract: *The National Guidelines for Stem Cell Research, 2013 and Draft Guidance document for regulatory approvals for Stem Cell and Cell Based Products (SCCPs), Dec 2013 tried to regulate the stem cell research and approvals procedure for release of Stem Cells and Cell Based Products. However, a number of gap areas have been missed out for the therapeutic applications of the cells, which has left the Stem Cell Industry widely perplexed. An effort has been made to identify these areas to be considered further by the regulatory agencies.*

The finalization of the National Guidelines for Stem Cell Research, 2013 jointly by the Indian Council of Medical Research and the Department of Biotechnology (The National Guidelines)[1] and the draft Guidance Document for Regulatory Approvals of Stem Cell and Cell Based Products (SCCPs), December 2013[2] by the Central Drugs Standard Control Organization (CDSCO Guidance) are welcome steps. These guidelines are an effort to complement each other and fill in the gaps and voids left in the minds of the researchers and the industry to streamline the application of stem cells for research and development and therapeutic use. All the effort made by these agencies involved in the development and finalization of comprehensive details and providing the guidance documents need to be appreciated.

The two documents however, have not brought cheers to the stem cell industry and the researchers alike. These documents may satisfy the basic researchers, who would benefit from promotional science and funding but all those involved with the translational research and therapeutic aspects of stem cells it means a slow death to the industry. Like the pharmaceutical industry the patients would be denied the indigenous genuine regenerative medicine therapy and would have to depend on imports of SCCPs from the multi-nationals.

The National Guidelines even though omit the word Therapy from the title of the Guidelines and emphasize that stem cells are still not a part of standard of care; hence there can be no guidelines for therapy until efficacy is proven and that these guidelines are intended to cover only stem cell research, both basic and translational, and not therapy. At the same time the Guidelines has gone beyond its Scope of therapy and a strong view has been taken to the fact that various clinics in India are offering largely unproven therapy, raising several ethical, legal and social issues and putting desperate patients at health and financial risks. The Guidelines states that every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice.

This has already created a ripple running through veins of various clinics and there is a panic among the sponsors as the implementation of the new Guidelines pose an imminent threat to all use of stem cell for therapeutic purposes, commercial or not commercial, as only very few of them have the required facilities for research and clinical trials. It has given a set back to the established industry to re-establish to meet the stringent requirement under the Guidelines to generate pre-clinical information and clinical trial data before commercialisation. It has also created a terror in the minds of the potential patients in receiving such therapies.

The CDSCO Guidance make it mandatory to run clinical trials for any use of stem cells for therapeutic applications even for types of cells prepared using standard established technologies and reagents. This would mean that the research at the institutional level would limit itself to publications and experimental studies. Any therapeutic use of the cells would require clinical trials and have to follow the requirements under the CDSCO Guidance. To fulfil the criterion of even getting Category I License for collection, processing, storage of SCCP for the purpose of test and analysis,

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it would require GMP facility, dedicated clean area in the hospitals/ clinics; and technically competent and trained personnel. The Guidance also require uniformity in manufacturing and process controls of SCCPs including source, cell collection or recovery methods and their safety testing, tissue typing etc. It might virtually means that any intent of clinical trial for commercial use and applications by the hospitals /clinics would not be possible. 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.

The new guidance does offer a ray of hope for import of the product and technology but such avenues would be very limited. The chance of indigenous technology emanating from the research institutions is also very remote as most of these institutions would have no facility of clinical trials to qualify for Category 1 license. Thus the implementation of the new Guidelines may pose an imminent threat to commercial use of such products and technologies. It would also give a set back to the established industry to re-establish to meet the stringent requirement under the Guidelines to generate pre-clinical information and clinical trial data before commercialisation.

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. Most of the research in India is through public funding and restricted to major institutions doing basic research. With existing mechanism the funding is difficult to come for small and medium industry, unless new mechanism of generating funding for stem cell research and therapy including liberal funding by the funding agencies is considered. Our report highlighted some of the possibilities.

The provision of IPR protection under guidelines to an extent may give some encouragement of investment by industry.

In India in recent years, liberal funding from the Ministry of Science and Technology and the Ministry of Health and Family Welfare, the stem cell research has attained new heights at par with developments abroad. This is very evident from the high quality presentations at international conferences. At the same time, 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 would that happen. At the same time, the application of genuinely approved therapies in India is very remote in near future, as very few genuine technologies are in pipe-line, resulting in disinterest to large industrial houses and investors and slow death to the stem cell therapy in India.

In some of our recent reports we raised regulatory issues and policy considerations[3-5] 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. We are sure there would be number of observations made by other authors also, which would bring further issues for consideration by the regulatory agencies.

The present document provides a brief on the guidelines and the impact it would have on the cellular therapies.

ICMR-DBT Guidelines, 2013

The new National Guidelines for Stem Cell Research are issued jointly by the Indian Council of Medical Research and the Department of Biotechnology in December 2013[1]. Prior to those Draft Guidelines were issued in March, 2012 which was modifications on the Guidelines for Stem Cell Research and Therapy of 2007.

These guidelines present significant improvement upon the Draft Guidelines 2012, in defining the role of all the stakeholders in details including the individual researchers, organizations, sponsors, oversight / regulatory committees and any others associated with both basic and clinical research on all types of human stem cells and their derivatives. More emphasis is on basic research involving preclinical, clinical trials and clinical research to prove efficacy, safety and utility of the cell.

The new guidelines follow the guiding policy of promoting scientific and ethical conduct of stem cell research while preventing premature commercialization and potential exploitation of vulnerable patients and taking into consideration new developments in research related to stem cells and regenerative medicine and scaffolds in tissue engineering.

The guidelines cover only the stem cell research both basic and translational and not for therapy. Basic research would further lead to involving preclinical, clinical trials and clinical research to prove efficacy, safety and utility of the cell types used. Guidelines prescribe strict procedures for sourcing and the use of stem cells by research institutions and provide ethical direction to scientists working in the field. Main emphasis is on research and proof on concept before the stem cells are put to therapeutic applications.

