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Cell and Gene Therapy Regulation in Malaysia: Current Pathways and International Comparison

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ABSTRACT

The regulation of cell and gene therapy products (CGTPs) is essential for ensuring their safety, efficacy, and timely access to the market. This article describes Malaysia's current regulatory framework for CGTPs, emphasizing available pathways such as priority review, conditional registration, facilitated registration, and orphan drug designation. Additionally, this study employs a comparative analysis to examine expedited regulatory pathways and orphan drug designations in the United States (US), European Union (EU), and Japan, highlighting key differences that impact CGTP approvals. Notably, Malaysia utilizes a broader regulatory approach, similar to the EU's Priority Medicines, in contrast to the US and Japan, which have specific pathways, such as Regenerative Medicine Advanced Therapy and the conditional and time-limited designation, respectively. The facilitated registration pathway introduced in Malaysia is unique among the reviewed jurisdictions. It relies on foreign regulatory assessments and subsequently accelerates market access in Malaysia. The study concludes that product registration holders can utilize existing regulatory pathways in Malaysia to expedite CGTP approvals. Furthermore, adopting a tailored regulatory framework similar to those in other regions could enhance Malaysia's ability to support the development and commercialization of CGTPs, ultimately improving both patient safety and access to these innovative treatments.

1. INTRODUCTION

"Cell and gene therapy products (CGTPs)", "advanced therapy medicinal products", "regenerative medicine advanced therapy (RMAT)" or "advanced therapy" represent an important advancement in medical science, providing promising therapeutic solutions for diseases previously considered incurable [1–4]. CGTPs are a diverse group of products that may originate from cells, tissues, or genes. They differ from traditional pharmaceuticals mainly because of the manipulation of living cells, the administration of genetically modified cells, and the expression of genes of interest in the human body [5,6]. As the discipline continues to evolve, regulatory frameworks must adapt to manage the scientific and clinical complexities while ensuring patient safety, treatment efficacy, and timely access [7–11].

In Malaysia, the regulation of CGTPs has increased in significance due to the worldwide progress in the field and the rising demand for innovative therapies. In response, the Malaysian Guidance Document and Guidelines for CGTPs were introduced in 2016, establishing the requirements for quality, safety, and efficacy [12,13]. This led to the initiation

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of mandatory product registration in January 2021, with full regulatory enforcement starting in January 2025 [14]. Notably, Malaysia's regulatory framework is also influenced by international standards. Although Malaysia holds the status of observer, as opposed to a member in the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use as of February 2025, it is working towards aligning its regulatory framework in reference to those of established authorities, such as United States (US), European Union (EU), and Japan [15,16]. The US, EU, and Japan are the founding country members of the ICH.

However, despite these developments, challenges persist in balancing the approval of CGTP while maintaining strong regulatory oversight, particularly in adapting international regulatory frameworks to the local context [11,17,18]. Hence, this article aims to evaluate Malaysia's regulatory framework for CGTPs, focusing on expedited review pathways such as priority review and the facilitated registration pathway. It further conducts a comparative analysis with regulatory systems in the US, EU, and Japan to identify structural differences and shared practices. The goal is to assess how Malaysia's evolving regulatory approach fits within the global landscape and to highlight opportunities for potential alignment and enhancement.

2. METHODS

2.1. Data sources

The data on Malaysian requirements and regulatory pathways were retrieved from the website of the National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia.

Information on the ICH and regulatory pathways in the US Food and Drug Administration (USFDA), the European Medicines Agency (EMA), and the Japanese Ministry of Health, Labour and Welfare (MHLW) was obtained from publicly available websites.

2.2. Study selection

All regulatory pathways pertaining to CGTPs in Malaysia were included for comparison. Similar pathways available in the US, EU, and Japan have been selected for further explanation and tabulated for differences.

2.3. Data extraction

The requirements for CGTPs have been extracted from the Drug Registration Guidance Document (DRGD) and the Guidelines for Registration of CGTPs in Malaysia (2016).

2.4. Comparability assessment

The websites of the US FDA, EMA, and Japan MHLW were referred to for information and comparison on the expedited pathways. Information from literature searches was used to complete the data when necessary information was not available in the primary regulatory documents. The comparability data was specifically focused on key eligibility criteria and their advantages to maintain consistency.

3. RESULTS

3.1. Regulatory model in Malaysia

The legislative basis for the registration and marketing authorization of pharmaceuticals, including CGTPs (classified as Biologics) in Malaysia, is the Control of Drugs and Cosmetics Regulation (1984) promulgated under the Sale of Drugs Act 1952 (ACT 368) [19,20]. NPRA, Ministry of Health Malaysia, is the National Regulatory Authority responsible for medicinal products, including New Chemical Entities (NCE), Biologics, Generics, Health Supplements, Natural Products, and Veterinary products.

NPRA acts as the secretariat to the Drug Control Authority (DCA), [20] to ensure only products that meet a certain level and requirement for quality, safety, and efficacy are marketed and used by the Malaysian population. Within NPRA, the review of the dossier for registration and Clinical Trial Import License (CTIL) or Clinical Trial Exemption (CTX) is conducted by the Center of Product and Cosmetic Evaluation. Note that CTIL and CTX are the licenses required for imported or locally manufactured products intended to be used in clinical trials [21].

3.2. Registration and requirements of CGTPs in Malaysia

NPRA has established a standard procedure for all pharmaceutical product registration. Since 2011, NPRA has been operating an online product registration system under the acronym QuEST3+ (Quality, Efficacy, and Safety 3+; the digit 3+ indicates the current system version) [22]. This web-based platform is developed based on the Association of Southeast

Table 1. Organization of a biological registration dossier: ICH-CTD versus ACTD.

Organization of product registration dossier	ICH-CTD	ACTD
Module /Part I	Administrative information and prescribing information	Table of content, administrative data & prescribing information including product labelling.
Module / Part II	Common technical document summaries	Quality document
Module / Part III	Quality	Non-clinical document (safety)
Module / Part IV	Non-clinical study reports (safety)	Clinical document (efficacy)
Module V	Clinical study reports (efficacy)	Not applicable

ACTD: ASEAN Common Technical Dossier; ICH-CTD: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Common Technical Dossier.

Asian Nations (ASEAN) Common Technical Dossier (ACTD) format. Specifically, the differences between the format of an ICH-Common Technical Dossier, as developed by regulators from ICH regions and ACTD, are depicted in Table 1 below. The main difference between the ICH-ACTD and ACTD is that the former is organized in Modules I to V, while the latter is in four parts, and they are distinct in organization [23,24].

