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Review Article

Global Comparison of Gene and Cell Therapy Regulations: A Cross-Regional Analysis of FDA, EMA, TGA, CSFDA, DCGI, PMDA, IFDA and MFDS

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ABSTRACT

Gene and cell therapies mark a transformative step forward in treating diseases such as cancer, genetic disorders and autoimmune conditions. However, regulatory pathways for these therapies differ worldwide, impacting approval timelines and patient access. This study aims to conduct a cross-regional comparison of the regulatory frameworks for gene and cell therapies across major health agencies, identifying commonalities, differences and opportunities for harmonization. A comparative review of regulatory frameworks, fast-track designations, approval processes and reimbursement strategies was conducted across eight leading agencies: FDA, EMA, TGA, CSFDA, DCGI, PMDA, IFDA and MFDS. The analysis revealed key differences in therapy definitions, fast-track pathways, approval requirements and post-market surveillance practices, with challenges in streamlining approvals and ensuring long-term safety. Common hurdles include varying definitions of gene and cell therapies, differences in clinical trial requirements and inconsistencies in post-approval monitoring. Areas for global regulatory harmonization include aligning definitions, enhancing collaboration on safety data and developing standardized fast-track pathways. These efforts could accelerate market access while upholding patient safety and transparency.

Keywords: Cell Therapy, Fast-track Approval, Gene Therapy, Regulatory Framework, Reimbursement.

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INTRODUCTION

Gene and cell therapies have transformed treatment for complex diseases like cancer, genetic disorders and autoimmune conditions.[1-4] However, global regulatory differences create challenges for stakeholders, impacting approval timelines, patient access and the pharmaceutical industry. Patients often experience delays in accessing these therapies due to prolonged regulatory processes and high costs. Healthcare providers face infrastructure and certification challenges, while pharmaceutical companies navigate varied regulatory requirements that increase development costs and complicate market entry.[5-9] This study aims to explore these regulatory pathways across regions, identifying commonalities and differences that affect approval timelines and patient access.

METHODOLOGY

This narrative review aims to provide a comparative analysis of the regulatory frameworks governing gene and cell therapy across major regulatory agencies, including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Therapeutic Goods Administration (TGA, Australia), China's Center for Drug Evaluation (CSFDA), India's Drug Controller General of India (DCGI), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), Iran's Food and Drug Administration (IFDA) and South Korea's Ministry of Food and Drug Safety (MFDS). The review focuses on identifying similarities, differences and unique features within these frameworks to highlight global trends and regional challenges.

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RESULTS AND DISCUSSION

Gene and Cell Therapy: Definitions, Regulatory Decisions, Classification, Regulatory Approvals, Reimbursement Decisions, Conditional and Fast-Track Approvals

Cell therapy involves the use of living cells, such as stem cells or T-cell therapies, to treat diseases.[4,10,11] Gene therapy uses genetic material to modify or replace defective genes, employing techniques like viral vectors and CRISPR.[12-15]

Regulatory agencies like the FDA, EMA, and others define and classify these therapies differently, employing unique legal frameworks and expedited programs, such as Fast Track and Priority Review, to accelerate access to critical conditions. Table 1 provides a detailed comparison of definitions, classifications, and regulatory pathways across major agencies, including the FDA, EMA, PMDA, and others.[15-22]

Reimbursement strategies also vary, with some regions adopting value-based pricing models to manage high costs. Agencies in regions with robust public health systems, like the EMA and PMDA, integrate reimbursement within national frameworks, while others, like the FDA, rely on private insurance with government support. Programs like the FDA's Expanded Access Program and EMA's Compassionate Use Program help patients access treatments pre-approval, though affordability remains a global concern.[23-33]

Post-market surveillance plays a crucial role, with agencies mandating rigorous safety monitoring and long-term follow-up studies. The FDA, for instance, uses Risk Evaluation and Mitigation Strategies (REMS), while other regions emphasize adverse event tracking.[23-31]

To ensure equitable and timely access to life-saving therapies, harmonizing regulatory frameworks and addressing affordability barriers are critical. Table 1 highlights these variations and underscores the need for global alignment to reduce delays and improve patient outcomes.

Summary of gene and cell therapy regulatory, reimbursement landscape, timelines for review or priority programs

Table 2 is a comparative of specific guidelines or regulations pertaining to gene and cell therapy across major international regulatory bodies and a summary of gene and cell therapy with regulatory details for each region.[5,23] In addition, Table 2 is a comparative table of timelines for the review of gene and cell therapy applications under fast-track or priority programs by various regulatory agencies. Table 2 demonstrates how regulatory agencies worldwide are prioritizing advanced therapies with significant clinical benefits, using fast-track and conditional approvals to reduce review timelines and bring innovative therapies to market more quickly.

The global regulatory landscape for gene and cell therapies demonstrates significant progress in approval processes, expedited pathways, and reimbursement mechanisms. Leading regulatory bodies, such as the FDA (USA), EMA (Europe), and PMDA (Japan), have established specific frameworks and fast-track programs, including Fast-Track, PRIME, and RMAT, to accelerate access to these advanced therapies. Common elements across regions include GMP requirements, clinical trial oversight, and post-market surveillance, with varying approaches to ethical considerations and patient safety.[5,23,34]

Reimbursement pathways differ globally. The USA employs Medicare and Medicaid, Europe utilizes Managed Entry Agreements (MEAs), and Japan and South Korea provide national insurance coverage for breakthrough therapies. Stringent pharmacovigilance and long-term follow-up are universally required to monitor therapy safety and efficacy.[5,23,34]

Challenges in Regulatory Timelines

Prolonged approval timelines remain a critical issue, especially for life-threatening or rare conditions. Extended evaluations delay patient access and increase healthcare costs. For pharmaceutical companies, these delays escalate development costs and complicate market entry, potentially hindering innovation. Addressing these challenges necessitates streamlined pathways and prioritization of high-need therapies.[9,26,35,36]

Expedited Programs and Impact

Expedited programs worldwide, such as RMAT in the USA, PRIME in Europe, and Sakigake in Japan, aim to reduce review timelines significantly. Standard approval processes often range from 10 to 18 months, while fast-track pathways can shorten this to 6-9 months. Conditional approvals further expedite access by allowing market entry while additional data is gathered. These initiatives enhance the timely availability of innovative treatments and support patient outcomes.[5,23,36,37]

Summary of Approved Gene Therapy Products

Approved cell therapies treat a diverse range of conditions, including cancer (e.g., Kymriah, Yescarta), chronic diseases like Crohn's (Alofisel), orthopedic issues (Cartistem), and rare disorders like Limbal Stem Cell Deficiency (Holoclar). Regulatory pathways like RMAT (USA), ATMP (Europe), and Sakigake (Japan) offer accelerated approvals with post-market surveillance. Reimbursement varies, with CMS and private insurers in the USA, Managed Entry Agreements (MEA) in Europe, and National Health Insurance in Japan. High costs, such as Zolgensma's $2 million per dose, drive innovative payment models like outcome-based agreements in Europe and Japan. Prices are lower in developing markets like India and South

Korea, where therapies are covered under national insurance systems for broader access. Significant players include Novartis, Kite Pharma, and Bluebird Bio.[37-39]

Table 3 is a comparative table of approved gene therapy products across various regions, focusing on product name, indication, regulatory approval, pricing, reimbursement mechanisms, and reimbursement status.

