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LETTERS

Current status of Regulatory perspectives on Stem Cell Therapy in India

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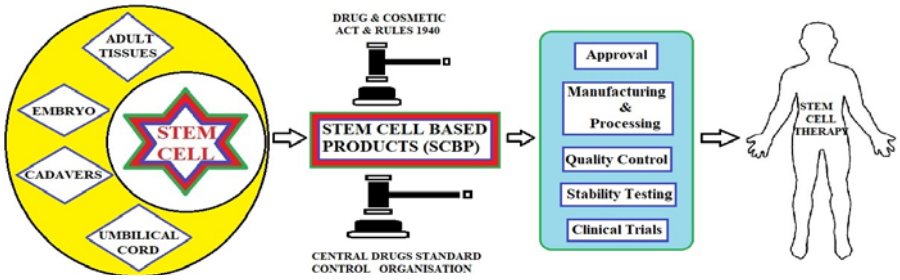
ABSTRACT



In the recent decade, regenerative medicines are emerging at fast pace in the field of therapeutics. Regenerative medicines have been used in curing severe diseases; mainly through restoration of stem cells. The stem cells are unspecialized cells which have an infinite proliferation capacity and can differentiate into all type of cells. These properties of stem cells to regenerate the functions of the tissues and organs are used in stem cell therapy. The ability of stem cells to regenerate and reconstruct the damaged tissue makes them an exciting area in medical treatment. Stem cell and stem cell-based products are used in the treatment of many diseases and support therapies. In India, the stem cell and cell-based products are supervised by the Central Drug Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare. CDSCO regulates the clinical trial approvals, monitoring, and approvals of drug manufacturing or new drugs and marketing authorization of stem cell-based products under the Drugs and Cosmetic Act 1940 and Rules. The focus of the present article is to provide information on the procedure of license approval for stem cells and cells based products in India. The article also include discussion on mandatory requirements of stem cell-based products like manufacturing and process controls, quality control, stability testing, labeling, and quality assurance.

Keywords: Regulatory Affairs, Master cells, Regulation Laws, Licensing Authority, Clinical Trials Approval.

INTRODUCTION

Stem cell therapy is a developing branch of medical science, and includes most recent regenerative medicines dealing with the restoration of function of cells and tissues for the patient suffering from serious diseases. Stem cell research has established the cell-based therapies for the cure of diseases which are not otherwise cured by conventional medicines and therapies. Stem cell research is focused on degenerative disorders in which the function of cells is severely affected and there is even the demise of certain cell types. These degenerative diseases might be treated by the use of stem cells, which can offer help and replace dead cells with new ones. Stem cell therapy has proved itself worthy in the treatment of various diseases such as coronary illness, diabetes, spinal line damage, and Parkinson's ailment.[1,2] Stem cells are defined as cells with infinite proliferation capacity and can differentiate in all types of cells, tissues, and organs. Stem cells do not have any specific structures, or specialized function is one of the best foundation properties of stem cells; that is why they are called "**Master Cells**" or "**All Purpose Cells**".[3]

Differentiation and self-renewal are two different properties of stem cells. The stem cells can give a boost to identical new stem cells that are also efficient to self-renewal, expansion, and differentiation, leading to maintenance of stem cell pool. Stem cells can progress to specialized cells with a particular

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function.[4,5] Based on the potency of stem cells, they are divided into four different types namely totipotent, pluripotent, multipotent, and unipotent.[6,7] The characteristics of stem cells are shown in Figure 1.

