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Navigating Regulatory requirements for Stem Cells Therapy- A review on Regulations of US, European Union, Japan and India

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Abstract

Regenerative medicine is an emerging branch of medicine holding tremendous power to cure in contrary to conventional treatment. Stem cells being at forefront of regenerative medicines holds unprecedented capability of self-renewal and cell differentiation, where this capability is the sole of the stem cell therapy. The cell therapy works by replacing the injured and collapsed cells with the regenerative ones in a chronic condition. But as there are always accompanying downsides with every benefit in this case it's the ethical consideration, risk and cost associated to the usage and treatment. This review article aims to analyze the status of both stem cell therapy and research by outlining the regulatory landscape for developing, manufacturing and conducting of stem cell therapy in the countries namely US, EU, Japan and India in a comparative mode. The unethical and unproven stem cell tourism happening worldwide will also be highlighted in this review. In the realm of life-threatening medical procedures, addressing regulatory loopholes is a matter of utmost importance. The need for well-coordinated, robust, and meticulously enforced regulations cannot be overstated. These comprehensive regulatory frameworks play a pivotal role in ensuring that scientific advancements in this domain are conducted with the highest levels of safety and ethical integrity.

Keywords: Stem cells, Regulations, Regulatory framework, Advanced Therapy Medicinal Products (ATMPs), Regenerative medicine, Stem cell tourism, Medical Tourism, Embryonic Stem Cells (ESC), CBER, FDA

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1. Introduction

Regenerative medicine has successfully permeated the domain of clinical practice, placing particular emphasis on harnessing the potential of human cells and among the several treatments one of them is the Stem cell therapy. (1,2) The roots of stem cells can be traced back into 1958, when Hungarian physician Georges Mathe embarked on a trailblazing and controversial experimental endeavor. Driven by the urgency to rescue six scientists who had endured hazardous levels of radiation exposure, Mathe embarked on a pioneering journey that involved the transplantation of bone marrow. (3,4) Despite the unfortunate loss of one patient, Georges Mathe's groundbreaking experiment demonstrated promising outcomes, with allogeneic bone marrow transplant though they were temporary improvements. (5) This experiment opened doors and illuminated potential of stem cell's effectiveness. Later on, in early 1960s Ernest McCulloch and James Till conducted a series of animal studies, unraveling the fundamental role of hematopoietic stem cells (HSCs) i.e., self-renewability in the complex process of blood development, which is one of the hallmarks of stem cells. Subsequently, in 1963 first case of leukemia was cured using bone marrow transplant by Georges Mathé. The inherent characteristics of Stem cells which exist in various states of potency, the multipotent, pluripotent, and totipotent serves as the foundation for regenerative therapy, which aims to address the deterioration or loss of cells and tissues within the body, (4) These pivotal moments propelled the field of stem cell research forward, opening new avenues for exploration and ignited a wave of scientific inquiries into the vast therapeutic possibilities offered by these cells. However, as this field is still progressing, the need for establishment of harmonized, robust, and well-regulated regulations and standards is of paramount importance. Implementing comprehensive regulatory frameworks helps safeguard against potential risks and ensures that scientific advancements in this domain adhere to rigorous ethical guidelines.

1.1 Classification of Stem Cells-

Stem are categorized based on their differentiating factor i.e., in what type of cell lineage the stem cell can develop into. There is typically three division or

classification of these cells which are Embryonic Stem Cells, Adult Stem Cells and Induced Pluripotent Stem cells. (6)

Embryonic Stem Cells having pluripotency as its differentiating factor it can be differentiated into any cell type with the capability of it developing into an organism. It is important to note that ESCs are distinct from the fertilized eggs which are found inside a woman's body but are the cells derived from early-stage embryos, typically at the blastocyst stage. Pluripotency makes ESC's extremely valuable for both research and medical applications but ethical issue restricts its use. (6,7)

Adult Stem Cell being multipotent or unipotent in nature can mature into a restricted range of cell type. Although these are typically found in majority of tissues throughout the body but relatively in small quantities therefore require expansion and enrichment. Hematopoietic Stem Cells, Mesenchymal Stem Cells, Neural Stem Cells, Epithelial Stem Cells, and Skin Stem Cells are among the various types of adult stem cells which can be sourced from fetus, umbilical cord, placenta, infant, child, or adult organ/tissue. (7) The category of adult stem cells, cord blood, fetal tissues come under multipotent where in cells are differentiated but in a limited number of matured cell types. (6,8) Despite being less adaptable than ESCs, adult stem cells nonetheless have a great therapeutic promise with being ethically less contentious.

Induced Pluripotent Cells are made to perform as a pluripotent cell by reprogramming or inducing the somatic/adult stem cell. This innovative genetic reprogramming technique, which was first identified in 2007, but due to constraints regarding low reprogramming and efficient differentiation, tumorigenicity and invasive procedures it requires several more years of study before it can be used to therapeutic therapies. (6,7)

1.2 Transplantation of Stem cells

The surgical procedure known as stem cell transplantation is alternatively referred to as bone marrow transplant or specifically Hematopoietic stem cell transplant, it entails the substitution of unhealthy cells with healthy ones. The transplant can be either be Autologous /Allogeneic /Syngeneic.

In situations where a perfect donor match is not accessible, alternative options like umbilical cord blood transplant, parent-child transplant, or haplotype mismatched transplant are feasible alternatives that are available. Perfect donor match is decided based on the maximum resemblance of human leukocyte antigens (HLA) of both donor and receiver. (9) In Autologous transplant, the receiver/ patient uses his/her own cells for treatment purpose by extracting, treating and returning back whereas in Allogeneic transplant cells of 'donor' are used maintaining anonymity of donor. Furthermore, the Syngeneic transplant being the rare-one as its possible only in identical twins. In the cord blood transplant, the blood from the cord is used post the delivery which is of no use whereas in the Parent-child transplant/ haplotype mismatched transplant cells of parents or sibling is used with 50% resemblance**.** Considering the transplant for preparing the patient for the transplant a high dose of chemotherapy (radiation therapy in some cases) is given which is also called as 'conditioning treatment'. Post this in the 'engraftment process', the healthy stem cells are infused into the bloodstream, once they reach the bone marrow formation of healthy new blood cells begins. (9,10)

