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Authors

Hashmi, Shahrukh K
Jamil, M Abdullah
de la Fuente, Josu
et al.

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Title: Futuristic Global CGT Regulations Based on an Analysis of Today's Leading Frameworks

Authors and Affiliations: *Shahrukh K. Hashmi [1], M. Abdullah Jamil [2], Josu de la Fuente [3], Johnny Mahlangu [4], Margareth C. Ozelo [5], Mark C. Walters [6], Asma Almannaei [7], Alok Srivastava [8], Hazza Alzahrani [9], Peihua Lu [10], Teruyo Arato [11], Gili Kenet [12], Kaori Nomura [13], Philippe Leboulch [14]*

[1] Research and Innovation Center, Department of Health, Abu Dhabi, UAE; Department of Medicine, Mayo Clinic, Rochester, MN, USA; Department of Computer Vision, MBZU of Artificial Intelligence, Abu Dhabi, UAE

[2] Medical College, Aga Khan University, Karachi 74800, Pakistan

[3] Department of Paediatrics, Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK; Department of Immunology & Inflammation, Imperial College London, London, UK.

[4] Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, the National Health Laboratory Service, Johannesburg, South Africa; Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

[5] Hemocentro UNICAMP, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Campinas, São Paulo, Brazil

[6] Department of Pediatrics, UCSF Benioff Children's Hospital Oakland, Oakland, California, USA

[7] Research and Innovation Center, Department of Health, Abu Dhabi, UAE

[8] Haematology Research Unit, St. Johns Research Institute; Department of Clinical Haematology, St. John's Medical College Hospital, St. John's National Academy of Health Sciences, Koramangala, Bengaluru, India.

[9] Oncology Center, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

[10] Hebei Yanda Lu Daopei Hospital, Langfang, China; Lu Daopei Institute of Hematology, Beijing, China.

[11] Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo, Japan.

[12] The National Hemophilia Centre, The Amalia Biron Thrombosis Research Institute, Sheba Medical Centre, Tel Hashomer, Tel Aviv University, Tel Aviv, Tel Aviv, Israel

[13] Advanced Clinical Research Center, Fukushima Medical University, Fukushima, Japan.

[14] Department of Medicine, Genetics Division and Harvard international Center for Genetic Disease (iCGD), Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Corresponding Author:

Shahrukh K. Hashmi MD MPH

RIC, Department of Health, Abu Dhabi, UAE. *Email:* Shashmi@doh.gov.ae

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Abstract

The advancement of Cell and Gene therapies (CGT) represents a pivotal shift in the treatment model for cancers and a broad spectrum of other diseases, particularly rare and orphan disorders. Despite major advances, information regarding global regulatory pathways is scarce and often perplexing, with technicalities essential to approval such as current Good Manufacturing Practice (cGMP), Good Laboratory Practices (GLP), Certificate of Pharmaceutical Product (CPP), Chemistry, Manufacturing, and Controls (CMC), and pathways that accelerate the approval process like orphan drug designation, priority review, and fast track designation being inadvertently marginalized or overcomplicated at times. Furthermore, the globalization of these therapies is crucially hampered by fragmented, economically unsustainable and often perplexing regulatory pathways. These regulatory challenges and the high cost of the traditional clinical trial model create significant bottlenecks for developers. We analyze the current frameworks in major jurisdictions, highlighting the technicalities in each, and propose a new, harmonized global blueprint for development and approval. Key components of this proposed framework include a shift towards advanced preclinical models, adaptive trial design, and patient-centric endpoints. Along with simplifying the processes for CGT developers (whether industry or academia), adopting this framework could increase the efficiency of CGT approvals, and lower the development costs which can help in achieving the goal of *bench to bedside to globalization*, directly translate to a more robust research atmosphere that benefits all by increasing the efficiency of CGT trial and product approvals in both developed and developing countries.

Introduction

In 1990, four-year old “bubble girl” Ashanthi DeSilva received a pioneering intervention - gene therapy for Severe-Combined-Immunodeficiency (SCID)(1). Conventionally, the treatment options available to Ashanti were either haploidentical bone marrow transplantation (BMT) or replacement of missing enzyme through regular infusions of pegylated adenosine-deaminase (PEG-ADA); however, neither were deemed appropriate (2). Having been submitted more than three years earlier, a gene therapy protocol had undergone more than three submissions, extensive formal written reviews, hours of public discussions, and went through at least seven regulatory entities/sub-entities (1). The question arose why it took so much time and multiple layers of regulators: was the procedure itself too complex and novel, the regulatory pathways unclear, or both?

Since then, much progress has been accomplished with a growing number of cell and gene therapy (CGT) products approved by the United States Food-and-Drug-Administration (US-FDA), the European Medicines Agency (EMA) and many others. Today, cell and gene therapy spans ex-vivo retroviral vector (RV), lentiviral vectors (LV), herpes simplex virus vector (HSVV), gene editing approaches (GE), and in-vivo adeno-associated virus vectors (AAVV) with many others in the pipeline. Targeted diseases include select “liquid” cancers by means of chimeric antigen receptor (CAR-T) cell immunotherapy, and “solid” tumors in clinical trials such as advanced melanoma, non-small cell lung cancer, recurrent or metastatic head and neck cancer, urothelial carcinoma. In addition, there are a variety of inherited disorders that have been targeted including beta-thalassemia, sickle cell disease, hemophilia A and B, adenosine-deaminase-deficiency, aromatic L-amino acid decarboxylase deficiency, cerebral adrenoleukodystrophy, metachromatic leukodystrophy, *RPE65* mutation-associated retinal dystrophy, Duchenne muscular dystrophy, spinal muscular atrophy, dystrophic epidermolysis bullosa and others (3–6).

Gene therapies are defined by the US-FDA as products that “that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms”. EMA defines it as biological product that “contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence” (7). While there may be subtle differences between the two definitions, both cover the most fundamental concepts of gene therapy.

Approval from regulatory bodies like the US-FDA, EMA, Centre for Drug Evaluation (CDE) / National Medical Products Administration (NMPA), Medicines and Healthcare products Regulatory Agency (MHRA), Pharmaceuticals and Medical Devices Agency (PMDA) and others is crucial in the development of CGT (**Figure 1**). In 1999, a patient enrolled in a phase 1 trial in the US, Jesse Gelsinger, died 4 days after gene therapy with adenoviral vector administration from multiorgan failure secondary to overwhelming immune reaction (8). In another trial (in Europe) which focused on treating X-linked severe combined immunodeficiency (SCID-X1), four out of 9 patients developed T-cell leukemia 30-68 months after treatment. Investigators identified “insertional mutagenesis” as the probable culprit (8). Insertional mutagenesis can be simply defined as the process where the viral vector integrates into unintended sites (sometimes hard to differentiate between unintended off-target versus toxigenic effects) within the genome, causing mutations such as silencing or aberrant expressions of proto oncogenes (LIM domain-only 2 (LM02) specifically in the case of SCID-X1) (8,9). Before reported in the SCID-X1 trial,

the risk of insertional mutagenesis was considered negligible, and regulatory bodies and investigators mainly focused on ensuring cell lines and viral vectors were not contaminated (10). A consequence of the insertional mutagenesis events was vector design modification to ensure safety, such as using self-inactivating (SIN) long terminal repeat (LTR) viral vectors or lentiviral vector designs, which reduce the probability of vector-mediated transactivation of neighboring genes (9). Incidences like these slowed down progress of gene therapy development and approvals in North America and Europe due to regulatory concerns, while on the other side of the world, NMPA approved their first gene therapy product for clinical use in 2003 (11).

