Available online on 15 Sep, 2021 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Open Access

Regulatory Framework for Regenerative Medicine in India

Vishnu Priya Cherukuri, SSND Balakrishna Ch*, Meghana Golla, Sree Greeshma Swetha Konagala, V L D Sai Swetha Penugonda, Sravanthi Addanki

Department of Pharmaceutical Regulatory Affairs, Shri Vishnu College of Pharmacy (Autonomous), Bhimavaram, Affiliated to Andhra University, Visakhapatnam, Andhra Pradesh, India

Abstract

Regenerative medicine is a promising field of approach to repair or regenerate human cells, tissue or organs that have been damaged by trauma, disease, or congenital issues. Regenerative medicine is used when the body is incapable to heal itself. Stem cell and gene therapies are key components to Regenerative medicine, as they open the door to unique therapeutic applications. Stem cells are special human cells that are commonly found in different organs and tissues including the blood, brain, bone marrow, skin, muscle, heart, and liver tissues. These cells have the potential to develop into different types of cells such as skin cells, muscle cells, brain cells, and nerve cells. Regenerative medicine may improve your health and quality of life in the future with many new therapies for organ failure, Alzheimer's, Parkinson's, chronic heart diseases, dental injuries and so on. Over the past two decades, cell therapies and gene therapies have made increasing public attention. So, there is a need to form a clear regenerative medicine regulatory framework in India. In this article, it is presented with different applications, challenges and regulations of regenerative medicine in India.

Keywords: Regenerative Medicine, Gene Therapies, Stem Cell therapy

Article Info: Received 02 Aug. 2021; Review Completed 05 Sep. 2021; Accepted 09 Sep. 2021

Cite this article as:
Cherukuri VP, Balakrishna Ch SSND, Golla M, Konagala SGS, Sai Swetha Penugonda V L D, Addanki S. Regulatory Framework for Regenerative Medicine in India. Int J Drug Reg Affairs [Internet]. 2021 Sep 15 [cited 2021 Sep 15]; 9(3):25-31. Available from:
http://ijdra.com/index.php/journal/article/view/479

DOI: 10.22270/ijdra.v9i3.479
*Corresponding author

1. Introduction

The medicinal products which have the potential to heal the tissues or organs which are damaged by the age, diseases or trauma and to renormalize congenital defects are known as regenerative medicines. Promising preclinical and clinical data support the possibility to treat the acute and chronic diseases by regenerative medicines in the fields of cancer, cardiovascular diseases and certain types of skin disorders etc. (1-3) Nowadays, transplantation techniques are used to treat organ or tissue failures and loss but they are limited by donor supply and immune reactions these limitations will be overcome by using regenerative medicines. The field of regenerative medicine encircles numerous strategies, involves the use of materials and De novo generated cells, various combinations thereof, to take the place of missing tissue, effectively replacing it structurally and functionally in order to heal the damaged tissue. (4) In India Gene Therapy medicinal products (GTMPS), Stem cell therapy (SCT) and Tissue engineering products (TEP) comes under the umbrella of regenerative medicine. The above-mentioned products are separately regulated in India, where as in USA and EU they are collectively regulated as Advanced Therapy Medicinal Products (ATMPS). India has large burden of many genetic disorders and unmet medical needs for which gene therapy prove to be a one and only solution to treat such ailments. However, it contains unique technical risks and ethical challenges. Recently one of the Chinese scientists misuse the gene therapy by making modifications in germlines but germline gene therapy is prohibited in many countries. With the use of CRISPER gene editing technique, he created twin babies who have resistance against HIV. He succeeded in creating resistance but unwanted mutations took place for which he punished with imprisonment and fine. (5) To overcome the misuse of gene therapy by scientists' stringent regulations and requirements to conduct clinical trials should be framed. Many countries around the world are developed rules and regulations. In India there is necessity to develop regulations regarding gene therapy to support scientists, clinicians and industries to develop regenerative medicinal products.

