

Review Article

REGULATORY PERSPECTIVE FOR GENE THERAPY PRODUCTS IN THE USA, EU AND JAPAN AND FUTURE ASPECTS

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ABSTRACT

Gene Therapy Products (GTPs) hold immense promise in revolutionizing medical treatments by altering genetic expressions to address various diseases. This study gives a summary of gene therapy products and their prospective uses, their historical development and several treatment options, as an in-depth exploration of the regulatory considerations for GTPs in the United States of America (USA), European Union (EU), and Japan, along with insights into future aspects of this field. A comprehensive discussion follows detailing the regulatory landscape and approval pathways in the USA, EU, and Japan. Programs that are exclusive to each area, such as PRIME (Priority Medicines) in the EU, USA's RMAT (Regenerative Medicines Advanced Therapy) designation and the Sakigake system in Japan are examined. Milestone meetings, approval requirements, and specific regulatory guidelines for GTPs in each region are also thoroughly covered. A list of approved GTPs and a glimpse into the future of the field. Anticipated trends include increasing investments, challenges related to production costs, expansion of manufacturing capabilities, and regulatory updates. The various regulatory strategies in each area and their efforts to balance patient access and safety will have a big impact on GTPs marketed in the future. Japan is well-positioned to maintain it's as a global leader in regenerative medicine and cell treatments because of its favourable regulatory environment and government backing.

Keywords: Gene therapy products, Medical treatments, Genetic expressions, Regulatory considerations, Regulatory landscape

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INTRODUCTION

Gene Therapy Products (GTP's) are the process of modifying the expression of genetic expression, and genetic alteration of living cells for therapeutic use. A gene therapy procedure is used to treat a disease by modifying a person's DNA. Numerous possible uses for gene therapy exist, including:

Replacing genes that are associated with the development of diseases with healthy genes. Disabling a disease-causing gene. Transposing altered or new genes into the body to treat disorders [1].

A spike in interest in gene therapy's past can be attributed to excessive expectations of a rapid transition from concept to clinical trials in the 1980s. However, a setback occurred in 1999 when a patient underwent gene therapy. Renewed hope emerged a decade later, with a wave of gene therapy start-ups emerging from 2008, facilitated by financial and pharmaceutical support. The significance attributed to gene therapy is exemplified by Juno Therapeutics' valuation of \$4 billion within a year of its founding in 2014. In the US, upon the approval of the first gene therapy, around 854 companies were involved in the field, projected to exceed 1085 companies by the close of 2020, with over 400 gene therapy studies underway. Gene therapy's applications encompass the prevention, treatment, or potential cure of hereditary disorders like cystic fibrosis, haemophilia, and sickle cell disease. Additionally, it holds promise for addressing cancers and infections such as Human Immunodeficiency Virus (HIV) [2]. Gene therapy may alter the way that cancer is treated, hereditary issues, and infectious disorders. Research and development for these diseases is underway and is currently the subject of research. A few examples of approved gene therapy medications are Tectus for beta cell acute lymphocytic leukaemia and Elevidys for Duchene muscular dystrophy [1].

A variety of gene therapy products are available

- Plasmid DNA: Genetically altered circular DNA that can be utilized to transfer therapeutic genes into human cells [1].

- Viral vectors: Viruses are the main source of gene therapy products because they have the natural ability to transfer genetic material to cells. At that point, utilizing infections that have been modified viruses without infection-causing abilities can be used as vectors for transmitting therapeutic genes to human cells [1]

- **Technology for human editing genes:** Changing the quality points is to remove undesirable qualities to maintain changed qualities or repair mutation in genes.

- **Patient-derived cellular GTPs:** The patient's cells are genetically modified (usually via a viral vector), and then reintroduced [1].

The costs associated with genome sequencing have been on the rise from \$100 to \$1 million for each genome in the past decade. This is largely attributed to the late 1990s scientific arms race to decipher the human genome, thus providing a better understanding of genetic code for the first time. As a result, the cost of gene sequencing showed a declining trend over five years; the graph is shown below in fig. 1 [3].

New treatments for previously incurable diseases have been made possible by deciphering the human genome. The advent of molecular methods for artificial genome transfer and alteration, such as virus-based infection mechanisms and the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/CRISPR Associated Protein 9 (Cas9) system, which allows for precise DNA slicing and subsequent natural DNA repair processes, has complimented genome sequencing [4].

Methods

USA

GTPs are a medical procedure that requires changing the genetic code of living cells. There are two ways to accomplish this: *Ex vivo*; involving the alteration of a patient's cells or *Ex vivo, In vivo, In vitro* in which the patient receives gene therapy right away. *Ex vivo* gene therapy is also known as somatic cell therapy. Gene therapy involves

the use of genetic alteration to mark cells for future identification and therapeutic use. Recombinant DNA materials which come under regulatory scrutiny are used to transmit genetic material for gene therapy [5].

Regulatory authorities have created a framework for the development of gene therapies usually, this framework also applies

to cell and tissue treatments. The Office of Tissues and Advanced Therapies (OTAT) is located within the Center for Biologics Evaluation and Research (CBER), a division of the US FDA. There are three programs designed to promote product development: fast track, breakthrough treatment, and RMAT. The breakthrough therapy and RMAT categories share many traits with the fast track designation, which was the first to be established [6].