The use of hematopoietic stem cells for treatment of various haematological, immunological and metabolic disorders has been excluded from the ambit of the Guidelines since the same has already been established as a standard of medical care. These guidelines also do not apply to research using non-human stem cells or tissues.

A strong view has been taken on unethical use by various clinics/ hospitals in India of offering largely unproven therapy, raising several ethical, legal and social issues leading to severe complications and putting desperate patients at health and financial risks. Accordingly the Guidelines have emphatically clarified that since the stem cells are still not a part of standard of care, the use of stem cells in patients must be done strictly within the purview of approved and monitored clinical trials with an intent to advance science and medicine and not as therapy until the efficacy of the cells is proven. Hence, the use of stem cell other than that for hematopoietic stem cell reconstitution for approved indications is investigational at present and every use of stem cells in patients outside an approved clinical trial shall be considered as malpractice.

The present Guidelines have taken in to consideration significant developments made in production of induced Pluripotent Stem (iPS) cells for generating histocompatible stem cells, growing stem cells without xenogenic feeder cells and developing well-defined media free from foetal calf serum. Efforts have been made to provide guidance for characterizing the cell product for therapy for its purity, safety and potency in an expeditious and cost-effective manner in order to harmonize them with the internationally revised guidelines.

Ethical Considerations in stem cell research includes health and safety of donors; informed consent from the donor, manufacture and quality assurance of stem cell products in terms of targeted differentiation of human ES or iPS cells, individualized processing of cells, adherence to quality control and assurances under GLP/ GMP/GTP conditions, characterization to develop clinical grade cells and regulation of stem cell research, particularly in relation to its translational role.

To meet the objective of fundamental tenets of beneficence, non-malfeasance, justice and autonomy to all research involving human subjects, all research involving the use of stem cells must be guided by the general principles laid down in the "Ethical Guidelines for Biomedical Research on Human Participants" published in 2006 by the Indian Council of Medical Research (ICMR).

The present guidelines have an additional layer of oversight with extended mandate of Review and Regulatory Oversight of Stem Cell Research given to the National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT). This mechanism of additional review has been accepted by the scientific community in the country and the required NAC- SCRT has become operational.

Guidance is provided for protection of IPR on the merits of each case. In case the IPR is commercially exploited, a proportion of the benefits shall be returned to the community, which has directly or indirectly contributed to the product, which may include potential beneficiaries such as patient and research groups.

The Guidelines has the scope of periodic evaluation of advances in the field by expert groups and appropriate modification of regulations as and when deemed necessary.

Taking into consideration the ethical concerns about the promotional advertisement by private banks, the present Guidelines ascertained that in absence of scientific basis for preservation of cord blood for future self-use, the offer of storage of cord blood for possible future use has been considered misleading for the public and lack comprehensive and accurate information to the consumer and this practice is not recommended. The Guidelines however, recommend that parents should be encouraged for voluntary donation to public cord blood banks for allogeneic transplantation and research purposes and in such cases, ID cards should be issued by the banks, to the donor to enable preferential access/benefits to donor/relatives, in future.

The Salient Features of The Present Guidelines Include

The Aim and Scope of the Guidelines is extended to all stakeholders including individual researchers, organizations, sponsors, oversight/regulatory committees and any others associated with both basic and clinical research on all types of human stem cells and their derivatives.

The present guidelines have retained the earlier classification of stem cell research and categorized the stem cell research into three areas viz. permitted, restricted and prohibited, according to the expected risk and level of supervision required for each category

Permitted Areas of Research

In vitro studies on pluripotent stem cell lines viz. ES or iPS cells, or Somatic Stem Cells (SSCs) from foetal or adult tissues, for understanding their basic biology; use of stem cell lines from sources outside the country as per the regulatory requirements of the country of origin and National Guidelines; In vivo studies in experimental animals, Establishment of new human ES cell lines from spare embryos or iPS cell lines from foetal/adult somatic cells; Umbilical Cord Blood stem cell banking; Clinical trials with clinical grade SSCs processed as per National GLP/ GMP / GTP guidelines.

Restricted Areas of Research

Creation of a human zygote by IVF, SCNT or any other method

for deriving ES cell line for any purpose unless clearly defined that research cannot be carried out with existing ES cell lines, or those that can be derived from spare embryos and minimum numbers of embryos/blastocysts required; Clinical trials using cells derived from the differentiation of human ES or iPS cells, or any stem cell after major manipulation, for which clearance is required; Clinical trials sponsored by multinationals, employing cell products developed outside India require prior approval of Health Ministry's Screening Committee (HMSC);The imports of biological materials for research and development as regulated by Government of India; Research involving introduction of human ES / iPS / SS cells into animals including primates; Studies on chimeras where stem cells from two or more species are mixed at any stage of development; Research in which the identity of the donors of blastocysts, gametes, or somatic cells from which the human ES/iPS cells were derived is readily ascertainable or could become known to the investigator would also require prior approval of NAC-SCRT through IC-SCR and IEC.

Prohibited Areas of Research

Research related to human germ line gene therapy and reproductive cloning; In vitro culture of intact human embryos, regardless of the method of their derivation, beyond 14 days of fertilization or formation of primitive streak, whichever is earlier; Clinical trials involving transfer of xenogeneic cells into a human host or clinical research on Xenogeneic-Human hybrids; Research involving implantation of human embryos into uterus after in vitro manipulation, at any stage of development, in humans or primates; Breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to gonadal cells.

Levels of Manipulation

Minimal manipulation involving no intended alteration in cell population or function; Substantial manipulation (or More than minimal manipulation) involving ex vivo alterations in the cell population including enhancement or depletion of specific subsets, expansion, cryopreservation, or cytokine based activation which is not expected to result in alteration of function; and Major manipulation where Genetic and epigenetic modification of stem cells, transient or permanent, which results in alternation of function.