2. Regulations specific to US

Stem cell research has captured a lot of notice in the United States by promising health betterment and significant advances in regenerative medicine. The products and devices pertaining cellular and gene therapy are referred as Human Cell Therapies or Products (HCT/Ps). In United States the Centre for Biologics Evaluation and Research (CBER), a division of Food & Drug Administration (FDA) is responsible for regulating these HCT/Ps products. Under the purview of CBER effective oversight, compliance and supervision is ensured. For surveillance CBER relies on the two key acts granted by the authority i.e., Public Health Service (PHS) Act and the Federal Food Drug and Cosmetic (FD&C) Act, by leveraging provisions of these acts regulatory framework is strengthened and enforced. (11) These stem cells products undergo a stringent regulatory procedure of safety, quality, efficacy evaluation and requires FDA's prior approval whereas the cellular products related medical devices requires premarket approval before getting market clearance. (12,13) The US-FDA first granted approval for a stem cell therapy product named Hemacord in 2011, an intravenous suspension used in progenitor transplant as an unrelated donor. (14) However, the first HCT/P was granted approval in April 2010 named Provenge (Stipuleucel-t), an autologous cellular immunotherapy designed to treat metastatic prostate cancer which is hormone refractory. (15,16) Whereas, Elevidys is the latest approved HCT/P product (as of July 7, 2023) which received its initial US approval on 22nd June, 2023. Elevidys, being a gene-based therapy product received accelerated approval for effectiveness in Duchenne muscular dystrophy (DMD) in pediatric patients (4-5 yrs) where there is a DMD gene mutation for sure. Its further approval will be based on the phase III confirmatory trials. (17) As of now these approved HCT/Ps have been given the go-ahead for the usage of certain malignancy, hematologic and immune system diseases and are acknowledged for their potential of providing therapeutic benefits and improved conditions. (18) The Office of Tissues and Advanced Therapies (OTAT) till now has approved thirty cellular and gene therapy products. (19) The FDA has issued guidance to help companies navigate the regulatory process for stem cell therapy. Cellular therapy includes cancer vaccines, immunotherapies, and various stem cells (hematopoietic, adult, and embryonic) for cures. (11)

2.1 Regulatory Structure

In US, stem cell products do not have specific regulations, it all falls under the oversight of HCT/Ps. Earlier the section 351 and section 361 of Public Health Service Act both were applicable for drugs as well as HCT/Ps. However, in 1990s two distinct regulatory tiers were established wherein section 351 dealt with drugs, devices, biological products whereas section and 361 dealt

with HCT/Ps and communicable diseases. The 21 CFR Part 1271 outlines the regulation for HCT/Ps in which various aspects related to donor eligibility, manufacturing practices, conduct of clinical trial and product labelling etc. are laid down. For the Products that tend to satisfy all the criteria in 21 CFR 1271.10 are mandated to receive FDA licensure and approval. However, if that particular product falls out of the aspects of 21 CFR 1271 then the product is bound to be regulated within the jurisdiction of Section 351 of PHS Act and FD&C Act. (20,21) Considering a product whether the 21 CFR Part 1271 will be applicable or not has been put forth in Figure.1 using a flowchart. (22)

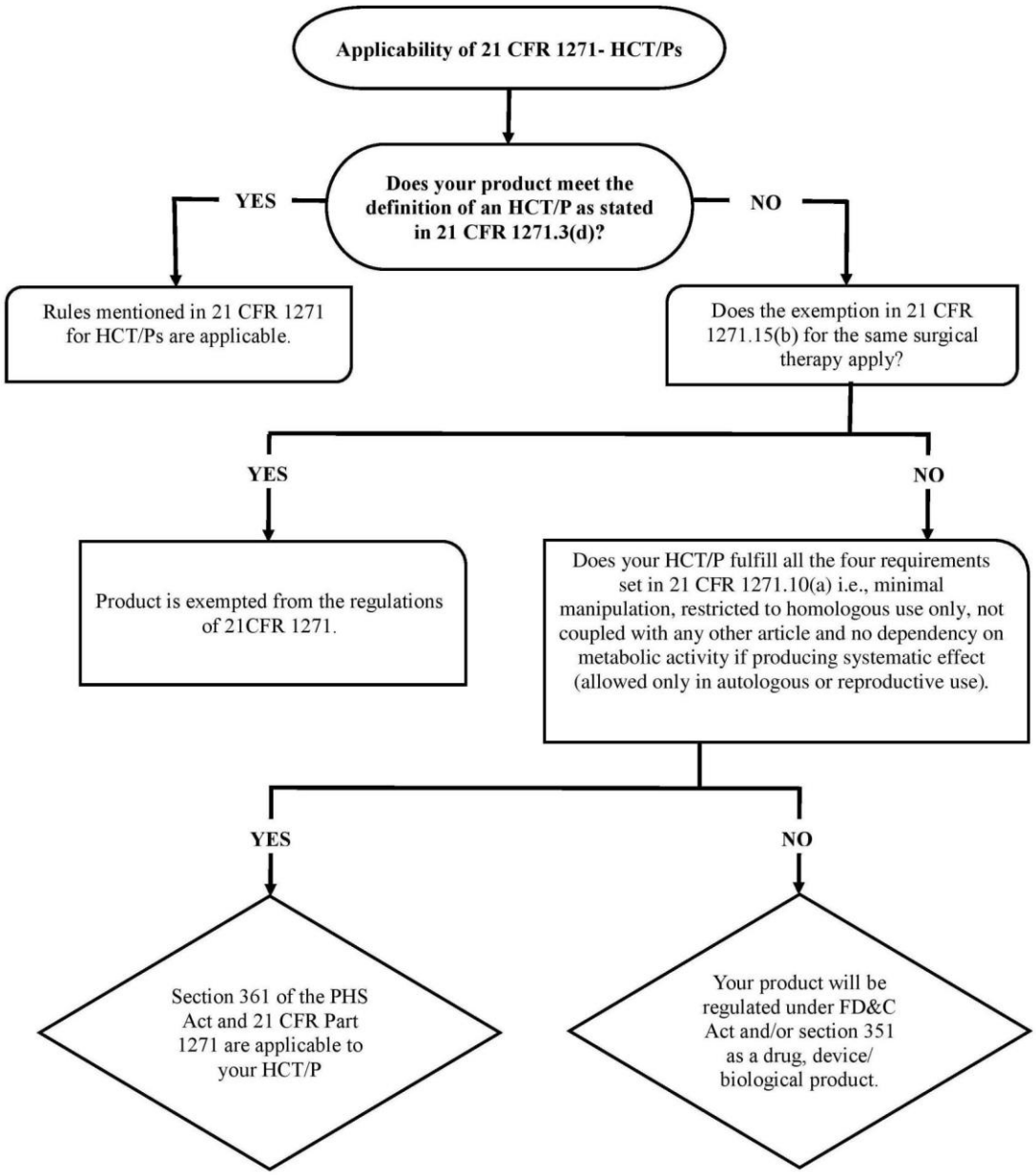

Figure 1. Flowchart illustrating applicability and exemption of 21 CFR 1271. CFR, Code of Federal Regulation; HCT/P, Human Cell Therapies or Products; PHS, Public Health Services; FD&C, Food Drug and Cosmetics Act