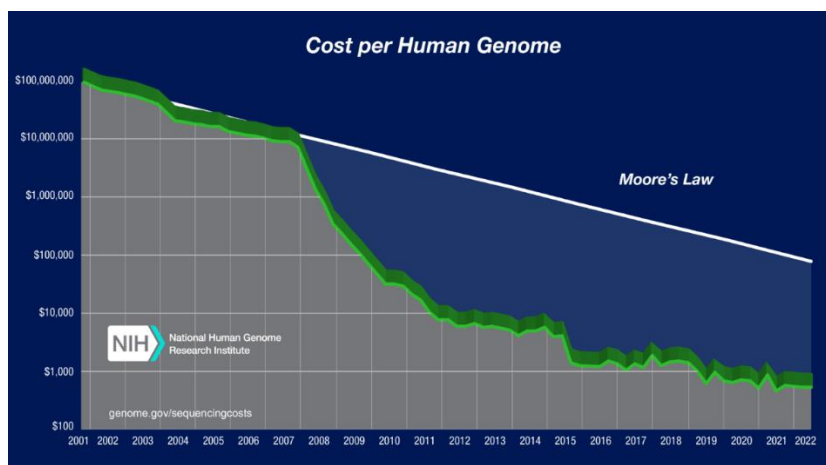


Fig. 1: The declining cost of the genome during the last decade [3]

Fast track designation

The applicant must file a Fast-Track Designation (FTD) application with the product description and intended use, along with all necessary supporting documentation. The USFDA is legally obligated to confirm that the requirements for fast-track designation have been met within 60 d of receiving the application. A summary of the requests handled by CBER during the review process and decision-making [7].

Breakthrough therapy designation

A Breakthrough Therapy Designation (BTD) is intended to facilitate the development and review of a drug to treat a serious condition in early clinical evidence suggesting that the drug may be more effective than existing therapies in one or more key clinical variables. The size of the treatment effect (which may include its duration) and the significance of the clinical outcome that was observed will both influence the improvement that exceeds that of standard therapy. Generally, initial clinical evidence must demonstrate a distinct advantage over conventional therapy. The USFDA does not expect breakthrough therapy applications to be submitted after the initial Biologics License Application (BLA), New Drug Application (NDA) or Supplement. USFDA must respond to applications for BTD and approve them within 60 d of receiving them [8].

Regenerative Medicine Advanced Treatment (RMAT)

It was established by the 21st Century Cures Act. It is a term specifically designated as a regenerative medicine advanced treatment; it was of great interest to the advanced therapy industry. The products eligible for RMAT are regenerative medicines therapies and preliminary clinical evidence suggesting a potential to address unmet medical needs. The sponsors should submit an RMAT application with an Investigation New Drug (IND) or amendment to an existing one.

The following information to be submitted are:

- A. An overview of the gene therapy conditions that are currently accessible
- B. Description of the statistical analysis and results

The RMAT designation should be submitted to the OTAT; the review is done within 60 d. If RMAT is rejected, OTAT will explain why the designation wasn't given [9].

Rolling Review (RR)

It refers to the practice of submitting the FDA components of a pharmaceutical company's NDA as they are finished rather than initiating the review process. Only entire components, such as a full Chemistry, Manufacturing and Controls (CMC) section, a full toxicological part, or a full clinical section, will be accepted by the agency. The pre-BLA meeting is where the preliminary agency agreement on rolling review for drugs designated as BTD, FTD, or RMAT is obtained [9].

Incentives for the development of therapeutics intended to treat rare diseases

Orphan designation

The Orphan Designation (OD) program grants orphan status to pharmaceuticals and biologics that are designed for the safe and efficient treatment, diagnosis, or prevention of uncommon illnesses or disorders that afflict fewer than 200,000 individuals in the USA. However, it is not envisaged that these medications and biologics would cover their development and marketing expenses [10].

Once an FDA-approved orphan medicine receives commercial authorization in the USA, it is eligible for seven years of market exclusivity. Even if the prevalence at the time of licensing is higher than expected, the market exclusivity is still in place because there is no necessity to re-apply or confirm eligibility for orphan designation at that time. The FDA will only withdraw a substance's designation as an orphan drug if it finds that the application was incomplete or contains incorrect information. This is different in the EU. During the seven-year window of market exclusivity, no other companies may sell medicine with the same active ingredient the same application or indication as the designated orphan drugs. The definitions in 21 CFR 316.3(b) are used to determine a drug's sameness. The concept of sameness applies to both small and large molecules. It refers to having the same active moiety in tiny molecules, regardless of the ester or salt. The FDA issued a draft guidance document explaining this definition in more detail for small molecules, synthetic peptides, and complex mixtures. The sameness of monoclonal antibodies and GTPs is likewise subject to FDA regulation [11].