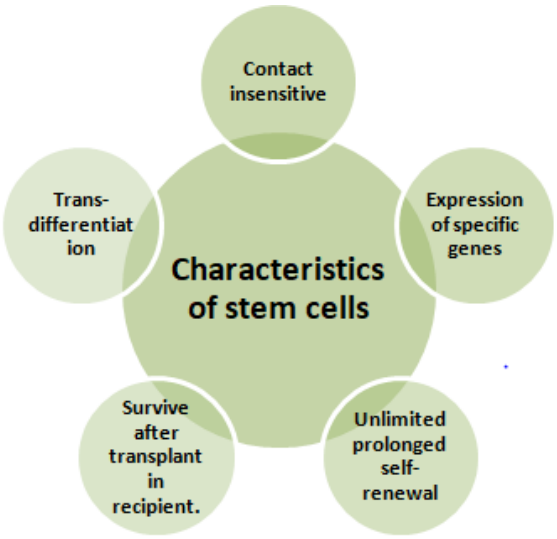

Figure 1: Characteristics of Stem Cells

Research on the stem cell started in the late 1800s after the advancement of the microscope, then scientists used *in vitro* fertilization of mammalian eggs, but very limited successes were achieved.[8] In 1959, the first *in vitro* fertilization technique was successfully used to produce rabbits. From the inner mass of blastocysts, stem cells are extracted and cultured in a petri dish. Major milestones of stem cell research[9,10] are shown in **Table 1**.

Table 1: Major milestone in stem cell research

Year	Stem Cell Research Area
1959	First *in vitro* fertilization (IVF).
1968	The first *in vitro* fertilization of the human egg.
1978	Human umbilical cord blood stem cells were discovered.
2000	Human ES cells derived from blastocysts.
2001	Blood cells successfully developed from ES cells.
2003	UK stem cell bank established.

SOURCES OF STEM CELLS

Various sources of stem cells are:[11,12]

- Spare embryos: Cells obtained from spare and leftover embryos that were not used by couples to have children in a fertility clinic.
- Cloned embryos: Stem cells are harvested from embryos that are cloned in the laboratory.
- Special purpose embryos: Embryos are produced by *in vitro* fertilization.
- Umbilical cords: Blood and tissue of the umbilical cord are the sources of stem cell, which has the potential for research work.
- Adult tissue: During surgery, stem cell of living adult is an alternate source of stem cells.
- Cadavers: From human post – mortem tissue, the surviving cells are isolated and reported.

STEM CELL THERAPY

In the 1980s, the first stem cell was collected from peripheral blood by apheresis. In the US, stem cell therapy was done on 20,000 patients by the National Marrow Donor Programme (NMDP).[13] Stem cell therapies include both form of stem cells: Embryonic stem cells and adult stem cells as shown in **Table 2.**[14]

Table 2: Difference between Embryonic stem cells and adult stem cells

Embryonic stem cells (ESCs)	Adult stem cells (ASCs)
ESCs are pluripotent cells capable of differentiating into any type of cells of the body.	Adult stem cells are Unipotent/Multipotent and can differentiate into their derived types of cells/tissue.
Large numbers of these cells can be easily cultured in vitro.	Rarely found, and difficult to grow in vitro.
Transplant rejection occurs with ESCs.	No transplant rejection occurs as it uses cells from the same patient's body.
The possibility of infection and teratoma formation.	No such possibility.
May induce an immune response.	Immune-privileged.
Ethically controversial.	No ethical issues.

For cell or tissue-based therapy, there are various regulative issues to control the efficacy, quality, and safety of SCBPs for clinical and commercial applications. So, appropriate standards and controls are used to maintain the safety, efficacy, and quality of the products.

Safety testing is demanding procedure, which includes assays for viral, endotoxin, microbial, mycoplasma, and fungal contamination. The clinical effectiveness of a product must be evaluated by using *in vitro* functional assays, after safety has been established.[15] The various advantages and challenges of stem cell therapy are shown in **Table 3**.

CLINICAL APPLICATIONS OF STEM CELL

Extensive research work is going on in the field of stem cell therapy for several diseases. Stem cell therapies include transplantation of the stem cells from bone marrow stem cells, peripheral blood stem cells, and skin replacement. Leukemia is a cancer of white blood cells or leukocytes which can be treated with bone marrow transplantation. In a bone marrow transplant, the patient's bone marrow stem cells are replaced with those from a healthy, matching donor. Existing bone marrow and abnormal leukocytes are first killed by using a combination of