The registration process involves the following steps:

i) Screening process

ii) Payment for processing and technical evaluation

iii) Technical assessment

iv) Presentation to the Drug Evaluation Committee (DEC)

v) Presentation to the Drug Control Authority (DCA)

vi) Final decision by the DCA for the generation of the registration number (MAL no)

During the screening process, all submissions will be checked to ensure completeness of information. This includes any special requirement-related documents, for example, any specific letter of intent related to any particular submission [e.g., Facilitated Registration Pathway (FRP)]. This is an addition to the complete sections in the dossier, comprising the particulars of the product, drug substance, drug product, nonclinical and clinical studies. Subsequently, the evaluation process will commence when all information is satisfactory at the screening stage and payment is made within 30 days of screening clearance.

The standard evaluation timeline is 245 working days, excluding the time taken for the applicant/product registration holder to respond to the list of questions regarding their products. Concurrently, during this review stage, comments or inputs from Key Opinion Leaders will be solicited, particularly regarding the safety and efficacy of the product. These comments will be incorporated into the overall product's assessment report to support the decision-making process.

Once the required information and supporting documents are deemed satisfactory, it will be presented to the DEC. If no further issues are identified, the submission will subsequently be tabled at the DCA meeting for final decision. Ultimately, this leads to the registration approval of the product, provided the committee deems that the application is safe, efficacious, and of quality. However, if the DCA members opine that the benefit does not outweigh the risks, the registration application could be rejected or registration could be withheld until the issue is resolved. In the event of rejection, Product Registration Holders (PRH) may conduct an appeal to the Minister of Health, Malaysia [16,20].

3.3. Oversight of CGTPs in Malaysia

The regulation of CGTPs has progressed through several milestones. In 2012, a technical working group was established, which led to the publication of guidance documents for CGTP registration in 2016 [25]. Furthermore, in 2017, Directive Bil 6/2017 introduced a voluntary registration process, in contrast to mandatory registration which was initially planned for January 2021 [12]. Directive Bil 19/2020, issued in 2020, allowed for transitional registration mechanisms, enabling CGTPs marketed prior to the full enforcement of regulations in 2021 to remain available under certain conditions [14].

This transition period, which extends from 2021 to 2024, aims to improve industry readiness while maintaining regulatory oversight, with the target for full compliance set for January 1, 2025[12,14,25]. During the transitional period, CGTPs marketed prior to 2021 may continue limited sales through a two-stage manual screening process. Stage 1 involves basic documentation, such as product information and evidence of safety, while Stage 2 requires more robust data, including completed nonclinical studies and ongoing early-phase clinical trials. Specifically, these mechanisms aim to prevent disruptions to patient access while encouraging the industry to prepare for full compliance [14]. Figure 1 below illustrates the regulation timeline for CGTPs in Malaysia.

Malaysia has introduced several expedited pathways (which will be explained further below), but current utilization for CGTPs remains limited. However, despite all efforts in facilitating CGTP registration, up to May 2025, only one CGTP product succeeded in gaining market access in Malaysia—for instance, Zolgensma, manufactured by Novartis Gene Therapies, Inc., Durham, US. Zolgensma, which is a gene therapy indicated for Spinal Muscular Atrophy (SMA), has been approved since February 2024. Notably, Zolgensma has been designated as an orphan drug and evaluated via the priority review pathway in Malaysia [26]. In its country of origin, the US, it has been approved since May 2019, followed by approval in the EU and Japan in March 2020 [26–29]. Apart from Zolgensma, no other CGTPs have been approved via the conditional or facilitated registration pathways to date.

3.4. Regulatory pathways in Malaysia

In addition to the standard regulatory pathway, Malaysia has introduced several alternative mechanisms, such as the priority review, the conditional registration pathway, and the facilitated registration pathway [16]. Orphan drug designation is available for drugs that address unmet medical needs and are indicated for rare diseases.

One of the advantages of having these pathways, except for conditional registration, is a shortened timeline review, reducing the standard 245 working days to a minimum of 120 working days [16]. For the facilitated registration pathway, the timeline will be in accordance with the type of review, whereby the abbreviated and verification review takes 120 and 90 working days, respectively [30]. Although the timeline for conditional registration follows the standard pathway of 245 working days, an application for priority review can be submitted for consideration [31]. However, the calculation of these days does not consider the time taken for the applicant or PRH to answer the related queries by NPRA.

3.4.1. Standard marketing authorization pathway

When the information required to demonstrate the quality, safety, and efficacy is sufficient, a product can be evaluated under the standard regulatory pathway. Typically, this includes the conduct of a pivotal Phase III clinical trial in a large number of patients in the intended population using the