FDA has also come up with expedited programs for regenerative medicines to foster innovation to satisfy the unmet medical need. These programs offer expedited pathway for development and approval of innovative products in timely manner. Herein the regenerative medicine is given with a designation which qualifies them for accelerated approval or priority review. (23) The various programs are put forth in a comparative manner in Table 1.

According to a recent study, in United States 700 clinics across the country provide unlicensed stem cell and regenerative medicine interventions (SCRIs) for range of illnesses like Neurological disease, muscular dystrophy, genetic disorders such as autism, and even COVID-19. (26) Due to lack of awareness considering the use of anything marketed as a regenerative medicinal product; FDA has come up with an official alert stating a list of regenerative products which are not- approved by FDA for any Neurological, Orthopedic, Cancer, cosmetic procedures or Covid-19 indications. (27) The discussion about the unproven offerings of such therapies will be further discussed in this review.

Table 1. Regulatory tools and Expedited programs for HCT/Ps by USFDA

Program	Eligibility Criteria	Nature of Program	Benefits	FDA Response timeline	When to submit	Reference
Fast Track Designation	Both clinical and non-clinical data required which has potential to address unmet medical need. **AND** Drug must be intended to treat serious condition.	Designation	• Facilitated development • Expedited development and review • Rolling review	Within 60 calendar days of receipt request	No later than pre-BLA or pre-NDA meeting. Request can be submitted with IND application or as an IND amendment.	(23,24)
Break-through Designation	Preliminary Clinical data is required and which is need to be demonstrated for substantial betterment than the existing therapies with one or more clinically significant endpoint. **AND** Drug must be intended to treat serious condition.	Designation	• All benefit of fast track • Intensive FDA guidance on efficacious drug development • Involvement of senior management as per organizational commitment	Within 60 calendar days of receipt request	no later than the end-of-phase 2 meeting. Request can be submitted with IND application or as an IND amendment.	
Regenerative Medicine Advanced Therapy	Preliminary Clinical data is required to prove clinical significance. Product intended must treat, modify, reverse or cure serious condition and address an unmet medical need.	Designation	• All benefit of fast track • Early interaction with FDA section 505(g)(5)	Within 60 calendar days of receipt request	Prior discussion with review division for possibility of accelerated approval during development	
Accelerated Approval	Drug must be intended to treat serious condition. **AND** demonstrated for providing substantial betterment than the existing therapies **AND** exhibits an impact on a clinical endpoint that may be evaluated sooner than irreversible morbidity or mortality (IMM)	Approval Pathway	Approval based on surrogate endpoint that will predict drug's clinical benefit.	Not specific	Request can be submitted with original BLA, NDA or efficacy supplement.	
Priority Review Designation	Drug must be intended to treat serious condition. **AND** provide a significant improvement in safety or effectiveness **OR** Any supplement that requests a labelling modification in response to a 505A report on a paediatric trial **OR** Medicine qualified for infectious disease **OR** Any application or supplement for a drug submitted with a priority review voucher.	Designation	Shorter clock for review of marketing application (6 months compared with the 10-month standard review)	CBER responses Within 60 calendar days of receipt of original BLA, NDA or efficacy supplement		
Orphan Designation	Intended for rare disease or condition Affects 200,000 person (or more orphan subset) in United States OR the cost of making and developing the drug in U.S. can't be recovered by sales.	Designation	• 7-year market exclusivity • Tax credit for qualified Clinical trial • Waiver for drug user fees.	Within 90 days of receiving the request, the FDA will review it and issue a decision.	Prior submitting marketing application sponsor may request designation anytime in the drug development process.	(25)
Revocation of Designation	If a product no longer satisfies the designation's precise qualifying requirements, designation may be revoked at a later stage of product development.					(24)

3. Regulations specific to Europe

In Europe Union (EU), the stem cell therapy products are subject to European Medicine Agency's (EMA) regulation. These are referred under a broad class of products i.e., Advanced Therapy Medicinal Products (ATMPs). (28) These are further sub classified into Gene Therapy Medicinal Products (GTMP), Tissue Engineered Products (TEP), Somatic Cell Therapy Medicinal Products (sCTMP) and Combined ATMPs (which combines medical device with GTMP/TEP/sCTMP). (29) To supervise the scientific progress and assessment of quality, safety, and effectiveness of ATMPs, the Committee for Advanced Therapies (CAT) was constituted as a dedicated committee within the EMA. Formation of CAT was in compliance with the Regulation (EC) No. 1394/2007 with the core role being diligent monitoring which will facilitate development. (30,31) The first ATMP to get the Market Authorization (MA) was Chondrocelect in November 2009 (15,32). However, the MA was later withdrawn by MA holder, TiGenix NV in July 2019 due to commercial reasons. (33) According to the January 2023 highlights from the Committee for Advanced Therapies (CAT), 24 ATMPs have so far been given market authorization. However, commission opinion is still pending for one ATMP i.e., Hemgenix which indicates its ongoing assessment. (32) Approved ATMPs cover diverse diseases: cancer, cardiovascular, musculoskeletal, immune & inflammation, neurological, and more, showcasing their broad potential. (34)

3.1 Regulatory Structure

EU's regulatory framework fosters cutting-edge product evaluation and approval while balancing patient needs for therapeutic progress. The legislative framework governing ATMPs has been laid down in Tissue and Cell Directive 2004/23/EC, specifying the safety and quality basis governing the tissues and cells. (35) In addition to this directive, the European Commission has further proposed and enacted the few more directives that were to be implemented in close cooperation with EU member states to assist in putting this fundamental act into effect. These directives have been mentioned in Figure 2, primarily associated marketing approvals, conduct of trial, preparation and processing etc. (36) This comprehensive legislative framework works in conjunction to ensure regulation and advancement within the European Union.