One of the first gene therapy approvals was alipogene tiparvovec (Glybera), which utilized an AAV vector aiming to treat lipoprotein-lipase deficiency. The Committee-of-Advanced-Therapies (CAT), established by the EMA to review CGT products, rejected the initial Glybera application in 2010 followed by Committee-on-Human-Medicinal-Products' (CHMP) decision. CHMP is responsible for the final recommendation to the European Union (EU). Following that, upon reevaluation, the CAT reversed its earlier ruling, but the CHMP's stance persisted. After a third review at the start of 2012, CHMP remained unsatisfied, although narrowly, missing the required majority by one vote. Finally, in the fourth review, Glybera received its marketing approval. Three rejections of Glybera were overcome before the go-ahead for use in the EU, demonstrating that gene therapy products are complicated not only from the developmental, but also regulatory perspectives (12). The case of Glybera also exemplifies the profound financial bottlenecks that can stall even scientifically successful therapies. The escalating costs associated with repeated applications resulted in the acquisition and liquidation of the initial pharmaceutical company by another entity before the final approval was granted (12,13). Such commercial uncertainty can deter investors, causing them to seek opportunities with more predictable returns. Therefore, mergers and acquisitions (M&A) have become a routine practice (for better or worse) in the business of CGT companies globally. This financial pressure is reflected in the recent investment trends. While CGT developers received a peak of 22.7 billion US\$ worth of investments in 2021 alone, that figure has dropped by 33% to 15.2 billion US\$ in 2024 (14).

Despite these financial headwinds neither the scientific vigor nor the importance of these therapies have diminished, with the scale on ongoing research underscoring this momentum (9). As of March 2023, there are 2,201 Phase 1 trials and 1,683 Phase 2, 3 trials (15). Concurrently, there are a total of at least 2,575 developers of gene therapy (16).

As of the writing of this paper, CGT is mainly being used for the treatment of cancers at 68.3% and with the cancer burden projected to increase worldwide, the utilization of CGT will likely continue to grow (12,15,17). Additionally, gene therapy is poised to be potentially curative for a plethora of genetic conditions, and can alleviate the suffering of millions of people worldwide (18).

However, CGT development is facing economic pressure, and coupled with the scientific complexity, necessitates a fundamental rethinking of the path to approval. In this paper, we analyze in technical detail the existing frameworks and expedited pathways for CGT manufacturing and approval. Based on this analysis, we propose a new, harmonized global blueprint leveraging adaptive trial designs, innovative endpoints, and modern manufacturing approaches to make the journey from bench to bedside to globalization faster, cheaper, and more predictable.

General Manufacturing Requirements and Essential Concepts

To better understand the essential requirements of CGT manufacturing, we will first briefly revisit the steps of manufacturing (**Tables 1 and 2**) (19–24). We will focus mainly on CGT for curative intent and will not be discussing supportive CGT (e.g. mesenchymal stromal cells) which are beyond the scope of this review.

Cell therapy, such as hematopoietic cell transplantation (HCT), aims at transferring allogeneic or autologous cells into a patient to alleviate symptoms or cure a disease whereas non-HCT CGTs involve the administration of genetic material into a patient for gene addition or gene editing, using carriers such as viral or non-viral vectors, whether in-vivo or ex-vivo (25). The autologous cellular and tissue-based products are not subject to regulatory oversight (in some jurisdictions) if they are collected and transplanted in the same procedure and same organ (homologous use) without significant manipulation, like bone grafts in orthopedic procedures or skin grafts in reconstructive procedures (26,27). The ex-vivo CGTs and allogeneic products require another layer of heightened safeguards for prevention of cross-contamination and the preservation of the Chain-of-Identity (COI) (28). A variety of artificial-intelligence based algorithms are available on supply-chain, and currently blockchain based COIs are being established in CGTs (29). The type of viral vector or novel capsid used is of prime importance from a regulatory perspective. There are at least five types of viral vectors used for CGTs and many under development: Type C retroviruses, lentiviruses, adenoviruses, adeno-associated viruses, and herpes simplex viruses. Rare deaths after adenovirus vector transfer, and leukemia occurrence in retrovirus patients have limited their usage, and AAV vectors are currently considered to be the safest option for most *systemic* gene therapies. According to a review observing viral vector trends, AAV vectors are currently the most popular in-vivo vector therapies (**Figure 2**) (21). Lentiviral vectors, however, dominate in most situations where life-long efficacy involves gene transfer into hematopoietic stem cells (besides the size of gene to be transferred). There are fundamental differences between the non-integrating and integrating viral vectors, as well as in their genotoxic risks, and a detailed description of similarities and differences of each of the viral vectors is beyond the scope of this review.

The development of viral vectors in the future should take full advantage of the progress in computational design and follow an innovative approach. Artificial intelligence (AI) based tools can now rapidly screen vast DNA libraries, using tools like Google's AlphaFold, and predict protein structures with incredible accuracy, allowing developers to design vectors in-silico for improved tissue targeting and optimal antigen binding (30) This innovative approach will be less time intensive than traditional methods which rely on laborious and costly trial and error wet lab screening, accelerating the pre-clinical design, de-risk candidates by increasing the probability of success and helping therapies reach the bedside faster (31)

Critical-Process-Parameters (CPPs) represent another fundamental aspect that requires attention. In viral vector production, the cultivation of mammalian cells involves an increased number of CPPs compared to other types of cultivations like bacterial or yeast. Maintaining control over these CPPs is essential in ensuring that the batch-to-batch variability remains minimal, which directly affects a product's critical-quality-attributes (CQA) (32,33). Another mandatory consideration in manufacturing gene therapy is the compliance of current Good-Manufacturing-Practice (cGMP) guidelines which vary across regions, but they usually serve the same purpose; “assure proper design, monitoring, and control of manufacturing processes and facilities” to ensure “the identity, strength, quality, and purity of drug products by requiring

that manufacturers of medications adequately control manufacturing operations” (34). cGMP is enforced by many regulatory agencies including US-FDA, MHRA and EMA, whereas World-Health-Organization (WHO) also has a version of cGMP followed in over a hundred countries (35–37). For a facility to be cGMP certified, the relevant regulatory body will award said certification upon inspection of the manufacturing systems, quality of raw materials, robustness of operating procedures (particularly quality management systems), product quality deviations and testing process, and the development and validation of a myriad of quality control (QC) tests that ensure the potency, purity, safety and identity of biologics (32,34).

Since cGMP certification is required for in-house production of gene therapy products and due to strict requirements in obtaining them, many companies choose out of house manufacturing via contract-development-and-manufacturing companies (CDMO), or in their own facilities at different locations in the world. Often, pharmaceutical companies that have the in-house manufacturing capacity acquire or partner with CDMO to expand production pipelines (21). Additionally, manufacturing processes for viral vectors are generally unautomated, low yielding processes, that require optimization and sometimes face difficulty in scaling-up (33). Scalability of CGT is an essential element in ensuring access to these therapies, and its critical importance was demonstrated a few years ago when the demand of a B-cell maturation antigen (BCMA) directed CAR-T cells for myeloma was far outstripped the supply due to production and scalability issues in the US (part of which may also be due to vector supply).

The entire process from *development to approval* can take over a decade and is estimated to cost more than two billion US\$ according to a study by Tufts University (incorporating costs for failures) (38). The development of a CGT involves multiple stages before reaching patients. Post-research and development (R&D) for a candidate product, the product enters preclinical research. This stage, conducted conventionally in animal models/species through in-vivo, ex-vivo, or both, assesses the safety and efficacy to prepare for human trials (32). Good-Laboratory-Practice (GLP), a quality system covering the organizational process and conditions for non-clinical laboratory studies, must be complied with during preclinical research (39). While the essentialness of GLP cannot be debated, the current reliance on multi-species animal testing for toxicology studies represents another major cost and time bottleneck. A more efficient and predictive future standard should be adopted, replacing the current model with a streamlined GLP- compliant toxicology study in advanced, human-cell-based platforms like organoids and spheroids. These platforms are essentially simplified organs and tissues grown from human cells to better predict a therapy’s effect. This approach provides more human-relevant data that could significantly accelerate the preclinical timeline from over a year to as little as a few months, without compromising on safety (40).

Subsequent clinical trials, approved by regulatory bodies based on the preclinical results proceed through phase 1-3 (in most cases), and may take several months to many years to complete (32). Trials must comply with ICH Good-Clinical-Practice (GCP) guidelines E6 (R3); a quality standard that covers multiple aspects of ethically conducting and reporting clinical trials involving human subjects. GCP, like the CGMP and GLP, is overseen by the relevant regulatory bodies (41). Regulatory bodies may also expedite reviews for therapies that uniquely serve small or specific patient populations (**Table 3**) (42–56). Following thorough analysis of the clinical trial performance, analyzing available treatment options, assessing potential risks and benefits, reviewing risk management strategies, and ensuring cGMP

guidelines have been followed by the manufacturer, the regulatory body would decide on the application. Decisions can come either in the form of an approval, denial, or a request for further information (32). This general pathway varies by region and authority, details of which are explored in subsequent sections for the large regulatory agencies.