Risk evaluation and mitigation strategies

The USFDA may demand a Risk Evaluation and Mitigation Strategy (REMS) for specific pharmaceuticals that have significant safety concerns

to assist in guaranteeing the benefits of the prescription outweigh its hazards. REMS are intended to reinforce medication usage habits that promote the medicine's safe use. Only a small number of pharmaceuticals need a REMS, even though all medications have labelling that educates healthcare stakeholders about prescription hazards [12].

FDA requirements on long-term follow-up examinations of gene therapy study participants

Pharmaceutical companies must comply with the FDA's post-marketing procedures even after clearance has been given. These include adhering to extra post-marketing duties, such as starting phase IV clinical trials, as well as recording and disclosing any adverse effects emerging after product introduction. The FDA CBER recently revised the "Long Term Follow-Up After Administration of Human Gene Therapy Products" which has since been replaced with the "Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events" [13]

Europe

GTPs contain therapeutic, preventive, or diagnostic genes. To treat various diseases including cancer, hereditary issues, or chronic disorders, they mainly work by injecting recombinant genes into the body [14]. One key aspect of the EU is that GTPs come under an umbrella class of products known as "Advanced therapy medicinal products" (ATMPs). Other products belonging to this category are somatic cell therapy and tissue-based therapies [15].

Prime

PRIME is an early Access Development to Support the technique that promotes the development of treatments with excellent public health potential, hence assisting patients in gaining access to novel medications. Early clinical data is used to demonstrate unmet medical needs, faster assessment standards are used to evaluate eligibility, non-clinical and possibly and non-tolerability evidence to support small business applicants [16].

The EMA's PRIME is a non-profit initiative that seeks to raise financing towards the creation of pharmaceuticals that meet medical needs. PRIME's goal is to streamline the development plans and accelerate the evaluation process to get drugs to patients faster. PRIME is based on improved interactions and early communications with agents.

PRIME's goal is to provide early and proactive assistance so that applications submitted by potential drug developers can be reviewed quickly. The quality of patient's lives may improve the faster they can get the drugs they need. The PRIME services are used to inform the regulatory frameworks, which also include fast evaluations and scientific guidance. A pharmaceutical product that has received marketing authorization and benefited from PRIME can be expected to increase the producer's chances of being accelerated. PRIME's objective is to involve drug developers early in the development process to enhance the quality of scientific data used to decide whether or not to apply for marketing approval. PRIME's early consultation and expert guidance also ensure that patients only take part in studies that are necessary for collecting the required data, making the most of limited resources [17].

Japan

In Japan, the phrase "Regenerative Medicinal Products" (also known as "SAISEI-IRYOUTOU-SEIHIN" in Japanese) refers to the products (apart from quasi-drugs and cosmetics) expressed in human or animal cells and transgenes to treat both human and veterinary diseases [18].

DISCUSSION

Classification

Class I-High risk

In regenerative therapy, the inner cell mass of preimplantation embryos is used to form pluripotent stem cells, also known as Embryonic Stem Cells (ES cells). Induced pluripotent stem (iPS) cells can be created through somatic cell reprogramming following the external production of specific transcription factors, while

transgenes (transgenic) or allogenic cells are used. A Ministry of Health Labour and Welfare (MHLW) health scientific council and a panel with particular certification in regenerative medicine oversee the review process. The initiation of a regenerative medicine therapy program cannot take place before the end of the usual 90 d Marketing Authorisation Holder Letter review period unless an extension of the review period has been granted [19, 20].

Class II-intermediate risk

This class comprises the bulk cell therapies for non-homologs and stem cell therapies using cultured cells, except class I. The strategy cannot be presented to the MHLW until it has received approval from the Specially Certified Regenerative Medicine Committee (SCRM). Treatments using regenerative medicine can begin following examination, approval, and submission [19, 20].

Class III-Low risk

This category includes cell therapies that are not stem cells or non-pharmacologic cell therapies that fall under class I or class II. Plans need to be submitted to MHLW after approval by a Certified Regenerative Medicine Committee [19, 20].

Sakigake designation

The Sakigake designation system, or "Sakigake," was developed by the MHLW as a component of the Sakigake administrative strategy to encourage the development of novel new medical items to successfully treat critical illnesses in Japan and Pharmaceuticals and Medical Devices Agency (PMDA)-Conditional and time-limitation approval for regenerative medicines [16, 21].

Strategy

MHLW announced its "strategy of sakigake" to set a benchmark for the effective implementation of innovative medical technologies. The "strategy" encompasses a broad scope of activities, from fundamental research to clinical research, approval review, safety precautions, insurance coverage, and international growth. One of the key projects of the "Strategy of Sakigake" is the "Sakigake Designation System," which supports Research and Development and early Clinical research in Japan to speed up the practical implementation of new medical products with the potential to be effective through priority consultations. MHLW will collaborate with PMDA to implement the plan [22].

Comparison study for GTPs

GTPs are regulated in the USA by the USFDA under Section 351 of the Biologics Act and the FDCA. In the EU, the EMA oversees them through amendments to Part IV of Annex I to the Staff Regulations of the European Communities (2001/83/EC) as per Directive No 107/2009/120/EC. In Japan, the PMDA governs GTPs under Chapter 1 of the PMDA, specifically sections 2 to 9. These regions have distinct approval pathways: the USA offers accelerated, BT, FTD, and OD pathways; the EU includes accelerated, conditional marketing authorization, PRIME Scheme, and orphan designation; and Japan provides priority review, OD, and SAKIGAKE pathway.