Responsibility of Investigator, Institution and Sponsor for Conduct of Stem Cell Research

Guidance is provided to scientists involved in research on human ES cells to work closely with monitoring/regulatory bodies and to demonstrate respect for autonomy and privacy to public concerns for donors of gametes, blastocysts, embryos or somatic cells for stem cell research and safeguard rights and dignity of human donors and aborted foetuses. Those working with human iPS cells need to be particularly careful with the vectors and genes used for induction of stemness against malignant transformation.

Sponsors shall also take note of their responsibilities and liabilities under various statutes, regulations and guidelines governing research and development in this field in the country. Emphasis is given to regular review of research to ensure highest degree of scientific rigor and resolution of ethical concerns.

Each institution shall maintain a register of its investigators conducting stem cell research and ensure follow of guidelines and regulations regarding the use of these cells. The institutions conducting stem cell research shall establish suitable mechanisms for creating awareness and communicating scientific evidences to the public. All records pertaining to clinical adult stem cell research must be maintained for a period of at least 5 years and those for ES/iPS cell research for atleast10 years.

The physician/scientist engaged in stem cell research shall endeavour to avoid any activity that leads to unnecessary hype, or unrealistic expectations in the minds of study subjects or public at large regarding stem cell therapy.

The study subject and other responsible family members must be given adequate and unbiased information about the trial protocol, its limitations and potential adverse effects.

Translational Research including Clinical Trials Using Stem Cells: Detailed guidelines are provided for both preclinical studies and clinical trials using stem cells and their derivatives for repair or regeneration of damaged tissues and organs in situations where application of this mode of therapy has not yet reached an accepted standard of medical care. Translational research for generating a safe and effective novel product based on fundamental research involves scientific, technical and entrepreneurial challenges besides, addressing the ethical, social, and regulatory issues.

Preclinical studies

Preclinical studies under the regulatory requirements for any new biological entity (NBE) are considered essential prior to the conduct of human clinical trials to establish safety of the product and the procedure and proof-of-principle, for achieving desired therapeutic effects, and evaluated both for early and late toxicities including immunogenicity and tumorigenicity. Study Design include defining well characterized and the source, dose and route of their administration, safety, distribution of cells, their survival, integration and functional outcome; use of Large animal models/non-human primates; preclinical toxicity studies in a certified GLP facility; interaction of stem cells with; and plan to

analyze potential toxicities arising due to abnormalities acquired during in vitro processing. Besides, approval by IC-SCR and IEC, approval from IAEC and CPCSEA is required for studies involving small and large animals respectively.

Clinical Research/Trial

Trials using clinical grade human stem cells are to be undertaken in compliance with Schedule Y of Drugs and Cosmetics Act and GCP Guidelines of CDSCO as well as ICMR-Ethical Guidelines for Biomedical Research involving Human. Guidance is provided for selection of the Trial Subjects; Approval and Monitoring with respect to the source and type of stem cells, autologous or allogeneic application, degree of manipulation and stage and purpose of research; Regulatory Approvals requiring registration with CTRI; approvals by IC-SCR, IEC, NAC-SCRT and DCGI as per degree of manipulation, type of cells including human ES cells, import of cells and the purpose of trial for licensing or marketing; and Monitoring of clinical trials for adverse events, reporting to the Data Safety Monitoring Board (DSMB).

Compensation

The institution and/or sponsor conducting clinical trials shall be responsible for insurance and compensation of the subjects recruited under the trial.

Tissue Engineering and Scaffolds in Stem Cell Research: The detailed guidelines for the use of scaffolds in stem cell research were considered beyond the scope of this document/ guidelines. However, as guidance for the organization, growth, and differentiation of cells in tissue-engineered constructs, the properties of the scaffold may not only provides physical support for the cells but also helps maintain the chemical and biological function restoration. Scaffold should be biocompatible and should provide a 3D template, porous architecture with a high surface area allowing for maximum loading of cells, cell-matrix interaction, tissue in growth and transportation of nutrients and oxygen; should be mechanically strong but biodegradable made of material that can be sterilized without compromising any structural or functional properties.

Use of Stem Cells for Therapeutic Purposes

Use of hematopoietic stem cell transplantation (HSCT) for hematological disorders is already approved for stem cell therapy. All stem cell therapy other than these is treated as investigational and required to be conducted in the form of only a clinical trial after obtaining necessary regulatory approvals. For such clinical trials the cells need to be of clinical grade; product for transplantation free from animal products and microbial contamination. Centres carrying out stem cell clinical trials and the agency/ source providing such cells for the trial need to be registered with the NAC-SCRT through IC-SCR.

Basic Research

Stem cells derived from various sources are extensively being used in basic research for the fundamental understanding of their multiplication, differentiation to other cell types, drug discovery and screening research and clinical research/ trials for human disease. Based on the cell type/tissue of origin, stem cells are classified into Somatic Stem Cells (SSCs), and Embryonic Stem Cells (ESCs). SSCs have limited differentiation capacity and may be multipotent or unipotent. ESCs on the other hand are pluripotent and this characteristic can also be generated by reprogramming of somatic cells, giving rise to induced Pluripotent Stem Cells (iPSCs). Guidelines have been provided for general considerations on derivation and characterization of human pluripotent stem cells for basic and clinical research. A new class of human stem cells, human iPS cells, derived from foetal or adult diploid somatic cells by forced expression of pluripotency, are genetically reprogrammed PSCs and they exhibit properties similar to a typical ES-cell line. Derivation of new ES or iPS cell lines from human embryonic or somatic cells respectively must adhere to the conditions for gamete, embryo and somatic cell donation and with prior approvals. Other areas for basic research identified include modelling of human disease, drug development and derivation of a new hES cell line whether from spare embryos or embryos created for the purpose and necessary clearances required for the same.

