DEVELOPMENT OF A REGULATORY GUIDELINE FOR CELL THERAPY MEDICINAL PRODUCTS IN THAILAND

By
MISS Patcharaphun KIDPUN

A Thesis Submitted in Partial Fulfillment of the Requirements
for Doctor of Philosophy (SOCIAL AND ADMINISTRATIVE PHARMACY)
Graduate School, Silpakorn University
Academic Year 2021

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นางสาวพัชราพรรณ กิจพันธ์

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By	Patcharaphun KIDPUN
Field of Study	(SOCIAL AND ADMINISTRATIVE PHARMACY)
Advisor	Associate Professor Rapeepun Chalongsuk

Graduate School Silpakorn University in Partial Fulfillment of the Requirements for the Doctor of Philosophy

.....Dean of graduate school
(Associate Professor Jurairat Nunthanid, Ph.D.)

Approved by

.....Chair person
(Associate Professor Siwanon Jirawatnotai , Ph.D.)

.....Advisor
(Associate Professor Rapeepun Chalongsuk)

.....Committee
(Assistant Professor Namfon Sribundit , Ph.D.)

.....Committee
(Assistant Professor PANOOPAT POOMPRUEK , Ph.D.)

.....Committee
(Assistant Professor Sineenart Krichanchai , Ph.D.)

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MISS PATCHARAPHUN KIDPUN : DEVELOPMENT OF A REGULATORY GUIDELINEFOR CELL THERAPY MEDICINAL PRODUCTS IN THAILAND THESIS ADVISOR : ASSOCIATE PROFESSOR RAPEEPUN CHALONGSUK

Treatment approaches have evolved rapidly and are being increasingly customized to specific diseases or particular patients, leading to the emergence of Advanced Therapy Medicinal Products (ATMPs). These ATMPs entail cell therapy medicinal products. These are emergence of new products. The objective of the research was to develop guidelines for the regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration. The research was a qualitative study conducted from March to September 2021. Three parts of the study included 1. Review of literature and related documents 2. Interviews with 34 key informants using a semi-structured questionnaire. Key informants were purposively selected from researchers or physicians conducting the study using cell-based therapy and regulators of these products and manufacturers and importers who are licensed with the Drug Act B.E. 2510 (1967). 3. Formulation of the guideline of cell therapy medicinal products to verify from all stakeholders, both in terms of use within medical institutions and drug registration, as well as sent the summary of the recommendations to the interviewees for reconsideration. The results found that: 1. To ensure patient safety using cell-based therapy within medical institutions, specific requirements for this service should be established including those for qualification of physicians providing the service, manufacturing site, standard of laboratory, medical institutions, medical practices, cell therapy medicinal products, and monitoring of the use of cell-based therapy 2. ATMPs: cell therapy medicinal products are different from other chemical or traditional biological drugs. Therefore, different regulations are developed, including the need to submit conditional approval with a Risk Management Plan, consideration without samples for testing before marketing authorization, certification of lot release, and retain samples. In particular, the autologous product is limited quantities and specific patients. Moreover, risk-based: SMP level 1 follow-up is applied. The extensive safety and efficacy post-marketing process should be carried out for two years, following which it should be maintained until lifelong. Additionally, Thai Food and Drug Administration (FDA) freely able to tailor-made following up procedure of patients in order to better protect patients. The regulation for providing services using ATMPs: cell therapy medicinal products in Thailand require collaboration from various organizations, such as the Department of Health Service Support, Thai FDA, Department of Medical Sciences, The Medical Council, and relevant Royal Colleges to ensure patient access and safety. However, cost-effectiveness evaluation to care for patients who untreatable previously standard therapy is ultimately recommendations for further research studies.

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MISS Patcharaphun KIDPUN

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CHAPTER I

INTRODUCTION

Significance and background

Treatment approaches, which combine new scientific knowledge and biotechnology innovations in cell-based, tissues, and gene, have evolved rapidly and are being increasingly tailored to specific diseases or particular patients. These novel treatments offer new opportunities for treating rare or previously uncurable diseases (1, 2). Innovative therapeutics widely known as Advanced Therapy Medicinal Products (ATMPs) (3), which can further be sub-classified into four main categories as somatic cell therapy medicinal products (4-8), gene therapy medicinal products (8), tissue engineered products and combined ATMPs as an incorporation between cells, tissues, genes and medical devices (3, 9). While such is usually being called ATMPs in the European Union (EU) and Thailand (10), it is being recognized as human cells, tissues, and cellular and tissue-based products (HCT/Ps) or biologic drug (type of the cells or gene) in the United States of America (USA) (11) or Regenerative Medicine (RM) in Japan (12, 13). ATMPs have been obtained a Marketing Authorization (MA) in the EU, the USA and Japan. As of April 2021, there are 18, 20 and 11 products available in the USA, the EU and Japan, respectively (11, 14-16). The highlighting aspect of ATMPs is the utilization of cells or tissues of humans from patients or volunteer donors. This is a marked differences from other drugs. As a result, ATMPs can be divided into two groups according to sources of the products. The first is autologous product, from which cells of individuals and specific patients are used. There are numerous advantages of this approach, including the minimization of risks from systemic immunological reactions or bio-incompatibility (17, 18). For example, KYMRIAH® and YESCARTA® products. Those products are an immune cellular therapy containing autologous T cells genetically modified an anti-CD19 on surface cancer cells (17-24). They were likely to be associated with better efficacy and safety in the treatment of relapsed or treatment resistant leukemia or lymphoma. Due to the

autologous source resulting in patient specific batches, these products truly represent personalized medicines. The second is allogeneic products which come from a single volunteer donor or a group of a small number of donors. Allogeneic-based products are being so largely manufactured that people call them off-the-shelf products. The challenges involve the selection of donors regarding communicable diseases and ethical issues, especially as allogeneic products dramatically consider the immune system (25). For example, PROCHYMAL® is an active ingredient from human bone marrow-derived mesenchymal stem cells for acute graft-versus-host disease treatment after the hematopoietic stem cell transplantation (26-28). TEMCELL® HS is an alternative treatment in case patients are not responsive to steroid during therapeutic processes. As the result, ATMPs are the most anticipated group of innovative medicinal products aiming to address life-threatening or untreatable conditions that do not respond to the standard treatment. As such, ATMPs have become an excellent candidate as adjunctive therapy in clinical practices which could widely impact prospective treatment strategies

ATMPs may be available in selected countries depending on the local legal framework. Regulation of ATMPs can be categorized into 2 main approaches. Firstly, medicinal products for human use (controlled by the national regulatory authorities) must be approved before their market launch. For example, the EU has Regulation (EC) 1394/2007 (so-called ATMPs Regulation), while the US has the Food, Drug & Cosmetics Act (FDCA) under 21 CFR 600-680 and Public Health Service Act section 351, and Japan uses Pharmaceutical Medical Device and other therapeutic product Act (PMD Act) to control RM. Secondly, ATMPs exemption from the medicine legislation is excluded from MA. For instance, clinical practices or hospital exemption (HE) in medical institutions are controlled by the exclusive, professional responsibility. This exception is made to comply with medical requirements. However, there may be additional specific laws to regulate them as Directive 2004/23/ EC, Directive 2006/17/ EC and Directive 2006/86/ EC in the EU while FDCA under 21 CFR 1271 in the USA, and The Act on the Safety of Regenerative Medicine (ASRM) in Japan. It is important to recognize the importance of safety and quality. As mentioned previously, ATMPs can be distributed in various ways to patients. Nevertheless, ATMPs were reported inefficacy or exaggerating

advertisement and abusing for unproven products or treatments, especially, at clinical setting that where are the easiest place and less restrictive accessibility (29). Moreover, A death was reported following a pulmonary embolism of a Korean patient who received an injection of stem cells at a Kyoto-based clinic (30, 31). The United States of America has three patients of over 75 years with age-related macular degeneration who went blind after intravitreal injections of the autologous adipose tissue-derived (32). Meanwhile, processes of ATMPs products are rigorously regulated approval under drug law because ATMPs are complex and innovative products. In some cases, it will not be feasible to use traditional regulations. The origin of ATMPs is the primary reason for their uniqueness that cell or tissue of ATMPs are derived from human. Their products may be specified to the administration procedures or invasive surgical procedures. Some products can persist in human bodies for a prolonged period after administration and they may proliferate and differentiate tumorigenicity. It reduces its effectiveness and increases adverse reactions to treatment (33, 34). In addition, the inherent characteristics of the products cause side effects that cannot be exactly monitored and followed up on the products (25, 35). Therefore, it is important to formulate a long-term follow up plan on the efficacy and the safety of ATMPs. Moreover, the traditional pharmacokinetics of absorption, distribution, metabolism, and elimination studies may not be feasible to ATMPs. Thus, biodistribution is also taken into consideration of biological substances associated with the surrogate markers. The benefits of some products may not be able to sufficiently proven because of limited population size during a period of clinical trials or poor understanding of scientific knowledge with products. Lastly, ATMPs are required significant financial supports which encompasses two concepts, reimbursement, and funding, and these need to be explored. For this reason, often, ATMPs have not yet been granted to become widely used extensively in the market. These challenges can be met in the development of ATMPs for commercialization.

By 2019, clinical trials to identify the number of ATMPs in development involved 1,052 ongoing studies. Most ATMPs studies are in cell-based therapy (36). Moreover, Thailand has also been studying cell therapy for a long time and ATMPs are mainly composed of cells. This study aims to investigate into the regulation of cell therapy medicinal products ahead of genes, tissues, and future integration of ATMPs,

as ATMPs mostly are compose of cells. Additionally, academic of medical institutions in Thailand have successfully adopted both patient's cells or donors. For example, the limbal stem cell transplants have been used very successfully to restore functional corneal epithelium (37). However, in the case of receiving stem cells from a donor, there is still immune resistance. Further, the CD19 CAR T cells are being developed for against the leukemic cells (38). Thailand is increasingly interested in developing cell therapies or advanced therapies that incorporate cells for medical problems. These do not correspond to standard treatment. Medical institutions in Thailand can provide cell therapies treatment by exempt of medical requirements via a medical practice on individual patients under exclusive professional responsibilities of medical practitioners to comply with an individual medical prescription for an individual patient. The produced cells for the individual patients are excluded from the Drug Act B.E. 2510 (1967) and its amendment that they are not complying with this law (39). Consequently, it is similar to how cell therapy is being allowed to be produced and used in a clinical setting without marketing authorization. Subsequently, some national regulatory authority worn against unauthorized products as inefficacy is not being assured and there may be problem related to safety (40). By nature, the claimed effects of unapproved ATMPs tend to be based on anecdotal evidence rather than clinical trials according to the regulatory frameworks. Their use is therefore associated with a risk of serious adverse events and lack of significant clinical benefits.

At present, Thailand, there are no specific guidelines or requirements for cell therapy in medical institutions. The remarks on Regulation (EC) 1394/2007 mentioning hospital exception (HE) should be excluded from the scope of this legislation while ensuring that community rules relating to quality and safety are not compromised (3) ASRM has also been enforced to clinical facilities in Japan, Australia and South Korea which released provision for operating within medical institutions. Therefore, Thailand should formulate specific regulations or rules for cell-based therapy at medical institutions to ensure the quality of treatments and protect the patients. At the same time, ATMPs type cell-based medicinal products are not being manufactured or imported. Nevertheless, Thai Food and Administration is the main role of protecting consumers' health by ensuring safety, quality and efficacy

of health products, including cell-based medicinal products. These products were regulated by under the national legislation and international agreements with Drug Act B.E. 2510 (1967) and its amendment (39). Any Marketing Authorization Application should comply with current Good Manufacturing Practice (specific: Good, Tissue Practice), Good Clinical Practices, Good Laboratory Practices and Good Pharmacovigilance Practices. This is mandatory for all medicinal products that have been granted MA. However, traditional regulations may not be suitable for ATMPs type cell therapy medicinal products that it sets out for mass production and different origin. Likewise, the limitation of number for enrolling in a clinical trial is difficult to approve drug registrations. Therefore, many countries have come up with guidelines for special approval for ATMPs such as Conditional approval, specific licensing scheme for ATMPs or RM and Expedited pathways.

In conclude, the confirmed data shows that drugs derived from cell-based are potential in the treatment of various diseases, and it is considered as new alternatives to treating undiscovered medical needs. Some evidences demonstrate sufficient data on safety and efficiency. However, Thailand should prepare guidelines of cell therapy medicinal products for both medical institutions and drug registration that regulations should evolve both to promote the potential approach and to safeguard the public. Subsequently, cell therapy medicinal products might impact on the treatment in the future. Moreover, Thailand lacks specific regulatory guidelines for cell therapy medicinal products of applicants and medical institutions. It is important to formulate guidelines for cell-based therapy that are suitable models for the regulations of cell therapy medicinal products, both in terms of use at medical institutions and drug registration in Thailand. In addition, public health will be protected before cell therapy medicinal products will become common in Thailand.

Research questions

This research seeks to address the following questions:

What are the suitable models for the regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration?

Research objectives

The objectives of this research were to study and develop:

1. Guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products that may be suitable for Thailand.

2. Guidelines for cell therapy medicinal product regulations in terms of drug registration that may be applicable in Thailand.

Benefits of the study

1. The stakeholders have a better understanding of the current situation and problems in relation to the regulation of cell therapy medicinal products in Thailand.

2. To identify the necessary regulatory requirements for cell therapy medicinal products in terms of use by medical institutions and drug registration to ensure quality, safety, and efficacy of the use of such products in Thailand in the future.

3. The suggestions to develop the policy of regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration which are potentially suitable for Thailand.

Scope of the research

The research was a qualitative study conducted from March to September 2021. Three parts of the study included:

1. Review of literature and related documents

2. Interviews with 34 key informants using a semi-structured questionnaire. Key informants were purposively selected from researchers or physicians conducting the study using cell-based therapy, regulators of these products, and entrepreneurs including manufactures and importers are licensed within the Drug Act B.E. 2510 (1967). In this research, many interviewees have experience in several different perspectives of cell therapy medicinal products in Thailand.

3. The formulation of recommendations for the regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration, and the distribution of the recommendations' summary to the interviewees for reconsideration.

Terminology definition

1. Advanced Therapy Medicinal Product (ATMPs) means any of the following medicinal products for human use. For example, gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), or tissue-engineered products (TEPs), and whether the product fulfills the definition of a combined ATMPs or not. ATMPs is presented as having properties for or is used in or administered to human beings to treat, prevent or diagnose diseases through the pharmacological, immunological, or metabolic action of its cells or tissues for human.

2. Somatic Cell Therapy Medicinal Products (sCTMPs) means

(a) contains or consists of cells or tissues that have been subject to substantial manipulation for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings to treat, prevent or diagnose disease through the pharmacological, immunological, or metabolic action of its cells or tissues

3. Gene therapy medicinal products (GTMPs) means

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings to regulate, repair, replace, add, or delete a genetic sequence;

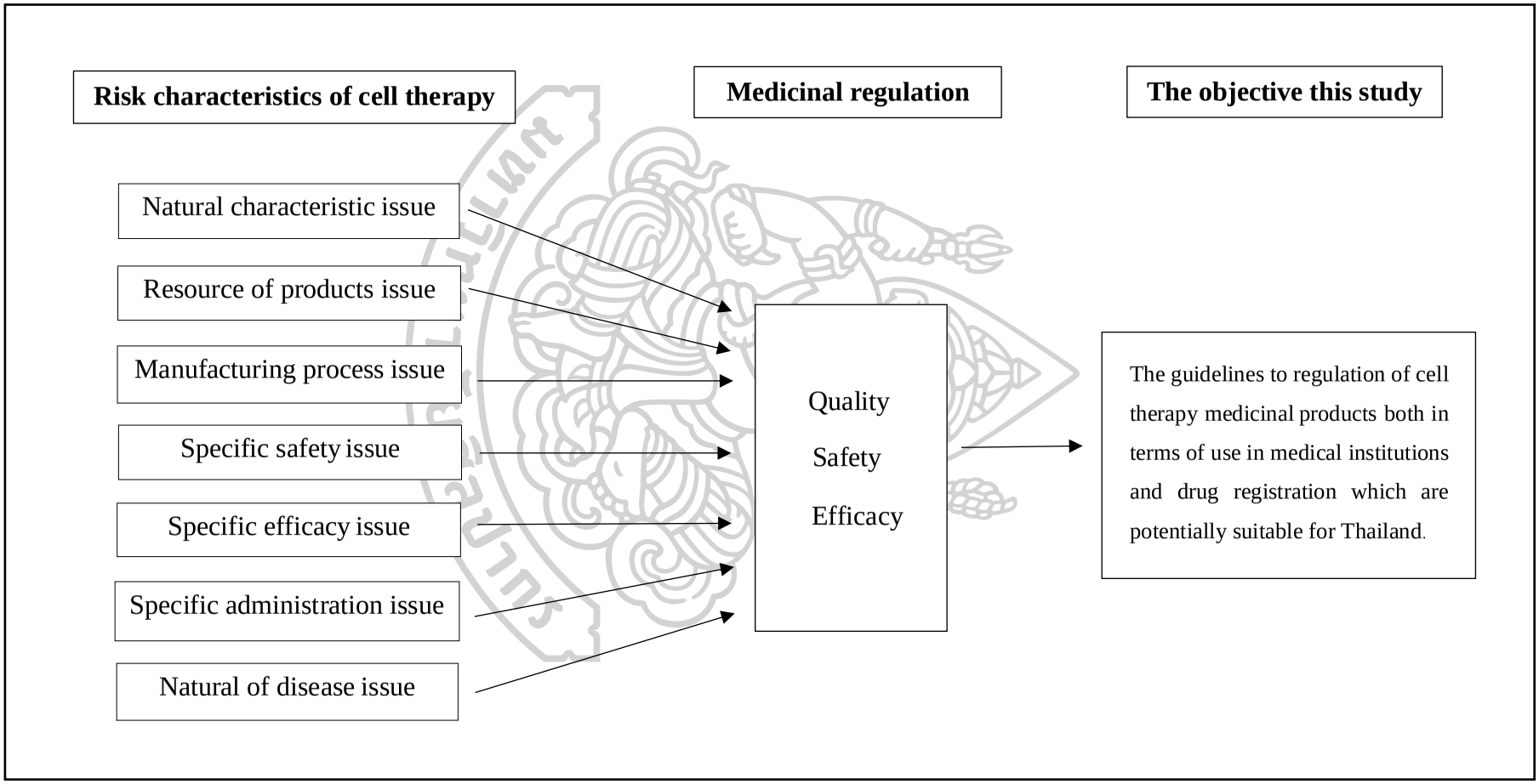
(b) its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of gene expression of this sequence.

4. Tissue Engineered Products (TEPs) contains or consists of engineered cells or tissues, and TEP means cells or tissues substantial manipulation modified and/or not intended to be used for the same essential functions

5. Combined ATMPs are incorporated between cells, tissue, gene, and medical devices.

6. Cell Therapy Medicinal Products consist of highly modified cells relevant to their intended clinical use and have been altered, or of cells that are not intended to be used for the same essential function(s) or advanced therapy encompass of human cells within medical institutions.

Conceptual framework



CHAPTER II

LITERATURE REVIEW

To develop suitable models for the regulation of cell therapy medicinal products in terms of use within medical institutions and drug registration in Thailand, researchers studied from related documents, articles, and various research by defining the study topics as follows:

1. Legal framework for cell therapy medicinal products in the United States of America, the Europe Union, JAPAN, AUSTRALIA, South KOREA, and THAILAND

2. The development of Advanced Therapy Medicinal Products (ATMPs) for drug registration

3. State-of-the-art knowledge on the regulation of Advanced Therapy Medicinal Products (ATMPs)

4. The production and distribution of cell therapy medicinal products

5. Post-Marketing Safety measures for cell therapy medicinal products

6. Risk-based approach

7. Researchers related to developing an approach for regulatory on cell therapy medicinal products

1. Legal framework for cell therapy medicinal products in the United States of America, the Europe Union, JAPAN, AUSTRALIA, South KOREA, and THAILAND

1.1 The United States of America

The United States (US) Food and Drug Administration (FDA) has jurisdiction over a wide range of health products, including food, tobacco, medicines, and medical devices in the United States. Within the USFDA, pharmaceutical therapeutics are regulated under either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) which is specifically responsible for the regulation of biologics products such as vaccines, blood products,

biopharmaceuticals, cells or tissues of humans as well as gene therapy products. The cells or tissues of humans as well as gene products are classified as biological drugs. USFDA is the legal authority to regulate human cells, tissues, and cellular and tissue-based products (HCT/Ps) by the Public Health Service Act (PHS Act) and the Food, Drug, and Cosmetic Act (FD&C Act) and their amendments. Oversight cells or tissues of human and gene therapy products fall to the Office of Tissues and Advanced Therapies (OTAT), which before re reforming in October 2016 was known as The Office of Cellular, Tissue, and Gene Therapies (OCTGT) located within CBER. Gene and cell therapy (GCT) products are regulated under Section 351 of the PHS Act and the FD&C Act related to 21 CFR parts 600–680 (Figure 1)(41). 351 Products are defined by exclusion; it is a biologic which does not meet the criteria of 361 Products as defined in the same legislation. 361 products cover products including tissue and bone transplants and are referred to as HCT/Ps that have a definition the following requirements must be met:

1. The HCT/P is minimally manipulated.

2. The HCT/P is intended for homologous use, as reflected by the labeling, advertising, or other indication of the manufacturer's objective intent.

3. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerning the HCT/P.

4. The HCT/P does not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function, or the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and is for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use (6, 41, 42).

361 products fall under Section 361 of the PHS Act and 21 CFR Part 1271 that do not require premarket approval. Therefore, gene and cell therapy (GCT) products, which are excluded from 361 products, are regulated as 351 Products. As 351 Products, GCTs must accept premarket approval requirements such as Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Investigational

New Drug (IND) Application, Good Clinical Practice (GCP) , and Good Pharmacovigilance Practices (GVP) after launch into the market.

In addition, the definition of minimal manipulations is significant to evaluate and categorize as to whether 351 products or 361 products. It means cutting, grinding, and shaping, soaking in an antibiotic solution, sterilization by ethylene oxide treatment or gamma irradiation, cell separation, lyophilization cryopreservation, and freezing that is without culture before administration to the patient (6). That do not change biological activity of cells or tissues. All of the above, the degrees of manipulations are a meaningful element of regulatory overseen of cells and tissues therapy medicinal therapy

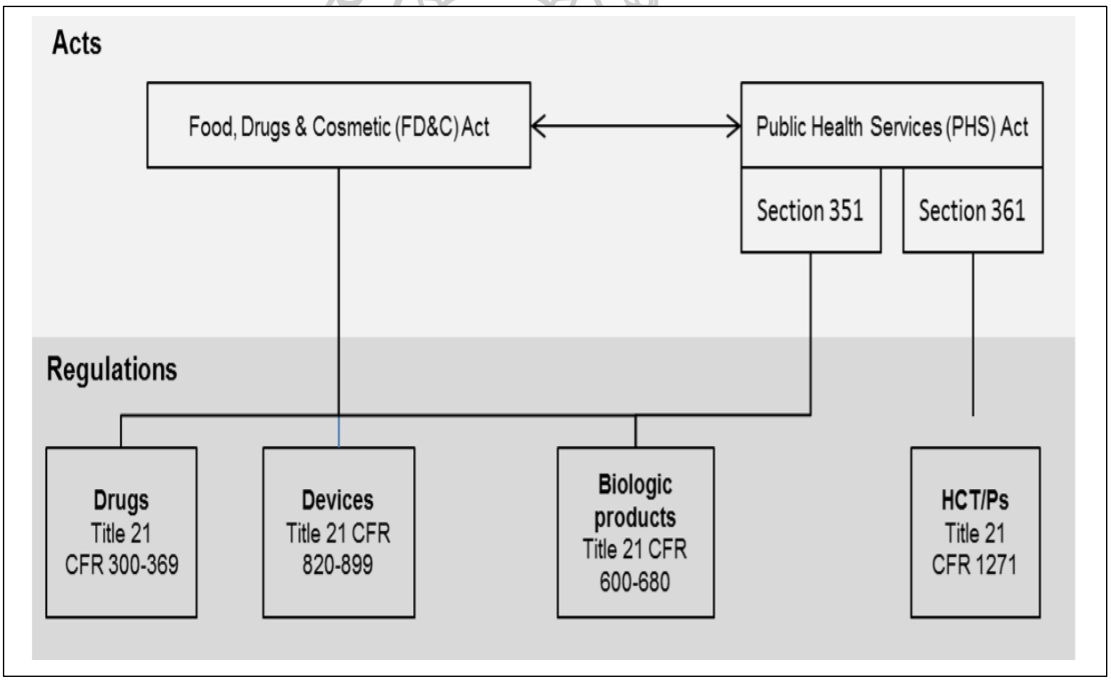


Figure 1 The difference between the Public Health Service Act (PHS Act) and the Food, Drug and Cosmetic Act (FD&C Act) (41)

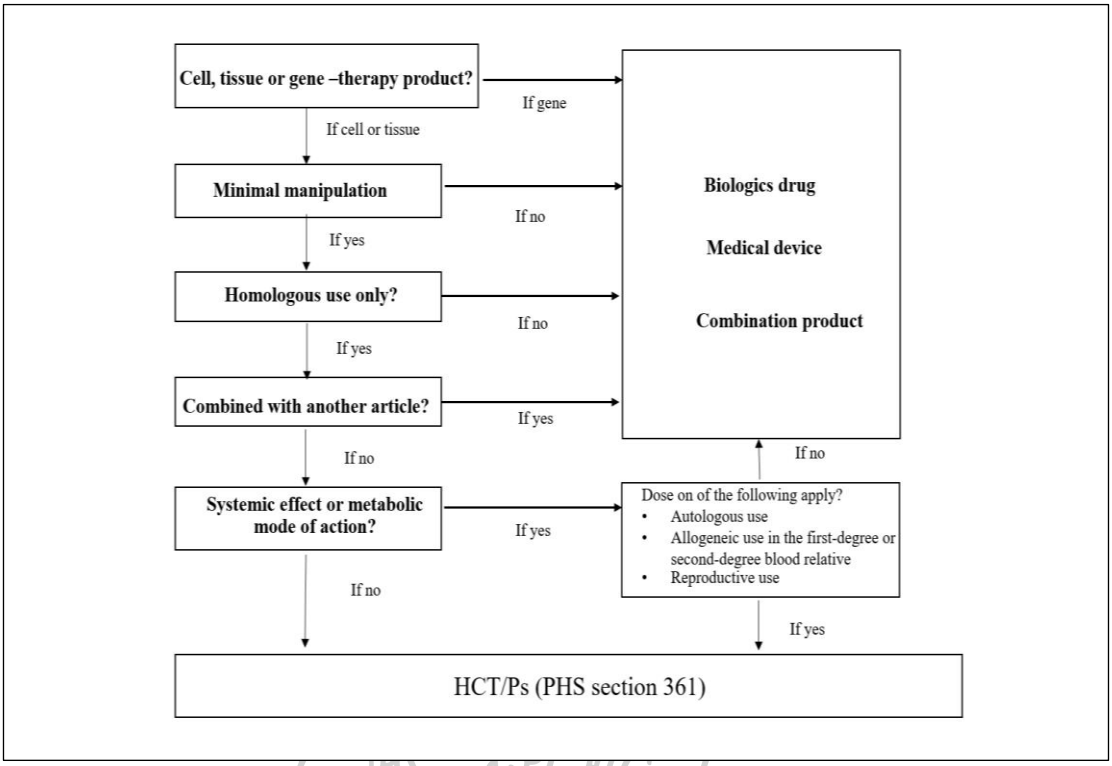


Figure 2 Classification of ATMPs between PHS section 351 and 361 (41)

1.2 The European Union

The European Medicines Agency (EMA) is the centralized regulatory body of the European Union (EU). Within the EMA, the Committee for Advanced Therapeutics (CAT) provides opinions and suggestions on Advanced Therapy Medicinal Products (ATMPs) that are the major responsibility of those products. However, planning was reviewed and approved by the Committee for Medicinal Products for Human Use (CHMP) for drug registration. Marketing Authorization (MA) approval in the EU can be divided into four groups as follows shown in Figure 3 (43).

1. The centralized procedure for medicinal registration is the approval by the European Commission (EC). The centralized procedure is valid throughout the entire the EU. The EMA is responsible for the scientific evaluation of applications under the centralized procedure. Additionally, ATMPs are required a centralized procedure.

2. The mutual recognition procedure is the approval of drug registrations affecting the market placement of medicinal products within each Member State (Related Member States).

3. The decentralized procedure is the approval of the registration of the drugs that are effective for sale and distribution in more than one country in the EU.

4. The national procedure for drug registration approval is applied only in countries that drug registration is effective for sale and distribution within the country's MA.

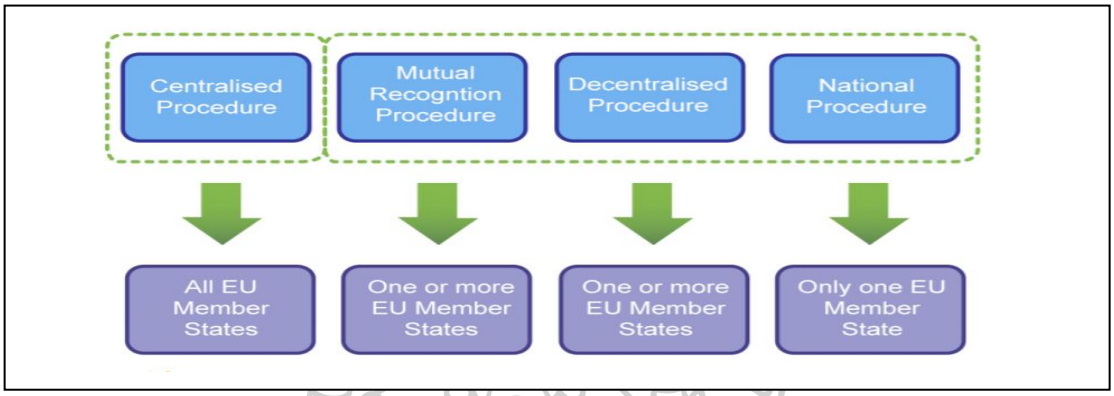


Figure 3 European marketing authorization approval procedures (43)

Somatic cell therapy medicinal products (sCTMPs), gene therapy medicinal products (GTMPs), and tissue-engineered products (TEPs) and combined between cell tissue or gene and medical devices are classified into the Advanced Therapeutic Medicinal Products (ATMPs) which are provided under the new Regulation (EC) 1394/2007 that so-called ATMPs Regulation (3). All ATMPs in the EU are required to obtain a MA via the centralized procedure, except for those falling under Article 3(7) of Directive 2001/83/EC (8) and Article 28 of Regulation (EC) 1394/2007, the so-called hospital exemption (HE). ATMPs under hospital exemption is the definition "…prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, to comply with an individual medical prescription for a custom-made product for an individual patient…" (3). HE is needed to define and harmonize for standardization among countries in the EU. If the ATMPs fall into HE schemes may be followed national competency authorization. ATMPs must comply with pharmaceutical regulations. The Marketing Authorization Application (MAA) has been made to ensure the quality, safety, and efficacy of all medicinal products for human use by the legislation of the pharmaceuticals before

permitted to marketing authorization. In general, ATMPs have to complete the same scientific and regulatory requirements as other medicinal products such as current Good Manufacturing Practice (cGMP), Good Laboratory Practice (GLP) , Investigational Medicinal Product Dossier (IMPD), Good Clinical Practice (GCP) , and Good Pharmacovigilance Practices (GVP). These requirements are ensured on quality, safety, and efficacy for those products.

ATMPs classification is conducted by the CAT on request of and on basis of information provided by a developer of a product based on genes, cells, or tissues and the outcome of the classification is therefore specific to the product under development that is divided into the following ways (9):

1. Somatic Cell Therapy Medicinal Products (sCTMPs) means

(a)contains or consists of cells or tissues that have been subject to substantial manipulation for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor.

(b) is presented as having properties for, or is used in or administered to human beings to treat, prevent or diagnose disease through the pharmacological, immunological, or metabolic action of its cells or tissues.

2. Gene therapy medicinal products (GTMPs) means

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings to regulate, repair, replace, add, or delete a genetic sequence.

(b) its therapeutic, prophylactic, or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of gene expression of this sequence.

3. Tissue Engineered Products (TEPs) contains or consists of engineered cells or tissues, and TEP means cells or tissues substantial manipulation modified and/or not intended to be used for the same essential functions.

4. Combined ATMPs are incorporated between cells, tissue, gene, and medical devices.

The key of classifying whether a cells or tissues product is categorized ATMPs as considering the level production of cells or tissues have been subject to substantial manipulation (more than minimal manipulation in terms of the US) so that biological characteristics, physiological functions, or structural properties relevant for the intended clinical use have been altered. Furthermore, Annex I of ATMPs regulation referred to cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification that are called minimal manipulations (3). Thus, the cells or tissues products are processed within minimal manipulation criteria that are excluded from ATMPs.

1.3 JAPAN

In Japan, ATMPs are well known as Regenerative Medicine (RM). Japanese National Diet has passed the Regenerative Medicine Promotion Act in May 2013 (12, 30). This law is a comprehensive policy to promote the RM developments as well as to protect those who accept RM. In line with this law, two related laws, the Act on the Safety of Regenerative Medicine (ASRM or RM Act) and the Pharmaceuticals and Medical Devices (PMD) Act (which is the revised Pharmaceutical Affairs Law (PAL)) (shown in Figure 4), which have dramatically reformed the Conditional approval for early phase after positive clinical data of RM from small numbers of patients that it can be performed RM only. The RM and PMD Acts were enacted in November 2013 and became law in November 2014. Japan has enacted two new laws related to the prophylactic, treatment, cure, mitigation, or prevention of disease using genes, cells, and tissues from human or animal cells. RM is defined by PMD Act and ASRM as follows:

(1) Processed human or animal cells intended for either: (a) the reconstruction, repair, or formation of the structure or function of the human (or animal) body (such as tissue-engineered products) (b) the treatment or prevention of human (or animal) diseases (such as cellular therapy products).

(2) Articles intended for the treatment of disease in humans (or animals) and are transgenes to express in human (or animal) cells.

"Processing" is defined by the PMD Act and ASRM, as follows

1) artificial expansion/ differentiation of cells and establishment of a cell line,

2) chemical treatment to activate cells or tissues,

3) modification of biological characteristics,

4) combination with noncell/non-tissue components, and/or

5) genetic modification of cells conducted for the treatment of diseases or repair or reconstruction of tissues.

"Processing" does not include the following operations:

1) separation and cutting of tissues,

2) isolation of specific cells (except for isolation following biological/ chemical treatments),

3) treatment with antibiotics,

4) washing,

5) sterilization by gamma-ray,

6) freezing,

7) thawing, and/or other procedures that do not use cells for different structures and functions from the original cells.

As mentioned previously, the terms of processing is the same means as more than minimal in the US and substantial manipulation in the EU.