2. Regulatory framework for regenerative medicinal products in India

India proactively released guidelines regarding gene therapy to overcome the misuse by scientists in December 13 2019. National guidelines regarding the procedures to be followed for developing and performing gene therapies to overcome inherited genetic or rare diseases in India were released by the apex health research body ICMR. Gene therapy technique uses gene modification procedures in these clinicians insert correct gene by making modifications in defective genes instead of using drugs and surgery. The document entitled "National Guidelines for Gene Therapy Product Development and Clinical Trials" has been released to enable treatment of diseases by gene therapy.

2.1 Classification of Gene Therapy

In India gene therapy was classified into two categories a. germ line therapy, b. somatic cell therapy.

a) Germ line gene therapy: This technique uses the modification of gametes which vertically transmits across the generations. But this technique is prohibited in India due to ethical and social considerations because if any mutation take place in one generation that effects not only current generation but also future generations.

b) Somatic cell therapy: This is the one and only accepted approach because it effects the targeted tissues, organs and cells in the patient and is not passed on to the subsequent generations.

2.2 GTAEC

Gene therapy field is associated with unique scientific and ethical, legal considerations for gene therapy products usage so this area should be monitored by additional expertise for efficient scientific and ethical evaluation. Gene Therapy Advisory Evaluation Committee was established at ICMR (Indian Council of Medical Research) under the aegis of Department of Health Research (DHR), Ministry of Health and Family Welfare, Government of India. This committee was composed of a core group of scientists and clinicians who have prior knowledge of gene therapy as well as representation of the government agencies (ICMR, DGHS, CDSCO, DBT, DST, MCI). This committee involved in the decision-making process regarding approval of gene therapy products. GTEAC have the authority to monitor the ongoing gene therapy clinical trials it also gives suggestions in designing of clinical trials. Pre IND meetings with GTEAC are also available if applicant has confusion regarding trails. (6)

Draft guidelines for stem cell research on India were proposed in 2002 and released in 2007 as Guidelines for Stem Cell Research and Therapy - GSCRT 2007 by an expert group constituted by ICMR and Department of biotechnology. These guidelines were revised rigoursly to make control over the stem cell research, recent revision took place in 2017 as National Guidelines for Stem Cell Research - NGSCR 2013.

As per the ICMR-DBT guidelines, there is no approved indication for stem cell therapy as a part of routine medical practice, other than the Hematopoietic stem cell Transplantation (HSCT/BMT). Accordingly, all stem cell therapy other than BMT shall be treated experimental. It shall be conducted only as clinical trial after prior approval from CDSCO. All such experimental trials shall be registered with CTRI.

Stem cell research was monitored by two committees one at national level focusing primarily on policy and the other a more self-regulatory system of review at institutional level. The National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) has been constituted and notified by Department of Health Research (DHR), Ministry of Health and Family Welfare, Govt. of India as an independent body of experts representing diverse areas of biomedical research, concerned government agencies and other stakeholders. The Institutional Committee of Stem Cell Research (IC-SCR), on the other hand, operates at the institutional level with members having specific expertise as per these guidelines. It is mandatory for them to register with NAC-SCRT and submit annual report on their scientific activities for effective functioning.

According to nature of experiment and source stem cell research on humans is categorized into following areas 1. Permissible area of research 2. Restricted area of research 3. Prohibited area of research. (7)

a. Permissible area of research

- Any invitro studies involving pluripotent stem cell lines
- In vivo studies in experimental animals (other than primates) with established cell lines
- Establishment of hES cell lines from unutilized left-over embryos of IVF programmes
- Establishment of Umbilical cord stem cell banks

b. Restricted area of research

- With the use of IVF, SCNT and other methods creation of zygote for the derivation of hES Clinical trials with the import of stem cells from the other countries by multinational sponsors is restricted
- Research using pluripotent stem cells on experimental animals including pluripotent stem cells at embryonic and foetal stage of development for differentiation and integration of human cells into animal cells
- Introduction of stem cells from different species that were mixed on the purpose of research into experimental animals including vertebrates is restricted

c. Prohibited area of research

- Any research related to genetic engineering and reproductive cloning
- Any research involving implantation of human embryo into uterus after in vitro manipulation at any stage of development in humans or primates
- Animals in which any of the human stem cells have been introduced at any stage of development should not be allowed to breed

