Advances in Bioresearch
Adv. Biores., Vol 15 (5) September 2024: 418-431

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.5.418431

Advances in Bioresearch

REVIEW ARTICLE

A Comparative Analysis of Stem Cell Research Implementation: Perspectives from India, Europe, and the United States

Nivethidha Subramanian, Raman Sureshkumar
Department of Pharmaceutics- Pharmaceutical regulatory affairs, JSS Academy of Higher Education & Research, JSS College of Pharmacy, Ooty, Nilgiris, Tamilnadu, India 643001
Email: nivethidhasubramanian@gmail.com, sureshcoonoor@jssuni.edu.in.

ABSTRACT
The potential of stem cells to revolutionize healthcare by offering novel treatments for various diseases and injuries is immense. However, the ethical and legal considerations surrounding the conduct of clinical trials for stem cell research are paramount. Effective collaboration among diverse stakeholders, including researchers, healthcare professionals, policymakers, and patients, is crucial for advancing stem cell research and facilitating the delivery of cutting-edge therapies to those in need. This paper provides an overview of the various types of stem cells currently utilized in healthcare and their emerging applications, alongside a comparative analysis of the status of stem cell research across different regions, particularly focusing on the United States, Europe, and India. While each country has its own regulations governing stem cell research and therapy development, there are common challenges associated with implementation. Therefore, it is essential to disseminate informative insights about the potential of stem cell-based therapies to enhance human health.
Keywords: *Stem cells, National guidelines, Regulatory frameworks, Healthcare innovation.*

Received 26.06.2024 Revised 02.08.2024 Accepted 11.09.2024

How to cite this article:
Nivethidha Subramanian, Raman Sureshkumar. A Comparative Analysis of Stem Cell Research Implementation: Perspectives from India, Europe, and the United States. Adv. Biores., Vol 15 (5) September 2024: 418-431.

INTRODUCTION

The Drugs and Cosmetics Act 1940 defines stem cells and their derivatives as "Drug" and categorizes them as Investigational New Drug (IND) or 'Investigational New Entity (INE)' when used for healing purposes. Thus, bioethical and regulatory standards must be adequately followed prior to commencing medical investigation (1). Illustration for Ethical Consideration in different regions is explained in (table 6) .Whilst stem cells have a significant regenerative and reparative role in grown-ups, their main duty in newborns is to transform and increase in number into the variety of cell categories and lineages essential for continuous growth (2). basic cells, which are not specific cells, exist all over the human body. They possess the ability to renew themselves and mature into any kind of cell in an organism. basic cells can be discovered in both grown-up and embryonic cells. There are numerous stages involved in the specialization procedure. The truth that a single-potential stem cell's developmental capacity decreases with each following phase restricts its capability to transform into as many diverse ty of cells as adaptable ones (3). There is immense potential for the repair and rejuvenation of injured or harmed tissues using stem cell-based therapies. A variety of grown-up stem cells, unborn stem cells, and iPSC stem cells are currently being used to cure a broad spectrum of diseases all around the globe. Because of their extensive use in bone marrow transplants over the past six decades to cure various blood-related cancers and illnesses, HSCs are the most utilized stem cell type in medical settings. In the 1960s, Tim and McCulloch acknowledged two characteristics of HSCs, specifically (i) their ability for self-renewal and (ii) their ability to produce all kinds of blood cells (4). Because of their simplicity of separation from multiple tissues, mesenchymal stem cells (MSCs) are the most popular and desired cell type for therapy after hematopoietic stem cells (HSCs). Moreover, several preclinical investigations have demonstrated that MSCs possess an anti-inflammatory and immune-modulating impact, which thus created stem cell biology. HSCs are a better stem cell category for grafting in the management of several blood conditions

because they are easy to extract from different origins including cord blood, peripheral blood, and bone marrow. Presently, over 50,000 bone marrow transplants are conducted each year across the globe, and they signify the acknowledged norm of treatment for several blood-linked illnesses (5). Illustration for Clinical trials and translations for clinical applications in different regions is explained in (table 7).The self-regeneration and variation potential of stem cells makes them sought-after targets for basic examination. Most of the investigation concentrates on recognizing the hereditary and ecological signs that exist in the stem cell environment, as well as variation factors (6,7). Stem cell therapy is linked with significant costs on a worldwide level. For example, Provenge®, a ego-cell therapy using dendritic cells from metastatic prostate cancer, and Prochymal®, a different bone marrow derived MSC treatment for GvHD, each have a price range of $100,000 and $200,000(8). Challenges in stem cell research-Before their utilization may be increased, progenitor cells require a significant amount more exploration. The Illustration for Patient Safety and Quality and Research funding in different regions is explained in (table 8). The progression of embryonic progenitor cells must first be better comprehended by scientists. The likelihood of the body rejecting the embryonic progenitor cells that are now available presents another challenge. Additionally, some individuals believe that utilizing progenitor cells derived from embryos violates ethical principles. Using adult multipotent progenitor cells presents challenges for scientists as well. Researchers are attempting to find a better approach to cultivating these cells because they are difficult to do in a lab. The body also contains trace amounts of these cells. There is a higher possibility that they could have DNA issues. In the United States, medical experiments utilizing stem cell therapy are actively being conducted (9). In recent times, medical centers that offer a variety of stem cell therapies have emerged. According to a 2016 investigation, there were 570 such establishments located alone in the United States. These establishments seem to offer stem cell-derived treatments for a variety of conditions, from sports-related afflictions to tumors. However, the vast majority of stem cell treatments are still only supported by theory and lack experimental confirmation. For example, exploration is being carried out on the potential therapeutic uses of stem cells obtained from amniotic fluid that doctors can retain after an amniocentesis examination. Medical centers are authorized by the Food and Drug Administration (FDA) to infuse patients with their own stem cells as long as those cells are used only for that intention Conversely, the FDA Trustworthy Authority has solely sanctioned the utilization of lymphoid antecedent cells, which are progenitor cells that generate blood. These, which are engendered from umbilical cord blood, are employed by healthcare providers to tackle conditions that impact blood production. For example, a physician can presently store blood from a reliable Origin after an infant is born and utilize it subsequently. The FDA releases a roster of the specific stem cell commodities it has approved, comprising umbilical cord blood, alongside the healthcare establishments that employ them, on its website Trusted Origin. It also cautions individuals to exercise prudence before undergoing any exploratory therapies since merely a limited quantity of stem cell therapies have genuinely progressed to the initial phase of a clinical investigation (10). Illustration for Research areas in different regions is explained in (table 10). Though different countries have their own guidelines for research and development of stem cells including treatment, there are certain issues pertaining to the implementation. Hence in this review an attempt has been made to include certain guidelines of different countries and difficulties in implementing them and Comparison of Regulatory Framework Issues for Stem Cell Research in Three Different Regions is explained in (table 4).