US-FDA

To seek regulatory approval in the US and its territories, interested parties need to seek approval of the US-FDA (57,58). Within the US-FDA, gene therapy is under the jurisdiction of the Division of Cellular, Tissue and Gene Therapies, which is under the Office-of-Tissues-and-Advanced-Therapies (OTAT), which reports to the Center-for-Biologics-Evaluation-and-Research (CBER) (**Figure 3**) (59). To proceed from the preclinical stage and start clinical trials, interested parties must submit and receive approval of an Investigational-New-Drug (IND) application, but before submitting a plethora of steps need to be taken (60).

First and foremost, the sponsor needs to design and develop a product. The developer at this stage needs to take important considerations in mind, namely the method by which gene addition or editing will be achieved, the type and degree of genomic modification desired for the therapeutic effect and the delivery method of the GE components (nuclease dependent or independent etc.). These considerations must be clearly defined during this phase including technical details e.g. homology directed repair (HDR) versus non-homologous end-joining (NHEJ) if applicable etc. The therapeutic editing threshold of the therapy also needs to be chosen during development. The US-FDA expects clear justification from the developer for this choice, and clinical data supporting the choice when available. Finally, the optimal delivery method should be defined. Method of delivery would depend on the nature of the therapy, whether it is ex-vivo or in-vivo; the appropriate choice should be made (viral vector considerations discussed above) (61).

The US-FDA (like most regulators) also requires sponsors to submit a cGMP compliant Chemistry-Manufacturing-and-Control (CMC) information with the IND. Any consequential changes to the CMC that may occur as the protocol progresses need to be submitted for review before being implemented. Lack of sufficient CMC details (including stability with a target shelf-life and a list of raw materials) can result in a on hold placed by the US-FDA due to failure to assess risks to subjects in the proposed study (62).

Following this, the rationale and proof-of-concept (POC) must be established. POC studies can be conducted via in-vitro models, animal species, or animal models. It should be noted that the use of non-human primates (NHP), multiple rodent, or non-rodent species is not necessarily a default, and the sponsor will be required to provide scientific justification for their choice, as sometimes non-standard test species like genetically modified rodents or large animals (sheep, goats etc.) may be acceptable. Collectively, the results from POC's serve to establish the rationale and feasibility of the proposed clinical trial, as well as guiding the preclinical toxicology and safety study designs (59,61,63,64).

Once initial POC studies have been carried out and data produced, the US-FDA is open to pre-pre-IND meetings (e.g. INTERACT) which are discussions with CBER which allows them to provide constructive feedback and advice based on the initial POC studies (59,65,66). The pre-IND phase of development may include therapeutic optimization of manufacturing with toxicology. The next step in the process involves toxicology/safety studies. Importantly, it should be noted that toxicology studies are expected to be GLP

compliant (discussed previously), unlike POC studies that do not collect safety endpoints (63). The complete and extensive requirements for IND can be found on the US-FDA's resource center (63). As a significant update to these preclinical safety requirements, the US-FDA announced in April 2025 its plans to phase out animal testing, focusing instead on AI based computational models and organoids (benefits discussed previously), signaling the regulatory desire to streamline and modernize the regulatory process for the 21st century (67).

Study participants must be selected in a manner that balances the overall risk-benefit, interpretability of results, lack of other treatment options etc. Some CGT products are developed specifically for the pediatric populations, in that case, often trials may be carried out in adult subjects to obtain initial safety data. CGT products also require long-term follow-up of participants to identify any late safety issues. Often, sponsors have separate protocols for long term monitoring and safety/efficacy (68).

After the clinical trials are completed and results of the last phase show promise, a Biologics-License-Application (BLA) is submitted to the US-FDA. Once approved, the therapy will be authorized to be distributed via specialized US-FDA approved sites (69,70) (**Figure 4**).

However, since CGTs often treat rare and orphan diseases, the US-FDA has special considerations in place to expedite the review process. These designations are breakthrough therapy designation, accelerated approval, regenerative-medicine-advanced-therapy (RMAT) designation, fast track designation, and priority review designation (71) (**Table 3**).

While the US-FDA's structured pathway has historically ensured a high standard of safety, reforms such as expedited pathways and the recent shift towards innovative preclinical testing signal a positive evolution in the regulatory policy and an ambition to set a new global standard.

EMA

Organizations seeking regulatory approval within the European Union (EU) will be required to consult EMA. The EMA was formed in 1995 with the goal of reducing costs incurred by companies in submitting separate marketing requests for approval in European-Union (EU) member states, in addition to protecting human and animal rights. It is responsible for recommending centralized marketing authorizations for all EU-member-states-and-European-Economic-Area (EEA) countries to the European Commission (EC), such that the single authorization granted by the EC will enable marketing and availability of said therapy in all of EU and EEA (72–74). The EMA operates a centralized approval pathways for what is defined as advanced therapy medicinal products (ATMP) which include gene and cell therapies and forwards recommendations to the EC. The EC then takes a legally binding decision based on EMA's recommendation (75).

Before being granted approval by the EC, applications are evaluated by the CAT, and then the CHMP (75). The CAT and CHMP are scientific committees under the EMA, and carry out most of the scientific evaluation work (74). Among other roles like regulating and supervising ATMP development in the EU, the CAT is responsible for drafting an initial opinion of the MAA submitted by pharmaceutical companies (76). This is done based on the quality, safety and efficacy of the ATMP based on preclinical and clinical data (75). These opinions are then further discussed by the CHMP, where a final opinion is generated and forwarded to the EC. The EC then makes its final decision based on CHMP's recommendations (73).

The EMA recommends a risk-based approach for ATMP development, with a priority given to safety of subjects throughout (77). Prior to clinical studies, the steps followed for the European market are somewhat similar to those in the US (77–79). As with the US-FDA, preclinical studies need to be compliant with GLP regulations, however regulations may differ from the US-FDA's as EU has separate Directives for GLP that are applicable across the EU and EEA (80).

As of January 1, 2023, EMA approved a regulation that allows a single application for clinical trials in multiple European countries rather than separate applications to each competent authority, and all initial trials must be submitted through the system. This system is called the Clinical Trial Information System (CTIS) and simplifies the process to initiate first-in-human (FIH) trials (79). Member State approval is still required for the trial to start; however, sponsors do not have to submit requests to each concerned competent authority in separate member states in the case of applying to multiple member states. A CTIS application consists of three parts: Forms and Member state concerned (MSC), Part 1, and Part 2. Forms and MSC must have the necessary form requirements, justification of trial category and justification for MSC selection. (81). It should be noted that although the CTIS submission may be equivalent to the IND submission to the US-FDA, there are additional requirements in the CTIS and therefore applications similar to the IND by sponsors located in the US, if not adapted to the additional requirements, would result in an incomplete application (82). This centralized procedure is a pioneering step in regional harmonization and can set the framework for *global harmonization*.

Once all three phases of clinical trials have been conducted, the next step of the approval process with EMA is to submit an eligibility request for an MAA. It should be noted that these requirements (GMP, GLP, GCP) may differ from those of the US-FDA as the EMA has its own directives issued for each of the above (80,83,84).

The EMA also offers scientific advice and protocol assistance throughout the development cycle, which it specially recommends for teams developing innovative medicine or responding to unmet clinical need, which is often the case with ATMP (85). (**Table 3**). An example of this would be the **priority medicines** (PRIME) scheme, which accelerates the review of medicines that may offer a significant advantage over existing treatments, especially for severe or life-threatening diseases (86). Additionally, the EMA offers an orphan designation to certain therapies that respond to rare medical conditions that only affect a handful of people. (87). It is important to note that more than half of the ATMP approved obtained orphan status (88). Companies based in the EU can also enjoy a plethora of benefits under the small and medium-sized enterprises (SME) which is important to incentivize startup companies to invest in CGT development (89). Furthermore, the EMA has established up Data Analysis and Real World Interrogation Network (DARWIN EU®), which aims to integrate real-world evidence collected from centers across the EU into the regulatory lifecycle, making regulatory oversight more adaptive and data driven (90).

