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Review

Regulatory systems and requirements for clinical trials of AAV-based gene therapies – Perspectives from six Asian countries or regions: Report from the 6th Asia Partnership Conference of Regenerative Medicine – April 20, 2023

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ABSTRACT

Gene therapies, which include viral-vector gene delivery, genome editing, and genetically modified cell therapy, are innovative treatments with the potential to address the underlying genetic causes of disorders and to provide life-changing value in terms of curing disease. Although adeno-associated virus (AAV)-based gene therapy is one of the most advanced types of gene therapy, far fewer AAV-based gene therapy studies have been conducted in Asia than in North America and Europe. The 6th Asia Partnership Conference of Regenerative Medicine (APACRM) was held on April 20, 2023 in Tokyo, Japan. APACRM Working Group 3 comprehensively analyzed the regulatory processes that occur prior to the initiation of clinical trials as well as the regulatory requirements for AAV-based gene therapies for six Asian countries or regions (China, India, Japan, Singapore, South Korea, and Taiwan). In this article, we report the outcomes of this conference, summarizing the regulatory requirements for initiating clinical trials for AAV-based gene therapies in terms of the laws, regulations, and guidelines for gene therapy; consultations or reviews required by the health authorities; points to consider for scientific reviews by the health authorities; and specific challenges to address when developing gene therapy products in these locations. Finally, we present several policy recommendations, including simplifying the regulatory review system for multiple scientific review areas; simplifying the regulatory consultation system; and providing training programs and regulatory guidance to support the advancement of gene therapy development in Asia.

Contents

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1. Introduction

Adeno-associated virus (AAV)-based gene therapy is at the forefront of cell and gene therapy (CGT). This advanced therapy has begun to offer transformative value as a potential cure, particularly for patients affected by rare diseases. However, Asia lags substantially behind North America and Europe in terms of the number of ongoing clinical studies on AAV-based gene therapies, as reported by the Alliance for Regenerative Medicine (ARM) in 2019 [1]. Considering the innovative nature of gene therapy, the regulatory framework for AAV-based gene therapy remains inadequately established, and it varies among Asian countries or regions (China, India, Japan, Singapore, South Korea, and Taiwan). The objective of the 6th Asia Partnership Conference of Regenerative Medicine (APACRM; April 20, 2023; Tokyo, Japan) was to promote regulatory harmonization of regenerative medicine products across Asia. The regulation of clinical trials for AAV-based gene therapies was a focal point of this conference. APACRM Working Group 3 (WG3) comprehensively summarized the Investigational New Drug (IND) process and the regulatory requirements for AAV-based gene therapies, drawing insights from 30 industry experts from these countries or regions. While the conference proceedings outline the regulatory requirements and consultation systems for each country or region, they omit the complete presentations [2].

Therefore, we comprehensively summarize the regulatory requirements for starting clinical trials of AAV-based gene therapies in these countries or regions, addressing 1) the laws, regulations, and guidelines for gene therapy; 2) the consultations or reviews required by the health authorities (HAs) before starting a clinical trial; 3) considerations regarding the Chemistry, Manufacturing, and Controls (CMC), nonclinical, and clinical aspects; and 4) the distinct challenges encountered in developing gene therapy products (GTPs). This article thus provides a side-by-side comparison of the regulatory requirements for initiating clinical trials of AAV-based gene therapies in these countries or regions. Furthermore, we provide policy recommendations aimed at advancing AAV-based gene therapies in Asia.

2. Regulatory requirements for starting a clinical trial of AAV-based gene therapy

2.1. China

In China, CGTs are classified as therapeutic biological products, according to the registration classification and document requirements for biological products. CGTs present many challenges in drug development and regulation that differ from those associated with traditional biological agents. CGT development may occur via 1) the investigational new drug (IND) track, in which CGTs are tested in clinical trials registered with the Center for Drug Evaluation (CDE) of the New Medical Product Administration (NMPA), or 2) the medical technologies track, in which CGTs are tested in investigator-initiated trials (IIT) conducted by individual hospitals and supervised by the National Health Commission (NHC). Qualified IIT data can be used to support IND submissions. Rapid global advancements in CGT, and its potential long-term therapeutic effects, have prompted the government to institute a series of regulatory reforms to expedite CGT development in China. More than 16 CGT-specific guidelines were published between 2017 and 2022, including five for cell therapy, seven for gene therapy, two for oncolytic viruses, and two for stem cell products.

The seven gene therapy-related guidelines address non-clinical studies, long-term follow-up studies, CMC, and clinical-risk management plans for gene therapies or genetically modified cell therapy products [3–9] (Table 1). To gain marketing approval and commercialize CGT products in China, sponsors must follow the IND track, in which the processes and timelines are aligned with those from other regions, such as with the policies of the United States Food and Drug Administration (USFDA). (Fig. 1).

Although the IND acceptance and review processes of the CDE and NMPA in China take longer than such processes in the US or Europe, the drug review process has been optimized to expedite New Drug Application (NDA) approval of CGTs; these expedited processes include the Priority Review Process, Breakthrough Therapy Designation, and the Conditional Approval Process. NDA reviews are meant to be completed within 200 days of the receipt

Table 1
Regulatory guidelines for gene therapies in the six Asian countries or regions.