The approval procedures for gene products are similar across the USA, EU and Japan, but there are differences in terms of timelines and requirements. Generally, the US FDA review process is longer, while the EU and Japan have relatively shorter approval timelines. All of these regions have mechanisms in place to quickly approve innovative products that address critical medical needs. As a result, gene product manufacturers must navigate each region's unique regulatory requirements and approval timelines to bring their products to market across these territories. The regulatory approval pathway for GTPs is shown below in fig. 2 [24].

Europe Japan USA

Milestone meeting

Type a meeting

Type A meetings are reserved for meetings that are necessary for the continuation of an ongoing product development program or to resolve a critical safety issue [26].

Table 1: Comparison study for GTPs in the USA, EU AND Japan [23]

Country	USA	EU	JAPAN
Name	GTP	ATMP	Regenerative Medicinal Products
Jurisdiction	USFDA	EMA	PMDA
Regulations	Section 351 of the Biologics Act and the FDCA.	Amendments to Part IV of Annex I of Annex I to the Staff Regulations of the European Communities (2001/83/EC) by Directive No 1072009/120/EC	Chapter 1 of the Pharmaceutical and Medical Devices Act, sections 2 to 9.
Approval Pathways	<ul style="list-style-type: none"> Accelerated BTD FTD OD 	<ul style="list-style-type: none"> Accelerated Conditional marketing authorization “PRIME” scheme OD 	<ul style="list-style-type: none"> Priority review OD Sakigake
Application submissions	Before conducting clinical trials, manufacturers submit an IND application to the FDA.	Manufacturers file an MAA with the EMA to apply for marketing authorisations.	Manufacturers submit a NDA to the PMDA to apply for marketing authorization.
Preclinical and clinical testing	Manufacturers are required to conduct preclinical and clinical studies in each of the three areas to assess quality, efficacy, and safety. In each location, preclinical and clinical research goes through three stages.		
Clinical trial phases	Phase 1, 2 and 3		
Review and process	The NDA is reviewed by the FDA for safety, effectiveness, and quality.	The EMA assesses the MAA and assesses safety, effectiveness, and quality.	The PMDA also examines the NDA and evaluates its safety, effectiveness, and quality.
Approval timeline	6-8 mo	210 d	12 mo
Additional data	Required	NR	NR
Priority review	The FDA has a "Priority Review" process for some drugs that can help reduce the time it takes to review a drug.	In addition, the EU also has expedited procedures for products with a high level of public health relevance.	As mentioned above, Japan have a priority review process for novel gene products.

*NR-Not required



Fig. 2: Approval pathway of GTP and RMP in EU, Japan and the USA consulting with agencies

Table 2: Milestone meetings in the US, EU and Japan

Country	Milestone meetings
USA	EOP2, Pre-IND, Pre-BLA, Pre-NDA
EU	CHMP scientific recommendations
JAPAN	PMDA Consultations on Quality, Non-Clinical, and Clinical Gene Therapy Protocols
<i>Information meetings</i>	
USA	Pre-IND meeting for RMAT; Type C meeting [25].

Type B meeting–Pre-IND, EOP 1and2, pre-phase

Type B meetings must be scheduled by the FDA no later than 60 d after the date of receipt of a formal request for a Type B meeting. The sponsor or applicant may request a meeting date later than 60 d from the date of request receipt. FDA will work with the sponsor or applicant to establish the earliest possible date to schedule a clinical hold [27].

Type C meeting

Type C meetings are any meetings between CBER or CDER and sponsor(s) for the development and assessment of a non-type A or non-type B product When the FDA gets a written request for a

meeting, they should schedule it at the latest after 75 d. If the sponsor or applicant requests a meeting later than that, we'll work with them to fig. out the earliest possible time [27].

Regulatory guidelines

USA

Comparability and manufacturing changes for human cellular and GTPs

The FDA, a sponsor of IND and BLA applications for Hematopoietic Stem Cells (HSCs) and GTE products, is guiding product

comparability and management of manufacturing changes for licensed and experimental Cell and Gene Therapy Products (CGTP).

This guideline aims to share the FDA's current opinion on

- 1) Reporting lifecycle management for CGTP.
- 2) Comparability analyses to evaluate changes in production that affect product quality [28].

Europe

ICH S12 guideline

This guideline aims to provide a set of general principles for conducting a non-clinical Business Development (BD) study related to gene therapy. This outlines the general principles for non-clinical Business Development (BD) evaluations. The Interpretation Considerations and utilization of DB results support non-clinical development strategies as well as clinical trial design. 3R (reduce, refine/replace) concepts are used in this guideline to accelerate GT product development while minimising unnecessary animal use. This guideline refers to GT products that have mediated (translated) the transmitted genetic material. Examples of GT products include *ex vivo* GM-modified human cells, Polymerase Chain Reaction (PCR)-derived nucleic acids (plasmids and RNA), and microorganisms (e. g., viruses, bacteria, and fungi) that have been genetically modified for transgenesis expression. These guidelines also apply to *in vivo* Nuclease Transfection (NUTS) and RNA instructions that are not specifically transcribed or translated using a non-viral delivery mechanism. While not yet recognised as a GT in many regions, oncogenes (non-genetically engineered viruses) that do not express transgenes remain subject to the recommendations in this document. This guideline does not apply to vaccines used as a preventive measure.