Banking of Umbilical Cord Blood and Other Biological Tissues Including Cell Lines

Each proposal for banking or for academic application of the banked tissue shall be carefully examined by the IC-SCR and IEC from the ethical angle to ensure access, equity and justice

Banking of Umbilical Cord Blood

Umbilical cord blood banks are permitted to be established in India and licensed by the CDSCO as per standard requirements and practices. Any other use of cord blood stem cells, HSC or MSC is considered experimental at present and permitted only under conditions of controlled clinical trial by the IC-SCR/IEC or NAC-SCRT through the IC-SCR as required under the provisions of the present guidelines. All cord blood banks must be licensed and monitored by the CDSCO. Guidance is provided in taking precautions for collection of umbilical cord blood for stem cells, preparation of detailed SOPs for release of umbilical cord units for clinical use and follow up plans to monitor the outcome of HSCT for assessing safety and efficacy of cord blood stem cell therapy.

Banking and Distribution of Human ES/iPS Cell Lines

Guidelines to be adapted for human ES/iPS stem cell lines require that donors of biological material give informed consent through a process approved by the IC-SCR and IEC; maintaining detailed meticulous records of cell culture; uniform tracking systems and guidelines for distribution of cells as per accepted standard procedures. The facility engaged in obtaining and storing human ES/iPS stem cell lines need to follow the standard practices of standardized protocols for banking and withdrawals and documentation required for investigators and sites that deposit cell lines.

Mechanism for Review and Regulatory Oversight of Stem Cell Research

Since research in the field is associated with unique ethical, legal and social issues that require additional oversight and expertise for efficient scientific and ethical evaluation, a separate mechanism for review and monitoring besides the Institutional Ethics Committee (IEC), in the form of Institutional Committee for Stem Cell Research (IC-SCR) at institutional level and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) at national level have been introduced. All institutes engaged in stem cell research must establish an Institutional Committee for Stem Cell Research (IC-SCR) with necessary expertise. Alternatively, IC-SCR can be constituted by inducting additional expertise in the existing IEC with the nomenclature as IC-SCR

Scope of the Committees

All institutions and investigators; public and private, carrying out research on human stem cells should be registered with the NAC-SCRT through IC-SCR; Research using human stem cells requires prior approval of IC-SCR for permitted research and of the NAC-SCRT for restricted research; Procurement of human embryonic stem cell lines from abroad or from laboratories/ banks in India require MTA; Clinical trials using genetically modified SSCs, and ES or iPS cells or derivatives require prior approval from the NAC-SCRT; All clinical trials using more than minimal manipulated cells and IND products require additional approval of Drug Controller General of India (DCGI); All clinical trials approved by DCGI for stem cell derived products shall be registered with the Clinical Trials Registry of India established by ICMR; and International collaborations shall have prior approval of respective funding agency as per its procedure or Health Ministry's Screening Committee (HMSC).

Function of NAC-SCRT and IC-SCR

The National Apex Committee for Stem Cell Research established by Department of Health Research (DHR), Ministry of Health and Family Welfare, Govt. of India is a multidisciplinary committee mandated to give general oversight of the field of stem cell research and therapy in India and formulation of policy related to it and review of specific controversial or ethically sensitive research and proposals for therapeutic use of stem cells/ differentiated derivatives. The Committee has the responsibility to examine scientific, technical, ethical, legal and social issues in the area of stem cell or their derivatives based research and therapy; Maintain a register of all institutions involved in any type of stem cell research and therapy including details of their IC-SCR; Reviews and approves specific research protocols falling under restricted category. It also addresses new unforeseen issues of public interest from time to time; Use of chimeric tissue for research; Review annual reports of these IC-SCRs.

Scope of NAC-SCRT

The scope of NAC-SCRT has been extended also to review and update the national guidelines for stem cell research and therapy periodically; along with CDSCO, to set up standards for safety and quality control, procedures for collection and its schedule, processing or preparation, expansion, differentiation, preservation for storage, removal from storage to assure quality of human stem cells or their derivatives; Respond to queries/ representations from all the stakeholders in the community, to controversial issues raised /received from NGOs, patients, individuals etc.; and Monitor any unethical practices related to stem cell research and/ or therapy being followed at any organization or any individual and bring them to the notice of relevant authorities.

Procurement of Biological Material for Research

Procurement of biological material as a source of stem cells for basic or translational research is permissible subject to approval by IC-SCR and IEC. Detailed guidance is provided for procurement of biological material from foetal and placental tissues, as well as gametes, blastocysts and somatic cells. Detailed independent informed consent need to be obtained for termination of pregnancy and for donation of the foetal material for research that includes permission for screening of the donor for transmissible infections and obtaining family history of genetic disorders, the purpose and use of donated foetal tissue etc. The process of procurement of gametes, blastocysts, or somatic cells for the purpose of generating new human ES/iPScell lines require consent for donation of blastocysts; no inducement for donation of gametes or embryos by way of payment or in lieu of medical services, no payments made for donation of somatic cells for use in SCNT or creation of iPS cell lines. Detailed informed consent module provides statements to the effect that the blastocysts or gametes will be used to derive human ES cells/cell lines only

for research purposes following the established procedures of ethical practices for procurement, culture, and storage of cells and tissues keeping in view the interest of the donors including compensation in case of any complication.

International Collaboration

All international collaboration are permitted as per the approved procedure of funding agencies (DST, DBT, ICMR etc.) or the Health Ministry's Screening Committee, following joint proposal with appropriate MOU.

Exchange of Biological Material for Research

All proposals for import/export of stem cells and their derivatives required for research and development including for clinical trials shall be examined by the IC-SCR and NAC-SCRT if necessary and the statutory requirements of approval from DCGI and the Govt. of India's guidelines. Established procedures would be followed for type of cells as per appropriate international guidelines for their packaging, labelling, handling and transport at ports without compromising their quality.

Public Participation

An interactive portal on the web would be created by NAC-SCRT, both for the public as well as scientists and professionals to provide reliable and up-to-date information about recent developments in the field and encourage suggestions and feedback for continuous improvement. Periodic interactions with the public/stakeholders will be held across the country by the experts and regulators.

Periodic Review of Guidelines

The unfolding of new developments and knowledge, both in basic and translational aspects, in the field of stem cells would be periodically reviewed and periodic changes to specific clauses and sections will be notified in the form of amendments to update the guideline document.