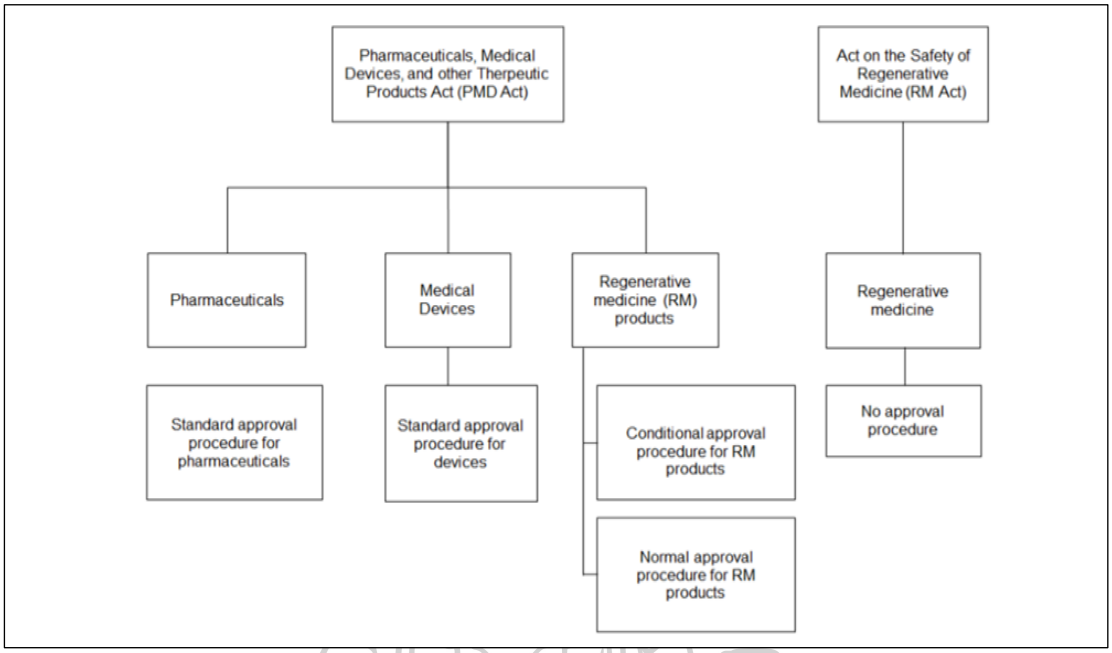


Figure 4 The difference between The RM Act and The PMD Act (41)

Japan Regulatory Frameworks for RM are generally classified into two categories

1. PMD Act (the previous name was Pharmaceutical Affairs Law (PAL)) is a law that has been in existence since the 1960s that regulates and supervises pharmaceutical products, medical devices, and quasi-drug. In 2013, RM emerges as a novel product that was regulated by the PMD Act. This law is the law that governs pharmaceutical companies/sponsors. To obtain approval to register RM into the market and to ensure quality, safety and efficacy after the product is released. Furthermore, the PMD Act introduced conditional time-limited approval. This approval is considered a case-by-case for RM products only, within a period agreed with Ministry of Health, Labor and Welfare (MHLW), normally a maximum of 7 years for data confirm after-market authorization. At the end of commitment time, the applicant must collect and demonstrate of safety and efficacy profile for re-evaluation approval (44). If the data are inadequate for supporting full approval, these products have to be withdrawn from the market at the end of the 7-year after post-marketing.

2. ASRM or RM Act This law was first drafted in April 2013 and then implemented in 2014 as a new law governing the manufacture of RM products. This

new law was enacted to specifically relate to the protection of RM products. Its goal is to promote, control, and prevent its use in clinical research, processing cells, or treating specific patients with medical practitioners. ASRM is a law that requires physicians or those involved such as medical institutions, educational institutions, and cell plants, to follow the requirements of this law. Moreover, this law divides RM products into three subcategories based on the level of risk (45, 46).

Class I: high risk. RM is encompassed of embryonic stem cells, induced pluripotent stem cells, transgene cells, and allogeneic cells. Researchers or medical institutions must submit a research protocol and ethical information to the specially certified regenerative medicine committee and the Health Science Council (HSC) of the MHLW. The experts' s specially certified regenerative medicine committee consists of approximately 10 to 15 experts. After the committees have approved the research protocol and ethics data. Researchers must submit research protocols and research ethics data to the HSC under the MHLW for re-approval. The HSC will use 90 days to consider granting a research protocol unless the review period is extended. If the HSC makes any revisions or recommendations, the investigator must follow through on them before RM products can be conducted in human studies.

Class II: moderate risk. RM is encompassed of mesenchymal stem cells. Researchers or medical institutions must submit research protocols and ethical information to the specially certified regenerative medicine committee. The experts' s specially certified regenerative medicine committee consists of approximately 10 to 15 experts. After the committees have approved the research protocol and ethics data. subsequently, Researchers must submit research protocols and research ethics data to the MHLW for notification.

Class III: low risk. RM is excluded from category 1 or 2. Researchers or medical institutions must submit research protocols and ethical information to a specially certified regenerative medicine committee. After the committees have approved the research protocol and ethics data. Subsequently, researchers must submit research protocols and research ethics data to the MHLW for notification.

The medical institutions have to report annually to MHLW and committees for RM, including (1) the number of patients who were administrated RM, (2) incidence

of diseases and disabilities related to RM, and (3) overall safety and efficacy evaluation of RM.

As mentioned previously, the two laws (ASRM and PMD Act) have different standards and objectives. Whereas the PMD Act is a law that regulates the RM products throughout the marketplace. It is strict requirements meet to Good Manufacturing Practice (GMP) , Good, gene, Cellular, and Tissue-based product manufacturing Practice (GCTP), Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Good Pharmacovigilance Practices (GVP). On the other hand, ASRM is a regulation related to research institutes, medical settings, and cell processors. However, their organizations still have to comply with ASRM rules to ensure quality, safety, and efficacy for those who accept the RM. Those differences between the PMD Act and ASRM Act where the first law focuses on standardizing the distribution of free RM across the market but the second law limits access.

1.4 AUSTRALIA

The Therapeutic Goods Administration (TGA) in Australia is a key role to regulate therapeutic products such as medicines, biological medicines excluded from human cell or tissue-based products, products containing live animal cells, tissues or organs, biologicals, and medical devices.

Cell-based products, tissue-based products, combination products (e.g., a cell therapy and a medical device), and immunotherapy products containing human cells (e.g., chimeric antigen receptor (CAR) T-cell therapy) are all included in the definition of biologicals, and their products are governed by the Australian Regulatory Guidelines for Biologicals (ARGB). For cell and gene products, the Advisory Committee on Biologicals (ACB) and the Office of Gene Technology Regulator (OGTR) have major responsibilities. Their committees include experts from various fields. The therapeutic goods are met Good Manufacturing Practice (GMP) inclusion on the Australian Register of Therapeutic Goods (ARTG), adverse event reporting, and compliance with TGA standards for therapeutic goods (47, 48).

Risk basis for classification for Biologicals (49)

In Australia, all biologicals have classified biologicals according to the level of risk to patients associated with their use. Their products will be categorized by the

level of processing applied to the biological (minimal manipulation or more than minimal manipulation the same in the EU, USFDA, and JAPAN) and the intended use of the product (homologous or heterologous use). Biologicals are categorized before inclusion on the Australian Register of Therapeutic Goods (ARTG) according to their risk. Each category is subject to differing levels of requirements of supporting efficacy and safety evidence. Their products should be classified into one of four classes,

Class 1 biologicals are low risk and have an appropriate level of external governance and clinical oversight. a biological is a Class 1 biological if:

(a) it is a faecal microbiota transplant product; and

(b) it is not advertised to consumers; and

(c) it is to be collected under the supervision or direction, or following the requirements, of a medical practitioner registered, in a State or internal Territory, as a medical practitioner; and

(d) each later step in the manufacture of it is to be carried out in a hospital by, or under the supervision or direction of, the practitioner (unless the step relates to the storage or testing of the biological, in which case it may instead be carried out by a person under a contract with the hospital in a State or internal Territory); and

(e) it is for use in a recipient who is a patient of the hospital with the recipient being under the clinical care of the practitioner.

The requirements of Class 1 biologicals must be needed as follows:

1. must comply with all applicable standards

2. must be mentioned in Schedule 16 (50)

3. must be included on the ARTG, following a declaration of compliance

4. does not require manufacturers to hold a GMP manufacturing license or certificate

5. does not require pre-market assessment of supporting data

At the time of publication of this guidance, only faecal microbiota transplant products (subject to certain conditions) are defined as Class 1 biologicals

Class 2 biologicals are low risk. The definition is the level of processing that has been subjected to only minimal manipulation and only for homologous use.

Class 3 Biologicals are medium risk. The definition is either: for homologous use, but has been prepared using more than minimal manipulation or for non-homologous use, regardless of whether they have been prepared using minimal manipulation or more than minimal manipulation. Characteristic between Class 2 and Class 3 Biologicals is shown in Figure 5 (49)

As mentioned previously, the terms of minimal manipulation is dramatically important to categorize the class of biologicals that usually be considered minimal manipulation as the following list: centrifugation, trimming, cutting or milling, flushing or washing, refrigeration, freezing, freeze-drying, the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents, irradiation for bioburden reduction (51). Additionally, homologous use is also significant that means cells or tissues are used for repair, reconstruct, replace or supplement to a person (the recipient), the same basic function or functions in the recipient as the original cells or tissues performed in the person from whom they were collected (donor) (52). The definition of both minimal manipulation and homologous use is the same as the EU, USFDA, and Japan.

Class 4 biologicals are high risk. The definition is the following biologicals are Class 4 biologicals:

(a) biologicals that comprise or contain cells, tissued or organ of live animal

(b) biologicals to which both of the following as:

(i) the biologicals comprise, contain, or are derived from human cells or human tissues that have been modified to artificially introduce a function or functions of the cells or tissues, including genetic modification of cells (CAR T cells)

(ii) the artificially introduced function or functions were not intrinsic to the cells or tissues when they were collected from the donor;

(c) pluripotent stem cells.

(d) biologicals derived from pluripotent stem cells.

Moreover, Class 4 biologicals maybe mean that subjected to prepare more than minimal manipulation and heterologous use.

Intended / Level of processing	Homologous	Non-homologous
Minimal manipulation	Class 2 (Low risk)	Class 3 (Medium risk)
More than minimal manipulation	Class 3 (Medium risk)	Class 3 (Medium risk)

Figure 5 Classification matrix for class 2 and 3 biologicals (49)

Autologous human cells and tissues (HCT) products excluded from TGA regulation (53)

On the other hand, some products were excluded from TGA regulation, For example, autologous human cells and tissues (HCT) products. Criteria for exclusion from TGA in terms of autologous HCT products is needed all of the following:

1. Collected from a patient who is under the clinical care of a medical or dental practitioner registered under a law of a State or an internal Territory

2. Manufactured by that medical or dental practitioner, or by a person or persons under the professional supervision of that medical or dental practitioner in a hospital (except storage and testing), for that patient who must be a patient of that hospital

3. Not advertised to consumers

Where one or more criteria are not met, including advertising to consumers, regulation by TGA will apply for those autologous HCT products.

The conditions for exclusion of these criteria do not include any restrictions on the level of manufacturing including beyond minimal manipulation and the intended use (homologous use or non- homologous use). Exclusion from TGA regulation is not exclusion from all regulations. There are requirements for prevention from the risks that may arise as a result of therapy with autologous HCT products. These requirements are required from medical and dental practitioners such as

1. Registered hospital setting under a law of a State or an internal Territory

Hospital institutions are accepted and controlled under various states, territories, and national provisions. Accreditation of hospitals is required in the hospital setting that performs autologous HCP products with patients. Licensing of hospitals has been approved by the Australian Health Ministers.

2. Registered medical and dental practitioners who conduct autologous HCT products. To maintain registration in their respective specialties, medical and dental practitioners are required to associate with continuing professional education, work within their scope of practice, and maintain recency of practice. Guidance for professional practice is contained in the code of conduct for registered medical practitioners and Good medical practice: A code of conduct for doctors in Australia. Medical and dental practitioners must be a key responsibility for the clinical care of the patient throughout treatment in which the autologous HCT products are used.

3. Criteria before conducting of autologous HCT therapy

Medical and dental practitioners should be consideration of the treatment being undertaken is necessary for safety and efficacy for patients that are supported by reliable clinical evidence. They should ensure that before treatment of any patient with a product that has not been authorized for use in Australia. Additionally, patient receives appropriate and adequate information about the material risks and benefits of that product to allow informed consent.

4. Autologous HCT Advertising is prohibited to consumers

1.5 South KOREA

The Ministry of Food and Drug Safety (MFDS), which is formally known as the Korean Food and Drug Administration, is the regulatory agency for food, drugs, biologic products, medical devices, and cosmetics in South Korea. Many products of cell-based, tissues and gene products as biologic products are made in South Korea and have been increasing in the market.

Cell-based, tissues and gene products

Cell-based, tissues and genes are biologic products, that were so-called advanced therapy, in South Korea that are regulated under the Pharmaceutical Affairs Act (PAA). In general, a cell therapy product is defined as a medicinal product

manufactured through physical, chemical, and/or biological manipulation such as *in vitro* culture of autologous, allogeneic, or xenogeneic cells. However, this definition does not apply to a case where a medical doctor performs minimal manipulation such as simple separation, washing, freezing, thawing, and other manipulations. Additionally, a gene therapy product is defined as genetic material or a medicinal product containing such genetic material intended to be administered to human beings for treatment of disease. If cell-based, tissues and genes are classified as biologic products. Thus, these products have required compliance with Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Investigational New Drug (IND) Application, Good Clinical Practice (GCP), and Good Pharmacovigilance Practices (GVP) by authorized MFDS (54).

Cell-based products excluded from MFDS regulation

Cell-based therapies have been minimally manipulated within medical institutions that are excluded from the definition of cell therapy products and are not regulated under PPA as biologic products. In this case, risk-based regulatory approaches will be applied and made a decision. However, these products are regulated under the Medical Service Act. Therefore, minimal manipulation is classified whether biological drugs or not that definition is the same as the EU, USFDA, Japan, and Australia. Although, minimally manipulated is key to categorizing cell-based products. Moreover, they must also be conducted in medical institutions. If not, those products are regulated by MFDS.

Specific considerations for Conditional approval of Cell-based products

In South Korea, Cell-based, tissues and gene products can be approved by Conditional approval as Japan, the EU, USFDA due to limited number in the clinical phase. Nevertheless, the sponsor must submit safety and efficacy data for re-evaluation and re-examination to confirm safety data after approving their products. The unique re-examination requirements for cell therapy products need to investigate of 600 patients in Korea or foreign countries in six years. However, sponsors must be provided and submit Periodic Safety Update Report (PSUR) and Risk Management Plan (RMP) that can contain specific measures to manage safety during the post-marketing phase such as long-term post-marketing clinical studies for gene or cell

therapy products that have possibly delayed adverse events due to proliferated and differentiated tumorigenicity (55, 56).

1.6 THAILAND

Thailand, Thai Food and Drug Administration (Thai FDA) is the role of supervision health products and consumer protection to receive health products that are quality, effective and safe for Thai people. Including, food, medicine, medical device, cosmetics, and hazardous substance. Regarding cell-based, gene and tissue-engineered products have been addressed intended to treat a serious condition that is classified as a drug. Those products are regulated under the Drug Act B.E. 2510 (1967) and its amendment (39) . Hence, the sponsor must be permitted by the national regulatory authority before manufacturing or import of their products. Basically, medicinal products will comply with regulatory requirements such as current Good Manufacturing Practice (cGMP), Good Laboratory Practice (GLP) , Investigational New Drug (IND) Application, Good Clinical Practice (GCP) , and Good Pharmacovigilance Practices (GVP). In 2018, the Thai FDA has promulgated the new regulation to control and monitor Advanced Therapy Medicinal Products (ATMPs) on 7 March 2018 (57) and signed guidelines on ATMPs for drug registration type cell-based therapy on 10 May in the same year (10).

This guideline can be classified into four categories as somatic cell therapy medicinal products (sCTMPs) gene therapy medicinal products (GTMPs), and tissue-engineered products (TEPs) and combined ATMPs and medical devices as follows:

1. Somatic cell therapy medicinal products contain or consist of cells or tissues that have been subject to substantial manipulation or intend to treat, preventing or diagnose.

2 Gene therapy medicinal products contain or consist of a recombinant nucleic acid used in or administered to human beings to regulate, repair, replace, adding or delete a genetic sequence and its therapeutic, prophylactic, or diagnostic effect .Gene therapy medicinal products shall not include vaccines against infectious diseases.

3. Tissue-engineered products contain or consist of engineering as well as used for regenerating, repairing, or replacing a human tissue.

4. Combined Advanced Therapy Medicinal Products means cell, tissue (viable or non-viable), or gene incorporated as an integral part of the product medical devices

Notability, Thailand refers a definition the types and meanings of each product category as defined by the EU.

Article 13 (2) of the Drug Act B.E. 2510 (1967) and its amendment do not regulate medical products for the treatment of a single patient under their supervision. This is exempt from the Drug Act B.E. 2510 (1967) and its amendment (39). They are, however, governed by the Thai Medical Council (medical law). There is currently no specific law or regulation governing cell-based therapy in medical institutions. Medical institutions, on the other hand, provide a more approachable service. Furthermore, some issues such as safety and quality, must be addressed. A few years ago, stakeholders offered to create (Draft) the Cell Therapy Act, which has since been implemented. The Cell Therapy Act is dedicated to protecting patients who accept cell therapy in the medical field.

2. The development of Advanced Therapy Medicinal Products (ATMPs) for drug registration

At the moment, advances in science, biology, technology, and genetics have the potential to create novel treatments such as cell-based therapy products, gene therapy products, and tissue-engineered products. They are well-known as ATMPs. These items fall under the category of biological drugs. The term "biologic drugs" refers to any substance of biological origin, including microorganisms, organs, and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of either human or animal origin and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells) (1, 8) .

ATMPs promise as treatments for previously untreatable disorders and new treatment options for conditions. Pieces of evidence demonstrate a helpful result for its. However, ATMPs are limited to approval into the market. Because ATMPs are complex and innovative products that may pose specific challenges to the design and administration procedures/delivery to the target site may be sometimes combined with specific surgery. ATMPs contain cells or tissues of human origin that must be controlled donor selection, manufacturing of process, quality in control, transport and handling conditions have the potential to negatively impact the quality and function of ATMPs. Likewise, in some cases, it will not be feasible to conduct traditional

pharmacokinetic (PK) study designs or dose-finding studies. It may be the principle of biodistribution biological substances associated with the surrogate markers (biomarker) . Some products can persist in humans for an extended period after administration or permanent effect even after the product itself is no longer present. The effects of the product might evolve. As the result, it is important to monitor and plan for long-term follow-up of efficacy and safety (33-35). However, the efficacy of some products for rare or life-threatening diseases may not be proven due to a small number of participants in clinical trials or a lack of scientific knowledge of relevant diseases. Subsequently, these products cannot be approved for drug registration. Autologous product, in particular.

As mentioned earlier, the nature of ATMPs is different from biopharmaceutical products that some requirements are not appropriate for ATMPs. Nevertheless, these barriers will be solved through understanding the early development of the drug life cycle until launching into the market. These factors can be found as follows:

1. Research and development (R&D)

Unlike chemically synthesized medicines, ATMPs contain human cells, tissues, or genes with unique features that cause the complexity of the manufacturing process. They are easy to change the surrounding condition. Those products can be caused to immune system resistance because of the diversity of the donors. Furthermore, biological characteristics, physiology, mechanism of action, and toxicology are complicated and intrinsically variable features. It takes approximately 30 years. To reach marketing authorization. Including, a large amount of the cost and human skills (58). The cells or tissues and genes studies have been increasing each year. for example, during the year 1999-2003, there were 34 studies, and later in the year 2004-2010, there were 333 studies, and in the year 2011-2015, there were 572 studies, In 2016, there were 939 studies involving advanced medical products (59). In 2019, there were 1,052 studies (36). The majority of studies were related to cell therapy medicinal products and were conducted between phases I and II. Those who were studied had a cancer illness that had been thoroughly researched. The primary and original groups for ATMPs development are education and the medical sector.

These developers will need a budget, as well as time and regulatory knowledge. As a result, the government should be required to assist.

2. Good Manufacturing Practice; GMP

ATMPs production is aided by advances in biotechnology as well as intrinsic differentiation. ATMPs are human cells or tissues that have a wide range of originality. These are life-saving medications, and their properties may change after being administered to humans. In most cases, immune resistance can led to the serious and life-threatening reactions, including significant manipulation of the method of preparation of the starting materials. Autologous product, in particular, is made to order. These issues are critical to consider when manufacturing ATMPs, and they are as follows:

1. Setting standards of quality and safety for the donation of human cells and tissues. Especially, allogeneic products are associated with immune response. The main issue of allogeneic products is considered the ethical and human rights of the pharmaceutical industry. This makes them different from other biological drugs that are non-human derived. Currently, Thailand has only the Thai Red Cross Society, which is a place to receive blood donations and stem cells from blood cells to treat without commercial benefits. Therefore, the industries have to realize this aspect.

2. Selection of suitable vectors for gene therapy products. The vector is a virus or non-virus. The choice of the vector depends on the purpose of the condition and the persistence of the intended therapeutic. The vector should be transcribed gene according to the appropriate location. Furthermore, it is not to be caused by mutations in the host cells.

3. The process of cultivation or proliferation of cells, tissues (Master Cell Bank, Working Cell Bank), or vectors that meet the requirements of the product both phenotype and bioactivity.

4. Manufacturing process and in-process control should be fulfilling the purpose of the product. Process parameters and in-process controls must be suitable for sensitivity and timely detection.

5. Process evaluation/validation to obtain products with the required properties, both phenotype and genotype, purity, potency, and compatibility of the product with other constituents such as matrix, scaffold, medical devices, biological

materials, biomolecules, toxicology and desired pharmacological effects. All of which require the selection of appropriate analytical methods. In the case of autologous product, there is a small number of products in each batch that is a patient-specific product. The number of each batch cannot be increased and limited other biopharmaceutical products which may affect the analysis method.

6. Stability testing such as storage condition (cold chain) and distribution. In the case of autologous product may have a short shelf -life after production. ATMPs are generally produced by cells or tissues that are logistic and distributed as cold chain, appropriate storage and handling conditions are significant.

ATMPs are sensitive and required consistency in a batch of production. Therefore, this is necessary to apply the principles of Good Manufacturing Practices (GMP) (60). GMP requirements are not only produced consistency, but also the safety aspect. GMP is a pharmaceutical quality assurance system.

3. Good Laboratory Practice; GLP

GLP is applied to *in vitro* and *in vivo* studies. This phase is proved of concept pharmacology, toxicology, and adverse events of the medicinal products. The traditional pharmacokinetics of absorption, distribution, metabolism, and elimination (ADME) studies may not be feasible to ATMPs. Non-clinic studies of ATMPs should be demonstrated biodistribution, trafficking, proliferation, viable cell rate, and transgene expression. There are considerations about the animal models in non-clinical experiments as follows. 1. selection of related to animal species, 2. age, 3. physiological characteristics, 4. route of administration, dose regimen, and 5. the stability of ATMPs in the study. Animal models are different from human responses that can usually not predict biological activity in humans. Often, animal models are restricted to forecast the risk and safe in humans. Hence, the processes in the non-clinical study should be complied with GLP to ensure that the studies were conducted in the appropriate conditions (61).

4. Good Clinical Practice; GCP

The clinical study involves the participation of human subjects. The importance of this clinical study period is;

1. Sufficient scientific data proofs of pharmacology and toxicology before initiation of the first-in-human study.

2. The rights, safety, and well-being of trial subjects are protected by Institutional Review Board / Independent Ethics Committee (IRB/IEC).

The clinical phase is required to comply with GCP principles as international standards. These standards ensure the quality, safety, and credibility of the research. ATMPs clinical studies in phase I are unable to include healthy volunteers and are randomized in clinical studies. Due to the small number of patients who participated in the clinical trial, it may be impossible to evaluate the statistical significance for ATMPs safety and efficacy that clinical benefit is insufficient for reasonable safe (62). Furthermore, follow-up is necessary to plan for long-term monitoring. The clinical trial was completed, but the patients should be followed over time or for the rest of their life.

5. Good Review Practice; GRP

ATMPs licensing considers quality, safety, and efficacy dossiers before Marketing Authorization. The limitation of number for enrolling in a clinical trial is difficult to approve drug registrations. Therefore, many countries have come up with guidelines for special approval for ATMPs. For example, Japan has established a new license for RM only that so-called condition time-limited approval. RM may be demonstrated or predict efficacy and safety rather than the potential risks. However, RM must be collected safety and efficacy data within the period agreed with MHLW (not more than 7 years). whilst the United States has the term Regenerative Medicine Advanced Therapy Designation (RMAT) (63). This approval is designed to help accelerate the development of ATMPs under the law The 21st Century Cures Act (Cures Act). Additionally, safety and efficacy data can be collected after approval to re-evaluate. On the contrary, RMAT is not exactly determined the time period for gathering data as condition time-limited approval in Japan.

6. Good Pharmacovigilance Practices; GVP

GVP is a follow-up after releasing into the market. Those products are monitor both the efficacy and safety of ATMPs. GVP can be categorized into two requirements as follows:

1. Post-Marketing Requirements (PMR) are under the guidelines of medicine which are studies that the sponsor must agree to conduct as a prerequisite for approval. The report of drug adverse reactions is required after drug approval.

2. Post-Marketing Commitment (PMC). The commitment of a post-market advanced medical product or an agreement between pharmaceutical companies and regulators. The FDA may require post-marketing studies to further assess the risks related to the administration of the product, either when product use is associated with unknown serious risk or when existing data are indicative of potential serious risk. Drug companies have to gather data from a clinical trial, observation to represent safety data following Marketing Authorization. Moreover, the FDA may either withdraw product approval or modify the labeled indication when arising new safety information. It is recommended that cell and gene therapy medicinal products be subjected to intensive follow-up within two years of acceptance. In humans, cell and gene therapy products are long-acting and persistent (64). As a result, depending on the nature and characteristics of the product, monitoring and follow-up may need to be extended. Because the safety profile of those who accept those products can be changed.

3. State-of-the-art knowledge on the regulation of Advanced Therapy Medicinal Products (ATMPs)

The originality of ATMPs is the primary reason for their uniqueness. Generally, ATMPs are derived from cells or human tissues, either healthy volunteers or patients. To date, the ATMPs legalized under the Marketing Authorization (MA) have been practically used in the European Union (EU), The United States of America (USA), and Japan. There are available 20 products in the USA, whereas 18 and 11 products were available in the EU and Japan, respectively (11, 15, 16). Currently, there are two sub-categories of ATMPs reflecting the source of the cells of tissues. 1. autologous product and 2. allogenic product. The autologous product is cells or tissues derived from patients themselves, whereas allogeneic products are derived from healthy donors.

1. Autologous product

This approach provides several advantages such as the minimization of risks from systemic immunological reactions, bio-incompatibility, and disease transmission associated with grafts or cells not cultivated from other individuals (17, 18). For example, KYMRIAH® (tisagenlecleucel), a lentiviral vector-encoded anti-CD19 Chimeric Antigen Receptor (CAR) agent modified from the patient's T cells, demonstrated a sustained efficacy without requiring any additional therapy. Pediatric and young adult patients who suffered from Acute Lymphoblastic Leukemia (ALL) with a history of treatment-refractory and relapsed observed an 83% overall remission rate within three months and 66% relapse-free survival during the first 18 months after receiving KYMRIAH® (65). The processes for manufacturing of CAR T cells are presented as Figure 6 (20, 66, 67) .Thus, the results led to the indication of KYMRIAH®, which is advisable for adult patients with relapsed or refractory diffuse large B-cells lymphoma (DLBCL) after two or more systemic lines therapy (22, 68, 69). The T cells source for producing KYMRIAH® is obtained from peripheral blood mononuclear cells, the enriched T cell source, then undergo transduction with a lentiviral vector containing the anti-CD19 CAR transgene. Consequently, the transduced T cells are expanded using the cell culture technique in a GMP facility. The final product is formulated into a suspension form followed by cryopreservation. Likewise, YESCARTA® (axicabtagene ciloleucel) is the other T cell-based product for treating diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cells lymphoma (PMBCL) in adult patients. Eligible patients who received YESCARTA® showed 83% objective response rate (ORR) with 58% complete remission rate (CR)(24, 70). Admittedly, the effectiveness of CAR T cells on the treatment of relapsed or refractory lymphoma has been observed worldwide

Tissue-engineered product (TEP) is the other type of autologous product. SPHEROX®, the autologous chondrocyte implantation (ACI), is an example of TEP approved in 2017 in the EU to treat and repair cartilage defects of the knees in adults (71). The major component of SPHEROX® is prepared from patients' chondrocytes. Chondrocytes are extracted by arthroscopy follow by tissue culturing for expansion in a dedicated laboratory. Subsequently, the implantation suspension of SPHEROX® is administered by intraarticular implantation to repair the defected area (72, 73).

Similarly, matrix-induced autologous chondrocyte implantation (MACI®) used patients' chondrocytes as the primary source of regenerative materials for the damaged area. MACI® uses a unique matrix membrane derived from porcine; thus, it may not be suitable for patients who are allergic to materials derived from pigs, cows, and ox. Nevertheless, MACI® has been approved in the EU and the US since 2013 and 2016, respectively. In 2014, MACI® has been withdrawn in the EU due to the absence of manufacturing sites and commercialization reasons. However, it was still commercialized in the US. MACI® provided elective treatment strategy to patients who suffer from single or multiple symptomatic, full-thickness cartilage defects of the knee with/ without bone involvement in adults (7 4) . Due to the mechanism of production and the nature of autologous product, it can be denominated as the most symbolic of contemporary personalized medicine (75).

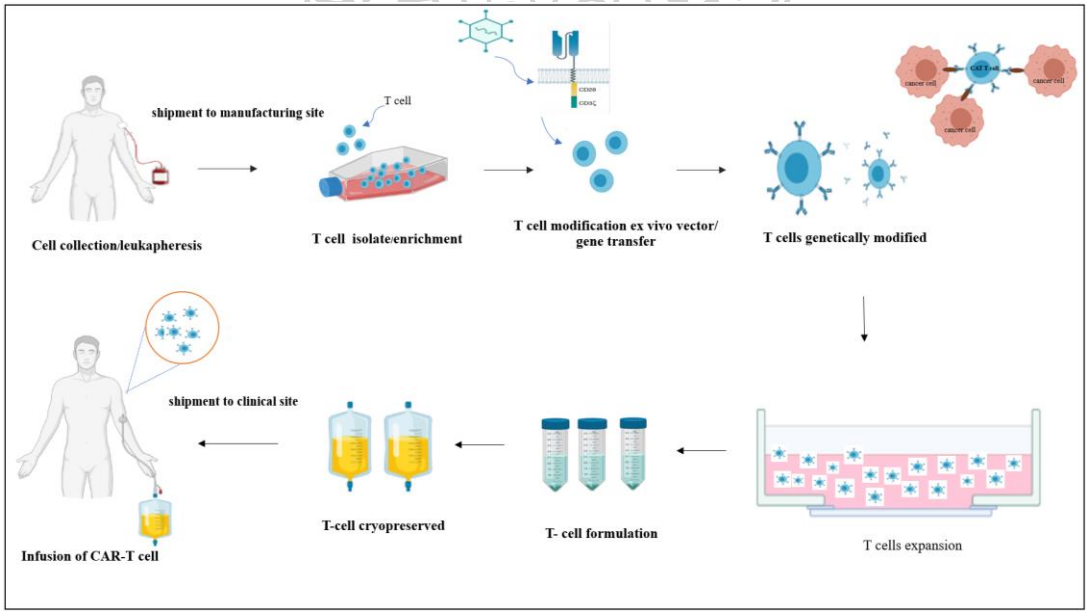


Figure 6 The processes for manufacturing of CAR T cells (20,66)

2. Allogeneic products

Allogeneic products are derived from a single donor or a pool of a small number of donors to provide a large batch for treating numerous patients. Allogeneic products are amenable to a scale-up-based manufacturing approach, suitable for an "off-the-shelf product" (25). However, the main challenge in manufacturing allogeneic products is the quality assurance of the products such as donor selection and donor characteristics. Moreover, using the allogeneic products in patients needs to consider

the compatibility between donor and recipient due to the concerning immune response after administering the products (76). Such incidents as seen in the case of TEMCELL HS® (approved in Canada and New Zealand in 2012, and Japan in 2015) (26, 28). The main therapeutic component of the product is derived from mesenchymal stromal cells (MSCs). Generally, MSCs are responsible for the tissue repairing process; thus, it has high intrinsic capability in proliferation and differentiation. In addition, MSCs cells have characteristics of low immunogenicity, potent anti-inflammatory modulator, the capability to accentuate the innate immune response, and others, which support their promising role in stem cells therapy (77, 78). MSC-based therapy demonstrated the achievement of 50% complete response within 6 weeks after the first infusion with more than a half reduction of the dose steroid used within 8 weeks. Thus, TEMCELL HS® was approved for acute graft-versus-host disease (aGVHD) after hematopoietic stem cell transplant (26, 79, 80). Although the novel biomedical products have been named differently such as biologic drugs (US), regenerative medicines (Japan), and ATMPs (Thailand and the EU), they present new curative possibilities for a range of patients (10-13). Unquestionably, patients who suffered from a life-threatening disease or poor quality of life in the long term such as cancers, neurodegenerative disorders, osteoarthritis, particularly in areas of previously untreatable illness would gain health benefits from accessing ATMPs. As such, stem cell tourism, a new trend of health tourism, has increased its recognition worldwide (81). People who could afford and were willing to invest in well-being would embark on their travel to other countries to receive treatments that may not be available where they live (81, 82). This trend has been driven by health consciousness behavior in which individuals seek the best possibility, using any source of information, to increase their quality of life (83, 84). Unfortunately, it is nearly impossible for most individuals to access the approved ATMPs since they are abided by the safety and efficacy legislation in each country's standard (85). Thus, it is crucial to establish the optimal solution balancing uncertainty regarding safety/efficacy and facilitate early access to new treatments in high medical need.

Concept of Regulation for Advanced Therapy Medicinal Products (ATMPs)

Regulation of ATMPs can be categorized into 2 main approaches as followed.

1. Medicinal product for human use

The regulatory authority in each country controls this category such as the US FDA (USA) and the European Medicines Agency (EMA) for the EU. ATMPs are classified as therapeutic agents due to their intrinsic capability to derive clinical effects comparably to the classical definition. Hence, the marketing authorization must be approved before launching the product to the population. Under this regulation, ATMPs are strongly required to have followed drug legislation and amendments established in each country. For example, Regulation (EC) 1394/2007– "ATMPs regulation" was specifically formulated to control ATMPs in the EU (3). In the USA, the regulations that involve controlling ATMPs are Title 21 of the Code of Federal Regulations part 600-680 under The Food, Drug & Cosmetics Act (FDCA) and section 351 of the Public Health Service provides (PHS) Act (86). Meanwhile, the pharmaceutical medical device and other therapeutic product Act (PMD Act) is the core principle of the current regulatory framework for ATMPs in Japan (ATMPs are called regenerative medicines in Japan). Furthermore, developers or sponsors have to adhere to a regulatory requirement, including the manufacturing process, quality control, non-clinical/clinical safety, and efficacy. Those requirements are generally aligned with the Good Manufacturing Practice; GMP, Good Laboratory Practice; GLP, Good Clinical Practice; GCP, Good Review Practice; GRP. Subsequently, successful product approval must be regulated through the post-marketing by Good Pharmacovigilance Practices; GVP.

As described earlier, regarding the complexity of ATMPs, those attributes were taken into account for the approval process. Due to its exceptional clinical benefit, especially in some life-threatening or rare diseases, a special early access pathway has been applied such as:

The Expedite program

The Expedite program was set for a new drug or novel medicine intended to treat a severe condition and demonstrate the potential to address an unmet medical need. As such, the main objective of the Expedite program is to offer early and

proactive support to medicine developers to optimize the generation of data based on risk and benefit of the product to patients. This type of program is available in many countries such as Fast Track Designation and Breakthrough Therapy Designation in the US (63, 87) and PRIME program (87-89) and Adaptive pathway in the EU (90). Including Japan has a SAKIGAKE Designation system (87, 91). Expedite program can be accelerated assessment of medicines applications by priority review or rolling review.

Conditional approval

The Conditional approval or Accelerated approval can be applied to the product that may present lesser than usual for the clinical data required, whereas the benefit of the product outweigh the risk. Such a risk may arise from lacking data in some areas; thus, additional data are still required (63, 87, 89, 92). Furthermore, regarding the marketing authorization, Conditional approval products could be withdrawn anytime if they violated the post-marketing scheme such as a report of severe adverse events or fail to achieve the additional regulatory requirements.

Specific licensing scheme for ATMPs or RM

A specific licensing scheme for ATMPs or RM is the scheme developed mainly for a particular circumstance. This scheme recognizes the importance of the length of time the product would be available for particular patients such as patients in a critical health condition or treatment does not exist today. Thus, under this scheme, the product would be readily approved as soon as the safety and efficacy have reached a justifiable standard. This type of regulation was firstly established in Japan and the US in 2016.