NMPA/CDE

The People's Republic of China is one of the pioneers in the CGT landscape, being one of the first countries to have approved a CGT (11). Presently, China is one of the top countries for ongoing clinical trials, along with the US (15,91).

Regulation in China is undertaken by various governmental organizations with interlinked role. An application can take one of two pathways based on the classification of the therapy: the drug track or the

medical technology track (92). The two tracks differ in regulations, and regulatory bodies depending on their (investigator-initiated trial) IIT status mainly (91) (**Figure 5**).

The drug track requires an IND submission to the Centre for Drug Evaluation (CDE), an affiliate institution of the NMPA, which is charged with reviewing the application. The CDE appoints a drug evaluation team (DET) to review the quality, safety and efficacy of products submitted in an IND or later in the BLA (93,94). Clinical trials are carried out under the regulatory oversight of the NMPA and compliance with GCP and cGMP will be mandatory in this pathway. Usually, pharmaceutical or biotechnology companies are the sponsor for clinical trials as these studies are conducted with the goal of achieving marketing authorization, which can be applied for following the clinical trials (93). Similar to the US-FDA, MHRA and EMA, the CDE has published guidelines and recommendations that address the technical aspects of the whole process such recommending sponsors illustrate the rationale of selecting an animal model, possibility of using an organoid model, technical points in for proof of concept studies, risk assessment of the therapy, CMC study strategy and adequate risk assessments (95).

The other pathway, medical technology track, is regulated by the National Health Commission (NHC) the successor of the Ministry of Health (MOH) (96). The medical technology track is usually initiated by academic or medical institutions to conduct clinical research and explore further rather than collect data for a MAA (93). These studies, which are essentially IITs, allow a for a more flexible approach during preclinical research in contrast to clinical trials which are more standardized (92). IIT's are regulated by the NHC and NMPA while quality supervision is the responsibility of the institution. Institutions are required to meet certain criteria to be eligible to conduct IITs such as having an established capacity for research, equipped with relevant personnel and risk control systems, and have institutional ethics committees and institutional academic committees to oversee and address ethical issues (93). Notably, IIT's can be converted into the "drug" track after an IND submission and is the chosen path for many CGT products in China, given they are conducted in accordance with GCP principles and demonstrate safety and effectiveness of the intervention with technical evidence (92,93).

As is the case with other frontrunning regulatory authorities like the EMA, MHRA and US-FDA, the NMPA/CDE also offers various designations that fast track a drug application (**Table 3**). Various CGT products have been granted these designations. In addition, NMPA also provides the option for developers to avail meeting throughout the development cycle like, pre-IND and pre-New Drug Application (NDA) to facilitate development (95).

MHRA

MHRA is the UK regulatory body responsible for overseeing the approval of medicines, including CGT. If tissues and cells are being used as starting materials in a medicinal product, the donation, procurement and testing of the cells are licensed and regulated by the Human Tissues Authority (HTA). Once the starting materials have been made available, medicines legislation applies and is regulated by MHRA.

Before submitting for formal approval, CGT require clinical trials for which Clinical Trial Authorization (CTA) is necessary. The pathway to obtain CTA includes an optional Pre-CTA Meeting where the sponsor discusses the clinical trial design, data requirements, and specific regulatory pathways, followed by submissions of Investigational Medicinal Product Dossier (IMPD) containing all relevant data related to the gene therapy product (including its manufacturing process, quality control and preclinical data),

clinical trial protocol (detailed description of the clinical trial's design, including endpoints, patient selection criteria, treatment regimens, and statistical methods), preclinical study reports (including data on safety, efficacy, pharmacology, and the vector's behavior), manufacturing and control information (details on the production of the gene therapy, the vector used, characterization of the gene construct, and details about the quality control processes). Once the Research Ethics Committee (REC) approves of the trial protocol, the MHRA reviews the application, issuing an approval to proceed with the clinical trial (48).

Once clinical trials have demonstrated acceptable safety and efficacy profiles, the gene therapy product may be submitted for MAA. This is done through the Centralized Procedure for gene therapies, which is recommended for orphan drugs and ATMP. Gene therapies are classified as ATMP under UK law. The pathway for MAA includes an optional pre-submission scientific advice meeting, a formal MAA dossier submission in Common Technical Document (CTD) format. The Committee for Advanced Therapies (CAT) then evaluates the scientific data, (including an assessment of clinical trial outcomes, manufacturing and quality control and risk-benefit profile of the therapy). Risk-benefit analysis is used to assess the long-term risk of adverse events, considering the nature of gene therapy and its potential benefits, including the post-marketing surveillance plan and any conditional approvals that might apply (**Table 3**). Once these steps are completed, a decision is awarded depending on MHRA assessment of safety and efficacy. The approval may come with conditions such as post-marketing commitments or restricted use. If refused, the sponsor is informed of the reasons and may be given the opportunity to resubmit with further data or modifications. Specific attention is paid to long-term monitoring, as gene therapies may have delayed side effects. The MHRA also requires plans for post-marketing surveillance to track the long-term effects of the therapy (97).

PMDA

CGTs have been handled within the framework of regenerative medical products since Japan amended the Pharmaceutical Affairs Law in 2014, separating them from drugs and devices regulations. Before commencing a clinical trial of an investigational CGT, the sponsor needs to provide details regarding the quality and non-clinical safety of the new investigational product. It is recommended that the sponsor request a scientific consultation with the responsible regulatory authority, the Pharmaceuticals and Medical Devices Agency (PMDA), to determine whether a clinical trial with the investigational CGT has a plausible rationale. In cases where CGTs do not meet criteria of regular approval, they may be granted a time-limited conditional approval, given that the results from clinical trials can predict efficacy and assure safety. This approval pathway allows the product to obtain a regular approval only after the sponsor conducts post-marketing studies required by the regulators and confirms the product's efficacy and safety (98,99).

In Japan, 21 CGTs were approved by 2024. Of these, 10 out of 12 cell products and 2 out of 4 in-vivo gene products are of Japanese origin, while all five ex-vivo gene products are developed globally. Three cell products and two in-vivo gene therapy products of Japanese origin are products with time-limited conditional approval. Two products did not receive regular approval due to failure to demonstrate the efficacy in post-marketing studies. Some clinical aspects at approval were summarized elsewhere (100).

Other countries

Since CGT is relatively new in some African and Asian countries, the regulatory authorities are gearing up in establishing guidelines and policies in this area. Among numerous ex-vivo and in-vivo CGTs, CAR-T cells appear very promising and, given that a lot of them are being approved for hematologic malignancies, their utilization both on-trial and off-trial continues to increase. Given that many inherited diseases are potentially cured by gene therapies e.g. hemoglobinopathies, hemophilia, metachromatic leukodystrophy, SMA-1 etc., it is imperative that policies and standards, besides comprehensive guidelines, be established in both developed and developing countries for utilization of gene therapy.

In India, indigenous CAR-T Cell products have followed local regulatory paths; and there is an on-going FIH lentiviral vector-based gene therapy for hemophilia which has also been processed as per local regulations results of which (first 5 patients) were recently published (101). Thailand has also become very active in CGT for malignancies (CAR-T cells) and inherited disorders, such as beta-thalassemia (102). In Saudi Arabia, at least two CAR-T cell therapies and one gene therapy, have been approved (103).

CD-19 CAR-T therapy is produced and approved in Israel as well, for use in leukemia or aggressive lymphoma patients (104). In GCC, many other countries, including UAE, have started making policies on CGTs to be utilized in their citizens.

In Brazil, since 2019, when the Brazilian Health Regulatory Agency (ANVISA) approved a clinical trial using gene therapy for hemophilia, several other products based on CGT have subsequently gained approval and obtained licenses. Notably, this encompasses two clinical trials dedicated to the national development of a product based on CAR T-cells for treating patients with lymphomas and leukemias. This initiative is crucial to ANVISA's broader efforts to foster regulatory collaboration with Brazilian researchers and developers. Its primary goal is to accelerate the development of advanced therapy products, ensuring their availability within the Unified Health System (SUS) (105).

A Blueprint for a Modernized CGT Framework

Having explored the current regulatory system for major jurisdictions worldwide, this section proposes a multi-pronged blueprint for a more efficient and globalized framework. As previously discussed, the preclinical phase is already evolving, with regulators beginning to embrace innovations like human models and in-silico designs to address long standing *preclinical* bottlenecks. However, the most significant and costly hurdles remain in the clinical phase.