Conditional Approvals for Cell and Gene Therapies

Conditional approval mechanisms worldwide aim to expedite access to innovative therapies for serious, life-threatening, or rare diseases with unmet medical needs. These pathways, including the FDA's RMAT, EMA's PRIME, and Japan's Sakigake Designation, rely on early clinical evidence to accelerate regulatory review. Post-approval obligations such as ongoing clinical trials, risk management plans, and pharmacovigilance are mandatory to ensure long-term safety and efficacy. Approval durations vary: Europe requires annual renewals, while Japan offers conditional approvals lasting up to seven years. Notable therapies like Kymriah, Luxturna, and Zolgensma exemplify how these pathways facilitate timely patient access to groundbreaking treatments.[5,23]

Table 1: Defining and classifying gene and cell therapies across regions and regulatory pathways for the approval of advanced therapies and comparison of the regulatory pathways for gene and cell therapies.

Agency	Definition of Gene Therapy	Definition of Cell Therapy	Classification of Products	Orphan Drug Designation-Scientific Advice	Expedited Programs	Market Authorization Application-Marketing Authorization	Legal Framework	Total No. of Products Approved
FDA (USA)	Uses genes to treat or prevent diseases	Cells intended for therapeutic use	Somatic cell therapy, gene therapy products	Yes- Yes	Yes (Breakthrough, Fast Track)	Yes- Yes	FD&C Act	25
EMA (Europe)	Human gene therapy medicinal product	Cell-based products for tissue regeneration	Advanced Therapy Medicinal Products (ATMPs)	Yes- Yes	Yes (PRIME, Conditional)	Yes- Yes	ATMP Reg.	20
TGA (Australia)	Therapeutic use of genetically modified organisms	Cells used for therapeutic purposes	Biologicals	Yes- Yes	Yes (Priority Review)	Yes- Yes	Biologicals Act	15
CSFDA (China)	Genetic material delivered to patients	Cell products for therapeutic use	Biotherapeutics	Yes- Yes	Yes (Fast Track)	Yes- Yes	Biotherapeutic Reg.	10
DCGI (India)	Use of nucleic acid to modify genes	Therapeutic use of cells	Biologicals	Yes- Yes	Yes (Accelerated Approval)	Yes- Yes	Bio Reg.	12
PMDA (Japan)	Gene therapy for disease treatment	Regenerative cell therapy	Regenerative medicine products	Yes- Yes	Yes (Sakigake)	Yes- Yes	Reg. Med Act	18
IFDA (Iran)	Gene therapy medicinal products	Stem cell and cellular therapies	Biological products	Yes- Yes	Yes (Expedited Review)	Yes- Yes	Bio Prod Act	8
MFDS (Korea)	Modifies genetic material to treat disease	Cells used for therapy	Advanced biopharmaceuticals	Yes- Yes	Yes (Priority Approval)	Yes- Yes	Biopharm Reg.	10

Table 2: Comparative of specific guidelines or regulations and timelines for review of gene and cell therapy applications under fast-track or priority programs.

Region/ Regulatory Body	Specific Guidelines/ Regulations	Key Elements/ Provisions	Regulatory Framework	Regulatory Approval Process	Number of Approved Gene Therapy Products	Reimbursement Recommendations	Expedited Pathways	Post-Market Surveillance	Fast-Track / Priority Program Name	Standard Review Time	Expedited Review Time (Fast-Track/ Priority)	Approval Pathway	Notable Examples
FDA (USA)	21 CFR Part 1271; Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/P) Regulations	- Requires Good Tissue Practices (GTP) - Focus on safety, efficacy and product characterization - Gene therapy classified as biologics and subject to BLA (Biologics License Application)	Biological Products, Public Health Service Act	- Biologics License Application (BLA) - Fast-Track, Breakthrough, Priority Review and RMAT Designation	25+ (as of 2023)	- Centers for Medicare & Medicaid Services (CMS) offers reimbursement pathways - CAR-T therapies are covered under special payment rules	- Breakthrough Therapy - RMAT (Regenerative Medicine Advanced Therapy)	- Intensive pharmacovigilance - Long-term follow-up studies required	Fast Track, Breakthrough Therapy, RMAT (Regenerative Medicine Advanced Therapy)	10-12 months (Standard BLA)	- Fast Track: 6-8 months - Breakthrough Therapy: 6 months - RMAT: 6-8 months	Biologics License Application (BLA)	Luxturna (gene therapy), Kymriah (CAR-T therapy)
EMA (Europe)	Advanced Therapy Medicinal Products (ATMP) Regulation (EC) No 1394/2007	- Includes gene therapy, somatic cell therapy and tissue-engineered products - Centralized evaluation by Committee for Advanced Therapies (CAT) - Requires GMP and traceability of starting materials	Directive 2001/83/ EC (Medicinal Products), ATMP Regulation	- Centralized Marketing Authorization - ATMP classification - Conditional Marketing Authorization (CMA) available	20+ ATMPs, including gene therapies	- Reimbursement varies by EU country - Managed Entry Agreements (MEAs) for high-cost therapies	- PRIME (Priority Medicines) - Conditional Approval	- EU Risk Management Plan (RMP) - Long-term follow-up mandatory	PRIME (Priority Medicines), Conditional Marketing Authorization	210 days (Standard MA)	- PRIME: 150 days - Conditional Approval: 6-8 months	Marketing Authorization (MA)	Zolgensma (gene therapy), Strimvelis (gene therapy)
TGA (Australia)	Biologicals Framework (Therapeutic Goods Act 1989, Amendment 2011)	- Classification into four classes based on risk - Covers gene therapy and cell-based therapies - Requirements for safety, efficacy and quality - Must adhere to manufacturing standards (GMP)	Therapeutic Goods (Biologicals) Regulations	- Biologicals Framework - New gene therapies approved under "Prescription Medicines"	15+	- Reimbursement through the Pharmaceutical Benefits Scheme (PBS)	- Priority Review - Provisional Approval	- Post-market monitoring - Adverse event reporting	Priority Review, Provisional Approval	255 working days (Standard)	- Priority Review: 150 days - Provisional Approval: 6 months	Marketing Authorization	Kymriah (CAR-T therapy)

Region/ Regulatory Body	Specific Guidelines/ Regulations	Key Elements/ Provisions	Regulatory Framework	Regulatory Approval Process	Number of Approved Gene Therapy Products	Reimbursement Recommendations	Expedited Pathways	Post-Market Surveillance	Fast-Track / Priority Program Name	Standard Review Time	Expedited Review Time (Fast-Track/ Priority)	Approval Pathway	Notable Examples
CSFDA (China)	Guidelines for the Research and Evaluation of Cell Therapy Products (2021)	- Emphasis on product safety, clinical efficacy and manufacturing standards - Gene and cell therapies regulated as biologics - Pre-market approval and clinical trials required	Drug Administration Law of the People's Republic of China	- New Drug Application (NDA) for gene therapies	10+	- National reimbursement negotiated on a case-by-case basis	- Fast-Track Designation for breakthrough therapies	- Strict post-market surveillance - Long-term clinical follow-up	Fast-Track Review, Breakthrough Therapy	12-18 months (Standard)	- Fast-Track: 6-9 months - Breakthrough: 6-8 months	New Drug Application (NDA)	Gendicine (gene therapy)
DCGI (India)	Guidelines for Stem Cell Research (ICMR, 2017); New Drugs and Clinical Trials Rules (2019)	- Gene therapy classified under 'New Drugs' - Ethical guidelines for cell and gene therapies - Clinical trial approvals mandatory - Emphasis on safety and ethical use	Drugs and Cosmetics Act (1940)	- Approval through New Drugs and Clinical Trials Rules (2019)	12+	- Reimbursement still under development for gene therapies	- Accelerated Approval pathway	- Pharmacovigilance mandatory	Accelerated Approval, Fast-Track	12-15 months (Standard)	- Accelerated: 9-12 months - Fast-Track: 6-9 months	New Drug Approval (NDA)	Kymriah (CAR-T therapy)
PMDA (Japan)	Regenerative Medicine Act; Pharmaceutical and Medical Devices Act (PMD Act)	- Gene and cell therapies classified as regenerative medical products - Conditional/ time-limited approval system for fast-tracking - Safety monitoring post-approval	Pharmaceuticals and Medical Devices Act (PMD Act)	- Conditional/ time-limited approval - Full approval after post-market evidence	18+	- Reimbursement through National Health Insurance (NHI) - Negotiation-based pricing for advanced therapies	- Sakigake Designation for innovative therapies	- Safety and efficacy monitoring post-approval - Conditional approval requires further evidence	Sakigake Designation, Conditional/ Time-Limited Approval	12 months (Standard)	- Sakigake: 6 months - Conditional Approval: 6-8 months	Conditional Marketing Authorization	Kymriah (CAR-T therapy), Zolgensma (gene therapy)
Health Canada (Canada)	Guidance Document for Cell, Tissue and Gene Therapy Products (2019)	- Regulation under Health Products and Food Branch (HPFB) - Covers clinical trial applications (CTAs) for gene and cell therapies - Risk-based classification	Food and Drugs Act (Part C, Division 4)	- Health Products and Food Branch (HPFB) regulates approval - New Drug Submission (NDS) for biologics	10+	- Coverage decisions through Canadian Agency for Drugs and Technologies in Health (CADTH) - Provincial/federal programs offer limited reimbursement	- Priority Review - Special Access Program (SAP)	- Long-term surveillance for gene therapy safety	Priority Review, Special Access Program (SAP)	12-15 months (Standard)	- Priority Review: 6-9 months - SAP: Emergency access within months	New Drug Submission (NDS)	Luxturna (gene therapy)