In Japan, the specific licensing scheme was established under the Pharmaceuticals, Medical Devices, and other therapeutic products Act (The PMD Act) . The PMD Act was promulgated in 2013 since the preceding Pharmaceutical Affairs Law (PAL) did not include the regulation of regenerative medicines. Consequently, the actual PMD Act came into effect a year after, on 25 November 2014. Under the PMD Act, regenerative medicine products will be conferred conditional or time-limited approval after safety and efficacy are confirmed or sufficiently evaluated. Subsequently, it is necessary to apply post-marketing

surveillance to the products after successful launching to the market. Generally, the criteria for specific licensing approval are including:

a) It meets the definition of regenerative medicine therapy.

b) Significant potential results in the early-phase for registration trials in terms of efficacy and safety.

c) Sponsors must conduct post-marketing clinical studies and so on to confirm the efficacy and safety and re-evaluated applications for regular approval within a predetermined period (no more than seven years) for the full license (12).

A few years later, in 2016, the US established the Regenerative Medicine Advanced Therapy Designation (RMAT) under the 21st Century Cures Act. This designation aimed to facilitate a more comfortable, fast-forward, and reduced cost for the manufacturers to submit their products (93). However, the eligibility criteria for RMAT designation is including (63).

a) It meets the definition of regenerative medicine therapy. These are methods of preparation more than minimal manipulation of human cells or tissue and heterologous use as well as gene therapy. Section 361 of the Public Health Service Act and 21 CFR part 1271 are exceptions to this RMAT scheme (4).

b) It is intended to treat, modify, reverse or cure a serious condition; and

c) Preliminary clinical evidence indicates that regenerative medicine therapy has the potential to address unmet medical needs for such conditions.

RMAT has more flexibility than the Fast Track and Breakthrough Therapy Designation as it has no obligation to demonstrate the substantial improvement of the efficacy over the existing therapies. RMAT only requires demonstrating that the product would be very likely to address the unmet medical need, which could subsequently be proven in the post-approval state using real-world evidence. In contrast, Fast Track and Breakthrough Therapy Designation are required to provide supporting information regarding the clinical benefit over the current treatment options as mandatory (63).

The new legal framework would likely facilitate the patient to access the ATMPs in parallel with the quality, safety and efficacy assurance of the products. Generally, some ATMPs products could produce long-lasting biological effects in patients, although the products undergo a single administration. As such, it is possible

to encounter adverse events after ATMPs administration; however, the time to events is likely to depend on the type of ATMPs. For example, stem cell-based ATMPs may derive delayed events as the cell's proliferation period require a certain amount of time to achieve the process of proliferation and differentiation. Therefore, stem-cell-based ATMPs could develop into inappropriate cell types or multiply unexpectedly, resulting in adverse events (33, 34, 94). Furthermore, the traditional approach of predicting pharmacokinetic profiles such as physiologically based pharmacokinetic modeling (PBPK) and population pharmacokinetics (PopPK) is not applicable for ATMPs due to their peculiar nature. Thus, it is of the highest importance in formulating the monitoring scheme for ATMPs products to promote post-marketing efficacy and safety reassurance. The EMA suggested 2-years close monitoring program for the cell-based and gene-based after administration of the product. After two years of close monitoring, the vigilance scheme would depend on the overall risk assessment of each product (34). On the other hand, the US FDA advised that cell integrate modified gene therapy could be extended to 15 years for following to assure any possible late adverse reactions (94, 95). Reasonably, the extended follow-up scheme is highly likely appropriate for monitoring ATMPs products as it would be useful in the detection and prevention of any delayed adverse reactions.

2. ATMPs exemption from the medicines legislation

ATMPs exemption from the medicines legislation is a component of the treatment intervention with ATMPs. Such as hospital exemption (HE), clinical practice in the dedicated institutions and Compassionate Use and Expand Access Program. In addition, the intervention has to be conducted by the exclusive, professional responsibility of a medical practitioner as a mandatory requirement to comply with an individual therapeutic prescription for a specialized product for each individual (96). Further described as:

1. Hospital exemption (HE) Noticeably, HE means "prepared on a non-routine basis according to specific quality standards and used within the same Member State in a hospital under the exclusive, professional responsibility of a medical practitioner, to comply with an individual medical prescription for a custom-made product for an individual patient" (3). Therefore, HE is out of the scope of the ATMPs Regulation, when an ATMPs is not intended to be marketed and not intended to be industrially

prepared. The EMA allows manufacturing of products falling under the HE to be authorized by the national community, subject to certain conditions, and leaves it to the Member States (MSs) to define the HE requirements within their legal framework. As a result, the requirements are widely different and slightly harmonized in each country (97). However, the conditions of Article 3(7) of the Directive specify as compulsory for exempted ATMPs that national traceability and pharmacovigilance requirements, as well as the specific quality standards, be equivalent to those provided for at the community level in respect of ATMPs for which a centralized procedure is required (98). This approach of implementation by the member states has led to differences in the way the HE has been interpreted and implemented throughout the EU. On the contrary, HE has the potential of facilitating innovation and patient access. These differences have created parallel paths to market access as well as diverse approaches are used between member states for HE authorization (97). As a consequence, inefficient or even unsafe ATMPs could potentially enter a market under the HE in MSs with lower data requirements, while in other MSs with higher requirements such a product would not be granted the HE. This would result in uncertainty and barriers to patient access, transparency, and incentives for developing ATMPs in the EU. Rapidly evolving technology in the area of ATMPs has brought exciting new opportunities for treating a range of diseases, including many currently considered incurable. Therefore, national competent authority considers safety, efficacy, and the eligibility criteria access to HE. It is critical to establish uniform standards for patient safety, product quality, and safety throughout the EU. It ensures that all patients are treated, which not only protects public health but also promotes widespread patient access to these novel therapies. The table 1 shows the various HE requirements in other EU countries (99, 100).

2. Clinical practice in dedicated institutions ATMPs as part of clinical interventions in Japan is under the scope of the Act on the Safety of Regenerative Medicine (ASRM regulation). ASRM was enacted in November 2013 and became law in November 2014 as it was first established due to the domestic incident of cell therapy failure that led to death (31). ASRM applies to physicians or those involved such as medical institutions, educational institutions, cell plants that wish to clinically develop stem cell-based interventions and must comply with the requirements of this

law. In addition, this law has classified RM products into three subcategories based on the level of the potential risks. Thus, ASRM has a scope that covers treatment procedures using ATMPs as a component concerning patients' safety concerns. Safety is of ultimate importance when considering applying unapproved ATMPs. There were reports of death following a pulmonary embolism of a patient who received an injection of stem cells-based ATMPs at a Kyoto-based clinic (30, 31). Likewise, three patients in the US over the age of 75 with age-related macular degeneration became blind after receiving intravitreal injections of autologous stem cells (32). In addition, ATMPs were reported inefficacy or exaggerating advertisement and abusing for unproven products or treatments at clinical setting that where are the easiest place and less restrictive accessibility. The application of ATMPs frequently requires dedicated medical skills that require numerous hours of practice. Thus, a high degree of good clinical practice is required to assure the equipotent execution between clinical sites. More importantly, these regulations are enforced to all manufacturing facilities either affiliated with a medical institution or not. On the other hand, the standards above may somewhat resemble the Good Tissue Practices (GTP); however, they are less rigorous than GMP. Many countries have been developing new legislation for ATMPs in clinical sites. In addition, this new legislation must be well-applicable following the context of socioeconomics and ethical perspectives.

3. Compassionate Use Program (CUP) and Expand Access Program (EAP). Some countries have the option to enter for severely debilitating disorders or unsatisfied treatment or patient cannot enter into clinical trial who may be exclusions criteria in clinical trial through unapproved products to decrease the suffering, facilitation to access new treatment and transparent that registered information before investigating. For example, CUP have been established referred to in Directive 2001/83/EC and Article 83 of Regulation (EC) 726/2004 as **"**a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorization or must be undergoing clinical trial**"**. This program has been conducted after allowing from agency of MSs that they must notify to the EMA. Pharmacovigilance requirements have been required and updated on a regular period

from the applicant. Moreover, the sponsor should ensure that patients can get to the new medicinal product during the period between authorization and post-market (8, 101). Similarly, the US FDA is also called EAP that aim and process are several similarities and different to the EMA. Common criteria, submitted and approved protocol before using that are needed in both countries. The difference of EPA can access to drug, biologic, or medical device while CUP access to medicinal products only. Also, EPA can use for individual or group patients but CUP applies a group of patients (more than one) (102, 103). Investigational drugs have not yet been approved or exactly demonstrated safety and efficacy data by FDA. Likewise, those products may be failed or success in treatment of disorders. Thus, intensive monitor is still necessary to earlier detect and prevent unexpected serious advert events.

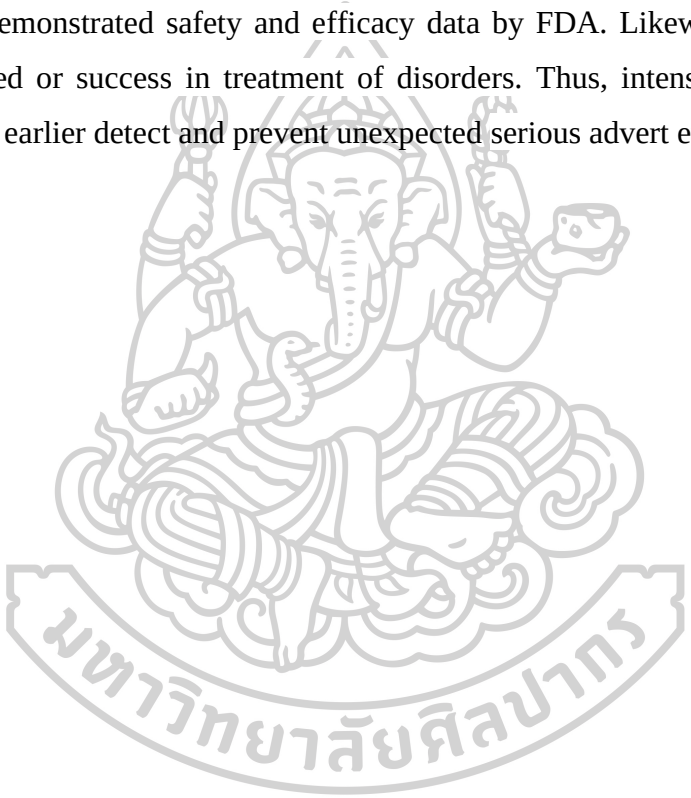


Table 1 The various HE requirements in other EU countries

Characteristic	Country							
	Germany	Netherlands	Finland	UK	France	Spain	Poland	Italy
definition for "prepared on the non-routine basis"	small quantities and in the case of based on a routine manufacturing procedure	10 patients per year, or a maximum of 50 patients per year	non-industrial manufacturing	A small scale and carried out in some hospitals	a small scale in hospitals, which is evaluated on a case-by-case basis	a small scale in hospitals, which is evaluated on a case-by-case basis	no more than 20-50 cases per year	a small scale in hospitals, which is evaluated on a case-by-case basis
eligibility criteria for products to be approved under HE.	preliminary benefit/risk assessment	HE for patient ineligible for a clinical trial (as CUP)	quality data are required	NA	HE requires the same clinical trials	quality, efficacy, and safety	NA	NA
Data entry requirements (Manufacturing & Quality)	Required	Required	Required	Required	Required	Required	Required	Required
Data entry requirements (Clinical)	Required	Required	Not required	Not required	Not required	Required	Required	Not required

Table 1 (continue)

Characteristic	Country							
	Germany	Netherlands	Finland	UK	France	Spain	Poland	Italy
GMP compliance	comply with the principles of GMP when within the institution	GMP requirements	comply with the principles of GMP	comply with the principles of GMP	GMP requirements	GMP requirements	GMP requirements	comply with the principles of GMP
ATMPs licensed under HE	All	All	All	All	All	only hospitals	All	Public institutes
Renewal of ATMPs licensed under HE	Non- defined	one year	Non- defined	Non- defined	5 years	initially granted for 3 years and then for 5 years	Non- defined	Non- defined
is a list of HE-ATMPs publicly available?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Medical practitioner registry	No	No	No	No	No	No	No	No

Table 1 (continue)

Characteristic	Country							
	Germany	Netherlands	Finland	UK	France	Spain	Poland	Italy
ATMPs registration under HE	Yes	NA	NA	NA	NA	Yes	NA	NA
Restricted when licensed products are available	No	Yes	Yes	No	Yes	No	No	Yes
Submit annual reports detailing the number of products manufactured under HE	Not required	Required	Not required	Required	Not required	Required	Not required	Required

Table 1 (continue)

Characteristic	Country							
	Germany	Netherlands	Finland	UK	France	Spain	Poland	Italy
Pharmacovigilance (PV)	PV set out in Regulation (EC) No. 1394/2007 apply AND local Qualified Person for PV AND establishment of PV and a risk management system	reference is made to the ATMP regulation, All AEs must also be reported on an annual basis or at the end of treatment	no explicit PV requirements have been set for HE-ATMPs	medical practitioners operating under HE in the UK are obliged to record and notify the MHRA	same quality, traceability, and PV standards as those set for centrally approved ATMPs	the named person is responsible for PV reporting. The licensed hospital must collect all information and report to regional authority as well as provide periodic safety reports	no explicit PV requirements have been set for HE-ATMPs	HE-ATMPs manufacturers are required to appoint Responsible Person who will report all AEs, including lack of clinical efficacy, to regional authority, and prescribing physicians are required to report serious and any other events
duration of follow up	The EMA's guidelines on safety and efficacy follow-up for ATMPs state that, about gene therapy medicinal products, it is expected that patients are followed for up to 15 years.							patients treated under HE must be followed for a minimum of 8 years

Remark**;** NA: not applicable

4. The production and distribution of cell therapy medicinal products

The unique aspect of most cell therapy medicinal products is that the starting materials are cells or tissues from patients or volunteer donors so the manufacturing process begins at a clinical site. Therefore, some cell therapy medicinal products are made from a patient's cells (autologous or one-to-one therapies) and those that are made from a donor's cells (allogeneic or one to many therapies). Allogeneic products are a single volunteer donor or a pool of a small number of donors may be adequate for the production of a master cell bank. Allogeneic products manufacturing can be done on an industrial scale or in mass quantities. Autologous product, on the other hand, is patient-specific products, made on a small scale or in one batch for one person, and has immunogenic compatibility because they are made from the patient's cells. The availability of autologous or allogeneic products will influence the production and distribution model in the following ways:

1. Centralized manufacturing has been the dominant model for large-scale production. Allogeneic products can be produced for industrial-scale manufacturing facilities and distributed to any place (67).

2. Decentralized or redistributed manufacturing divides manufacturing capacity across geographic regions, responsive manufacturing, customized to the end-user, and is an attractive solution to overcome challenges facing the autologous of cell therapy medicinal products manufacturing chain (104).

3. Point Of Care Manufacturing (POC). Manufacturing and administration are within the near area. In some cases, cell therapy medicinal products have a relatively short shelf-life after production (105, 106). Moreover, cell therapy medicinal products have been manufactured and administered at POC, which has involved the production of therapies within medical institutions to reduce cost and time delivery. Those products are unapproved medicines by the National Regulatory Authority (107).

Allogeneic therapies can be manufactured and delivered in the same way that biologic drugs or traditional centralized manufacturing. Autologous therapies, on the other hand, differ from traditional pharmaceuticals in that they take into account the product's natural characteristics, supply chain, transport time, traceability, and logistics cost.

5. Post-Marketing Safety measures for cell therapy medicinal products

Cell therapy medicinal products are approved by National Regulatory Authority (NRA) to ensure that novel medicines are effective and safe before they are released to the market. In some cases, the clinical data for safety and efficacy may be less than usual, if the benefit of the product outweighs the risk such as Conditional approval. However, adverse events are not always discovered during a clinical study. NRA is concerned with an area in which knowledge is rapidly evolving and experience is limited. Furthermore, some adverse drug events (ADEs) are only known after a drug has been approved for marketing. Since the safety profile in clinical trials is limited due to the size of the study population, study inclusion and exclusion criteria, and short-time follow-up. For this reason, post-marketing monitoring is critical for patients who have received novel medicine, particularly new chemical entries or novel modes of action such as cell therapy medicinal products and gene therapy medicinal products. The World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems”. The process of post-marketing is designed for the collection, minimization, and evaluation of information relevant to the risk-benefit balance of medicinal products after they launch into the market. Post-marketing surveillance can be categorized into 3 main approaches as follows:

Category 1 is the legal basis to the marketing authorization as spontaneous reporting or Individual Case Safety Reports (ICSRs). Spontaneous reporting has been defined as an unsolicited communication by a healthcare professional or pharmaceutical manufacturer to the NRA that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme (ICH 2003). Spontaneous reporting is a voluntary report by healthcare professionals and marketing authorization holders to the national competent authority that is called passive surveillance. In addition, spontaneous reporting or ICSRs can be submitted via a system of NRA by the paper-based or electronics base. The spontaneous reporting system is a generally used and relatively inexpensive method of collecting information on post marketing. Their reports may be emerged signals detection of

possible unexpected adverse reactions or changes in the severity of drug after launching to market. Unfortunately, one of the major problems was collected underreporting of ADR exists due to lack of punishment (108).

Category 2 is specific obligations only in case of a conditional or other commitment between NRA and pharmaceutical company. Such as

2.1 Periodic Safety Update Reports (PSURs) are essential pharmacovigilance documents that are intended to provide the new safety experience of a medicinal product to competent authorities at the time points post-authorization. Since the patient's safety profile may change as a result of the expansive distribution. The PSURs' goal is to present a comprehensive and pivotal analysis of the product's risk-benefit balance in the context of cumulative risk and benefit information. PSURs are required six monthly PSURs submissions should be continued following initial placing on the market in the EU and until two full years of marketing experience in the EU has been gained. Then, PSURs should be submitted once a year for the following two years and thereafter at three-yearly intervals. PSURs are monitored and evaluated by NRA. In addition, Safety variations can be impacted or changed activity related to the task in the Risk Management Plan (RMP) that the product information can be modified when any changing effect to the safety profile (109).

2.2 RMP is a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating assessment of the effectiveness of those interventions. RMP document should be submitted at the time of with the dossier. Moreover, RMP can be modified any time a product’s lifecycle when meeting new safety data such as PSURs, ICSRs or spontaneous reporting. The EU-RMP is a role model that has led to its implementation in other countries. They contain two parts. Part I is consists of a safety specification and a pharmacovigilance plan and Part II is consists of an evaluation of the need for risk minimization of activity (routines or additional) and risk minimization plan. Most aspects of RMP are incorporated into the concept ICH-E2E. Normally, RMP should be considered based on the level of the risk for products (110).

2.3 Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the United States Food and Drug Administration (USFDA) was established in 2007. REMS is required for certain medications with serious safety concerns to help

assure the benefits of the medication outweigh its risks. Sponsors develop the REMS program based on required elements that consist of 5 parts as I. Administrative Information, II. REMS Goals (specific safety measures to mitigate a serious risk), III. REMS Requirements (elements to assure safe use), IV. REMS Assessment timetable as well as V. REMS Materials (material or a tool for reduced risk). Then, USFDA reviews and approves the REMS before releasing. The aim of REMS is the same as RMP in the EU. They are tools for identification, assessment, monitoring, and minimization of the risk to patient safety (111).

2.4 Early Post-marketing Phase Vigilance (EPPV) was established in Japan. This program is exclusive monitoring ADEs that maybe arise out in the first 6 months after launch to market. Marketing authorization holders are required to provide the safety information to health care professionals and to collect ADR information intensively for the time frame by visiting hospitals periodically. The period is monitored to the first biweekly for 2 months and then monthly for 4 months later. Applicants have to submit a safety report to Pharmaceuticals and Medical Devices Agency (PMDA) 2 months later. Potential signals may have emerged during a new drug's early post-marketing period.

2.5 Post-Authorization Safety Studies (PASS) are designed to take into account safety information for drugs that have limited safety data at the time of marketing authorization. In general, national competent authorities may require Conditional approval PASS as a commitment at the time of authorization. National competent authorities and applicants are assigned a time frame to complete a safety profile to ensure safety (112).

2.6 Post-Authorization Efficacy Studies (PESS) may be required by NRA either as a commitment at the time of authorization or in the post-authorization phase. Normally, Conditional approval may be required PESS by competent authorities. PESS is performed after the marketing authorization and aims principally to further evaluate the efficacy of the medicinal product. The intention is to confirm efficacy data that are available at the time of the initial authorization.

Categories 1 and 2 do not apply to Category 3. Marketing Authorization Holder (MAH) has specific safety concerns such as evaluating the effectiveness of

risk-mitigation activities conducted or financed by applicants. It is not mandatory by authorities who do not bind the regulation.

Nonetheless, cell therapy medicinal products are a novel product that should be provided to address risk management systems that are based on the risk of specific products. This overview of the approach is an illustration of post-marketing safety measures, which differ depending on the risk of medicinal products and comprehensive data. In 2008, the European Medicines Agency introduced the current guideline for safety and efficacy monitoring of ATMPs including cell therapy medicinal products. The extended follow-up scheme is ideal for monitoring ATMPs products because it aids in the detection and prevention of any delayed adverse reactions. As a result, it is critical to formulate a monitoring scheme for cell therapy medicinal products to promote the efficacy and safety of licensed medicinal products.

6. Risk-based approach

The assessment of the benefit-risk in the context of a new drug application is one of the most important steps in its development. Cell therapy medicinal products are intrinsically different nature other traditional drugs. Those cell therapy medicinal products may be related to specific risks to the patient. They are determined by various risk factors, which are based on the manufacturing, donor procurements, biological activity, administration, and storage and distribution of the product that these data might accumulate from previous experience with the same product and/or the same class of products. Thus, the risk-based approach is regulatory sciences relating to the quality, safety, and efficacy of medicinal products and to justify any deviation from the requirements of medicinal regulation and key concept to decide for approval. It provides all of the stages in the development of the product lifecycle. Risk identification should start as early as possible steps and all of the time through the process of development. The definition is as follows:

Risk-based approach: a strategy to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorization application dossier.

Risk: a potential unfavorable effect that can be attributed to the clinical use of the ATMPs and is of concern to the patient and/or to other populations such as health care professionals and caregivers.

Risk factor: a qualitative or quantitative characteristic that contributes to a specific risk following the handling and/or administration of cell therapy medicinal products.

Risk profiling: a methodological approach to systematically integrate all available information on risks and risk factors to obtain a profile of each risk associated with specific medical products (113). The Methodology of Risk Profiling follows as

1st step: To identify risks associated with the clinical use of the cell therapy medicinal products.

The risk-based approach starts with the identification of risks associated with the clinical use of the cell therapy medicinal products. Risk identification should start as early as product development and all the time during the development of product phase as well as can be supported by reference to scientific data.

2nd step: To identify product specific risk factors contributing to each identified risk.

Any relevant risk factors that may contribute to the identified risk should be identified by the applicant. These risk factors could be related to the product's nature and composition, the characteristics of living donors, the manufacturing process, nonclinical and clinical aspects, product storage and distribution, administration procedures, and patient follow-up. Consequently, risk factors may be emerged during any product development process. These risk factors have been controlled by the applicant's that they are primary responsibilities.

3rd step: To map the relevant data for each identified risk factor against each of the identified risks. To evaluate the contribution of each risk factor to an identified risk. This is represented by the relationship between risk factors and identified risks.

4thstep: To conclude on the risk factor – risk relationships. To conclude on the risk factor-risk relationships.

The risk-based approach has been admired and accepted to the utility for applying pharmaceutical products. Moreover, recommendations for the applicants should be earlier interaction with agencies when making decisions to new risks that have never previously occurred bring to manage and mitigate potential issues.

Quality risk management

Many aspects of the pharmaceutical industry such as GMP, GLP, GCP, GRP, and GVP, incorporate risk management principles. This concept is a proactive approach and an effective tool for ensuring medical quality. Thus, quality risk management contributes to a scientific and practical approach to drug approval decision-making. It provides documented, transparent, and reproducible methods for carrying out steps of the quality risk management process based on current knowledge about assessing the risk's probability, severity, and, in some cases, detectability. Figure 7 depicts a model for quality risk management that can be divided into four steps.

1. Risk Assessment: There are 3 sub-groups in risk assessment

1.1 Risk identification: The applicant should be considered in all areas the development. Risk identification is associated with any relevant risk to the patient and other stakeholders.

1.2 Risk analysis is the process of calculating the risk associated with the hazard.

1.3 Risk evaluation is decision making and setting out the ways to reduce the risks. Those have adequate information and resource that are available.

2. Risk Control is divided into two sections

2.1 Risk reduction focuses on strategies for risk factor control or mitigation.

2.2 Risk acceptance is the agreed of risk or eliminative risk. Risk acceptance depends on the level of the hazard that may be considered case by case approach.

3. Risk Communication is the sharing of information about risk and risk management between the decision-makers and other communications might include those among interested parties such as regulators and industry, industry and the patient, within a company, industry, or regulatory authority.

4. Risk Review should be implemented. It is the basic process to monitor and review after existing interventions for minimizing risk. Furthermore, multiple changes can occur and impact the risk-benefit balance that the minimization activity will be

modified and reduced product risk to assure quality, safety, and efficacy (114). The overview of a typical quality risk management process is provided as Figure 7 (114).

The quality risk management process can be shifted into the basic risk management cycle. This is conceptually in the same or similar principles. The risk management cycle shows Figure 8 (111, 115).

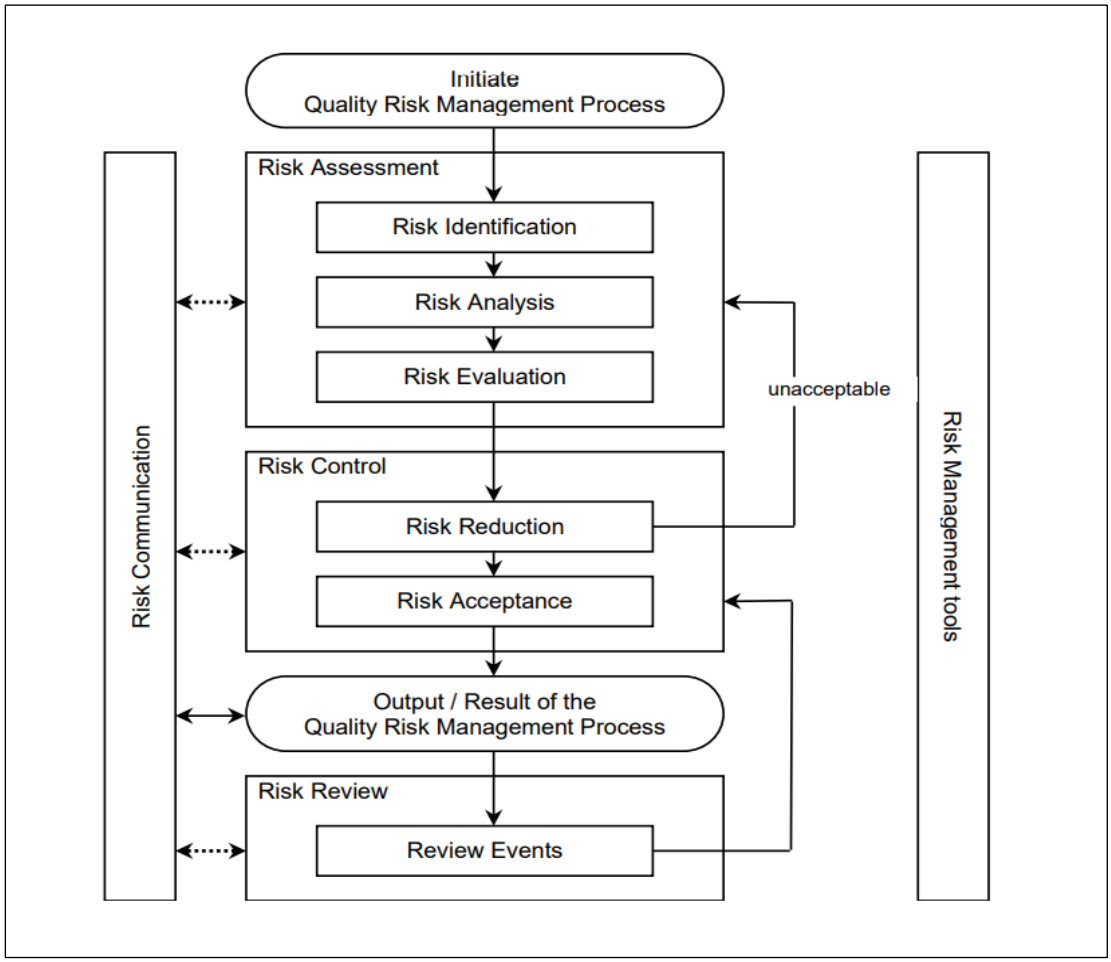


Figure 7 Overview of a typical quality risk management process (114)

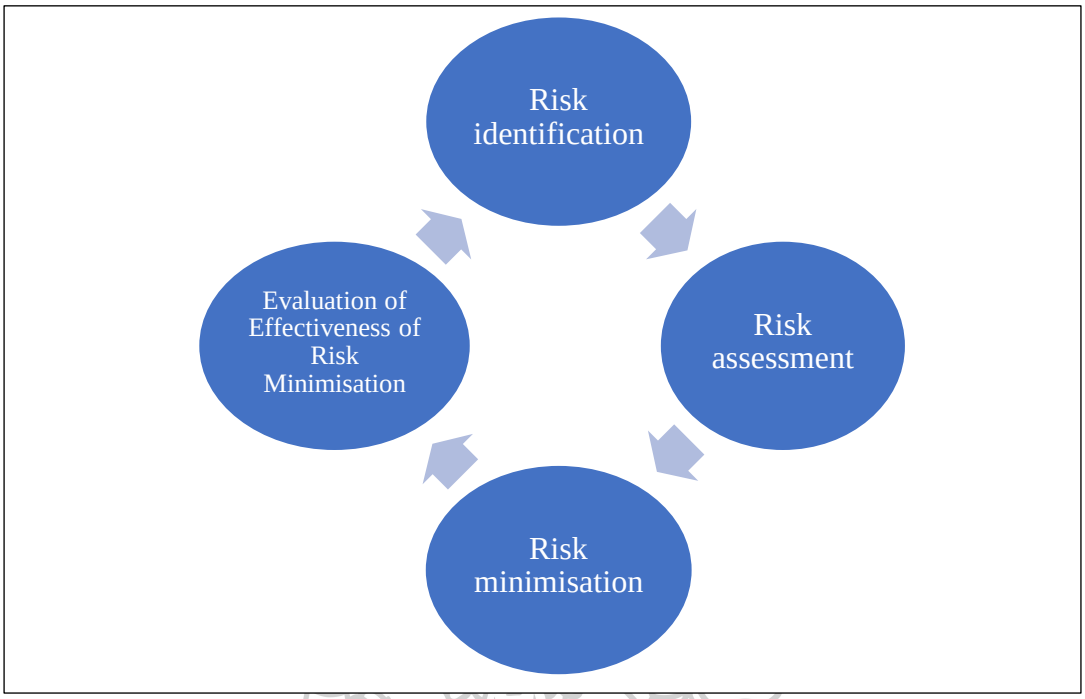


Figure 8 The basic risk management cycle (111,115)

7. Researchers related to developing an approach for regulatory on cell therapy medicinal products

Geoffrey Banda and group (2018) (116) had studied the current innovation ecosystem of Regenerative Medicine (RM) in the United Kingdom. The study approach, purposive sampling was used to get 18 interviews from 10 RM companies/organizations in the United Kingdom. This study was focused on the value chain gap and the influence of the innovation ecosystem. It found that 3 main problems.

1. Nonintegrated value chains were caused by 1) manufacturing; few cGMP plants and lack of capacity for clinical production 2) clinical adoption; lack of collaborations between therapy manufacturers and clinicians 3) translational services limit of a contract manufacturing organization such as CAR T cells.

2. Technology and delivery gaps define as 1) different for autologous and allogeneic therapies related to manufacturing model, distribution model, and cost of goods. especially autologous therapy 2) logistic issues; cell product is a living drug that changes according to the shipping and condition storage 3) regulation and

reimbursement systems for therapies. Secondly, an ultimate cost is a barrier to access for the patient.

3. Disproportionate governance can be defined 2 points as a pioneer's disadvantage and limited patients for clinical trials. 1) Pioneers incur the costs of learning how to manage the regulatory process and that of helping the regulators to learn. It is coherence and ability between developers and regulators and 2) RM can be treated for rare diseases. As a result, the number of clinical trials may be limited of participants and designed of clinical studies challenges. Hence, those issues are related to unapproved licensing.

Renske M.T and group (2018) (117) discovered that the purpose of this study was to assess the challenges faced by companies developing ATMPs in Europe. This study was a survey-based cohort study among commercial ATMPs developers. It found that most developers were small or medium-sized enterprises (65%) and Most companies developed cell-based medicinal products (53%), followed by GTMPs (46%) and combined ATMPs (1%). The intended therapeutic field for ATMPs had developed oncology (29%), ophthalmology (15%), and hematology (14%) respectively. The top three challenge domains were regulatory (34%), technical (30%), and scientific (10%). Moreover, financial challenges (covered two themes reimbursement and funding), clinical challenges, and human resource management challenges were reported from this study.

Benjamin M Davies and group (2017) (118) had studied to perceived barriers the adaptation of cell therapies in multi-stakeholder. In this research, the questionnaire was used via email to participants who were clinicians, researchers, and commercial including, regulatory professional experts in 13 countries such as North America, the United Kingdom, and other parts of Europe. The results of the study showed that the three biggest barriers to adoption as identified by each group: 1) Clinicians demonstrated the most of barrier cost-effectiveness, manufacturing, and regulation, respectively 2) Commercial demonstrated the most of barrier reimbursement, manufacturing, and cost-effectiveness, respectively 3) Researchers demonstrated the most of barrier manufacturing, efficacy, and reimbursement, respectively.

John Gardner and Andrew Webster (2016) (119) investigated stakeholders' efforts to overcome these innovation barriers and thus facilitate the emergence of

useful RM therapies. This study is conducted through interviews with three domains in the United Kingdom: regulatory, health economic, and clinical development. It was discovered that three domains are critical to the adoption and patient access to innovative therapies.

1. The regulatory system should not obstruct patients' access to products, but it should provide confirm safety and efficacy data. Many counties were designed to make patient access easier. Consequently, clinicians and regulators must engage in dialogue as soon as possible when there is a considerable medical need for therapeutic developments.

2. Innovative biomedical therapy faces a health economics challenge in terms of reimbursement and payment systems. Since RM is a high-cost treatment. Moreover, the payer will provide based on robustly clinical effectiveness data.

3. The clinical challenge for an innovative therapy is determining how it will be adopted and implemented in current clinical practice. These are complex and novel therapies that health care providers have used for technical and staff training, and logistical and delivery infrastructures within the clinical setting.

Rosario Isas and group (2016) (120) had studied that the aims to fill an empirical gap in the literature by exploring how cell-based therapies and products (CTP) manufacturing facilities navigate Canadian regulatory and commercialization environments, which together drive the translation of novel CTPs from bench to bed. This paper used a combination of purposeful and snowball sampling strategies to recruit participants that select participants based on roles and responsibilities at CTP such as CTP manufacturing, regulatory affairs, management, science, medicine, and commercialization. A semi-structured interview was used for participants. It found that four major themes emerged in exploring what shapes regulatory and commercial environments for CTPs as follows:

1) Managing regulatory uncertainty caused by the inability to classify CTPs within existing regulatory categories for approval and commercialization. Because these products have inherent characteristics and do not fall under the jurisdiction of the Canadian regulatory framework.

2) Creating a business case in which the market potential of a CTP is determined in large part by demonstrating its safety and effectiveness. Financial partners and regulators must support the successful development of a business case.

3) Standardizing manufacturing procedures that mobilize CTPs from a research and development phase to commercialization. Indeed, they need to develop for harmonization.

4) Formulating network between academic researchers, regenerative medicine industries, and regulators is potential for developing responsible commercialization processes.

SOFIEKE DEWILDE and group (2016) (121) conducted research to identify major roadblocks that may explain the low success rate of ATMPs implementation in clinical care. This study consisted of interviews with various stakeholders involved in ATMPs development in the Netherlands such as academic research groups, national authorities, and patient organizations. Following the completion of the interviews, questionnaires were sent to the stakeholders based on the obstacles mentioned in the interviews. This study is the result of significant obstacles.