The traditional, linear phase 1-3 clinical trial model is economically unsustainable, creating a “valley of death” between early stage and late-stage development (106). According to global data, around 50% of CGT products are unsuccessful in progressing from phase 1 to phase 2, with failure rates increasing to nearly 75% in phase 2-3 transition. Composite success rates for CGT are low being only 5% (107,108). Each phase of clinical trials is extremely time-and labor intensive, with out-of-pocket cost estimates in the US ranging around 30, 65 and 250 plus million US\$ for phases 1,2, and 3 respectively (109) An estimate for the fully capitalized (out-of-pocket plus cost-of-capital) makes the total cost of a successful therapy even higher, at about 2.6 billion US\$ (38).

This leads to a vicious cycle of low success rates and high costs, which deters investment and puts a strain on the resources of developers. To recoup the costs of development, the few therapies that do gain regulatory approval are often priced at exorbitant amounts. This strategy transfers the financial burden to patients and an already stressed healthcare system, creating significant barriers to access. Ultimately, this creates a paradox where scientifically brilliant therapies are developed, but the underlying economic model limits their reach and impact, failing all stakeholders: innovators, investors, patients and regulators (110).

To address these bottlenecks, we propose a shift to a more flexible and efficient adaptive design. The proposed pathway starts with developers conducting a preclinical phase, where candidate design, efficacy and therapeutic studies are conducted in-silico and/or in organoids and humanoids. Once these parameters have been confirmed, and after consultation with the regulatory agency, the developer submits an IND application. Upon IND approval, FIH phase 1 trials (incorporating innovative strategies) begin.

The simplest of these are “basket” and “umbrella” trials. A basket trial tests a single therapy across multiple different diseases that share a common molecular biomarker, while an umbrella trial investigates multiple different therapies within a single disease. Perhaps the most powerful and efficient trial design would be platform trials. Like umbrella trials, platform trials evaluate multiple therapies for a single disease, with the added flexibility of adding or removing treatments during the trial (111). These strategies, while not widely used, have resulted in success stories in the real world. Larotrectinib and Pertuzumab have achieved regulatory approval, in both the US and EU, based on basket and platform designs, respectively (112). Once a candidate has shown good efficacy and safety in innovative phase 1 trials, the regulatory body should meet and approve the next phase, a pivotal (registration) trial. Designed in consultation with the regulatory agency, the registration trial will be statistically powered to generate substantial evidence of effectiveness. Crucially, the trial will move beyond traditional single endpoints and instead utilize patient centric, composite endpoints, utilizing newer statistical methods such as win ratios. Briefly, win ratio is a statistical method of analysis that compares two cohorts of patients using multiple pre-specified and hierarchically ranked endpoints and compares each patient in the two groups in a pairwise fashion, to determine the therapy's overall clinical benefit beyond a single measure like progression-free survival. This method has been used successfully in cardiovascular trials such as the TRILUMINATE trial (113). By providing definitive evidence of efficacy in a single, efficient study, the pivotal trial model can replace costly traditional phase 2 and 3 trials (114). Currently, the US-FDA facilitates the use of novel trial designs through its Complex Innovative Trial Design (CID) Pilot Program. However, the scope of this program is limited, as it accepts only a small number of proposals each year, excluding first-in-human (FIH) studies (115).

Beyond trial efficiency, the vector's design is of paramount importance from a safety perspective. At present, CGT approvals have mostly been centered around ex-vivo therapies such as CAR-T cells, with all of the current 7 US-FDA approved CAR-T therapies being ex-vivo, and utilizing either Lentiviral or Retroviral vectors (4). However, recent studies have demonstrated hematological cancers in CAR-T cell and gene therapy recipients (116–118). Considering these findings, investigators will continue to develop strategies to increase the long-term safety of these products by alternating vectors and methods of delivery. As such, regulatory authorities, developers, and clinicians should all be ready for this change. The two latest studies demonstrating severe adverse events both utilized lentiviral vectors for gene

delivery, demonstrating that the design of the vector is critically important from a safety perspective as the expression of transgene near the integration may increase the risk of oncogenesis (117,118).

Early phase studies to investigate whether lipid nanoparticles (LNPs) and various transposons can be optimized as an alternative to viral vectors have been initiated, following the resounding success of mRNA COVID-19 vaccines (119). This may also help with another major concern in globalization of CGTs, as ex-vivo therapies may not be a practical option for many developing countries due to expense, rapid availability issues (including supply-chain), and many other factors.

Investigations are currently ongoing to develop in-vivo CGTs for malignant and non-malignant conditions, which may be a possible solution towards globalization of CGT. In-vivo therapies may have the advantage of being more economical, practical, and theoretically safer as chemotherapy regimens may not necessary for conditioning (119). Anticipating these changes, regulatory bodies, in addition to ensuring the vectors aren't causing translational mutagenesis, will also need to focus on minimizing "off-target effects", which are comparatively more concerning with in-vivo therapies with viral vectors.

A more robust and carefully monitored long term follow-up plan, for clinical trials, would be crucial to ensure safety of these groundbreaking but often unpredictable therapies (120). In general, the long-term follow-up plan should be individualized for cellular therapies versus gene therapies given actuarial life expectancy differences in the populations on which these therapies are utilized. Many CAR-T cell therapies will be utilized for middle-aged and elderly individuals (especially for myelomas and lymphomas), whereas majority of the systemic gene therapies currently available for clinical use in various jurisdictions will be used in younger populations (e.g. pediatric or adolescent patients). Thus, for pharmacovigilance purposes for real-world studies, a long-term plan is necessary from a regulatory perspective for CGTs before they are being commercialized.

Conclusions:

As the approval pathways vary from country to country, and timelines for approvals also differ, the global expansion of CGT is a very complicated process since patients needing these therapies are distributed globally particularly in low- middle- income countries [LMIC], where the actual burden of inherited disorders (which may be cured by gene therapies) may be even higher proportionately to well-resourced nations.

Moreover, the cost of these CGTs is significantly high and may initially lead to access disparities, unfortunately. Reduction of the direct cost for gene therapies is complicated, however, a conscious systematic effort jointly by regulators and developers of the CGT (academia or industry) should be undertaken (ideally prior to initiating clinical trials), especially when the ethical dilemma of life-saving CGT products for rare/orphan diseases versus cost/distribution is a main consideration for globalization. One method to lower costs and increase throughput is to integrate innovative strategies in every phase of drug development. Beyond lowering development costs, innovative payment models will be essential for ensuring these novel therapies reach the patients who need them.

Recognizing and validating the needs of all stakeholders in CGT is essential to advance in a collaborative manner; the need of regulators to ensure safety of the novel therapy, the patients' demand for relief from

rare diseases that are conventionally incurable, and the desire of pharmaceutical & biotechnology developers to market therapies without delays in development. To mitigate delays in the approval process without compromising on safety, the following strategies are suggested: a unified regulatory framework in a region/country rather than multiple authorities with differing requirements, greater emphasis on communication between regulators, developers (industry or academia), and end-users (clinicians) is necessary. Multiple regulatory agencies judging a specific therapy can lead to delays in approval as seen with the case of Glybera, as such, every country or region should ideally have one authority that conducts a robust evaluation. Delays and rejections may also occur due to regulators' uncertainty regarding the minute details in the expectations from developers set by the agencies. Dedicated channels of communication and real-time feedback at every stage of the process can help set expectations early on. EMA's centralized approval framework can be a good example to achieve global access.

Countries whose CGT programs are in infancy should consider facilitating and expediting reviews of therapies approved by their well-experienced counterparts internationally. For the major players of the CGT industry, a greater emphasis on inter-agency equivalation should be made early on, and preferably the clinical trials should be international, so that such therapy approvals can be translated to worldwide access. Afterall, the translation of the overall goal of bench-to-bedside is measured by time-to-commercial approval, and then time-to-market, and currently, consideration is the *global market* consistent of both developed countries and LMICs.