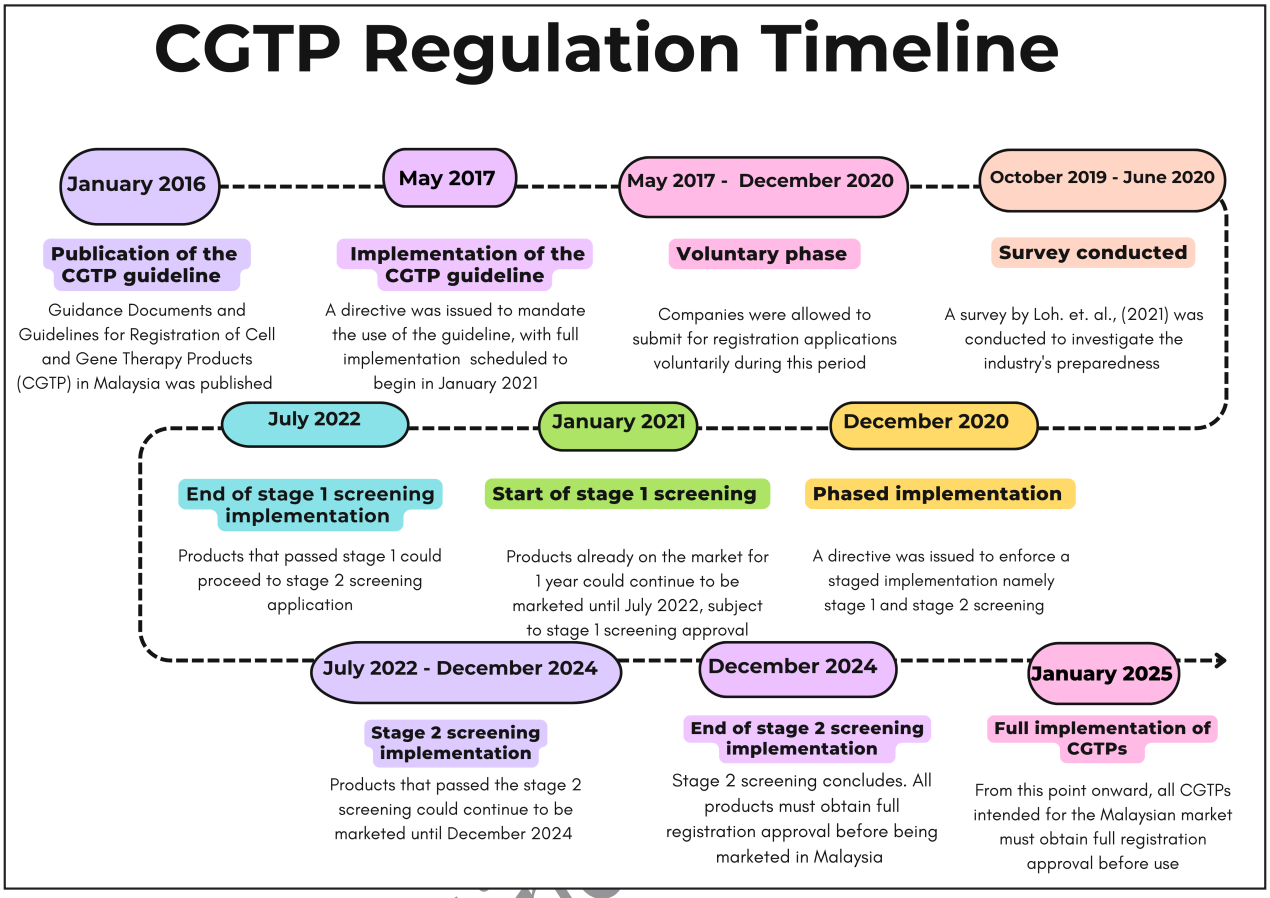

Figure 1. A chronology on the CGTP Regulation Timeline summarized from NPRA directives.

clinically relevant endpoint. Prior to this, the demonstration of proof of concept, mechanism of action, and safety is expected to be confirmed via the pre-clinical studies in relevant animal models or via *in vitro* methodology. Furthermore, justifications are to be provided for all study design approaches used. The principles of Good Laboratory Practice in accordance with the Organization for Economic Co-operation and Development principles are expected to be followed for safety and toxicity studies [32]. Whenever there is incompliance, justification should be provided. Thus, the acceptance of the justification will be assessed on a case-by-case basis.

During the review, the PRH will be given 6 months from the first correspondence date to submit the required data/ information or documentation, and failure to do so may lead to rejection [16].

3.4.2. Expedited review in Malaysia

3.4.2.1 Priority review pathway

Understanding the need for faster access to medications or treatments for patients, especially for life-threatening diseases, NPRA has developed a few regulatory pathways to cater to this need. Among them is priority review. This pathway applies to NCE products, Generics and Biologics, including CGTPs [33].

The criteria for granting priority review are detailed in Appendix 12 of the DRGD. Eligible requirements include those that address unmet medical needs, life-saving therapies for serious illnesses with no local alternatives, crucial pharmaceuticals during pandemics or endemics, and products that fulfill specific needs. Moreover, new formulations as required by the DCA, including the first or first three locally manufactured generic or biosimilar products, as well as NCE and Biologics products tested in the Malaysian population as part of Phase III clinical trials, are also eligible for a priority review, as explained in the guidance document [33].

PRH has 1 month from the date of payment confirmation to formally request priority review from the Director of NPRA. With the requirement of complete documentation submission during screening, the DEC will issue the final approval. As the aim of this pathway is to provide timely access to vital therapeutics, the review period is reduced to 120 working days for NCEs and Biologics, and 100 working days for Generics products. However, despite the shortened review period, compliance with all applicable legal requirements remains mandatory under this application method [33].

Zolgensma, currently the only approved CGTP in Malaysia, was evaluated via this pathway following its designation as an orphan drug. Details regarding the orphan drug designation are provided in *Section 3.4.2.4 Orphan drug designation* below.

Besremi, containing ropeginterferon alfa-2b as the drug substance, has also been reviewed via this pathway. Besremi is indicated for the treatment of Polycythaemia Vera (PV) in adults with symptomatic splenomegaly. As of June 2024, there was no first-line treatment option approved by the DCA for patients with PV. Furthermore, conventional interferons and hydroxyurea have been used as off-label treatment for PV. Hence, Besremi was granted priority review and was approved in June 2024 in Malaysia [34]. It is worth noting that Besremi is not a CGTP but classified under biologics. However, considering that CGTPs are regulated within the broader classification of biologics, the use of Besremi is considered suitable for contextual and explanatory purposes.

3.4.2.2. Conditional registration pathway

It is acknowledged that a full clinical trial involving all phases (i.e., Phase I, Phase II, and Phase III) is required for registration approval in Malaysia. Nevertheless, under certain conditions, products that have demonstrated efficacy and safety based on early clinical data, such as a Phase II clinical study, can be considered for conditional approval [31].

The detailed explanation on the conditional registration is as outlined in the "Guidelines on Conditional Registration for New Chemical Entities and Biologics second Edition (2020)".

Malaysia's conditional registration process for NCE and Biologics enables quicker access to critical medicinal products. This particularly applies to those that address unmet medical needs, medicinal products for seriously debilitating and life-threatening diseases, drugs categorized as orphan medicines, or products to be used in emergencies. Notably, this pathway allows products to be conditionally registered based on early clinical data rather than requiring full, comprehensive data upfront, as for the standard pathway. Furthermore, this provisional approach permits drugs with promising safety and efficacy profiles to be used in patients while additional data to confirm their efficacy and safety are gathered. In the guidance document, emphasis has been made that although complete clinical data is not immediately required, there must be sufficient preliminary evidence demonstrating the product's potential therapeutic benefits, and the risk profile is manageable [31].

Therefore, to be qualified for conditional registration, the drug must have already been approved by at least one of the eight reference regulatory authorities recognized by the DCA. For instance, EMA, EU, USFDA, US, Health Canada, Canada, Pharmaceuticals and Medical Devices Agency (PMDA), Japan, Swissmedic, Switzerland, Therapeutic Goods Administration, Australia, United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA), United Kingdom and the Agence Nationale de Sécurité du Médicament et des Produits de Santé, France. Notably, conditional registration only applies to initial product approvals and does not cover post-registration applications for additional indications except on a case-by-case basis. The conditional registration is valid for 2 years, with the option of renewing twice for an additional 2 years each time [31].