This recommendation does not cover chemically synthesized oligo-equivalent products produced without a biotechnological manufacturing process. Excretion describes the release of a GT substance through the skin (pustules, wounds, wounds), secretions (urine, saliva, nasopharyngeal secretions, etc.) or secretions. The purpose of this recommendation is not to include the assessment of a GT product's nonclinical elimination profile. Additionally, this suggestion does not cover the study of the genomic and germline integration of GT products (29).

This guideline discusses the following.

Study population

Species, strains, and genders that are pertinent to the study should be included in the population. Additionally, consideration of the known mechanisms of action should be made while choosing animal models and the potential for Immune-Mediated Adverse Events (IMAEs).

Dosing

The maximum acceptable dosage for the species and predicted human exposure levels should be taken into consideration when choosing doses. It is important to choose dosing plans that will result in steady-state serum concentrations and simulate human exposure.

Study duration

The study's duration needs to be sufficient to allow for IMAE manifestation. Studies should also assess the likelihood of immunogenicity during repeated administrations and lengthy treatment durations.

Immunogenicity testing

It is important to conduct immunogenicity testing to evaluate the likelihood that binding and neutralising antibodies may arise.

Safety endpoints

The mode of operation of the product and the possibility of IMAEs should be taken into consideration while choosing the safety

endpoints. These have to contain histology, clinical indicators, and other pertinent information.

Dose-response

To establish the connection between dosage and the incidence of IMAEs, dose-response research may be required.

Sensitization studies

Sensitization tests can be required in some circumstances to determine the likelihood of cross-reactivity with endogenous proteins (30).

Japan

Regulations concerning certain regenerative medicine products

Regulatory frameworks for GCT clinical studies

In Japan, clinical research is conducted in two distinct forms: clinical trials and clinical research. Certain studies are conducted in medical facilities, while others are conducted in clinical research. Different review procedures must be followed to ensure that the study plans are approved before they can be implemented. MHLW has the authority to authorize both forms of clinical research in Japan. Based on the research findings, the MHLW can grant approvals for the marketing of products to the public or the provision of the technology to the public through the National Health Insurance System. Additionally, General Conventional (GCT) technologies in health research are also available. The agreement between a doctor and a patient allows for the establishment of private practices in clinics and hospitals. This classifies some of these "medical care" GCTs which examine medical care practices such as health research even though they are not conducted to advance knowledge [31].

Consultation with pharmaceutical affairs and notification of clinical trials

The PMDA requires sponsors to submit a clinical trial strategy to the PMDA (also known as a "Clinical Trial Notification"). Before authorizing the clinical research project, the PMDA is required by Article 80-2 of the PMD Act to assess the submission for 30 d. As well-known regenerative medicine products are complex, sponsors must complete a Pharma Affairs Consulting on Research and Development Strategy with the PMDA before they can submit a Clinical Trial Notice. Based on product specifications, adequacy of preclinical testing, details on the animal or human-derived components, and more, the PMDA will assess the efficacy and safety in this case. Review fees are required for the Pharmaceutical Affairs Consultation, although they are not required for Clinical Trial Notifications. Under certain circumstances, a 90% discount may be eligible for start-up enterprises or academic institutions. PMDA Consultations can be divided into several categories, so sponsors can discuss topics like clinical trial design (subject to additional fees). Clinical trials are included under GCP in regenerative medicine products (ICH-E6) [32].

There are several guidelines on GTP, GCP, and GCTP; the recent guidelines are:

GTP-Standards of biological raw materials, Operational guideline Q and A, PFSB/ELD, FSB/MDRMPE Administrative Notice, 2015

GCP-Procedure for remote inspection as a part of compliance inspection on drugs and regenerative medical products, PMDA/CPE Notification No. 0525001, 2022.

GCTP-Ministerial ordinances on GCTP for regenerative medical products, Q and A #3, PSEHB/CLD Notification No. 0629-1 [33]

Future aspects

USA

Increasing public and commercial funding in the field of cell and gene therapy

Cell and gene therapy businesses are drawing more private and governmental investment despite the low number of approvals.

Over the past ten years, private equity and capital investment in the life sciences has grown significantly. The surge of investment in firms that provide cell and gene therapy is also noteworthy. For example, investment has increased

dramatically, going from USD 362 million in 2020 to around USD 68 billion in 2021. As a result, it is anticipated that the need for outsourcing will rise, the expansion of the cell and gene therapy manufacturing industries.