GLOBAL MARKET SEGMENTATION

Stem cell therapy is described using Cell Origin, Purpose, and Category as the market sections. The market is split into umbilical cord/early stem cells, mesenchymal stem cells derived from fat tissue, mesenchymal stem cells derived from bone marrow, and other cell origins. The market is categorized into tumors, skeletal disorders, cuts and wounds, heart conditions, digestive system illnesses, and other purposes based on the type of purpose. The market offers two types of transplants: similar and self-transplants. Similar transplants are further divided into children and adult groups. Illustration for Intellectual property in different regions is explained in (table 9) Adult and pediatric self-transplants are further divided into categories. Geographically, the market is examined in North America (the United States, Canada, and Mexico), Europe (Germany, France, the United Kingdom, Italy, Spain, and other regions of Europe), Asia-Pacific (China, Japan, Australia, India, South Korea, and other parts of Asia-Pacific), and LAMEA (Brazil, South Africa, Saudi Arabia, and other regions of LAMEA)) (11).

INDIA

The foundation of stem cell treatment in India is the utilization of stem cells and products derived from them in all invasive procedures conducted by medical professionals as a component of regular care therapies. The most commonly employed stem cell treatments include bone marrow transplants and therapies utilizing umbilical cord blood (12). They serve as India's primary standards for clinically

relevant stem cell research. These recommendations were updated in 2013 and again in 2017 (6) making them more rigorous than the first rules that were released in 2007/2013. The NGSCR has outlined and distinguished between restricted, forbidden, and allowed stem cell research (12).
They have also depicted important, significant alteration. The Central Drug Standard Control Organization (CDSCO)/DCGI, which reports to the Ministry of Health and Family Welfare (MoHFW), is responsible for supervising the quality, production, and administration of stem cells. Fig. 1(13) offers an illustration of the regulation of stem cell research in India. As per the New Drugs and Clinical Trials (2019) Act, SCBPs are subject to control in India as "New Drug," where "New Drug" is employed to identify any stem cell-derived product or gene therapy product intended for clinical usage medication SCBP is designed to be given to patients that is created from stem cells. As indicated by the NGSCR, 2017, an Institutional Committee for Stem Cell Research (IC-SCR) must be formed prior to commencing a clinical trial for stem cell therapy (12)(14). Regulations and legislation for stem cell research in India is given in (table 1).

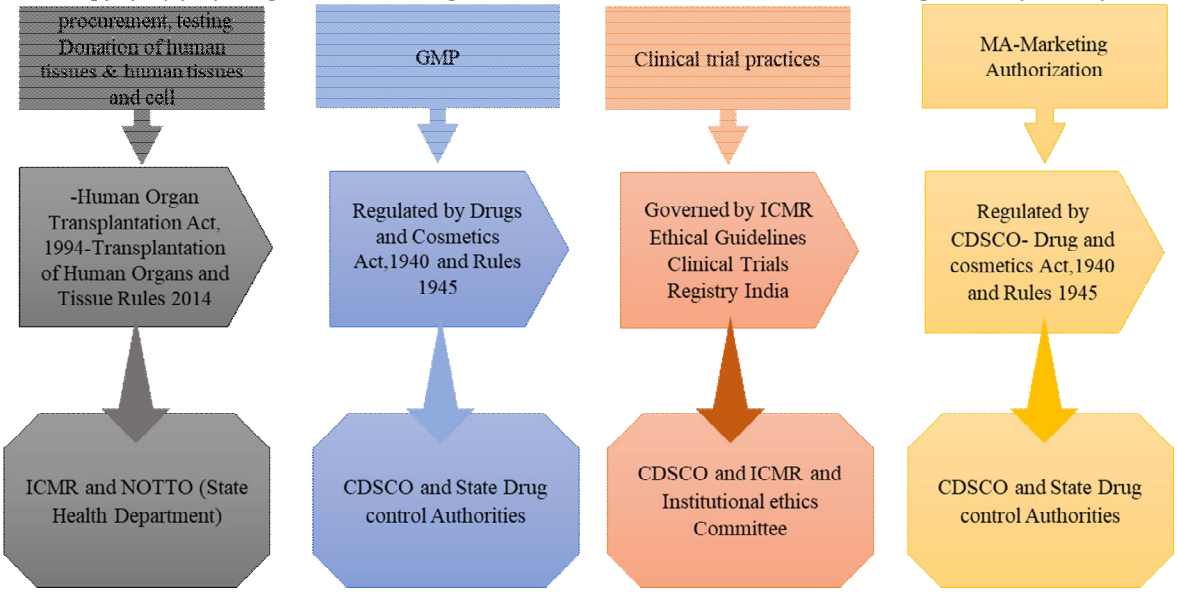

Fig 1. Illustration for Stem Cell Research Regulation in India Essential Features of the NGSCR Guidelines 2017.

Three wide divisions were employed to classify stem cell investigation:
a) Lawful Stem Cell Investigation: In this circumstance, the rules allowed for the formation of novel hESC/(iPSC) lines.
b) Constrictive Stem Cell Investigation: In agreement with the criteria, any investigation employing human preimplantation embryos engendered during IVF or IUI procedures necessitates prior authorization from the committee.
c) Forbidden Stem Cell Investigation: This classification encompasses reproductive cloning experiments and gene treatment for human germ lines, and human embryos surpassing 14 days post-fertilization [15][16]. Illustration for regulatory framework in different regions is explained in (table 5).

TABLE 1: Regulations and Legislation for Stem Cell Research in India

Category	Legislations/Guidelines	Regulatory bodies/ department
National guidelines	National Stem Cell Guidelines for Research, 2017	The Indian Council of Medical Research (ICMR) and the Department of Biotechnology (DBT)
Fraudulent advertisements for stem cell	Chapter 6 - the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002	The Medical Council of India (MCI) state medical councils.
	The Objectionable Advertisements Act- The Drugs and Magical Remedies Act, 1954	The Directorate General of Health Services
	The Schedule J of the Drugs and Cosmetics Act, 1940	The Advertising Standards Council of India (ASCI)

Regulations for (CT)clinical practices	The Medical Council of India Act, 1956 The Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulations, 2002 Section 304-A of the Indian Penal Code; The Civil Law of Torts. Consumer Protection Act, 1986 Proposed Amendments in Drugs and Cosmetics Rules, 1945	State medical councils and MCI State medical councils and MCI law enforcement agencies such as police and courts. forums for consumers CDSCO

EUROPE

The management and regulatory frameworks that control the stem cell investigation-medical conversion sequence in Europe are varied, mirroring the broad spectrum of social, cultural, economic, and historical conditions. In the area, 'gentle' laws, such as expert regulations, financing strategies, and principles of behavior, are included with 'solid' laws (such as laws and agreements), offering supplementary instruments for management and implementation. Importantly, irrespective of the method, ethical deliberations have tremendously increased in importance as a normative tool for formulating European policy [17]. The growth of separate groups that function on both a local and worldwide level has coincided with the progress of the stem cell (SC) field worldwide. These establishments have endeavored to establish the limits of responsible progress while advocating adaptable standards and supervision, with different levels of achievement. The Regulations on Stem Cell Investigation and Medical Use (hereinafter: Regulations) by the International Society for Stem Cell Research (ISSCR) are one prominent example of this [18]. Illustration for stem cell research regulation in Europe is explained in fig.2.