Additionally, products granted conditional registration must meet specific obligations. These include, but are not limited to, enhanced and continuous safety monitoring, as well as the periodic submission of clinical data for verification of clinical efficacy, as part of the post-marketing strategy. To ensure transparency, clear labelling indicating the conditional status of the registration or indication should be made available, informing both healthcare providers and patients about the provisional nature of the registration. In some instances, additional health professional education and patient registry establishment may be necessary as additional risk minimization activities. By demanding continuous proof of the product's efficacy and safety in real-world settings, this system strikes a balance between the pressing need for innovative treatments and the safety measures required to preserve the public's health [31].

The conditional registration pathway was first introduced in May 2018 [35]. Over time, improvements have been made, including the explicit inclusion of vaccines in addition to medicinal products, and the "Guidance and Requirements on Conditional Registration of Pharmaceutical Products during Disaster" document was incorporated into the revised version in December 2020. Although the timeline for the conditional registration pathway is set at 245 working days, a priority review application can be made, contingent upon consideration by the DEC, which will reduce the timeline to 120 working days if approved [31].

At present, no CGTP has received approval via this specific regulatory pathway. Nonetheless, Lunsumio is chosen to exemplify the procedural steps involved. Although Lunsumio is not categorized as a CGTP, it is a biologic product. As previously mentioned, CGTPs are regulated within the broader classification of biologics. Hence, the use of Lunsumio as an example is considered appropriate for contextual and explanatory purposes.

Lunsumio, indicated for the treatment of adult patients with relapsed or refractory Follicular Lymphoma who have received at least two prior systemic therapies, is an example of a conditionally approved product. Additionally, Lunsumio contains mosunetuzumab as its active ingredient, approved in September 2024 based on the results of a clinically meaningful objective response rate, complete response, and duration of response, while demonstrating a clinically manageable safety profile. Lunsumio will need to fulfill certain conditions to verify its efficacy and safety, to confirm that the benefits outweigh the risks [36].

3.4.2.3. Facilitated registration pathway

Beginning in March 2019, the Facilitated Registration Pathway: Abbreviated and verification has been introduced. This pathway leverages the assessment and inspection outcomes from a reputable regulatory authority, reducing duplication of effort and allowing NPRA to focus on a risk-based approach [37].

Facilitated registration pathway review can be considered a complete evaluation when an NCE product, generics, and biologics, including CGTPs, have been approved by the World Health Organization (WHO) Collaborative Registration Procedure or by at least one agency from any DCA reference country within 3 years of submission. It can also be considered if the product has been approved via the ASEAN Joint Assessment (JA) procedure, based on the revised guideline in November 2023 [38].

As a limited independent review is conducted in this pathway, a declaration on the sameness of documents, except for Malaysia's specific requirement, should be submitted. However, approvals granted by selected institutions under exceptional circumstances, such as the current scientific knowledge being insufficient to provide comprehensive data (e.g., conditional marketing authorization), are not eligible for this pathway [30].

Specifically, two main review styles have been introduced: verification, which confirms identical dossier information, and abbreviated, which involves a limited assessment depending on trusted sources. Regardless of review style, all submissions must adhere to technical dossier standards, demonstrate product consistency, and fulfill the ASEAN-specific requirements whenever applicable. The verification process is conducted within 30 working days, whereas the abbreviated review is completed within 90 working days [30].

A further clarification of the operational aspects of the pathway was laid down in the Frequently Asked Questions in June 2024. Main issues include the continual requirement for Annex 1 (declaration statement by the applicant) and Annex 2b (dossier checklist for facilitated registration pathway) at the point of submission, even in the absence of raw validation data. Notification of the intent must be made to NPRA, with dossier alignment confirmed against selected reference agencies. Notably, discrepancies or incomplete submissions may result in application rejection or re-routing to the usual method. Approved products must comply with ASEAN requirements, including stability studies (except for cold chain products) and country-specific requirements. Constant communication between applicants and NPRA should ensure that any further documentation required is provided [30,38,39].

Kauliv, Vyepti, Arexvy, Yuflyma, and Yesafili are examples of biologic products that have been reviewed and approved via the Facilitated Review Pathway in 2024. Hence, EMA has been chosen as the reference drug regulatory agency for all products mentioned [40–44].

3.4.2.4. Orphan drug designation

As some CGTPs might fall under the category of orphan drug, it is worth considering this designation as eligible products will be automatically evaluated via the priority review pathway with an assessment timeline of 120 working days [45].

Orphan medicines refer to pharmaceutical products designed for the treatment, prevention, or diagnosis of rare, life-threatening, or chronically debilitating conditions recognized in the Malaysian Rare Disease List. The list follows four key criteria for inclusion: the compulsory presence of confirmed cases within Malaysia, an estimated prevalence of fewer than 1 in 4,000 people (determined through expert opinions and available local epidemiological data), the severity of the disease, and formal approval from the National Rare Disease Committee under the Ministry of Health, Malaysia. Additionally, these medicines are considered when no satisfactory diagnostic, preventive, or therapeutic options are available, or if existing treatments do not provide significant benefits to individuals affected by the condition [46,47].

The designation process includes considerations and input from the DEC, which requires submission to contain comprehensive product information, proposed indications, scientific rationale, and supporting evidence [46,47].

Furthermore, the decision on the designation is made within 45 working days, with successful applications granted priority evaluation. The benefits of obtaining the designation include possible price waivers for Good Manufacturing Practice (GMP) inspections and loosened data requirements (such as acceptance of Phase II). Conversely, PRH is obliged to provide safety updates and perform comprehensive post-marketing surveillance, and failure to comply with these requirements may result in designation revocation [47]. As of June 2024, four biologics products have been approved as orphan drugs: Enspryng by the product registration holder Roche, Nexviazyme and Xenpozyme, both from Sanofi-Aventis, and Zolgensma by Novartis for the indications Neuromyelitis Optica Spectrum Disorder (NMOSD), Pompe Disease, Niemann-Pick Disease A and B, and SMA, respectively [48]. Out of the four products mentioned, Zolgensma, which is currently approved for registration in Malaysia, is in the category of cell and gene therapy [26].

In September 2024, two additional biologic products, i.e., Soliris and Ultomiris, were approved via the orphan drug designation. Note that both products were developed by AstraZeneca. Soliris has been granted orphan drug designation for the indication of Paroxysmal Nocturnal Haemoglobinuria, atypical Haemolytic Uraemic Syndrome, myasthenia gravis, and NMOSD. On the other hand, Ultomiris has been designated as an orphan drug for the same indication as Soliris except for NMOSD [49,45].

Consolidated information on all available pathways in Malaysia is tabulated as per Table 2 below.