Country or region	Issued year	Guidelines	Contents
China	2021	Technical Guideline on Nonclinical Studies and Evaluation of Gene Therapy Products (Draft) [3]	Provides suggestions for GTP development for non-clinical aspect.
	2021	Technical Guidelines for Non-clinical Study and Evaluation of Genetically Modified Cell Therapy Products (Draft) [4]	Provides suggestions for genetically modified cell therapy product for non-clinical aspect.
	2022	Guideline for Long-term Follow-up Clinical Research of Gene Therapy Products (Draft) [5]	Long-term follow-up research of GTPs
	2022	Technical Guideline for Clinical Risk Management Plan of Biologics Marketing Application for Cell Therapy Products of Chimeric Antigen Receptor-T (CAR-T) [6]	Discusses risk management planning for drug registration application for CAR-T cell.
	2022	Technical Guideline for Pharmaceutical Study and Evaluation of Cell-based Immunotherapy Products [7]	Discusses the pharmacological research and development in drug registration applications for cell-based immunotherapy products.
	2022	Technical Guideline for Pharmaceutical Study and Evaluation of In-vivo Gene Therapy Products (Draft) [8]	Discusses the pharmacological research and development in drug registration applications for in-vivo GTPs.
	2022	Technical Guideline for Pharmaceutical Study and Evaluation of Ex-vivo Gene Therapy Products (Draft) [9]	Discusses the pharmacological research and development in drug registration applications for ex-vivo GTPs.
India	2017	National Ethical Guidelines for Biomedical and Health Research involving Human Participants [40]	Guidelines for dealing with ethical issues in human genetic testing and gene therapy research
	2019	National Guidelines for Gene Therapy Product Development and Clinical Trials [12]	Guidelines providing a broad framework on the ethical, scientific, and regulatory requirements for those who aspire to test GTPs.
	2021	National Policy for Rare Diseases [41]	The Indian national policy for rare diseases. Discusses the challenges as well as the development of a centre of excellence, and how it can provide support in rare-disease treatment.
Japan	2018	Standard for Biological Ingredients [16]	Guidelines requiring investigation of viral testing or manufacturing records for biological ingredients of human or animal origin. The scope includes secondary biological ingredients used for manufacturing of primary bioingredients
	2019	Guideline on Ensuring the Quality and Safety of Gene Therapy Products [17]	Guidelines for gene therapy development, particularly for CMC and preclinical studies, to be consulted before starting a clinical study in Japan
	2020	Points to Consider for Efficient Consultation on Regulatory Strategies related to Quality and Safety from the Initial Stage of Development of Regenerative Medicine Products (Preclinical Safety) [18]	Guidelines to consider in terms of preclinical safety perspectives when conducting a consultation on regulatory strategies related to quality and safety
	2021	Points to Consider for Efficient Consultation on Regulatory Strategies related to Quality and Safety from the Initial Stage of Development of Regenerative Medicine Products (Quality) [19]	Guidelines to consider in terms of quality perspectives when conducting a consultation on regulatory strategies related to quality and safety
Singapore	2021	Health Products (Cell, Tissue and Gene Therapy Products) Regulations [42]	CTGTP definition and classification; regulations for the manufacture, import, supply, presentation, and registration of CTGTP products, and on duties and obligations
	2021	Health Products (Clinical Trials) Regulations [22]	Clinical trials of CTGTPs
	2021	Health Products (Clinical Research Materials) Regulations [43]	Regulations on clinical trial research materials including CTGTPs
South Korea	2020	Guideline on Long-term Follow-up of Advanced Biopharmaceutical Products [26]	Describes the long-term follow-up required for stem cells-based products (up to 5 years), gene therapies using viral vectors (up to 15 years), and xenogeneic products (up to 30 years).
	2021	Guidance on Non-clinical Assessment of Gene Therapies [27]	Guideline providing information about the required non-clinical documents and considerations about general toxicity, immunogenicity, tumorigenicity, biodistribution, and efficacy studies
	2022	Guideline on the Requirements for Quality Dossier of Cell and Gene Therapy Products [28]	Guideline providing information about CMC requirements in the IND dossier for CGT products
	2022	Guideline on the Quality Control of mRNA-based Gene Therapy Products [29]	Guideline providing technical considerations for setting up CMC of mRNA-based GTPs
	2022	Guideline on the Quality Control of Gene Therapy Products [30]	Guideline providing technical considerations on the CMC of GTPs using viral or non-viral vectors and gene-modified cells
	2023	Guideline on the Quality and Nonclinical Evaluation of Plasmid DNA Based Gene Therapy Products [31]	Guideline providing technical considerations on the CMC and nonclinical studies of GTPs using nonviral delivery of plasmid DNAs
Taiwan	2018	Guidance on Chemistry, Manufacturing and Controls of investigational Viral Vector Gene Therapy Products [33]	Guideline providing suggestions for CMC requirements of viral vector GTP development and manufacturing
	2020	Guidance on Nonclinical Pharmacology and Toxicology of Investigational Gene Therapy Products [34]	Guideline providing suggestions for nonclinical pharmacology and toxicology requirements of GTP development and manufacturing
	2020	Guidance on Clinical Trial of Gene Therapy products [35]	Guide the gene therapy products for IND application review, including vectors with recombinant nucleic acid, genetically modified microorganisms or viruses, and genetically modified cells such as CAR-T cells.

Table 1 (*continued*)

Country or region	Issued year	Guidelines	Contents
	2021	Guidance on Chemistry, Manufacturing and Controls Development Strategies of Genetically Modified Cells in Regenerative Medicine Products [36]	Guideline providing suggestions for CMC requirements of genetically cell development and manufacturing
	2022	Guidance on Safety considerations for adeno-associated virus (AAV) gene therapy products [37]	Guideline providing suggestions for CMC requirements of AAV gene therapy product development and manufacturing in safety considerations
	2022	Guidance on Application of Gene Therapy products [38]	Guideline for the review of registration of GTPs and for long-term follow-up observations, including for vectors comprising recombinant nucleic acid sequences, genetically modified microorganisms or viruses, and genetically modified cells such as CAR-T cells
	2023	Guidance on Long-term Follow-up Clinical Research of CART Products [39]	Guideline providing strategies and suggestions for the long-term follow-up of clinical trial research on CAR-T products

GTP, gene therapy product; CAR-T, chimeric antigen receptor-T; CMC, chemistry, manufacturing, and controls; CTGTP, cell, tissue and gene therapy product; IND, investigational new drug; CGT, cell and gene therapy; mRNA, messenger ribonucleic acid; DNA, deoxyribonucleic acid; AAV, adeno-associated virus.