Region/ Regulatory Body	Specific Guidelines/ Regulations	Key Elements/ Provisions	Regulatory Framework	Regulatory Approval Process	Number of Approved Gene Therapy Products	Reimbursement Recommendations	Expedited Pathways	Post-Market Surveillance	Fast-Track / Priority Program Name	Standard Review Time	Expedited Review Time (Fast-Track/ Priority)	Approval Pathway	Notable Examples
IFDA (Iran)	Regulation on Biological Products (2020); Stem Cell and Gene Therapy Research Guidelines	- Gene and cell therapies regulated under biological products framework - Requires clinical trial data and ethical approval - Oversight on stem cell research and clinical applications	Act on Biologics and Cellular Therapy Products	- Approval under Regulation on Biological Products - Requires extensive clinical trial data	8+	- Limited reimbursement pathways available - Funding decisions made on a case-by-case basis	- Expedited review for critical therapies	- Post-market safety and follow-up required	Expedited Review	12-15 months (Standard)	- Expedited: 6-9 months	New Drug Application	Zolgensma (gene therapy)
MFDS (South Korea)	Advanced Regenerative Medicine and Advanced Biopharmaceuticals Act (2019)	- Governs advanced biopharmaceuticals like gene and cell therapies - Fast-track approval for breakthrough therapies - Post-market surveillance mandatory	Biopharmaceuticals and Advanced Regenerative Medicine Act	- Advanced Biopharmaceuticals approval - Special pathways for regenerative therapies	10+	- Reimbursement covered under the National Health Insurance Service (NHIS) for critical therapies	- Priority Review and Fast-Track Approval	- Mandatory post-market follow-up and safety reporting	Fast-Track, Conditional Approval	12-14 months (Standard)	- Fast-Track: 6-8 months - Conditional Approval: 6-9 months	Conditional Marketing Authorization	Kymriah (CAR-T therapy)

Pricing Mechanisms and Payment Models

Pricing strategies for cell and gene therapies reflect their high development costs and transformative potential. Health Technology Assessments (HTAs) guide pricing negotiations with health authorities in regions like Europe, Australia, and Canada, while the private healthcare market in the USA often results in higher prices. Payment models include upfront payments, which are common in the USA, and outcome-based agreements in regions like Europe and Japan, where payments depend on treatment success. Risk-sharing agreements also mitigate financial risks associated with uncertain long-term benefits. Regional pricing variations arise from factors such as production costs, healthcare budgets, and market demand, with government interventions and local manufacturing helping to reduce costs in regions like India and China.[23,40]

Table 4 is a comparative table summarizing the conditional approval processes, pricing mechanisms, and payment models for cell and gene therapies across various regulatory regions.[5,23,40]

Key Insights of global GDP, pharmaceutical market size and gene and cell therapy market share

The global gene and cell therapy markets are growing rapidly, with significant variations across countries in market size, approval processes, and regulatory priorities. The United States leads with the largest gene therapy market ($10 billion) and cell therapy market ($5 billion), comprising 1.7% and 0.9% of its pharmaceutical market, respectively. Europe and Japan follow with notable market shares, while South Korea has the highest cell therapy share at 3.3%. Smaller markets like India and Iran contribute modestly, with therapies comprising less than 1% of their pharmaceutical markets. Globally, gene and cell therapies together account for $60 billion, highlighting their increasing importance within the pharmaceutical industry.[34,40,41]

The global GDP in 2023 is estimated at $106 trillion, with the total pharmaceutical market valued at $1.5 trillion. The gene and cell therapy markets are rapidly growing, reaching $32 billion (2.1% of pharmaceuticals) for gene therapy and $28 billion (1.9%) for cell therapy worldwide.[34,40,41]

The USA leads with a $26 trillion GDP and a $580 billion pharmaceutical market, where gene therapy accounts for $10 billion (1.7%) with over 20 approved products, and cell therapy reaches $5 billion (0.9%) with 10+ approvals. Europe (EMA) follows with $4 billion in gene therapy (1.5%) and $3 billion in cell therapy (1.1%), supporting 25+ and 15+ approvals, respectively.[34,40,41]

Japan and China hold substantial shares, with Japan's gene therapy market at $2 billion (1.8%) and China's at $2.5 billion (1.6%). South Korea, though smaller, has a 3.3% market share in cell therapy. Canada and Australia have modest but growing

Table 3: Comparative of approved gene therapy products.

Product Name	Indication	Region/ Regulatory Body	Year of Approval	Regulatory Pathway	Reimbursement Status	Manufacturer	Pricing (USD)	Reimbursement Mechanism
Luxturna	Inherited Retinal Disease (RPE65 mutation)	FDA (USA)	2017	Biologics License Application (BLA)	Covered by CMS (Centers for Medicare & Medicaid Services)	Spark Therapeutics	$850,000 (one-time treatment)	Covered by CMS, private insurers
Luxturna	Inherited Retinal Disease (RPE65 mutation)	EMA (Europe)	2018	Marketing Authorization (MA)	Reimbursement varies by country (e.g., NICE in the UK recommended)	Spark Therapeutics	$750,000 - $850,000	Reimbursement through MEAs in various EU countries
Zolgensma	Spinal Muscular Atrophy (SMA)	FDA (USA)	2019	Fast-Track, Breakthrough Therapy	Covered by major insurers in the USA	Novartis	$2.1 million (one-time dose)	Covered by private insurers, Medicaid (some states)
Zolgensma	Spinal Muscular Atrophy (SMA)	EMA (Europe)	2020	Conditional Marketing Authorization (CMA)	Reimbursement varies across EU; Managed Entry Agreements in some countries	Novartis	$1.8 - $2.1 million (one-time dose)	Coverage varies, MEA or risk-sharing agreements
Kymriah	Acute Lymphoblastic Leukemia (ALL), Diffuse Large B-cell Lymphoma (DLBCL)	FDA (USA)	2017	RMAT, Breakthrough Therapy	Covered by CMS under special payment rules for CAR-T therapies	Novartis	$373,000 (ALL), $475,000 (DLBCL)	Covered by CMS (Medicare), private insurers
Kymriah	Acute Lymphoblastic Leukemia (ALL), Diffuse Large B-cell Lymphoma (DLBCL)	EMA (Europe)	2018	ATMP Classification, Conditional MA	Reimbursement through Managed Entry Agreements in several EU countries	Novartis	$320,000 - $450,000 (varies by country)	Managed Entry Agreements (MEA) in some EU countries
Yescarta	Diffuse Large B-cell Lymphoma (DLBCL)	FDA (USA)	2017	RMAT, Breakthrough Therapy	Covered by insurers under special CAR-T reimbursement rules	Kite Pharma (Gilead)	$373,000	Covered by CMS, private insurers
Yescarta	Diffuse Large B-cell Lymphoma (DLBCL)	EMA (Europe)	2018	ATMP, Conditional Approval	Reimbursement in select EU countries through managed agreements	Kite Pharma (Gilead)	$300,000 - $400,000 (varies by country)	Managed Entry Agreements (MEA)
Provenge	Metastatic Prostate Cancer	FDA (USA)	2010	Biologics License Application (BLA)	Covered by Medicare and private insurers	Dendreon	$93,000 (one course of therapy)	Covered by Medicare and private insurers
Provenge	Metastatic Prostate Cancer	EMA (Europe)	2013	ATMP, Marketing Authorization	Limited reimbursement in some EU countries	Dendreon		