Draft CDSCO Guidance, December, 2013

This Draft Guidance Document is based on the recommendations of the High Powered Committee set up in June, 2013[2] and is subsidiary to the amendments made in 2013 to the Drugs and Cosmetics Act (DCA), 1940. The new rules proscribed there under the amendment in DCA mandates that all stem cells and cell based products that can be used for therapeutic purposes shall be referred as Stem Cell and Cell Based Products (SCCPs) and all activities related to their usage i.e. manufacture/isolation/ collection, storage and transplantation into patients must be done only under a license or permission that would be granted by the DCG(I) / CDSCO. It addresses both autologous and allogeneic SCCPs.

The rules and regulations in this Guidance Document are applicable to all organizations such as hospitals, private clinics, institutes, universities, tissue banks and companies who wish to obtain a license for the use of SCCPs for therapeutic purposes in India. Failure to comply with the conditions of this document or using SCCPs without a CDSCO / DCG(I) license shall lead to penalties as per the provision of the Drugs and Cosmetics Rules. The document provide the background information, the technical definition of SCCPs and details of various licensing / permission categories, requirements necessary to demonstrate proof of concept, pharmacological safety and designing of pharmacodynamic / pharmacokinetic studies.

The Salient Features of The Present Guidelines Include

SCCPs is defined as a new drug, which includes all vaccines, rDNA derived drugs, Stem Cell and Cell Based Products, unless certified otherwise by the Licensing Authority under Rule 21 of Drugs and Cosmetics Act.

The document provides guidance for collection, isolation storage, manufacturing, quality control, preclinical studies and clinical trials with SCCPs by Hospitals (Corporate or Government), Clinics, Companies, Research Institutes, University Departments and Cell Banking Centres.

The general consideration for clinical application of stem cells include: source of cells, isolation and characterization of cells, methods of expanding the cells, nature of substrates used, quantification of stem cells, differentiated cells in the expanded population, stability of the differentiated The SCCP sub-division within the Biological Division of CDSCO shall advertise through their website/press announcement requesting interested parties to apply for a license to manufacture/isolate/collect and/or store and/or conduct clinical trials and commercial use of SCCPs.

Four categories are identified for licenses/approvals of SCCPs: Category 1: License for collection, processing, storage of SCCP for the purpose of test and analysis, Category 2: Approval of Clinical Trial Protocols for generation of safety and efficacy data, Category 3: Approval/permission for manufacture or import of SCCP as a IND/New Drug, and Category 4: License for manufacture or import for storage, sale and distribution.

Category I

In this category, the applicant shall get a license certifying that the applicant's facility is fit for doing work on SCCPs. This would be an entry level license and all other licenses would be issued only to those parties which possess the Category 1 License from CDSCO. Issue of Category 1 license would need of minimal requirement of GMP facility for collection, processing, manufacturing and storage of SCCPs for clinical trials; dedicated

clean area in the hospitals/clinics for isolation and infusion of SCCPs into patients and post infusion patient care; technically competent and adequately trained personnel to handle such type of work; and adherence to all Safety Norms in the laboratories and clinical areas.

The procedure to get a license for clinical trials in this category would include:

- Applications would be invited from Universities/Institutes/ Hospitals/Clinics/ Companies (only for intended commercial use and doing clinical trials with SCCPs)
- The Institutional Ethics Committee (IEC)/Institutional Committee Stem Cell Research and Therapy (ICSRT) at the applicant's institution must be registered with CDSCO/ DCG(I).
- Joint Inspection by CDSCO & Experts
- Recommendations sent to DCGI
- DCG(I) grant the License in Form 29X that the Facility is suitable for work with SCCPs for collection, processing, storage, test and analysis (in vitro and in animals) only.

Category 2

Under this category, approval shall be given for specific protocols for generating efficacy and safety data by doing clinical trials/ commercial usage of SCCPs. Category 2 approval would be given only at locations that have been licensed as a Category 1 facility.

The following procedure will be followed for processing applications in Category 2.

- Applications will be received only from Category 1 Licensees
- In case of imported SCCP direct clinical trial application including detailed protocols can be received.
- Joint Evaluation and GCP inspection by CDSCO and Approved Experts
- Recommendations sent to DCGI
- NOC/Approval from DCGI that the proposed protocol is suitable for obtaining, and/or storing and/or using SCCPs of permissive/restricted classes as classified in the ICMR-DBT Guidelines.

Category 3

This category of approval/permission would be given only at locations which have obtained Category 1 and 2 license and approval. This approval/permission would be given for manufacturing or for importing SCCPs as new drugs.

The procedure will be as follows:

- Applications will be accepted only from Category 1 and 2 Licensees. In case of imported SCCP clinical trial report done under Category 2 along with the application will be reviewed
- Joint Evaluation of Proposal by SCCP Expert Committee
- Recommendations sent to DCGI
- DCG (I) approves the permission to manufacture or import SCCP as New Drug in Form 46/46A (for indigenous) or 45/45A (for imported) that SCCP of the applicant is a new SCCP drug of permissive/restricted class.

Category 4

This license would be of the highest category and would be given only to those who have Category 3 permission for manufacture or import of SCCP as a new drug.

The procedure for the getting this license would be as follows:

- Applicants who have Category 3 approvals will apply to DCG (I).
- Joint Inspection by CDSCO & Experts. In case of imported SCCP, the license will be granted only after inspection of overseas manufacturing facility.
- Recommendations sent to DCGI
- DCG(I) shall grant the License for indigenous SCCP

Detailed guidance has been provided on mandatory requirements for manufacturing and usage of SCCPs which require: Classification of SCCPs as autologous or allogenic; Manufacturing and process controls of SCCPs including source, cell collection or recovery methods and their safety testing, tissue typing; Banking procedures, its strategy and methods; Materials used during manufacturing and its source as human/animals; Requirements of manufacturing process including location and surroundings, collection and storage of cellular and regenerative products source, personnel, testing and production controls, quality control and assurance, storage of finished product, testing of SCCPs, labelling, maintenance of records, master formula records and requirements for processing of cellular and regenerative products.