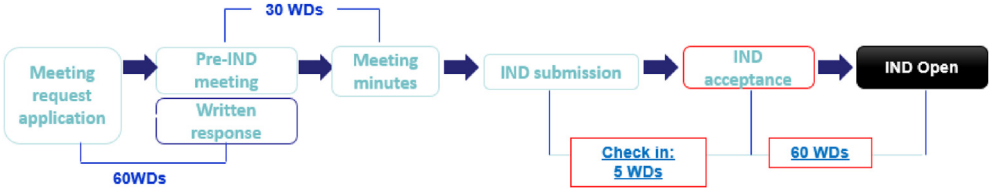

Fig. 1. Investigational New Drug (IND) process of China's Center for Drug Evaluation (CDE) [10] WD, Working Day.

of the original submission; for CGTs, this can be reduced to 130 days, if Priority Review is granted. Therefore, for qualifying applications, these expedited regulatory pathways make the CGT review process more efficient, especially for highly innovative products from small- or mid-sized companies. We expect that further guidelines will be released to help of novel CGT products transition from basic research to clinical application in China.

2.2. India

According to the New Drug and Clinical Trials Rules (2019) issued by the Ministry of Health & Family Welfare, GTPs are designated as drugs [11]. The National Guidelines for Gene Therapy Product Development and Clinical Trials (2019) issued by the Indian Council of Medical Research (ICMR), the primary guideline, provides a broad framework for the ethical, scientific, and regulatory requirements for these advanced therapies [12]. The sequence followed by any institution to obtain approval for GTP development is shown in Fig. 2. The timeline for approval of CMC aspects by the Institutional Biosafety Committee (IBSC) and the Review Committee on Genetic Manipulation (RCGM) of the Department of Biotechnology is approximately three months; thereafter, preclinical study protocols must be approved by the RCGM, and approval by the Institutional Animal Ethical Committee (IAEC) may take a further three months. Once a preclinical study is completed, an application for clinical trial approval is submitted to the Indian FDA, which may take approximately 4–6 months to provide approval.

The RCGM is responsible for validating the appropriateness of the preclinical data package, which includes data on acute and chronic toxicity, the biodistribution profile of the GTP, gene integration, tumorigenicity, reproductive and developmental toxicity, immunotoxicity, and an assessment of the GTP's environmental impacts. For GTPs that will be administered to humans, quality is of the utmost importance. Quality evaluation includes assessing product purity, safety, identity, and strength. The raw materials should be of high quality and should be manufactured under Good Manufacturing Practice (GMP) conditions. In order to receive approval, each batch of the GTP must be appropriately tested to ensure that sterility and GMP conditions are maintained during all critical processes. GTP storage and shipment stability data should be available.

The clinical trial protocol is scientifically reviewed by the Gene Therapy Advisory and Evaluation Committee (GTAEC) of the ICMR, the Subject Expert Committee (SEC) of the Indian FDA, and the Institutional Ethics Committee (IEC). The protocol should include information about the disease and details of the population of patients under consideration. Details of the patients' molecular and clinical data should be included, so that they can be considered for the GTP trial. The expected risks of the GTP and the rationale for conducting the clinical trial should be explained. The primary inclusion criterion should be clearly described, and should be supported by imaging, biochemical, structural, and morphological evidence. Such clinical trials are mostly single-arm trials; therefore, historical data and the natural history of the disease can be provided. Testing must be conducted for pre-existing neutralizing antibodies against the vectors used in the GTP to detect adverse immune responses to the GTP. In order to assess the endpoints, the study design should consider the natural history of the disease, patient stratification, disease stage of the intervention, and the duration of post-GTP treatment.

Several challenges exist in developing GTPs in India. These include the need to first obtain study approval from various committees (such as the IBSC, IAEC, and RCGM), including preclinical study approval. Similarly, for clinical trials, GTAEC approval is required before the clinical protocol is approved by the SEC. Simplifying the Indian regulatory system, so that different types of approval can be granted by a single committee, would expedite the process of conducting studies; this would promote the rapid development of GTPs in India.

2.3. Japan

In Japan, gene therapy clinical trials must comply with the Pharmaceutical and Medical Device (PMD) Act [14] and the Act on

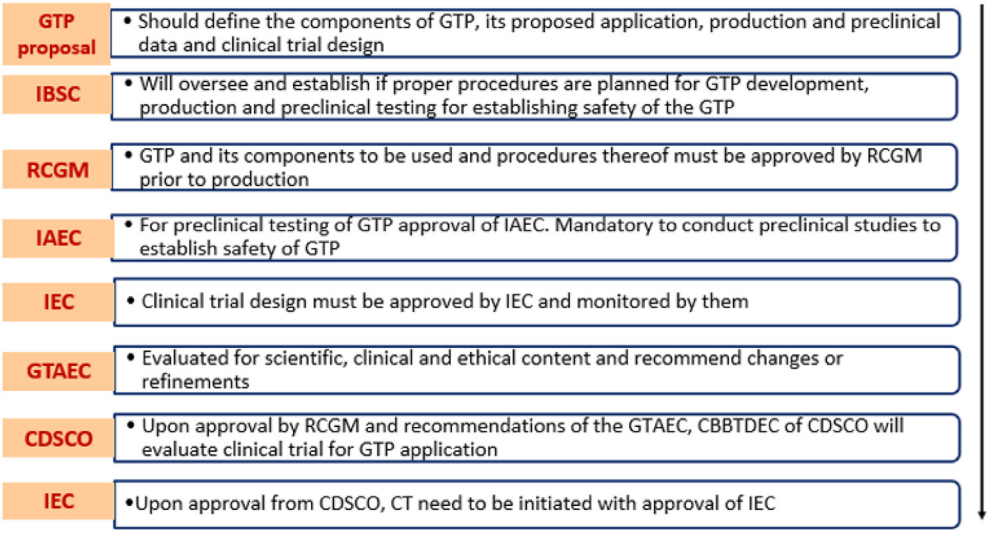

Fig. 2. Indian Guidelines for Gene Therapy Product Development [13]. GTP, gene therapy product; IBSC, institutional biosafety committee; RCGM, review committee on genetic manipulation; IAEC, Institutional Animals Ethics Committee; IEC, Institutional Ethics Committee; GTAEC, Gene Therapy Advisory and Evaluation Committee; CBBTDEC, Cell Biology Based Therapeutic Drugs Evaluation Committee; CDSCO, Central Drug Standard Control Organization; CT, clinical trial.