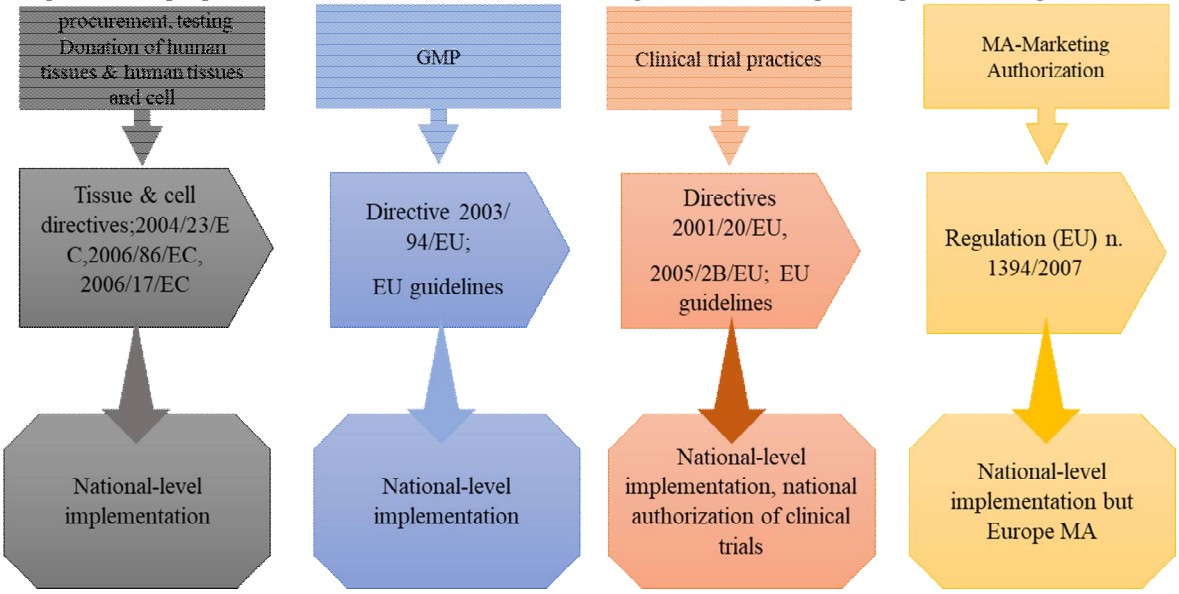

Fig 2. Illustration for Stem Cell Research Regulation in Europe.

They offer up-to-date criteria for policy, ethics, and science. Since their creation in 2006, the ISSCR guidelines have been acknowledged as more than just a symbol for "usual law" in all of the world's jurisdictions. This is because they have assisted in the understanding and implementation of policy, increased public awareness of moral issues, and directed scientific practice. The ISSCR altered its Guidelines, embracing stringent guidelines for the regulation of clinical research, the transformation of SC-based therapies, and a markedly reorganized set of recommendations for the supervision of in vitro SC projects [19]. Since criteria are meant to represent community standards and, in this manner, to supplement national frameworks for research governance, they have the potential to have an impact on policy developments [20]. Moreover, while both rigid and flexible rules influence how SC research is conducted, it is uncertain how European policy frameworks perform in comparison to evolving global norms, such as those reflected in the ISSCR recommendations. Furthermore, it is not apparent what triggers or how European nations' policies differ from one another. Comprehending these practices could assist in identifying any governance and policy gaps, contradictions, or hurdles. Furthermore, it might

illuminate how governance frameworks might empower researchers to act responsibly throughout the innovation process. To acquire these observations, this article examines the progression of SC protocols in 46 distinct European nations. Considering the Guidelines, we explore significant moral and administrative matters related to contested applications, like qualification criteria, supervision processes, and execution approaches. Comparative investigations provide an opportunity to promote global standardization and comprehension of regional establishments. The European area serves as an exceptional portrayal since it encompasses a range of foreign policy approaches. Hence, evaluating the domains of similarity, disparity, and progress in this locality may assist in global policy deliberations and growth [20]. Drugs for human use that stem from genes, tissues, or cells are referred to as advanced therapy medical products (ATMPs). They offer groundbreaking fresh opportunities for the healing of sickness and injury.

Three classifications can be utilized to classify ATMPs.

Gene-therapy drugs: These encompass genes in them that possess curative, preventative, or diagnostic impacts. They operate by introducing "recombined" genes into the body, usually to heal a variety of ailments, such as hereditary conditions, tumors, or enduring illnesses.

Somatic-cell treatment drugs: These include cells or tissues that have been changed to modify their biological characteristics or cells or tissues that are not meant to be used for the identical essential objectives in the body. Integrated genes are portions of DNA that are created in the lab by combining DNA from diverse origins.

Tissue-engineered medicines: These include cells or tissues that have been modified so they can be employed to repair, revitalize, or replace human tissue. They can be used to manage, diagnose, or avert diseases [21]. Regulations and legislation for stem cell research in Europe is given in (table 2).

TABLE 2: Regulations and Legislation for Stem Cell Research in Europe

Category	Legislations/Guidelines	Regulatory bodies/ department
EU Stem cell Research Guidelines	EU Directive 2004/23/EC on Human tissues and cells EU Directive 2001/83/EC on medical products EU Directive 2001/83/EC on clinical trials	European commission European Medicines agency (EMA) EGE, European commission (Ethical Guidance)
Regulations for fraudulent advertisements	EU consumer protection regulations (directive 2005/29/EC)	European commission and National Consumer Protection Authorities
Regulations for clinical practices	EU Directive 2001/20/EC on clinical trials European Group on Ethics in Science and New Technologies (EGE)	National Regulatory authorities (NRAs), EMA (for certain clinical trails) EGE, European commission (ethical Guidance)

USA - United States of America

The USA Food and Drug Administration has issued four ultimate guidance Documents to tackle how the organization desires to aid and accelerate the progress of rejuvenating medicine products, including human cells, tissues, and cellular and tissue-based goods (HCT/Ps). These papers are a fragment of a comprehensive policy framework. These instruments for aid emphasize the FDA's dedication to aiding in the creation of innovative, state-of-the-art therapeutic substitutions for patients and uphold the agency's risk-based, adaptable regulatory system [22].