1. Inadequate financial support can be divided into 2 groups as financial support for research and development until Marketing Authorization (MA) phase and reimbursement after MA or hospital exemption (HE) approval.

2. Regulatory knowledge: Lack of knowledge and documentation needed to prepare for MA. Stakeholders would be helpful for a knowledge platform to support the development route of ATMPs to share knowledge or provide from an expert during the various stages of the development process. Thus, a national ATMPs development knowledge platform could be established.

3. Rapidly evolving field: The ATMP field is innovative, complex, and dynamic.

4. Study-related problems: The study-related problems were reported such as limited availability of human starting material including participant in clinical trial, raw materials for manufacturing.

5. Collaborations with all stakeholders such as manufacture, researcher, clinician, regulator, funding agency, payer, and patient advocacy groups.

In conclusion, Treatment approaches have been greatly developed and improved with scientific advancement, better knowledge regarding biotechnology, and the technicality of cell-based, tissues and genes therapies. All these have led to the so-called Advanced Therapy Medicinal Products (ATMPs) or Regenerative Medicine (RM) as called normally in Japan. According to the emergence of this new product, different from products generally derived from chemical and biological sources, As the result, new kinds of regulations are needed. ATMPs represent an immense hope for the suffering patients and their caregivers, but should also be handled as novel pharmaceuticals associated with high uncertainty and insufficient experience. In addition, the number of limits patients are enrolled in a clinical trial. Thus, Appropriate regulations are dramatically significant not only in safeguarding public health that who accepted but also facilitated innovation of therapies. Subsequently, Novel therapies have tremendous costs that be handled the development process until deliver to patients. The prices are hindered by affordability and reimbursement by payers. Furthermore, the rigorous pieces of evidence were considered for cost-effectiveness only. Finally, Collaboration is the key factor of the ecosystem to support researchers, manufacturers, regulators, clinicians, funding agencies, and patient advocacy groups to succeed in the area of commercialization processes.

CHAPTER III

METHODOLOGY

The research methodology used in this dissertation is qualitative. More specifically, the essential data is gathered using three basic methods: Pursuing that, 1) documentary review from existing literature and secondary sources, 2) semi-structured interviews with stakeholders based on non-probability random sampling using purposeful and snowball sampling strategies, and 3) formulation of the guideline. This research was approved by the Institute Review Committee for Human Research at Silapakorn University No. REC 64.0126-011-0192 on 25 March 2021.

Research methodology

1. Documentary review

The present review aims to aid in the development of interview questions for the main component of this study. To gather the essential national and international data, the researcher focuses on the European Union, the United States of America, Japan, Australia, and South Korea which are home to the world's leading innovators, manufacturers, and stringent regulatory authorities for cell therapy pharmaceutical products. The researcher's primary concerns are the licensing of cell therapy medicinal products and the control of activities linked to the use and production of these products in medical institutions. Interview questions were developed based on theories established in the existing academic literature and on documents published by both the private and public sectors regarding guidelines, law, and/or regulations about advanced therapy medicinal products and cell-based medicinal products. More specifically, the researcher reviews publicly available documents such as the homepage of the European Medicines Agency (www.ema.europa.eu), U.S. Food and Drug Administration (www. fda. gov) , the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan (www. pmda. go. jp/ english/) , Therapeutic Goods Administration (TGA) (www.tga.gov.au), the Korea Food & Drug Administration (KFDA) (www. mfds. go. kr/ eng/) , and Thai FDA (https://www.fda.moph.go.th/).

Furthermore, the researcher searched PubMed, Google scholar and Web of science databases for the research articles, review articles and systematic reviews. The researcher also conducted between March 2019 and December 2020. The keywords were used for the databases searches as regulation of cell therapy medicinal products, regulation of regenerative medicine products, regulatory framework for Advanced Therapy Medicinal Products or cell therapy, and regulatory aspects of Advanced Therapy Medicinal Products or cell therapy. In addition, English and Thai language publication will be included in this review only. The scope of the review being the following:

1. 1 Guidelines for regulating cell therapy medicinal products for medical institutions.

1. 2 Guidelines for regulating cell therapy medicinal products for drug registration.

1. 3 Qualifications of medical institutions providing treatment using cell therapy medicinal products.

1. 4 Qualifications of laboratories providing treatment using cell therapy medicinal products.

1.5 Problems, obstacles, and suggestions for regulating cell therapy medicinal products, in terms of drug registration and usage by medical institutions.

The researcher then formulates particular questions to be used in the research's subsequent interview stage based on the information gathered above.

2. Semi-structured interviews with stakeholders

The researcher selects participants based on non-probability random sampling using the purposeful and snowball sampling strategies. Interviews were conducted between March and July 2021 to obtain the opinions of the relevant stakeholders regarding the design of a suitable regulatory environment for cell therapy medicinal products in Thailand (Appendix A) . Interviews are based on a semi-structured approach, in which the key topics are discussed with each interviewee while allowing the interviews to flow naturally and additional issues to arise during the discussions. Each interview is recorded and transcribed. The questions are different depending on the background and expertise of the interviewees, there are also some common ones for all the informants. Examples of these questions include:

1. How should cell therapy medicinal products be regulated in Thailand, in terms of both drug registration and the qualifications of medical institutions providing related treatments? (Should there be any additional organization(s) established or the law(s) enacted to ensure the quality, safety, and/or efficiency of related treatments?)

2. What are the potential problems, obstacles, or resolutions for the regulation of cell therapy medicinal products in terms of drug registration and medical institutions providing related treatments in Thailand? (Selected based on the characteristics of the key informants, including whether they can likely provide insights into drug registration or use of cell therapy medicinal products by medical institutions)

3. Suggestions for regulations of cell therapy medicinal products for drug registration and use by medical institutions in Thailand.

4. Who was on the expert group that oversaw the regulation of cell therapy medicinal products? (Selected based on the characteristics of the key informants, including whether they can likely provide insights into drug registration or use of cell therapy medicinal products by medical institutions)

The objectives of semi-structured questions for the interviews with stakeholders are as follows.

Table 2 Objectives and concept of semi-structured interview for key stakeholders

Objectives	**Concept of interviews**
1. The qualifications of medical institutions that are sufficient for them to provide safe and high-quality treatments using cell therapy medicinal products.	-What are the qualifications of medical institutions that are sufficient for them to provide safe and high-quality treatments using cell therapy medicinal products (medical institutions requirements, medical institutions registration, quality control)?
2. The qualification of a medical practitioner sufficient for providing cell therapy medicinal products for treatments.	-What are the key qualifications of a medical practitioner that are sufficient for providing cell therapy medicinal products treatments? -What should the professional team consist of (multidisciplinary)? -Should cell therapy medicinal products be subject to the ethic code set out by the medical council concerning the same issues the medical council B.E. 2552 (2009) rule?
3. Guidelines to regulate cell therapy medicinal products for drug registration that are suitable in the Thai context.	-Should guidelines for regulating cell therapy medicinal products be different from the ones used for traditional biological products? -What should be the right model to regulate cell therapy medicinal products? (manufacturing, importer and autologous, allogeneic products) -How are follow-up procedures of patients administered with cell therapy medicinal products?
4. The qualifications of laboratories are sufficient for them to provide safe and quality the treatment using cell therapy medicinal products.	-What are the qualifications of laboratories sufficient for them to provide safe and high-quality treatments using cell therapy medicinal products?

Table 2 (continue)

Objectives	Concept of interviews
5. The qualifications of cell banks about cell therapy medicinal products	-How is the establishment of cell banks or the criteria for the donation of human cells for the pharmaceutical industry and medical institutions?
6. Issues, obstacles, and suggestions for the development or regulation of cell therapy medicinal products in medical institutions contexts	-How are situation(s) and trend(s) in terms of production of cell therapy medicinal products within medical institutions for patients? -How are treatment standards of cell therapy medicinal products in medical institutions? -What are the follow-up procedures for patients administered with cell therapy medicinal products? -What should be the right model to regulate cell therapy medicinal products within medical institutions? -What are the issues, obstacles, and suggestions for the development or regulation of cell therapy medicinal products in medical institutions?
7. Issues, obstacles, and suggestions of development or regulation for cell therapy medicinal products in commercial contexts	-How are the situation(s) and trend(s) of the production of cell therapy medicinal products in commercial contexts? -Should guidelines for regulating cell therapy medicinal products be different from ones used for traditional/existing pharmaceutical products? -What should be the right model to regulate cell therapy medicinal products? (manufacturing, importer and autologous, allogeneic products) -How are follow-up procedures of patients administered with cell therapy medicinal products? -What are issues, obstacles, and suggestions for the development or regulation of cell therapy medicinal products in commercial contexts?

Key stakeholders

In total, ten stakeholders are chosen to represent various organizations, including medical institutions, private companies, and the public sector that are key players in various aspects of cell therapy medicinal products in Thailand. For each group of stakeholders, we select participants based on non-probability random sampling using the purposeful and snowball sampling strategies. Table 3 shows the ten stakeholders and the qualifications of qualifying informants within each group. The groups of stakeholders consist of colleague three institutions: medical institutions, private companies, and public policy sectors. Medical institutions are those with potential interest in providing treatment using cell therapy medicinal products or advanced therapy consisting of the cell for patients in Thailand. Private companies are the main manufacturers and/ or importers of biological pharmaceutical products. Finally, the public policy sectors are those involved in the regulation. The full list is as follows.

1. The Department of Health Service Support (HSS) is a division of the Ministry of Public Health organization. That organization is a collection of departments tasked with overseeing Thailand's medical institutions.

2. The Thai Food and Drug Administration (Thai FDA) is a division of the Ministry of Public Health. This is a set of departments tasked with guaranteeing the safety, quality, and efficacy of consumable items to protect consumers' health. Drugs and cell therapy medicinal products are included.

3. The Thai Medical Council is responsible for medical practitioner regulation.

4. The Red Cross Society is responsible for donor recruitment for hematopoietic stem cell transplants.

5. Science-based or academic institutions such as Ramathibodi Hospital, Siriraj Hospital, and King Chulalongkorn Memorial Hospital are interested in using cell therapy medicinal products or advanced therapy consisting of the cell for patients.

6. Institute of Biological Products by the Department of Medical Sciences (DMSc) is in the authority of quality testing and assurance of biological products for licensure, and it is known in Thailand as the national control laboratory.

7. Bureau of Laboratory Quality Standards by the Department of Medical Sciences (DMSc) is responsible for quality assurance and accreditation for public health laboratories (Accreditation Body).

8. Companies in Thailand that manufacture or import biological drugs. The latter group is usually companies in Thailand whose parent companies are international pharmaceutical companies that have already been manufacturing ATMPs (of which cell therapy medicinal products are a subset) and launched the products into the market. Companies that have been researching ATMPs are also included in this category.

In addition, the researcher contacted with the first of key informant in each of the sectors that was a gateway to led to other key informants as follows

1. A member of the Department of Medical Sciences is involved in the working group and secretary of developing standards of cell-based therapy laboratories.

2. A member of Thai FDA is main a responsibility of developing the ATMPs regulatory framework.

3. A member of Institute of Biological Products by the Department of Medical Sciences is main a responsibility for quality testing and assuring of biological products for licensing.

4. The subsidiary importers biologic medicines company's head of regulatory affairs is licensed under the Drug Act B.E. 2510, and the parent company has already been permitted to sell ATMPs on the market.

5. The Drug Act, B.E. 2510, grants a license to the head of regulatory affairs of a biologic drug company.

Notably, each interviewee gave their informed consent before participating in the study.

Table 3 The key qualifications of informants

The key qualifications of informants	**Number of key informants (n)**
1. A member of the committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council	4 (P11, P12, P13, P14)
2. A member of the Board of Directors of the Medical Council of Thailand or an Executive of the Thai Medical Council or one who was previously a member of the Board of Directors	2 (P21, P22)
1. An expert in the field of quality control and safety of biologic drugs or cell therapy medicinal products 2. An expert in the field of analysis, quality assurance, and risk assessment of biologic drugs or cell therapy medicinal products 3. An expert in the field of development of management systems and standardization of laboratory analysis of biologic drugs or cell therapy medicinal products AND with experience of no less than 5 years	2 (P31, P32)
1. An expert involved in the working group (Draft) Act on Cell Therapy B.E… with experience no less than 5 years	2 (P41, P42)
1. The biologic manufacturing companies in Thailand	6 (P51, P52, P53, P54, P55, P56)
1. An expert in the area of regulation of cell therapy medicinal products or biologic drugs (pre-marketing) 2. An expert in the area of regulation of cell therapy medicinal products or biologic drugs (post-marketing) 3. An expert in the area of regulation of cell therapy medicinal products or biologic drugs (Health Product Vigilance Center) AND with experience of no less than 5 years	4 (P61, P62, P63, P64)

Table 3 (continue)

The key qualifications of informants	Number of key informants (n)
1. The head of the National Blood donation laboratory or the Stem Cell laboratory or 2. An expert in the area of the Stem Cell laboratory AND with experience no less than 5 years	1 (P71)
1. An expert in the field of developing management systems and quality control systems for cell-based laboratories 2. An expert in the field of audit or certification of public health laboratories AND with experience of no less than 5 years	2 (P81, P82)
1. Acting in the position of head of the center or involved in clinical research and development for cell therapy medicinal products or advanced therapy consist of the cell for patients such as Ramathibodi Hospital, Siriraj Hospital, and King Chulalongkorn Memorial Hospital	7 (P91, P92, P93, P94, P95, P96, P97)
1. The biologic drugs importers. These are usually companies in Thailand whose parent companies are international pharmaceutical companies that have already been manufactured ATMPs (of which cell therapy medicinal products are a subset) and launched the products into the market. Companies that have been researching ATMPs are also included in this category.	7 (P101, P102, P103, P104, P105, P106, P107)

Key stakeholders were categorized into 2 groups as follows the research objectives.

1. To study and develop guidelines for the regulation of medical institutions concerning the use and production of cell therapy medicinal products which are potentially suitable for Thailand. Key stakeholders were (P11, P12, P13, P14), (P21, P22), (P41, P42), (P63, P64), (P71), (P81, P82), (P91, P92, P93, P94, P95, P96, P97). Moreover, there are three key informants who give important information which is in the domain of more than one group within the first objective.

2. To study and develop guidelines for the regulation of cell therapy medicinal products in terms of drug registration which are potentially suitable for Thailand. Key stakeholders were (P31, P32), (P51, P52, P53, P54, P55, P56), (P61, P62, P63, P64), (P101, P102, P103, P104, P105, P106, P107).

3. Formulation of the guideline

Information collections from all participants were conducted through interviews by the researcher until new issues no longer emerged and saturation was reached. Additionally, information collections also encompassed document reviews. After that, data were verified by triangulation with data from documentary review and data from interviews. The researcher who conducted the interviews and one other researcher created specific data extraction forms using Microsoft Excel. Selected issues were identified in Microsoft Excel that can be classified 2 ways as 1. Guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products and 2. Guidelines for cell therapy medicinal product regulations in terms of drug registration. We formulated the guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products and drug registration by identifying recurring themes from document review and interviews including issues with important implications on quality, safety and efficacy. Our guideline is not being derived directly from existing guidelines of any countries, but from our research. In cases of discrepancies between documentary reviews and interviews, the final calls would be based upon the unanimous views of the researchers. Consequently, the guideline of regulations for cell therapy medicinal products (Appendix B) , both in terms of use at medical institutions and use for drug registration in Thailand was formulated to send them off to all interviewees to final reviews. The final reviews of opinions of informants are considered as being representative of the groups whereby the informants belong. The guidelines for cell therapy medicinal product regulations were selected based on the characteristics of the key participants whether they are drug registration or medical institutions. The guideline can be rank by each questionnaire as agree, partially agree, or disagree. Similarly, stakeholders can recommend and discuss to respond to guideline during the consideration. So that, the answers would be in accordance with the opinions of the key informants.

Data collection

According to the document review, the researcher reviews publicly accessible documents such as the homepage of the European Medicines Agency, U.S. Food and Drug Administration, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, Therapeutic Goods Administration (TGA) , the Korea Food & Drug Administration (KFDA), and Thai FDA. Furthermore, PubMed, Google scholar and Web of science databases are considered to formulate the regulation of cell therapy medicinal products. Similarly, based on semi-structured interviews with stakeholders, each informant received a semi-structured interview form at least three days before the interview. The interviewees chose the date and time of the interview. Each interview lasted 45-60 minutes and was voice-recorded with the interviewee's permission. The essential topics/ questions were explored with each person while allowing the conversation to run naturally and for other issues to surface during the session. Following the interview, the researcher returned an interview transcript to each interviewee within one week to verify and re-validate the summarized content. The researcher allowed for the possibility of collecting additional information in the future should new issues or information arise during the interview with other interviewees. Subsequently, after the interview transcripts were validated, the researcher analyses the interview scripts from all the stakeholders, looking for common themes/problems/issues associated with the most appropriate models for the regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration. Finally, the researcher established the guidelines to the regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration from document review and interview. The guidelines were sent to all participants for final making decision that were selected based on the characteristics of the key participants whether they are drug registration or medical institutions. In addition, the guidelines are taken into consideration by all key informants for three weeks. The researcher will follow up at least three around one week apart.

Data analysis

Based on the interviews, the researcher identified important subjects. In addition, the researcher examines crucial topics in light of the concerns raised in the literature. The overall purpose was to identify critical obstacles and best practices to develop guidelines for regulating cell medicinal products for use by medical institutions and drug registration in Thailand. Qualitative information was used in content analysis, in which the researcher collected data and analyzed data that came from document reviews and interviews in order to verify and confirm the data. Following that, the researcher created the guidelines based on an analysis of the documentary and interviews with stakeholders. Participants can express their opinion by ticking various boxes (‘agree’, ‘partially agree’ or ‘disagree) with various issues and they can write additional recommendations. The appropriate guideline is constructed by identifying issues that most participants agree upon. As for additional recommendations from participants, they are categorized according to emerging themes. Lastly, the guidelines were gathered from key informants to final making decision, and the important findings were presented once more.

CHAPTER IV

RESULTS

This research examined the creation of regulatory guidelines for cell therapy medicinal products in Thailand. The researcher revealed the specifics of the research findings in accordance with the following objectives:

1. Guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products that may be suitable for Thailand.

2. Guidelines for cell therapy medicinal product regulations in terms of drug registration that may be applicable in Thailand.

The research process divided into 3 phases as follows:

Phase I Documentary review

Phase II Semi-structured interviews with stakeholders

Phase III Formulation the guideline of cell therapy medicinal products

1. Documentary review

The researcher used the results of the documentary review to interview key informants and studied the essential national and international data on cell therapy medicinal product licensing and the control of activities related to the use and production of these products in medical institutions from related works of literature. The following is a summary of the findings.

Principle of regulation of cell therapy medicinal products can be divided into 2 major aspects as:

1. The extent to which cells or tissues are manufactured (beyond minimal or substantial manipulation) or the intended application (homologous use or heterologous use). They are medications that are classified as regulated therapeutic products for human use. The United States, the European Union, and South Korea have all implemented this key principle. In addition, the definition of minimal manipulations is significant to evaluate and categorize into ATMPs sub-classification as cell therapy medicinal products. In the US for the FDA, it means cutting, grinding,

and shaping, soaking in an antibiotic solution, sterilization by ethylene oxide treatment or gamma irradiation, cell separation, lyophilization cryopreservation, and freezing that is without culture before administration to the patient. Similarly, for the EMA, it means cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification. Also, Japan means separation and cutting of tissues, isolation of specific cells (except for isolation following biological/ chemical treatments) , treatment with antibiotics, washing, sterilization by gamma-ray, freezing, and thawing. Moreover, these activities do not change the biological activity or function of cells. All of the foregoing, as well as the levels of manipulation, are an important part of the regulatory oversight of cell therapy medical therapy.

2. The aim of cell therapy medicinal products is to be distributed throughout the market or in medical practice in medical facilities for a single patient who is under the sole management of a professional. Those products do not rely on a level of manipulation. Japan, Australia, and Thailand are among the countries that have implemented this key principle.

As a result, cell therapy medicinal products are classified into two primary regulatory approaches to access patients as follows.

1. The regulation of cell therapy medicinal products for clinical practice in medical institutions

Clinical experience in medical facilities qualifies cell therapy medicinal products for exemption from the medicines regulation. Furthermore, the intervention must be carried out by a medical professional as a legal obligation for each individual to follow a unique treatment prescription and can be further described as:

Medical practices in medical institutions

Medical practices in medical institutions are exempted from any pre-launching campaigns to the market. Some counties draw up the requirements for the cell processing facility or medical institutions must adhere to a series of standard operating procedure guidelines. Such regulation can be seen in the EU (Directive 2004/ 23/ EC, Directive 2006/ 17/ EC and Directive 2006/ 86/ EC) , the US (21 CFR 1271) and Japan (The Act on the Safety of Regenerative Medicine, ASMR) .

Moreover, Japan uses ATMPs product as part of clinical interventions, clinical research, processing facilities and production in medical institutions is under the scope of ASMR regulation. ASMR was first established due to a domestic incident of cell therapy deficiency that led to a death.

Qualifications of laboratories or manufacturing sites providing treatment using cell therapy medicinal products

Requirements for the qualifications of laboratories or manufacturing sites are required as organization and management, personnel who are involved in providing cell-based therapy, equipment and materials, facilities/premises, documentation and records, including screening measures or tests of human cells, processing and process controls and quality system checks. Furthermore, major adverse reactions and medical treatment reports must be reported to the appropriate authorities. Cell processing facilities and laboratories that perform cell-based treatments must obtain a license or notification from the national authorities. Current Good Tissue Practice (cGTP) requirements are expected to carry out in cell production within medical institutions due to ensure the quality and safety of cell therapy medicinal products. The standards above may somewhat resemble the Good Tissue Practices: GTP. However, they are less rigorous than the GMP requirements. Nevertheless, the processing facility and laboratories must be authorized by national authorities as an assurance of quality, safety and efficacy for cell therapy medicinal products.

Qualifications of medical institutions providing treatment using cell therapy medicinal products

Many counties have established guidelines for the use of cell-based therapy in medical facilities. In South Korea, for example, those products are manufactured with minimal manipulation. Their products are controlled as medications if they are not subjected to minimal alteration. Furthermore, before performing treatments on patients, medical institutions must be registered with national jurisdictions. Similarly, several counties set the rules for doing interventions at medical facilities. Australia, for example, established rules such as recognized physicians and medical facilities, no advertising to patients, and pre-determined criteria before treatment. Furthermore, before acceptance, patients are given accurate risk and benefit information.

In recent years, medical practitioners in Thailand have put more interest in implementing cell therapy medicinal products or advanced therapy encompassing human cells within medical institutions to resolve the treatment challenge in life-threatening diseases. Some success stories were seen from the local medical institution where the stem cell-based therapy on limbal epithelial transplantation was performed and CAR T cells in B-cell Acute Lymphoblastic Leukemia (ALL) and Diffuse Large B-cell Lymphoma (DLBCL). However, there has not been any explicit regulation regarding any use of ATMPs for cell therapy medicinal products as part of the treatment intervention within medical institutions in Thailand as of today. A few years ago, the government as a regulatory sector and stakeholders attempted to establish a Cell Therapy Act for clinical practice standardization (in public and private clinical site). This law, however, has yet to be enacted. The Cell Treatment Act (draft) is a key instrument for protecting public health for patients who have accepted cell therapy.

2. The regulation of cell therapy medicinal products is overseen as medicinal products for human use or drug registration

The national regulatory authorities in each country controls medicinal product for human use, such as the United States Food and Drug Administration (US FDA) for the USA, the European Medicines Agency (EMA) for the EU, Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Therapeutic Goods Administration (TGA) in Australia, the Ministry of Food and Drug Safety (MFDS) in South Korea, and Thai FDA in Thailand. Cell therapy medicinal products are classified as medicinal products based on legal definitions. As a result, those products are regulated by national regulatory authorities. They must comply with the requirements of the medicines legislation before launching. Those requirements are generally abided by the Good Manufacturing Practice: GMP, Good Laboratory Practice: GLP, Good Clinical Practice: GCP, and Good Review Practice: GRP. Following that, Good Pharmacovigilance Practices (GVP) must be used to regulate and monitor the product after it has been approved. National regulatory bodies oversee all of these steps to ensure the quality, safety, and efficacy of cell therapy pharmaceutical products used by permitted patients. Traditional medicinal product

regulation can be used to cell therapy medicinal goods in terms of drug registration, which is divided into three steps.

Pre-marketing authorization process

Advances in biotechnology and advanced therapies have assisted the production of cell therapy medicinal goods. The products present a unique difficulty, as they are based on either the patient's cell or a healthy volunteer donor as beginning material. The origin of the beginning material used in the manufacturing process of the products can be classified as autologous or allogeneic. When patients receive incompatible human cell products, immunological responses can often result in significant and life-threatening complications. As a result, autologous product has a number of advantages for the immune system. Furthermore, Autologous product, in particular, are custom-made, costing a lot of money and requiring a lot of procedural distribution. These challenges are critical to consider when manufacturing cell therapy medicinal products as a means of establishing quality and safety standards for cell-based therapy donation, procurement, testing, manufacturing process and in-process control, process evaluation/validation, preservation, storage, and distribution. Good Laboratory Practice; GLP is applied to *in vitro* and *in vivo* studies. This phase is proved of concept pharmacology, toxicology, and adverse events of the medicinal products. The traditional pharmacokinetics of absorption, distribution, metabolism, and elimination (ADME) studies may not be feasible for cell therapy medicinal products. Non-clinic studies of ATMPs should demonstrated biodistribution, trafficking, proliferation, viable cell rate, and transgene expression. In addition, an animal model should be predicted clinical experiments in the human phase. Good Clinical Practice; GCP involves the participation of human subjects. The clinical phase is required to comply with GCP principles as international and national standards. These standards ensure the quality, safety, and protection of the rights of the human being enrolled in the study. Cell therapy medicinal products clinical studies in phase I are unable to include healthy volunteers and are randomized in clinical studies. Due to the small number of patients who participated in the clinical trial, it may be impossible to evaluate the statistical significance for safety and efficacy that clinical significance is inadequate for acceptable approved products.

Moreover, GMP and cGTP are also taken into account when producing cell therapy medicinal products.

Marketing authorization process

Cell therapy medicinal products differ from other chemical medications and traditional biologic drugs in several ways. As a consequence, regulatory approval for cell therapy medicinal products is based on natural characteristics. The regulatory path chosen will be determined by the product's characteristics, the target patient population and disease prevalence, and the limited quantity of products, particularly autologous products. Many countries have designed flexible and expedited pathways to success for drug registration. For example, In the EU, the PRIME scheme is the main mechanism and focuses on expediting and optimizing the development of priority medicines. The USA has an available Breakthrough Therapy Designation, Fast Track Designation mechanism for novel therapy and the Regenerative Medicine Advanced Therapy Designation (RMAT) under the 21st Century Cures specific for support cell and gene therapy products. Japan has been developed SAKIGAKE Designation schemes that aim to expedite the rapid authorization of new medicines. Furthermore, PMD Act announce a new regulated specific for Regenerative Medical products that are time-limited condition approved and last for a maximum of 7 years. However, those products have taken advantage of dedicated approval schemes for medicinal products providing positive clinical benefits, especially in situations of unmet medical needs. At the same time, many countries determine criteria for Conditional approval as unmet medical needs, seriously debilitating, life-threatening diseases. In the initial phase, less comprehensive data than normally required has demonstrated a positive benefit-risk, but where further data needs to be collected for evaluation again. Conditional approval was established to access novel drugs timely and predict the benefit of products at Marketing Authorization Application (MAA).

Post-marketing authorization process

Generally, some cell therapy medicinal products can produce long-lasting biological effects in patients, although the products undergo a single administration. As such, it is possible to encounter adverse events or loss of efficacy after administration. For example, stem cells may derive delayed events as the cell proliferation period requires a certain amount of time to achieve the process of

proliferation and differentiation. Therefore, stem cells or cell-based could develop into inappropriate cell types or multiply unexpectedly adverse events. Thus, it is of the highest importance in formulating a monitoring scheme for cell therapy medicinal products to promote post-marketing efficacy and safety. Stringent regulatory authorities recommended for surveillance period. The EMA suggested a 2-years intensive follow-up for the cell-based therapies after exposure. After two years of close monitoring, the vigilance scheme would relate to the overall risk assessment of each product. On the other hand, US FDA advised that the follow-up period could be extended to 15 years when cells combine with gene therapies to assure any possible late adverse reactions. Hence, the extended follow-up scheme is highly likely appropriate for monitoring cell therapy medicinal products as it would be useful in the detection and prevention of any delayed adverse reactions.

As mentioned previously, the concept of traditional biologic drugs can be applied, but the unique characteristics of cell therapy medicinal products should also be taken into account.

3. Problems, obstacles, and suggestions for regulating cell therapy medicinal products in terms of drug registration and usage by medical institutions

According to the development of a novel medicinal product, cell therapy medicinal products are different from pharmaceuticals generally derived from chemical and biological sources. Moreover, cell therapy medicinal products are promised for the suffering patients, but should also be handled as novel pharmaceuticals associated with high uncertainty and insufficient experience due to a lack of circumspect knowledge of these products which have emerged recently. As the result, the barriers are revealed to the development of cell therapy medicinal products. The vast majority of the interventions in this early stage were focused on the creation of experimental medicines based on human genes and/or cells in university hospital settings, where there was a lack of regulatory expertise and marketing understanding. Moreover, facilities for clinical-grade cell manufacture as the under-resourced medical institution cannot invest in these expensive plants, for example, GMP are key manufacturing cost. Similarly, the lack of human skill in cell-based therapies knowledge, and finance issues. In the case of commercialization, the

following domains of characteristics in the industry's challenge for cell therapy medicinal products are described. Manufacturing and process in control of products that are necessary for quality, safety, and efficacy are scientific issues. Cell therapy medical products have emerged and differed from traditional drugs in terms of the regulatory environment, which has been optimized for new products. Furthermore, the number of patients recruited in a clinical trial has an impact on approval. As a result, appropriate regulations are critical not only in protecting public health but also in facilitating the development of new therapies for patients. Finally, as they traverse the long and risky journey to market, early-stage cell therapy companies must be prepared to raise sufficient finance to survive. Novel medicines have high costs after they are released to the market, and their prices are hampered by payer reimbursement and affordability. Furthermore, due to a lack of time and expertise, it is difficult to demonstrate cost-effectiveness, which leads to payment challenges from healthcare providers. As a result, politicians must design the program to allow patients access to the products.

2. Interviews with stakeholders

Characteristics of key informants

The general information of key informants of each group are presented in Table 4. Key informants were categorized into 2 groups as follows the research objectives.

1. To study and develop guidelines for the regulation of medical institutions concerning the use and production of cell therapy medicinal products which are potentially suitable for Thailand. Key stakeholders were (P11, P12, P13, P14), (P21, P22), (P41, P42), (P63, P64), (P71), (P81, P82), (P91, P92, P93, P94, P95, P96, P97). Moreover, there are three key informants who give important information which is in the domain of more than one group within the first objective.

2. To study and develop guidelines for the regulation of cell therapy medicinal products in terms of drug registration which are potentially suitable for Thailand. Key stakeholders were (P31, P32), (P51, P52, P53, P54, P55, P56), (P61, P62, P63, P64), (P101, P102, P103, P104, P105, P106, P107).

In addition, some key informants hold multiple occupational positions with multiple responsibilities.

Table 4 General information of the key informants of each group

Personal information	Group 1 Number (n=4)	Group 2 Number (n=2)	Group 3 Number (n=2)	Group 4 Number (n=2)	Group 5 Number (n=6)
Gender					
Female	-	-	1	1	5
Male	4	2	1	1	1
Age (years)					
< 40	-	-	-	-	1
41 - 50	-	-	1	-	2
51 - 60	1	1	-	2	2
61 - 70	3	1	1	-	1
> 70	-	-	-	-	-
Duration of experiences (years)					
1 – 5	1	1	-	-	-
6 - 10	-	-	-	-	-
11 - 15	3	-	-	-	3
16 - 20	-	1	-	-	1
20 and above	-	-	2	2	2
Job position					
Executive of the director	2	2	1	1	4
The head of the department	2	-	1	1	2
Practitioner	2	-	1	-	-

Table 4 (continue)

Personal information	Group 6 Number (n=4)	Group 7 Number (n=1)	Group 8 Number (n=2)	Group 9 Number (n=7)	Group 10 Number (n=7)
Gender					
Female	2	1	2	3	4
Male	2	-	-	4	3
Age (years)					
< 40	2	-	-	-	1
41-50	1	-	-	4	3
51-60	-	1	2	2	3
61-70	1	-	-	1	-
> 70	-	-	-	-	-
Duration of experiences (years)					
1 – 5	-	-	-	-	-
6 – 10	1	-	-	1	1
11 – 15	2	-	-	3	1
16-20	-	-	-	2	2
20 and above	1	1	2	1	3
Job position					
Executive of the director	1	1	2	-	1
The head of the department	1	1	2	7	5
Practitioner	2	-	-	-	1

The objective 1 Guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products that may be suitable for Thailand.

1. Interviews with stakeholders

1.1 The introduction of application for cell therapy medicinal products in Thailand

From an interview with key informants, a group of researchers, and academic medical center, In 2021, cell therapy medicinal products have been applied for treatments to individual patients in clinical research that patients are under the exclusive professional responsibility of medical practitioners at teaching hospitals such as Ramathibodi Hospital, Siriraj Hospital, and King Chulalongkorn Memorial Hospital. Cells are derived from the patient's cells or related donor that they may be genetically modified of T cells (Chimeric Antigen Receptor (CAR) T cells) or cells culture only such as NK cell, a limbal stem cell. After that, they are returned to the same patients, which are well-known personalized medicine that are specific-patients, as cancer and limbal stem cells deficiency. Their information was agreed with the government's cell-based laboratories. Cell production was provided to the academic medical center in the clinical research phase only. Moreover, the cells are used from the patient's cells such as mesenchymal stem cells from bone marrow. Their researches have been conducted after sufficient safety and efficacy profile to ensure safety. *(P81, an expert in the field of developing management systems and quality control systems for cell-based laboratories-DMSc, interview, 23 April 2021)* However, safety and efficacy data remain to be followed.

"… Cancer cellular immunotherapy excellence center pursue its research in two key areas: (1) development of Natural Killer cells; and (2) treatment of leukemia and lymphoma with CAR T cells, which is currently in phase I for human study …" *(P96,* a group of researchers, and academic medical center, *interview, 24 June 2021)*

"… The limbal stem cell transplantation for corneal disease was conducted in the clinical research. As for now, it is being considered as the standard treatment

by the Medical Council of Thailand … ” *(P14, the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council & P91, a group of researchers, and academic medical center, interview, 27 April 2021)*

“… The function of the government's cell-based laboratories is to produce cells to feed clinical researches in academic medical centers only … ” *(P81,an expert in the field of developing management systems and quality control systems for cell-based laboratories-DMSc, interview, 23 April 2021)*

In 2021, in Thailand, cell therapy medicinal products have not been used for treatment to many patients or off-the-shelf products. Due to the complexity of the manufacturing process. Furthermore, finished products have used patients’ cells as so-called personalized medicine. So that, cell therapy medicinal products have still been conducted by clinical research in Thailand. In particular, cell therapies were performed within private hospitals where there are more issues to consider than public hospitals such as sufficient efficacy and safety data, right to information, and service fees. *(P96, a group of researchers, and academic medical center, interview, 24 June 2021) , (P12, the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council & P21, the Board of Directors of the Thai Medical Council, interview, 21 March 2021)*

1.2 Key informants' opinions to the models for use of cell therapy medicinal products within medical institutions

The models for use of cell therapy medicinal products for patient treatments within medical institutions in Thailand can be considered into four categories as

1) Medical practices on cell therapy medicinal products.

2) Cell production is derived from a patient's cells based on a medical prescription within medical institutions.

3) Cell production is derived from a donor for a specific patient based on a medical prescription within medical institutions.

4) Cell production is derived from a donor for many patients within medical institutions.