the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Genetically Modified Organisms (GMOs) (hereafter, "Cartagena Act") [15]. Two important additional guidelines, standards for biological ingredient and guideline on ensuring the quality and safety of gene therapy product, are applied [16,17] (Table 1). When a GTP clinical trial is conducted, the sponsor must follow regulatory procedures based on the Cartagena Act and obtain approval for Cartagena Type 1 use from the Ministry of Health, Labor, and Welfare (MHLW) and the Ministry of Environment (MoE), before the start of the clinical trial.

Moreover, before a GTP clinical trial starts in Japan, regulatory science consultations on both quality and preclinical safety are required. Consultations on the clinical study protocol and on the regulatory procedures for Cartagena Type 1 use may also be required. Such GTP clinical trials conventionally require eight consultations with regulatory authorities including informal preliminary meetings (Fig. 3). These activities can proceed in parallel.

The purpose of the preclinical safety consultation is to obtain feedback on the adequacy of the preclinical safety data package from the Pharmaceuticals and Medical Devices Agency (PMDA) to ensure patient safety before the clinical trial starts. Aspects reviewed by the regulatory authority include general toxicity, gene integration, tumorigenic and oncogenic potential, reproductive and developmental toxicity, immunotoxicity, and the risk of emergence of replication-competent viruses [18].

As with the preclinical safety consultation, the CMC consultation with the PMDA provides feedback on whether the quality-data package is sufficient to start the clinical trial. The main regulatory review points are compliance of the primary and secondary raw materials with the standards for biological ingredients and product quality in terms of manufacturing, safety, stability, and the consistency of materials manufactured using different methods [19]. Although consultation is not mandatory for clinical trials, sponsors should carefully consider the necessity of such consultation based on the scientific novelty and challenges of the clinical protocol, patient safety, and future appropriate marketing authorization applications. The key points of the regulatory review are the efficacy endpoints and safety evaluation methods of the clinical trial, GTP dosage and administration, and the long-term follow-up period. Applications for Cartagena Type 1 use of GTPs are reviewed by the PMDA to ensure that environmental impacts in terms of transmission to third parties are prevented and to ensure appropriate handling of the product while conducting the clinical trial. Following PMDA review, Cartagena Type 1 use is approved by the MHLW and MoE. Both sponsors and healthcare professionals at clinical study sites should handle GTP products in accordance with the approved methods.

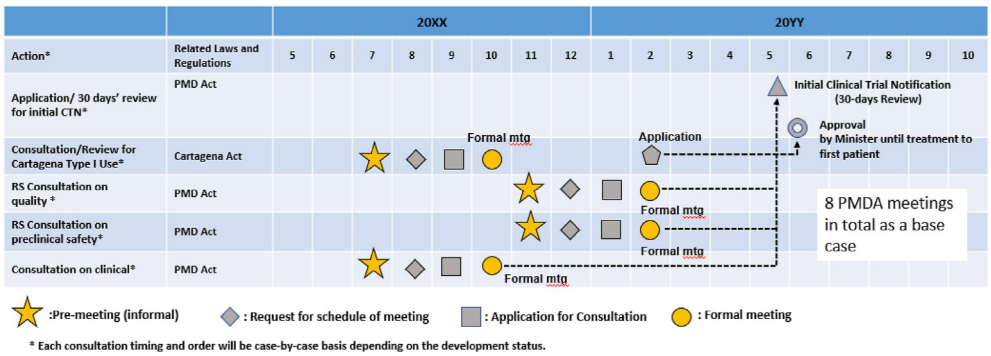

Fig. 3. Necessary Health Authority (HA) Consultations and Reviews Required Before Starting an Initial Clinical Trial in Japan [20]. PMD, pharmaceutical and medical device; CTN, clinical trial notification; RS, regulatory science; PMDA, Pharmaceuticals and Medical Devices Agency.

Before starting a GTP clinical trial in Japan, multiple formal consultations are required and an approval for Cartagena Type 1 use must be obtained. Preparation for these activities requires considerable time and resources. Delays in these activities significantly impact the amount of time required to start a clinical study.

2.4. Singapore

The Health Products Act, which came into effect on March 1, 2021, regulates cell, tissue, and GTPs (CTGTPs) [21]. CTGTPs are health products intended for use in humans for therapeutic, preventive, palliative, or diagnostic purposes, and are risk stratified into two classes, lower risk (Class 1) and higher risk (Class 2).

Clinical trial consultation is voluntary. Sponsors can seek early scientific and regulatory advice from the Innovation Office of the Health Sciences Authority (HSA). CTGTP clinical trials require Clinical Trial Authorization (CTA), and must comply with the Health Products (Clinical Trials) Regulations [22] and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice guidelines [23]. Typical evaluation timeline is 60 working days for a Class 2 CTGTP CTA. CTAs are submitted concurrently to the HSA and the relevant Institutional Review Board (IRB) for review and approval.

For CTGTP applicants for both registration and CTA, applicants must submit the environmental risk assessment (ERA) dossier to the Genetic Modification Advisory Committee (GMAC) for review and approval for release. ERA approval is a necessary document required by the HSA as part of the CMC dossier for CTA evaluation. The GMAC approval timeline can be up to 6 months. Applicants, including companies and research institutions/laboratories, are advised to submit a dossier to the GMAC for review. Applicant can refer to the GMAC's “Checklist of Information Required for GMAC Review, Environmental Risk Assessment of GMO-Related Gene Therapy Products” [24]. Applicants are required by regulation to submit the GMAC's recommendations on environmental risk assessment for GTPs (including genetically modified cells) as part of the dossier submission to the HSA for clinical trials or product registration applications.