3. Miracles of Regenerative Medicine

The field of Regenerative Medicine is evolving and it could have immense potential in developing new treatments for various unmet medical needs.

3.1 In Alzheimer's Disease

Alzheimer's Disease is a progressive neurodegenerative disorder characterized by the degeneration and loss of neurons in the brain. Progression of Alzheimer's Disease leads to decline in memory, judgment impairment, behavioural problems, problem-solving skills, dementia and, eventually death. Currently, there are no effective medications to treat Alzheimer's Disease. Evidence supports that stem cells may play a valuable role in slowing Alzheimer's progression through enhancing neurogenesis and replacement of lost neurons. (8)

3.2 In Dentistry

Regenerative medicine is a promising field in dentistry to repair and restore the damaged teeth to get natural structure and function. Dental tissues are frequently damaged due to tooth decay, and they can be treated by synthetic or metal dental fillings or crowns, which needs additional damage to the teeth by drilling to prevent the loss of an entire tooth. Regenerative medicine has the potential to change the conventional treatment of dental injuries owing to its property to dental tissues. (9) Stem cells play a significant role in dental regenerative medicine, and they are used for bone regeneration, periodontitis, and immature necrotic pulp regeneration. In addition, no treatment reported adverse effects that may have been related with cell transplantation. (10)

3.3 In Heart Failure

Heart failure is one of the leading causes of death worldwide. Regenerative medicine is the most promising treatment for Heart failure. Heart failure occurs when the heart being incapable to pump sufficient amount of blood around the body due weak heart muscles. Stem cell-based therapies could save the lives of people living with heart failure by replacing lost and damaged cells. Stem cells have the potential to regenerate the heart muscle, repair damaged myocardial cells and restore the structure and function of the heart. Cardiac cell-based treatments have been performed with different types of cells, including stem cells, skeletal myoblasts, aspirated bone marrow cells, pluripotent stem cells (PSCs), and endothelial progenitor cells, such as embryonic stem cells (ESCs). (11)

3.4 In Leukaemia

Leukaemia is a malignant progressive disease caused by increased number of abnormal white blood cells in your body. This will suppress the formation of normal blood cells, leading to anaemia and other symptoms. Regenerative medicine has significant therapeutic potential to restore impaired blood cells. A stem cell therapy involving hematopoietic progenitor cell transplantation can be used to restore healthy bone marrow in patients with leukaemia. This procedure restores the immune system by infusing healthy blood-forming stem cells into the body. (12)

3.5 In Diabetes

Diabetes is a chronic disease that occurs due to the loss or dysfunction of insulin-producing β-cells in the pancreas. Diabetes complications, such as high blood sugar, Diabetes, cardiovascular problems and, in the long-term, multi-organ damage, and leads to premature death. Stem cells have the potential to develop into a variety of cell types, including insulin-producing β-cells. Thus, stem cells therapy is a hopeful source for the treatment of Diabetes. However, crucial work remains to be done for the clinical application of these stem cells to cure diabetes. (13)

4. Regulatory approval procedures for regenerative medicine in India

Regenerative medicines undergo same regulatory procedures as that of conventional pharmaceutical products. Approval takes 6-24 months from the date of submission of application.