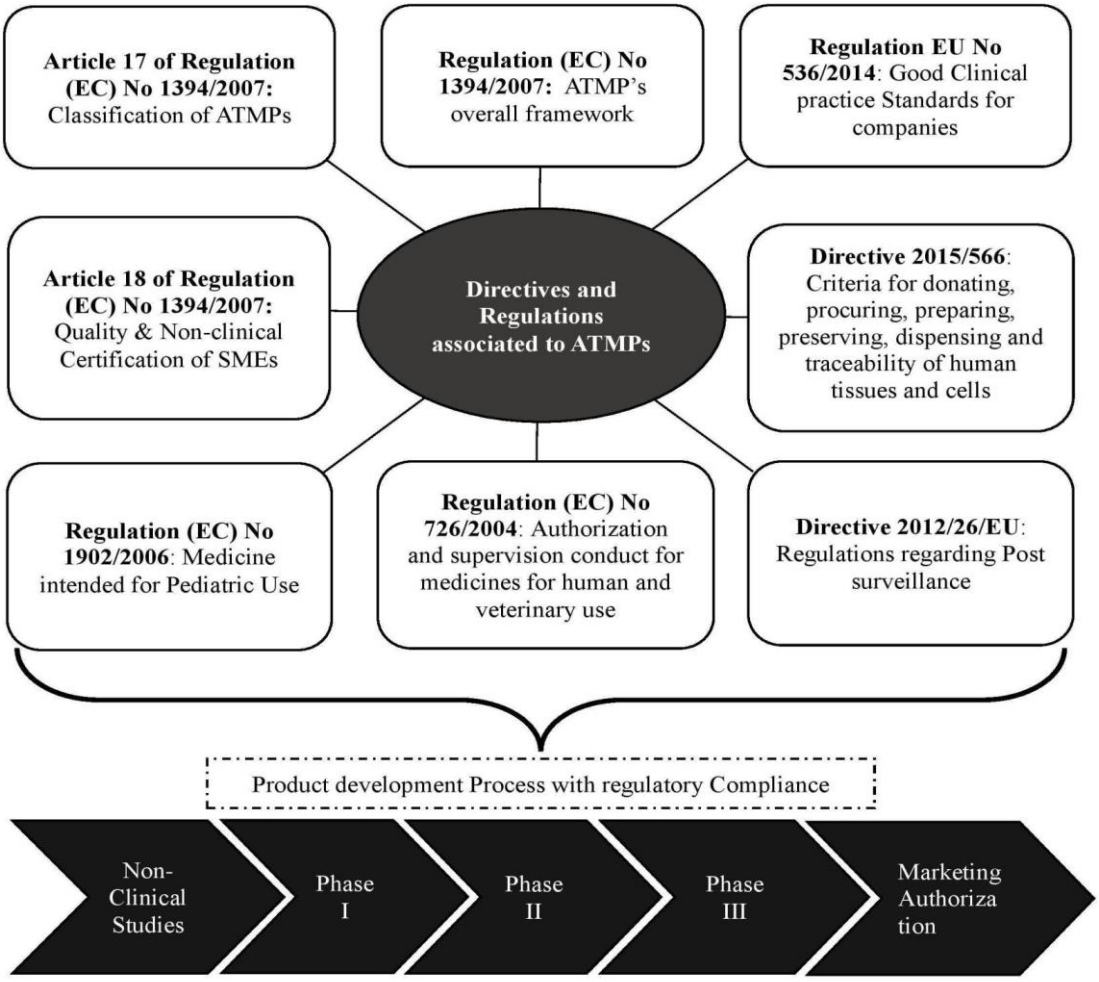

Figure 2. Regulation and Directives associated to development of ATMPs in EU. ATMPs, Advanced Therapy Medicinal Products; EC, European Commission; EU, European Union; SMEs, Small and Medium sized Enterprises

Table 2. Regulatory tools and Expedited programs for ATMPs by EMA

Program	Eligibility Criteria	Nature of Program	Benefits	EMA Response timeline	When to submit	Reference
Prime designation	Innovated medicine must demonstrate the capabilitty to meet medical requirements as prevention, onset and duration of the given condition which is not met yet. OR improving the mobidity or mortality of disease, clinically meaningful outcome.	Designation	• Fosters early dialogue with EMA which helps sponsor in data collection for high quality MA applications. • Kick-off meetings with rapporteur and EMA experts • Appointment of PRIME scientific coordinator • Oppourtunity to involve stakeholder as HTA, patients and US-FDA • Confirmation of potential accelerated assessment • expedite examination	EMA responds 40 days later the request.	Sponsor engaged in exploratory clinical trials (Phase 1) can request on preliminary clinical evidence.	(40)
Conditional Approval	• Positive Benefit-Risk Ratio • Submission of comprehensive data post authorization • Medicinal product addresses unmet demand of medicine. • Patients benefit of accessing the medicine greater than requirement of additional data.	Conditional approval Valid for one-year, annual renewals permitted.	Grant of Conditional MA without the submission of comprehensive data instantly but to be submitted within the agreed timeframe by EMA. Grant of standard MA after data submission	EMA takes up to 210 working days for assessment of application for MA of new medicinal product.	Requests have to be made at pre-submission meetings six to seven months before applications are filed.	(41)
Accelerated Assessment	• Intended medicine must be therapeutically innovative and must be of great interest to public health. • Availability of strong evidence.	Priority Review	• Reduction in time of assessment of application and faster approval. • Improved and early access of treatment to the patient.	Post submission of sufficient justification CHMP can reduce the timeframe from 210 days to 150 days.	Requests have to be made at pre-submission meetings six to seven months before applications are filed. Applicant can receive confirmation during the clinical development phase as per the PRIME scheme.	(42)