The first two final guidance documents are:

Producers should be aware of the regulatory requirements set forth by the FDA for cell therapy goods, as well as those established by researchers and medical professionals. Human cells, tissues, and cellular and tissue-based products (HCT/P), as defined by the FDA under Title 21 of the Code of Federal Regulations (CFR) Part 1271.3(d), are "items containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." A few instances that fit this description include HSCs/progenitor cells made from peripheral blood or CB, modified self-chondrocytes, and epithelial cells on an artificial framework. If the therapy does not fulfill the description of HCT/P in 21 CFR 1271.3(d), such as blood components/derivatives (for instance, PRP) and slightly altered BMA, then the regulations in 21 CFR Part 1271 do not apply. If the therapy does not satisfy the description of HCT/P in 21 CFR 1271.3(d), such as blood components/derivatives (for instance, PRP) and slightly altered BMA, then the regulations in 21 CFR Part 1271 do not apply [23]. For treatments that match the description of

HCT/P in 21 CFR 1271.3(d), further details on how HCT/P is regulated are given in 21 CFR 1271.15(b). An institution is free from complying with 21 CFR Part 1271 if it acquires and administers HCT/P from the same individual, during the exact surgical operation, and in its original condition (as per the "identical surgical process (ISP) exception" in 21 CFR 1271.15(b)) [23][24]. In every other situation, the algorithm proceeds to the demands in 21 CFR 1271.10(a). Pursuant to the demands delineated in this title, the HCT/P must be slightly modified, fabricated for a similar purpose, not blended with other active components, without a systemic impact, or if it does, administered autologously or to first- or second-degree blood relatives [23]. Without prior authorization or a biologics license application, solely under section 361 of the Public Health Service (PHS) Act and the regulations in 21 CFR Part 1271, a system of regulatory standards governing disease transmission. Otherwise, if the cellular therapy does not meet the criteria under 21 CFR 1271.10(a), the Federal Food, Drug, and Cosmetic (FD&C) Act, or section 351 of the PHS Act, and relevant regulations, regulate cell treatment as a biological product. In this instance, the establishment would be obligated to enroll the treatment, put forth an application for biologics permit for legal promotion, and possess an investigational new drug (IND) request if the treatment is still in the trial phase. Prior approval before market release would also be essential for the cellular therapy [23][24]. The significance of being well-informed about the regulations is emphasized by the FDA's recent strict enforcement initiatives to safeguard patients from the hazards of illicit products being distributed as HCT/P in violation of section 361 of the PHS Act and rules in 21 CFR Part 1271. In May 2018, the FDA lodged a complaint against a stem cell facility for providing patients with their own, non-compliant SVF. The FDA contended that following removal from the patient, the isolated SVF no longer represented fatty tissue and that the therapeutic utilization of the SVF differed from its natural function as fatty tissue (i.e., not intended for analogous use). The Florida judge ruled in support of the FDA on June 3, 2019. The stem cell clinic argued that CFR 1271.15(b) and 21 CFR 1271.10(a) are applicable to its SVF products, but the judge disagreed, perceiving the situation as a breach of national legislation and the items as "drugs" necessitating extensive prior authorization under the FD&C Act. The stem cell hospital was directed by the court on June 25, 2019, to stop providing SVF services until additional FDA compliance. The FDA has released several warnings to other hospitals utilizing root cells and products obtained from umbilical cords as well as the SVF hospital [25][26]. Contrary to predictions, a federal magistrate in California dismissed a government request brought by the government against a stem cell clinic simultaneously with the earlier accusation. The FDA stated during the trial that the establishment was using illegal SVF treatments that are altered before insertion to treat degenerative conditions. The FDA alleges that the fat tissue extraction phase was where the alteration occurred, leading to the development of an SVF product that is not covered by the SSP exception. The defendant contended that all stipulations in 21 CFR Part 1271 are fulfilled because their SVF is unaffected despite the removal of fat tissue [27]. Throughout the trial, the SSP abnormality was considered easy by the court, and it was alleged that it did not require the substitution of all removed tissue, akin to coronary artery bypass surgeries where the extracted blood and additional artery are not inserted. In view of this rationale, the judge determined that the SSP anomaly applied to the SVF product because the original host tissue was taken out during the collection process without altering the SVF composition in any other manner. The court ruled that the FDA's implementation of the SSP anomaly "must adhere to the limits of rational comprehension, a prerequisite an organization can overlook" since it is "unreasonable and creates inconsistencies in enforcement.". Illustration for stem cell research regulation in USA is explained in (fig.3).

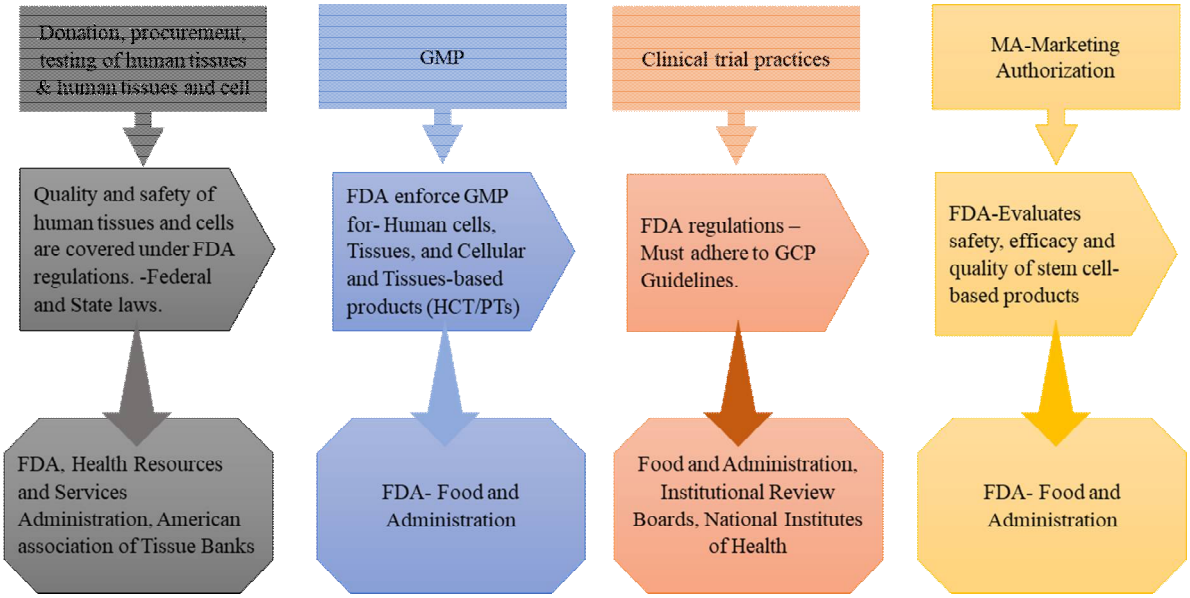

Fig 3. Illustration for Stem Cell Research Regulation in USA.

These examples emphasize the uncertainty and possible weakness of the FDA rules governing the usage of cellular therapy items. Besides that, other multiple cell items, such as BMAC, still get utilized as HCT/P in compliance with section 361 of the PHS Act and the regulations in 21 CFR part 1271 without having obtained FDA notifications [28]. Regulations and legislation for stem cell research in the USA is given in (table 3).

TABLE 3 Regulations and Legislation for Stem Cell Research in USA.