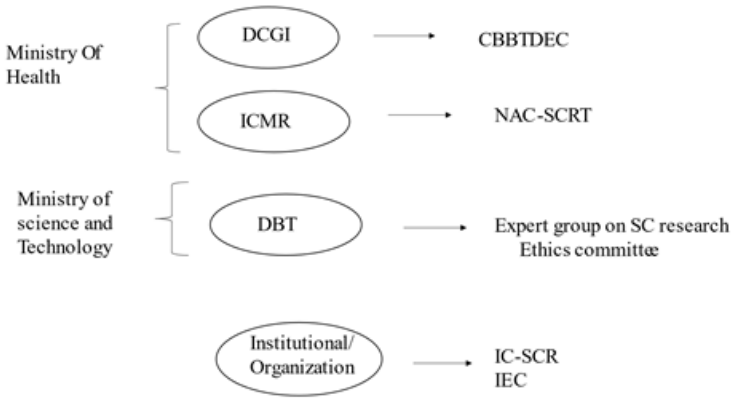

Figure 1. Mechanism of oversight and review

DCGI: Drug controller general of India; ICMR: Indian council of medical research; DBT: Department of Biotechnology; NAC-SCRT: National Apex Committee; IC-SCRT: Institutional committee; CBBTDEC: Cellular biology based therapeutic drugs evaluation committee. (14)

4.1 Expedited Approval Procedures in India

Two types of procedures are available in India to expedite the drug approval procedure for the benefit of the patients. (15) They are 1. Conditional Approval, 2. Fast Track Approval.

a) Conditional Approval

If the benefit of immediate availability outweighs the risk of less comprehensive data, then the conditional approval process applicable. Conditional marketing authorization valid for one year and can be renewed annually. The marketing authorization holder will be required to complete ongoing studies to confirm the benefit risk is positive. Once comprehensive data on the product have been obtained then the conditional marketing authorization is converted into standard marketing authorization e.g. Stempeucel got marketing authorization via conditional approval.

b) Fast track approval

An investigational new drug that is intended to treat a serious condition, and for which nonclinical or clinical data demonstrate the potential to address an unmet medical need in patients with such condition, can receive fast track designation. Advantages of Fast track designation include actions to facilitate development and expedite review of the product, such as the possibility for rolling review if CDSCO determines, after preliminary evaluation of clinical data submitted by a sponsor, that the fast-track product may be effective.

5. Challenges involved in Regenerative medicines manufacturing in India

India has no unified national policy for regenerative medicine. To date, India has separate guidelines for some regenerative medicine subsectors such as stem cells, while other subsectors have no dedicated regulations such as nanotechnologies and 3D bioprinting.

There are mainly 4 challenges involved as follows:

5.1 Manufacturing expenses

Cell therapy manufacturing processes are generally highly expensive. Since Scaling up from limited laboratory facilities to automated systems for bulk production will largely be based on costs, there will be requirement of higher standards financial and time planning. As a first-generation technology, there is involvement of higher stakeholders' tolerance for higher pricing, which lasts only for a limited time period.

5.2 Design quality

Post collection of sufficient evidence of clinical effectiveness of regenerative medicines, bioreactor technologies are considered for the manufacture of regenerative medicine products. But if there are any changes even minor process changes at this stage will require new validation of the product performance. So, in the case of automation, robots manually reproduce the existing inefficient manual processes due to which the products are often based on obsolete technologies. Ultimately, the manufacture of regenerative medicines sometimes misses the opportunity to improve their quality by innovating process design.

5.3 Biomaterials challenges

The trends in material selection will eventually have a major impact on the manufacturing process. So, challenges relating to biomaterials is mostly concerned with their selection than the manufacturing process. The traditional synthetic biodegradable polymers and a few bioactive ceramics that have been manufactured through conventional routes are commonly used but, now are no longer considered ideal as there is involvement of critical nano structural features, may involve self-assembly and environmental responsiveness, they may not be compatible with normal top-down manufacturing and therefore could require changes in the production process.so, attention is now being turned towards biomaterials that have more relevant biological properties.