Hospital Exemption	• ATMP prepared on non- routine basis w.r.t quality standards • Must be used and manufactured under same member state in hospital with sole responsibility of professional. • Customized products as per the prescription • Quality and safety related community regulations not to be overruled.	Exception	Waiver for submission of MAA.	Relative to individual member state.	Relative to individual member state.	(39)
Orphan Designation	• Medicinal product must be intended for life threatening disease or condition. • Condition must prevail in more than 5 people among 10,000 OR the cost of making and developing the medicine in EU can't be recovered by sales. • If similar to pre-existing, it must have clinically 'significant benefit' than those existing.	Designation	• Protocol Assistance (Specific Scientific Advice) • Market exclusivity for 10 years • Fee reductions	The Committee for Orphan Medicinal Products (COMP) takes maximum of 90 days after validation	Sponsor can request a pre-submission meeting at least two months before the intended submission date, if he feel he could be benefitted.	(43)
Pediatric Designation	• Intended for life-threatening, chronically debilitating, or disabling disease. • Clinically significant and beneficial in pediatric. • Either PIP or waiver in place	Designation/ Development Program	• 6- month extension period for medicinal product authorized by all member state • Protocol Assistance (Specific Scientific Advice) • Fee reductions	PDCO responds within 10 days if re-examination elapsed it takes more 3o days after which the final decision by EMA comes within 10 days.	The Pediatric Investigation Plan should be submitted early during product development and not later than ending the PK studies i.e., during phase 1 trials.	(44)

From a scientific and regulatory perspective, it is difficult to produce potential new medications to treat unmet medical needs and bring in market on quick basis. To encourage and promote such innovation expedite development program were introduced. The PRIME designation was launched in March 2016 by EMA with a primary goal of accessibility of important therapies more quickly and efficiently to the patient (37). PRIME scheme was restricted to products being developed and to be approved in EU through centralized pathway. Some of the tools associated to PRIME are scientific advice, conditional approval and accelerated assessment, which formerly existed but have coalited with the PRIME designation and function independently too, these have been discussed in detail in Table 2. The products under the PRIME scheme, designations such as orphan and pediatric are authorized centrally but on the other hand the customized cell products which are also called as Hospital Exempted (HE) products are authorized by member state (38). As per the provision of Article 28 of Regulation 1394/2007/EC (39), the member state holds the responsibility of national traceability, pharmacovigilance, and quality criteria for HE products. This exemption of centralized evaluation also exempts the need for submission of marketing authorization application (MAA) to CAT and CHMP for evaluation. (31,39) The detailed overview of features of PRIME scheme, various designations and HE exemptions are given in table 2.

As per the CAT quarterly highlights and approved ATMPs report of January 2023, a total of 116 ATMPs were listed down from 2016 till 2023. Among these 116, total off 50 ATMPs were granted with the PRIME eligibility. (32)

EMA acknowledges ATMP market's challenges of high development costs, dedicated facilities, and complex regulatory processes. However, recognizing these challenges EMA is actively engaged in efforts to tackle them and provide support for development of new and innovative ATMPs. (45)

4. Regulations specific to Japan

In Japan, cellular products are referred to as Regenerative medicinal products. Similar to US and Europe even Japan don't have separate regulations for stem cell products but are in coalition with gene therapy products. The overseeing of regenerative medicine in Japan is primarily done by the Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA). PMDA operates under MHLW and is entrusted for making recommendations for approval to the MHLW and evaluating the safety and efficacy. (46) Back in 1995, Japan faced criticism regarding unorganized regulatory framework which was highlighted in the report published by *Nature medicine*. However, as an answer to it Japan has made significant strides in its regulatory structure over the past 20 years.

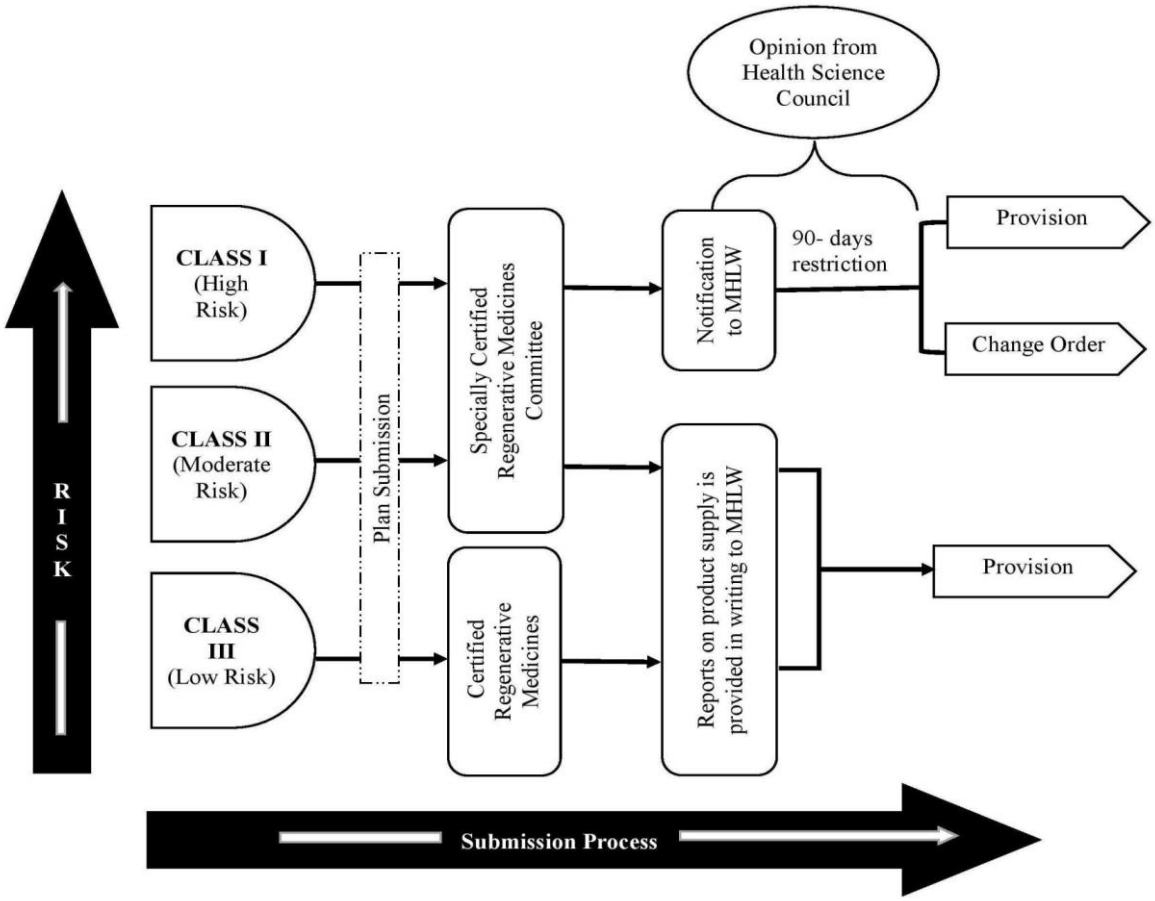

Figure 3. Illustration of flow of regulatory procedure for various classes of regenerative medicine in Japan. MHLW, Ministry of Health, Labour and Welfare

Table 3. Regulatory tools and Expedited programs for regenerative medicines by PMDA.