Table 3: Advantages and Challenges of Stem Cell Therapy

Advantages	Challenges
Low rejection rates of adult stem cell	High immune rejection rates of embryonic stem cell
Can be transformed into pluripotent stem cells	Adult stem cells have a defined cell type
No communicable disease transmission	Collection of any form of stem cell is a difficult process
Minimal post-procedural recovery time	Therapy is a costly process
Avoid surgery and its many complications and risks	Ethical and Moral issues

chemotherapy and radiation. Then, healthy stem cells from the donor's bone marrow are introduced into the patient's bloodstream. Juvenile diabetics or Type 1 diabetics also cured with the help of stem cell therapy. Some of the recent research and clinical applications in this field is review as follow:-

Wang et al., reviewed that the successful transplantation of *in vitro* cultured autologous chondrocyte, which suppresses the secretion of inflammatory factors and clinically helps in the treatment of osteoarthritis. The polymer scaffolds are platelet-rich plasma which is injected along with the MSCs, cytokines, or growth factor for better efficacy into the articular cavity in the form of suspension helps in the treatment of osteoarthritis.[16] *Műzes et al.,* suggested that the intensive immunosuppression of autoreactive lymphocytes clinically helps in hematopoietic stem cell therapy in autoimmune disorders. The use of hematopoietic stem cell therapy completely alters the immune system by removing the previous T-cells with new healthy T-cells in the treatment of autoimmune disorders.[17] *Borlongan et al*., analyzed that laboratory and clinical experience with mesenchymal stem cell therapy may lead the future translational research on stem cell-based regenerative medicine for stroke in neurological disorders. The safety of stem cell therapy in a clinical trial has been reported. But for enhancing the efficacy of therapy, finding an optimal regimen of cell dose, route of administration, and timing is required.[18] *Daryabari et al*., researched the uterine bioscaffolds, which have the prominent potential for regeneration and angiogenesis for the whole uterus and employed *in vitro* and *in vivo* studies. The biocompatibility and recellularization of bioscaffolds have confirmed by the immunohistochemical or histological evaluation of harvested grafts.[19] *Ozdemir et al*., reviewed that the mesenchymal stem cells help in recovering in autoimmune diseases and graft versus host ailments by differentiating the M1 phenotype of pro-inflammatory and M2 phenotype of anti-inflammatory of macrophages which are strong immunomodulatory cells researched in various clinical studies.[20] *Guo et al*., suggested that effective and ingenious therapy for the treatment of smoke-inhalation-induced acute lung injury researched on exosomes secretion by mesenchymal stem cells.[21] *Lodola et al.*, demonstrated that the contraction rate of the patient-specific cardiac is optically boosted by using conjugated polymer films as a transducer in an *in vitro* cell model. Conjugated polymer films follow the coupling mechanism of photothermal effect by photostimulation which enhances the contraction rate of cardiac muscle cells.[22] *Papa et al*., developed a clinically alternative source of human hematopoietic stem cells for allogeneic bone marrow transplantation by ex vivo cultured CD34+ cells isolated from Umbilical cord blood cells.[23] *Lin et al*., reviewed the novel approach in the regeneration of dental and orthopedic defects, co-cultured the calcium phosphate cement scaffolds with stem cells, in clinical practice. *In vivo* studies, calcium phosphate cement scaffolds enhance the affinity of cell and bone prevascularization and form new blood vessels or bones.[24] *Filho et al*., researched that mesenchymal stem cell therapy helps in promoting the neuroregeneration by slowing the progression of Parkinson's disease by given therapy in clinical trials. Mesenchymal stem cells regenerate the cells which produced the bioactive molecules helps in the progression of neuroregeneration and decreased the amelioration of Parkinson's diseases. [25]

Some of the clinical applications of stem cells or stem cell therapies are discussed here. Several diseases including cancer can be cured by stem cell therapies. Some of them are mentioned above. There are many therapies for cancer cells other than stem cell therapy such as photodynamic therapy. In photodynamic therapy, selective drugs are introduced on the cancer cells with the help of irradiation light with reactive oxygen species, which kills the cancer cells.[26] Some radiological particles or nanoparticles are also used for tracing the cancer cells. The special physio-chemical properties of the radiolabeled nanoparticles help in tracing of the intense area of cancer cells which improve the efficacy of therapeutic drugs and reduce toxicity.[27]