Table 3: A few examples of approved GTPs

Product name	Company	Treatment	Year
U S A [34]			
Abecma (Idecabtagene vicleucel)	Celgene Corporation. [A division of Bristol-Myers Squibb]	Refractory multiple myeloma	2021
Adstiladrin	Ferring Pharmaceuticals A/S	High-risk blood cancer	2022
Alloccord (HPC, cord blood)	Medical Center for Children at Cardinal Glennon SSM	Donor-derived hematopoietic progenitor cells	2013
Breyanzi	Bristol-Myers Squibb	Large B-cell lymphoma, or LBCL	2022
Carvykti (Ciltacabtagene autoleucel)	Janssen Biotech	Refractory numerous myeloma	2023
Elevidys	Sarepta Therapeutics	Duchenne muscular dystrophy (DMD)	2023
Zolgensma	Novartis Gene Therapies	Type I Spinal Muscular Atrophy	2023
Europe (35)			
Abecma	Bristol-Myers Squibb Pharmaceutical EEIG	Kahler's disease	2021
Breyanzi	Bristol Meyers Squibb Pharma EEIG, IR	Cancer of white blood cells	2022
Carvykti	Janssen Cilag International N. V.	Refractory multiple myeloma	2022
Hemgenix	CSL Behring GmbH	Hemophilia B	2023
Imlygic	Amgen Eu-rope B. V.	Melanoma	2015
Kymriah	Novartis Europharm Ltd., IRL	Beta-cell non-Hodgkin lymphoma	2018
Libmeldy	Orchard Therapeutics	Early-onset MLD	2020
JAPAN (36)			
Idecabtagene vicleucel	Abecma	Multiple myeloma	2022
Darvadstrocel	Alofisel	Mesenchymal stem cell advanced therapy	2021
Lisocabtagene maraleucel	Breyanzi	Kill CD19-positive cancer cells	2021
Ciltacabtagene autoleucel	Carvykti	Refractory large B cell lymphoma	2022
Beperminogene per plasmid	Collatogene	Cytomegalovirus promoter	2019
Teseraturev	Delytact	Malignant Glioma	2021
An autologous human myoblast derived cell sheet.	Heart Sheet	Acute myocardial infarction (AMI)	2015

High production costs for gene and cell therapy

Cell treatments are expensive because of the cells and the therapy, the relatively low production quantities, and the numerous manual operations required by the present techniques. Compared to gene therapy, which can have manufacturing prices between USD 500,000 and USD 1 million, excluding R and D expenses, cell therapy treatments are projected to cost more than USD 100,000 per patient. As a result, both manufacturers and healthcare providers will face significant challenges related to the cost of cells and GTPs.

Expansion of CDMOS's manufacturing capabilities for cell and gene therapies

The fast growth in demand for cell and gene treatments has caused a rapid evolution in the manufacture of these medicines. Higher yields and reduced Cost Of Goods Sold (COGS) are required as a result of these medicines' expanded use (for instance, in treating increasingly widespread illnesses). Contract Development and Manufacturing Organizations (CDMOs) have invested a lot in this area recently, making several sizable acquisitions and expanding their geographic reach by setting up production facilities. These additions will facilitate the production of cell and gene treatments and give CDMOs prospects for expansion to offer these services [37].

Europe

In Europe, there are substantial obstacles, especially on the access side. Europe has been a wonderful pioneer in the field in many respects, having approved the first gene therapy and having a top-notch regulatory organization. However, Europe is now lagging in several important measures, most likely as a result of the interaction of challenging regulatory and reimbursement issues. Seven of the 23 ATMPs that the EU has authorized have been taken off the market. By the end of June 2022, there were 2% fewer developers based in Europe than there were five years prior, while the proportion in North America rose by 42% and the proportion in Asia-Pacific rose

by 271%. Additionally, clinical trial participants no longer have early access to investigational treatments. The H1 2022 Report emphasizes how the pipeline for clinical trials in Europe is getting smaller, especially for early-stage studies. There could be fewer approvals in Europe moving forward than there otherwise would be due to the drop in clinical trials. The EU will update its pharmaceutical laws for the first time in a generation; the proposal is anticipated in 2023. The project will have a significant impact on whether patients in Europe will have access to ATMPs for years to come by balancing affordability and access, among other issues [38].

Japan

The regulatory framework in Japan is one of the primary factors contributing to the highest number of cell treatments in that nation. The Regenerative Medicine Promotion Act was a new law that Japan passed in 2014 to hasten the discovery and approval of regenerative medicine, including cell treatments. By permitting conditional approval of regenerative medicine products based on the results of preliminary clinical studies, this rule reduced the time and resources required for clinical development.

Regenerative medicine research and development have also received considerable funding and support from the Japanese government, which has contributed to the favourable atmosphere for the industry's expansion. One example of this is the founding of the Japan agency, which offers financing and assistance for the study and development of regenerative medicine.

The ageing population of Japan and the prevalence of particular illnesses like Parkinson's disease and cancer have also had an impact on the need for cell therapies. Many Japanese companies have focused on developing and marketing cell therapies to address these unmet medical needs. Japan is a world leader in regenerative medicine and cell therapies because of its supportive regulatory environment, substantial market potential, and government funding and support. Additionally, cell therapies cost less than gene therapies, simplifying reimbursement [39].