Program	Eligibility Criteria	Status	Benefits	PMDA Response timeline	When to submit	Reference
Sakigake Designation	• The innovative product must be first developed and approved in Japan. • Must show prominent effectiveness in comparison to existing therapy.	Designation	• Consultation for clinical trial on priority basis with reduction of in wait time from 2 months to 1 month. • Pre-application consultation • Abbreviated review time from 12 months to 6 months, post the result of phase 3 trials. • An assigned manager as concierge for entire process • Extension in the re-examination period during the post marketing surveillance • Coalition with scientific expert.	The initial result by Evaluation and Licensing Division (ELD) is notified within 30 days whereas review opinion by PMDA comes within 60 days	Request to be submitted as early as possible or in early phase of clinical trial (phase1 or 2a).	(52)
Conditional and term limited approval	• Medicine must address unmet requirement of medical field • Promising anticipation of results based on the early trial data (Safety and Efficacy). • The post marketing surveillance must be conducted for standard approval within predetermined period • Positive benefit to risk ratio	Conditional approval. Valid for not more than 7 years. [NAGAI]	• Evaluation of Safety and efficacy in shorter time compared to existing process • Accelerated approval timeline based on limited data • Early access of treatment to the patient	PMDA	During early phase of clinical study based on safety and efficacy data	(53)
Orphan Designation approval	• The products are anticipated to be utilized by less than 50,000 patients and MHLW designated for priority review. • Medicine indicated for serious disease or condition	Designation	• Priority review • Abbreviated review time from 12 months to 9 months. • Market exclusivity of 10 years • Financial incentives		During early phase of clinical study based on safety and efficacy data	(53)

To establish a clear national strategy for regenerative medicine, The Regenerative Medicine Promotional Act in association of two acts, those are a) Act on the Safety of Regenerative Medicine (RM Act) and b) Amended Pharmaceutical Affairs Law (PAL), also known as the Pharmaceuticals and Medical Devices Act (PMD Act) were enacted in May 2013. (47) The RM and PMD acts were introduced in 2013 and enforced officially in 2014, basically in relation to the significant changes to the conditions for the clinical application. (48) Prior until now, clinical research using human stem cells was subject to just one main set of guidelines "Guidelines on Clinical Research Utilizing Human Stem Cells" but however now researchers have to comply with the RM Act and its provision in delivery of regenerative medicine which has been mandated in November 2014. Also, the RM Act covers both private practice and clinical research while the PMD Act focuses on the early market access. (47) In September 2015, TEMCELL HS Inj, the first stem cell product was given approved under the RM Act, which is a Human (allogeneic) bone marrow-derived mesenchymal stem cell. (49) This milestone approval is considered a breakthrough in the domain of regenerative medicine in Japan, as it holds the distinction of being the initial stem cell product being commercially viable.

4.1 Regulatory Structure

Generally, every country has regulations for stem cells, aimed at improving disease conditions with limited product alterations, and offers expedited programs for faster patient access. However, Japan sets itself apart by the implementation of a unique format of classification of regenerative medicines, similar to how most of the countries have a risk-based classification for medical devices. The products are classified in a descending order Class I (highest risk), including novel cells like iPSCs, genetically modified embryonic stem cells, and xenogeneic/allogenic cells. Class II comprises cell therapies with somatic stem cells or cultured cells, while Class III includes cell therapies using somatic and non-cultured cells (low risk). (46) The classification determines the level of regulatory oversight i.e., shown in Figure 3, including requirements for clinical trials, regulating committee and approval processes. (50,51)

Similar to other regulatory agencies, Japan has an expedited program known as the SAKIGAKE Designation for innovative products. This designation encouraging R&D and early clinical research/trials in Japan by providing priority consultations, evaluations, and reviews for novel medical products with potential considerable efficacy to address unmet medical needs. (52) Various regulatory tools such as orphan designation and conditional approval, also do exist in Japan to accelerate the approval and market entry, the features of various such tools are explained briefly in table 3.

As of May 2023, Japan has 18 Regenerative medicinal products approved. (53) According to a recent report regenerative medicine as of March 2023 is valued at ~¥25 billion (~$185.5 million) and is expected to reach ¥1.1 trillion ($8.2 billion) by 2040. (54) Japan's regulatory framework is considered relatively permissive compared to other countries but gathering treatment data and evaluating regenerative medicine therapies' efficacy and safety remains crucial. As continuous improvement and safety assurance is still the need of time.

5. Regulations specific to India

India has established separate set of guidelines for research and therapy oriented to stem cells, unlike other countries which have combined regulation for stem cell and gene therapy. As per the Drugs and Cosmetics Act of 1940, stem cells and their derived substances are denoted as "drugs" and designated as Investigational New Drug (IND) when used for medical treatment. (55) To regulate the ethical and safe utilization of stem cells first attempt was made by the Indian Council of Medical Research (ICMR) and Department of Biotechnology (DBT) collectively in 2007. A Comprehensive set of regulations governing the research and therapy using Stem cells was developed. (56) This guideline when firstly prepared had to go through subsequent revisions in 2013 and 2017. In 2007 the guideline was titled as "Guideline for Stem Cell Research and Therapy" which was revised and retitled as "Guideline for stem cell Research" in 2013 as till then no therapies were proven for its efficacy therefore stem cell therapy was not considered as therapy or a way of cure. (57) The subsequent revision of 2017, the "National Guideline for Stem Cell Research" was prepared considering the scientific and technological developments as well as the associated challenges. (58) In India, the Central Drugs Standard Control Organization (CDSCO) is entrusted for approving Stem cell products, while various screening committees including the Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC), Technical Committee and apex Committee which play very crucial role in the evaluation process. (59) In India the only approved use of stem cell treatment is restricted to hematopoietic stem cell transplantation (HSCT) for hematological diseases and not for any other indication. Notably, the very first successful allogenic Bone marrow transplant was done in India took place in 1983. (60) However, the very first patented stem cell product to get market clearance by the Drug Controller General of India (DCGI) is Stempeucel received its approval in 2016. It is indicated for the treatment of critical limb ischemia and knee osteoarthritis. It is also being explored for various other indications as Diabetic foot ulcer, acute respiratory distress syndrome (ARDS) due to Covid-19 later pneumonia in severe cases and; Platelet Activating Factor (PAF) due to Crohn's disease. Stempeucel® has been successful in the phase II trials by showing promising results in the mentioned indications. Stempeucel® is anticipated to be available in market by 2024 with DCGI's approval. (61,62)