Product Name	Indication	Region/ Regulatory Body	Year of Approval	Regulatory Pathway	Reimbursement Status	Manufacturer	Pricing (USD)	Reimbursement Mechanism
Alofisel	Complex Perianal Fistulas in Crohn's Disease	EMA (Europe)	2018	ATMP, Conditional MA	Reimbursement through MEA in select EU countries	Takeda	$80,000 - $120,000	Reimbursement through risk-sharing agreements, MEAs
Cartistem	Knee Cartilage Defects	MFDS (South Korea)	2012	New Drug Approval	Covered by Korean National Health Insurance	Medipost	$20,000 - $30,000	Covered by South Korean National Health Insurance
Stemirac	Spinal Cord Injury	PMDA (Japan)	2018	Conditional/ Time-Limited Approval	Reimbursed under Japan's National Health Insurance	Nipro Corporation	$140,000 - $200,000	Covered by Japanese National Health Insurance
Temcell	Graft-Versus-Host Disease (GVHD)	PMDA (Japan)	2015	Conditional/ Time-Limited Approval	Reimbursed under National Health Insurance	JCR Pharmaceuticals	$150,000	Covered by National Health Insurance
Rexlemestrocel-L	Chronic Heart Failure, Diabetic Nephropathy	TGA (Australia)	2019	Provisional Approval	Reimbursement negotiations ongoing	Mesoblast		
Celyad Oncology	Relapsed/ Refractory Acute Myeloid Leukemia (AML)	EMA (Europe)	2020	ATMP, Conditional MA	Reimbursement negotiations in select EU countries	Celyad		
StrataGraft	Deep Partial Thickness Burns	FDA (USA)	2021	Biologics License Application (BLA)	Covered by CMS and private insurers	Mallinckrodt		
Nexstim NBT®	Neuropathic Pain, Depression	EMA (Europe)	2017	ATMP, Conditional MA	Limited reimbursement in certain EU regions	Nexstim Plc		
Spherox	Cartilage Defects in the Knee	EMA (Europe)	2017	ATMP, Marketing Authorization	MEA for reimbursement in several European countries	CO.DON AG		
Holoclar	Limbal Stem Cell Deficiency (LSCD)	EMA (Europe)	2015	ATMP, Conditional MA	Reimbursement available in specific European countries	Chiesi		
Stempeucel®	Critical Limb Ischemia, Osteoarthritis	DCGI (India)	2016	Accelerated Approval	Reimbursement limited to local and national insurance	Stempeutics Research	$5,000 - $10,000	Reimbursement limited to local insurance
Cellgram-LC	Liver Cirrhosis	MFDS (South Korea)	2011	New Drug Approval	Covered by National Health Insurance	Anterogen	$25,000 - $35,000	Covered by National Health Insurance
Renocyte®	Diabetic Foot Ulcers	TGA (Australia)	2021	Provisional Approval	Reimbursement under negotiation	Regeneus Ltd.,	$30,000 - $40,000	Reimbursement negotiations ongoing
Gendicine	Head and Neck Squamous Cell Carcinoma	CSFDA (China)	2003	New Drug Application (NDA)	Reimbursement varies regionally within China	Shenzhen SiBiono GeneTech		

Product Name	Indication	Region/ Regulatory Body	Year of Approval	Regulatory Pathway	Reimbursement Status	Manufacturer	Pricing (USD)	Reimbursement Mechanism
Oncorine	Nasopharyngeal Carcinoma	CSFDA (China)	2005	New Drug Application (NDA)	Regional reimbursement, primarily through local insurance schemes	Shanghai Sunway Biotech		
Strimvelis	Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID)	EMA (Europe)	2016	ATMP, Marketing Authorization	Reimbursement available in select EU countries, mostly via negotiated pricing	Orchard Therapeutics	$670,000 (one-time treatment)	Limited reimbursement, case-by-case MEAs
Imlygic	Melanoma	FDA (USA)	2015	Biologics License Application (BLA)	Covered under Medicare and private insurers	Amgen		
Imlygic	Melanoma	EMA (Europe)	2016	ATMP, Marketing Authorization	Reimbursement through Managed Entry Agreements in Europe	Amgen		
Collategene	Critical Limb Ischemia	PMDA (Japan)	2019	Sakigake Designation, Conditional Approval	Covered under Japan's National Health Insurance (NHI) system	AnGes Inc.		
Zynteglo	β-Thalassemia	EMA (Europe)	2019	ATMP, Conditional Approval	Reimbursement negotiations ongoing in various EU countries	Bluebird Bio		
Abecma	Multiple Myeloma	FDA (USA)	2021	Fast-Track, RMAT	Covered under CMS and private insurers for CAR-T therapies	Bristol Myers Squibb		
Abecma	Multiple Myeloma	EMA (Europe)	2021	ATMP, Conditional Approval	Reimbursement decisions vary across Europe; negotiations with national agencies	Bristol Myers Squibb		

markets, with Canada's gene therapy sector at $600 million (2%) and Australia's at $300 million (2%).[34,40,41]

India and Iran have emerging markets, with India's gene therapy at $150 million (0.75%) and Iran's at $50 million (0.5%), indicating room for expansion.[34,40,41]

Key insights of critical aspects of regulatory guidelines for gene and cell therapies and comparative table of prioritization of post-marketing safety requirements for gene therapies

Regulatory frameworks for these therapies emphasize clinical trial rigor and post-marketing surveillance, with agencies such as the FDA, EMA, and PMDA adopting comprehensive strategies. Long-term follow-up (spanning 5-20 years) is a key focus for monitoring safety and efficacy. Agencies like the FDA prioritize pharmacovigilance and risk management through detailed Risk Management Plans (RMPs) and periodic reporting. Expedited pathways, such as Fast Track (USA) and PRIME (Europe), aim to accelerate approvals, with timelines ranging from 4 to 12 months. Regional differences in clinical trial requirements, post-market monitoring, and approval timelines reflect diverse approaches to fostering innovation while ensuring patient safety. Table 5 is a comparative table summarizing the critical aspects of regulatory guidelines for gene and cell therapies, focusing on clinical trial requirements, post-market surveillance and risk management strategies across various agencies.[15,23]

Table 4: Comparative table summarizing the conditional approval processes for cell and gene therapies and pricing mechanisms and payment models.