Category	Guidelines/Legislations	Department/Agency
US Stem cell Research Guidelines	Food and Drug Administrations (FDA) Regulations on stem cell therapies National Institutes of Health (NIH) Guidelines for Human stem cell Research (2009) Stem Cell therapeutic and Research Act (2005) Public Health Service Act (PHSA) Section 498A (2009) Stem cell Research Enhancement Act (2007,2009) 21 CFR Part 1271(Human Cells, Tissues, and Cellular and Tissue- Based Products)	Food and Drug Administrations (FDA) National Institutes of Health (NIH) HHS HHS HHS/NIH FDA
Regulations for fraudulent advertisements	FDA Regulations on Advertising and Promotion of Drugs Including Stem Cell Therapy FTC Act (Section 5)- Prohibition Against Deceptive Advertising. Stem Cell Therapy Warning Statement Rule Federal Food, Drug, and Cosmetics Act (FD&C Act)- Prohibitions on Misbranding and False Advertising FDA's "Consumer Alert" on stem cell Therapy Scams	Food and Drug Administration (FDA) Federal Trade Commission (FTC) Federal Trade Commission (FTC) FDA FDA and FTC
Regulations for clinical practices	Clinical trials involving stem cells must follow federal regulations and ethics guidelines	FDA – NIH- Institutional Review Boards (IRBs)- State health department

TABLE 4 Comparison of Regulatory Framework Issues for Stem Cell Research in Three Different Regions.

PARAMETERS	INDIA	US	EU
Regulatory agency	CDSCO	US FDA	EMA
Framework for regulation	Lack of consistent norms; absence of regulations for medical institutions	Challenging FDA regulation; unregulated clinics	Member states' rules differ from one another; uncontrolled clinics
Ethical consideration	Assent was obtained after being informed	Contributor consent is an ethical consideration	Donor approval; embryonic stem cells
Clinical trials	Limited rigorous experiments; challenges with long-term monitoring	Prerequisite for rigorous FDA clinical trials	difficulties with clinical trial harmonization
Patient safety and quality	Unverified treatments; problems with quality assurance	Hazardous therapies are offered by unregulated clinics	Clinics without regulations; possible security risks
Research funding	Fluctuating funding availability; resource competition	Funding concerns and disparities	Funding differences between nations
Intellectual property	Challenges in safeguarding intellectual property	Patent disputes and opposition	Differentiated patent laws and protection
Regulatory harmonization	A lack of consistency and diverse state regulations	The requirement for consistency among various state regulations	Divergent legal systems across the member states
Translations for clinical applications	Regulatory barriers; balancing safety and innovation	Balancing safety and innovation	Regulatory barrier to cutting-edge medicines
Global collaboration	Possibilities for collaboration; challenges with data sharing	Security and collaboration in research	Problems with Collaborative Research
Equitable access	Accessibility to treatments is accessible to all socioeconomic levels	Issues with Cost and Insurance Coverage	differences in access between member states
Public awareness and education	Inaccurate information being disseminated; misinformation	Inaccurate information; exaggerated patient expectations	Required for accurate information sharing
International collaboration	Possibilities for collaboration; exchanging knowledge.	Cooperation in international research	Difficulties in global collaboration.

Framework for Regulation

TABLE 5 Illustration for regulatory framework in different regions.

INDIA	The Department of Biotechnology and the Indian Council of Medical Research, led by Dr. Geeta Jotwani, introduced updated guidelines for Stem Cell Research in 2017. These regulations, overseen by regulatory bodies, prioritize ethical standards and thorough clinical studies to ensure the safety of patients and uphold the quality of healthcare services in India [29].
USA	The United States oversees stem cell treatments based on risk assessment standards, similar to natural products. Apart from slightly altered methods, the Food and Drug Administration enforces laws from 1938 and 1902 to ensure safety and approval [30].
EUROPE	The EUCelLEX initiative is analyzing the legal frameworks within Europe concerning the utilization of stem cells, with the goal of proposing enhancements to regulations that will facilitate the effective use of stem cells. Goal 1: Examine laws at both the national and European levels regarding the utilization of stem cells. Goal 2: Evaluating existing regulations on stem cells, looking ahead to potential modifications, and proposing enhancements. Goal 3: The European Union is delving into the regulations surrounding public-private partnerships as they make progress in the field of pharmaceuticals utilizing stem cells [31].

Remarks Organizations in the United States, European Union, and India are responsible for overseeing ethical practices in the field of stem cell research. In India, the standards set in 2017 prioritize both health literacy and ethical conduct. The National Institutes of Health in the US establish guidelines that reflect American values, while laws in the EU align with European standards. Each entity prioritizes the interests specific to their respective regions.

Ethical Consideration

TABLE 6 Illustration for Ethical Consideration in different regions.

INDIA	As per regulations set by CDSCO, it is required to conduct video screening for the detection of six different infections: HIV-1, HTLV, CMV, HBV, HCV, and Treponema pallidum. This is necessary in specific circumstances to ensure safety and compliance. The sharing of donated intellectual property is being reevaluated, with the aim of benefiting both contributors and communities through potential commercialization opportunities [29].
USA	The limitations on funding faced by Congress are the primary factor influencing the development of laws regarding stem cell research in the United States. The National Institutes of Health (NIH) oversees research involving human stem cells, including human embryonic stem cells (hESC), and considers ethical implications when determining funding regulations and providing supervision. [32][33][34].
EUROPE	The guidelines set forth by the European Commission in 2005/62/EC outline the standards for air quality systems within the community, while the air guideline established by the European Parliament and Council in 2002/98/EC focuses on ensuring safety and quality in the handling of human air. It is imperative for transfusion facilities to comply with both air quality regulations and standards for their products. (35).

Remarks The moral principles surrounding the exploration of stem cells vary from country to country: In India, the emphasis is on healthcare and local benefits, while the United States prioritizes progress, and the European Union is committed to upholding ethical standards.

Clinical trials and Translations for clinical applications

TABLE 7 Illustration for Clinical trials and translations for clinical applications in different regions.

INDIA	Clinical trial and Translational studies including stem cell related clinical trials: Guidelines for utilizing Special Containment Procedures Division in research on tissue regeneration and well-being. Preliminary examination: (a)Approval is needed from the IEC (humans), IAC (small animals), and CPCSAE (primate species) before proceeding. (b) Encompass inquiries on immunological rejection, local and systemic biodistribution, and safety. (c)Explore animal samples for dose-dependent harm, considering effects on growths, genetic material, and maturation. Medical experiments: Clinical trials (a) Enrollment with the CTRI and obtaining prior authorization from CDSCO, IEC, and IC-SCR is mandatory. Approval from these regulatory bodies is necessary for any changes to be made. (b)A post-research phase that continues for at least two years is mandatory. (c)It is necessary to establish a committee to supervise data security.(d)Any undesirable occurrences that occur during clinical experiments must be communicated via IC-SCR to IEC, CDSCO, and NAC-SCRT.(e)Trial transcripts must be kept for at least 15 years [29].
USA	In order to assess the risk of a product, the FDA requires thorough testing on animals. Some medical facilities might provide inaccurate details about experiments without the required Investigational New Drug application. Weaknesses in security exploit FDA guidelines concerning stem cell treatment. Proceed with caution.[36] Translational studies including stem cell related clinical trials: NIH and NCATS support the FDA in its oversight of US stem cell research. ClinicalTrials.gov has trial documentation. The Stem Cell Translation Lab advances iPSC technology in healthcare by providing thorough control that guarantees safe, efficacious medicines [37][38].
EUROPE	The EU Regulation 536/2014 accelerates the approval of clinical trials through designated platforms, streamlining the authorization process for medical studies in the European Union. As of 2016, its efficiency is pending evaluation. [39].Translational studies including stem cell related clinical trials: Studies carried out in the European Union and European Economic Area, including investigations on stem cells, are documented in the European Union Clinical Trials Register. This encompasses research on children as well as medical interventions governed by Directive 2001/20/EC. Advanced therapy medicinal products, which may involve the use of embryonic cells, are overseen by the European Medicines Agency [40].