Detailed guidance is also provided for Characterization of SCCPs, which includes: cell identity, cell purity, potency and testing for tumourigenicity; Quality control and release of SCCP; Stability testing; Container and closure system; Labelling; Quality Assurance of SCCPs; In-process controls including Batch numbering System and Validation of the manufacturing process; Product tracking; Pre-Clinical Studies including Pharmacodynamics, Toxicology: systemic toxicity as well as tumorigenicity study in SCID mice; Clinical studies including pharmacodynamics, pharmacokinetics, dose finding studies, clinical efficacy, clinical safety and pharmacovigilance and risk management plan

The Formats of applications, requirements and details for all SCCPs have been annexed with the CDSCO Guidelines.

Discussions

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. However, 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. The use of permitted autologus cells considered to be safer therapy with minimal danger of rejection, requiring more than minimal manipulation, is also made subject to regulations.

The new guidelines are discussed in respect of published reports on policy considerations for stem cell research and therapeutic requirements.

Challenges

Successful therapy of stem cells involves number of challenges. Regenerative medical technology is difficult to evaluate. The length of time and capital resources required for stem cell research is the biggest challenges; Gestation period is very long and costs involved are very exorbitant. Sustained funding is difficult to arrange from Government resources as big companies are not interested in funding cell therapies; and early-stage start-up companies/ small cell therapy developers are not in a position to fund clinical trials. 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 largely unproven therapy to unsuspecting patients.

Limitations

Translating research to develop a commercially viable stem cell-based therapy has number of limitations of complexity, innovation, regulatory flexibility and reimbursements. CDSCO Guidance to great extent would curtail unapproved therapies but nothing has been said about the fate of ongoing therapies by a number of clinics / hospitals including some of the prestigious hospitals. The funding agencies can address other issues on research funding for developments of cellular products, up scaling and necessary infrastructure; research limitations on large animals and clinical trials, joint development of products between academicians and industry; and generating skills.

Legal Issues

The Draft Guidelines are silent on how the absence of legal measures will be able to curb unethical stem cell medical practices. There is nothing in the Guidelines to outlaw, prohibit or punish those carrying out stem cell treatments. 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 possible harmful risk associated with unapproved stem cell therapies are making regulatory agencies and patients sceptical about potential of stem cell therapies, necessitating the need for controlled clinical studies to provide evidence on safety and efficacy claims of such therapies. The laws and regulations must differentiate clearly between standard therapies and other cellular therapies approved for marketing and clinical trials.

Under the Guidelines 2013, 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 guidelines at present are silent on legal measures on unethical use. National Apex Committee for Stem Cell Research and Therapy has been set up to govern the stem cell-related research and therapy but has no legal powers to curb unethical stem cell medical practices. At present, if a consumer has a complaint against cellular therapy provider, the government has no power to act on the complaint. The Guidelines are totally silent on how to prohibit or punish those carrying out unethical stem cell treatments.

The Ministry of Health and Family Welfare, Government of India introduced a Bill before the Rajya Sabha in August 2013 to regulate clinical trials and related issues including exports by way of further amending the Drugs and Cosmetics Act 1940, which will be called as the Drugs and Cosmetics (Amendment) Act, 2013 and have the provision of legal measures, once the law is enacted. Emphasis will be mainly given around regulation, ethical supervision of trials, compensation of trial subjects etc.

Government of India has initiated some steps towards regulating stem cell therapies. The Ministry of Health has issued Drugs and Cosmetics (3rd Amendment) Rules 2011 for manufacture of blood products and collection, processing, testing, storage, banking and release of umbilical cord blood stem cells under the Drugs

and Cosmetics Act, 1940 which will govern cord blood stem cells.

Some of the provisions of the proposed act are already considered in the draft guidance document of CDSCO. The definition of 'New Drug' and 'manufacturing process' is defined in detail. Accordingly prior permission of Central Licensing Authority is made mandatory for the manufacture of any new drug. The state licensing authority before issuing any license for manufacture of a new drug shall ensure that the permission from the Central Licensing Authority has been obtained by the manufacturer of new drug prior to applying to the state authority.

As per the aforesaid Bill, the Central Government shall constitute an authority to be known as the 'Central Drugs Authority', which would l be empowered to specify regulations, guidelines, norms, structures and requirements for effective functioning of the Central Licensing Authority and the State Licensing Authorities including review, suspend or cancel any permission, license or certificate issued by these authorities.

The 2013 Bill envisages penal actions against the person conducting clinical trial for violation and non-compliance of the provisions relating to the conduct of such clinical trials, in terms of fine and imprisonment. Provision is also made of compensation in case of an injury or death of a person occurs due to the clinical trial, by the person conducting such clinical trials.

Unethical Advertisements

The claims pertaining to benefits of stem cell therapy are frequently been published in newspapers. Such advertisements definitely raise expectations in the minds of general public. Reporting of such medical achievements in the Internet or newspapers by way of advertisements/ publications by the doctors involved in stem cell therapy research are in gross violation of the guidelines laid by Government of India. The National Guidelines clearly states under the subject, "Responsibility for Conduct of Stem Cell Research: Investigators, Institutions and Sponsors" that the physician/scientist engaged in stem cell research and therapy shall ensure that no hype or unrealistic expectations are created in the minds of subjects or public at large regarding stem cell therapy. Efforts made so far have not been able to curtail the mushrooming of the clinical healthcare entities providing unapproved therapies by soliciting unsuspecting patients through electronic and print media.

Questionable Safety of Stem Cell Therapy

Developments in the field of regenerative medicine and stem cell research are relatively new and are associated with complicated ethical, social and legal issues. Very little pre-clinical data on animal models is available and most of the treatment modalities have not gone through rigorous clinical trials to ensure the safety of the treatments. A large number of hospitals and industry involved in cellular therapies have started providing treatment for which stringent safety aspects are yet to be established. Doctors/ clinics have started treating a wide range of diseases by believing that the use of adult stem cells is safe. There is a need to curb expansion of these unethical services failing which there is a strong apprehension that the unethical medical practices may grow tremendously out of control of any regulatory/legal bodies or otherwise.