Region/Regulatory Body	Pathway Name	Eligibility Criteria	Expedited Pathways	Post-Approval Requirements	Duration of Conditional Approval	Pathway Name	Eligibility Criteria	Expedited Pathways	Post-Approval Requirements	Duration of Conditional Approval	Example Products Approved
FDA (USA)	Accelerated Approval, RMAT	Serious or life-threatening diseases; unmet medical need	Breakthrough Therapy, Fast Track, RMAT	Post-marketing studies, long-term follow-up	Indefinite (if post-market commitments fulfilled)	Accelerated Approval, RMAT	Serious or life-threatening diseases; unmet medical need	Breakthrough Therapy, Fast Track, RMAT	Post-marketing studies, long-term follow-up	Indefinite (if post-market commitments fulfilled)	**Kymriah**, **Yescarta**, **Zolgensma**
EMA (Europe)	Conditional Marketing Authorization (CMA)	Life-threatening or seriously debilitating conditions	PRIME, Conditional MA	Annual renewal of conditional approval, post-market surveillance	One year, renewable annually until full data provided	Conditional Marketing Authorization (CMA)	Life-threatening or seriously debilitating conditions	PRIME, Conditional MA	Annual renewal of conditional approval, post-market surveillance	One year, renewable annually until full data provided	**Luxturna**, **Alofisel**, **Zynteglo**
TGA (Australia)	Provisional Approval Scheme	Serious conditions with unmet medical need	Priority Review, Provisional Approval	Ongoing data submission, risk management plans	Maximum of 6 years, or until full data provided	Provisional Approval Scheme	Serious conditions with unmet medical need	Priority Review, Provisional Approval	Ongoing data submission, risk management plans	Maximum of 6 years, or until full data provided	**Rexlemestrocel-L**, **Provenge**
PMDA (Japan)	Conditional/ Time-Limited Approval	Serious diseases; early evidence of effectiveness	Sakigake Designation, Priority Review	Post-market clinical studies, additional evidence collection	7 years, extension possible if required	Conditional/ Time-Limited Approval	Serious diseases; early evidence of effectiveness	Sakigake Designation, Priority Review	Post-market clinical studies, additional evidence collection	7 years, extension possible if required	**Stemirac**, **Temcell**, **Collategene**
MFDS (South Korea)	Conditional Approval (Fast Track)	Serious diseases, particularly rare or life-threatening	Fast Track Approval	Ongoing clinical studies, post-marketing surveillance	Initial approval for 5 years, can be extended	Conditional Approval (Fast Track)	Serious diseases, particularly rare or life-threatening	Fast Track Approval	Ongoing clinical studies, post-marketing surveillance	Initial approval for 5 years, can be extended	**Cartistem**, **Cellgram-LC**
CSFDA (China)	Conditional Approval	Urgent clinical needs, orphan drugs, or major diseases	Priority Review, Special Approval	Post-market studies, pharmacovigilance	5 years, subject to renewal	Conditional Approval	Urgent clinical needs, orphan drugs, or major diseases	Priority Review, Special Approval	Post-market studies, pharmacovigilance	5 years, subject to renewal	**Gendicine**, **Oncorine**
DCGI (India)	Accelerated Approval	Rare diseases or life-threatening conditions	Accelerated Approval, Fast Track	Post-marketing studies, risk management plans	2-4 years, with potential for extension	Accelerated Approval	Rare diseases or life-threatening conditions	Accelerated Approval, Fast Track	Post-marketing studies, risk management plans	2-4 years, with potential for extension	**Stempeucel®**, **Itolizumab**
Health Canada (Canada)	Conditional Marketing Authorization (NOC/c)	Conditions with unmet medical need, early clinical evidence	Priority Review, NOC/c	Ongoing data submission, post-market surveillance	Reviewed annually, extension if necessary	Conditional Marketing Authorization (NOC/c)	Conditions with unmet medical need, early clinical evidence	Priority Review, NOC/c	Ongoing data submission, post-market surveillance	Reviewed annually, extension if necessary	**Kymriah**, **Yescarta**
IFDA (Iran)	Conditional Approval (Accelerated)	High-impact medical needs, serious or rare diseases	Accelerated Review	Post-approval studies, ongoing surveillance	3-5 years, with extension options	Conditional Approval (Accelerated)	High-impact medical needs, serious or rare diseases	Accelerated Review	Post-approval studies, ongoing surveillance	3-5 years, with extension options	**Cell-based cancer therapies** (ongoing review)

The approval processes, key guidelines, expedited pathways, and post-marketing surveillance for gene and cell therapies vary across global regulatory agencies. Most agencies follow a three-phase clinical trial process, but approval mechanisms and fast-track programs differ significantly.[25,42]

Approval Processes & Key Guidelines

The FDA (USA) requires an Investigational New Drug (IND) application, followed by Phase I-III trials and a Biologics License Application (BLA) under 21 CFR Part 312 & 600. The EMA (Europe) follows a similar path but mandates a Clinical Trial Application (CTA) and Marketing Authorization Application (MAA) governed by ICH E6 and EU CT Regulation. Australia (TGA) and Canada (Health Canada) use CTA-based approvals, while China (CSFDA), India (DCGI), Japan (PMDA) and South Korea (MFDS) require New Drug Applications (NDA) for final market approval. Iran (IFDA) adheres to GCP guidelines and follows a Market Authorization process.[25,42]

Expedited Pathways

The USA offers multiple fast-track options, including Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval, with 6-12-month timelines. The EMA provides PRIME, Accelerated Assessment, and Conditional Marketing Authorization, with some approvals processed within 120-150 days. TGA (Australia), PMDA (Japan), and MFDS (South Korea) offer Priority Review and Conditional Approval, which takes between 150-180 days. China (CSFDA) follows Breakthrough Therapy Designation and Conditional Approval with a 6-12 months timeframe. India's DCGI uses Accelerated Approval and Fast Track Designation, taking 6-12 months. Iran's IFDA has Accelerated and Conditional Approval, requiring 6-12 months.[25,42]

Post-Marketing Surveillance

All agencies enforce post-marketing monitoring to ensure safety and efficacy. The FDA mandates Risk Evaluation and Mitigation Strategies (REMS) and Periodic Safety Update Reports (PSURs). The EMA, Japan, Canada, and Australia require Risk Management Plans (RMPs), with additional long-term follow-ups. China, India, Iran, and South Korea have implemented post-market surveillance and adverse event reporting to track therapy risks.[25,42]

Timelines for Expedited Approvals

The fastest approvals occur in the USA (6 months for Fast Track and Breakthrough Therapy), Japan (6 months for Sakigake Designation), and EMA (4 months for PRIME). Accelerated programs in China, India, Iran, and South Korea range from 6 to 12 months. Australia and Canada have 150-180 days expedited pathways.

In summary, while regulatory frameworks differ, all agencies emphasize accelerated access, stringent clinical trials, and robust post-market surveillance to ensure the safety and effectiveness of gene and cell therapies.[25,42]

Table 5: Critical aspects of regulatory guidelines for gene and cell therapies and a comparative table of prioritization of post-marketing safety requirements for gene therapies.