Remarks Three nations have regulatory bodies—the United States, the European Union, and India—that oversee ethical medical research. The Food and Drug Administration (FDA) is responsible for overseeing clinical trials in the US, the European Medicines Agency (EMA) reviews medications in the EU, and the Central Drugs Standard Control Organization (CDSCO) oversees the use of stem cells in India.

Patient Safety and Quality and Research funding

TABLE 8 Illustration for Patient Safety and Quality and Research funding in different regions.

INDIA	The guidelines indicate that product testing should encompass safety, biodistribution, immune rejection studies, immune rejection examinations, studies on the toxicity of a single dose and multiple doses, tumor-causing potential, genetic damage, examinations on toxicity during development, and studies on the dispersal within the body in relation to patient safety and the quality of stem cell products. Clinical investigation needs to be submitted to CTRI for registration and authorized by the IC-SCR, IEC, and CDSCO. A minimum 2-year follow-up period is necessary. The establishment of a DSMB is required for each inquiry. Through IC-SCR, all adverse incidents must be reported to IEC, CDSCO, and NAC-SCRT. Experiment records should be retained for at least 15 years [29]. The Department of Biotechnology (DBT), the Department of Science and Technology (DST), and the Indian Council of Medical Research (ICMR) are just a few of the departments and institutions that the Indian government has acknowledged for both theoretical and practical stem cell investigation. Moreover, apart from aiding enterprises in India, the work conducted in this realm has resulted in the construction of state-of-the-art facilities at over 40 prominent health research institutions. The ICMR created the 2017 National Guidelines for Stem Cell Research (RGSCR) following global norms. The administration has endorsed the ethical and educational principles of stem cell exploration via stem cell investigation guidelines. Hematopoietic cell transplantation (HCT) ought to be the preferred method for treating blood-related conditions, as stated in RGSCR-2017.To control medical experiments and novel medications, containing xenografts and products derived from human cells and stem cells, the authorities have issued the New Drug and Clinical Experiment Regulations, 2019..These guidelines consist of numerous clauses that aim to enhance the openness and responsibility of the medication authorization procedure as well as to progress novel medication advancement. The complete funding assigned by the Indian Council of Medical Research (ICMR) for scholarships and particular tasks engaging stem cells throughout the three previous years was as below: 2019 ($4,36,19,531/-), 2020 ($68,82,564/-), and 2021 ($3,08,34,008/-). The Department of Biotechnology (DBT) has granted funding for research on the basic concepts of stem cells, early and advanced translational research, the advancement of gene editing technology for potential healing uses, and the creation of animal models for different human illnesses. The monetary value that the DBT has disbursed in this area over the previous three years and the present year is Rs. 7345.58 Lakh. This information was stated in a written reply presented to the Lok Sabha today by Dr. Bharati Pravin Pawar, the Union Minister of State for Health, and Family Welfare [41].
USA	Each medical operation possesses benefits and drawbacks. However, untested stem cell treatments can be exceedingly hazardous. Attendees at a communal FDA gathering, for example, emphasized numerous serious unfavorable incident happenings. A single individual encountered vision impairment subsequent to an ocular stem cell infusion. A distinct patient developed a spinal growth subsequent to an infusion into the spinal cord. Other possible safety concerns for unproven treatments include: • Replies at the administrative facility, • The capacity of cells to move away from their location of insertion and transform into undesirable cell varieties or to replicate. • the incapacity of cells to operate as anticipated. the development of tumours [36]. Investigation on stem cells in the US is funded by the National Institutes of Health (NIH). The National Institutes of Health is the biggest public supporter of medical investigations worldwide. In the financial year 2022, the NFH acquired $45 billion in support, most of which was utilized to finance inquiries focused on enhancing well-being and decreasing sickness and disability. Novel treatments and progress facilitated by NIH-supported examination have aided individuals in extending their lifespan and enjoying a better state of well-being, while simultaneously establishing the foundation for forthcoming scientific exploration. The NIH will not back any new or rival grant propositions for investigations involving the grafting of human multipotent stem cells into vermin that is not a human embryo at the pre-gastrulation phase. Research grants that encompass costs for or engage in research transferring human pluripotent cells into non-human vertebrate animal embryos at the pre-gastrulation stage will not be considered by the National Institutes of Health (NIH). On an individual basis, ongoing NIH funds will be deliberated with the recipients. NYSTEM, which was founded in 2004 with a $3 billion bond proposal and extended in autumn 2020 with a $5.5 billion ballot question, was less famous than California's esteemed initiative and no more obtains state funding for stem cell research. [42][43][44][45][46][47].
EUROPE	To ensure a high level of protection for human health, Directive 2002/98/EC sets guidelines of excellence and security for the gathering and examination of human blood and blood parts, irrespective of their planned utilization, as well as for their handling, retention, and dissemination when planned for transfusion. EUTCD class cell lines are formed and stored in HTA-approved facilities in line with the EU Tissue and Cells Directives (EUTCD), enabling them to be utilized as a

	foundation for the advancement of cellular treatments. EUTCD class cell lines are formed and stored in HTA-licensed facilities in line with the EU Tissue and Cells Directives (EUTCD), enabling them to be utilized as the foundation for the advancement of cellular therapies. (48,49). The European Union's Horizon 2020 exploration and development program offers financial support for European stem cell exploration. EuroStemCell, a partnership of over 400 stem cell and regenerative medicine organizations in Europe, provides unbiased resources for understanding stem cells. The European Union's Horizon 2020 exploration and advancement plan has granted funding for them [50].

Remarks Ensuring the safety and availability of healthcare services is of utmost importance in healthcare policies in the United States, European Union, and India. Challenges include cultural practices in India, the state of infrastructure in the US, laws in the EU, and funding for research on stem cells.

Intellectual Property

TABLE 9 Illustration for Intellectual property in different regions.