4. EXPEDITED REGULATORY PATHWAYS AND ORPHAN DRUG DESIGNATION IN US, EU, AND JAPAN

The expedited regulatory pathways in the US, EU, and Japan share common goals of facilitating faster access to innovative therapies while balancing safety and efficacy. The US has multiple pathways, including RMAT, fast track, breakthrough therapy, priority review, and accelerated approval, providing different levels of support depending on the available data [50,51]. The European Union Priority Medicines (EU's PRIME) scheme and accelerated assessment prioritize early engagement and regulatory support, while Japan's SAKIGAKE designation fosters early innovation and conditional approval mechanisms for regenerative medicines [52–56]. Moreover, orphan drug incentives across all regions provide financial and regulatory benefits to support drug development for rare diseases [57–60]. The eligibility criteria and key benefits of each program in the US, the EU, and Japan are as described in Tables 3, 4, and 5, respectively.

5. DISCUSSION

The discussion now shifts from reporting regulatory pathways to analyzing their alignment and divergence with international practices, as well as evaluating Malaysia's position in facilitating access to advanced therapies.

Table 2. Expedited pathways, key eligibility criteria and advantages / key features.

Expedited pathway	Key eligibility criteria	Advantages / key features
Priority review Applicable to NCE, Generics and Biologics	1. The indication is for: i. Unmet medical needs (e.g. medicines for rare diseases, new vaccines, etc.) with no treatment options locally available, ii. Life-saving such as for treatment/ prevention of serious medical conditions (e.g. anticancer, antiretroviral, etc.) with no treatment options locally available, iii. Treatment/ prevention in pandemic/ endemic situations, for the interest of public health, iv. Emergency supply/ crucial for treatment purpose according to the current needs in the country, v. Supply to the Ministry of Health Malaysia under circumstances where alternative product with the same active ingredient is unavailable, vi. Population's specific needs (e.g., religious purpose) 2. Product which involves a change in the formulation due to the decision/ instruction by the Drug Control Authority (DCA), for the purpose of formulation improvement with appropriate scientific justification(s), 3. New application for products that have been registered with the same active ingredient for which the registration has been cancelled/ withdrawn due to issues other than safety issues. Priority review will be considered based on individual/ case to case basis and involves product that is crucial for treatment purpose. 4. Product which is the first *generic/ biosimilar product, or the first three locally manufactured generic/ biosimilar product. **No generic/ biosimilar product has been registered by DCA at point of consideration on granting Priority Review* **During product evaluation, the priority review status granted can be cancelled in the event that the condition (4) is no longer fulfilled.* 5. New Chemical Entity (NCE) or biologics product with a phase III global, multicentre pivotal clinical trial conducted locally in Malaysia for the treatment of diseases of public health significance (e.g., hepatitis, HIV, COVID-19, etc.). A minimum of 5% of the total number of randomised subjects are subjects in the clinical studies conducted at study sites in Malaysia.	1. Reduced timeline to 120 working days for Biologics, 100 working days for Generics products
Conditional registration pathway Submission of registration application based on early clinical data such as Phase II clinical study	1. Approved by at least one of eight reference regulatory authorities recognised by DCA i.e. EMA, US FDA, Health Canada, PMDA, Swissmedic, TGA, UK MHRA, ANSM. 2. Strong justification provided for either: i. Medicinal products or vaccines for seriously debilitating diseases or life-threatening diseases OR ii. Medicinal products or vaccines to be used in emergency situations OR iii. Orphan medicine 3. Justification on ability to fulfil the requirements in relation to all points as follow: i. Positive risk-benefit balance of the product ii. High possibility on ability to provide comprehensive data iii. Fulfilment of unmet medical need iv. The benefits of immediate availability to public health outweighs the risk of less comprehensive data than normally required, based on registration requirements. 4. Proposal submission on completion of ongoing or new studies, or the collection of pharmacovigilance data	1. Early access to market in contrast to obligation to complete Phase III study for standard pathway 2. Potential to full registration if conditions are met.

Continued

Expedited pathway	Key eligibility criteria	Advantages / key features
Facilitated registration pathway Assessment based on the evaluation report from established regulatory authorities	Abbreviated review WHO Collaborative Registration Procedure (CRP) The product should have/is as per items below: 1. Screening stage approval via QUEST system. 2. Valid GMP certification from PIC/s member or WHO. 3. Identical in all aspects of the drug substance and drug product except for container closure system and pack size to meet ASEAN stability requirements (if applicable). Different drug product manufacturing site or brand name can be considered if clearly justified. 4. Declaration letter to confirm identical Drug Master File (DMF) with WHO CRP application if DMF is submitted. However, for Biologics, the whole drug substance dossier is expected. Products approved by at least any one regulatory authority recognized by DCA i.e. EMA, US FDA, Health Canada, PMDA, Swissmedic, TGA, and UK MHRA. The product should have the following items: 1. Submission application in QUEST system within 3 years from the approval date of chosen reference drug regulatory agency 2. Declaration on authenticity of assessment report, list of Question & Answer (Q & A) and all relevant documents 3. Valid certification of manufacturing facilities from any PIC/S members 4. Identical in all aspects of the drug substance and drug product except for container closure system and pack size to meet ASEAN stability requirements (if applicable). Different drug product manufacturing site or brand name can be considered if clearly justified 5. Declaration letter to confirm identical Drug Master File (DMF) with WHO CRP application if DMF is submitted. However, for Biologics, the whole drug substance dossier is expected. 6. No rejection, withdrawal, suspension, approval via the appeal process or pending deferral by any reference drug regulatory agency for quality, safety and/or efficacy reasons in relation to the product and its intended use (indications, dosage information and patient group). 7. Identical information in the proposed Package Insert (PI)/ Patient Information Leaflet (PIL) to that approved by the reference drug regulatory agency, except for country-specific information. 8. The proposed indication, dosing regimen, patient groups and or direction for use is the most stringent among those approved by the reference drug regulatory agencies. A supplemental clinical assessment report from the reference drug agency that approved the most stringent indication, dosing regimen, patient group and/or direction for use should be submitted when the chosen reference drug regulatory agency does not bear the most stringent indication, dosing regimen, patient group and/or direction for use. Reports from public domain are acceptable. Differences in dosage regimen to meet local practices are allowed for vaccines. 9. Products which are approved via a full evaluation process by the reference drug agency will be considered. Products approval via exceptional circumstances such as conditional marketing authorisation or equivalent process is not eligible for this pathway. Verification Review ASEAN Joint Assessment (JA) Procedure 1. Products from the priority therapeutic areas and indications that are periodically posted on ASEAN national regulatory agency websites. 2. Products outside priority area can be submitted for consideration with condition that the products have been approved by 'stringent' NRA defined by WHO, prequalified by WHO, or assessed through special regulatory pathways such as EU Article 58 or US FDA tentative approval. 3. The manufacturer is a PIC/S-GMP compliant site (document verification only, no inspections foreseen)	1. Reduced timeline to 30 working days for verification process 2. Reduced timeline to 90 working days for abbreviated review