Regulatory Agency	Clinical Trial Requirements	Post-market Surveillance	Risk Management Strategies	Long-term Follow-up Studies	Pharmacovigilance	Risk Mitigation	Proportion of Focus (%)
FDA (USA)	- Pre-IND meeting required - Phase I, II, III trials- IND application submission- Clinical hold mechanism	- REMS (Risk Evaluation and Mitigation Strategy) - Periodic Safety Update Reports (PSURs)- Long-term follow-up required	- REMS programs for risk mitigation - Risk communication requirements- Risk assessment plans	Mandatory for most gene therapies; typically 15-20 years	Robust, with REMS programs, frequent updates required	Comprehensive REMS with risk communication and mitigation strategies	Long-term Follow-up: 40% Pharmacovigilance: 35%Risk Mitigation: 25%
EMA (Europe)	- Scientific advice before clinical trials - Phase I, II, III trials- CTA (Clinical Trial Application) submission	- Risk Management Plan (RMP) - Periodic Benefit-Risk Evaluation Report (PBRER)- Long-term safety monitoring	- Risk Management Plan (RMP) - Risk minimization measures- Safety monitoring and signal detection	Required; duration varies, often up to 15 years	Extensive; includes RMPs, periodic safety reports and signal detection	RMPs include detailed risk minimization measures	Long-term Follow-up: 35% Pharmacovigilance: 40%Risk Mitigation: 25%

Regulatory Agency	Clinical Trial Requirements	Post-market Surveillance	Risk Management Strategies	Long-term Follow-up Studies	Pharmacovigilance	Risk Mitigation	Proportion of Focus (%)
TGA (Australia)	- Pre-IND consultation - Phase I, II, III trials- CTA (Clinical Trial Notification)	- Risk Management Plan (RMP) - Periodic Safety Update Reports (PSURs)- Post-market surveillance studies	- Risk Management Plan (RMP) - Post-market monitoring - Risk minimization strategies	Long-term follow-up is generally required; duration varies	Standard pharmacovigilance practices; include PSURs and regular updates	Risk Management Plans with risk minimization strategies	Long-term Follow-up: 30% Pharmacovigilance: 45%Risk Mitigation: 25%
CSFDA (China)	- Pre-Clinical Trial Consultation - Phase I, II, III trials- IND application submission- Clinical trial registration	- Post-market surveillance requirements - Adverse event reporting- Long-term monitoring studies	- Risk management requirements in registration - Risk control measures- Adverse event management	Required; long-term follow-up typically 5-10 years	Basic pharmacovigilance; less extensive than some regions	Risk management requirements in registration with ongoing monitoring	Long-term Follow-up: 25% Pharmacovigilance: 35%Risk Mitigation: 40%
DCGI (India)	- Pre-clinical and clinical trial approval - Phase I, II and III trials - Clinical Trial Registry submission	- Post-market surveillance - Adverse drug reaction reporting- Periodic safety updates	- Risk minimization plans - Post-marketing safety monitoring - Risk communication requirements	Long-term follow-up is often required; up to 5-10 years	Standard pharmacovigilance; includes adverse drug reaction reporting	Risk management plans with post-marketing monitoring	Long-term Follow-up: 30% Pharmacovigilance: 40%Risk Mitigation: 30%
PMDA (Japan)	- Pre-IND consultation - Phase I, II and III trials - Clinical Trial Notification (CTN) submission	- Risk Management Plan (RMP) - Long-term follow-up required- Periodic safety reports	- Risk Management Plan (RMP) - Safety monitoring- Risk assessment and mitigation strategies	Mandatory; often 5-10 years for long-term follow-up	Comprehensive; includes RMPs and regular safety updates	Detailed risk management strategies in RMPs	Long-term Follow-up: 35% Pharmacovigilance: 40%Risk Mitigation: 25%
Health Canada	- Pre-Clinical Trial Application (CTA) meeting - Phase I, II, III trials- CTA submission	- Risk Management Plan (RMP) - Periodic Safety Update Reports (PSURs)- Post-market surveillance studies	- Risk Management Plan (RMP) - Risk communication requirements- Risk assessment and mitigation strategies	Required; generally 5-10 years of follow-up	Includes RMPs, periodic safety reports and long-term monitoring	Risk Management Plans with detailed strategies	Long-term Follow-up: 30% Pharmacovigilance: 40%Risk Mitigation: 30%
IFDA (Iran)	- Clinical Trial Application (CTA) submission - Phase I, II and III trials - Pre-market approval	- Post-market surveillance - Adverse event reporting- Safety monitoring	- Risk assessment plans - Post-market risk management - Risk mitigation strategies	Long-term follow-up is often required; up to 5 years	Basic pharmacovigilance; includes reporting adverse events	Risk management with post-market surveillance	Long-term Follow-up: 20% Pharmacovigilance: 40%Risk Mitigation: 40%

Regulatory Agency	Clinical Trial Requirements	Post-market Surveillance	Risk Management Strategies	Long-term Follow-up Studies	Pharmacovigilance	Risk Mitigation	Proportion of Focus (%)
MFDS (South Korea)	- Pre-IND consultation - Phase I, II and III trials - Clinical Trial Notification (CTN) submission	- Risk Management Plan (RMP) - Periodic Safety Update Reports (PSURs)-Long-term follow-up studies	- Risk Management Plan (RMP) - Safety monitoring- Risk communication and mitigation measures	Long-term follow-up required; duration varies, often up to 10 years	Includes comprehensive pharmacovigilance; PSURs and safety updates	Risk management strategies in place with regular reviews	Long-term Follow-up: 30% Pharmacovigilance: 40% Risk Mitigation: 30%

Gene and cell therapy challenges

Gene and cell therapy regulatory frameworks face several challenges, including approval bottlenecks and discrepancies in safety monitoring protocols. A key issue is the varying definitions and classifications across regions, leading to approval delays and market-entry barriers. For example, the FDA broadly defines gene therapy as products that alter genetic material. In contrast, the EMA defines it more specifically as involving recombinant nucleic acid sequences for therapeutic or diagnostic purposes. These differences require companies to adapt applications for each agency, slowing international development.[26,33,43]

Approval bottlenecks are another significant challenge, particularly in agencies with fewer expedited pathways. While the FDA and Japan's PMDA offer accelerated approval options, other agencies, such as South Korea's MFDS, provide fewer fast-track pathways, causing delays in patient access to therapies. Additionally, therapies conditionally approved in the U.S. often face further delays in regions with less-developed regulatory systems, such as Iran.[26,33,43]

Safety monitoring protocols also vary widely, with some agencies imposing more stringent requirements. The FDA mandates intensive long-term follow-up for gene therapies, while countries with limited healthcare infrastructure may focus surveillance primarily on high-risk therapies, leading to gaps in safety data and inconsistent patient safety.[26,33,43]

These regulatory challenges affect various stakeholders. Patients face delayed access to therapies, particularly in regions with fragmented approval processes. Healthcare providers must navigate varying safety protocols, limiting access to advanced therapies in under-resourced facilities. Pharmaceutical companies bear the cost of navigating different regional regulations, requiring tailored clinical trials and compliance efforts. Addressing these challenges by harmonizing definitions, aligning safety standards, and expanding fast-track options could streamline global access.[26,33,43]

Trends for gene and cell therapies

Recent trends indicate a potential path for harmonization. Many agencies now offer expedited approval pathways for therapies targeting unmet medical needs, such as the FDA's Fast Track and Breakthrough Therapy designations, EMA's Conditional Marketing Authorization, and Japan's Sakigake designation. These common pathways could support mutual recognition agreements, streamlining global access.[10,26,43,44]

There is also growing alignment in post-market safety monitoring, with agencies like the FDA and EMA requiring long-term surveillance for high-risk therapies. Similarly, Australia's TGA and Japan's PMDA implement stringent post-market requirements. This convergence in safety monitoring could reduce duplicative surveillance efforts across regions.[10,26,43,44]

Additionally, most agencies are recognizing gene and cell therapies as distinct from traditional pharmaceuticals, which may lead to standardized classification and terminology. Lastly, as gene therapies become more expensive, a shift toward value-based reimbursement models is emerging, with the EMA promoting outcome-based models in Europe and similar discussions in the U.S. and Australia. By leveraging these trends, regulatory bodies could develop a more unified and efficient global approach to gene and cell therapies.[10,26,43,44]

FINDINGS AND RECOMMENDATIONS

There are significant differences in how international regulatory agencies define and evaluate gene and cell therapies. Streamlining approval processes and harmonizing regulations may help reduce the barriers to global access for these innovative treatments. Recommendations include adopting common guidelines for clinical trial requirements and post-market surveillance.