5.4 Supply chain challenges

- The clinical supply chains required to deliver regenerative medicines therapies are conceivably the most complex in the industry, even more than for biologic medicine. There are mainly 2 challenges involved as follows:

  (i)Currently, billions of dollars are being spent on regenerative medicine research and clinical studies, resources are yet to be allocated to the management and delivery of innovative medical therapies at scale.

  (ii)Furthermore, progress by the pharma industry in coming into compliance with the FDA's regulations for regenerative medicines has been obtuse.

  This makes the process of bringing regenerative medicines at scale to the market even more challenging.

- Nanomaterial scaffolds are key to regenerative medicine innovation, as previously noted. It is, therefore, pertinent to analyse the current national policy on nanotechnology in India. Research programs in nanotechnology were started in early 2000s in India alongside support for stem cells. In both cases i.e, Research programs and national policies, the potential risks to health and the environment were not initially given importance.

- By 2010, the government had acknowledged the risks of nanotechnology (16), and recently drafted the "**Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries**". (17,18)

- These guidelines acknowledged that, though nanotechnology has the potential to address health issues related to the repair of damaged organs, there are a number of safeties, environmental, ethical and regulatory issues associated with the creation of artificial materials for diagnosis or delivery of new drugs and the creation of artificial tissues. However, these draft guidelines failed to analyse various issues in great details. It largely provides a checklist

while handling nanomaterials in a laboratory. It can be argued that the lack of clarity on safety and regulatory standards has hampered innovation as some companies cite this absence as a reason to avoid investing in the area. (19) Although 3D bioprinting is a promising area in the regenerative medicine ecosystem, it brings regulatory challenges both at the level of production methods and products. (20)

5.5 Additional Key Points that are challenging are

- Indian regulatory agencies not assessing the ethical and social issues linked to the Stechnology as like UK/EU and the USA.
- Regenerative medicine faces the challenge of ensuring that novel materials can cope with traditional infection risks posed by any type of surgery.
- Many transplanted regenerative materials are prone to bacterial infections which post administration of antibiotics following stem cell transplantation may also disturb the balance of intestinal microbiota and increase the risk of infections. (21)
- These risks are particularly relevant to India in light of the general burden of infectious disease and drug-resistant infections combined with the twin conditions of antibiotic overuse and underuse across different socioeconomic healthcare settings. (22)

6. Products approved in India till 2021

6.1 APCeden

APCeden is manufactured by APAC BIOTECH. APCeden is an autologous monocyte-derived mature dendritic cell vaccine. It was approved in India in 2017 for the treatment of prostate cancer, ovarian cancer, colorectal cancer, and Non-Small Cell Lung carcinoma.

6.2 Stempeucel (STEMPEUTICS RESEARCH PVT)

Stempeucel is manufactured by STEMPEUTICS RESEARCH PVT. An ex-vivo cultured adult allogeneic mesenchymal stromal cell therapy for the treatment of Critical Limb Ischemia. Conditionally approved in India in 2017.

6.3 Ossron

An autologous bone cell implantation for the treatment of bone defects in patients caused by degeneration, drugs, intense physical stress, diet, genetics, obesity, smoking, alcohol or disease. Approved in S. Korea in 2009, approved in India in 2017. (23)

7. Conclusion

Regenerative medicine is a major revolutionary advancement in medical treatment. It has the potential to cure serious diseases and conditions where existing therapies do not provide satisfactory solutions. There are also many regenerative medicines in the clinical pipeline that are in their early stages of development. Although the therapeutic potential of regenerative medicine is exciting, the cost of regenerative medicine development and manufacturing is more expensive. This leads to higher prices and eventually delays the market access. So, there is an urgent need for regulatory framework to incentivize the regenerative medicine research in India. Reimbursements and governmental support also needed for regenerative medicine to treat patients with chronic diseases.