2.5. South Korea

South Korea enacted the “Advanced Regenerative Medicine and Advanced Biopharmaceutical Safety and Support Act” in August 2020 [25]. This act classifies products into four categories: cell therapy, gene therapy, tissue engineering therapy, and combination therapy. Accordingly, the IND process in AAV-based gene therapy is regulated by new laws, related regulations, and guidelines. The South Korean Ministry of Food and Drug Safety (MFDS) has published several new guidelines; six guideline documents related to gene therapy have been revised or published since this act was enacted. These guidelines address nonclinical assessment, quality's IND dossier, quality assessment, and long-term follow-up study for gene therapies using viral or nonviral vectors, genetically modified cells, or mRNAs [26–31] (Table 1).

The technical considerations and data required for gene therapy clinical trial applications in South Korea are not significantly different from those required in other countries or regions. The main concerns regarding the use of viral vectors include genome integration, off-target effects, uncontrolled expression of transgenes, immunogenicity, persistent infection, and latent reactivation. South Korea abides by the Cartagena Protocol on Biosafety to the Convention on Biological Diversity, and therefore requires that an environmental risk assessment (ERA) be conducted when gene therapies will be imported or exported, but not during the IND process.

The National Institute of Food and Drug Safety Evaluation (NIFDS) of the MFDS is responsible for conducting IND review of all therapeutic drugs, including gene therapies. Pre-IND consultations or reviews of specific topics are available before an IND application is submitted. IND documents can be prepared in a Common Technical Document (CTD) format. The first IND review takes up to 30 working days from submission of an IND application. Upon receipt of a review result, the sponsors can submit revised documents with itemized answers within 30 working days or request an extension of the due date. The MFDS provides an expedited review process and conditional approval pathways for CGT products for treat serious illnesses or rare diseases. The program includes a tailored review, with a rolling review process, priority review with designated MFDS staff, and conditional approval, which allows for marketing approval after the Phase II clinical trial, with the condition of performing a Phase III trial. This approval process is expected to reduce the time required by 3.5–4.5 years when all three programs are applied. Long-term follow-up, for up to 15 years after treatment, is required for gene therapies, depending on the specific characteristics and safety concerns of the gene therapy.

2.6. Taiwan

In Taiwan, the Pharmaceutical Affairs Act currently governs the GTP regulatory framework [32]. Two draft acts related to gene therapies are currently being examined (the Regenerative Medicine Act and Regulation of Regenerative Medicinal Products); once approved, these will become specialized laws. The Taiwan Food and Drug Administration (TFDA), an agency of the Ministry of Health and Welfare (MOHW), oversees the enforcement of laws and regulations related to food, cosmetics, medicine, and medical devices, as well as licensing, permits, and authorization. It aims to ensure safety, efficacy, and quality by implementing comprehensive lifecycle management system that adheres to international standards. The Center for Drug Evaluation (CDE), supported by the MOHW, enhances clinical trial quality, approval processes, and transparency in drug and device reviews. Seven gene therapy-relevant guideline documents address the following aspects: CMC, nonclinical pharmacology and toxicology, clinical trials, safety considerations of AAV GTPs, product registration, and long-term follow-up study for either gene therapies or genetically modified cells [33–39] (Table 1).

The review process for clinical trial applications varies depending on the checkpoints and timelines applied. For GTPs, which are categorized as an emerging field in biotechnology, the review process involves three categories. The first is an expedited review, which does not require a committee meeting, and takes 30 days to complete. This review is appropriate when either of two conditions is met: 1) the study is a multiregional clinical trial (MRCT) conducted in one of ten reference countries, excluding first-in-human studies; or 2) the study concerns regenerative medicine with the same laboratory procedure that had a previously approved IND by Taiwan FDA (TFDA) and was initiated by same investigators, but not available for pivotal clinical trials.

For clinical trials that do not meet the criteria for this expedited process, but that qualify for pre-submission consultation and subsequent revisions based on the consultant's feedback, the review process takes 45 days. When a committee-based review is required, the process takes 150 days. To ensure the safety and effectiveness of GTPs prior to clinical trials, IND applications must include the clinical protocol, informed consent forms, participant recruitment strategies, and other necessary materials. The Investigator's Brochure, safety data, investigator's qualifications, and any additional materials required by the Ethics Committee to ensure clinical

trial's safety and ethical standards, are also essential components of the application.

Nonclinical studies and evaluation, which are essential, are subject to two sets of guidelines: the first is Good Laboratory Practice (GLP) for Non-clinical Laboratory Studies, and the second, Guideline for Non-clinical Safety Studies for Medicinal Products. These guidelines, which align with the international standards and practices set out by the US FDA and the Organisation for Economic Cooperation and Development (OECD), cover proof-of-concept studies, safety, pharmacology, biodistribution, shedding, toxicity, genotoxicity, and tumorigenicity study. Shedding studies are unnecessary in non-clinical evaluations if the shedding model of the GTP is known. Shedding should not be confused with biodistribution, which pertains to the distribution of the carrier or viral population within the body from the application site. Shedding can be assessed via biodistribution tests or other non-clinical studies using animal models.

Taiwan's high-quality, efficient, and cost-effective clinical trial environment, coupled with its National Health Insurance system, makes it an appealing destination for clinical trials. This has led to the establishment of local clinical trial offices by numerous major international pharmaceutical companies, thus accelerating regulatory improvements and CGT company's development.