Continued

Expedited pathway	Key eligibility criteria	Advantages / key features
Orphan drug designation Pharmaceutical products intended for the treatment, prevention, or diagnosis of rare, life-threatening or chronically debilitating conditions recognized in the Malaysian rare disease list	1. "A medicine, vaccine or *in vivo* diagnostic agent that is primarily intended to treat, prevent or diagnose a rare disease as listed in the Malaysian rare disease list"; and 2. No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized; or, if such a method exists, the medicinal product must be of significant benefit to those affected by the condition.	1. Loosened data as listed below: i. Phase II clinical data acceptance ii. Stability study data and storage condition of the product according to Zone IVb requirements are not mandatory iii. Protocol of analysis, analytical method validation and Certificate of Analysis for at least 1 batch instead of 3 batches iv. The product may be manufactured in countries whose health authorities are not members of the (PIC/S). v. Possible GMP inspection fee waivers vi. Submission of an annual safety report if the submission of PSUR/PBRER every 6 months for the first 2 years and once a year for the following 3 years could not be submitted. 2. Priority review upon approval; 120 working days of assessment timeline

Abbreviations: European Medicines Agency (EMA), EU, United States Food and Drug Administration (US FDA), US, Health Canada, Canada, Pharmaceuticals and Medical Devices Agency (PMDA), Japan, Swissmedic, Switzerland, Therapeutic Goods Administration (TGA), Australia, and United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA), United Kingdom and The Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), France. Pharmaceutical Inspection Cooperation Scheme (PIC/S).

Table 3. Eligibility criteria and key benefits for each program in US.

Designation	Criteria	Key benefits
Fast track	Treats serious conditions with potential to address unmet needs	Expedited review, frequent FDA interactions, rolling review submission
Breakthrough therapy	Substantial improvement over existing therapies based on preliminary clinical evidence for treatment of serious conditions	Senior manager FDA involvement, facilitated development and expedited assessment
Regenerative medicine advanced therapy (RMAT)	Meets the definition of regenerative medicine therapy, treat, modify, reverse or cure serious conditions, and addresses unmet needs based on preliminary clinical data	Early interactions for surrogate endpoints, benefits of Fast Track and Breakthrough designations
Priority review	Significant improvement over existing therapies in safety or efficacy for serious conditions	Reduced review time from 10 to 6 months
Accelerated approval	Uses surrogate endpoints for serious, prolonged disease conditions	Early patient access with post-marketing studies required
Orphan drug designation	Affects <200,000 patients or unprofitable within 7 years for vaccines, diagnostics or preventive drugs	Tax credits, user fee exemptions, 7-year market exclusivity

Source: US Food and Drug Administration [50,51,59].

Table 4. Eligibility criteria and key benefits for each program in EU.

Designation	Criteria	Key benefits
Accelerated Assessment	Major public health interest, substantial improvement over existing treatments and fulfils unmet medical need	Review timeline reduced from 210 to 150 days, early engagement with CHMP Rapporteurs, dedicated procedural manager (PM) assigned
PRIME (PRIority MEdicines)	Unmet medical need, significant therapeutic advantage based on preliminary data	Early rapporteur appointment, regulatory support through roadmap & development tracker, potential for accelerated assessment
Conditional Marketing Authorization	Positive benefit-risk balance despite limited data, targets life-threatening diseases	Early approval with post-marketing obligations, renewal and eventual transition to marketing authorization.
Orphan drug designation	Prevalence <5 in 10,000 or insufficient market return, significant benefit over existing methods, no satisfactory method of diagnosis, prevention or treatment exists, for life-threatening or chronically debilitating diseases	Fee reductions, 10-year market exclusivity, protocol assistance

Source: European Medicine Agency [52,53,57,58,62]

Table 5. Eligibility criteria and key benefits for each program in Japan.

Designation	Criteria	Key benefits
SAKIGAKE	First developed and anticipated approval in Japan, radical improvement over existing therapies	Priority consultation and review, dedicated PMDA manager, post-marketing support
Priority review	Orphan drugs for severe diseases showing apparent improvement of medical care	Reduced evaluation timeline from 12 to 9 months
Conditional & time-limited approval	Regenerative medicine products showing probable clinical benefit via surrogate endpoints	7-year conditional approval with post-marketing studies
Orphan drug designation	<50,000 patients, high medical need, theoretically supported via strategic development	Financial subsidies, priority review, extended re-examination period up to 10 years, regulatory guidance and consultation

Source: Japan Ministry of Health, Labour and Welfare [55,56,61,63,68].

However, while there might be similarities between these pathways and those in other ICH countries (i.e., the US, the EU, and Japan), the FRP is unique to Malaysia. Unlike expedited pathways in the US (e.g., RMAT) or Japan (e.g., SAKIGAKE), which emphasize early access based on limited clinical data, Malaysia's FRP accelerates market entry by leveraging prior approvals from recognized reference authorities, conserving regulatory resources, and focusing internal review efforts on higher-risk products [30]. The list of eligible reference authorities has been expanded beyond the original scope of just the US and EU, to include those recognized by the WHO, JAs from ASEAN member states, and other reference countries accepted by the DCA. Consequently, this demonstrates Malaysia's move toward broader regulatory harmonization. Hence, PRH should take this opportunity to make use of the program, which will eventually lead to faster market access in Malaysia.

The priority review program in Malaysia is parallel to the priority review in the US and Japan, and it includes an accelerated assessment in the EU. All pathways reduce assessment timelines to 120 working days, 6 and 9 months, and 150 days as opposed to 245 working days, 10 and 12 months, and 210 days for standard reviews, respectively [2,33,50,53,61]. Specifically, in Malaysia and the US, eligibility criteria for serious or life-threatening diseases are prioritized, although Malaysia additionally considers local context as a criterion, e.g., local manufacturing site [33,50]. Unlike the US, which mandates superiority over existing therapies, Malaysia's and the EU's frameworks emphasize the absence of treatment alternatives [33,50,53]. Compared to Japan's approach, it only limits priority review to orphan drugs or significant improvements in clinical care [2,61]. On the other hand, Malaysia's approach aligns with global trends in expediting critical therapies, but is broader in scope as it incorporates domestic health priorities. Malaysia would benefit from more stringent prioritization criteria to optimize resource allocation. Additionally, Malaysia would have a strengthened system by implementing greater transparency in review outcomes (e.g., the number of products granted priority review and their outcomes, or the incorporation of regulatory pathway approval status in product technical assessment summaries), which are elements increasingly standard in mature regulatory systems. The differences associated with the pathways are tabulated in Table 6 below.