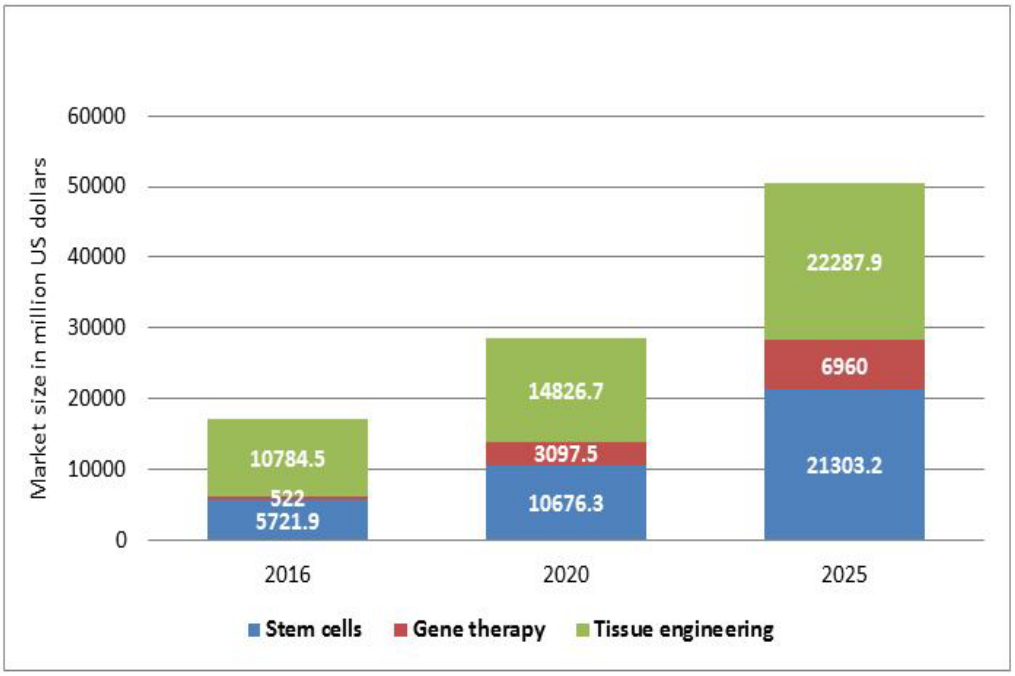

Figure 2. Global regenerative medicines market by therapy type (24)

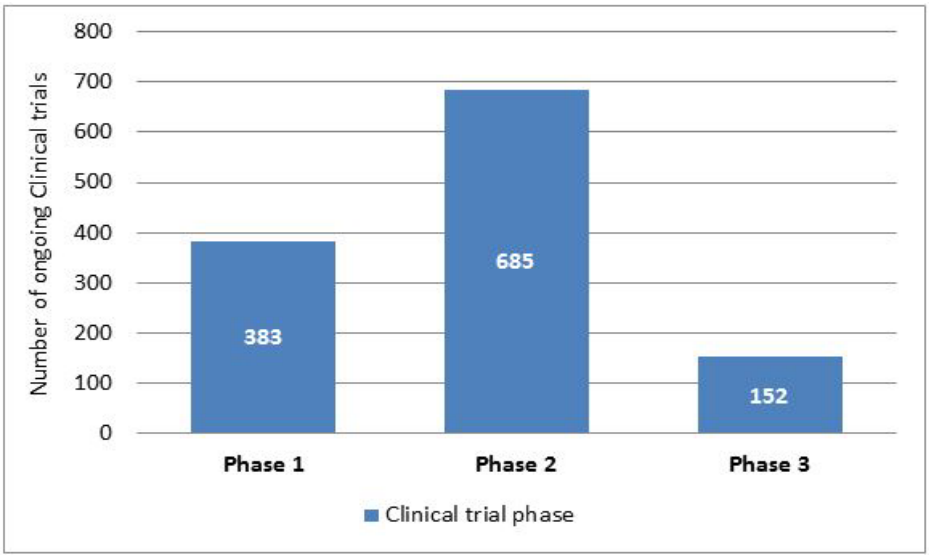

Figure 3. Number of ongoing clinical trials for regenerative medicine worldwide in 2020, by phase (25)