3. Regulatory guidelines for gene therapies in six Asian countries or regions

These six Asian countries or regions have established or revised guidelines pertaining to CMC, nonclinical and clinical aspects of gene therapies (Table 1). A noteworthy focus in these guidelines is the attention to long-term follow-up in clinical studies, an area of particular interest given the unique attributes of gene therapy. Taiwan and China have formulated seven sets of guidelines and documents related to gene therapy, reflecting the establishment of more new regulatory frameworks within these Asian countries or regions. This regulatory effort is indicative that Taiwan has conducted the most AAV-based gene therapy development, and in China, many China local AAV-based GTPs have recently started clinical trials [2]. In Japan, the HAs place a distinct emphasis on the biological ingredients of gene therapy, exemplified by the establishment of the “Standard for Biological Ingredients”, which provides a regulatory framework for biological ingredients and aims of mitigating the risk of viral infection.

4. Points to consider for each product development area for six Asia countries or regions

The following is the overarching summary of considerations for CMC and non-clinical and clinical aspects specific to the gene therapy development in these Asian countries or regions (Table 2), although the details of requirements differ by countries or regions.

4.1. CMC aspects

For raw materials such as human serum albumin, cells utilized in viral vector production, and fetal bovine serum, including secondary materials, Japan mandates strict adherence to its “Standards for Biological Ingredients”. In terms of manufacturing methods and quality control in product development, sponsors are obligated to deliberate on specifications, in-process testing, and characterization testing of both the drug substance (DS) and finished drug products (DP), and to consider the justifications for using specific parameter settings. Product-related impurities such as the presence of incomplete vectors in viral-vector products, evaluation of process-related impurities, and ancillary materials, and all outcomes of characterization tests should be presented. The safety evaluation of the finished product against endotoxins and infectious substances necessitates careful consideration. When the investigational product and the test substance used in nonclinical safety studies are manufactured by different manufacturing processes, sponsors should explain the differences of the manufacturing process and quality attributes, alongside confirmation of quality similarity between the methods. In terms of the stability of the developed product, sponsors should consider conditions ranging from DS, DP, transportation, to in-use storage, encompassing factors such as expected shelf life, storage temperature, and container closure system. These aspects must be described at the time of IND submission.

4.2. Preclinical and clinical aspects

For preclinical aspects in the gene therapy development, specific preclinical assessments for using vital vectors such as gene integration assessment, biodistribution/shedding studies and assessing risk of emergence of replication-competent viruses are considered crucial.

Regarding the clinical aspects, the risks associated with GTPs and the rationale for conducting specific clinical trials should be clarified. Because gene therapies often target rare diseases, the patient pool is often limited, and large-scale clinical trials may not be feasible. Gene therapy clinical trials are typically single-arm studies, hence historical data and the natural history of the target disease must be obtained in the case.

Testing is required for pre-existing neutralizing antibodies to vectors used in GTPs to detect adverse immune responses and possible reductions in efficacy. The study design should consider the natural history of the disease, patient stratification, disease stage of the intervention, duration of post-treatment follow-up to assess the endpoints, and patient age, especially in pediatric populations. The inclusion of healthy volunteers in the control group for gene therapy trials is generally impractical. The rationale for a dose regimen involving an optimal balance between safety and efficacy, dosing frequency, and administration route should be discussed with regulatory agencies.

Clinical safety monitoring and prevention/treatment of immune responses to GTP should be set considering target organs and expected adverse events in non-clinical and clinical studies. Long-term follow-up of patients should be considered depending on the regulatory guidelines, disease characteristics, and vectors. The follow-up time, which may vary for certain diseases owing to their natural history, pathophysiology, or clinical sequelae, must be justified by the sponsor.

5. Specific challenges in gene therapy development in six Asian countries or regions

Table 3 summarizes the challenges in gene therapy development in six Asian countries or regions. In this section, the common key challenges are categorized, and possibilities for collaboration and policy implications to improve regulatory systems are highlighted.

5.1. Regulatory review system

In China, there is a persistent lack of uniformity in management systems and review documents, with some of the general requirements for biological products or the general laws related to drugs being potentially inapplicable to CGT products. The CDE in China has released numerous CGT-specific guidelines that, upon implementation, could be subject to negotiations with HAs.

Table 2
Points to consider in each product development area for the six Asian countries or regions.

Product Development Area	Points to Consider
CMC	• Compliance of primary and secondary raw materials used in the manufacturing process • Manufacturing method and quality control method of the developed product • Safety and consistency of products manufactured using different methods • Evaluation of risk of emergence of replication-competent viruses • Product stability
Preclinical	• Pharmacology/proof-of-concept • Safety pharmacology • Biodistribution/shedding: assess the in vivo distribution, persistence, and clearance or release of products outside the body • General toxicity: confirm the appropriateness of the experimental settings including the selection of animal species, maximum dose, duration of monitoring, and safety evaluation measures • Genotoxicity • Gene integration: evaluate the possibility of vector integration into chromosomes and the risk of unintended gene integration into germ cells • Reproductive and developmental toxicity: evaluate potential adverse effects on reproductive aspects including fertility, embryonic and fetal development, pre- and postnatal development, and maternal function • Immunotoxicity: assess potential adverse effects on the immune system • Carcinogenicity/tumorigenicity: evaluate the carcinogenic or tumorigenic potential of the GTP • Emergence of replication-competent viruses: assess the risk of emergence of replication-competent viruses via recombination by mutated or endogenous viral fragments
Clinical	• Knowledge of the etiology, epidemiology, pathology, clinical course, treatment, and prognosis of the target disease • Expected risks arising from the mechanisms of action of gene therapy products, and the rationale explaining why gene therapy should be conducted • Rationale for the dose, dosing frequency, and injection site • Adequate assessment of antibody formation and of unanticipated immune responses against the vector or expressed protein • Patient number: as the patient pool is limited, large-scale clinical trials may not be possible. • In clinical trials, it may not be possible to include healthy subjects as a control. • Enrolment of vulnerable population – if pediatric population is enrolled, it must address ethical considerations. • Route of administration (RoA) of GTP: Sponsors should provide adequate justification for choosing a certain RoA by giving evidence of pre-clinical data or providing evidence from other similar trial of GTP. • Consideration of immunosuppression to reduce immune responses to GTP. • The study should include safety, immunological, and efficacy endpoints; these may be surrogate or disease specific. • Follow-up time period may differ depending on the natural history, pathophysiology, or clinical sequalae of the disease, and must be justified by the sponsor. • Planned observation of vectors administered to subjects, biological distribution and survival of transgenic cells, expression pattern of target gene, presence or absence of proliferative virus, and clinical symptoms associated with administration

CMC, chemistry, manufacturing, and controls; RoA, route of administration; GTP, gene therapy product.