CONCLUSION

GTPs compliance with regulations in the USA, EU, and Japan reflects how quickly this area is developing and changing. Gene therapy has the potential to fundamentally alter illnesses from cancer to inherited problems are treated. Even while the regulatory systems share elements like milestone meetings and safety evaluations, each area has developed unique ways and strategies to accelerate the development and approval of GTPs. To hasten the development of gene therapy USA has adopted initiatives including RMAT, FT, and BTM. While Japan's Sakigake system promotes the development of innovative medical items, the EU's PRIME program supports the prompt evaluation of new therapies. These programs highlight regulatory organizations dedication to promoting innovation and meeting unmet medical needs. GTPs that has received approval show the true achievements made in this field and offer hope to patients with rare diseases that were formerly incurable. As the environment for gene therapy keeps evolving, it will be crucial to properly overcome regulatory concerns like production costs, accessibility, and safety. As seen by the increased investments and development of manufacturing capabilities, people are becoming increasingly interested in and confident in the possibilities of gene therapy. The combined efforts of regulatory agencies, researchers, and business sectors will be crucial to realizing the full potential of GTPs. As regulators work to find a balance between patient access and safety, this will eventually change the face of medicine and patient care.

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AUTHORS CONTRIBUTIONS

OBPK played a comprehensive role by conceptualizing and designing the study and was involved in literature search, data acquisition and analysis, statistical analysis, manuscript preparation, editing, and review. SM supported in study design and was actively involved in content preparation, data synthesis, manuscript preparation, editing, and review of the same. MP helped in the study conceptualization and review of the manuscript.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. What is gene therapy? In: FDA. Available from: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy> [Last accessed on 25 Jul 2023]
2. Nhlbi. Genetic therapies-benefits and risks. NHLBI, NIH. Available from: <https://www.nih.gov/health/genetic-therapies/benefits-risks> [Last accessed on 15 Aug 2023]
3. The cost of sequencing a human genome. Available <https://www.genome.gov/about-genomics/fact-sheets/sequencing-human-genome-cost> [Last accessed on 07 Aug 2023]
4. Celec P, Gardlik R. Gene therapy using bacterial vectors. *Front Biosci (Landmark Ed)*. 2017 Jan 1;22(1):81-95. doi: 10.2741/4473, PMID 27814603.
5. Razi Soofiyani SR, Baradaran B, Lotfipour F, Kazemi T, Mohammadnejad L. Gene therapy, early promises, subsequent problems, and recent breakthroughs. *Adv Pharm Bull*. 2013;3(2):249-55. doi: 10.5681/apb.2013.041, PMID 24312844.
6. How to navigate global regulatory frameworks and expedited programs for gene therapy development in the U. S., EU, and Japan>premier research. Available from: <https://premier-research.com/blog-how-to-navigate-global-regulatory-frameworks-expedited-programs-for-gene-therapy-development-in-the-u-s-eu-japan> [Last accessed on 15 Aug 2023]
7. Fast track designation request performance. In: FDA. Available from: <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/fast-track-designation-request-performance> [Last accessed on 25 Jul 2023]
8. Breakthrough therapy. In: FDA. Available from: <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy> [Last accessed on 25 Jul 2023]
9. Vaggelas A, Seimetz D. Expediting drug development: FDA's new regenerative medicine advanced therapy designation. *Ther Innov Regul Sci*. 2019 May 1;53(3):364-73. doi: 10.1177/2168479018779373, PMID 29895180.
10. Designating an orphan product: drugs and biological products. In: FDA. Available from: <https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products> [Last accessed on 15 Aug 2023]
11. Heard JM, Vrinten C, Schlander M, Bellettato CM, Van Lingen C, Scarpa M. Availability, accessibility and delivery to patients of the 28 orphan medicines approved by the European Medicine Agency for hereditary metabolic diseases in the MetabERN network. *Orphanet J Rare Dis*. 2020 Jan 6;15(1):3. doi: 10.1186/s13023-019-1280-5, PMID 31907071.
12. Risk evaluation and mitigation strategies | REMS. In: FDA. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems> [Last accessed on 15 Aug 2023]
13. Postmarketing requirements and commitments: reports. In: FDA. Available from: <https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports> [Last accessed on 16 Aug 2023]
14. Eichler HG, Pignatti F, Schwarzer Daum B, Hidalgo Simon A, Eichler I, Arlett P. Randomized controlled trials versus real world evidence: neither magic nor myth. *Clin Pharmacol Ther*. 2021 May 1;109(5):1212-8. doi: 10.1002/cpt.2083, PMID 33063841.
15. Eichler HG, Pignatti F, Schwarzer Daum B, Hidalgo Simon A, Eichler I, Arlett P. Randomized controlled trials versus real world evidence: neither magic nor myth. *Clin Pharmacol Ther*. 2021 May 1;109(5):1212-8. doi: 10.1002/cpt.2083, PMID 33063841.
16. Sakurai A. Pharmaceuticals and Medical Devices Agency regenerative medicine and gene therapy in Japan Pharmaceuticals and Medical Devices Agency (PMDA)/Q5A(R2) EWG Deputy Topic Leader (MHLW/PMDA); 2013.
17. PRIME: priority medicines | European Medicines Agency. Available from: <https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines> [Last accessed on 25 Jul 2023]
18. PDF. Gene therapy. Principles and potential applications. Available from: https://www.researchgate.net/publication/11647636_gene_the_rapy_principles_and_potential_applications
19. Azuma K. Regulatory landscape of regenerative medicine in Japan. *Curr Stem Cell Rep*. 2015 Jun 1;1(2):118-28. doi: 10.1007/s40778-015-0012-6.
20. Maeda D, Yamaguchi T, Ishizuka T, Hirata M, Takekita K, Sato D. Regulatory frameworks for gene and cell therapies in Japan. *Adv Exp Med Biol*. 2015 Sep 19;871:147-62. Available from: <https://pubmed.ncbi.nlm.nih.gov/26374217> [Last accessed on 25 Jul 2023]
21. Tanaka M, Idei M, Sakaguchi H, Kato R, Sato D, Sawanobori K. Achievements and challenges of the Sakigake designation system in Japan. *Br J Clin Pharmacol*. 2021 Oct 1;87(10):4027-35. doi: 10.1111/bcp.14807, PMID 33694268.
22. Strategy of SAKIGAKE. Available from: <https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html> [Last accessed on 25 Jul 2023]
23. Sato Y, Ono S. Regulatory environment and approvals in cell and gene therapy products between Japan, the USA, and the EU. *Ther*