5.1 *Regulatory Structure*

In India back in 2013 an additional review measures by establishing two review committees: the Institutional Committee for Stem Cell Research (IC-SCR) and National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) they were introduced as a second layer of oversight to oversee stem cell research on both institutional and national scales. (63) Institutional Committee for Stem Cell Research (ICSCR) and Institutional Ethics Committee (IEC) registration is

necessary for organizations carrying out research or clinical trials on stem cells. Additionally, the involved facilities are mandated to be certified with Good Manufacturing Practices (GMP) and Good Laboratory Practices (GLP) as well as they must be mandatorily registered with NAC-SCRT and CDSCO. Clearance from CBBTDEC, IC-SCR and NAC-SCRT for conduction of clinical trial is must. (64,65) The guideline also describes about the minimal, substantial and major manipulation of stem cells as well as points out the restricted, prohibited and permitted research activities. In India, the transplantation of minimally manipulated homologous stem cells is allowed only for certain hemopoietic diseases for which prior approval is not required, these permitted diseases are listed down in Annexure III of the guideline. For the diseases that are not listed down they require IC-SCR, IEC and CDSCO approval even if it's a concurrent trial taking place in India. Products are also eligible for conditional market approval until phase IV stage, which are continued only if found satisfactory. (58,59) The Research using newly established embryonic stem cell/induced pluripotent stem cell (iPSC) lines is "permissible" whereas establishment of Embryonic Stem cell (ESC) lines using in vitro fertilization (IVF), intracytoplasmic sperm injection, and somatic cell nuclear transfer in preimplantation human embryos is considered as "restrictive" research. Certain research involving genome modified human embryo, reproductive cloning, germ line gene therapy, xenogeneic cells or Xenogeneic-Human hybrids, animal breeding with human stem cells are completely prohibited. (55) With this the usage of stem cells for human administration is permitted only in the context of clinical trial and nowhere else. (66)

India's regulations are still in making whereas the existing ones are lacking behind in governance due to its regulatory loopholes i.e., no strict supervision against the illegal stem cell treatment offerings. However, it will take time but eventually there will be proper set of regulation along with proper enforcement of those regulation. As the SCR criteria are always changing, and stronger provisions will always be needed in accordance with shifting worldwide norms.

6. Stem Cell Tourism

Stem Cell tourism is an unethical practice where in the patient travels from a country to another to receive unproven and unapproved stem cell therapies in the hope of getting better or cured. The hope associated with the endless capacity of stem cells cannot be denied and also holds truth in some sense but this hope often eclipses the need to acknowledge the downside of these unproven and unapproved therapies. The hope of being cured is so high that it often blinds to see the importance of evidence-based medicine, thorough scientific assessment and regulatory oversight before opting for such treatment. (67) Cure and betterment in the cases of neurological condition, cardiovascular diseases, diabetes, cosmetics etc. is been highly promoted. (68) These markets of stem cell tourism thrive on false advertisement and therapies those are promoted as a sure fire solution for indications which are neither officially approved nor have ever been part of any clinical trial conduct. (69) Additionally, countries that promote such unproven therapies are those whose regulations are either unclear or not in place. The countries leading the race of offering such unethical treatments are Canada, United States (US) and United Kingdom (UK) whereas Mexico, India, Thailand, Malaysia and Singapore are the destination for medical tourism. (67,70) Thailand excels in affordable clinical services and tourism amenities, but competes with Japan, South Korea, and Malaysia for regional dominance and attracting patients worldwide. (70) Herein, globalization plays a huge role by not restraining regional constrain. In spite of such unethical conduct happening all over the world this industry is still booming in billon dollars. The major reason behind the difficulty to track and regulate this sector can be said as is its reliance on online operation. (67,71) The challenge that arises with tracking is the emergence of a new clinic on the shutdown of other, this being a never-ending cycle. (71) According to a study more than 400 websites are offering such stem cell-based treatments for a broad spectrum of condition also another study examined 21 countries across 5 continents were virtually offering and promoting therapies. (67,72)

Despite the enormous promise of stem cell treatment, it is critical to address the issue of inflated expectations around it. Its use must be clearly constrained in order to guarantee that it is exclusively applied for recognized and approved treatments only. There is immense need to educate physician, scientist and patient about the benefits and risks (most importantly the risks). Along with this it's necessary to take crucial steps to address the legislative loophole in order to protect patients by being tricked in the hope of cure and to regulate effectively. (67)

7. Safety and Ethical Viewpoint

The innate propensity of stem cells to branch out into diverse cell types holds huge opportunities in the fields of regenerative medicines, drug discovery as well as disease modelling. However, this brings with it a very sensitive issue i.e., ethical and safety consideration which necessarily have to be addressed to ensure morally responsible practices. As with the discussion of ethics it brings multiple tangents of sensitive concerns along with it such as protection of human rights and dignity, responsible research, maintenance of public trust, assured safety and efficacy post the treatment etc. These concerns have arisen due to versatility of hESC's pluripotency which has become a positive as well as negative, on one hand a single cell type can be created into distinct cell types whereas on the other hand its highly difficult to manage their behaviour due to high tumorigenic property. (73) The usage of ESCs has always been a debatable as well as a controversial topic, some say and believe that according to moral perspective embryos are as valuable as a living individual even they do hold a moral status and should not be exploited in the name of scientific research or advancement. On the other side some people also believe utilization of extra spare In-Vitro Fertilization (IVF) embryo which will anyway be killed or destroyed is lesser disrespectful, well there is no end to this discussion. (74) While considering the right and dignity of an individual but also the urge to pursue scientific advancement, researchers are moving towards and exploring the usage of iPSCs which works as an alternative to hESCs. These are morally superior due no destruction of embryos and

meanwhile are striking balance between scientific progression and ethical consideration. However, even with the use of iPSCs the assurance of safety and effectiveness when seen on long-term basis is still questionable. (73) Anyhow, this is a never-ending ethical debate where there no definite answer can be quoted, as science do holds importance but it can't overweigh the rights and dignity of an individual. Additionally, being a complex ethical, scientific, and cultural issue, this argument thus requires a thoughtful discussion and new firm harmonized regulations.