India has complex regulatory systems for initiating gene therapy clinical studies, necessitating multiple approvals from various committees; approval is required from the IBSC, IAEC, and RCGM for preclinical studies and CMC are required. This can take 13–15 months, potentially hindering the development of gene therapy. Additionally, clearance from the GTAEC of the ICMR and the SEC of the CDSCO is mandatory for clinical trial approvals. Streamlined, single-window clearance for preclinical and clinical studies would significantly expedite the initiation of clinical trials.

5.2. Regulatory consultation system

In China, preliminary consultations before Pre-IND meetings require comprehensive supporting documents, with the possibility of multiple rounds or resubmissions. Sponsors are encouraged to engage with the CDE, especially regarding innovative drugs, including CGT products. In Japan, sponsors must complete several HA consultations dealing with CMC, nonclinical, and clinical aspects before CTN submission. Preliminary HA reviews assess the sufficiency of the preclinical safety data and the quality of the investigational products; such reviews are essentially mandatory for a smooth CTN review within the 30-day timeframe. This consultation process requires approximately three months from application to completion, including both the preliminary and formal meetings, and any delay in consultation could significantly impact clinical trial initiation. Preparing the documentation for the multiple mandatory consultations entails substantial information and sponsor resources.

5.3. Regulatory guidance

In Taiwan, specialized laws regarding CGTs are still being developed. The Pharmaceutical Affairs Act regulates CGTs, although some of its requirements may not be entirely appropriate for CGT products. To support the growing CGT industry in Taiwan, government efforts are therefore required to expedite the launch of these revised laws.

In Japan, the HA requires adherence to the “Standards for Biological Ingredients.” The regulatory focus is on compliance in terms of the primary and secondary raw materials used in manufacturing. This poses significant workload for sponsors with not only primary raw material but also secondary raw material suppliers.

5.4. GMO requirements

In Japan and Singapore, GMO product approval confirming that it satisfies the Cartagena protocol is required before a clinical study of gene therapy is started. The standard timeline from application to approval is up to 6 months in both countries.

5.5. Lack of expertise in CGT

Compared with the US and countries in the EU, these Asian countries or regions are less experienced in CGT development and need more expertise in the CMC, nonclinical and clinical studies of CGT products. The regulatory bodies in these countries or regions should offer consultations and training opportunities to researchers

Table 3
Specific challenges for gene therapy development in the six Asian countries or regions.

Asian country or region	Issue	Details	Points for improvement
China	Lack of uniformity on management systems or review documents.	Some of the general requirements for biological products or general drug-related laws may not be applicable to CGT products.	Many CGT specific guidelines have been released and put into effect. There is potential for negotiation with HAs.
	Preliminary consultation before Pre-IND meetings	Many supporting documents are required to request Pre-IND meetings, and several rounds of Pre-IND meetings or resubmission of IND documents may happen.	Communications with the CDE regarding innovative drugs, including CGT products, should be encouraged.
India	Requires approval for pre-clinical studies and CMC from different committees	GTP proposal requires approval from IBSC, IAEC, and RCGM before submission and it takes 13–15 months (including the time to conduct the studies)	Single-window clearance of pre-clinical studies will save a substantial amount of time when initiating clinical trials.
	Clinical trial approval must be obtained from different committees	The CT proposal must be approved by both the ICMR (GTAEC committee) and the Indian FDA (SEC)	Single-window clearance to obtain the approval could be expedited (it currently takes 9–12 months).
Japan	Necessary to complete several PMDA consultations before CTN submission	The PMDA conducts preliminary reviews of preclinical safety data sufficiency and of investigational product quality. These consultations are essentially mandatory for smooth review of a CTN in 30 days.	**Timelines:** The time period required for each consultation is approximately 3 months from application to completion. Delay of consultation will give impact on start of clinical trial. **Documents:** Preparing the documentation requires large amounts of information and substantial resources.
	Obtain approval for Cartagena type I use as planned	GMO handling procedures to prevent exposure to the external environment and transmission to third parties are described in Cartagena type I usage. Approval is required before starting treatment of the first patient in the clinical study.	**Timelines:** It takes 3–6 months to obtain approval. Delayed approval will give impact the enrolment of Japanese patients. **Documents:** Preparing the documentation requires large amounts of information and substantial resources.
Singapore	Approval for environmental risk assessment from the GMAC	The GMAC ERA approval is required as part of a CTA. However, the GMAC approval timeline can be up to 6 months. Approval is required as part of submission requirement to the HSA.	The GMAC timeline should be factored into CTA planning.
	Evaluation timeline of CTGTP clinical trials	This requires 60 working days, which is a substantial period.	Advance planning is required to account for these requirements.
	Conduct research on gene therapies in Singapore	Separate GMAC approval must be obtained for research.	Familiarity with local requirements is needed as this requirement is distinct from conventional IRB/EC approvals.
	GCP/GDP considerations for the transportation and storage of gene therapy IMP	Special storage and temperature requirements.	It is necessary to ensure that all parties are adequately trained and that there are facilities for proper storage of IMP.
South Korea	Long-term follow-up	Long-term follow-up is currently required for the maximum time period for almost all types of gene therapies. This places substantial cost and time burdens on CGT companies.	Gene therapies with low risks of adverse effects should be exempted from long-term follow-up, or allowed to apply follow-up periods that are shorter than the maximum period. Regulatory science to provide scientific basis for the regulations, as well as safety data, is required.
	License for "Management Business for Human Cells etc"	This is a new license launched within the Regenerative Bio Act. Briefly, it is required for companies providing cells as a starting material for CGT products. It is mandatory for companies developing cell therapies or ex vivo gene therapies, including those providing cells for use within the same company. Obtaining this license requires extra work in addition to that required to obtain the manufacturing license.	The license for "Management Business for Human Cells etc" should be exempted or combined with the GMP manufacturing license for companies manufacturing cells as starting materials of their own products.
Taiwan	Specialized laws regarding CGT are under consideration	CGT is governed by the Pharmaceutical Affairs Act. However, some requirements within this act may not be applicable to CGT products	Government efforts are required to approve these laws faster, to support the growth of the CGT industry
	Need more non-clinical and clinical expertise in CGT products	Limited information is available for CGT in non-clinical and clinical trials for companies intending to conduct clinical trials and to demonstrate the safety and efficacy of their products.	Regulatory bodies need to have more experience of reviewing submissions from various companies and countries. They could provide additional consultations and training to researchers and companies seeking to develop CGT products.