Regulatory Perspectives of Stem Cell Therapy in India

A regulative blueprint for stem cells based products in India was settled by the Ministry of Health and Family Welfare (MHFW), Government of India, in the month of June 2013. These regulations or Guidance for stem cells were recommended by a committee and the amendment or new regulations came under the D&C Act, 1940 in 2013. Isolation, processing, manufacturing, and quality of stem cells and stem cells based products are regulated by Central Drug Standard Control Organization (CDSCO) /DCGI under the supervision of the MHFW.[28] According to CDSCO, Stem cell therapy is defined as "the admixture of tissue and cellular-based products which resolve the problem of diseases by providing effector function cells or support the treatment of other diseases".[29] According to CDSCO the SCBPs are classified as

Autologous SCBPs:

The donor and recipient of SCBPs are the same. Mesenchymal stromal cells (MSCs) and mononuclear cells are isolated from the tissue of the recipient patient. After minimal manipulation, MSCs are used for clinical trials for generating the data and for making claims.

Allogeneic SCBPs:

The donor and recipient of SCBPs are different. Mononuclear cells and mesenchymal stem cells that have been confined from the other cells/tissues of a matched cadaveric and live donor are allogeneic cells.

APPROVAL PROCESS OF SCBPS IN INDIA

The aspirant is needed to submit the application to the Biological Division of CDSCO for a license to manufacture, collect, isolate, store, and regulate the clinical trials and profitable use of SCBPs. For the approval of clinical trials, the applicant is required to fill Form 44 and submit it to CDSCO or can be submitted online at the SUGAM portal. The application is reviewed by the Institutional Ethical Committee and the Institutional Committee on Stem Cell Research and Therapy and forwarded to the Licensing Authority. The license is approved by the DCGI, and clinical trials are initiated after obtaining the approval of license from DCGI. In the Clinical Trials Registry of India (CTRI), clinical trials must be registered.[30] Applicants are shortlisted by a technical committee after the screening of a prescribed format that is submitted by the applicant for issuing a license. An application is evaluated by the evaluation committee.[31] Name and address of licensed Umbilical Cord Stem Cell Blood Bank[32] issued by CDSCO are given on the website of CDSCO. Four types of licenses/approvals (**Table 4**) in India:

Table 4: Four types of licenses/approvals issued by CDSCO

Type	Licenses/Approvals
Type 1	To provide a license for collection, processing, storage of SCBP for test and analysis.
Type 2	Approval of Clinical Trial Protocols for the generation of safety and efficacy data.
Type 3	Approval/permission for manufacture or import of SCBP as an IND/New Drug.
Type 4	To provide a license for manufacture or import for storage, sale, and distribution.

Type 1: Type 1 licenses are entry-level type license given when applicants fulfill the requirements on stem cells. Type 1 license is given for analysis and testing of collected, processed, stored SCBPs from CDSCO. Type 1 License is compulsory for all other license's approval process.

Type 2: Type 2 licenses are given to those applicants who are doing clinical trials for generating the safety and efficacy data for commercial usage of SCBPs, approved by CDSCO as shown in **Figure 2**. It is important that Type 2 approvals are given to those who have already a Type 1 license.

Type 3: Type 3 licensed is given to those applicants who only manufacture or for import of SCBPs as new drugs and given to only those location which is already approved for Type 1 and Type 2.

Type 4: In this category, the license is given for import, manufacture, sale, storage, and distribution of SCBPs. It is a superlative form of an approval process. The license approval procedure of IND and NDA are shown in **Figure 3**.[28]