LIMITATIONS

The study is limited by the availability of data on certain regulatory frameworks and differences in reporting standards across regions. Further research is needed to assess the long-term impact of regulatory differences on patient outcomes.

CONCLUSION

Gene and cell therapies are revolutionizing medicine by offering new treatments for previously untreatable diseases, but the global regulatory landscape remains fragmented. Harmonizing standards could accelerate approval processes and improve access to these life-saving therapies. Pricing is influenced by factors like innovation and regional healthcare systems, with countries like Europe, Japan, and South Korea adopting sophisticated models such as outcome-based payments, while India and China emphasize affordability through local production and price controls. The USA and Europe lead the global market, with strong growth also seen in South Korea, China, and emerging markets like India and Iran, reflecting the increasing adoption of these advanced treatments worldwide.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FDA: U.S. Food and Drug Administration; **EMA:** European Medicines Agency; **TGA:** Therapeutic Goods Administration; **CSFDA:** China State Food and Drug Administration; **DCGI:** Drug Controller General of India; **PMDA:** Pharmaceuticals and Medical Devices Agency; **IFDA:** Iran Food and Drug Administration; **MFDS:** Ministry of Food and Drug Safety; **ATMPs:** Advanced Therapy Medicinal Products; **GMP:** Good Manufacturing Practice; **GTP:** Good Tissue Practices; **BLA:** Biologics License Application; **RMAT:** Regenerative Medicine Advanced Therapy; **CMS:** Centers for Medicare & Medicaid Services; **CAT:** Committee for Advanced Therapies; **CMA:** Conditional Marketing Authorization; **MEAs:** Managed Entry Agreements; **RMP:** Risk Management Plan; **NDA:** New Drug Application; **PMD Act:** Pharmaceuticals and Medical Devices Act; **NHI:** National Health Insurance; **CADTH:** Canadian Agency for Drugs and Technologies in Health; **HPFB:** Health Products and Food Branch; **SAP:** Special Access Program.

REFERENCES

1. Hanna E, Rémuzat C, Auquier P, Toumi M. Gene therapies development: slow progress and promising prospect. J Mark Access Health Policy. 2017;5(1):1265293. doi: 10.1080/20016689.2017.1265293, PMID 28265348, PMCID PMC5328344.
2. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present and future. Stem Cell Res Ther. 2019;10(1):68. doi: 10.1186/s13287-019-1165-5, PMID 30808416, PMCID PMC6390367.
3. Arabi F, Mansouri V, Ahmadbeigi N. Gene therapy clinical trials, where do we go? An overview. Biomed Pharmacother. 2022;153:113324. doi: 10.1016/j.biopha.2022.113324, PMID 35779421.
4. Hoang DM, Pham PT, Bach TQ, Ngo AT, Nguyen QT, Phan TT, *et al*. Stem cell-based therapy for human diseases. Signal Transduct Target Ther. 2022;7(1):272. doi: 10.1038/s41392-022-01134-4, PMID 35933430, PMCID PMC9357075.
5. Galli MC, Serabian M, editors. Regulatory aspects of gene therapy and cell therapy products. A global perspective. Cham: Springer International; 2015.
6. Conlon TJ, Mavilio F. The pharmacology of gene and cell therapy. Mol Ther Methods Clin Dev. 2018;8:181-2. doi: 10.1016/j.omtm.2017.12.007, PMID 29687036, PMCID PMC5908264.
7. Maruyama Y, Noda S, Okudaira S, Sakurai A, Okura N, Honda F. Regulatory aspects of cell and gene therapy products: the Japanese perspective. Adv Exp Med Biol. 2023;1430:155-79. doi: 10.1007/978-3-031-34567-8_9, PMID 37526847.
8. Ikonomou L, Cuende N, Forte M, Grilley BJ, Levine AD, Munsie M, *et al*. [international Society for Cell & Gene Therapy Position paper]. International Society for Cell & Gene Therapy Position Paper: Key considerations to support evidence-based cell and gene therapies and oppose marketing of unproven products. Cytotherapy. 2023;25(9):920-9. doi: 10.1016/j.jcyt.2023.03.002, PMID 37517865.
9. S S KD, Joga R, Srivastava S, Nagpal K, Dhamija I, Grover P, *et al*. Regulatory landscape and challenges in CAR-T cell therapy development in the US, EU, Japan, and India. Eur J Pharm Biopharm. 2024;201:114361. doi: 10.1016/j.ejpb.2024.114361 [epub]. PMID 38871092.
10. El-Kadiry AE, Rafei M, Shammaa R. Cell therapy: types, regulation and clinical benefits. Front Med (Lausanne). 2021;8:756029. doi: 10.3389/fmed.2021.756029, PMID 34881261, PMCID PMC8645794.
11. Khaddour K, Hana CK, Mewawalla P. Hematopoietic stem cell transplantation. In: Treasure Island, (FL): StatPearls Publishing; Updated 2023 May 6. StatPearls [Internet]. p. 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536951/.
12. Roth TL, Marson A. Genetic disease and therapy. Annu Rev Pathol. 2021;16:145-66. doi: 10.1146/annurev-pathmechdis-012419-032626, PMID 33497260, PMCID PMC9704033.
13. Sayed N, Allawadhi P, Khurana A, Singh V, Navik U, Pasumarthi SK, *et al*. Gene therapy: comprehensive overview and therapeutic applications. Life Sci. 2022;294:120375. doi: 10.1016/j.lfs.2022.120375 [epub]. PMID 35123997.
14. Li X, Le Y, Zhang Z, Nian X, Liu B, Yang X. Viral vector-based gene therapy. Int J Mol Sci. 2023;24(9):7736. doi: 10.3390/ijms24097736, PMID 37175441, PMCID PMC10177981.
15. Halioua-Haubold CL, Peyer JG, Smith JA, Arshad Z, Scholz M, Brindley DA, *et al*. Regulatory considerations for gene therapy products in the US, EU and Japan. Yale J Biol Med. 2017;90(4):683-93, PMID 29259533, PMCID PMC5733859.
16. Petricciani J, Hayakawa T, Stacey G, Trouvin JH, Knezevic I. Scientific considerations for the regulatory evaluation of cell therapy products. Biologicals. 2017;50:20-6. doi: 10.1016/j.biologicals.2017.08.011 [epub]. PMID 28888427.
17. Schaut W, Shrivastav A, Ramakrishnan S, Bowden R. Search, identification and curation of cell and gene therapy product regulations using augmented intelligent systems. Front Med (Lausanne). 2023;10:1072767. doi: 10.3389/fmed.2023.1072767, PMID 36950510, PMCID PMC10025403.
18. Malech HL, Garabedian EK, Hsieh MM. Evolution of gene therapy, historical perspective. Hematol Oncol Clin North Am. 2022;36(4):627-45. doi: 10.1016/j.hoc.2022.05.001 [epub], PMID 35773053, PMCID PMC9296588.
19. Giommetti A, Papanikolaou E. Advancements in hematopoietic stem cell gene therapy: A journey of progress for viral transduction. Cells. 2024;13(12):1039. doi: 10.3390/cells13121039, PMID 38920667, PMCID PMC11201829.
20. Qiu HY, Ji RJ, Zhang Y. Current advances of CRISPR-Cas technology in cell therapy. Cell Insight. 2022;1(6):100067. doi: 10.1016/j.cellin.2022.100067, PMID 37193354, PMCID PMC10120314.
21. Khoshandam M, Soltaninejad H, Hamidieh AA, Hosseinkhani S. CRISPR, CAR-T and NK: current applications and future perspectives. Genes Dis. 2024;11(4):101121. doi: 10.1016/j.gendis.2023.101121, PMID 38545126, PMCID PMC10966184.
22. Deneault E. Recent therapeutic gene editing applications to genetic disorders. Curr Issues Mol Biol. 2024;46(5):4147-85. doi: 10.3390/cimb46050255, PMID 38785523, PMCID PMC11119904.
23. Lee S, Lee JH. Cell and gene therapy regulatory, pricing and reimbursement framework: with a focus on South Korea and the EU. Front Public Health. 2023;11:1109873. doi: 10.3389/fpubh.2023.1109873, PMID 36908458, PMCID PMC9998493.
24. Mohammadian Gol T, Zahedipour F, Trosien P, Ureña-Bailén G, Kim M, Antony JS, *et al*. Gene therapy in pediatrics - Clinical studies and approved drugs (as of 2023). Life Sci. 2024;348:122685. doi: 10.1016/j.lfs.2024.122685 [epub]. PMID 38710276.
25. Cai Y, Sui L, Wang J, Qian W, Peng Y, Gong L,*et al*. Post-marketing surveillance framework of cell and gene therapy products in the European Union, The United States, Japan, South Korea and China: a comparative study. BMC Med. 2024;22(1):421. doi: 10.1186/s12916-024-03637-z, PMID 39334246.
26. Drago D, Foss-Campbell B, Wonnacott K, Barrett D, Ndu A. Global regulatory progress in delivering on the promise of gene therapies for unmet medical needs. Mol Ther Methods Clin Dev. 2021;21:524-9. doi: 10.1016/j.omtm.2021.04.001, PMID 33997101, PMCID PMC8099595.
27. Pimenta C, Bettiol V, Alencar-Silva T, Franco OL, Pogue R, Carvalho JL, *et al*. Advanced therapies and regulatory framework in different areas of the globe: past, present and future. Clin Ther. 2021;43(5):e103-38. doi: 10.1016/j.clinthera.2021.02.006 [epub]. PMID 33892966.
28. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. J Mark Access Health Policy. 2015;3. doi: 10.3402/jmahp.v3.29321, PMID 27123175, PMCID PMC4802687.
29. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. J Mark Access Health Policy. 2020;8(1):1715536. doi: 10.1080/20016689.2020.1715536, PMID 32082514, PMCID PMC7006635.
30. Gonçalves E. Value-based pricing for advanced therapy medicinal products: emerging affordability solutions. Eur J Health Econ. 2022;23(2):155-63. doi: 10.1007/s10198-021-01276-2 [epub] 2021 Jun 9, PMID 34106364, PMCID PMC8882079.