Irrespective of these critical aspects in developing CGT and the need for rapid globalization, what does not change is the scrutiny (via real-world evidence generation, pharmacovigilance, and direct reporting) that the regulators and CGT developers need to pay *after* approval of these products for years post-treatment, as this is a new era, and one can never predict the long-term effects of any novel therapy. By embracing a framework built on advanced preclinical designs, efficient adaptive trials, and a robust commitment to long-term pharmacovigilance, the global community can build a framework that fulfils the transformative promise of cell and gene therapy for the 21st century and beyond.

References

1. Anderson WF. September 14, 1990: the beginning. *Hum Gene Ther* [Internet]. 1990 [cited 2024 Jan 22];1(4):371–2. Available from: <https://pubmed.ncbi.nlm.nih.gov/1981846/>
2. Anderson WF, Blaese RM, Culver K. The ADA human gene therapy clinical protocol: Points to Consider response with clinical protocol, July 6, 1990. *Hum Gene Ther* [Internet]. 1990 [cited 2024 Jan 22];1(3):331–62. Available from: <https://pubmed.ncbi.nlm.nih.gov/11642817/>
3. Medicines Agency E. Advanced therapy medicinal products approvals Extension of indication of authorised ATMPs Overview of product-related activities. 2024 [cited 2024 Jul 27]; Available from: www.ema.europa.eu/contact
4. Approved Cellular and Gene Therapy Products | FDA [Internet]. [cited 2024 Jul 27]. Available from: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>
5. FDA grants accelerated approval to lifileucel for unresectable or metastatic melanoma | FDA [Internet]. [cited 2024 Jul 27]. Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-lifileucel-unresectable-or-metastatic-melanoma>
6. FDA approves first cancer treatment for any solid tumor with a specific genetic feature | FDA [Internet]. [cited 2024 Jul 27]. Available from: <https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature>
7. Wirth T, Parker N, Ylä-Herttuala S. History of gene therapy. *Gene* [Internet]. 2013 Aug 10 [cited 2024 Jan 22];525(2):162–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/23618815/>
8. Heelan B. History of Gene Therapy Products. *Handb Cell Gene Ther From Proof-of-Concept through Manuf to Commer* [Internet]. 2023 Jan 1 [cited 2024 Jan 24];1–12. Available from: <https://www.taylorfrancis.com/chapters/edit/10.1201/9781003285069-1/history-gene-therapy-products-bridget-heelan>
9. Medicines Agency E. Reflection paper on management of clinical risks deriving from insertional mutagenesis. [cited 2024 Jan 24]; Available from: www.ema.europa.eu
10. Wu C, Dunbar CE. Stem cell gene therapy: the risks of insertional mutagenesis and approaches to minimize genotoxicity. *Front Med* 2011 54 [Internet]. 2011 Dec 27 [cited 2024 Jan 24];5(4):356–71. Available from: <https://link.springer.com/article/10.1007/s11684-011-0159-1>
11. Guo J, Xin H. Chinese gene therapy. Splicing out the West? *Science* [Internet]. 2006 Nov 24 [cited 2024 Jan 22];314(5803):1232–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/17124300/>
12. Ylä-Herttuala S. Endgame: glybera finally recommended for approval as the first gene therapy drug in the European union. *Mol Ther* [Internet]. 2012 Oct [cited 2024 Jan 22];20(10):1831–2. Available from: <https://pubmed.ncbi.nlm.nih.gov/23023051/>
13. Glybera | European Medicines Agency [Internet]. [cited 2024 Feb 24]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/glybera>
14. Investments by Year.

15. GTCT (a873679) [Internet]. [cited 2024 Jan 24]. Available from: <https://a873679.fmphost.com/fmi/webd/GTCT>
16. Cell and Gene Therapy Sector Data - Alliance for Regenerative Medicine [Internet]. [cited 2024 Jan 24]. Available from: <https://www.alliancerm.org/data>
17. Worldwide cancer data | World Cancer Research Fund International [Internet]. [cited 2024 Jan 24]. Available from: <https://www.wcrf.org/cancer-trends/worldwide-cancer-data/>
18. How Gene Therapy Can Cure or Treat Diseases | FDA [Internet]. [cited 2024 Jan 24]. Available from: <https://www.fda.gov/consumers/consumer-updates/how-gene-therapy-can-cure-or-treat-diseases>
19. Vega-Mercado H. Gene Therapy Products Basics and Manufacturing Considerations. Handb Cell Gene Ther From Proof-of-Concept through Manuf to Commer [Internet]. 2023 Jan 1 [cited 2024 Feb 7];35–48. Available from: <https://www.taylorfrancis.com/chapters/edit/10.1201/9781003285069-4/gene-therapy-products-humberto-vega-mercado>
20. General Chapters: <1046> CELL AND GENE THERAPY PRODUCTS [Internet]. [cited 2024 Feb 7]. Available from: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1046_viewall.html
21. Nishida Y, Kodama K, Sengoku S. The gap between development and manufacturing in gene therapy: Strategic options for overcoming traps. Drug Discov Today. 2023 Feb 1;28(2):103429.
22. eBook: Gene Therapy—From Set-Up to Scale-Up - US. [cited 2024 Feb 7]; Available from: <https://www.thermofisher.com/us/en/home/global/forms/ebook-gene-therapy-from-set-up-to-scale-up.html>
23. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. “Off-the-shelf” allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov [Internet]. 2020 Mar 1 [cited 2024 Feb 7];19(3):185–99. Available from: <https://pubmed.ncbi.nlm.nih.gov/31900462/>
24. Vega-Mercado H. Cell Therapy Products: Basics and Manufacturing Considerations. Handb Cell Gene Ther From Proof-of-Concept through Manuf to Commer [Internet]. 2023 Jan 1 [cited 2024 Feb 7];49–64. Available from: <https://www.taylorfrancis.com/chapters/edit/10.1201/9781003285069-5/cell-therapy-products-humberto-vega-mercado>
25. Gene therapy - RaDaR [Internet]. [cited 2024 Feb 8]. Available from: <https://registries.ncats.nih.gov/glossary/gene-therapy/>
26. CFR - Code of Federal Regulations Title 21.
27. Regulatory for Cellular Therapies [Internet]. [cited 2024 Feb 25]. Available from: <https://www.aabb.org/regulatory-and-advocacy/regulatory-affairs/regulatory-for-cellular-therapies>
28. Different Approaches | ASGCT - American Society of Gene & Cell Therapy | [Internet]. [cited 2024 Feb 8]. Available from: <https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-approaches>
29. Industrialize cell and gene therapy with IBM Personalized Medicine Platform | IBM [Internet]. [cited 2025 Jan 20]. Available from: <https://www.ibm.com/blockchain/resources/personalized-medicine/>

30. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. *Nature* [Internet]. 2021 Aug 26 [cited 2025 Sep 22];596(7873):583–9. Available from: <https://www.nature.com/articles/s41586-021-03819-2>
31. Fleming N. How artificial intelligence is changing drug discovery spotlight /631/45 /639/705/117 /631/154 /706/703/559 n/a. *Nature*. 2018 May 31;557(7707):S55–7.
32. Wright JF. Quality Control Testing, Characterization and Critical Quality Attributes of Adeno-Associated Virus Vectors Used for Human Gene Therapy. *www.biotechnology-journal.com* [Internet]. 2020 [cited 2024 Feb 8]; Available from: <https://doi.org/10.1002/biot.202000022>
33. Emerson J, Kara B, Glassey J. Multivariate data analysis in cell gene therapy manufacturing. *Biotechnol Adv*. 2020 Dec 1;45:107637.
34. Facts About the Current Good Manufacturing Practices (CGMP) | FDA [Internet]. [cited 2024 Feb 8]. Available from: <https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmp>
35. Nally JD. Good manufacturing practices for pharmaceuticals. 2007 [cited 2024 Feb 8];398. Available from: https://books.google.com/books/about/Good_Manufacturing_Practices_for_Pharmac.html?id=3R5RDCTt9MoC
36. eCFR:: 21 CFR Part 210 -- Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General [Internet]. [cited 2024 Feb 8]. Available from: <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-210#210.1>
37. GMP/GDP Inspectors Working Group | European Medicines Agency [Internet]. [cited 2024 Feb 8]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-manufacturing-practice/gmp-gdp-inspectors-working-group>
38. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ* [Internet]. 2016 May 1 [cited 2025 Sep 22];47:20–33. Available from: <https://pubmed.ncbi.nlm.nih.gov/26928437/>
39. A Guide to Good Laboratory Practice (GLP) | SafetyCulture [Internet]. [cited 2024 Feb 9]. Available from: <https://safetyculture.com/topics/good-laboratory-practice-glp/>
40. Ingber DE. Human organs-on-chips for disease modelling, drug development and personalized medicine. *Nat Rev Genet* [Internet]. 2022 Aug 1 [cited 2025 Sep 22];23(8):467–91. Available from: <https://www.nature.com/articles/s41576-022-00466-9>
41. Good clinical practice | European Medicines Agency [Internet]. [cited 2024 Feb 9]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-clinical-practice>
42. Fda, Cber. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry. 2019 [cited 2024 Jul 27]; Available from: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
43. Expanded Access | FDA [Internet]. [cited 2024 Jul 27]. Available from: <https://www.fda.gov/news-events/public-health-focus/expanded-access>