CGT, cell and gene therapy; HA, health authority; IND, investigational new drug; CDE, center for drug evaluation; CMC, chemistry, manufacturing, and controls; IBSC, institutional biosafety committee; IAEC, institutional animals ethics committee; RCGM, review committee on genetic manipulation; CT, clinical trial; ICMR, Indian council of medical research; GTAEC, gene therapy advisory and evaluation committee; FDA, federal drug administration; SEC, subject expert committee; CTN, clinical trial notification; GMO, genetically modified organism; GMAC, genetic modification advisory committee; ERA, environmental risk assessment; CTA, clinical trial authorization; HSA, health sciences authority; CTGTP, cell, tissue, and gene therapy product; IRB, institutional review board; EC, Ethics Committee; GCP, good clinical practice; GDP, good distribution practice; IMP, investigational medicinal product; GMP, good manufacturing practice.

and companies developing CGT products. Communication and sharing of review experiences and knowledge between the regulatory bodies of these countries or regions will help to streamline regulatory reviews as well.

6. Conclusion

This article describes the regulatory requirements for starting clinical trials of AAV-based gene therapies in six Asian countries or regions. We found that Asian countries or regions are still evolving with accumulating experience and expertise of GTP development and reflecting in the regulation of AAV-based gene therapies, but divergent regulatory schemes and processes require multiple improvements. As policy implications, we propose the following items to harmonize the regulatory requirements for GTP development as well as help enhancing the capability of GTP development in the Asian countries or regions, although we understand that different regulatory and legal systems are existed in each country or region and complete regulatory harmonization is not realistic.

- Simplifying the regulatory review system for multiple scientific review areas
- Simplifying regulatory consultation system for multiple consultations and setting clear guidance for the meeting requirement
- Developing training programs on GTP development
- Developing new GTP regulatory guidelines based on recent scientific findings
- Simplifying or waiving the GMO approval currently required before starting a first clinical study.

In the coming APACRM, we will also consider to compare the gene therapy regulations in Asia with those of the US and EU for a broader understanding and discussion. We hope that the relevant regulatory agencies and trade associations will continue to collaborate to improve or harmonize their regulatory systems for AAV-based gene therapies, thus promoting the development of gene therapies in Asia.

Abbreviations

AAV, Adeno-Associated Virus; ARM, Alliance for Regenerative Medicine; CDE, Center for Drug Evaluation; CDSCO, Central Drug Standard Control Organization; CDx, Companion Diagnostics; CGT, Cell and Gene Therapy; CMC, Chemistry, Manufacturing, and Controls; CT, Clinical Trial; CTA, Clinical Trial Authorization; CTD, Common Technical Document; CTGTP, Cell, Tissue, and Gene Therapy Product; CTN, Clinical Trial Notification; DNA, Deoxyribonucleic Acid; DS, Drug Substance; EC, Ethics Committee; ERA, Environmental Risk Assessment; EU, European Union; FDA, Federal Drug Administration; FIRM, Forum for Innovative Regenerative Medicine; GCP, Good Clinical Practice; GDP, Good Distribution Practice; GLP, Good Laboratory Practice; GMAC, Genetic Modification Advisory Committee; GMO, Genetically Modified Organism; GMP, Good Manufacturing Practice; GTAEC, Gene Therapy Advisory and Evaluation Committee; GTP, Gene Therapy Product; HA, Health Authority; HSA, Health Sciences Authority; IAEC, Institutional Animals Ethics Committee; IBSC, Institutional Biosafety Committee; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IEC, Institutional Ethics Committee; IIT, Investigator-Initiated Trials; IND, Investigational New Drug; IMP, Investigational Medicinal Product; IRB, Institutional Review Board; MFDS, Ministry of Food and Drug Safety; MoE, Ministry of Environment; MHLW, Ministry of Health, Labor, and Welfare; MOHW, Ministry of Health and Welfare; MRCT, Multiregional Clinical Trial; mRNA, Messenger Ribonucleic Acid; NDA, New Drug Application; NHC, National Health Commission; NIFDS, National Institute of Food and Drug Safety Evaluation; NMPA, New Medical Product Administration; OECD, Organisation for Economic Cooperation and Development; PMD, Pharmaceutical and Medical Device; PMDA, Pharmaceuticals and Medical Devices Agency; RCGM, Review Committee on Genetic Manipulation; RoA, Route of Administration; RS, Regulatory Science; SEC, Subject Expert Committee; TFDA, Taiwan Food and Drug Administration; US FDA, US Federal Drug Administration; WD, Working Day; WG3, APACRM Working Group 3.

Author contributions

Conceptualization: H.M., A.J.Z., P.K.G., M.K., W.K.C., C.W.C., and B.C.: Data Curation, H.M.; Writing – Original Draft, H.M.; Writing – Review & Editing, H.M., A.J.Z., P.K.G., M.K., W.K.C., C.W.C., and B.C. All of the authors have approved the final article for publication.

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