31. Gomes KL, da Silva RE, da Silva JB, Bosio CG, Novaes MR. Post-marketing authorisation safety and efficacy surveillance of advanced therapy medicinal products in Brazil, the European Union, the United States and Japan. Cytotherapy. 2023;25(10):1113-23. doi: 10.1016/j.jcyt.2023.06.005 [epub]. PMID 37436339.
32. Mora A, Barnes L, Divine C, Frey N, Fuchs C, Hayes B, *et al*. The cell and gene therapy Consortium's perspective on harmonizing data collection for patient enrollment, therapy ordering and scheduling and cell collection. Transplant Cell Ther. 2023;29(11):653-65. doi: 10.1016/j.jtct.2023.08.011 [epub]. PMID 37604251.
33. Sanchez-Guijo F, Vives J, Ruggeri A, Chabannon C, Corbacioglu S, Dolstra H, *et al*. Current challenges in cell and gene therapy: a joint view from the European Committee of the International Society for Cell & Gene Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT). Cytotherapy. 2024;26(7):681-5. doi: 10.1016/j.jcyt.2024.02.007 [epub]. PMID 38416085.
34. van Overbeeke E, Michelsen S, Toumi M, Stevens H, Trusheim M, Huys I, *et al*. Market access of gene therapies across Europe, USA and Canada: challenges, trends and solutions. Drug Discov Today. 2021;26(2):399-415. doi: 10.1016/j.drudis.2020.11.024 [epub] 2020 Nov 24. PMID 33242695.
35. Salzman R, Cook F, Hunt T, Malech HL, Reilly P, Foss-Campbell B, *et al*. Addressing the value of gene therapy and enhancing patient access to transformative treatments. Mol Ther. 2018;26(12):2717-26. doi: 10.1016/j.ymthe.2018.10.017 [epub], PMID 30414722, PMCID PMC6277509.
36. Lapteva L, Purohit-Sheth T, Serabian M, Puri RK. Clinical development of gene therapies: the first three decades and counting. Mol Ther Methods Clin Dev. 2020;19:387-97. doi: 10.1016/j.omtm.2020.10.004, PMID 33209964, PMCID PMC7658574.
37. Chancellor D, Barrett D, Nguyen-Jatkoe L, Millington S, Eckhardt F. The state of cell and gene therapy in 2023. Mol Ther. 2023;31(12):3376-88. doi: 10.1016/j.ymthe.2023.11.001 [epub], PMID 37927037, PMCID PMC10727993.
38. Ma CC, Wang ZL, Xu T, He ZY, Wei YQ. The approved gene therapy drugs worldwide: from 1998 to 2019. Biotechnol Adv. 2020;40:107502. doi: 10.1016/j.biotechadv.2019.107502 [epub] 2019 Dec 27. PMID 31887345.
39. Shchaslyvyi AY, Antonenko SV, Tesliuk MG, Telegeev GD. Current state of human gene therapy: approved products and vectors. Pharmaceuticals (Basel). 2023;16(10):1416. doi: 10.3390/ph16101416, PMID 37895887, PMCID PMC10609992.
40. De Luca M, Cossu G. Cost and availability of novel cell and gene therapies: can we avoid a catastrophic second valley of death?: can we avoid a catastrophic second valley of death? EMBO Rep. 2023;24(2):e56661. doi: 10.15252/embr.202256661 [epub], PMID 36592141, PMCID PMC9900339.
41. Cornetta K, Bonamino M, Mahlangu J, Mingozzi F, Rangarajan S, Rao J. Gene therapy access: global challenges, opportunities and views from Brazil, South Africa and India. Mol Ther. 2022;30(6):2122-9. doi: 10.1016/j.ymthe.2022.04.002 [epub], PMID 35390542, PMCID PMC9171243.
42. Franco P, Jain R, Rosenkrands-Lange E, Hey C, Koban MU. Regulatory pathways supporting expedited drug development and approval in ICH member countries. Ther Innov Regul Sci. 2023;57(3):484-514. doi: 10.1007/s43441-022-00480-3 [epub] 2022 Dec 3, PMID 36463352, PMCID PMC9734413.
43. Carvalho M, Sepodes B, Martins AP. Regulatory and scientific advancements in gene therapy: state-of-the-art of clinical applications and of the supporting European regulatory framework. Front Med (Lausanne). 2017;4:182. doi: 10.3389/fmed.2017.00182, PMID 29124055, PMCID PMC5662580.
44. Kohn DB, Chen YY, Spencer MJ. Successes and challenges in clinical gene therapy. Gene Ther. 2023;30(10-11):738-46. doi: 10.1038/s41434-023-00390-5, PMID 37935854.

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