The conditional registration pathway, which accepts Phase II clinical trials for review in Malaysia, shares considerable similarities to the EU's conditional marketing authorization and the US's accelerated assessment designation [31,50,62]. All accept surrogate or intermediate endpoints under conditions of unmet need and require post-marketing commitments.

Table 6. Comparison of priority review pathways.

Regulatory Pathway	US	EU	Japan	Malaysia
Designation	Priority review	Accelerated Assessment	Priority review	Priority review
Eligibility criteria	Treats serious conditions; significant safety/efficacy improvement	Major public health interest; substantial therapeutic innovation	Orphan drug status or clear improvement in medical care	Addresses unmet medical needs, life-saving treatments, public health emergencies
Key benefits	Reduces review time from 10 to 6 months	Reduces evaluation time from 210 to 150 days; early CHMP engagement	Reduces review time from 12 to 9 months	Reduces evaluation time from 245 to 120 working days

Source: US Food and Drug Administration, [50] European Medicine Agency, [53] Japan Ministry of Health, Labour and Welfare, [56, 61, 63, 68] National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia [33].

Table 7. Comparison of conditional registration pathways.

Regulatory pathway	US	EU	Japan	Malaysia
Designation	Accelerated approval	Conditional marketing authorization	Conditional and time-limited approval	Conditional registration pathway
Eligibility criteria	Conditions with prolonged disease course; relies on surrogate or intermediate clinical endpoints	Addresses serious public health needs; positive benefit-risk balance despite limited data	Applicable exclusively to regenerative medicine products; probable clinical benefit demonstrated through surrogate endpoints	Positive benefit-risk balance, fulfilment of unmet medical need, potential for comprehensive data
Key benefits	Earlier patient access	Earlier market access, potential transition to full authorization	Approval valid for 7 years, earlier patient access	Facilitates earlier market access, potential for full registration
Post-marketing studies required	Yes	Yes	Yes	Yes

Source: US Food and Drug Administration, [50] European Medicine Agency, [62] Japan Ministry of Health, Labour and Welfare, [61, 63, 68] National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia [31].

Moreover, as the guideline for conditional registration in Malaysia was developed in reference to the guideline in the EU, it is not unexpected that there are many similarities to the pathway in the EU. Both Malaysia and the EU require a product to be for a serious or life-threatening target disease, for a limited orphan patient population, and with no alternative treatment options at the point of submission [31,62]. Furthermore, all programs require a post-marketing study for confirmation of efficacy and safety [2,31,51,61,62]. The validity of the conditional approval is 1 year in the EU, while in Malaysia, it is 2 years [31,53]. In the US, accelerated approval does not carry a defined validity period. However, it is contingent upon the timely completion of post-marketing confirmatory trials. Approval may be revoked if these trials fail to confirm clinical benefit, if the product is deemed unsafe or ineffective, or if the sponsor does not fulfill post-approval obligations. Additionally, misleading promotional activities may also warrant withdrawal [50]. In Japan, the pathway is only applicable to regenerative medicine products [63]. These comparisons indicate Malaysia's alignment with global conditional approval practices, while also highlighting areas for ongoing regulatory refinement. Table 7 below tabulates the differences regarding the conditional registration pathways.

The orphan drug designation systems in Malaysia, the US, the EU, and Japan share a common objective of promoting treatment, including diagnosis, for rare and serious diseases, albeit having differences in eligibility thresholds and the breadth of incentives offered. In particular, the definition of rare diseases, ranging from fewer than 1 in 4,000 in Malaysia to fewer than 200,000 people in the US, was based on the prevalence of the countries [45,46,59,64]. Moreover, extensive support was provided in the US, EU, and Japan, including tax benefits, user fee exemptions, regulatory guidance, and market exclusivity of up to 10 years [58,59,63–67]. Additionally, Japan further extends its support through financial subsidies and priority review specifically for orphan drugs [68]. Both the EU and Japan add regulatory support, which is an important tool in increasing the likelihood of registration approval in the respective countries. It is also worth noting that the US, EU, and Japan work closely on the issues related to orphan medicines [64–66,68]. However, Malaysia's mechanism of orphan drugs remains modest, offering possible GMP inspection fee waivers, reduced data requirements, and priority review. Unlike other systems, Malaysia incorporates approval from the national expert committee, highlighting its emphasis on localized evaluation [45,46]. In summary, the differences mentioned reflect varying levels of regulatory maturity and strategic

Table 8. Comparison for orphan drug designation.

Regulatory Pathway	US	EU	Japan	Malaysia
Designation	Orphan drug designation	Orphan drug designation	Orphan drug designation	Orphan drug designation
Eligibility criteria	Diseases affecting <200,000 people; vaccines, diagnostics, or preventive drugs must be unprofitable within 7 years post-approval	Life-threatening/chronic diseases, prevalence <5 in 10,000, must offer significant benefit	Diseases affecting <50,000 patients; high medical need, no alternatives	Prevalence <1 in 4,000; no satisfactory treatment, significant benefit
Key benefits	Tax incentives, user fee exemptions, 7-year exclusivity	Fee reductions/exemptions, 10-year exclusivity, regulatory support	Financial subsidies, regulatory guidance, tax benefits, priority review, extended re-examination (10 years)	Possible GMP inspection fee waivers, reduced data requirements, priority review

Source: US Food and Drug Administration, [59, 64] European Medicine Agency, [57, 58] Japan Ministry of Health, Labour and Welfare, [68] National Pharmaceutical Regulatory Agency, Ministry of Health, Malaysia [46, 47].

priorities in addressing rare disease treatment access. The comparison regarding the orphan drug designation in the US, EU, Japan, and Malaysia is as per Table 8 below.

In relation to the early engagement strategy, Malaysia's Pre-Submission Meeting (PSM) is a voluntary consultation service that serves as an avenue for applicants to clarify regulatory or technical issues [69]. Although it is not tied to any pathways, it echoes the supportive functions of the US Breakthrough Therapy (or RMAT for Regenerative Medicines), the EU's PRIME, and Japan's Sakigake Designation [50,52,55,63,70,71]. These international pathways, however, include formalized processes and regulatory assignment of an FDA senior manager, a Committee for Medicinal Products for Human Use rapporteur, or PMDA concierge, consequently providing structured guidance [50–52,55,69]. Malaysia's PSM, though helpful, lacks similar strategic integration into product development timelines, representing an area for potential enhancement [69].