1) Medical practices on cell therapy medicinal products.

"Medical profession" means any profession that performs to humans' activities of examination, diagnosis, treatment, disease prevention, midwifery, visual correction by contact lens insertion, acupuncture for therapeutic or anesthetic purpose, and shall include surgical act, radiation use, injection of medicine or any substance, insertion of any object into the body for birth control, beautification, and fitness. Medical practice is performed by a medical practitioner for examination, diagnosis, treatment, disease prevention. *(The Medical Profession Act B.E. 2525 (1982)* In the terms of medical practices, The Thai Medical Council is a role to regulate and control of medical profession such as medical profession on organ transplantation and medical practice on stem cell transplantation in The Medical Council Regulations on Medical Ethics Preservation, B. E. 2549 (2006) . However, clinical researchers are allowed for participants and IEC/IRB before conducting.

From an interview with key informants, two groups of the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Medical Council and the Thai Medical Council gave more information. In 2009, The Thai Medical Council promulgated the regulations on stem cell transplants for therapeutic purposes as well as specific members of committees on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Medical Council of Thailand. Since stem cells are overclaimed during inadequate safety and efficacy data, they are compelled to pay exorbitant fees for access. Thus, specific members of committees are responsible for approving protocols and certifying standard treatments with stem cells. Nevertheless, the clinical research must be approved by the Human Research Ethics Committees of the owner institution before submitting a protocol to the medical council.

"… Prior to 2009, stem cells were misunderstood, and their treatments are on the verge of commercialization. Hematopoietic stem cells have been approved for use (HSCs). As a result, the use of stem cells for other disorders is still considered clinical research, and those therapies will not be charged…." *(P11, the Committee*

on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council), interview, 17 March 2021)

At present, The Thai Medical Council have established standard treatment with hematopoietic stem cell transplantation for hematology diseases while the limbal stem cell for cornea limbal epithelial transplantation has been being considered by the committees on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells for approved standard treatment. Beyond that, due to a lack of safety and efficacy data, the scope of the two illnesses is currently a clinical study that have been approved by The Thai Medical Council before conducting.

2) Cell production is derived from a patient's cells based on a medical prescription within medical institutions.

In this case of cell therapies, Cells are modified or cultured cells in the external body after completely conducted come back into the same patient that those activities are defined within the scope of drug manufacturing that refer from the Drug Act B. E. 2510 (1967) . Thai FDA is a responsible body for ensuring that drug manufacturing is carried out in accordance with national and international law.

Drug means any substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or other animals. *(Drug Act B.E. 2510 (1967))*

Drug manufacturing means to make, mix, prepare or process, transform and divide to be packaged whether there is a label or not. *(Drug Act B.E. 2510 (1967))*

Certainly, Cells are classified as drugs. Consequently, any activities of manufacturing, selling and import are regulated by the Thai FDA that those activities must be allowed by the Thai FDA before conducting regarding section 12 under the Drug Act B. E. 2510 (1967) . However, Manufactured drug by the ministry, the government agency and the government departments responsible for disease prevention and disease therapy, the Thai Red Cross Society, the Government Pharmaceutical Organization are exception from section 13 (1) and manufactured within responsibility from medical professional ***" … production of medicines according to the prescription of a medical professional for an individual patient or according to the prescription of a veterinary practitioner for an individual animal***

…” *(Drug Act B.E. 2510 (1967))* are excluded from section 13 (2) the Drug Act B.E. 2510 (1967). Consequently, they are not compliant with the Drug Act B.E. 2510 (1967). From an interview with key informants, a group of researchers and academic medical centers have opinions on section 13 (2) that aim to be flexible and accessible for unapproved medicine or unavailable therapy previously in Thailand. It is so-called compassionate use. Although, this treatment approach may be unsafe and ineffective because it has not been approved by an accredited body.

Key informants, a group of researchers, and academic medical center have perspectives for mandatory principles of care for patients as follows

1. based on scientific evidence and code of conduct
2. positive of benefits than risk

So, the excluded from section 13 (2) the Drug Act B.E. 2510 (1967) intends to use and produce cell therapy medicinal products within medical institutions such as culture plans/laboratory and administration at the same place that cannot distribute to other places. *(P14, the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council & P91, a group of researchers, and academic medical center, interview, 27 April 2021) , (P92, a group of researchers, and academic medical center, interview, 30 April 2021)*

“… Medical professions have been permitted to perform medical practices on individual patient according to the Medical Profession Act and they should also take into account the appropriate code of conduct … ” *(P14, the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council & P91, a group of researchers, and academic medical center, interview, 27 April 2021)*

“… For example, Siriraj Hospital has cell culture room and transplant building are in separated buildings that is co-instituted an institution, but they cannot not be transferred elsewhere… ” *(P14, the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the*

Thai Medical Council & P91, a group of researchers, and academic medical center, interview, 27 April 2021)

3) Cell production is derived from a donor for a specific patient based on a medical prescription within medical institutions.

Cell-based therapies can be used cells from related blood or donor with human leukocyte antigen (HLA) of compatibility. Those cells are modified before performing. Those processes are classified as drug manufacturing according to the definition of the Drug Act B.E. 2510 (1967).

However, these cases of 2 and 3 may be overlapped jurisdictions between cell therapy medicinal products items and cells created for an individual patient by an exclusive medical practitioner under Article 13 (2) of the Drug Act B.E. 2510 (1967). Recently, patients' cells products have been approved by the EMA, the US FDA, and other countries. Those products are labeled a trade names KYMRIAH® (tisagenlecleucel), YESCARTA® (axicabtagene ciloleucel), SPHEROX® (spheroids of human autologous matrix-associated chondrocytes), and MACI® (autologous cultured chondrocytes on porcine collagen membrane). As a result, medicinal products have been registered that they are not a lot of quality but more specific to patients. This circumstance might be a gray area between medical products and manufacture of prescription by medical practitioners who prescribes for a specific patient under Article 13 (2) of the Drug Act B.E. 2510 (1967).

4) Cell production is derived from a donor for many patients within medical institutions.

In Thailand, Cell production has been not derived from a donor for many patients within medical institutions. Nevertheless, cell-based therapies as allogeneic products or free distribution must be approved and under the Drug Act B.E. 2510 (1967). *(P96, a group of researchers, and academic medical center, interview, 24 June 2021)*

From an interview with key informants, a group of researchers, and academic medical center, shared their opinions in favor of the cell-based therapies are high-risk products, they should not be exempt from section 13(2) of the Drug Act B.E. 2510

(1967) . These products are regulated rather than being sold without conditions or based on the decisions of a single physician.

" … ATMP should not exempt from section 13(2) because of high-risk products…" *(P96, a group of researchers, and academic medical center, interview, 24 June 2021)*

" … Cell manufacturing is not simple as cream preparation, cell manufacturing is a complex process that must be provided a quality control … " *(P97, a group of researchers, and academic medical center, interview, 26 July 2021)*

According to key informants in the same group, section 13 (2) of the Drug Act B.E. 2510 (1967) has a broad scope. *(P94, P95, a group of researchers, and academic medical center, interview, 18 June 2021)* Therefore, regulation and follow-up are needed for cell-based therapies at medical institutions. *(P71, the Nation blood center of The Thai Red Cross Society, interview, 14 June 2021)* As mentioned previously, all of the key informants, a group of researchers, and academic medical centers agree with cell-based therapies as a novel treatment of various diseases and new alternatives to treating undiscovered medical needs. However, oversight of use within medical institutions will be needed. If oversights are inadequate, problems related to misuse and safety may arise because there is a legal procedure that can be carried out under section 13 (2) of the Drug Act B.E. 2510 (1967).

At the same time, some key informants a group of researchers and academic medical centers, cell-based therapies are not regulated under drug registration due to small production and specific patients. If it must approval, it will high prices. Drug registration will be made a barrier to affordability and restrictions to patients. Cell-based therapies as personalized medicine should not be regulated on drug registration or exemption of sector 13 (2). *(P96, a group of researchers, and academic medical center, interview, 24 June 2021)*

" … ATMP must be regulated. However, oversight is not be authorized products only … " *(P96, a group of researchers, and academic medical center, interview, 24 June 2021)*

"…There should be regulation between Article 13 (2) and drug registration of the Drug Act B.E. 2510 …" *(P97, a group of researchers, and academic medical center, interview, 26 July 2021)*

2. Formulation the guideline of cell therapy medicinal products

After literature reviews and interviews with key informants were conducted, the researchers combined the data from two sources and performed triangulation. Subsequently, the data were classified in accordance to regulation, oversight, and control of cell therapy medicinal products for uses in medical institutions or issues with implications on quality, safety and efficiency of the products. The guideline consists of further details on the criteria for the classification of cell therapy medicinal products used in medical institutions, including issues related to recommendations of the regulation of ATMPs. Examples are lists of diseases for cured by ATMPs, qualification of medical practitioners, qualifications of laboratories or manufacturing sites, medical procedures, qualification of medical institutions, the kind of cell therapy medicinal products which are used in medical institutions, the measurement of post-treatment follow-up, and the issues related to ATMPs. Finally, the guideline for medical institutions' regulations regarding the use of cell therapy medicinal products was developed. It is being presented in Table 5.

3. Recommendations for regulations on service provision on cell therapy medicinal products in medical institutions: Thailand

Thailand has not allowed the service of cell therapy medicinal products in medical Institutions. Exceptionally, hematopoietic stem cell transplants were approved by the Thai Medical Council and they are excluded. *(P41, the legal affair division-HSS, interview, 1 April 2021)* The researcher collected data from documentary reviews and interviews with key informants for content analysis. Data

were categorized and classified to recommendations for the regulation of medical institutions in relation to the use of cell therapy medicinal products in Thailand. The researcher formulated the guideline from documentary review and interviews with key informants. The guideline was sent to all key informants for reconsideration, verification and commendation. For all of 17 participants, the guideline responds to 16 participants. Uncompleted response 3 participants. In the case that incomplete the guideline is submitted, the researcher contacted key informants who submit them and ask key informants to kindly complete the guideline. Some informants agree to complete the sections of the guideline which is of relevance to their expertise. In all cases, all answered questions are taken into account in the analysis pursued in this paper. The result of opinions on the regulation of medical institutions in relation to the use of cell therapy medicinal products are presented in Table 5.

Table 5 The opinions on the regulation of medical institutions in relation to the use of cell therapy medicinal products

The requirements of medical institutions in relation to the use of cell therapy medicinal products	**opinions (n=16)**		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
1. Background			
1.1 Cell therapy medicinal products are defined as 1. Minimally manipulated 2. Intended for homologous use only 3. Cells do not alter the relevant biological characteristics of cells 4. Manufactured and used within the same medical institutions The products that meet all of the requirements are classified as low-risk products, which are controlled by the Thai Medical Council and Sanatorium Act. On the other hand, the products that do not meet at least one requirement are classified as high-risk products.	14	1	-
1.2 Regarding section 13 (2) under the Drug Act, B.E. 2510, ATMPs (high-risk cell therapy medicinal products) should not grant permission. These products must be controlled. Each medical practitioner is not the sole decision-maker.	12	1	2
1.3 ATMPs (high-risk cell therapy medicinal products) in medical institutions can be classified into four groups 1. Clinical research use 2. Compassionate use 3. Manufactured and used within medical institutions 4. The approved products by Food and Drug Administration (FDA)	13	2	-

Table 5 (continue)

The requirements of medical institutions in relation to the use of cell therapy medicinal products	**opinions (n=16)**		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
1. Background			
1.4 Clinical research of ATMPs (high-risk cell therapy medicinal products) must be approved by the institutional ethical committee only. A review and approval from the Thai Medical Council are not needed.	10	1	4
1.5 The compassionate use of ATMPs (high-risk cell therapy medicinal products) should be reviewed by the institutional ethical committee before they are used in patients.	12	2	1
2. Recommendations for the regulation of ATMPs (high-risk cell therapy medicinal products) in medical institutions			
2.1 Lists of diseases for ATMPs (high-risk cell therapy medicinal products) used in medical institutions			
2.1.1 The Thai Medical Council and the relevant Royal College announce the lists of diseases or guidelines for cell treatment. **or** 2.1.2 At least phase II clinical trials are conducted by the researchers to demonstrate safety and efficacy profiles. After that, the data are summited to the Thai Medical Council or the relevant Royal College to review and approve for the treatment.	7	7	-
2.1.3 Conditions for ATMPs (high-risk cell therapy medicinal products) uses in medical institutions should be established, for example, the unregistered products, lack of sufficient data supporting safety and efficacy, or contraindicated in patients.	11	1	3

Table 5 (continue)

The requirements of medical institutions in relation to the use of cell therapy medicinal products	opinions (n=16)		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
2.2 Qualifications of medical practitioners			
2.2.1 The medical director is responsible for ATMPs (high-risk cell therapy medicinal products) uses in medical institutions.	14	-	-
2.2.2 The Thai Medical Council and the Royal College establish qualifications for medical practitioners, which are suitable for treatment.	14	1	-
2.2.3 The medical practitioners who are experts in the disease area have been certified by the Thai Medical Council or the approved organizations.	13	1	1
2.2.4 The medical practitioners pass the training courses approved by the Thai Medical Council and the Royal College.	16	-	-
2.2.5 There are registration systems for medical practitioners who use ATMPs (high-risk cell therapy medicinal products) for treatment.	15	-	1
2.3 Other qualifications			
2.3.1 A qualified person, who is assigned to produce cells from medical practitioners and nurses, must pass the training courses and must be certified.	13	2	-

Table 5 (continue)

The requirements of medical institutions in relation to the use of cell therapy medicinal products	opinions (n=16)		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
2.4 Qualifications of laboratories or manufacturing sites			
2.4.1 The medical institutions must be registered as a manufacturing site according to the Drug Act, B.E.2510.	9	7	-
2.4.2 The manufacturing site meets the requirements of the Good Manufacturing Practice (GMP).	10	5	-
2.4.3 The manufacturing protocols of the manufacturing site comply with Good Manufacturing Practice (GMP)	13	2	-
2.4.4 Standards of the cell-therapy laboratory, released by the department of medical sciences that are used as the reference or guideline and applied for the medical institutions in Thailand.	10	5	-
2.4.5 The operation is in accordance with the current Good Tissue Practices (cGTP).	13	2	-
2.5 Medical procedure			
2.5.1 The Thai Medical Council and the Royal College approve the safety and efficacy of medical procedures for ATMPs (cell therapy medicinal products).	13	2	-
2.5.2 Members of the medical institutions' committee, including internal or external experts, review and approve the uses of ATMP (cell therapy medicinal products) such as conditional approval that takes place in medical institutions.	8	7	-

Table 5 (continue)

The requirements of medical institutions in relation to the use of cell therapy medicinal products	opinions (n=16)		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
2.6 Qualifications of medical institutions			
2.6.1 ATMPs (high-risk cell therapy medicinal products) should be used in the medical institutions that are registered by the Department of Health Service Support, the Ministry of Public Health.	14	1	-
2.6.2 During the initial phase, ATMPs (high-risk cell therapy medicinal products) should be used in hospitals only.	12	1	2
2.6.3 The medical institutions must be accredited and the license must be renewed annually.	15	-	-
2.7 The ATMPs: a type of cell therapy medicinal products (High risk)			
2.7.1 ATMPs (high-risk cell therapy medicinal products) can be classified into two groups. 1. The approved cell therapy medicinal products by FDA are distributed to medical institutions. 2. The unproven ATMPs (high-risk cell therapy medicinal products) must be used in the medical institutions where they are manufactured.	13	2	-
2.7.2 The ATMPs type of cell therapy medicinal products (high risk) are unproven by the FDA. These products should be accepted for quality and process control. The members of the committee in medical institutions include internal or external experts who consider for approval. Such conditional approval must conduct within medical institutions.	10	5	-

Table 5 (continue)

The requirements of medical institutions in relation to the use of cell therapy medicinal products	opinions (n=16)		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
2.8 Post-treatment follow-up			
2.8.1 There should be a post-treatment follow-up for monitoring the safety and efficacy of ATMPs (high-risk cell therapy medicinal products). Especially, intensive follow-up is required during the first two years of the treatment.	13	3	-
2.8.2 Adverse event report, medical report, production report, and the number of patients who are treated with ATMPs (high-risk cell therapy medicinal products) should be submitted to the Ministry of Public Health to collect the data directly to the central database.	11	4	-
2.8.3 The government officers are allowed to reach medical institutions immediately in case there are emergent events that affect the patient's safety or to suspend the cell therapy administration.	14	-	-
2.8.4 There should be random inspection or complaint reporting channels.	15	-	-
2.8.5 There should be organizations that are responsible for the consideration of the safety and efficacy of ATMPs (cell therapy medicinal products) in order to evaluate the cell therapy treatment. If the medical institutions are not able to provide effective service, they have to discontinue the service.	14	1	-

Table 5 (continue)

The requirements of medical institutions in relation to the use of cell therapy medicinal products	**opinions (n=16)**		
	Agree (n)	**Partially agree (n)**	**Disagree (n)**
2.9 Miscellaneous			
2.9.1 Advertising of ATMPs (high-risk cell therapy medicinal products) not directly to consumers is prohibited.	13	-	2
2.9.2 ATMPs (cell therapy medicinal products) that are manufactured in the medical institutions should be canceled if there are registered products (import or manufacture) by FDA are available because they have clear evidence supporting their benefits over risks.	5	2	8
2.9.3 ATMPs (cell therapy medicinal products) should be considered in the reimbursement system because it is high efficacy but expensive treatment.	12	2	-

From Table 5, key informants (14 out of 16) shared their opinions in favor of the cell therapy product risk rating within medical institutions based on a risk-based approach. High-risk cell therapy medicinal products referred to the EU and the US FDA as follows 1. minimally manipulated 2. intended for homologous use only 3. cells do not alter the relevant biological characteristics of cells and 4. manufactured and used within the same medical institutions. The products that meet all of the requirements are classified as low-risk products. On the other hand, the products that do not meet at least one requirement are classified as high-risk products that those products have to establish specific requirements for regulation at medical institutions. However, 2 out of 16 informants worked in the legal affair division of HSS. They disagreed and said, there are no additional requirements for cell-based therapy within medical institutions because medical practitioners are responsible for their own practices. Key informants (13 out of 16) agreed that ATMPs high-risk cell therapy medicinal products in medical institutions can be classified into four groups which in each case should be controlled difference. The result of the research is emphasized specific regulation on ATMPs high-risk relation to the use of cell therapy medicinal products in medical institutions. These are requirements as follows:

1. Lists of diseases for ATMPs high-risk cell therapy medicinal products used in medical institutions

Key informants (11 out of 16) agreed that the use of ATMPs high-risk cell therapy medicinal products in medical institutions should be established condition. For example, unregistered products, lack sufficient data to establish their safety and efficacy, or are contraindicated in patients. On the other hand, 3 out of 16 informants were researchers, and some worked in academic medical center. They disagreed and believed that limits on the use of certain therapeutic products should not be imposed since they obstruct access to medical care. Furthermore, the high prices of registered products may make reimbursement impossible. Additionally, key informants (7 out of 16) worked the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and the Board of Directors of the Thai Medical Council, and a group of researchers, in academic medical center. Those consisted of 2 and 5 informants, respectively. Their opinion partially agreed and proposed that lists of diseases for cell therapies must be

approved by the Thai Medical Council only that is the authorized body for approval. If therapies have not been approved, they are still clinical studies. The Thai Medical Council must take into account scientific evidence to demonstrate safety and efficacy of the medical treatments, and may, further, request scientific opinions from the relevant Royal College. However, the final consideration depends on judgment of the Thai Medical Council.

2. Qualifications of medical practitioners

Key informants more than 13 out of 16 agreed on all qualifications of medical practitioners. For examples, the medical director is responsible for ATMPs high-risk cell therapy medicinal products uses in medical institutions, the Thai Medical Council and the relevant Royal College establish qualifications for medical practitioners. Moreover, the medical practitioners must be expertise in the disease area of patients, pass the training courses approved by the Thai Medical Council and the relevant Royal College, and be registered medical practitioners. One key informant had roles and responsibilities related to the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council, and the Board of Directors of the Thai Medical Council provided an opinion to renew the medical registration to up-to-date information. Otherwise, one of key informant, who worked as researchers, in academic medical center, partially agreed and commented, in the case of ATMPs: cell therapy medicinal products, those products have been authorized by the FDA that have not to require. Because the application must comply with the conditions of drug registration such as indications, and qualifications of physicians. In addition, one of key informant worked in the Bureau of Laboratory Quality Standards of DMSc disagreed and argued that the medical practitioners must be expertise in the cell-based therapies that have been certified or approved by the Thai Medical Council. It should be performed like other drugs.

At the same time, another person involved with ATMPs high-risk cell therapy medicinal products at medical institutions who is assigned to produce cells from a medical practitioner as medical technologists or scientists, nurses who care for patients, and pharmacists who are involved with manufacturing facilities certified

under GMP standards to ensure product quality. They must have the necessary training and certifications. However, 2 out of 16 informants were researchers, and some worked in academic medical center partially agreed and addressed that people involved with ATMPs who performs duties on stem cells transplantation. They also must be obtained training and certifications.

3. Qualifications of manufacturing sites or laboratories for cell therapies

Key informants (13 out of 16) believed that GTP should be applied for manufacturing sites and clinical sites for cell therapies. Also, one key informant involved in the field of regulation of post-marketing in the Thai FDA recommended. That the quality of systems should be taken into account for cell-based production. In the case of manufacturing sites, it can be classified into two approaches as 1. ATMPs high-risk cell therapy medicinal products in medical institutions must be registered a manufacturing site according to the Drug Act B.E.2510 (1967) that are accepted by key informants (9 out of 16). Those opinions were being recognized by all of key informants consisting of a group of researchers, who work in academic medical center, one key informant from pre-marketing Thai FDA, the Nation blood center of the Thai Red Cross Society, and, one key informant from the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and the Board of Directors of the Thai Medical Council.And, then, the remaining key informants, 7 out of 16 key informants, accepted that the Standards of the cell-therapy laboratory released by DMSc can be used at medical institutions during an early stage. In the latter case, HSS should consider and endorse the standards of the cell-therapy laboratory. Because health services are carried out within medical institutions which are regulated by Sanatorium Act, B.E.2541 (1998). Furthermore, a key informant, who engaged in the field of audit or certification of public health laboratories of DMSc pointed out that to achieve cell therapy in Thailand, standards for cell manufacturing sites and clinical facilities should be established. In the event of standard for manufacturing sites within medical institutions, it can be categorized into three approaches as 1. key informants (13 out of 16) consisted of those who worked the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical

Council and the Board of Directors of the Thai Medical Council, Thai FDA, the legal affair division of HSS, the Nation blood center of The Thai Red Cross Society and all of the members of a group of researchers, and academic medical center. They accepted the manufacturing protocols of manufacturing site are compliance with GMP. Those are composed of 2, 2, 2 ,1 and 6 informants, respectively. 2. key informants (10 out of 16) consisted of the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and the Board of Directors of the Thai Medical Council, Thai FDA, the legal affair division of HSS, the Nation blood center of the Thai Red Cross Society and some key informants in a group of researchers, and academic medical center. Those are composed of 2, 2, 2, 1, and 3 informants, respectively. Their opinions acknowledged the manufacturing site meet the requirements of the GMP. In particular, free distribution into other places. One key informant, who worked in the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council, had an opinion that GMP certification or GMP compliance is to ensure the quality of products. On the contrary, it is difficult to be implemented in medical institutions. And 3. key informants (10 out of 16) consisted of the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and the Board of Directors of the Thai Medical Council, the legal affair division of HSS, the Nation blood center of The Thai Red Cross Society, the Bureau of Laboratory Quality Standards of DMSc and some key informants are members of a group of researchers, worked in academic medical center. Those are composed of 2,2,1,1 and 4 informants, respectively. They agreed an initial phase, standards of the cell-therapy laboratory had been reviewed and established by DMSc and relevant government agencies can be applied at medical institutions. A key informant who worked in the area of pre-marketing for Thai FDA mentioned, standards of the cell-therapy laboratory should comply with GMP. Also, two key informants of group of researchers, and academic medical center gave more information that standards of the cell-therapy laboratory is suitable for minimal manipulation cell-based therapies. Additionally, some key informants who were researchers, and worked in academic medical center addressed about accredited body for cell-therapy laboratory. DMSc serves as Thailand’s national

accrediting body, supporting and creating quality assurance systems and providing laboratory accreditation services to all government and private laboratories in the area of medicine. Subsequently, it gathers knowledge and experts for assessment and grant laboratory accreditation in both public and private.

4. Medical practice

Key informants (13 out of 16) admitted that medical practice is approved by the Thai Medical Council or the relevant Royal College before conducting. However, 2 out of 16 key informants who had roles and responsibilities related to the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and the Board of Directors of the Thai Medical Council, and one key informant in a group of researchers, and academic medical center. Their opinions partially agreed and introduced that medical practice is approved by the Thai Medical Council only. Members of the medical institutions' committee, including internal or external experts, review and approve the uses of ATMPs: cell therapy medicinal products such as Conditional approval that takes place in medical institutions if medical practice is not accepted by the Thai Medical Council. ATMPs high-risk cell therapy medicinal products within a healthcare facility should be approved by the Thai Medical Council, Thai FDA, and HSS before conducting, according to key informants (8 out of 16) that consisted of two key informants of the legal affair division of HSS, one key informants of Thai FDA, one key informants of the Nation blood center of the Thai Red Cross Society, one key informants of the Bureau of Laboratory Quality Standards of DMSc, and three key informants in a group of researchers, worked in academic medical center. The primary responsible entities in the fields of medical professions, cell therapy medicinal products, and medical institutions are three organizations. Moreover, key informants, a group of researchers, and academic medical center, more gave information, currently, cell-based therapies are used in medical institutions that are unproven by the Thai Medical Council. Those treatments were carried out in accordance with Section 13 (2) of the Drug Act B.E. 2510 (1967) and with the approval of committees within a medical facility because they were carried out solely within the confines of the medical facility.

5. Qualifications of medical institutions

Most key informants (15 out of 16) have reached the conclusion that medical institutions must be accredited and renewed annually. Similarly, Key informants (14 out of 16) agreed medical institutions where used ATMPs high-risk cell therapy medicinal products are registered and added service on ATMPs high-risk cell therapy medicinal products by HSS. One of key informant in a group of researchers, and academic medical center partially agreed and suggested, should be registered laboratories. Key informants (12 out of 16) agreed about during the initial phase, these products should be used in hospitals only. Although, one key informant who worked in the field of regulation of pre-marketing the Thai FDA recommended that medical institutions must be conducted in teaching hospitals or academic medical centers only. Because some treatments are required extra equipment, personnel with excellent skills such as bone marrow transplantation, intensive care unit as CAR T cells treatment and an expert clinician in the field of hematology and oncology. In addition, the risks of the products should be considered related to the level of a medical setting. Alternatively, 2 out of 16 informants who worked in the legal affair division of HSS disagreed and provided information, currently, healthcare facilities are admitted for outpatients only those medical practitioners have been approved about diploma or residency training by Thai Medical Council, they will be using ATMPs high-risk cell therapy medicinal products for treatment.

6. The ATMPs: a type of cell therapy medicinal product (High risk)

Key informants (13 out of 16) accepted that ATMPs: a type of cell therapy medicinal product (High risk) can be classified into two groups. 1. The approved cell therapy medicinal products by FDA are distributed to any medical institutions. And 2. The unproven ATMPs (high-risk cell therapy medicinal products) must be used in the medical institutions where they are manufactured. However, one key informant of The Bureau of Laboratory Quality Standards of DMSc partially agreed and mentioned that one should be establish standards of the cell-therapy laboratory to produce cell-based for prescription within medical facilities. Also, one key informant with the roles and responsibilities related to the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical

Council and the Board of Directors of the Thai Medical Council partially agreed and mentioned that cell therapy medicinal products were approved by Thai FDA only. In the case of unproven ATMPs (high-risk cell therapy medicinal products), three key informants in a group of researchers, and academic medical center and a key informant of the Nation blood center of The Thai Red Cross Society partially agreed and offered information. It is excluded from section 13 (2) the Drug Act B.E. 2510 (1967) that is manufactured within responsibility by a medical professional. For this reason, the Thai FDA should be released new legislation to close the gap. Furthermore, drug manufacturing has been used under Section 13 (2) that is considered and approved by the members of committees within a medical facility. Because it is conducted within own medical facility as well as medicinal products are controlled by medical practitioners that they are unproved by external agencies. In the future, these products should be accepted for quality and process control. Thai FDA may involve with certified manufacturing facilities and quality of products in medical institutions because of expertise in an area of this field.

7. Post-treatment follow-up

Key informants (15 out of 16) supported that there should be channels for random inspections and complaint reporting. Also, government officers can conduct immediate inspections in medical institutions if any emergent events endanger the patient's safety or if cell therapy administration is halted. Similarly, key informants (14 out of 16) accepted that evaluation of safety and efficacy should be operated to renew or punish medical institutions. Moreover, a significant informant proposed by a key informant who worked in the area of post-marketing Thai FDA that the product's quality be monitored as well. Key informants (13 out of 16) admitted that ATMPs high-risk cell therapy medicinal products should be monitored for safety and efficacy. Intensive follow-up is especially important during the first two years of treatment. Following that, the period of follow-up can be extended as needed. Nevertheless, key informants suggested that should be imposed establishment bodies to monitor. In addition, Thai FDA should take into account for monitoring. Furthermore, key informants (11 out of 16) agreed that adverse event reports, medical reports, production reports, and the number of patients treated with ATMPs high-risk cell

therapy medicinal products should be submitted to the Ministry of Public Health. Meanwhile, key informants (4 out of 16) consisted of one key informant of the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and the Board of Directors of the Thai Medical Council, one key informant of the Nation blood center of The Thai Red Cross Society, and two key informants in a group of researchers, and academic medical center who partially agreed and mentioned that all reports should be submitted to IRB/IEC own institution or Thai FDA (if necessary). Besides, two key informants commented, all report should be summited to HSS, the Thai Medical Council, the Thai FDA for data to be collected directly into the central database.

8. Miscellaneous

Key informants (13 out of 16) acknowledged that advertising of ATMPs (high-risk cell therapy medicinal products) is prohibited. On the contrary, two key informants were consisted of the one who worked in the Bureau of Laboratory Quality Standards of DMSc and in a group of researchers, and academic medical center. They had disagreed and claimed, ATMPs high-risk cell therapy medicinal products are classified as a drug that those products can be applied advertising regulation under the Drug Act B. E. 2510 (1967) . Also, people have enough knowledge to make decisions for cell-based therapy. Regulatory agencies must forbid misinformation and overclaim for their therapies. Key informants (12 out of 16) supported that ATMPs: cell therapy medicinal products should be considered for reimbursement to improve patient access. Alternatively, 2 out of 16 key informants worked in the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council and in a group of researchers, and academic medical center partially agreed that reimbursement should be considered given adequate safety and efficacy as certified by the Thai Medical Council or responsibility bodies. Nonetheless, financial condition of the country should also be taken into account. According to 8 out of 16 key informants, they made up of the Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council, the legal affair division of HSS, the Nation blood center of the Thai Red

Cross Society, the Bureau of Laboratory Quality Standards of DMSc, and some key informants in a group of researchers, and academic medical center. Those consisted of 1,2,1,1, and 3 informants, respectively. Their opinions consist of disagreement and argument about terminating cell-based therapies production when cell therapy medicinal products are authorized. These products are manufactured in medical institutions should not be canceled if there are registered products (imported or manufactured) by the FDA due to hinder innovation in domestic. Likewise, these products have a high price impact on inaccessible therapy. Cell-based therapy within medical institutions, on the other hand, can be revoked if unsafe and inefficient data is obtained.

The objective 2 Guidelines for cell therapy medicinal product regulations in terms of drug registration that may be applicable in Thailand.

1. Interviews with stakeholders

1.1 The introduction of application for ATMPs: cell therapy medicinal products in Thailand.

1.1.1 The biologic manufacturing companies in Thailand

Based on interviews with all key informants, a group of biologic manufacturing companies was selected. They were aware of ATMPs, which are cell therapy medicinal products. However, they only skim the surface of product information without going into depth. These are new therapies that include cells, tissue, genes, or vectors. Similarly, cell therapy medicinal products consist of cells, stem cells and progenitor cells. They have received marketing authorization in other countries. Only one company is interested in manufacturing with ATMPs. It has been being developed for industrial pharmaceuticals. In 2014, the initial phase began with clinical research for treatment at an academic medical center which was supported by government and public sectors (donations). After that, it was supported by funding from outside agencies as commercialization, there is an expansion of clinical research for specific patients within medical institutions to distribution into the market in terms of medicinal products. CAR T cells are provided the first product of their company that they combine between cells and genes. Manufacturers, on the other hand, are not interested in the area of ATMPs cell therapy medicinal products for a variety of reasons, including the company's lack of target products, high investment, limited products as autologous product, unclear in the business model, and uncertainty surrounding the potential benefits and risks of these technologies.

1.1.2 The biological drugs importers

Based on key informant interviews, a group of biologic drug importers as all of 7 participants whose parent companies are international pharmaceutical companies were identified. These firms imported chemical and biological medicines, but not ATMPs: cell therapy medicinal products. Four of the seven companies have already manufactured ATMPs and released their products to the market. Otherwise, one company knew that the parent company has ATMPs launched to market. This

company is also interested in bringing ATMPs to approval in Thailand to get access to the innovative medicines that these products are to treat incurable disorders such as B-cell Acute Lymphoblastic Leukaemia (ALL), Diffuse Large B-cell Lymphoma (DLBCL) and spinal muscular atrophy. The company expects the government to support the payment system. At present (2021), the parent company does not grant Marketing Authorization Application (MAA) in Thailand that these reasons are presented as follows:

1. Manufacturing plants are scarce. ATMPs-type autologous product, in particular, have been designed differently than other drugs. Cells are collected at a clinical site after they have been delivered to the manufacturing site and returned there. The processes have taken approximately 21 days. The parent company may expand manufacturing facilities throughout the regions in the future.

2. Traceability system. ATMPs-type autologous product is manufactured as a single lot from the patient being treated. Thus, the chain of the identity of the patient samples is crucial to assure the right product is returned to the right patient. The cells of an autologous product are processed on-site at the clinical site into the manufacturing site and back to the clinical site again. As the result, the autologous product is complicated more than allogeneic products, for instance, the processes of manufacturing, distribution model including administration. While allogeneic products have been produced for immediate consumption that is called off the shelf products. *(P101, The biologic drugs importers, interview, 5 April 2021)*

The biologic manufacturers and biological drug importers were exposed as a result of interviews with all relevant sources. Currently, ATMPs: cell therapy medicinal products are not high on the agenda of the pharmaceutical industry in Thailand. Due to the unique nature of the product, particularly as an autologous product that has never been authorized in Thailand and the limited number of available products, it will require significant investment, including policy, regulation, and government promotion.

1.2 Guidelines to the regulations of ATMPs: cell therapy medicinal products in terms of drug registration, which are potentially suitable for Thailand.

All key informants of manufacturers and importers agree with the principle of new biological drugs are still be applied that they are similar to ATMPs: cell therapy medicinal products in many aspects such as origin from human as well as evaluation needs to quality, safety, and efficacy that key points for medicinal products. As for now (in 2021), the entrepreneurs have little attention to these products. Additionally, they will be more released to the market-specific regulatory requirements that have to be modified or added as like the EU or Japan. Nevertheless, the extreme difference between ATMPs: cell therapy medicinal products and biologic medicines is an amount of quantity manufacturing that autologous product is tailor-made as a single lot for the patient. The patient's cells are used to formulate for finished products. Since biologic medicines are manufactured in mass production for many patients.

"… medicinal products are approved by the Thai FDA, they will be used to everyone… " *(P31, The Institute of Biological Products-DMSc, interview, 23 March 2021)*

"…autologous product must be approved marketing authorization. unlike, it has been granted from the Thai FDA… " *(P31, The Institute of Biological Products-DMSc, interview, 23 March 2021)*

"… there is no lot or batch or mass production because its product for one person only… " *(P32, The Institute of Biological Products-DMSc, interview, 25 March 2021)*

"… it is made to order only … " *(P51, The manufacture of biologic drugs, interview, 19 April 2021)*

From all interviewees, the regulation of traditional medicinal products can be applied to ATMPs: cell therapy medicinal products in terms of drug registration that divided into three processes as follows.