44. Early Access to Medicines Scheme - Information for Applicants - GOV.UK [Internet]. [cited 2025 Jan 20]. Available from: <https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams>
45. Conditional Marketing Authorisations, exceptional circumstances Marketing Authorisations and national scientific advice - GOV.UK [Internet]. [cited 2025 Jan 20]. Available from: <https://www.gov.uk/guidance/conditional-marketing-authorisations-exceptional-circumstances-marketing-authorisations-and-national-scientific-advice#guidance-for-uk-marketing-authorisations-under-exceptional-circumstances>
46. Guidance on “non routine.”
47. REGULATION (EC) NO 1394/2007 ON ADVANCED THERAPY MEDICINAL PRODUCTS (“THE ATMP REGULATION”).
48. Advanced therapy medicinal products: regulation and licensing in Great Britain - GOV.UK [Internet]. [cited 2025 Jan 20]. Available from: <https://www.gov.uk/guidance/advanced-therapy-medicinal-products-regulation-and-licensing>
49. Designating an Orphan Product: Drugs and Biological Products | FDA [Internet]. [cited 2024 Jul 27]. Available from: <https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products>
50. Gothi D, Dhingra D, Sharma M, Kaur K. Regulatory considerations for cellular and gene therapy products in EU and US: A comparative analysis.
51. Conditional marketing authorisation | European Medicines Agency [Internet]. [cited 2024 Jul 27]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/conditional-marketing-authorisation>
52. Cox EM, Edmund A V., Kratz E, Lockwood SH, Shankar A. Regulatory Affairs 101: Introduction to Expedited Regulatory Pathways. Clin Transl Sci [Internet]. 2020 May 1 [cited 2024 Jul 27];13(3):451–61. Available from: <https://pubmed.ncbi.nlm.nih.gov/31909876/>
53. Yao X, Ding J, Liu Y, Li P. The New Drug Conditional Approval Process in China: Challenges and Opportunities. Clin Ther. 2017 May 1;39(5):1040–51.
54. Luo X, Qian F, Yang L, Li Y, Yang Y. Assessment of the breakthrough-therapy-designated drugs granted in China: A pooled analysis 2020-2022. Drug Discov Today [Internet]. 2022 Dec 1 [cited 2024 Jul 27];27(12). Available from: <https://pubmed.ncbi.nlm.nih.gov/36154876/>
55. Li G, Liu Y, Xie C, Zhou Q, Chen X. Characteristics of expedited programmes for cancer drug approval in China. Nat Rev Drug Discov. 2021 Jun 1;20(6):416.
56. Early Access to Medicines Scheme: Overview - GOV.UK [Internet]. [cited 2025 Jan 20]. Available from: <https://www.gov.uk/government/publications/early-access-to-medicines-scheme-overview>
57. What does FDA do? | FDA [Internet]. [cited 2024 Feb 10]. Available from: <https://www.fda.gov/about-fda/fda-basics/what-does-fda-do>
58. FDA History | FDA [Internet]. [cited 2024 Feb 10]. Available from: <https://www.fda.gov/about-fda/fda-history>
59. Chen T. Pre Pre-IND and Pre-IND Interactions for Cell and Gene Therapy Products. 2017;

60. THE PATH TO NEW GENE THERAPY: 7 Steps to IND | Lovelace Biomedical [Internet]. [cited 2024 Feb 10]. Available from: <https://www.lovelacebiomedical.org/the-path-to-new-gene-therapy-7-steps-to-ind/>
61. Fda, Cber. Human Gene Therapy Products Incorporating Human Genome Editing; Guidance for Industry. [cited 2024 Feb 10]; Available from: <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance->
62. Fda, Cber. Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) Guidance for Industry. 2020 [cited 2024 Feb 12]; Available from: <https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common->
63. Cber. Guidance for Industry Preclinical Assessment of Investigational Cellular and Gene Therapy Products. 2009 [cited 2024 Feb 12]; Available from: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
64. Wensky A, Dcept C/, Ptb /. Preclinical Considerations for Products Regulated in OCTGT.
65. Interactions with Office of Therapeutic Products | FDA [Internet]. [cited 2024 Feb 11]. Available from: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/interactions-office-therapeutic-products>
66. OTP INTERACT Meeting | FDA [Internet]. [cited 2024 Feb 11]. Available from: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/otp-interact-meeting>
67. FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs | FDA [Internet]. [cited 2025 Sep 22]. Available from: <https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs>
68. Fda, Cber. Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products _____ Guidance for Industry. 2015 [cited 2024 Feb 12]; Available from: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
69. Clinical Trials Process | ASGCT - American Society of Gene & Cell Therapy | [Internet]. [cited 2024 Feb 12]. Available from: <https://patienteducation.asgct.org/gene-therapy-101/clinical-trials-process>
70. Fda, Cber. Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products Guidance for Industry. [cited 2024 Feb 12]; Available from: <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance->
71. Fda, Cber. Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry. 2019 [cited 2024 Feb 12]; Available from: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.
72. Obtaining an EU marketing authorisation, step-by-step | European Medicines Agency [Internet]. [cited 2024 Feb 24]. Available from: <https://www.ema.europa.eu/en/human-regulatory->

- overview/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step
73. History of EMA | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/about-us/history-ema>
 74. Salmikangas P, Schuessler-Lenz M, Ruiz S, Celis P, Reischl I, Menezes-Ferreira M, et al. Marketing regulatory oversight of advanced therapy medicinal products (ATMPs) in europe: The EMA/CAT perspective. *Adv Exp Med Biol*. 2015 Sep 19;871:103–30.
 75. Obtaining an EU marketing authorisation, step-by-step | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step#ema-inpage-item-13176>
 76. Committee for Advanced Therapies (CAT) | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat>
 77. Medicines Agency E. Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials. 2019 [cited 2024 Feb 25]; Available from: www.ema.europa.eu/contact
 78. Non-clinical development i i ? What to do.
 79. CHMP, GTWP. COMMITTEE FOR THE MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) GUIDELINE ON THE NON-CLINICAL STUDIES REQUIRED BEFORE FIRST CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS DRAFT AGREED BY GENE THERAPY WORKING PARTY ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION AGREED BY SAFETY WORKING PARTY GUIDELINE ON THE NON-CLINICAL STUDIES REQUIRED PRIOR TO CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS. 2007 [cited 2024 Feb 25]; Available from: <http://www.emea.europa.eu>
 80. Good laboratory practice compliance | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-laboratory-practice-compliance>
 81. Clinical Trials Information System | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/clinical-trials-human-medicines/clinical-trials-information-system>
 82. IMPD requirements. [cited 2024 Feb 25]; Available from: www.topra.org
 83. Good clinical practice | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-clinical-practice>
 84. Good manufacturing practice | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-manufacturing-practice>
 85. Scientific advice and protocol assistance | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance>