6. LESSONS FROM INTERNATIONAL CGTP IMPLEMENTATION

The regulatory experiences of advanced jurisdictions, namely the US FDA, EMA, and PMDA, offer valuable lessons on the challenges of implementing expedited pathways for CGTPs. Nevertheless, while these frameworks highlighted the advantage of faster access to novel therapies, they also come with trade-offs related to regulatory rigor, post-approval monitoring, and the reliability of clinical evidence [72]. One of the critical issues worth focusing on is the conditional regulatory pathway, whereby surrogate endpoints are often used in early-phase trials to predict clinical benefit in place of traditional, long-term efficacy and safety data [73].

Additionally, the use of surrogate endpoints has been associated with a lack of ability to predict meaningful clinical outcomes consistently [73]. Surrogate endpoints also have limited validity in the context of long-term safety and efficacy [73]. This is exemplified by the product, Kymriah, which was approved based on surrogate markers like B-cell aplasia, but its sustained efficacy beyond short-term remission remains under post-marketing evaluation [73].

In Japan, conditional approval of HeartSheet based on limited early-stage data raised concerns about the reliability of non-randomized trials in predicting therapeutic benefit. Although post-marketing studies were required, their implementation was delayed, reflecting a common challenge in CGTP approvals where early patient access often occurs before comprehensive real-world validation [74]. Furthermore, products such as Temcell and reclassified therapies like JACE have demonstrated impediments in ensuring long-term safety oversight and in adapting established treatments to fit within accelerated regulatory pathways.

Additionally, manufacturing and quality control challenges in CGTPs also complicate accelerated approvals [75]. Therapies granted breakthrough or Sakigake designations have encountered difficulties maintaining their quality control, also known as Chemistry, Manufacturing, and Controls standards [75]. This is exemplified by the need to resolve issues with the manufacturing process, including product stability, short half-life, and analytical validation [71]. This post-approval commitments require specifications and test-methods revision, which further demands specialized regulatory and scientific capacity [71].

Beyond scientific uncertainty, accelerated approvals transfer a significant burden of evidence generation to the post-marketing phase, which requires high levels of workforce and financial commitment from sponsors [70,73]. Between 2018 and 2022, up to 70% of FDA approvals required confirmatory Phase III trials. Many of the trials were delayed, inconclusive, or failed to verify anticipated benefits [73]. Moreover, this burden is anticipated to be particularly heavy for CGTPs due to the complex manufacturing processes and individualized treatment protocols. Resource strain is experienced by sponsors, marketing authorization holders, and regulatory agencies, particularly due to the obligation to meet statutory review timelines while managing increased volumes of post-market follow-up commitment [17,70,76].

Collectively, the risks mentioned underscore the need for Malaysia and other emerging regulators to balance the speed of access with scientific caution, ensuring the benefits are not limited to only faster patient access, but more importantly, are safe, transparent, and evidence-driven. Additionally, this should be considered without overextending regulatory personnel or compromising staff sustainability.

However, while the above were derived from the international regulatory models, the regulatory adaptation must also be considered within the context of the ASEAN

level. There is a glaring challenge regarding regulatory harmonization in ASEAN. In particular, each country in the ASEAN region has its own framework with specific guidelines (if any) and requirements for CGTPs, making it challenging to create a unified regulatory approach for CGTPs. This includes differences in regulating development plans, clinical research, market approval, and ultimately patient access [15,76–79].

Additionally, a significant inequality in infrastructure, including laboratories and experienced technical personnel among ASEAN member states, creates a barrier for harmonization. These are exemplified by differences in stem cell processing facilities, technical expertise, and resources available for CGTPs regulation and oversight [78,80].

It has also been reported that ethical considerations, particularly in the use of autologous cells and innovative practices, require careful regulation to ensure safety and efficacy. Differences in ethical standards, such as views on gene editing, stem cell use, and human tissue sourcing, pose challenges in regional harmonization. Some countries are more restrictive than others, leading to fragmented policies and regulatory uncertainty for developers [81].

From a domestic standpoint, Malaysia faces unique implementation challenges, despite having introduced the CGTP regulatory framework in 2016. Hence, it has been highlighted that there is a significant gap in the nation's regenerative medicine ecosystem, including the lack of clear clinical and manufacturing standards and ethical controversies [82]. Additionally, there is institutional fragmentation between regulatory, research, and health service bodies. This is particularly evident with the use of embryonic stem cells [82]. Apart from this, lack of funds, specialized equipment, and skilled personnel contribute to the challenge in CGTPs development [82]. Overall, this may inhibit or delay the complete optimization of the expedited pathways that are currently in place in Malaysia.

7. FUTURE RECOMMENDATION

In light of the challenges previously mentioned, Malaysia should approach the development of its own CGTP regulatory framework with strategic caution and incremental steps. As opposed to immediate replication of CGTP-specific, fast-track programs like the FDA's RMAT or Japan's conditional and time-limited designation, Malaysia could begin by establishing a conditional approval mechanism tied to post-marketing obligations. It draws from the strengths and learning from the limitations of established systems. Early regulatory collaboration with mature agencies, the use of shared scientific assessments, and the adoption of risk-based evaluation models can help reduce the review burden while maintaining quality. Moreover, the introduction of a national CGTP registry and active surveillance infrastructure would be essential to track real-world outcomes and fulfill post-approval commitments. By focusing on validation of surrogate endpoints, harmonized standards, and transparency in regulatory expectations, Malaysia can build a robust, agile, and trusted system that facilitates innovation without compromising patient safety or clinical credibility. Over time, with accumulated regulatory experience and industry feedback, Malaysia may consider introducing a formalized expedited pathway for CGTPS, tailored to local health system needs, resource constraints, and pharmacovigilance capacity.

8. CONCLUSION

In summary, Malaysia has established a range of regulatory pathways that align with international standards while addressing local requirements. The regulatory oversight of CGTP is evolving in response to scientific advancement, providing a structured framework for its regulation. Nevertheless, despite CGTP regulations being in place since 2021, only one product, Zolgensma, has been successfully registered to date, a considerably lower number compared to other biologics [25]. Further investigation is warranted to understand the factors limiting CGTP approvals in Malaysia and, consequently, their availability to patients. CGTPs offer the potential to eliminate or repair disease-causing cells, providing curative approaches that address unmet medical needs and enable highly personalized precision medicine [83].

Unlike the US and Japan, which offer specific programs like RMAT designation and conditional or time-limited approvals for CGTPs, Malaysia currently lacks a dedicated program for these therapies. However, applicants can utilize existing pathways that offer various benefits and considerations to streamline the approval process. Therefore, enhancing and expanding these mechanisms could improve Malaysia's capacity to support the safe and efficient development of CGTPs, ultimately enhancing patient access to these advanced treatments.

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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This study does not involve experiments on animals or human subjects.

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