Acknowledgements

We would like to express our sincere gratitude to Shri Vishnu College of Pharmacy (Autonomous), Bhimavaram, Affiliated to Andhra University, Visakhapatnam, Andhra Pradesh, India

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Jaklenec A, Stamp A, Deweerd E, Sherwin A, Langer R. Progress in the Tissue Engineering and Stem Cell Industry "Are we there yet?" Tissue Engineering Part B: Reviews [Internet]. 2012 [cited 2020 Dec 07];18(3):155-166. Available from: http://terpconnect.umd.edu/~jpfisher/index_files/L1.pdf
2. Bailey A, Mendicino M, Au P. An FDA perspective on preclinical development of cell-based regenerative medicine products. Nature Biotechnology [Internet]. 2014 [cited 10 December 2020];32(8):721-723. Available from: https://pubmed.ncbi.nlm.nih.gov/25093890/
3. Mendelson A, Frenette P. Hematopoietic stem cell niche maintenance during homeostasis and regeneration. Nature Medicine [Internet]. 2014 [cited 2020 Dec 13];20(8):833-846. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4459580/
4. Bajaj P, Schweller R, Khademhosseini A, West J, Bashir R. 3D Biofabrication Strategies for Tissue Engineering and Regenerative Medicine. Annual Review of Biomedical Engineering [Internet]. 2014 [cited 2021 Jan 04];16(1):247-276. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4131759/
5. Patrick Baert A. That 'CRISPR Babies' Scientist Was Just Sentenced to Jail in China [Internet]. ScienceAlert. 2019 [cited 2021 Jan 10]. Available from: https://www.sciencealert.com/chinese-scientist-has-been-sentenced-to-three-years-jail-for-gene-editing-babies
6. National Guidelines for Gene Therapy Product Development and Clinical Trials [Internet]. 2021 [cited 2021 Jan 14]. Available from: https://www.nhp.gov.in/NHPfiles/guidelines_GTP.pdf
7. National Guidelines for Stem Cell Research [Internet]. Dbtindia.gov.in. 2021 [cited 2021 Jan 16]. Available from: http://www.dbtindia.gov.in/sites/default/files/National_Guidelines_StemCellResearch-2017.pdf
8. Sivandzade F, Cucullo L. Regenerative Stem Cell Therapy for Neurodegenerative Diseases: An Overview. International Journal of Molecular Sciences [Internet]. 2021 [cited 2021 Jan 22];22(4):2153. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7926761/
9. Regenerative medicine - Wikipedia [Internet]. En.wikipedia.org. 2021 [cited 2021 Jan 26]. Available from: https://en.wikipedia.org/wiki/Regenerative_medicine
10. Yamada Y, Nakamura-Yamada S, Konoki R, Baba S. Promising advances in clinical trials of dental tissue-derived cell-based regenerative medicine. Stem Cell Research & Therapy [Internet]. 2020 [cited 2021 Jan 27];11(1). Available from: https://stemcellres.biomedcentral.com/articles/10.1186/s13287-020-01683-x
11. Nasser M, Qi X, Zhu S, He Y, Zhao M, Guo H et al. Current situation and future of stem cells in cardiovascular medicine. Biomedicine & Pharmacotherapy [Internet]. 2020 [cited 2021 Feb 03];132:110813. Available from: https://reader.elsevier.com/reader/sd/pii/S0753332220310064?token=B420858EDAF9F48D9D31C85BA04DD03F3CEB278C42F6FC5EF2CC54FCFC859148A1AEE87829D02CBB83D18358FF72FEBD&originRegion=eu-west-1&originCreation=20210630111844
12. Dessie G, Derbew Molla M, Shibabaw T, Ayelign B. Role of Stem-Cell Transplantation in Leukemia Treatment. Stem Cells Cloning [Internet]. 2020 [cited 2021 Feb 04];132:110813. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7493021/