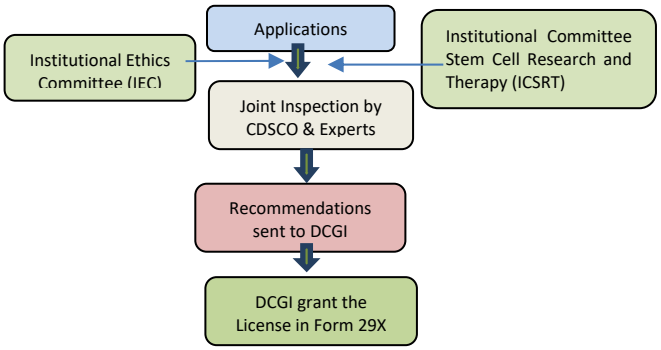

Figure 2: License Approval Process of Type 2 of SCBPs in India

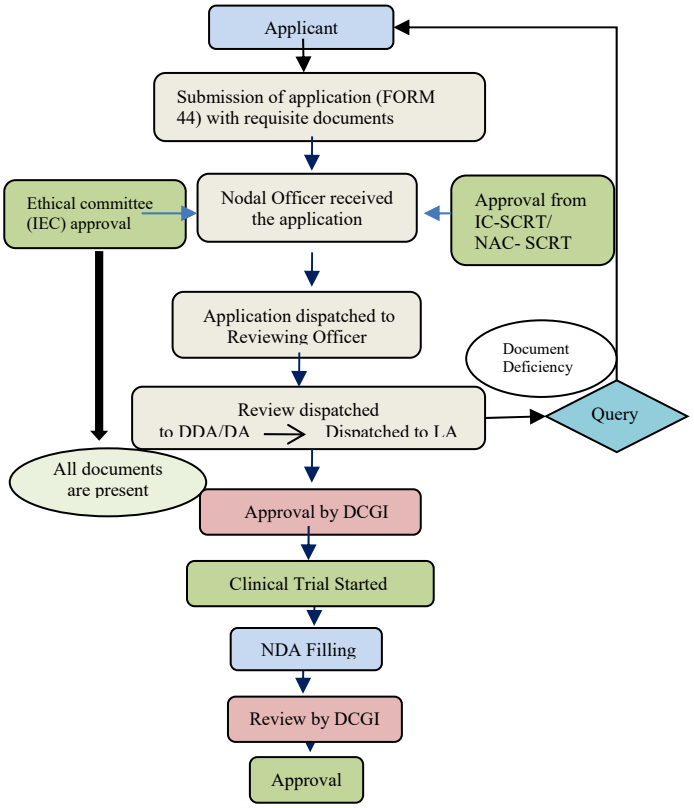

Figure 3: Approval of IND and NDA Process for SCBPs according to CDSCO in India

OTHER REGULATORY REQUIREMENTS FOR SCBPS IN INDIA

Other regulatory requirements for stem cells and cells based product for clinical trial and new drug approval are mention below:[28,33,34]

Manufacturing and Process Controls of SCBPs

Details of collection, processing, purification, manufacturing, and preparation of cells for final products and details of components and material used during manufacturing are described.

Source of SCBP and Cell Collection

SCBPs can be collected from two categories of sources: autologous (recipient and donor of SCBPs are the same) and allogeneic (recipient and the donor of SCBPs are different persons). SCBPs can be used as primary cells are used after washing and centrifugation (minimal manipulation). Not more

than six passages for stem cells are recycled in therapy. The Collections of stem cells are done from a working cell bank or a master cell bank.

All important information about cells and tissue source and their type are provided. The donor's SCBPs are prepared *in vivo* or not; if yes, which type of enzymes should be documented used for SCBP preparation. All the information about the collection and recovery method of SCBPs includes name/type of cell and location of the collection, and shipping conditions, etc. should be documented.

SCBPs Banking Procedures

SCBPs bank has two categories: Master Cell Bank and Working Cell Bank. The cells are collected from a single source and have a uniform composition with defined culture conditions are represent the master cell bank. When cells are extracted from more than one vials of cells and collected from more than one donor and cryopreserved after subculture, it represents a working cell bank.

Materials Used During Manufacturing

Based on the origin of the source, materials used for manufacturing are materials derived from human sources. The suitability of compounds of human origins like immunoglobulins, albumin, etc. should be evaluated before use. For the material derived from an animal source, compliance with regulatory guidelines is strictly required.

Manufacturing Process

The most important thing is to precisely design and validate the requirements of the manufacturing process of SCBPs and to describe the types of manipulation used for SCBPs processing. The manufacturing area and procurement area should be separate from each other. All information about the manufacturing process like transportation and their procedure, storage condition, and holding times should be described. If biodegradable materials are used, attention should be required. All requirements of the manufacturing process should comply with the GMP and Schedule M.