1. Pre-marketing authorization process

Marketing authorization is not only chemical drugs, but also biological drugs intended to ensure quality, safety, and efficacy. Chemical drugs registration must be demonstrated as quality, safety, and efficacy documents only. However, biological drugs must be needed.

1.1 The documents demonstrating quality, safety, and efficacy data, which are organized regarding ASEAN COMMON TECHNICAL DOSSIER (ACTD) or ICH COMMON TECHNICAL DOSSIER (ICH CTD) forms and

1.2 Results of finished products' quality testing from Institute of Biological Products of the DMSc.

The importers are not worried about the preparation of quality, safety, and efficacy documents. Since documents comply with international standards and the parent company prepares documents that can use the same documents that have been approved for registration. Additionally, Biological drugs are required for finished products' quality testing from the Institute of Biological Products of the DMSc for confirmatory quality of finished products before authorization. However, the autologous product may be performed so infrequently due to the limited amount of quantity that Marketing Authorization Holder (MAH) provides documents to demonstrate a substitute for finished product quality testing. GMP certification is the key to ensuring the quality, consistency, and accuracy of the products. *(P32, The Institute of Biological Products-DMSc, interview, 25 March 2021)* Despite this, the allogeneic products have a large amount of material available for analysis. It is necessary to comply with the traditional regulations. *(P63, pre-marketing Thai FDA, interview, 17 June 2021)* From the Institute of Biological Products of DMSc point of view re-testing must consider based on the cost-effectiveness of the analytical method for new drug because the amount of use is a few in Thailand and sometimes the product is exempt from certification of lot release after approval. *(P31, The Institute*

of Biological Products-DMSc, interview, 23 March 2021), (P32, The Institute of Biological Products-DMSc, interview, 25 March 2021)

2. Marketing authorization application process

The biologic manufacturers and biological drug importers agreed that ATMPs cell therapy medicinal products should be flexible approval with natural characteristics because of limited patient number and personalized medicines.

"…In the clinical trial phase, if there are 20 patients into the trial, they will request registration…" *(P51, The manufacture of biologic drugs, interview, 19 April 2021)*

Additionally, Conditional approvals can be applied for approved these products. Conditional approvals based on less comprehensive data but with demonstrated positive benefit-risk balance at the MAA and an expectation of complete data in the near future. After, the applicants are provided comprehensive data on efficacy and safety to submit for full licensing. Similarly, Expedited pathways have been also expanded to major public health interests, life-threatening conditions, and unmet medical needs. *(P51, The manufacture of biologic drugs, interview, 19 April 2021)* , *(P101, The biologic drugs importers, interview, 5 April 2021)* Alternatively, *some key informants, a g*roup of biologic manufacturing companies more gave information. Marketing Authorization (MA) evaluation should be elaborated to prevent down-regulation that affects quality, efficacy, and safety after the MA. *(P55, The manufacture of biologic drugs, interview, 7 June 2021)* From an interview with key informants, a group Medicines Regulation Division of Thai FDA more gave information. ATMPs: cell phase should be monitored for both safety and efficacy because some side effects such as cancer cells or malignant cells, may emerge after the event. ATMPs: cell therapy medicinal products are generally used as a single treatment for long-term efficacy in humans.

New medicinal products have been authorized in Thailand that are required specific requirements as Risk-based approach Safety Monitoring Program: SMP. Risk-based approach SMP is the condition for early follow-up after free distribution

that is classified based on risks into four classes level 1 is the highest risk and 2, 3, and 4 lower risks respectively.

Risk-based approach SMP: level 1 means medicinal products provide less comprehensive data, but with demonstrated positive benefit-risk balance at the MAA but medicinal products are needed to use for a life-threatening condition, unmet medical needs, and the major public health interest. Thereby, they must be followed intensive monitoring such as active surveillance and registry patients. The period of follow-up is at least two years.

Risk-based approach SMP: level 2 means medicinal products are as new chemical entities, new indications, new combinations, and new biological drugs. The period of follow-up is two years.

Risk-based approach SMP: level 3 means medicinal products are as a new delivery system, new route of administration, new dosage form, new strength. The period of follow-up is one year.

SMP levels 1-3 must include intensified/stimulated reporting both before and after entering the market, for example, adding text to drug labeling and package leaflet, qualified person to contract with Thai FDA, watch list important identified and potential risks, inform side-effect to health care professional before 1 month drug distribution and after 2,4,6, after drug distribution sent a summary to Thai FDA by 8 mouths, report of manufacture, import, distribution and adverse events. Following that, the MAH or the manufacturer submits comprehensive data to the Thai FDA under a duration of conditions based on Risk-based approach:SMP for full approval

Risk-based approach SMP: level 4 means follow-up medicinal products are an exception from level 1-3 that have been used spontaneous reporting system for monitoring. Spontaneous reporting is a voluntary report by healthcare professionals and MAH to the National Regulatory Authority (NRA) that is called passive surveillance. ATMPs: cell therapy medicinal products can be applied concepts of new biological drugs. Currently, the Thai FDA is developing Conditional approval that Risk Management Plan (RMP) is required for Conditional approval. RMP has not been required for MAA. Excluding Biosimilar, Erythropoietin, and Botulinum toxin A are needed to summit. *(P63, pre-marketing Thai FDA interview, 17 June 2021)*

3. Post-marketing authorization process

All key informants from manufacturers and importers agree that the most important step for ATMPs: cell therapy medicinal products is the post-marketing process. In addition, all key informants from manufacturers, importers and regulators accepted that ATMPs: cell therapy medicinal products should be applied RMP or might be added specific requirements on ATMPs: cell therapy medicinal products due to difference from other drugs. *(P62, HPVC-Thai FDA, interview, 27 March 2021)* RMP is needed to be evaluated and reviewed by many establishments as the Medicines Regulation Division, Health Product Vigilance Center (HPVC) of Thai FDA, and clinicians who review clinical documents should collaborate for decision making on RMP. *(P61, HPVC-Thai FDA, interview, 28 April 2021)* In addition, RMP should be re-evaluated to keep the data up to date regarding the dynamic of safety data such as the updated Periodic Safety Update Report (PSUR) documents. *(P61, HPVC-Thai FDA, interview, 28 April 2021)*

Moreover, the autologous product is made to order, limited quantity and unavailable product in the market. Hence, the follow-up will be established for safety follow-up should be used as 1. patients register 2. manufacturing sites and 3. medical institutions. *(P51, The manufacture of biologic drugs, interview, 19 April 2021)* or added on inspection of MAH's Pharmacovigilance system for monitoring activity of ATMPs: cell therapy medicinal products. *(P105, The biologic drugs importers, interview, 19 June 2021)* The post-marketing process should link and deliver information between the public and private organizations including an established central database to collect safety and efficacy profiles as well as investigation when problems are caused by these products. Moreover, ATMPs: cell therapy medicinal products are new therapy that knowledge and experience are limited. follow-up monitoring is essential. Efficacy and safety follow-up can be applied the Adverse Events Following Immunization: AEFI on ATMPs: cell therapy medicinal products that it involves with Thai FDA, Department of Disease Control, DMSc, the entrepreneurs, and medical institutions. *(P63, pre-marketing Thai FDA, interview, 17 June 2021), (P64, post-marketing Thai FDA, interview, 25 June 2021)*

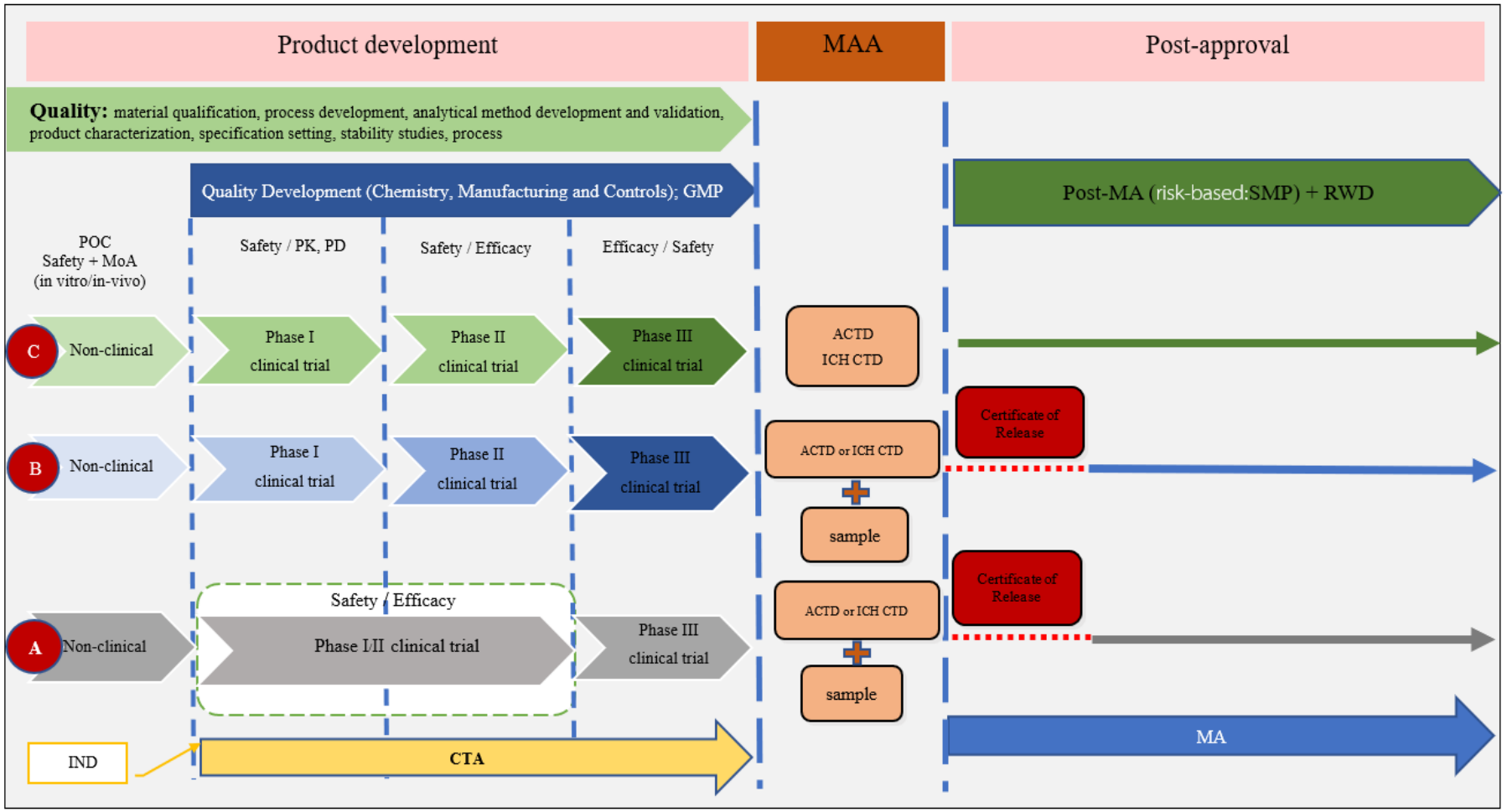
After MA, medicinal products are moved widely to the patients. Nevertheless, biologic drugs are required to have a certificate of lot release, according to a Ministry of Public Health announcement: lists of lot release control of biological products must be certified before selling or delivering to users. The following biological drug lists must have a certificate of lot release.

1. Vaccines including allergens used in treatment or disease prevention
2. Serum
3. Blood-derived or plasma-derived products
4. Diagnostic agents including allergens used in the diagnosis of diseases that are directly applied to the human body that is not medical devices according to medical devices law.

Because of their complexity and inherent variability, their biological products are released by the National Control Laboratory. As a result, it is critical to ensure the consistent quality of each lot before it is released to the market. Thailand's considerations for a certificate of the release include a review of the summary production protocol, transportation details and quality during transportation and independent testing (selected testing). *(P31, The Institute of Biological Products-DMSc, interview, 23 March 2021) (P32, The Institute of Biological Products-DMSc, interview, 25 March 2021)* On the other hand, Currently, ATMP: cell therapy medicinal products are not included in the list of lot release control of biological products due to new biological products after the announcement of this requirement.

Figure 9 synthesizes information from interviews of reviews of document regarding the processes of drug registration for chemical drugs, biological drugs, and ATMPs, i.e., cell therapy medicinal products (122). Research and development steps are important for the delivery of active substance for mechanism of action in body through *in vitro* and *in vivo*, leading to proofs of concepts of pharmacology, toxicology, and mitigation against adverse drug events. Moreover, manufacturing processes can be made compiled with GMP. After that, clinical trial on humans can be performed, but FDA would need to approve it first. Clinical trial phrase is divided into 3 sub-classes. Firstly, experiments were to be conducted in healthy volunteers to verify safety. Secondly, experiments were to be conducted in patients to confirm safety and efficacy. Thirdly, the experiments were to be scaled to more patients and a

thousand of patients may be enrolled for therapeutic confirmatory. However, in the case of cell therapy medicinal products, it will not be possible to conduct traditional pharmacokinetic (PK) study designs such as absorption, distribution, metabolism and excretion like traditional drugs. Nonetheless, the study should demonstrate the quality of biodistribution of biological substances, viability, persistence, trafficking and growth of cells. After clinical study is completed, information regarding quality, safety, and efficacy should be documented and submitted to the FDA for authorization. Evaluation of marketing authorization is not only important for chemical drugs, but also for biological drugs to ensure quality, safety, and efficacy. While chemical drugs registration only requires demonstration of quality safety and efficacy, biological drugs also need results from the quality testing of finished products from the Institute of Biological Products of the DMSc. After marketing is authorized, new medicinal products are required to be monitored according to risk-based approach SMP requirements. In addition, certification of lot release is required for some biological drugs before it can be sold to user.



Remark: C; chemical drugs B; biologic drugs A; ATMPs: cell therapy medicinal products MAA; Marketing Authorization Application GMP; Good Manufacturing Practice GTP; Good Tissue Practice RWD; Real-World Data CTA; Clinical Trial Authorization IND; Investigation New Drug MA; Marketing Authorization POC; Proof Of Concept MoA; Mechanism of Action

Figure 9 The processes of drug registration for chemical drugs, biological drugs, and ATMPs: cell therapy medicinal products in Thailand

2. Formulation the guideline of cell therapy medicinal products

After literature reviews and interviews with key informants were conducted, the researchers combined the data from two sources and performed triangulation. Subsequently, the data were classified in accordance to regulation, oversight, and control of cell therapy medicinal products for drug registration or issues with implications on quality, safety and efficiency of the products. The guideline consists of further details on the requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration as pre-marketing authorization process, marketing authorization process, and post- marketing authorization process. Finally, the guideline for medical institutions' regulations regarding the use of cell therapy medicinal products was developed. It is being presented in Table 6.

3. Recommendations for regulations on service provision on ATMPs: cell therapy medicinal products for drug registration: Thailand

At present, Thailand has not been authorized ATMPs: cell therapy medicinal products bring to the market. The researcher collected data from documentary review and interviews with key informants to content analysis. Data was categorized and classified to recommendations for ATMPs: cell therapy medicinal products in terms of drug registration. The researcher formulated the guideline based on a review of the documentary material and interviews with key informants. All key informants were asked to complete the guideline for consideration, verification and commendation and praise. The 19 participants are divided into two groups as the regulator group, which has six participants, and the sponsor group, which has thirteen participants. The questionnaire elicited responses from 19 people. 5 participants have uncompleted responses (3,2 participants each other group, respectively). In the case that incomplete the guideline is submitted, the researcher contacted key informants who submit them and ask key informants to kindly complete the guideline. Some informants agree to complete the sections of the guideline which is of relevance to their expertise. In all cases, all answered the guideline is taken into account in the analysis pursued in this paper. Table 6 summarizes the findings of opinions on the regulation for drug registration. In Table 6, All key informants have opinions as follows.

1. Pre-marketing authorization process

Most key informants (18 out of 19), who were five of regulators and thirteen of sponsors, shared their opinions in favor of the manufacturing process of ATMPs: cell therapy medicinal products that must be adhered to GMP and GTP standards before launching. In addition, five regulators and twelve sponsors were among the key informants (17 out of 19). They accepted the unidirectional idea that autologous product is novel medicinal products and specific patients. Moreover, autologous product was obtained from the patient's cells that may be divergent a conventional manufacturing process. As a result, autologous product differs greatly from other drugs that have been registered. Meanwhile, two key informants, who consisted of pre-marketing Thai FDA and the manufacturer of biologic drugs, proposed that allogeneic products are like as traditional biologic drugs such as mass of manufacture and general patients. Also, key informants (14 out of 19), who were five of regulators and nine of sponsors, agreed and provided information, these products are defined as new biologic drugs under the Drug Act B.E. 2510 (1967) and referred to definition by Thai FDA. However, one key informant of the manufacture of biologic drugs disagreed and mentioned, since these products have already been developed and approved for sale in other countries.

2. Marketing authorization application process

With reference to key informants (14 out of 19) commented, Urgent approval and Conditional approval can be implemented of ATMPs: cell therapy medicinal products. Likewise, some key informants of sponsors and regulators mentioned, the criteria should be clearly defined as a life-threatening condition, unmet medical needs, and urgent cases impact on public health under approved and reviewed by the committees. Moreover, abridge verification able to be applied for urgent approval to reduce the time for review documents. On the contrary, one key informants, who was post-marketing Thai FDA, disagreed and addressed, it is not necessary for Urgent approval on ATMPs: cell therapy medicinal products. In the case of Conditional approval, Thai FDA can establish a criteria or additional safety and efficacy requirements after post-marketing to confirm a positive benefit. Alternatively, key informants of sponsor as the biologic drugs importers (3 out of 19) partially agreed

and disagreed (1 out of 19) as well as suggested that data and information from reference countries or previous studies should also be shared and submitted to Thai FDA for Conditional approval. Key informants (12 out of 19), who worked four of regulators and eight of sponsors, reached agreement that Conditional approval may be required for RMP and PSUR. Furthermore, one key informant of HPVC Thai FDA partially agreed and proposed an important aspect that PSUR should be reported period time that determined by NRA for collecting new safety experience post-authorization. PSUR should not be reported only once at the end of a time condition when using a risk-based approach SMP. Key informants (12 out of 19), who were three of regulators and nine of sponsors, agreed about Expedited pathways on ATMPs: cell therapy medicinal products. Key informants (4 out of 19) consisted of regulator and sponsor. They partially agreed and offered to determine for life-threatening conditions and unmet medical needs and urgent cases impact on public health. Similarly, two key informants, who worked HPVC and pre-marketing Thai FDA, addressed those Expedited pathways should be granted specific researches or manufactures in Thailand only. Due to support to pioneers. Also, Expedite pathways should also take into account the availability of all relevant sectors, respectively.

According to most key informants (14 out of 19), They consisted of four of regulators and ten of sponsors who opinion should be available in registered medical institutions under the HSS. Alternatively, some key informants (2 out of 19) consisted of HPVC Thai FDA and the biologic drugs importers who disagreed and partially agreed, respectively and advised, ATMPs: cell therapy medicinal products should only be used in hospitals. Furthermore, key informants (13 out of 19) who were three of regulators and ten of sponsors, admitted that manufacturers or MAH are required to certificate at medical institutions and to train healthcare providers on product and drug administration. Autologous product or matched allogeneic product, in particular, are required to ensure safety. On the other hand, one key informants, who worked pre-marketing Thai FDA disagreed and mentioned that should be regulated by the government only.

Key informants (13 out of 19) who employed four of regulators and nine of sponsors, recognized that the evaluation of ATMPs: cell therapy medicinal products is

performed by using the general principles of biological drugs to ensure quality, safety, and efficacy. In addition, one key informants of the Institute of Biological Products DMSc recommended ATMPs of document profiles should be placed a greater emphasis on cell resource, procurement, and testing than traditional biologicals. Considerations of finished products' quality testing from the Institute of Biological Products of DMSc should be reached the following criteria as objective of the tests, laboratory capabilities, quantity of samples, cost, global standard operating procedures, and cost-effectiveness. Nevertheless, key informants two groups of regulators and sponsors (3 out of 19) partially agreed and one of key informant in a group of regulators disagree and commented that cost, the number of samples and cost-effectiveness do not relate to quality, safety, and efficacy of products that these conditions should not be included in consideration of testing analysis. On the other hand, one of key informant in a group of sponsors disagree and said that finished products' quality testing should be excluded from MAA due to restriction of samples, cost, short shelf-life, condition of storage, and laboratory capacity for re-testy.

Referring to 9 key informants, they consisted of three of regulators and six of sponsors. Marketing Authorization Application (MAA) of ATMPs: cell therapy medicinal products required for submission to Thai FDA include the documents demonstrating quality, safety, and efficacy data, and results of finished products' quality testing from the Institute of Biological Products of the DMSc were accepted. Simultaneously, key informants (7 out of 19), who were two of regulators and five of sponsors, partially agreed and proposed the documents demonstrate quality, safety, and efficacy data that are organized in accordance with ICH CTD, which has been granted to the majority of products in the EU and the USA. According to a key informant of pre-marketing Thai FDA, RMP has to submit at the MAA. All key informants have different opinions on finished products' quality testing before the MA. Key informants a group of regulators gave more information, the capacity of laboratories can be provided to analyze the test and allow government agencies other than the Institute of Biological Products of the DMSc because of decrees limitation of testing. Key informants a group of sponsors claimed that limited the quantity, price,

condition of storage, and laboratory capabilities impact on finished products' quality testing. As the result, the government agency should exempt this requirement.

As retention samples are required by sections 25 (6) and 27 (6) of the Drug Act B.E. 2510 (1967), Allogeneic products must be followed. On the contrary, some key informants of sponsor argued the manufacturing processes can be verified by GMP certified. Also, these products were restricted available of limitations, price, storage condition. Concurrently with Autologous product, 8 key informants, who are two of regulators and six of sponsors, admitted that these requirements should be an exception. Due to product limitations, price, storage condition. Meanwhile, one key informant of the biologic drugs importers debated those manufacturers will not send containers and labels to importers in the absence of medicines because they serve as control materials to prevent counterfeiting. However, three key informants a group of regulators provided information, indicating that the amount of material available for testing on these requirements is not limited. As such, they will be followed a conventional requirement. In the case of a limited amount of material, other appropriate measures such as storage time within the expiration date and limited sample retention, should be prepared.

DMSc performs a certificate of lot release procedure after the MA before selling or delivering biological drugs to users. This requirement is mandated by Ministry of Health Law B.E. 2555 (2012) lists of biological product lot release control. As of now, ATMPs: cell therapy medicinal products are not in the list of lot release control of biological products due to new products after the promulgation of this requirement. A group of sponsors (8 out of 19) agreed on exceptional exemption. Due to poor manufacturing volume, storage, and pricing. On the other hand, key informants consisted of three regulators and four sponsors (7 out of 19) disagreed with the exemption of certifications of lot release for cell therapy medicinal products. In addition, 3 out of 19 key informants, who were two of regulators and one of sponsors, partially agreed and proposed that Thai FDA and relevant agencies should consider depending on risk-based balance or added requirement that suitable feature on ATMPs: cell therapy medicinal products and should research worldwide practice

in depth, consult with the maker and adapt the conditions to suit the type of product. Specifically, autologous product is personalized products.

3. Post-marketing authorization process

Most key informants of five regulators and thirteen sponsors were among the key informants (18 out of 19) shared their opinions in favor of an established central database that is important to link and deliver information between the internal and external organizations. However, one key informant, who worked HPVC Thai FDA, warned about confidential information between government and private agencies. Similarly, most key informants (17 out of 19) consisted of those in six regulators and eleven sponsors who accepted that their products should be subjected to long-term monitoring for safety and efficacy data by RMP that it should be re-evaluated every 1-2 years. Alternatively, key informants (3 out of 19), who were one HPVC Thai FDA and two sponsors, partially agreed and HPVC Thai FDA commented, re-evaluation should be performed whenever new data is received that is intended to provide a new safety experience of a medicinal product at the post-authorization stage. On the other hand, one key informant of sponsor disagreed to re-evaluated of RMP due to burden of staff and MAH. According to key informants (17 out of 19), they were composed of five regulators and twelve sponsors who agreed that the Thai FDA should provide inspection of the pharmacovigilance system for ATMPs: cell therapy medicinal products domestic manufactures and imports when products have occurred problems. One key informants of sponsor suggested that should comply with international standards.

Referring to key informants (15 out of 19) , they were composed of four regulators and eleven sponsors who agreed that the most important step for ATMPs: cell therapy medicinal products is the post-marketing process because of higher risks than other drugs. Some key informants (4 out of 19) consisted of regulator and sponsor, who partially agreed and mentioned that most products may be administered a single dose but they are long-acting in a body. As a consequence, it is critical to monitor the safety and efficacy of patients who have received treatment. Also, two key informants a group of regulators partially agreed and provided information. The pre-marketing authorization process is also important. If the drugs are deemed unsafe

and ineffective, they will not be approved at the time of MA. As well as, key informants (15 out of 19), who were five regulators and ten sponsors, have reached the conclusion that the intensive post-marketing process of ATMPs: cell therapy medicinal products should be conducted in the 2-year interval after that, extended lifelong patients. Additionally, some informants (3 out of 19) a group of sponsors partially agreed and more provided information, the government should support to collaboration between entrepreneurs and clinicians who perform ATMPs cell therapy medicinal products. Also, one of the key informants which is a group of regulators mentioned that on the basis of product risks, standard follow-up can be used. Key informants (15 out of 19), who were five regulators and ten sponsors, agreed that safety and efficacy data are required post-marketing. Furthermore, a key informant, who worked post-marketing Thai FDA, offered quality of products shall also be followed.

Six regulators and eight sponsors were among the key informants (14 out of 19). Their opinion concurred in the decision reached that authority bodies should formulate specific requirements for ATMPs: cell therapy medicinal products due to superior risks than other drugs. Some key informants (5 out of 19) of sponsors who partially agreed and mentioned, specific requirements should be considered and reviewed from worldwide to optimize for long-term monitoring. The concept of AEFI was accepted by 12 key informants, who worked were three regulators and nine sponsors, AEFI can be applied for monitoring these products. However, two key informants, who worked as HPVC Thai FDA disagree and mentioned that AEFI is defined as the oversight for vaccines only. It may be used not only in active surveillance but also passive surveillance as spontaneous reporting.

Key informants (11 out of 19), who were three regulators and eight sponsors, acknowledged that post-marketing program can be applied risk-based SMP principle. However, two regulators and four sponsors partially agreed and gave additional opinions, ATMP: cell therapy medicinal products ought to follow a risk-based SMP level 1 and active vigilance. Moreover, if risk-based SMP and RMP documents are submitted, the Thai FDA should consider the duplication of both documents. And, Thai FDA must determine the responsible departments for the assessment and

monitoring of risk-based SMP and RMP. At the same time, two of key informants comprised sponsor and regulator who disagree and said, according to risk-based SMP level 1, the period for follow-up should not be limited for at least two years.

4. Miscellaneous

Key informants (15 out of 19), who were three regulators and twelve sponsors, acknowledged that ATMPs: cell therapy medicinal products should be considered for reimbursement, However, two key informants of the Institute of Biological Products-DMSc and sponsor disagreed and mentioned that the financial issue must be addressed by national competent bodies. Key informants (11 out of 19), who were three regulators and eight sponsors, agreed on an overview of drug registration of ATMPs: cell therapy medicinal products that MA include condition and standard approval. However, two key informants a group of regulators disagreed and suggested that ATMPs be considered Conditional approval and renewed only to keep up with technological development. The approval of conditional and standardized registrations is also a continuous process. Moreover, key informant a group of sponsors (5 out of 19) partially agreed and provided information that authorization of ATMPs: cell therapy medicinal products should be applied as a result of evaluation national stringent authority that Thai FDA is willing to accept to shorten the time period for MA. Furthermore, on condition and standard approval for ATMPs: cell therapy medicinal products, active surveillance should be used. However, post-authorization surveillance should be practical and not an impediment to patients' access.

Table 6 The opinions on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
1. Pre-marketing authorization process						
1.1 Manufacturing process of ATMPs (cell therapy medicinal products) for marketing must be followed the Good Manufacturing Practice (GMP) under the Drug Act, B.E. 2510, and the relevant annexes. The Good Tissue Practice (GTP) must be also considered.	5	13	-	-	-	-
1.2 ATMPs (cell therapy medicinal products) are classified as the new biologic drugs.	5	9	-	3	-	1
1.3 ATMPs (cell therapy medicinal products; subcategory: autologous product) are the new biologic drugs that different from the traditional ones.	5	12	-	-	-	1
1.4 ATMPs (cell therapy medicinal products; subcategory allogeneic products) are the new biologic drugs that are different from traditional ones.	3	11	2	2	-	-

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
2. Marketing authorization application process						
2.1 Evaluation of ATMPs (cell therapy medicinal products) is performed using the same principle as that of biological drugs in terms of quality, safety, and efficacy.	4	9	1	4	-	-
2.2 Documents for marketing authorization application of autologous product or matched allogeneic product that required for submission to Thai Food and Drug Administration (Thai FDA) include: 1. The documents demonstrating quality, safety, and efficacy data, which are organized regarding ASEAN COMMON TECHNICAL DOSSIER (ACTD) or ICH COMMON TECHNICAL DOSSIER (ICH CTD) forms and 2. Results of finished products' quality testing from the Institute of Biological Products of the Department of Medical Sciences.	3	6	2	5	-	2

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
2. Marketing authorization application process						
2.3 Documents for marketing authorization application of allogeneic products that required for submission to Thai FDA include: 1. The documents demonstrating quality, safety, and efficacy data, which are organized regarding ASEAN COMMON TECHNICAL DOSSIER (ACTD) or ICH COMMON TECHNICAL DOSSIER (ICH CTD) forms and 2. Results of finished products' quality testing from the Institute of Biological Products of the Department of Medical Sciences	3	6	2	5	-	2
2.4 Considerations of finished products' quality testing from the Institute of Biological Products of the Department of Medical Sciences are based on the following criteria: - Objective of the tests - Laboratory capabilities - Quantity of samples - Cost - Global standard operating procedures - Cost-effectiveness The cost of quality testing is considered a part of the total cost for drug research, development, and registration processes. Therefore, it affects the market prices of the drugs.	2	10	1	2	1	1

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
2. Marketing authorization application process						
2.5 There should be a protocol facilitating approval of ATMPs (cell therapy medicinal products) for life-threatening conditions and unmet medical needs in urgent cases.	3	11	1	2	1	-
2.6 The conditional approval should be considered for ATMPs (cell therapy medicinal products).	5	9	-	4	-	-
2.7 In the conditional approval, the marketing authorization holders should be allowed to conduct the post-marketing studies for evaluating the safety and efficacy of the drugs. In addition, the post-marketing data should be considered for the permanent registration or cancellation of the registration of the drugs (if the data is insufficient to prove their safety and efficacy).	5	9	-	3	-	1
2.8 The conditional approval must include the risk management plan (RMP) and the updated Periodic Safety Update Report (PSUR) documents.	4	8	1	4	-	1

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
2. Marketing authorization application process						
2.9 The ATMPs (type of cell therapy medicinal products) should be established expedite programs as other countries, such as 1. Fast Track Designation in the USA 2. Breakthrough Therapy Designation in the USA 3. Priority Medicine Scheme in the EU 4. SAKIGAKE Designation in JAPAN	3	9	2	2	-	1
2.10 Regarding the requirements of sections 25 (6) and 27 (6) of the Drug Act, B.E. 2510, medicinal products or retained samples must be kept if they are manufactured and imported. Autologous product or matched allogeneic product are the exceptions for these requirements; however, their labels, package inserts, drug containers, and the relevant documents must be kept	2	6	3	4	-	3
2.11 Regarding the requirements of sections 25 (6) and 27 (6) of the Drug Act, B.E. 2510, allogeneic products or the retained samples must be kept if they are manufactured and imported.	4	5	1	5	-	3

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	opinions (n=19)					
	Agree (n)		Partially agree (n)		Disagree (n)	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
2. Marketing authorization application process						
2.12 Certificates of lot release of ATMPs (cell therapy medicinal products) are not required because the drugs are not in the lists of lot release control of biological products.	-	8	2	1	3	4
2.13 ATMPs (cell therapy medicinal products) should be available in the registered medical institutions under the Department of Health Service Support, Ministry of Public Health.	4	10	-	1	1	1
2.14 Medical institutions should be evaluated by manufacturers or marketing authorization holders before receiving the permission for ATMPs (cell therapy medicinal products) uses, especially autologous product or matched allogeneic product, because they are collected and transported to manufacturing sites to ensure the constant standard between transportation and treatment.	3	10	1	3	1	-
3. Post-marketing authorization process						
3.1 The post-marketing process is the most important step for ATMPs (cell therapy medicinal products).	4	11	2	2	-	-

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	opinions (n=19)					
	Agree (n)		Partially agree (n)		Disagree (n)	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
3. Post-marketing authorization process						
3.2 Like other medicinal products, a risk-based approach safety monitoring program should be applied in the post-marketing process of ATMPs (cell therapy medicinal products).	3	8	2	4	1	1
3.3 The specific protocol for monitoring ATMPs (cell therapy medicinal products) uses should be designed because the products have a higher risk than other drugs.	6	8	-	5	-	-
3.4 The specific protocol for monitoring ATMPs (cell therapy medicinal products) uses should include the following components. -Medical institutions are registered for ATMPs (cell therapy medicinal products) service. -Health care providers such as physicians, pharmacists, nurses, and transportation staff have sufficient knowledge and skills. -The equipment for maintaining the quality of medicines -Availability of antidotes for emergency events -There must be a traceability system to track the process of the drug manufacturer, transportation, storage, distribution, and treatment -Patient confidentiality such as consent form	5	10	1	2	-	-

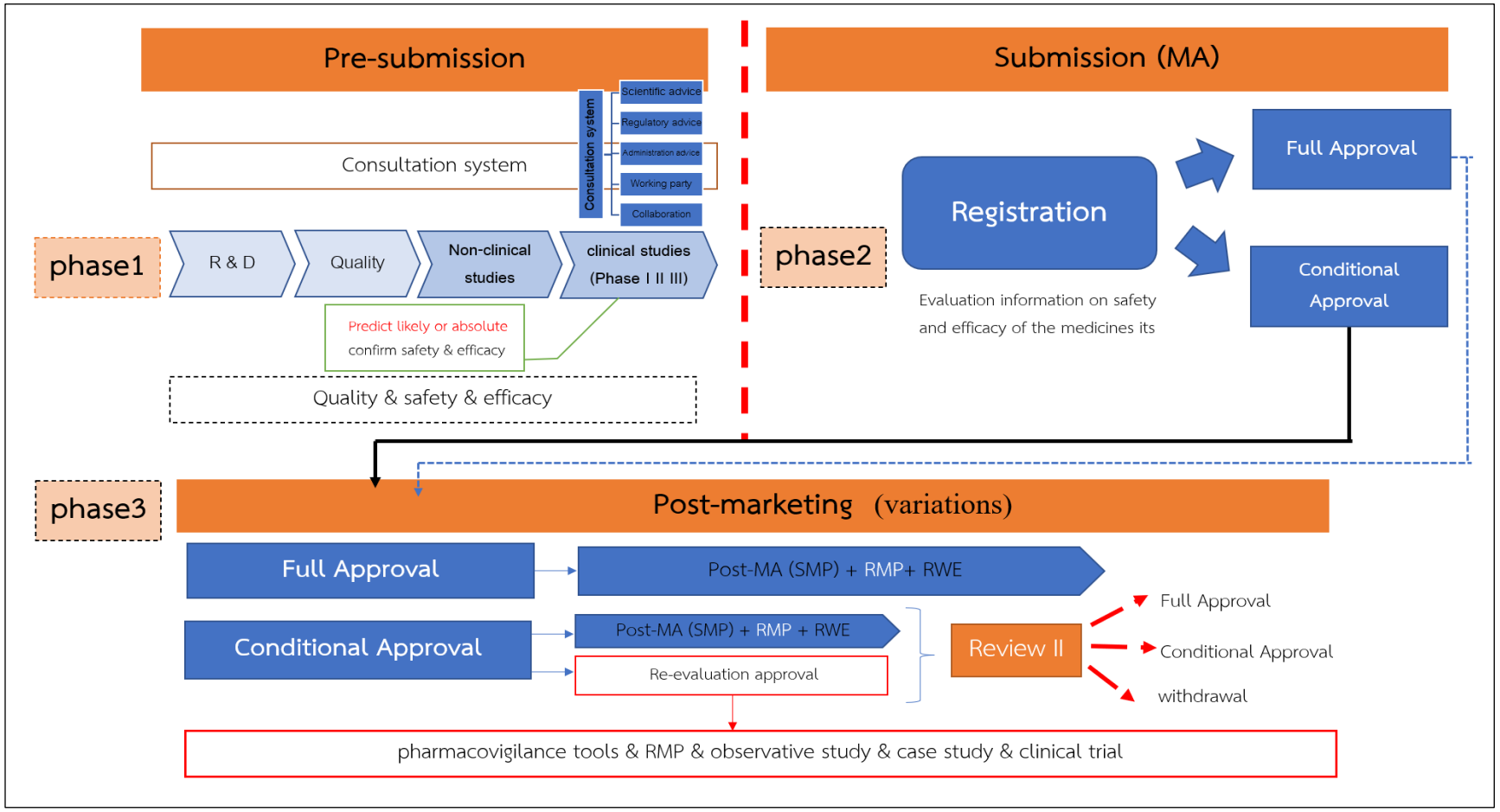
Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
3. Post-marketing authorization process						
3.5 Risk Management Plan (RMP) should be considered for registration of ATMPs (cell therapy medicinal products).	6	11	-	2	-	-
3.6 RMP should be reviewed every 1-2 years to keep the data up to date regarding the dynamic of safety data.	5	10	1	2	-	1
3.7 The intensive post-marketing process of ATMPs (cell therapy medicinal products) should be conducted in the 2-year interval such as patient registration or the follow-up system for all patients.	5	10	1	3	-	-
3.8 Safety and efficacy data of ATMPs (cell therapy medicinal products) should be monitored in the post-marketing process.	5	10	1	2	-	1
3.9 The concept of Adverse Events Following Immunization (AEFI) should be applied for the post-marketing process of ATMPs (cell therapy medicinal products).	3	9	1	3	2	1
3.10 The central database is important to link and deliver information between the internal and external organizations.	5	13	1	-	-	-

Table 6 (continue)

The requirements on the regulation of ATMPs: cell therapy medicinal products in terms of drug registration	**opinions (n=19)**					
	Agree (n)		**Partially agree (n)**		**Disagree (n)**	
	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)	Regulators (n)	Sponsors (n)
3. Post-marketing authorization process						
3.11 Thai FDA should provide the pharmacovigilance system inspection of ATMPs (cell therapy medicinal products) manufactures and imports	5	12	-	1	-	-
4. Miscellaneous						
4.1 ATMPs (cell therapy medicinal products) should be considered in the reimbursement system because it is the high efficacy but expensive treatment	3	12	-	-	1	1
4.2 Overview of drug registration on Advanced Therapy Medicinal Product (ATMPs) (cell therapy medicinal products) in terms of drug registration	3	8	-	5	2	-

4.2 Overview of drug registration on ATMPs: cell therapy medicinal products in terms of drug registration



Remark: RWE: Real-World Evidence, RMP: Risk Management Plan, SMP: Safety Monitoring Program

CHAPTER V

CONCLUSION AND DISCUSSION

This study looked into the creation of regulatory guidelines for cell therapy medicinal products in Thailand. The research findings are presented in accordance with the following goals:

1. Guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products that may be suitable for Thailand.

2. Guidelines for cell therapy medicinal product regulations in terms of drug registration that may be applicable in Thailand.