86. PRIME: priority medicines | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/prime-priority-medicines>
87. Orphan designation: Overview | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview#ema-inpage-item-18416>
88. Iglesias-Lopez C, Obach M, Vallano A, Agustí A. Comparison of regulatory pathways for the approval of advanced therapies in the European Union and the United States. *Cytotherapy* [Internet]. 2021 Mar 1 [cited 2024 Feb 25];23(3):261–74. Available from: <https://pubmed.ncbi.nlm.nih.gov/33483292/>
89. Support to SMEs | European Medicines Agency [Internet]. [cited 2024 Feb 25]. Available from: <https://www.ema.europa.eu/en/about-us/support-smes>
90. Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (EMA) [Internet]. [cited 2025 Sep 22]. Available from: <https://www.ema.europa.eu/en/about-us/how-we-work/data-regulation-big-data-other-sources/real-world-evidence/data-analysis-real-world-interrogation-network-darwin-eu>
91. Li W, Chen J. Institutional Framework for the Management of Human Genetic Resources in China. *Hum Gene Ther* [Internet]. 2021 Dec 1 [cited 2024 Mar 5];32(23–24):1495–500. Available from: <https://pubmed.ncbi.nlm.nih.gov/34278804/>
92. Yin C, Gao J, Li G, Hu H, Zhou L, Lu S, et al. Gene and cell therapies in China: booming landscape under dual-track regulation. *J Hematol Oncol* [Internet]. 2022 Dec 1 [cited 2024 Mar 5];15(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/36199142/>
93. Wu W, Wang Y, Tang Z, Gao Y, Huo Y. Regulatory oversight of cell therapy in China: Government's efforts in patient access and therapeutic innovation. *Pharmacol Res*. 2020 Aug 1;158:104889.
94. Wang Y, Qiu T, Liang S, Toumi M. An Overview of Cell and Gene Therapy Development in China. *Hum Gene Ther* [Internet]. 2022 Jan 1 [cited 2024 Mar 4];33(1–2):14–24. Available from: <https://pubmed.ncbi.nlm.nih.gov/34235966/>
95. Lu J, Xu L, Wei W, He W. Advanced therapy medicinal products in China: Regulation and development. *MedComm* [Internet]. 2023 Jun [cited 2024 Mar 5];4(3). Available from: <https://pubmed.ncbi.nlm.nih.gov/37125239/>
96. Li W, Chen J. Institutional Framework for the Management of Human Genetic Resources in China. *Hum Gene Ther* [Internet]. 2021 Dec 1 [cited 2024 Mar 4];32(23–24):1495–500. Available from: <https://pubmed.ncbi.nlm.nih.gov/34278804/>
97. Guidance on licensing biosimilars, ATMPs and PMFs - GOV.UK [Internet]. [cited 2025 Jan 20]. Available from: <https://www.gov.uk/guidance/guidance-on-licensing-biosimilars-atmps-and-pmfs>
98. Reviews | Pharmaceuticals and Medical Devices Agency [Internet]. [cited 2024 Jul 27]. Available from: <https://www.pmda.go.jp/english/review-services/reviews/0001.html>
99. List of Approved Products | Pharmaceuticals and Medical Devices Agency [Internet]. [cited 2024 Jul 27]. Available from: <https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html>

100. Arato T, Nomura K. Cell and gene therapy approvals in Japan and the need for international harmonization. *Nat Biotechnol* [Internet]. 2024 Jan 1 [cited 2024 Jul 27];42(1):13–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/38191662/>
101. Srivastava A, Abraham A, Aboobacker F, Singh G, Geevar T, Kulkarni U, et al. Lentiviral Gene Therapy with CD34+ Hematopoietic Cells for Hemophilia A. *N Engl J Med* [Internet]. 2024 Dec 9 [cited 2025 Jan 20]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/39655790>
102. Luanpitpong S, Klaihmon P, Janan M, Kungwankiatichai S, Owattanapanich W, Kunacheewa C, et al. Point-of-care manufacturing of anti-CD19 CAR-T cells using a closed production platform: Experiences of an academic in Thailand. *Mol Ther Oncol* [Internet]. 2024 Dec 19 [cited 2025 Jan 20];32(4). Available from: <https://pubmed.ncbi.nlm.nih.gov/39507317/>
103. Warda W, Fakih R El, Alrasheed N, Alkhaldi M, Hamideddin N, Alqudairy H, et al. Large Scale In-House Point-of-Care Manufacturing of Clinical Grade Autologous Anti-CD19 CAR T Cells in Saudi Arabia. *medRxiv* [Internet]. 2024 Jun 12 [cited 2025 Jan 20];2024.06.11.24308741. Available from: <https://www.medrxiv.org/content/10.1101/2024.06.11.24308741v1>
104. Kedmi M, Shouval R, Fried S, Bomze D, Fein J, Cohen Z, et al. Point-of-care anti-CD19 CAR T-cells for treatment of relapsed and refractory aggressive B-cell lymphoma. *Transplant Cell Ther* [Internet]. 2022 May 1 [cited 2024 Jul 27];28(5):251–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/35218999/>
105. Silva Junior JB, Rodrigues e Silva AA, Melo FCC, Kumoto MC, Parca RM. Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Consensus on genetically modified cells. Special Article: Advanced therapy medicinal products in Brazil: regulatory panorama. *Hematol Transfus cell Ther* [Internet]. 2021 Nov 1 [cited 2024 Jul 27];43 Suppl 2(Suppl 2):S68–77. Available from: <https://pubmed.ncbi.nlm.nih.gov/34794800/>
106. Butler D. Translational research: Crossing the valley of death. *Nature*. 2008 Jun 12;453(7197):840–2.
107. Global Trends in R&D 2025 - IQVIA [Internet]. [cited 2025 Sep 22]. Available from: <https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2025>
108. Clinical Development Success Rates and Contributing Factors 2011-2020 | BIO [Internet]. [cited 2025 Sep 22]. Available from: <https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020>
109. Research and Development in the Pharmaceutical Industry | Congressional Budget Office [Internet]. [cited 2025 Sep 22]. Available from: <https://www.cbo.gov/publication/57025>
110. The New Economics Of Cell And Gene Therapy [Internet]. [cited 2025 Sep 22]. Available from: <https://www.cellandgene.com/doc/the-new-economics-of-cell-and-gene-therapy-0001>
111. Sathian B, Teijlingen E van, Banerjee I, Asim M, Kabir R. The Promising Future for Complex Innovative Trial Design in Clinical Research. *Nepal J Epidemiol* [Internet]. 2023 Mar 31 [cited 2025 Sep 22];13(1):1256. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10225021/>
112. Position Paper Innovation in Clinical Trial Design: A review of The Clinical Trial Design Landscape A white paper by the EFPIA Clinical Trial Design Taskforce on behalf of the EFPIA Clinical Research Expert Group. [cited 2025 Sep 22]; Available from: www.efpia.eu

113. Sorajja P, Whisenant B, Hamid N, Naik H, Makkar R, Tadros P, et al. Transcatheter Repair for Patients with Tricuspid Regurgitation. *N Engl J Med* [Internet]. 2023 May 18 [cited 2025 Sep 22];388(20):1833–42. Available from: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa2300525>
114. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J* [Internet]. 2012 Jan [cited 2025 Sep 22];33(2):176–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/21900289/>
115. Complex Innovative Trial Design Meeting Program | FDA [Internet]. [cited 2025 Sep 22]. Available from: <https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program>
116. FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies | FDA [Internet]. [cited 2024 Oct 21]. Available from: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous>
117. Kobbe G, Brüggemann M, Baermann B-N, Wiegand L, Trautmann H, Yousefian S, et al. Aggressive Lymphoma after CD19 CAR T-Cell Therapy. *N Engl J Med* [Internet]. 2024 Oct 3 [cited 2024 Oct 19];391(13):1217–26. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa2402730>
118. Duncan CN, Bledsoe JR, Grzywacz B, Beckman A, Bonner M, Eichler FS, et al. Hematologic Cancer after Gene Therapy for Cerebral Adrenoleukodystrophy. *N Engl J Med* [Internet]. 2024 Oct 10 [cited 2024 Oct 19];391(14):1287–301. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa2405541>
119. Mullard A. In vivo CAR T cells move into clinical trials. *Nat Rev Drug Discov* [Internet]. 2024 Oct 16 [cited 2024 Oct 21];23(10):727–30. Available from: <https://www.nature.com/articles/d41573-024-00150-z>
120. Singh M, Brooks A, Toofan P, McLuckie K. Selection of appropriate non-clinical animal models to ensure translatability of novel AAV-gene therapies to the clinic. *Gene Ther* [Internet]. 2024 Jan 1 [cited 2024 Oct 21];31(1–2):56–63. Available from: <https://pubmed.ncbi.nlm.nih.gov/37612361/>