Characterization

For the development of cellular products, characterization and identification of SCBPs can be challenging. The characterization of SCBPs includes cell identity, cell purity, impurities involvement, the potency of the cell, and tumorigenicity throughout the development and manufacturing process. Some characterizations of the cellular components are Cell Identity, Cell Purity, Impurities, Potency, and Tumorigenicity. [35]

Quality control of SCBP

The materials used in the production process and final formulated products which are used to administer in human subjects should be exposed to quality control testing. All acceptable values range should be mentioned. Quality control testing should be done for each lot of manufactured products. At every step or whenever possible, quality control testing should be done. At the time of the submission of the application, all performed tests for quality control should be validated. [36]

Stability Testing

In all phases of clinical trials, stability testing should be operated to establish the chemical and physical limits of the SCBPs, which is planned during the proposed clinical investigation. Stability testing is used in the manufacturing process and is described as in-process stability testing and final product stability testing. To ensure the stability of products at the period of cryopreservation and holding steps of SCBPs should be adequately described. Stability testing of raw materials and stem cell products should be described. Final products or formulations should be free from impurities and should pass all the stability testing before commercial launch. The final product should be stable at a specific temperature which needs to be mentioned on the label. When the SCBPs are transported to the clinical trial area from the manufacturing area; temperature, time, packaging, and shipping conditions should be described. The potency, integrity, and sterility of the product should be demonstrated as per the stability protocol, are maintained under the proposed transporting conditions.

Exchange/Procurements of stem cells and stem cell lines

Mandatory approval by Institutional Committee on Stem Cell Research and Therapy (IC-SCR) and Institutional Ethical Committee (IEC) for exchange or procurement of stem cell lines are required to be obtained for basic and clinical research. A voluntary informed consent form must be collected in advance for abortion/termination of pregnancy, gametes, blastocysts, somatic cells, human ESC/iPSC, and for the donation of the fetal material for research. Sufficient time should be given to the parents for making a decision regarding the donation. At ports, applicable international guidelines should be followed for their handling, labeling, packaging, and transportation of stem cell lines. Prior approval/No Objection Certificate does not require, for import of stem cell lines for basic research from any government agencies. During clinical trials, such cells are not acceptable for commercial purposes or human applications. All stem cells and their products required for R&D, including in clinical phases, shall be examined by the IC-SCR and IEC along with their material transfer agreement. After clearance from CDSCO, stem cells or stem cell lines required for clinical trials and originating from countries outside India are imported.[33]

Container and closure system

Information on container and closure system as per GMP should be provided. Before the commercial launch, the container and closure system must be compatible with the products that should be demonstrated. The containers used for storage are sterilized, and sterilization procedures should be described. For the transport of products, packaging should be required, and additional data of packaging material should be informed.

Labeling, Quality Assurance (QA) and Product Tracking

Before the commercial launch, final products should be labeled. The investigational product must be labeled as: "New Drug for Investigational Use Only". The label must contain the information of product name, date of product manufacturing, expiry date, storage conditions, and two particular patient

identifiers is recommended under Schedule Y. From the source of the cell to final stem cell and cell-based products, the quality assurance system should be established and demonstrated. Quality Assurance system should be established for specific SCBPs include new drug category of SCBP, delivered a consistent quality product in all respect of In-process controls, Batch numbering System, and Validation of the manufacturing process. A well-established segregation system and product tracking should be for all the products. Tracking of all products from the recipient to donor or from donor to the recipient must be done. A well-established arrangement should mention all the descriptions of products from the collection to use of the product. The product is segregated from other products and is ensured by the well-established system.

Pre-Clinical Studies

The efficacy and safety of SCBPs and regenerative products are assessed by preclinical studies. Preclinical studies are conducted as per GLP facilities and the Schedule Y guidelines.

Pharmacodynamic studies

Pharmacodynamic studies are described as what the drug does to the body. Optimum efficacy of SCBPs and side effect of drugs are studied in pharmacodynamic studies by using an animal model. Advanced route of administration and potential mechanism of action of the drug are also studied.