Conclusion

Documentary review

According to the document review, Advanced therapy medicinal products (ATMPs): cell therapy medicinal products are being seen as a novel medicine and a novel treatment option in medicine. Currently, ATMPs: cell therapy medicinal products have been invented to address the ineffectiveness of traditional treatments applied to particular diseases such as cancers and neurodegenerative diseases. Moreover, the products have unique challenge which is dependent upon originating materials which are either cells of patients or of healthy volunteer donors. The source of originating material related to the manufacturing process of the products can be categorized into autologous and allogeneic products. Additionally, the products have intrinsic differences associated with natural characteristics that diverge from conventional pharmaceutical products. These medicinal products have been granted with marketing authorization in the EU, the US, Japan and other countries. On the other hand, patient can gain access to the unauthorized marketing authorization of ATMPs within clinical settings whereby the treatments can be produced and used only at national level. However, the safety of such uses is needed to be taken into considerations because severe adverse events after access to those products are being reported. Thus, there are two approaches to regulate ATMPs and these are as

followed: 1. ATMPs: cell therapy medicinal products with exemption from the medicine legislation. The evidence is presented by some countries for the regulation of medical institutions. For example, in Japan, the requirements were established for responsibility to safety and quality of Regenerative Medicine (RM) such as classification of RM, manufacturing facility registration, manufacturing facility requirements, standards for clinical practice and reported adverse event and medical treatments. In Australia, there are requirements for prevention from the risks that may arise as a result of therapy with cell therapy medicinal products such as registration of clinical setting and clinician. Moreover, treatment criterion has been established prior to treatment. In South Korea, cell-based therapies have been minimally manipulated within medical institutions only. Additionally, in the UK, Point Of Care Manufacturing (POC) is built up for the production and application of cell therapies in clinical settings. To ensure the quality of production, POC require equipment and infrastructure, qualified personnel, and adverse event reporting. And 2. Medicinal product for human use. The concept of new biologic drugs as GMP, GLP, GCP, GRP, and GVP can be applied. Furthermore, some countries have purposefully drawn up a flexible and expedited pathways to success for drug registration such as PRIME in the EU, Breakthrough Therapy Designation, Fast Tract Designation, and RMAT in the US and SAKIGAKE Designation in Japan. Similarly, Conditional approval has taken into consideration for medicinal products when they demonstrate early benefits, especially, high unmet medical needs or previously uncured disorders. After cell therapy medicinal products authorized by national regulatory agencies, post-marketing phase was essential period to confirm safety and efficacy. Stringent regulatory authorities recommended 2-years of intensive follow-up for the cell-based therapies after exposure. After two years, the vigilance scheme would relate to the overall risk assessment of each product. In other word, risk-based approach must be performed. On the other hand, US FDA advised that the follow-up period could be extended to 15 years when cell combine with gene therapies to assure any possible delayed adverse reactions. Meanwhile, the EU made a suggestion of 5 years. However, the unique characteristics of ATMPs: cell therapy medicinal products

should also be taken into account, in particular, autologous product which differs from other traditional drugs.

Interviews with stakeholders and formulation of the guideline to verify from all stakeholders

Based on the information gleaned from interviews, the model of access to cell therapy medicinal products for treatment can be divided into four major approaches (Figure 10), which are as follows.

1. Clinical research use

2. Investigational drugs have been utilized for life-threatening disorders or unsatisfied treatment or patient cannot enter into clinical trial that have been not approved. The program is normally known as Compassionate Use Program.

3. Cell-based therapies service by manufactured and used within medical institutions

4. The approved products by Food and Drug Administration (FDA)

The result of the research is emphasized specific regulation on ATMPs high-risk relation to the use of cell therapy medicinal products in medical institutions and drug registration. These are requirements as follows:

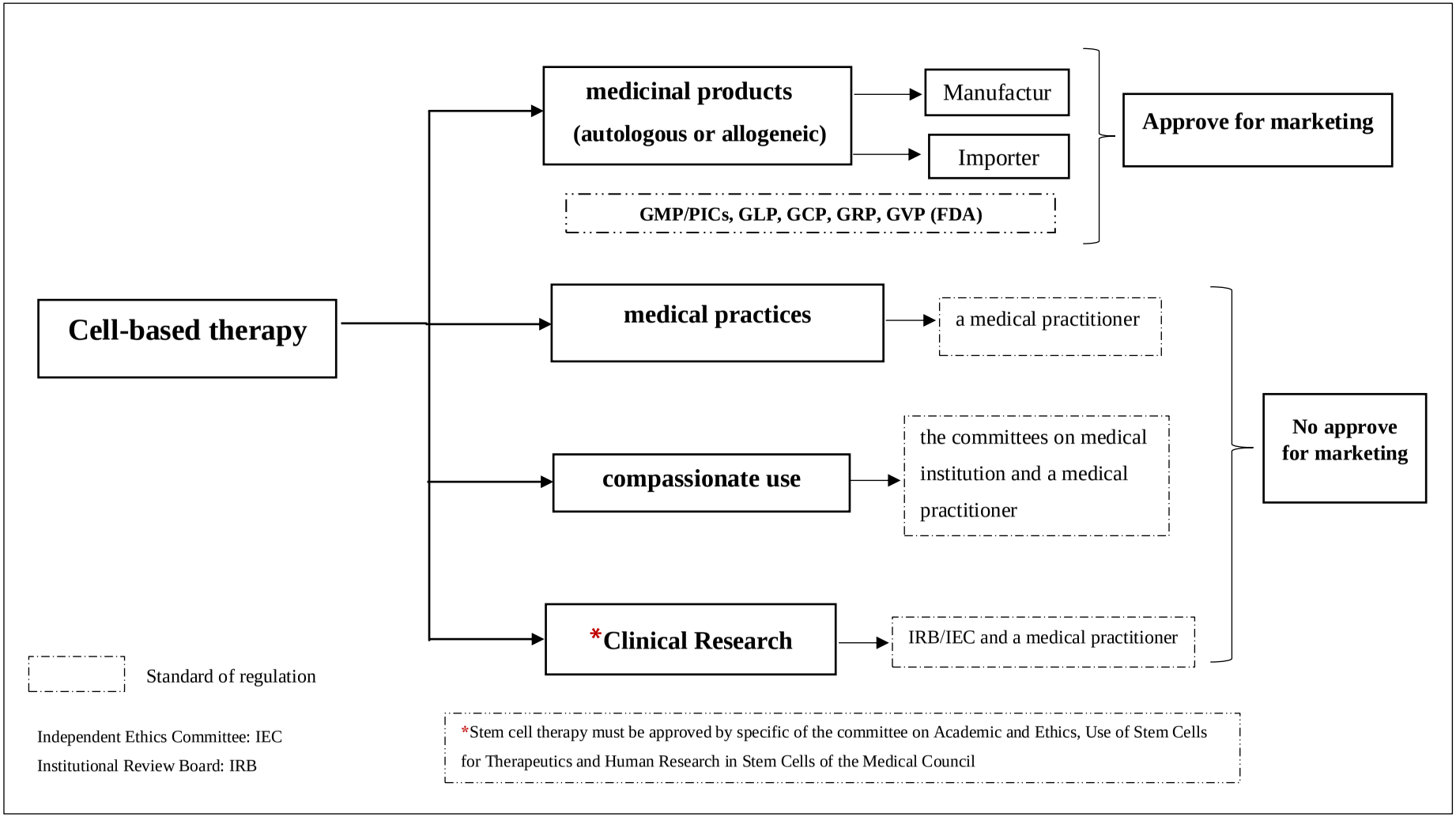


Figure 10 The model of access the using cell therapy medicinal products for the treatment

1. Guidelines for medical institutions' regulations regarding the use of cell therapy medicinal products that may be suitable for Thailand.

Currently, Thailand has not approved standard treatment with cell-based therapy. Apart from hematopoietic stem cell transplantation for hematology diseases. However, cell-based therapies have been used by patients at academic medical centers. This is under circumstances medical practices or production and use of cells within medical institutions by prescription that are excluded from the Drug Act B.E. 2510 (1967). The result of the research found most key informants do not agree with produced and used cells in medical institutions within the responsibility of a medical professional that excepted from section 13 (2) the Drug Act B.E. 2510 (1967). Because the manufacturing process is complicated and needed for quality control. For this reason, cell-based therapies must be classified depending on the risk-based approach. Low risk can be regulated by a medical professional and Sanatorium law that is classified referred to the definition of the EU and US FDA. If high risk must add specific requirements as follows.

1. Qualification of medical practitioners must be expertise in the disease area of patients, pass the training courses approved by the Thai Medical Council and the relevant Royal College, registered systems and medical director is responsible for high-risk cell therapy medicinal products used in medical institutions. The Thai Medical Council or HSS is key the obligation.

2. Qualified Persons who are involved in cell therapy other than medical practitioners such as scientists or medical technologists who are educated and assigned to produce cells from medical practitioners, nurses, and pharmacists.

3. Qualifications of manufacturing sites can be divided into two categories.

3.1 Medical institutions are registered manufacturing sites according to the Drug Act B.E. 2510 (1967) in terms of high-risk cell therapy medicinal products. Produced and used high-risk cell therapy medicinal products within medical institutions should comply with GMP. However, they should meet GMP certificated facilities when those products are free distribution.

3.2 Medical institutions are accreted standards of the cell-therapy laboratory by DMSc.

4. Medical institutions are registered by HSS that initial period needs to perform in hospitals only. Medical institutions are evaluated and renewed every year by HSS.

5. Medical practice is approved by the Thai Medical Council. Additionally, the Thai FDA may be involved with the evaluation of high-risk cell therapy medicinal products.

6. Follow-up is required to monitor the safety and efficacy of ATMPs high-risk cell therapy medicinal products. Specifically, intensive monitoring for the first two years after acceptance. Furthermore, an adverse event report, a medical report, a production report, and the number of patients treated with ATMPs high-risk cell therapy medicinal products should be submitted to HSS, the Thai Medical Council and Thai FDA to collect data for renewal assessment. Government officers can conduct immediate inspections in medical institutions if any emergent events endanger the patient's safety or if cell therapy administration is halted. Furthermore, there should be channels for random inspections and complaint reporting.

7. Miscellaneous

1. Advertising of ATMPs high-risk cell therapy medicinal products is prohibited directly to consumers.

2. ATMPs high-risk cell therapy medicinal products are manufactured in medical institutions should not be withdrawn if there are registered products (imported or manufactured) by the Thai FDA.

3. ATMPs high-risk cell therapy medicinal products should be considered in the reimbursement system to access and afford for patients.

2. Guidelines for cell therapy medicinal product regulations in terms of drug registration that may be applicable in Thailand.

Thailand has not yet authorized ATMPs: cell therapy medicinal products to be brought to market. Due to the high cost of investment, lack of knowledge and expertise, regulations, policy, and product limitations (in particular, autologous product). Entrepreneurs have little interest in these products (1 importer and 1

manufacturer only). As a result, the principle of new biological drugs is still being applied to ATMPs: cell therapy medicinal products, which are similar in many ways. However, as ATMPs become more widely available, specific regulatory requirements for ATMPs: cell therapy medicinal products must be modified or added, as shown below.

1. Pre-marketing authorization process

The manufacturing process of ATMPs: cell therapy medicinal products for marketing must be followed the GMP and GTP requirements. Those products are classified as new biological drugs according to the definition of the Thai FDA. Cells are provided from the patient's cells or related blood or donor that they are components of the finished product. Particularly, the autologous product is approved extremely differently from other drugs.

2. Marketing authorization application process

ATMPs type of autologous and allogeneic product are limited as the quantity, price, condition of storage, and laboratory capabilities impact on finished products' quality testing, certificate of lot release, and retain sample. Thereby, Thai FDA and authority bodies should consider based on the risk of products and add other requirements that re-testing without samples. Additionally, RMP should be submitted for registration.

ATMPs: cell therapy medicinal products should be considered Conditional approval that is required RMP and PSUR. Conditional approval, Urgent approval, and Expedited pathways should be provided for a life-threatening condition, unmet medical needs, and urgent case impact on public health under approved and reviewed by the committees. Moreover, Expedited pathways should be granted specific researches or manufacturers to support pioneers in Thailand only.

Service on ATMPs: cell therapy medicinal products should be registered medical institutions under the HSS and trained about products and administration drug by manufacturers or MAH to ensure the safety.

3. Post-marketing authorization process

The most important phase for ATMPs: cell therapy medicinal products is the post-marketing process. Along with the risks associated with the products and single-dose administration. These products are should be monitored quality, safety, and efficacy data by RMP as well as risk-based SMP level 1 with active surveillance. RMP should be reviewed every 1-2 years or when it meets new data. The concept of AEFI should be applied. Thai FDA should establish inspection for ATMPs cell therapy medicinal products manufactured and imports.

4. ATMPs cell therapy medicinal products should be considered in the reimbursement system but the financial issue must be explored.

Discussion

The regulation of cell therapy medicinal products can be classified 2 approaches as 1. medical institutions concerning the use of cell therapy medicinal products and 2. drug registration.

1. In this case, the regulation to medical institutions in relation to the use of cell therapy medicinal products. The results of study were found that all key informants agreed upon that in order to ensure patient safety using high-risk cell-based therapy, specific requirements for this service should be established including those for qualification of physicians providing the service, manufacturing site, standard of laboratory, medical institutions, medical practices, cell therapy medicinal products and monitoring of the use of cell-based therapy. The results are consistent with the other countries requirements. For example, ARSM in Japan is provide unique stipulations as manufacturing facility registration, manufacturing facility requirements, standards for clinical practice, and classification based on risk to the quality of control (12, 45). Australia has been registered hospital settings and medical and dental practitioners who conduct treatment as well as criteria before cell-based therapy (53). In South Korea, Cell-based therapies have been minimally manipulated within medical institutions that are regulated under the exclusive professional responsibility of a medical practitioner. If they meet not this criterion, they will be registered (54). Those new requirements are required when novel therapies are

expanded to protect the patients who accept them. Similarly, In the United Kingdom, a new regulatory framework known as Point-Of-Care is emerging (POC). It can be defined as the development and use of cell therapies in clinical settings to increase flexibility. Clinical settings such as quality control, equipment and infrastructure, qualified personnel, adverse event reporting, and manufacturing site auditing, must be covered. Thus, the control site should be designed that it will oversee the manufacturing site and send the data to The Medicines and Healthcare products Regulatory Agency (MHRA) due to assure quality, safety, and efficacy that the manufacturing sites are exempt from GMP standards. This is a challenging aspect of POC manufacture. The main tackles are equipment and infrastructure, qualified personnel, regulation, and supply chains (107). POC requirements are less stringent than drug registration requirements, which facilitates innovation and patient access into clinical settings. Due to high price of authorized product (123, 124). This is consistent with the findings that some key informants argued that it is difficult for medical institutions which want to produce cell-based therapies to be certified as a drug manufacturing facility. Similarly, standards of the cell-therapy laboratory released by the department of medical sciences can be used at medical institutions during an early stage. Japan, on the other hand, is permitted to have a separate manufacturing and clinical site but where are inspected by MHLW and PMDA (12, 45, 125, 126). In the current situation, Thailand is classified as producing and distributing other clinical settings that are governed by the Drug Act B.E. 2510 (1967). The requirements, however, must be clearly stated. Otherwise, there are various interpretations like HE in the EU. This is important to establish homogeneous standards for patient safety and product quality (99, 100).

Thailand, the use and production of cell therapy medicinal products within medical institutions are novel treatments and high risk that manufacturing process, quality of control, administration, and side effect are complicated. Their products need a specific requirement for safety. These agree with the findings from this research found that produced and used cell-based therapy within medical institutions is needed specific requirements which can be carried out through legal provision as

other countries such as add on condition with section 13 (2) the Drug Act B.E. 2510 (1967), promulgation new regulation for cell-based therapy or add a condition with section 15 of the Sanatorium Act, B.E. 2541 (1998) (127). Those new measures are involved with the Thai Medical Council and the relevant Royal College is determined a qualification of medical practitioners, and prepare a training course. The HSS is the responsibility of qualifications of medical institutions and services. The DMSc accreditation of standards of the cell-therapy laboratory. Finally, Thai FDA may be necessary to increase the role of the regulatory agency for an unproven product such as high-risk products that they are regulated manufacturing site, control of the process, quality control, or approved high-risk products that are produced and used within medical institutions only. However, the specific requirements are excluded from clinical research that is regulated by Independent Ethics Committee or Institutional Review Board.

2. The regulation to cell therapy medicinal products in terms of drug registration

As of now, the principle of new biological drugs is still being used because they are similar to ATMPs in many aspects and entrepreneurs are not much interested in these products. However, they may be designed specifically to meet the needs of ATMPs: cell therapy medicinal products, particularly autologous product, as opposed to other traditional medicines. As a result of the discoveries, ATMPs: cell therapy medicinal products must adhere to GMP and GTP standards before being released in accordance with international requirements. Furthermore, ATMPs: cell therapy medicinal products should be flexible approval with natural characteristics such as limited patient number, personalized medicines, rare disease impact on the evaluation of quality, safety, and efficacy data before marketing authorization. At present, many countries have come up with Conditional approval for ATMPs. It may be demonstrated or predicted efficacy and safety rather than the potential risks by an intermediate endpoint. Additionally, safety and efficacy data can be collected after approval to re-evaluate. Conditional approval is applied to the EU, the US, and Japan (12, 63, 87, 89). Besides, Expedite pathways have been designed and applied in other

countries such as Fast Track Designation and Breakthrough Therapy Designation in the US, as well as Priority Medicine Scheme and Adaptive pathway in the EU, were established for a new drug or novel medicine intended to treat the life-threatening conditions and unmet medical needs in urgent circumstances. Japan, for example, has a SAKIGAKE Designation system to support Japanese pioneers in the research and development of novel therapies that first emerged in Japan (63, 87-90). On top of those criteria, Conditional approval, Urgent approval, and Expedite pathways should be clearly identified criteria for use such as life-threatening conditions and unmet medical needs, and urgent circumstances impact on public health only, Moreover, their schemes have to close monitoring and re-evaluation to confirm safety and efficacy data in further information.

According to key informants agreed that ATMPs, particularly autologous product, will be subject to one-of-a-kind regulations. New types of regulations are required. Because patient cells are used to produce the medicine, production is relatively limited, production is made to order and the product is made specifically for the patients that natural characteristics of the product related to a distribution model, transport time, traceability, regulations and requirements for marketing authorization. Those finding were consistent with the previous research of Geoffrey Banda and the group (117, 128). Hence, the government and relevant authority bodies should consider and provide documents to demonstrate a substitute for finished product quality testing to confirm the quality, safety, and efficacy of those products. According to the recommendation of the EMA and Pharmaceutical Inspection Co-operation Scheme: PIC/S, ATMPs: cell therapy medicinal products may be excluded from re-testing before launching when those product limit of samples or short shelf-life. However, the manufacturing processes must be certified by GMP facilities (114, 129) and the manufacturer or MAH must provide a valid document such as amount of quantity, shelf- life, quality control of the products.

The result found that the post-marketing period is critical for ATMPs: cell therapy medicinal products due to the single treatment and risks. Cells may proliferate and differentiate, resulting in increased adversity and decreased efficacy (33, 34, 87).

Key informants shared their opinions in favor of intensive monitoring within 2-year interval. After that, extended lifelong patients. To be sure, RMP is an important tool for monitoring success (115). Also, PSUR should be reported period time that determined by NRA for collecting new safety experience post-authorization. PSUR should not be reported only once at the end of a time condition for new medicinal products. These results are consistent with the EMA recommendation. For patients who have received ATMPs, the EMA suggested a 2-year close monitoring program for the cell-based treatments after administration of the products because treatments entail relatively new biologics and new mechanism of action. Moreover, adverse events may arise during the early phase after administration (34). After two years of close monitoring, the vigilance scheme would depend on the overall risk-based approach of each product. Safety and efficacy follow-up shall be considered for ATMPs: cell therapy medicinal products. In addition, cells combine with modified gene therapy have been recommended that a follow-up period since pre-administration, 3, 6 and 12 months after administration, and then yearly for a minimum of 5 years after that may be considered related to clinical data that can be extended so long as possible when meet any risks (130). Meanwhile, US FDA advised that the follow-up period could be extended to 15 years to assure any possible late adverse reactions for modified gene therapies (95, 131). On the other hand, key informants in this study advised for long-term follow-up or the rest of their lives. Hence, the extended follow-up scheme is highly likely appropriate for monitoring ATMPs products as it would be useful in the detection and prevention of any delayed adverse reactions.

Due to the extreme cost, key informants accepted that the government shall support reimbursement system and promote innovative products. Japan, for example, has a reimbursement system for RM (12). Some countries do not have a financial plan to promote themselves. Patients are unable to access treatment that has come at a high cost. ATMPs, such as GLYBERA®, are being phased out of the market due to commercial reason (132-134). According to John Gardner and Andrew Webster, Geoffrey Banda and group, Renske M.T and group, Rosario Isas and group, Benjamin

M Davies and group, and SOFIEKE DEWILDE and group, the tremendous price is obstructed to patients' accessibility and affordability (116-121).

At the same time, regulations are outdated and cannot catch up with technological progress as all knowledge regarding ATMPs is limited. So, Regulations must be improved like Regulation (EC) No 1394/2007 (3), The Food, Drug & Cosmetics Act (FDCA) and Public Health Service Act (PHS Act) section 351 (86), Pharmaceutical medical device and other therapeutic product Act (PMD Act) in Japan (44, 45) and Regulatory pathways for autologous human cells and tissues products in Australia (135) . Their laws are formed after released newly products.

This research provided a snapshot for the recommendation for regulation of cell therapy medicinal products in Thailand, both in terms of use within medical institutions and drug registration. Finally, laws and regulations are critical for ATMPs: cell therapy medicinal products, which are new technology products. Furthermore, laws can either protect or impede the development of innovations. Other countries have introduced new requirements that are either different or similar to those in their own countries. Thus, policymakers in Thailand have to consider the safety and efficacy concerns of the candidate products in the highest regard when drafting the new legislation. The new legislation should be adapted and optimized based on the standards of other countries, which have successfully used ATMPs: cell therapy medicinal products in real clinical practices. Additionally, this new legislation must be well-applicable in terms of socioeconomics and ethical perspectives. As a result, this is a challenge for regulators or policymakers who must apply knowledge of risk-based balance or risk management to make decisions to protect and not hinder new therapies.

Recommendations for further research studies

Researchers should investigate the cost and value of the cell-based therapy approach to support the Ministry of Public Health's policy of using evaluated cost-effectiveness to care for patients who were previously untreatable with standard therapy, thereby promoting the use of cell-based therapy in the healthcare system.

Limitation

1. This study investigated the creation of regulatory guidelines for cell therapy medicinal products in Thailand. In terms of medical institutions and the use of cell therapy medicinal products, all key informants are public organizations, including a group of researchers and academic medical centers, and the findings do not reveal a private sector perspective obstacle.

2. The Patient Advocacy Groups (PAGs) are not included in this study; however, they are parts of the key aspects of using cell-based therapy and in protecting the rights of patients. Moreover, PAGs are the main player in clinical transformation of cell therapies as they bring about positive changes to regulatory process, infrastructure improvement, stability of markets and policy reimbursement.

3. Those who would analyze these questionnaires must be aware that the returned questionnaires are often incomplete.

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APPENDEX

APPENDIX A

Questionnaire for interview

1. English
2. Thai

The Questionnaire

The Questionnaire consists of 3 main parts as follows:

Part 1: Personal information of interviewees such as job position, work experience, and role as well as the responsibility of work

Part 2: The objectives of this research were to study and develop:

1. Guidelines to the regulation of medical institutions concerning the use and production of cell therapy medicinal products which are potentially suitable for Thailand.

2. Guidelines to the regulation of cell therapy medicinal products in terms of drug registration which are potentially suitable for Thailand.

Part 3: The questions commonly inquire for all the informants

3.1 How should cell therapy medicinal products be regulated in Thailand, both in terms of use within medical institutions and drug registration? Should there be any additional organization(s) established or the law(s) enacted to ensure the quality, safety, and/or efficiency of related treatments? (Selected based on the characteristics of the key informants, including whether they can likely provide insights into the use of cell therapy medicinal products by medical institutions or drug registration)

3.2 What are the potential problems, obstacles, or resolutions for the regulation of cell therapy medicinal products in terms of use within medical institutions and drug registration? (Selected based on the characteristics of the key informants, including whether they can likely provide insights into the use of cell therapy medicinal products by medical institutions or drug registration)

3.3 What are your recommendations for cell therapy medicinal product regulation in terms of use in medical facilities and drug registration? (Selected based on the characteristics of the key informants, including whether they can likely provide insights into the use of cell therapy medicinal products by medical institutions or drug registration)

3.4 Who was on the expert panel that oversaw the regulation of cell therapy pharmaceuticals? (Selected based on the characteristics of the key informants, including whether they can likely provide insights into drug registration or use of cell therapy medicinal products by medical institutions)

The questionnaire for interview group 1: The Committee on Academic and Ethics, Use of Stem Cells for Therapeutics and Human Research in Stem Cells of the Thai Medical Council (code 1X)

Name: …… Organization: ……

Date of interview: …… Time at interview: ……

Date of the recheck for transcripts by interviewees: …..……

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with cell therapy medicinal products on the medical institutions in Thailand?

The questions	**The answer**
1. How would you define the role and responsibilities of the Medical Council's Academic and Ethics committee, as well as the use of stem cells for therapies and human research in stem cells?	
2. Who composed the Medical Council's formulations on Academic and Ethical committee, the use of stem cells for medicines, and human research in stem cells?	
3. What are the criteria for approving a stem cell therapy protocol or standard treatment?	
4. How would you define the procedures for following up after the protocol has been approved?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 2: The Thai Medical Council (code 2X)

Name: …… Organization: ……

Date of interview: …… Time at interview: ……

Date of the recheck for transcripts by interviewees: ……..……

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with cell therapy medicinal products on the medical institutions in Thailand?

The questions	The answer
1. How would you describe the role and responsibility of The Thai Medical Council?	
2. Is cell therapy approved for treatment by the Thai Medical Council? How is the procedure going?	
3. What are the requirements for a medical practitioner to undertake cell therapy medicinal product treatments?	
4. What are the quality standards of cell therapy services?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 3: Institute of Biological Products of Department of Medical Sciences (code 3X)

Name: …… Organization: ……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ……...

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with ATMPs: cell therapy medicinal products on drug registration in Thailand?

The questions	**The answer**
1. How would you describe the role and responsibility of The Institute of Biological Products Department of Medical Sciences?	
2. What kind of products are classified as biologic drugs, including ATMPs: cell therapy medicinal products?	
3. In terms of biological drug registration, how would you describe The Institute of Biological Products Department of Medical Sciences?	
4. If this is the case, ATMP imports and production, as well as cell therapy medicinal products, must be registered in Thailand. What function does the Institute of Biomaterial Department of Science play in product regulation?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 4: The legal affair division department of Health Service Support (code 4X)

Name: …… Organization: ...……

Date of interview: …… Time at interview: .……...…

Date of the recheck for transcripts by interviewees: ……

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with cell therapy medicinal products on the medical institutions in Thailand?

The questions	**The answer**
1. How would you describe the legal affairs section of the Department of Health Service Support's mission and responsibilities?	
2. How would you describe Act of Cell Therapy's history?	
3. What are the requirements for medical institutions to provide cell therapy treatment to patients?	
4. What are the requirements for laboratory quality standards for treating cell therapy patients?	
5. How would you describe the cell laboratory assessment? What should it be?	
6. What are the requirements for a medical practitioner to undertake cell therapy treatments?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 5: The manufacture of biologic drugs in Thailand (code 5X)

Name: …… Organization: ...……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ……

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with ATMPs: cell therapy medicinal products on drug registration in Thailand?

The questions	The answer
1. How would you describe your company's general information?	
2. What is your company's drug development strategy like?	
3. What do you think the differences are between ATMP: cell therapy medical products registration and biological drugs?	
4. If that's the case, ATMP: cell therapy medical products will need to be registered in Thailand. What is the status of the regulatory system for this product?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 6: Thai Food and drug administration (Thai FDA) (code 6X)

Name: …… Organization: ...……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ..……...

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with ATMPs: cell therapy medicinal products on drug registration in Thailand?

The questions	The answer
1. How would you describe the role and responsibility of the Thai FDA?	
2. What does the approval process look like for ATMP: cell therapy medicinal products and biologics drugs?	
3. How would you describe the Thai FDA regulatory framework for ATMP: cell therapy medicinal products?	
4. How would you describe the ATMP: cell therapy medical products follow-up process?	
5. What are your recommendations for follow-up of ATMP: cell therapy medicinal products?	
6. What do you think the future holds for ATMP: cell therapy medicinal products importers and manufacturers in Thailand?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 7: Nation blood center of The Thai red cross society (code 7X)

Name: …… Organization: ...……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ..……

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with cell therapy medicinal products on the medical institutions in Thailand?

The questions	The answer
1. How would you describe the role and responsibility of the Thailand National Stem Cell Donor Registry?	
2. How would you characterize the pharmaceutical industry's drug development strategy?	
3. How would you describe Thailand National Stem Cell Donor Registry's stem cell establishment and cord blood bank?	
4. How would you describe the donor registry criteria?	
5. How would you define the pharmaceutical industry's or medical institutes' quality requirements for cell therapy?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 8: The Bureau of Laboratory Quality Standards of Department of Medical Sciences (code 8X)

Name: …… Organization: ...……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ……...……...

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with cell therapy medicinal products on the medical institutions in Thailand?

The questions	**The answer**
1. How would you describe the role and responsibility of The Bureau of Laboratory Quality Standards of the Department of Medical Sciences?	
2. How would you describe the laboratory quality requirements for cell therapy?	
3. How would you describe laboratory quality certification for cell therapy?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 9: The medical institutions involved in clinical research and development for cell therapy or advanced therapy consist of the cell for patients (code 9X)

Name: …… Organization: ...……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ..……

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with cell therapy medicinal products on the medical institutions in Thailand?

The questions	The answer
1. How would you describe the general facts about cell therapy utilization?	
2. How would you describe the overlapping jurisdictions between cell therapy medicinal products items and cells created for an individual patient by an exclusive medical practitioner under the Drug Act B.E. 2510 (1967)?	
3. How would you describe the medical institution's standard of medical practice and follow-up after cell therapy treatment?	
4. How would you describe the medical institution's regulation of cell therapy?	
5. How would you describe the challenges and roadblocks to cell therapy application in medical institutions?	

Part 3: The questions commonly inquire for all the informants

The questionnaire for interview group 10: The importers of biologic drugs in Thailand (code 10X)

Name: …… Organization: ...……

Date of interview: ……. Time at interview: ……...…

Date of the recheck for transcripts by interviewees: ……..

Part 1: General information such as job position, work experience, role, and responsibility of work

Part 2: What is the regulation for suitability with ATMPs: cell therapy medicinal products on drug registration in Thailand?

The questions	The answer
1. How would you describe of general information of your company?	
2. How would you describe your companies' drug development strategy?	
3. What do you think the differences are between ATMP registration: cell therapy medicinal products and biological drugs?	
4. If that's the case, ATMP: cell therapy medical products will need to be registered in Thailand. What is the status of the regulatory system for this product?	