Table 4. Summarisation of Regulatory framework of US, EU, Japan and India as discussed in this article.

Sr. no.	Parameters	United states	European Union	Japan	India
1.	***Cell based products are referred as-***	HCT/Ps, Human cells, tissues, and cellular and tissue-based products	ATMPs, Advanced therapy medicinal products	Regenerative Medical Products	Stem Cells & Cell Based products (SCCPs)
2.	***Classification***	A. Minimally manipulated B. More than minimally manipulated	A. GTMP, Gene therapy medicinal product; B. sCTMP, Somatic cell therapy medicinal product; C. TEP, Tissue-engineered product	A. Class I - high risk B. Class II - medium risk C. Class III - low risk''	A. Restrictive B. Permissive C. Prohibited
3.	***Regulating body***	CBER, FDA	CAT, EMA	PMDA	CBBTDEC, CDSCO
4.	***Expedite Program***	Breakthrough, Fast track and Regenerative Medicine Advanced Therapy(RMAT) Designation	Priority Medicines (PRIME) Scheme	Sakigake Designation	-
5.	***Approval Timeline***	10 months (Standard assessment), 6 months (Priority review)	210 days (Standard assessment), 150 days (accelerated assessment)	10 months (Standard assessment), 6 months (Priority review)	Not Specified
6.	***Conditional approval***	Accelerated Approval	Conditional Marketing Authorization	Conditional and term limited approval	Conditional Approval
7.	***Orphan & Pediatric Designation***	Present	Present	Present	Absent
8.	***Informed Consent***	Written consent Required	Written consent Required	Written consent Required	

8. Conclusion

While countries may vary in terms of their progress and specific regulations, the fundamental principle regarding the use of embryonic stem cells remains consistent: there are restrictions with the usage of embryonic cell lines and minimal manipulation of the cell line. When legislation is examined on a country-by-country basis, it becomes apparent that the United States, European Union, and Japan share some similar approaches beyond manipulation restrictions which is there in India too. These include the implementation of expedited schemes and additional tools such as conditional or accelerated approval systems. A comparison of the legal framework of the four nations is presented in Table 4. It draws attention to the parallels and discrepancies between respective regulatory structures.

Despite the existence of regulations in each country, concerns regarding the lack of clarity and effective enforcement of these regulations still persist. This situation raises the issue of potential malpractice and unethical practices within the domain of research and therapy of stem cell such as operation of unapproved clinics, the emergence of stem cell tourism, the promotion of openly marketed cell therapies, and the unfortunate consequences of patients undergoing unproven and potentially harmful treatments. Therefore, an urgent and imperative need exists for a comprehensive and harmonized regulatory framework with robust measures, including stringent enforcement actions and penalties that effectively addresses these concerns is required. In order to secure the future of regenerative medicine, it is crucial to put patient's safety first while promoting the growth of rigorous, evidence-based stem cell research.

Expert Opinion

The review paper delves into the intricate realm of stem cell regulations across the United States, the European Union (EU), Japan and India, while also highlighting on

the practice of stem cell tourism. This comprehensive approach will serve as a valuable resource for researchers, policymakers, and healthcare professionals worldwide, offering a well-rounded understanding of the multifaceted landscape surrounding stem cell research and therapy. Addressing ethical consideration linked to both stem cell tourism, research, conduct and consequences of these unregulated treatments, this paper will actively contribute to ongoing global conversations on patient safety and ethical standards. Furthermore, it will be useful for education and awareness campaigns and will emphasize on better policy making with reduction in unapproved stem cell tourism that's happening. This paper will serve as a catalyst for positive change in this dynamic field.

Key areas for improving stem cell regulations in the United States, European Union, Japan, and India, as well as addressing challenges associated with stem cell tourism, encompass a range of critical considerations. This includes the need for standardized international regulations and harmonization efforts to ensure consistency in stem cell research and therapy practices. Enhancements in ethics, informed consent procedures, and rigorous oversight are crucial for safeguarding patient rights and safety. Promoting transparency in clinical trials, increasing public awareness, and educating healthcare professionals as well as the citizens are essential steps in creating a more informed ecosystem. Additionally, the establishment of accreditation programs, international collaboration, and mechanisms for monitoring and adapting to scientific developments are vital for fostering responsible stem cell research and therapy while combating the risks posed by unregulated stem cell tourism.

More study in this area can serve as a foundation for more informed policymaking, ensuring that regulations strike a balance between stimulating innovation and safeguarding ethical standards and patient safety. It can also contribute to the evolution of ethical guidelines, enhance patient safety by identifying risks associated with best regulatory practices. Moreover, research can drive regulatory innovation to adapt to scientific advancements, educate both the public and healthcare professionals.

In the next upcoming years, we can anticipate several noteworthy developments in stem cell regulations across the world, as well as in the context of stem cell tourism. International collaboration and efforts to standardize regulations may gain traction, fostering consistency in stem cell research and therapy practices globally. Ethical considerations are expected to evolve in response to scientific advancements, while streamlined approval processes may expedite the clinical translation of well-established stem cell therapies. To counter the risks associated with stem cell tourism, regulatory agencies may intensify oversight and introduce stricter penalties for non-compliant clinics. Furthermore, the heightened awareness of data privacy and security concerns in the context of patient information and genetic data may lead to enhanced regulatory measures. Increased research funding, continued public education initiatives, and the potential for international guidelines for stem cell tourism all contribute to a dynamic regulatory landscape poised for evolution in the coming years.

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