Toxicology

In healthy and preferably rodent animals, safety and toxicology of SCBPs should be conducted. The study must include the route of administration according to the intended clinical trial indication, dosage, migration, survival, engraftment, differentiation, and proliferation. Single-dose toxicity study in at least one rodent species should be observed as per schedule Y guidelines. In rodent animals, repeated fixed-dose toxicity studies should be observed in pre-clinical studies, i.e. 14 days, 28 days, or 90 days. In clinical trials, standard and developmental toxicology studies are to be conducted in rodents. A repeated dose toxicity study should include the immunogenicity assessment report. Tumorigenicity potential in immunodeficient mice should be evaluated to understand differentiation and inappropriate cell proliferation. A minimum of six months period is necessary for the evaluation of the tumorigenicity.

Clinical Studies

In clinical studies, pharmacodynamic, pharmacokinetic, and dose-finding studies are conducted on human participants. The requirements of clinical trials should comply with Schedule Y and the same as for other medicinal products. Some studies are conducted in clinical trials are the mechanism of action studies, pharmacodynamic studies, pharmacokinetic studies, randomized clinical trials, and dose-Finding Studies. CTRI (Clinical Trials Registry of India) registered all the clinical trials on stem cell and tissue-based products. The clinical trials are conducted as per National GMP guidelines or schedule Y and license approved by DCGI/CDSCO. [37,38]

Pharmacodynamic studies and Pharmacokinetic studies

Drug efficacy evaluated with suitable pharmacodynamic markers in human participants. Degradation rate, compatibility, and functionality should be evaluated for a mixture product of stem cell and non-cellular components. A pharmacokinetics study means what the body does to the drug. The proliferation, viability, and functionality of products shall be discussed here. Different methodologies and their utility should be discussed.

Dose-finding studies

The quality and potency of the product are obtained by non-clinical development. To identify the minimal, optimal, and maximal dose, phase I and II studies are designed. The lowest dose where expected effects are observed is called a minimal effective dose. The range of doses where expected results are observed in clinical trials with their efficacy and tolerability called optimal effective dose range. The dose where the clinical safety studies show compatible benefit-risk ratio with less adverse effects called safe maximal dose.[39]

Clinical Efficacy and Clinical Safety

Using relevant endpoints of clinical trials, the efficacy of the drug in the targeted patient population is demonstrated. When optimal therapeutic results are achieved, the dose-schedule is demonstrated. A benefit-risk ratio of the drug is evaluated for the target population. Adverse effects are detected after the safety evaluation based on the safety database. The benefit-risk ratio of the products is estimated for the justification of clinical safety in a targeted patient population.[40,41]

Risk Management Plan and Pharmacovigilance

Description of the pharmacovigilance and durability of the product should be done routinely. To supervise the specific safety issues i.e. lack of efficacy, there are special studies. Special pharmacoepidemiological studies of SCBPs should be evaluated. Biological characteristics and traceability of SCBPs should be described.[42]

CONCLUSION

The fast-emerging market in medicines is stem cell research and stem cell therapy. Stem cell therapy helps to regenerate the lost or damaged tissues in body and support in therapies. Stem cell therapy used to cure the different types of diseases like immunodeficiency, Parkinson and diabetics, etc.; which are otherwise difficult to be cured by conventional medicines. According to CDSCO, “Stem cell and tissue-based products will be new drugs except if ensured in any case by the Licensing Authority under Rule 21 of the D&C Act. A new drug will continue to be treated as a new drug if it is not included in Indian Pharmacopoeia or a period of four years from the date of its first approval, whichever is earlier.” In India, these products are regulated by CDSCO to ensure that the safety, efficacy, and potency meeting the GMP, GTP, and GCP requirements. The clinical trials (CTs) are operated to collect the efficacy and safety data comply with the requirements of schedule Y and registered with the clinical trial registry of India (CTRI). In India, there are some shortcomings in the regulatory framework of stem cell therapies. A significant space still exists between the researches of laboratory and approved stem cell-based products. More stringent, clear, and concise laws need to be introduced to regulate and enable scientific progression in the area of stem cell therapy. A risk-based path of SCBPs is to be

practiced while awarding regulatory stem cell approvals. The conditional marketing authorization would be a viable reach beyond negotiating on patient safety and reduction in the time period of license approvals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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