13. Pan G, Mu Y, Hou L, Liu J. Examining the therapeutic potential of various stem cell sources for differentiation into insulin-producing cells to treat diabetes. Annales d' Endocrinologie [Internet]. 2019 [cited 2021 Feb 08];80(1):47-53. Available from: https://www.sciencedirect.com/science/article/pii/S0003426618311788?via%3Dihub
14. Lahiry S, Choudhury S, Sinha R, Chatterjee S. The National Guidelines for Stem Cell Research (2017): What academicians need to know?. Perspectives in Clinical Research [Internet]. 2019 [cited 2021 Mar 06];10(4):148. Available from:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6801994/
15. Qiu T, Hanna E, Dabbous M, Borislav B, Toumi M. Regenerative medicine regulatory policies: A systematic review and international comparison. Health Policy [Internet]. 2020 [cited 2021 Mar 12];124(7):701-713. Available from: https://pubmed.ncbi.nlm.nih.gov/32499078/
16. Beumer K, Bhattacharya S. Emerging technologies in India: Developments, debates and silences about nanotechnology. Science and Public Policy [Internet]. 2013 [cited 2021 Mar 24];40(5):628-643. Available from: https://academic.oup.com/spp/article/40/5/628/1676774
17. Guidelines and Best Practices for Safe Handling of Nanomaterials in Research Laboratories and Industries [Internet]. Dst.gov.in; 2021 [cited 2021 Apr 03]. Available from: https://dst.gov.in/sites/default/files/Draft-Guidelines%20.pdf
18. Draft Guidelines for Safe Handling of Nanomaterials [Internet]. Economic and Political Weekly. 2021 [cited 2021 Apr 25]. Available from: https://www.epw.in/journal/2016/23/commentary/draft-guidelines-safe-handling-nanomaterials.html
19. Beumer K. Travelling risks: How did nanotechnology become a risk in India and South Africa?. Journal of Risk Research [Internet]. 2017 [cited 2021 Apr 29];21(11):1362-1383. Available from: https://pure.rug.nl/ws/portalfiles/portal/76825405/Travelling_risks_How_did_nanotechnology_become_a_risk_in_India_and_South_Africa.pdf
20. LI P, FAULKNER A. 3D Bioprinting Regulations: a UK/EU Perspective. European Journal of Risk Regulation [Internet]. 2017 [cited 2021 May 04];8(2):441-447. Available from: https://www.cambridge.org/core/journals/european-journal-of-risk-regulation/article/3d-bioprinting-regulations-a-ukeu-perspective/ADC91ED03B04BDA7FBDF06BBCE5CD2B2
21. Taur Y, Xavier J, Lipuma L, Ubeda C, Goldberg J, Gobourne A et al. Intestinal Domination and the Risk of Bacteremia in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation. Clinical Infectious Diseases [Internet]. 2012 [cited 2021 May 07];55(7):905-914. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3657523/
22. Laxminarayan R, Chaudhury R. Antibiotic Resistance in India: Drivers and Opportunities for Action. PLOS Medicine [Internet]. 2016 [cited 2021 May 12];13(3):e1001974. Available from: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001974
23. Alliance for Regenerative Medicine. 2021 [cited 2021 May 22]. Available from: https://alliancerm.org/available-products/
24. Regenerative medicines market value worldwide by therapy type 2016-2025 | Statista [Internet]. Statista. 2021 [cited 2021 Jun 25]. Available from: https://www.statista.com/statistics/871252/regenerative-medicines-market-value-worldwide-by-therapy-type/
25. Ongoing clinical trials for regenerative medicine by phase 2020 | Statista [Internet]. Statista. 2021 [cited 2021 Jun 30]. Available from: https://www.statista.com/statistics/1088694/regenerative-medicine-clinical-trials-by-phase-and-therapy/