- Innov Regul Sci. 2023 Mar 1;57(2):227-37. doi: 10.1007/s43441-022-00455-4, PMID 36112305.
24. Sato Y, Ono S. Regulatory environment and approvals in cell and gene therapy products between Japan, the USA, and the EU. *Ther Innov Regul Sci.* 2023 Mar 1;57(2):227-37. doi: 10.1007/s43441-022-00455-4, PMID 36112305.
 25. Zhang J. Regulatory considerations to accelerate cell and gene therapy development; 2021.
 26. OTP Type a meetings. In: FDA. Available from: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-type-meetings> [Last accessed on 16 Aug 2023]
 27. Fda, Cder. Guidance for industry formal meetings between the FDA and sponsors or applicants; 2009. p. 301-796. Available from: <https://www.fda.gov/cber/guidelines.htm> [Last accessed on 13 Aug 2023]
 28. Manufacturing changes and comparability for human cellular and gene therapy products. In: FDA. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/manufacturing-changes-and-comparability-human-cellular-and-gene-therapy-products> [Last accessed on 25 Jul 2023]
 29. Ema. Step. Committee for Medicinal Products for Human Use ICH S12 Guideline on nonclinical biodistribution considerations for gene therapy products ICH S12 Guideline on nonclinical biodistribution considerations for gene therapy products; 2023. Available from: www.europa.eu/contact [Last accessed on 25 Jul 2023]
 30. Medicines Agency E. Committee for Medicinal Products for Human Use. In: ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products; 2021. Available from: <https://www.ema.europa.eu/contact> [Last accessed on 25 Jul 2023]
 31. Maeda H. The current status and future direction of clinical research in Japan from a regulatory perspective. *Front Med (Lausanne).* 2021 Jan 13;8:816921. doi: 10.3389/fmed.2021.816921, PMID 35096908.
 32. Moriyama Y. Clinical trial notifications and Clinical trial notifications and scientific consultation scientific consultation system in Japan system in Japan; 1994.
 33. Provisional Translation. Ministry of health, labour and welfare questions and answers (q and a) on points to consider for ensuring the reliability in utilization of data from registry or medical information database in applications for marketing approval and re-examination for regenerative medical products; 2023.
 34. Approved cellular and gene therapy products. In: FDA. Available from: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products> [Last accessed on 25 Jul 2023]
 35. PEI. Gene therapy medicinal products with a valid marketing authorisation- Paul-Ehrlich-institute. Available from: <https://www.de/en/medicinal-products/atmp/gene-therapy-medicinal-products/gene-therapy-node.html> [Last accessed on 25 Jul 2023]
 36. Review reports: regenerative medical products. In: Pharmaceuticals and Medical Devices Agency. Available from: <https://www.pmda.go.jp/english/review-services/reviews/approved-information/0004.html>.
 37. Cell and gene therapy manufacturing services market drivers and opportunities. Markets and Markets. Available from: https://www.marketsandmarkets.com/market-reports/cell-gene-therapy-manufacturing-services-market-180609441.html?gclid=CjwKCAjw5remBhBiEiwAxL2M94d_G161UicjoTkj8yN703GLwEh0LdvS3aB_an30JX1G7qdsHCgAlhoCeFcQAvD_BwE [Last accessed on 07 Aug 2023]
 38. The Cell and Gene Therapy Sector. In: A wave is coming—are we ready; 2023. Available from: <https://invivo.com/IV146781/the-cell-and-gene-therapy-sector-in-2023-a-wave-is-coming--are-we-ready> [Last accessed on 07 Aug 2023]
 39. Cell and gene therapies for rare disorders treatment in Japan. Available <https://www.delveinsight.com/blog/cell-and-gene-therapies-for-rare-disorders-treatment> [Last accessed on 07 Aug 2023]