Role of Local Bodies

Most of the countries have instituted their own regulations and safeguard measures for research and therapeutic use of stem cells. The scale and quality of regulations have widened imbalance between the research and application and requires more harmonization in cellular therapy. Some of the considerations include:

- Guidelines should clearly differentiate amongst 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.
- Ensure common understanding of trial registration, data reporting and safety standards that would ensure that the patients are provided sufficient information to increase their level of knowledge and understanding about the stem cell research and therapies.
- Ensure patients are provided sufficient information on technologies and therapies approved within the regulatory systems.
- Ensure patients are aware of their rights and able to differentiate between the validated and fraudulence therapies.
- Independent ethics committees may be provided significant role in situations where the regulations protecting the rights of the patients are weak
- Weightage given to information and evaluations provided by professional and industry-based organizations offering cell therapies.

Role of Funding Agencies

Development of the industry is very important because of the wide potential of stem cell therapy in healthcare needs for treatment of incurable tissue degenerative diseases. Sustained funding need to be committed both from Government as well as private resources. There has to be separate funding mechanism for stem

cell research. The funding agencies will have to be innovative in identifying priorities/ funding patterns to support both stem cell research for proof of concept, upscale and manufacture of therapeutic product. Cell therapy companies have to become very creative in their sources of financing for which different funding possibilities and modules need to be explored.

Funding agencies may consider regenerative medicine as a high priority area for funding; public funding routed through translational research facilities; support and nurture early stage researches and small cell therapy developers; evolve Public–Private Partnerships models; encourage collaborations and co-development of therapy/product; funding from beneficiary foundations. Besides funding, the agencies also ensure that patients have access to experts, assessment of emerging technology / treatments and professional; awareness creation of stem cell based products and therapies among stake holders; skill generation through cooperation and consultation with industry; consultancy / guidance for starting new ventures in stem cells, like banking facilities; and facilitation of technology scouting. The agencies also invest in infrastructure to support centralized facilities like GMP facilities for testing, standards and characterization of stem cells; low-temperature bank of stem cells and tissues; centres of excellence in states; and development of animal models based on the requirements.

Post-Manufacture Activities

The National Guidelines 2013 limit itself mostly to research and development of stem cells and experimental studies. CDSCO Guidance would provide licence licenses/approvals of procedures for test and analysis, clinical trial protocols for generation of safety and efficacy data, approval/permission for manufacture or import of SCCP as an IND/New Drug, and for license for manufacture or import for storage, sale and distribution. These guidelines do not provide any information on regulations for post-manufacture use of stem cells (drug), guidance to the patients on their rights, patients advisory for stem cell therapy, guidelines to distinguish fraudulence cell therapies; guidance for cellular therapy providers, physicians, hospitals / clinics to ensure that their activities are in com¬pliance with all relevant regulatory authorities and ethics committee requirements.

Role of the Investigators

National Guidelines has outlined the role of investigators in providing cellular therapy to ensure that their activities are in compliance with all relevant regulatory authorities and ethics committee requirements to ensure safety of the patients; comply with good clinical practice (GCP) standards; ensure fair advertising for clinical trials and/or experimental therapies; publish clinical trials and their results, including adverse event or side-effects and negative results; and follow the ethics of cellular therapy including disclosing any financial interest. The guidelines have put the onus on the investigators that no hype or unrealistic expectations are created in the minds of subjects or public at large regarding stem cell therapy, which is a welcome initiative.

Patients Advisory for Stem Cell Therapy

In absence of rigorous and formal clinical trials, some laboratories and practitioners are offering stem cell procedures without following the existing regulations. Patients are being offered false promises for treatment for incurable, potentially untreatable diseases. In order to educate the patients and their families contemplate voluntarily accepting new procedures, the national regulatory bodies need to ensure the patients to educate themselves on the specific treatment including all costs, potential risks, potential benefits and expected outcomes; the treatment being offered through informed consent in local language document that the patient or family member can understand and clarify through questioning; treatment procedure steps and how patient follow up is handled; reporting procedures of the treatment, their results and outcomes; and obtain a disclosure of all potential expenses related to the therapy as well as compensation against complications.

Patients Rights

Investigators providers of cellular therapies should respect the rights of patients seeking medical treatment the fundamental right to seek treatment for their diseases; the right to information regarding the safety and efficacy record of the cell treatment; and the right to informed consent.

Guidelines to Distinguish Fraudulence Cell Therapies

Patients their relatives and general public also need to understand the difference between the formal clinical trials resulting from the innovative practice of medicine where their rights are protected and risks are communicated; and the fraudulent cell therapy practice where there is no demonstration of competency or protections and the information is execrated. This they can judge by evaluating evidence from peer-reviewed publications, professional society presentations and scientific recognition; safety, regulatory history and reputation of the investigator and clinic; accuracy of the information provided o- in the informed consent of the risks, benefits, costs, safety, compensation for injury, investigator conflicts of interest and alternative therapies.

Stem Cell Policies on hESC

India follows the policy to allow creation of hESCs from excess

IVF embryos. However, SCNT is allowed with restrictions. In terms of hESC research, countries are following different policies. In a recent survey countries have been grouped in five broad categories of Very permissive allowing research with hESCs derivation from multiple sources even the creation of embryos for research purposes; Permissive with restrictions allowing research with hESCs derived solely from surplus IVF embryos and embryos created for research and prohibiting the creation of embryos solely for research purposes; Restrictive by default where legislation is not explicit but national practices are quite restrictive in practice for any hESC research; Very restrictive where legislation explicitly bans research on hESCs; and Unlegislated, where there is no specific legislation concerning hESCs research.

Growth of Industry

The limit of stem cell therapy would influence the growth potential of the stem cell industry at large and may limit 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 pro¬tocols. This would add to the limiting issues of inadequate research funding; unknown therapeutics outcomes; reproducibility issues in clinical trials; and poor understanding of underlying mechanism; Major hurdles recognised in this emerging industry include regulatory pathway, clinical translation, and reimbursement of the new products. Start-up companies have difficulties to access capital and investors based investment.