INDIA	IPR in Stem cell research, therapy and Regenerative medicines -As per Patents Act, 1970: Any development must fulfill these three basic conditions to obtain a patent, particularly: 1. The uniqueness 2. An innovative step 3. Industrial Significance If they fulfill all the requirements mentioned above, stem cell treatment and regenerative treatments are qualified for patent safeguard. Part 3 of the Patents Act of 1970 includes a catalog of items that are not regarded as innovations. Consequently, it ought not to be considered an innovation for the objectives of part 3 of this Act. The concern does, nonetheless, arise given part 3(b) of this act's extensive coverage [51].
USA	On behalf of the United States, the Office of International Intellectual Property Enforcement (IPE) is assigned with promoting the efficient safeguarding and implementation of intellectual property rights (IPR) globally. For the safeguarding of intellectual property rights (IPR), the US has a strong legal system. The structure comprises of laws, regulations, and recommendations that encompass intellectual property rights (IPR) such as patents, trademarks, copyrights, trade secrets, and others. The U.S. Copyright and Trademark Office (USCTO) is where trademarks and patents are recorded in the nation. The Library of Congress' Copyright Office is responsible for registering copyrights in the United States. Several organizations have also been created by the US government to enforce IPR laws and regulations. These organizations include the Department of Justice (DOJ), the Federal Bureau of Investigation (FBI), the U.S. International Trade Commission (ITC), and U.S. Customs and Border Protection (CBP).. It is important to emphasize that, depending on the kind of IPR concerned, intellectual property rules may be intricate. Seek advice from a lawyer or other legal expert if you have particular worries about intellectual property rights in the United States [52][53].
EUROPE	A constant increase in trade connections can be measured among the most of the participants, who work together with a few industrial/commercial enterprises. Most of the participants also collaborate with other public organizations to exchange information and methodologies. This indicates that the investigation of stem cells is a highly interdisciplinary subject with close connections to commerce. With the support of public-private alliances in this field, this is likely to worsen. Yet, it's also crucial to understand that cell therapies are only one of several possible translational paths for stem cell investigation, and they may not even be the one in which the largest European pharmaceutical firms are investing. The majority of attendees concurred that it was essential to reduce the range and impact of so-called "penetrate through rights" in biomaterials and linked platform technologies, while a smaller percentage of them disagreed or displayed indifference in this matter. They were also worried about the influence of these rights. As collaborations between each sector, including public and private and the establishment of mutual resources expand, the conventional limits between public and private licensing conditions might potentially cause issues [54].

Remarks Research on stem cells faces challenges in the United States, European Union, and India due to issues related to intellectual property rights. These challenges stem from differences in laws across regions, as well as conflicts regarding patents

Research areas.

TABLE 10 Illustration for Research areas in different regions.

INDIA	1.Permitted Areas of Research- Creation of fresh embryonic stem cell 2.Restricted Areas of Research- Creation of a human **zygote by IVF, SCNT** 3.Prohibited Areas of Research- Clone reproduction, intact human embryos are cultured in vitro [55].
	1. Permitted Research: Adult stem cell exploration is broadly accepted and not subject to substantial federal restrictions. Adult stem cells are additionally known as somatic or tissue-

USA	specific stem cells. - Provoked pluripotent stem cells (iPSCs): iPSC research, in which grown-up cells are reprogrammed to exhibit attributes similar to embryonic stem cells, is usually permitted. multipotent stem cells (iPSCs). 2. Restricted Research: Embryonic stem cells from humans (hESCs) are limited for use in investigation by the federal government. Only hFSC lines formed before August 9, 2001 or those formed after that date with the appropriate informed consent and without federal financing may be utilized for investigation through the NIH. Federal financing is usually not accessible for studies involving new hFSC lines formed after August 9, 2001.Cloning: Under national rules, the act of duplicating humans for use in reproduction is prohibited. 3. Prohibited Research: Duplication Cloning: According to federal law, it is prohibited to generate a duplicated human being through the procedure of duplication cloning. Limitations on the Utilization of Embryonic Tissue in Research: The utilization of embryonic tissue in research is bound by restrictions, primarily linked to the origin and permission for acquiring the tissue [56].
EUROPE	1. Permitted Research: The utilization of multipotent stem cells (hPSCs) in basic investigation is commonly endorsed within the EU, subject to ethical and legal limitations. Fetal stem cells (ESCs) and generated multipotent stem cells (iPSCs) are often utilized for a range of research endeavours in this. 2. Prohibited Research: In various EU countries, specific types of investigation concerning human embryos were either banned or subjected to stringent controls. For example, while exploration involving the disposing of human embryos was subjected to heightened ethical & legal examination, the creation of embryos for investigative aims (such as human cloning) was often prohibited. 3. Restricted Research: Several countries have placed restrictions on specific stem cell research techniques, such as chimera research, which entails merging human and animal cells to generate novel species, or germ line editing, which alters the genes of heritable embryos [50].

Remarks In India, there are regulations in place allowing for the development of new types of embryonic stem cells, with limitations on the creation of zygotes. In contrast, the European Union has laws that permit the use of pluripotent stem cells, and the United States is in favor of conducting research on adult stem cells.

CONCLUSION

The employment of stem cell-based therapies to address a range of illnesses and injuries demonstrates significant potential. It is crucial to follow both moral and legal demands in order to guarantee the safety and efficiency of these treatments. Additional to the factors considered in this article, further investigation is needed to fully understand stem cell mechanisms and potential applications. To promote uniformity and comprehension of internal frameworks, this composition underscores the need for continuous investigation and advancement in the area, as well as the importance of partnerships between public and private entities and global policy deliberations. Ultimately, we contend that stem cell exploration holds the potential to revolutionize the implementation of regenerative medicine and amplify the standard of living for countless individuals globally.

ACKNOWLEDGEMENT

The authors would like to thank the Department of Science and Technology - Fund for Improvement of Science and Technology Infrastructure (DST-FIST) and Promotion of University Research and Scientific Excellence (DST-PURSE) for the facilities provided for conducting research.

REFERENCES

1. Indian Council of Medical Research. (2017). National guidelines for stem research. Retrieved from
2. Dekoninck, S., & Blanpain, C. (2019). Stem cell dynamics, migration and plasticity during wound healing. *Nature Cell Biology, 21*, 18-24.
3. Zakrzewski, W., Dobrzyński, M., Szymonowicz, M., & Rybak, Z. (2019). Stem cells: past, present, and future. *Stem Cell Research & Therapy, 10*, 68.
4. Becker, A. J., Mc, C. E., & Till, J. E. (1963). Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. *Nature, 197*, 452-454.
5. Aljurf, M., et al. (2019). Worldwide Network for Blood & Marrow Transplantation (WBMT) special article, challenges facing emerging alternate donor registries. *Bone Marrow Transplantation, 54*, 1179-1188.
6. Yokohama-Tamaki, T., et al. (2015). CXCR4/CXCL12 signaling impacts enamel progenitor cell proliferation and motility in the dental stem cell niche. *Cell and Tissue Research, 362*, 633-642.
7. Polisetti, N., Zenkel, M., Menzel-Severing, J., Kruse, F. E., & Schlötzer-Schrehardt, U. (2016). Cell adhesion molecules and stem cell-niche-interactions in the limbal stem cell niche. *Stem Cells, 34*, 203-219.
8. Soria-Juan, B., et al. (2019). Cost-effective, safe, and personalized cell therapy for critical limb ischemia in type 2 diabetes mellitus. *Frontiers in Immunology, 10*, 1151.