Monitoring the Use of SCCPs

While ICMR-DBT Guidelines desist from the therapeutic aspects of stem cells, CDSCO Guidance has prescribes strict rules for collection, processing, storage, test, analysis, manufacture and distribution of SCCPs. These guidelines have added to the confusion of the physicians, patients and the public at large on who would monitor the use of the controlled and testified SCCPs in the patients. Unlike any pharmaceutical drug, the preparation and use of SCCPs would require continuous monitoring by the regulatory agency both at the central and the state level. The drug controllers would have to assume higher responsibilities. CDSCO may take the help of NAC-SCRT to set up standards for safety and quality control of procedures and processes assure quality of human stem cells or their derivatives, but to oversee applications of SCCPs, CDSCO may have to set up a Separate Body with major representations from the industry/sponsors and social groups.

The following issues would need further clarifications

Bone marrow/cord blood derived stem cells have been used for haematological reconstitution over years. Mesenchymal stem cells from bone marrow, cord tissue, fat and dental pulp have shown potential reprogramming and differentiations of cartilages, bone, muscles etc. and considered safe and do not cause any adverse events when used in therapy. However, most of the investigators, hospitals/ clinics did not generate any pre-clinical and clinical data and depending on the published safety report, they have been involved over the years in use of these cells for therapeutic purposes. Strict compliance with the new regulation would mean closure of the facility/delay in generating the capacity to provide therapy even to terminally ill patients. The regulators may have to consider the interest of such patients on compassionate ground and consider some mid way / relaxation to the existing facilities for limited period.

Some of the established companies in the field along with others have received permission from NAC-SCRT as per earlier practice for use of specific cells for running clinical trials for specific conditions / therapies. How such trials and other similar trials would be impacted for manufacture and distribution under the new CDSCO Guidance, where specific protocols would be followed?

The ICMR Guidelines regulates both basic and clinical research on all types of human stem cells and their derivatives by individual researchers, organizations, sponsors, oversight / regulatory committees. The studies would include both the pre-clinical experimental studies as well it may include clinical studies requiring clearances of the IEC, IC-SCR and NAC-SCERT wherever necessary. 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 would cause confusion and unnecessary problems for the cellular therapy developers. The regulatory agencies may consider complimenting the two guidelines for the benefit of investigators.

The National Guidelines permit the use of hematopoietic stem cell transplantation (HSCT) for haematological disorders as an already approved therapy for stem cells. Most of hospitals and clinics are taking benefit of this blanket approval even without having the necessary facility and without following the rigorous evaluation of product and offering largely unproven therapy. These entities collect the human samples; send it to various laboratories around the country and abroad for separation and preparation of cells for autologus therapy without following the

normal procedures of collection, storage and transfer. Most of these therapies involve substantial manipulation or one can say more than minimal manipulation and are must be subjected to regulatory clearances. There is no monitoring of such facilities. The arrays of guidelines have created doubts and confusion in the minds of the therapy providers and the consumers of such therapies. Necessary clarifications by the regulatory agencies may further clarify so as to whether the National Guidelines:

- Provide immunity to such hospitals/ clinics/ institutions, cellular therapy providers?
- What was the basis of giving blank clearance to hematopoietic stem cell transplantation?
- Have these technologies gone through the necessary scrutiny of the requirements of the existing guidelines by regulatory agencies?
- Can a clinical trial at one hospital (facility) for a particular application/disease can be extrapolated as a blanket approval to other hospital/clinic/facility?
- If the basis of blanket approval is reference to studies abroad, can application of other approved therapies abroad for the technologies and conditions of proven therapy abroad could become a basis of clearances in India?
- How do the regulatory bodies plan to address the issue of 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?

The National Guidelines although did not put any guidance for therapeutic use of the stem cells and cell based products. However, these guidelines stress upon that all products intended for administration in humans shall be properly labelled and fulfil the laid down acceptance, release and stability criteria including details of procedures to provide reproducible production of large quantities of well-defined clinical grade cells. The laboratory shall be duly accredited or certified, and file the CMC (Chemistry, Manufacturing and Control) documents for regulatory purposes and necessary approvals. These guidelines infringe upon the mandate of the CDSCO Guidance. All these processes of accreditation of the laboratory / facility for production and release of clinical grade stem cells would be governed under the CDSCO Guidance and would have to follow the strict requirements for getting the DCGI approvals. The role of institutions would limit to basic and experimental studies on stem cell research.

The Regulatory Bodies Need to Address the Following Issues:

- National guidelines have warned against creation of unnecessary hype regarding the benefits of the stem cells? The regulators must ensure a ban on advertising/publicity in electronic / print media or otherwise for anti-ageing, health and beauty benefits with stem cell therapy and make it punishable offence;
- Enact laws which enforce the treating doctors/clinics/ institutions to monitor treated patients of Stem Cell therapy for minimum five years before the treatment is advertised for general public and proper data bank is prepared on its long term safety;
- Drug Controller Authority may issue license to any centre for specific treatment / indication only. Any violation is considered unproven therapy and shall be made punishable offence;
- Enact laws to obtain regular report by officers of Drug Controller on inspection of the facilities provided in the clinic for manufacture stem cells for therapeutic use on regular basis;
- Enact law by which government officer/department can be held liable in case gross violation of the Act if takes place by the doctor/clinic/institution situated in their jurisdiction.
- A registry at the central level should maintain total information on the patients having stem cell therapy including the type of cells used, indication in which used, side effects noted etc.;
- ICMR and DBT responsible for stem cell research may upload and update on their portals projects being funded and highlights of significant results;
- The regulatory agencies incorporate necessary amendments to make the guidelines complementing both research and therapy favouring the end-users;
- GOI ensures that pending Bill is passed at the earliest and notification issued before it becomes difficult to manage unethical use of stem cell therapies.

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