9. Stanford Medicine Children's. (n.d.).
10. Biggers, A., Railton, D., & Sharon, A. (2021). Medical News Today.
11. Allied Market Research. (n.d.). Stem cell therapy market statistics, segments.
12. Department of Biotechnology. (n.d.). National guidelines for stem cell research–2017.
13. George, B. (2011). Regulations and guidelines governing stem cell-based products: Clinical considerations. *Perspectives in Clinical Research, 2*, 94–99.
14. NACSCRT. (n.d.). IC-SCR Registration.
15. Moradi, S., et al. (2019). Research and therapy with induced pluripotent stem cells (iPSCs): social, legal, and ethical considerations. *Stem Cell Research & Therapy, 10*(1), 34.
16. International Society of Stem Cell Research. (2021). Though the limit of 14 days is now removed by the International Society of Stem Cell Research in 2021.
17. Rosario, I., Ginoza, M., Jongsma, K., Lars, A., & Morris, F. (2022). Mending the gaps: ethically sensitive cells and the evolution of European stem cell policy. *Regenerative Medicine, 17*(5), 581-595.
18. Lovell-Badge, R., et al. (2021). ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 update. *Stem Cell Reports, 16*(6), 1398-1408.
19. Baylis, F. (2021). ISSCR guidelines fudge heritable human-genome editing. *Nature, 594*, 333.
20. European Commission. (n.d.). Horizon Europe: research and innovation funding programme until 2027. (Accessed on 15 September 2023).
21. European Medicines Agency. (n.d.). Advanced therapy medicinal products: Overview. (accessed on 4 September 2023).
22. U.S. Food and Drug Administration. (n.d.). FDA Framework for the Regulation of Regenerative Medicine Products. (accessed on 4 September 2023).
23. U.S. Food and Drug Administration. (2020). Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation Homologous Use - Guidance for Industry and Food and Drug Administration Staff. (accessed on 21 September 2023).
24. U.S. Food and Drug Administration. (2017). Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions Answers Regarding the Scope of the Exception; Guidance for Industry. (accessed on 21 September 2023).
25. Bloomberg Law. (2019). INSIGHT: FDA's Aggressive Enforcement Against Stem Cell Companies Starting to Ripen. *US Law Week.* (accessed on 21 September 2023).
26. U.S. Food and Drug Administration. (2019). Statement on stem cell clinic permanent injunction FDA's ongoing efforts to protect patients from risks of unapproved products. *FDA Statement.* (accessed on 21 September 2023).
27. Los Angeles Times.* (2020). Column: Judge Hands FDA a Loss On Stem Cell Clinics. (accessed on 21 September 2023).
28. El-Kadiry, A. E.-H., Rafei, M., & Shammaa, R. (2021). Cell Therapy: Types, Regulation, and Clinical Benefits. Frontiers in Medicine, 8.*
29. Lahiry, S., Choudhury, S., Sinha, R., & Chatterjee, S. (2019). The National Guidelines for Stem Cell Research (2017): What academicians need to know? *Perspectives in Clinical Research, 10.*
30. Board on Health Sciences, P., et al. (2014). *Stem Cell Therapies: Opportunities for Ensuring the Quality and Safety of Clinical Offerings: Summary of a Joint Workshop.* National Academies Press (US).
31. European Commission. (n.d.). European stem cell regulations | EUCELLEX Project | Results in brief | FP7. *CORDIS.*
32. Alchetron. (n.d.). Stem cell laws and policy in the United States. (accessed on 27 September 2023).
33. Academike. (n.d.). Legal issues relating stem cell research. =(accessed on 27 September 2023).
34. King, N. M. P., & Perrin, J. (2014). Ethical issues in stem cell research and therapy. *Stem Cell Research & Therapy, 5*, 85.
35. Worel, N., et al. (2023). A guide to the collection of T-cells by apheresis for ATMP manufacturing—recommendations of the GoCART coalition apheresis working group. *Bone Marrow Transplantation, 58*(7), 742-748.
36. U.S. Food and Drug Administration. (n.d.). FDA warns about stem cell therapies. Accessed on 21 September 2023).
37. Ferry, N. (2017). European regulation for therapeutic use of stem cells. *Bio-Medical Materials and Engineering, 28*, S3-S7.
38. Listl, S., & Klouche, M. (2006). The European Blood Directive (Directive 2002/98/EC) in the Context of the European Community Legislation. *Transfusion Medicine and Hemotherapy, 33*(5), 374-383.
39. O'Shea, O., & Abranches, E. (2020). UK Stem Cell Bank. *Stem Cell Research, 49*, 102019.
40. Press Information Bureau, Government of India. (2022, February 11). Research in regenerative medicine. (accessed on 22 September 2023).
41. Statista. (n.d.). Stem cell research funding by National Institutes for Health. Retrieved from (accessed on 22 September 2023).
42. National Institutes of Health. (n.d.). Guidelines for human stem cell research. Retrieved from (accessed on 22 September 2023).
43. National Institutes of Health. (n.d.). NIH stem cell research. Retrieved from (accessed on 22 September 2023).

44. National Institutes of Health (NIH). (n.d.). Grants & Funding. Retrieved from (accessed on 22 September 2023).
45. National Institutes of Health (NIH). (n.d.). NIH Grants Policy Statement: Human stem cell research. Retrieved from (accessed on 22 September 2023).
46. Science. (n.d.). New York state ends stem cell research funding. Retrieved from (accessed on 22 September 2023).
47. EuroStemCell. (n.d.). About EuroStemCell. Retrieved from (accessed on 21 September 2023).
48. Zachariades, N. A. (2013). Stem Cells: Intellectual Property Issues in Regenerative Medicine. Stem Cells and Development, 22, 59-62.
49. The United States Patent and Trademark Office (USPTO). (n.d.). About Us. Retrieved from (Accessed on 27 September 2023).
50. US Patent and Trademark Office. (n.d.). U.S. Patent and Trademark Office. (Accessed on 27 September 2023).
51. Rial-Sebbag, E., et al. (2018). Governing stem cells & regenerative medicine in Europe: The vision and recommendations from the EU CelLEX project.
52. NCATS. NIH. (n.d.). Stem Cell Information. (Accessed on 27 September 2023).
53. O'Brien, T., Creane, M., Windebank, A. J., Terzic, A., & Dietz, A. B. (2015). Translating stem cell research to the clinic: a primer on translational considerations for your first stem cell protocol. Stem Cell Research & Therapy, 6, 146.
54. Mousaei Ghasroldasht, M., Seok, J., Park, H.-S., Liakath Ali, F. B., & Al-Hendy, A. (2022). Stem Cell Therapy: From Idea to Clinical Practice. International Journal of Molecular Sciences, 23.
55. Boopalan, D., Pandian, R., & Kesavan, G. (2021). Prospects for Stem Cell-Based Regenerative Therapies in India. StemJournal, 3, 11-21.
56. eMedicineHealth. (n.d.). Is Stem Cell Research Illegal in the United States? Retrieved from (Accessed on 27 September 2023).