Part 3: The questions commonly inquire for all the informants

แบบสัมภาษณ์

แบบสัมภาษณ์ประกอบด้วยกัน 3 ส่วนหลัก ดังนี้

ส่วนที่ 1. ข้อมูลทั่วไปของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์งานวิจัย

2.1 การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

2.2 การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการอนุมัติทะเบียนตำรับยาที่เหมาะสมกับประเทศไทย

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน ดังนี้

3.1 การกำกับ ดูแล เซลล์บำบัดควรเป็นอย่างไรเพื่อให้ประชาชนมีความปลอดภัย (มีหน่วยงานใด หรือกฎหมายใดที่เกี่ยวข้อง หรือต้องออกเพิ่มเติม)

3.2 ปัญหาและอุปสรรคการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดของประเทศไทย (ทั้งรูปแบบการบำบัดรักษาโรคภายในสถานพยาบาล และการอนุมัติทะเบียนตำรับยา เลือกตามลักษณะของผู้ให้ข้อมูลสำคัญ)

3.3 ข้อเสนอแนะอื่นๆ ต่อการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดที่เหมาะสมกับประเทศไทย (ทั้งรูปแบบการบำบัดรักษาโรคภายในสถานพยาบาล และการอนุมัติทะเบียนตำรับยา เลือกตามลักษณะของผู้ให้ข้อมูลสำคัญ)

3.4 บุคคลใดบ้างที่มีประสบการณ์ หรือ เชี่ยวชาญ ด้านการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดหรือการนำเซลล์บำบัดไปใช้ในการรักษาผู้ป่วย

ผู้ให้ข้อมูลสำคัญกลุ่ม 1 คณะกรรมการวิชาการและจริยธรรมการใช้เซลล์ต้นกำเนิดเพื่อการรักษาและการทำวิจัยในคนด้านเซลล์ต้นกำเนิดของแพทยสภา (รหัส 1X)

ชื่อผู้ให้ข้อมูลสำคัญ หน่วยงานแพทยสภา วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

คำถาม	คำตอบ
1. บทบาท หน้าที่ของคณะกรรมการวิชาการและจริยธรรมการใช้เซลล์ต้นกำเนิดเพื่อการรักษาและการทำวิจัยในคนด้านเซลล์ต้นกำเนิดคืออะไร	
2. องค์ประกอบของคณะกรรมการวิชาการและจริยธรรมการใช้เซลล์ต้นกำเนิดเพื่อการรักษาและการทำวิจัยในคนด้านเซลล์ต้นกำเนิดเป็นอย่างไร	
3. คณะกรรมการวิชาการและจริยธรรมการใช้เซลล์ต้นกำเนิดเพื่อการรักษาและการทำวิจัยในคนด้านเซลล์ต้นกำเนิดมีหลักเกณฑ์การพิจารณาโครงการวิจัยและการอนุมัติการรักษาที่เป็นมาตราฐานอย่างไร	
4. กระบวนการติดตามหลังการอนุมัติให้ดำเนินการวิจัยในคนด้วยเซลล์ต้นกำเนิดเป็นอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 2 คณะกรรมการแพทยสภา หรือ ผู้บริหารแพทยสภา หน่วยงานแพทยสภา (รหัส 2X)

ชื่อผู้ให้ข้อมูลสำคัญ แพทยสภา วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. บทบาท หน้าที่ของแพทยสภาคืออะไร	
2. ปัจจุบันแพทยสภารับรองการนำเซลล์บำบัดมาใช้ในการรักษาโรคอะไรบ้างและมีกระบวนการพิจารณาอย่างไร	
3. คุณสมบัติของผู้ประกอบวิชาชีพเวชกรรมที่ได้รับอนุญาตให้สามารถบำบัดรักษาผู้ป่วยด้วยเซลล์บำบัดควรมีลักษณะอย่างไร	
4. มาตรฐานใดที่เกี่ยวข้องกับการให้บริการเกี่ยวกับเซลล์บำบัดและควรเป็นอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 3 สถาบันชีววัตถุ กรมวิทยาศาสตร์การแพทย์ (รหัส 3X)

ชื่อผู้ให้ข้อมูลสำคัญ สถาบันชีววัตถุ กรมวิทยาศาสตร์การแพทย์ วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการอนุมัติทะเบียนตำรับยาที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. บทบาทหน้าที่ของสถาบันชีววัตถุ กรมวิทยาศาสตร์การแพทย์คืออะไร	
2. ขอบเขตของยาชีววัตถุ ครอบคลุมผลิตภัณฑ์ประเภทใดบ้างและหมายรวมถึงผลิตภัณฑ์เซลล์บำบัดหรือไม่ อย่างไร	
3. สถาบันชีววัตถุ กรมวิทยาศาสตร์ มีส่วนเกี่ยวข้องกับการขึ้นทะเบียนตำรับยาชีววัตถุอย่างไร	
4. หากมีการนำผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด มาขึ้นทะเบียนที่ประเทศไทย บทบาทหน้าที่ของสถาบันชีววัตถุต่อการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เหล่านี้เป็นอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 4 กองกฎหมาย กรมสนับสนุนบริการสุขภาพ (รหัส 4X)

ชื่อผู้ให้ข้อมูลสำคัญ กองกฎหมาย กรมสนับสนุนบริการสุขภาพ วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. บทบาทหน้าที่ของกองกฎหมาย กรมสนับสนุนบริการสุขภาพคืออะไร	
2. ประวัติความเป็นมาของ ร่าง พรบ. ว่าด้วยเซลล์บำบัด พ.ศ.	
3. คุณสมบัติสถานพยาบาลที่มีความเหมาะสมสำหรับการบำบัดรักษาโรคด้วยผลิตภัณฑ์เซลล์บำบัดควรเป็นอย่างไร	
4. คุณสมบัติห้องปฏิบัติการเซลล์ทางการแพทย์ที่มีความเหมาะสมสำหรับการบำบัดรักษาโรคด้วยผลิตภัณฑ์เซลล์บำบัดควรเป็นอย่างไร	
5. การตรวจประเมินสถานพยาบาล ห้องปฏิบัติการเซลล์ทางการแพทย์ควรเป็นอย่างไร	
6. คุณสมบัติของผู้ประกอบวิชาชีพเวชกรรมที่เหมาะสมสำหรับการบำบัดรักษาโรคด้วยผลิตภัณฑ์เซลล์บำบัดควรเป็นอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 5 ผู้ประกอบการไทยที่ผลิตยาชีววัตถุภายในประเทศ (รหัส 5X)

ชื่อผู้ให้ข้อมูลสำคัญ บริษัท วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการอนุมัติทะเบียนตำรับยาที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. ข้อมูลทั่วไปของบริษัท	
2. ทิศทางการพัฒนาผลิตภัณฑ์ยาของบริษัทเป็นอย่างไร	
3. การขึ้นทะเบียนตำรับยาของผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดมีความแตกต่างหรือเหมือนกับยาชีววัตถุหรือไม่ อย่างไร	
4. ในความคิดของท่านหากมีการผลิตผลิตภัณฑ์การแพทย์ขั้นสูงชนิดเซลล์บำบัดในประเทศควรมีระบบควบคุมอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 6 สำนักงานคณะกรรมการอาหารและยา (รหัส 6X)

ชื่อผู้ให้ข้อมูลสำคัญ สำนักงานคณะกรรมการอาหารและยา วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการอนุมัติทะเบียนตำรับยาที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. บทบาทหน้าที่สำนักงานคณะกรรมการอาหารและยาคืออะไร	
2. การกำกับ ดูแล ควบคุมผลิตภัณฑ์ยาชีววัตถุ กับผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด มีความแตกต่างหรือเหมือนกับยาชีววัตถุหรือไม่ อย่างไร	
3. การขึ้นทะเบียนผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดควรเป็นอย่างไร	
4. ผลิตภัณฑ์ยามีการติดตามหลังออกสู่ตลาดเป็นอย่างไร	
5. การติดตามความปลอดภัยจากการใช้ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดควรเป็นอย่างไร	
6. แนวโน้มการผลิต หรือ นำสั่ง ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดในประเทศไทย	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 7 ศูนย์บริการโลหิตแห่งชาติ (รหัส 7X)

ชื่อผู้ให้ข้อมูลสำคัญ ฝ่ายธนาคารเซลล์ต้นกำเนิดเม็ดโลหิต หน่วยงานสภากาชาดไทย

วันที่ เวลา น. วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. ข้อมูลทั่วไปของฝ่ายธนาคารเซลล์ต้นกำเนิดเม็ดโลหิต สภากาชาดไทย	
2. ทิศทางการพัฒนาผลิตภัณฑ์ยาของสถานเสาวภา สภากาชาดไทยเป็นอย่างไร	
3. การจัดตั้งธนาคารเซลล์ต้นกำเนิดเม็ดโลหิต และธนาคารเลือดจากรก (cord blood bank) แห่งชาติเป็นอย่างไร	
4. หลักเกณฑ์การบริจาคเซลล์ต้นกำเนิดเม็ดโลหิตเป็นอย่างไร	
5. การนำเซลล์มาใช้เพื่อทางอุตสาหกรรมยาหรือการใช้เพื่อการบำบัดรักษาโรคภายในสถานพยาบาลควรมีมาตรฐานใดเข้ามาเกี่ยวข้อง	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 8 กรมวิทยาศาสตร์ทางการแพทย์ (รหัส 8X)

ชื่อผู้ให้ข้อมูลสำคัญ สำนักมาตรฐานห้องปฏิบัติการ กรมวิทยาศาสตร์ทางการแพทย์ วันที่

เวลา น. วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. บทบาทหน้าที่ของสำนักมาตรฐานห้องปฏิบัติการ (สมป.) กรมวิทยาศาสตร์ทางการแพทย์คืออะไร	
2. คุณสมบัติของห้องปฏิบัติการเซลล์ทางการแพทย์ควรเป็นอย่างไร	
3. การตรวจประเมินเพื่อรับรองห้องปฏิบัติการเซลล์ทางการแพทย์ควรเป็นอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่ม 9 โรงพยาบาลที่นำเซลล์บำบัดมาใช้เพื่อการรักษาผู้ป่วย (รหัส 9X)

ชื่อผู้ให้ข้อมูลสำคัญ โรงพยาบาล วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. ข้อมูลทั่วไปของการนำผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลเป็นอย่างไร	
2. ประเด็นคาบเกี่ยวระหว่างผลิตภัณฑ์ยากับการผลิตยาตามใบสั่งของผู้ประกอบวิชาชีพเวชกรรมที่สั่งสำหรับคนไข้เฉพาะราย ภายใต้มาตรา 13 (2) ของพรบ. ยา พ.ศ. 2510 และที่แก้ไขเพิ่มเติม	
3. มาตรฐานการรักษาตลอดจนการติดตามหลังการรักษาด้วยผลิตภัณฑ์เซลล์บำบัดภายในสถานพยาบาลควรเป็นอย่างไร	
4. แนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาล ควรเป็นอย่างไร	
5. ปัญหา อุปสรรคของหน่วยงานที่มีความประสงค์ต้องการผลิตผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาล	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

ผู้ให้ข้อมูลสำคัญกลุ่มที่ 10 ผู้ประกอบการที่นำหรือสั่งผลิตภัณฑ์ยาชีววัตถุเข้ามาในประเทศไทย (รหัส 10X)

ชื่อผู้ให้ข้อมูลสำคัญ บริษัท วันที่ เวลา น.

วันที่ถอดเทปตรวจสอบ:

ส่วนที่ 1. คำถามที่เกี่ยวข้องกับข้อมูลทั่วไป

1.1 ข้อมูลทั่วไป ประสบการณ์การทำงานของผู้ให้ข้อมูลสำคัญ

1.2 หน้าที่ หรือ ความรับผิดชอบของผู้ให้ข้อมูลสำคัญ

ส่วนที่ 2. คำถามที่เกี่ยวข้องกับวัตถุประสงค์: การพัฒนาแนวทางการกำกับ ดูแล ควบคุมผลิตภัณฑ์เซลล์บำบัดเพื่อการอนุมัติทะเบียนตำรับยาที่เหมาะสมกับประเทศไทย

คำถาม	**คำตอบ**
1. ข้อมูลทั่วไปของบริษัท	
2. ทิศทางการพัฒนาผลิตภัณฑ์ยาของบริษัท	
3. การขึ้นทะเบียนตำรับยาของผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดมีความแตกต่างหรือเหมือนกับยาชีววัตถุหรือไม่ อย่างไร	
4. ในความคิดของท่านหากมีการผลิตผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดในประเทศควรมีระบบควบคุมผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดอย่างไร	

ส่วนที่ 3. คำถามที่ถามผู้ให้ข้อมูลสำคัญทุกคน

APPENDIX B

Questionnaire

1. English
2. Thai

Code .....

Questionnaire

The Guidelines on the regulation of advanced therapy medicinal products (ATMPs) (cell therapy medicinal products) in medical institutions

Terminology Definition

Minimal manipulation is referral definition from 2 main organizations as

1. USFDA means cutting, grinding, and shaping, soaking in antibiotic solution, sterilization by ethylene oxide treatment or gamma irradiation, cell separation, lyophilization, cryopreservation, and freezing.

2. EMA means cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.

Note: Please mark √ in the box (□) which match with your opinion towards the following statements and fill your additional comments in the remarks column.

Agree: you agree with the mentioned statement.

Partially agree: you partially agree with the mentioned statement.

Disagree: you disagree with the mentioned statement.

Questions	Opinion	Remarks
1. Background		
1.1 Cell therapy medicinal products are defined as 1. Minimally manipulated 2. Intended for homologous use only 3. Cells do not alter the relevant biological characteristics of cells 4. Manufactured and used within the same medical institutions The products that meet all of the requirements are classified as low-risk products, which are controlled by the Thai Medical Council and Sanatorium Act. On the other hand, the products that not meet at least one requirement are classified as high-risk products.	☐ Agree ☐ Partially agree ☐ Disagree	
1.2 Regarding the section 13 (2) under the Drug Act, B.E. 2510, ATMPs (high-risk cell therapy medicinal products) should not grant permission. These products must be controlled. Each medical practitioner is not a sole decision- maker.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
1.3 ATMPs (high-risk cell therapy medicinal products) in medical institutions can be classified into four groups. 1. Clinical research use 2. Compassionate use 3. Manufactured and used within medical institutions 4. The approved products by Food and Drug Administration (FDA)	☐ Agree ☐ Partially agree ☐ Disagree	
1.4 Clinical research of ATMPs (high-risk cell therapy medicinal products) must be approved by the institutional ethical committee only. A review and approval from the Thai Medical Council are not needed.	☐ Agree ☐ Partially agree ☐ Disagree	
1.5 The compassionate use of ATMPs (high-risk cell therapy medicinal products) should be reviewed by the institutional ethical committee before they are used in patients.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2. Recommendations for the regulation of ATMPs (high-risk cell therapy medicinal products) in medical institutions		
2.1 Lists of diseases for ATMPs (high-risk cell therapy medicinal products) used in medical institutions		
2.1.1 The Thai Medical Council and the relevant Royal College announce the lists of diseases or guidelines for the cell treatment. **or** 2.1.2 At least phase II clinical trials are conducted by the researchers in order to demonstrate safety and efficacy profiles. After that, the data are summited to the Thai Medical Council or the relevant Royal College to review and approve for the treatment.	☐ Agree ☐ Partially agree ☐ Disagree	
2.1.3 Conditions for ATMPs (high-risk cell therapy medicinal products) uses in medical institutions should be established, for example, the products that are unregistered, lack of sufficient data supporting safety and efficacy, or contraindicated in patients.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.2 Qualifications of medical practitioners		
2.2.1 The medical director is responsible for ATMPs (high-risk cell therapy medicinal products) uses in medical institutions.	☐ Agree ☐ Partially agree ☐ Disagree	
2.2.2 The Thai Medical Council and the Royal College establish qualifications for medical practitioners, which are suitable for treatment.	☐ Agree ☐ Partially agree ☐ Disagree	
2.2.3 The medical practitioners who are experts in the disease area have been certified by the Thai Medical Council or the approved organizations.	☐ Agree ☐ Partially agree ☐ Disagree	
2.2.4 The medical practitioners pass the training courses approved by the Thai Medical Council and the Royal College.	☐ Agree ☐ Partially agree ☐ Disagree	
2.2.5 There are registration systems for medical practitioners who use ATMPs (high-risk cell therapy medicinal products) for treatment.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.3 Other qualifications		
2.3.1 A qualified person, who is assigned to produce cells from medical practitioners and nurses, must pass the training courses and must be certified.	☐ Agree ☐ Partially agree ☐ Disagree	
2.4 Qualifications of laboratories or manufacturing sites		
2.4.1 The medical institutions must be registered as a manufacturing site according to the Drug Act, B.E.2510.	☐ Agree ☐ Partially agree ☐ Disagree	
2.4.2 The manufacturing site meet the requirements of the Good Manufacturing Practice (GMP).	☐ Agree ☐ Partially agree ☐ Disagree	
2.4.3 The manufacturing protocols of manufacturing site comply with Good Manufacturing Practice (GMP).	☐ Agree ☐ Partially agree ☐ Disagree	
2.4.4 Standards of the cell-therapy laboratory, released by the department of medical sciences that are used as the reference or guideline and applied for the medical institutions in Thailand.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.4.5 The operation is accordance with the current Good Tissue Practices (cGTP).	☐ Agree ☐ Partially agree ☐ Disagree	
2.5 Medical procedure		
2.5.1 The Thai Medical Council and the Royal College approve safety and efficacy of medical procedure for ATMPs (cell therapy medicinal products).	☐ Agree ☐ Partially agree ☐ Disagree	
2.5.2 Members of the medical institutions' committee, including internal or external experts, review and approve the uses of ATMP (cell therapy medicinal products) such as conditional approval that takes place in medical institutions.	☐ Agree ☐ Partially agree ☐ Disagree	
2.6 Qualifications of medical institutions		
2.6.1 ATMPs (high-risk cell therapy medicinal products) should be used in the medical institutions that are registered by the Department of Health Service Support, the Ministry of Public Health.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.6.2 During the initial phase, ATMPs (high-risk cell therapy medicinal products) should be used in hospitals only.	☐ Agree ☐ Partially agree ☐ Disagree	
2.6.3 The medical institutions must be accredited and the license must be renewed annually.	☐ Agree ☐ Partially agree ☐ Disagree	
2.7 The ATMPs: a type of cell therapy medicinal products (High risk)		
2.7.1 ATMPs (high-risk cell therapy medicinal products) can be classified into two groups. 1. The approved cell therapy medicinal products by FDA are distributed to medical institutions. 2. The unproven ATMPs (high-risk cell therapy medicinal products) must be used in the medical institutions where they are manufactured.	☐ Agree ☐ Partially agree ☐ Disagree	
2.7.2 The ATMPs type of cell therapy medicinal products (high risk) are unproven by the FDA. These products should be accepted for quality and process control. The members of the committee in medical institutions include internal or external experts who consider for approval. Such conditional approval must conduct within medical institutions.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.8 Post-treatment follow-up		
2.8.1 There should be a post-treatment follow-up for monitoring the safety and efficacy of ATMPs (high-risk cell therapy medicinal products). Especially, intensive follow-up is required during the first two years of the treatment.	☐ Agree ☐ Partially agree ☐ Disagree	
2.8.2 Adverse event report, medical report, production report, and the number of patients who are treated with ATMPs (high-risk cell therapy medicinal products) should be submitted to the Ministry of Public Health in order to collect the data directly to the central database.	☐ Agree ☐ Partially agree ☐ Disagree	
2.8.3 The government officers are allowed to reach medical institutions immediately in case there are emergent events that affect the patient's safety or to suspend the cell therapy administration.	☐ Agree ☐ Partially agree ☐ Disagree	
2.8.4 There should be random inspection or complaint reporting channels.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.8 Post-treatment follow-up		
2.8.5 There should be organizations that are responsible for the consideration of safety and efficacy of ATMPs (cell therapy medicinal products) in order to evaluate the cell therapy treatment. If the medical institutions are not able to provide effective service, they have to discontinue the service.	☐ Agree ☐ Partially agree ☐ Disagree	
2.9 Miscellaneous		
2.9.1 Advertising of ATMPs (high-risk cell therapy medicinal products) not directly to consumers is prohibited.	☐ Agree ☐ Partially agree ☐ Disagree	
2.9.2 ATMPs (cell therapy medicinal products) that are manufactured in the medical institutions should be cancelled if there are the registered products (import or manufacture) by FDA are available because they have the clear evidence supporting their benefits over risks.	☐ Agree ☐ Partially agree ☐ Disagree	
2.9.3 ATMPs (cell therapy medicinal products) should be considered in the reimbursement system because it is the high efficacy but expensive treatment.	☐ Agree ☐ Partially agree ☐ Disagree	

Comments

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Thank you all for your cooperation in answering the questionnaires

Code .....

Questionnaire

The Guidelines on the regulation of advanced therapy medicinal products (ATMPs) (cell therapy medicinal products) in terms of drug registration

Terminology Definition

1. Autologous product is derived from an individual's cells, which patient-specific products.

2. Allogeneic products are derived from a single donor, or a pool of a small number of donors to provide a large batch for treating numerous patients, exception monozygotic twin.

3. Matched allogeneic product is derived from sibling or related donor that donor is compatible of human leukocyte antigen (HLA) with the patient which patient-specific products.

Note: Please mark √ in the box (□) which match with your opinion towards the following statements and fill your additional comments in the remarks column.

Agree: you agree with the mentioned statement.

Partially agree: you partially agree with the mentioned statement.

Disagree: you disagree with the mentioned statement.

Questions	Opinion	Remarks
1. Pre-marketing authorization process		
1.1 Manufacturing process of ATMPs (cell therapy medicinal products) for marketing must be followed the Good Manufacturing Practice (GMP) under the Drug Act, B.E. 2510 and the relevant annexes. The Good Tissue Practice (GTP) must be also considered.	☐ Agree ☐ Partially agree ☐ Disagree	
1.2 ATMPs (cell therapy medicinal products) are classified as the new biologic drugs.	☐ Agree ☐ Partially agree ☐ Disagree	
1.3 ATMPs (cell therapy medicinal products; subcategory: autologous product) are the new biologic drugs that different from the traditional ones.	☐ Agree ☐ Partially agree ☐ Disagree	
1.4 ATMPs (cell therapy medicinal products; subcategory allogeneic products) are the new biologic drugs that are different from traditional ones.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2. Marketing authorization application process		
2.1 Evaluation of ATMPs (cell therapy medicinal products) is performed using the same principle as that of biological drugs in terms of quality, safety, and efficacy.	☐ Agree ☐ Partially agree ☐ Disagree	
2.2 Documents for marketing authorization application of autologous product or matched allogeneic product that required for submission to Thai Food and Drug Administration (Thai FDA) include: 1. The documents demonstrating quality, safety, and efficacy data, which are organized regarding ASEAN COMMON TECHNICAL DOSSIER (ACTD) or ICH COMMON TECHNICAL DOSSIER (ICH CTD) forms and 2. Results of finished products' quality testing from the Institute of Biological Products of the Department of Medical Sciences.	☐ agree ☐ partially agree ☐ disagree	

Questions	Opinion	Remarks
2.3 Documents for marketing authorization application of allogeneic products that required for submission to Thai FDA include: 1. The documents demonstrating quality, safety, and efficacy data, which are organized regarding ASEAN COMMON TECHNICAL DOSSIER (ACTD) or ICH COMMON TECHNICAL DOSSIER (ICH CTD) forms and 2. Results of finished products' quality testing from the Institute of Biological Products of the Department of Medical Sciences	☐ Agree ☐ Partially agree ☐ Disagree	
2.4 Considerations of finished products' quality testing from Institute of Biological Products of the Department of Medical Sciences are based on the following criteria: - Objective of the tests - Laboratory capabilities - Quantity of samples - Cost - Global standard operating procedures - Cost-effectiveness The cost of the quality testing is considered a part of the total cost for drug research, development, and registration processes. Therefore, it affects the market prices of the drugs.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.5 There should be a protocol facilitating approval of ATMPs (cell therapy medicinal products) for life-threatening conditions and unmet medical needs in urgent cases.	☐ Agree ☐ Partially agree ☐ Disagree	
2.6 The conditional approval should be considered for ATMPs (cell therapy medicinal products).	☐ Agree ☐ Partially agree ☐ Disagree	
2.7 In the conditional approval, the marketing authorization holders should be allowed to conduct the post-marketing studies for evaluating safety and efficacy of the drugs. In addition, the post-marketing data should be considered for the permanent registration or cancellation of registration of the drugs (if the data is insufficient to prove their safety and efficacy).	☐ Agree ☐ Partially agree ☐ Disagree	
2.8 The conditional approval must include the risk management plan (RMP) and the updated Periodic Safety Update Report (PSUR) documents.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.9 The ATMPs (type of cell therapy medicinal products) should be established expedite programs as other countries, such as 1. Fast Track Designation in the USA 2. Breakthrough Therapy Designation in the USA 3. Priority Medicine Scheme in the EU 4. SAKIGAKE Designation in JAPAN	☐ Agree ☐ Partially agree ☐ Disagree	
2.10 Regarding the requirements of section 25 (6) and 27 (6) of the Drug Act, B.E. 2510, medicinal products or the retained samples must be kept if they are manufactured and imported. Autologous product or matched allogeneic product are the exceptions for these requirements; however, their labels, package inserts, drug containers, and the relevant documents must be kept.	☐ Agree ☐ Partially agree ☐ Disagree	
2.11 Regarding the requirements of sections 25 (6) and 27 (6) of the Drug Act, B.E. 2510, allogeneic products or the retained samples must be kept if they are manufactured and imported.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
2.12 Certificated of lot release of ATMPs (cell therapy medicinal products) are not required because the drugs are not in the lists of lot release control of biological products.	☐ Agree ☐ Partially agree ☐ Disagree	
2.13 ATMPs (cell therapy medicinal products) should be available in the registered medical institutions under the Department of Health Service Support, Ministry of Public Health.	☐ Agree ☐ Partially agree ☐ Disagree	
2.14 Medical institutions should be evaluated by manufactures or marketing authorization holders before receiving the permission for ATMPs (cell therapy medicinal products) uses, especially autologous product or matched allogeneic product cells, because they are collected and transported to manufacturing sites in order to ensure the constant standard between transportation and treatment.	☐ Agree ☐ Partially agree ☐ Disagree	
3. Post-marketing authorization process		
3.1 The post-marketing process is the most important step for ATMPs (cell therapy medicinal products).	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
3.2 Like other medicinal products, a risk-based approach safety monitoring program should be applied in the post-marketing process of ATMPs (cell therapy medicinal products).	☐ Agree ☐ Partially agree ☐ Disagree	
3.3 The specific protocol for monitoring ATMPs (cell therapy medicinal products) uses should be designed because the products have a higher risk than other drugs.	☐ Agree ☐ Partially agree ☐ Disagree	
3.4 The specific protocol for monitoring ATMPs (cell therapy medicinal products) uses should include the following components. -Medical institutions are registered for ATMPs (cell therapy medicinal products) service. -Health care providers such as physicians, pharmacists, nurses, and transportation staff have sufficient knowledge and skills. -The equipment for maintaining the quality of medicines -Availability of antidotes for emergency events -There must be a traceability system to track of the process of drug manufacturer, transportation, storage, distribution, and treatment. -Patient confidentiality such as consent form	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
3.5 Risk Management Plan (RMP) should be considered for registration of ATMPs (cell therapy medicinal products).	☐ Agree ☐ Partially agree ☐ Disagree	
3.6 RMP should be reviewed every 1-2 years to keep the data up to date regarding the dynamic of safety data.	☐ Agree ☐ Partially agree ☐ Disagree	
3.7 The intensive post-marketing process of ATMPs (cell therapy medicinal products) should be conducted in the 2-year interval such as patient registration or the follow-up system for all patients.	☐ Agree ☐ Partially agree ☐ Disagree	
3.8 Safety and efficacy data of ATMPs (cell therapy medicinal products) should be monitored in the post-marketing process.	☐ Agree ☐ Partially agree ☐ Disagree	
3.9 The concept of Adverse Events Following Immunization (AEFI) should be applied for the post-marketing process of ATMPs (cell therapy medicinal products).	☐ Agree ☐ Partially agree ☐ Disagree	
3.10 The central database is important to link and deliver information between the internal and external organizations.	☐ Agree ☐ Partially agree ☐ Disagree	

Questions	Opinion	Remarks
3.11 Thai FDA should provide the pharmacovigilance system inspection of ATMPs (cell therapy medicinal products) manufactures and imports.	☐ Agree ☐ Partially agree ☐ Disagree	
4. Miscellaneous		
4.1 ATMPs (cell therapy medicinal products) should be considered in the reimbursement system because it is the high efficacy but expensive treatment.	☐ Agree ☐ Partially agree ☐ Disagree	

Comments

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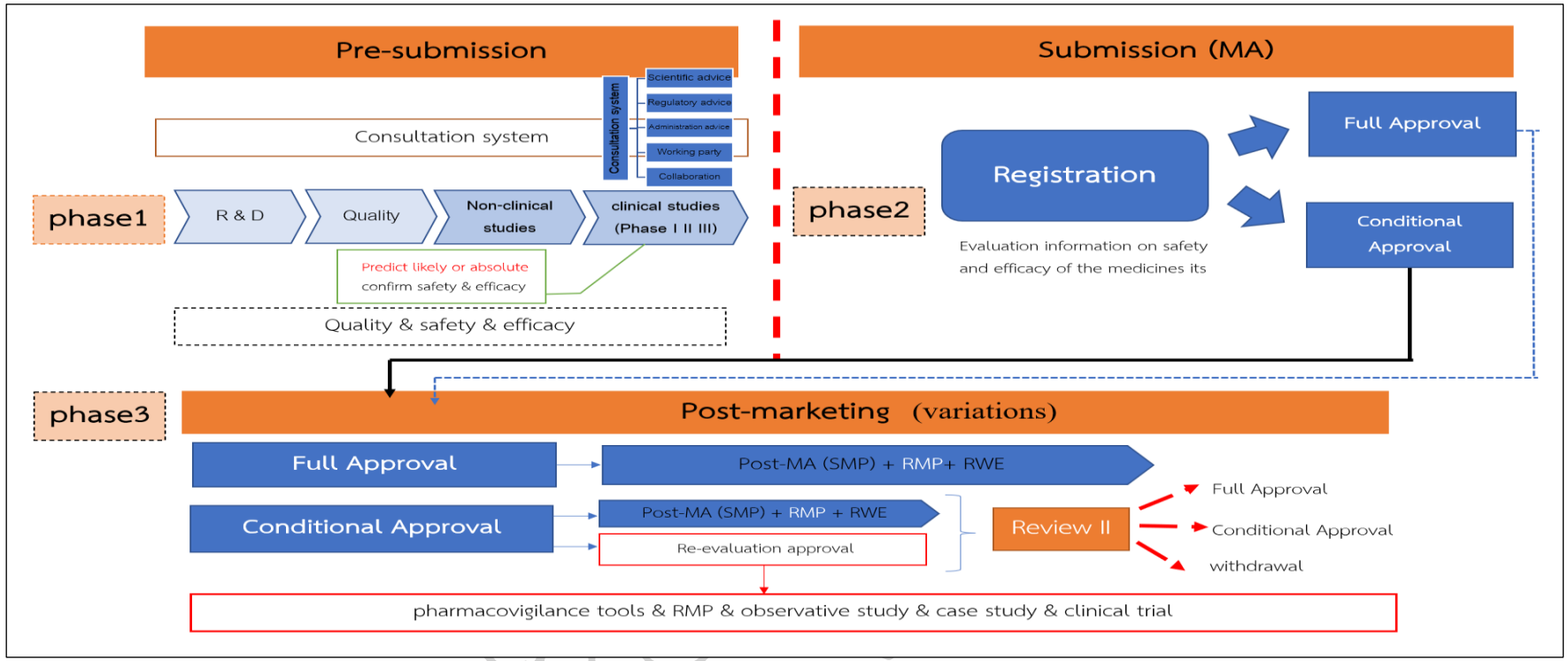
Overview of drug registration on Advanced Therapy Medicinal Product (ATMPs) (cell therapy medicinal products) in terms of drug registration



RWE; Real World Evidence

☐ Agree
☐ Partially agree
☐ Disagree

Remarks

.....

.....

Thank you for your cooperation in answering the questionnaires.

แบบสอบถาม โครงการวิจัย การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัด ที่เหมาะสมกับประเทศไทย

<u>วัตถุประสงค์งานวิจัย</u>

การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

<u>คำชี้แจง</u>

1. หลังจากที่ท่านได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้เนื่องจากท่านเป็นผู้ที่มีประสบการณ์ มีความเชี่ยวชาญ และเป็นผู้ปฏิบัติงานที่เกี่ยวข้องกับผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายใสถานพยาบาลของประเทศไทย ผู้วิจัยได้เก็บข้อมูลจากการสัมภาษณ์ท่านระหว่างเดือนมีนาคม – กรกฎาคม พ.ศ. 2564

2. ผู้วิจัยได้จัดทำบทสรุปแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์ผลิตภัณฑ์เซลล์เพื่อการบำบัดรักษาโรคภายในสถานพยาบาล จากการสัมภาษณ์และศึกษาเอกสารที่เกี่ยวข้อง เพื่อให้ท่านลงความคิดเห็นอีกครั้ง (รายละเอียดตามเอกสารแนบ)

3. ขอความร่วมมือจากท่านในการตอบแบบสอบถามตามความเป็นจริงเพราะข้อมูลที่ท่านตอบทุกข้อมีค่าและมีประโยชน์อย่างมาก เพราะถ้าหากขาดข้อมูลข้อใดข้อหนึ่งไป จะส่งผลทำให้การที่จะนำข้อมูลไปวิเคราะห์ขาดความสมบูรณ์และไม่สามารถนำไปใช้ประโยชน์ในการวิจัยได้ ขอความกรุณาส่งคืนแบบสอบถามภายใน**<u>สามสัปดาห์</u>** (***ภายในวันที่ 9 กันยายน 2564***) หลังจากที่ท่านได้รับ

4. หากท่านมีข้อสงสัยหรือข้อเสนอแนะประการใดกรุณาติดต่อ ผู้วิจัย น.ส. พัชราพรรณ กิจพันธ์ โทร 082-2716421 E-mail: <u>patcharaphun_k@yahoo.com</u> (สามารถติดต่อได้ตลอด 24 ชั่วโมง)

ผู้วิจัยหวังว่าจะได้รับความร่วมมือในการตอบแบบสอบถามเป็นอย่างดี และใคร่ขอขอบพระคุณ ท่านมา ณ โอกาสนี้ด้วย

ขอแสดงความนับถือ

น.ส. พัชราพรรณ กิจพันธ์

(ผู้วิจัย)

รหัส .....

การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลที่เหมาะสมกับประเทศไทย

<u>นิยามคำศัพท์</u>

minimal manipulation อ้างอิงจาก 2 หน่วยงานหลัก คือ

1. The USFDA คือ cutting, grinding, and shaping, soaking in antibiotic solution, sterilization by ethylene oxide treatment or gamma irradiation, cell separation, lyophilization, cryopreservation, and freezing และ

2. The EMA คือ cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification

<u>คำชี้แจง</u> โปรดใส่เครื่องหมาย / ลงในช่อง ☐ หน้าข้อความให้ตรงกับความเป็นจริงของท่านมากที่สุด หรือเติมข้อความในช่องว่างที่กำหนด

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
1. ข้อมูลเบื้องต้น		
ผลิตภัณฑ์เซลล์บำบัดที่มีลักษณะ ดังนี้ 1. minimally manipulated 2. intended for homologous use only 3. cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells 4. ดำเนินการผลิตและใช้ภายในสถานพยาบาลเดียวกัน ต้องเป็นไปตามข้อกำหนดทุกข้อที่กล่าวมา จะถูกจัดว่าเป็น**<u>ผลิตภัณฑ์ความเสี่ยงต่ำ</u>** การกำกับ ดูแล ให้อยู่ภายใต้ความรับผิดชอบของผู้ประกอบวิชาชีพ และกฎหมายสถานพยาบาล แต่หากอยู่นอกเหนือจากที่กล่าวมาเพียงข้อใดข้อหนึ่งผลิตภัณฑ์ชนิดนั้นจะถูกจัดว่าเป็นผลิตภัณฑ์ความเสี่ยงสูง	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2. ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) **ไม่ควร**ถูกอนุโลมตามมาตรา 13 (2) ของ พรบ. ยาฯ เพราะเป็นผลิตภัณฑ์ที่มีความเสี่ยงสูงต้องมีการกำกับ ดูแลที่เหมาะสมมากกว่าการใช้โดยไม่มีการควบคุมใดๆ หรือเกิดจากการตัดสินใจของผู้ประกอบวิชาชีพกรรมเพียงคนเดียว	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
3. ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) รูปแบบการรักษาเพื่อผู้ป่วยภายในสถานพยาบาลสามารถเป็นไปได้ 4 กรณี 1. การวิจัยภายในสถานพยาบาล (clinical research) 2. การรักษากรณี compassionate use 3. การเปิดบริการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดที่ผลิตและใช้ภายในสถานพยาบาลเท่านั้น 4. การใช้ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ที่ได้รับการอนุมัติขึ้นทะเบียนจากหน่วยงานควบคุมยา	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
4. การวิจัยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) ภายในสถานพยาบาล (clinical research) ผ่านคณะกรรรมการจริยธรรมการทำวิจัยในคนของสถาบันที่ผู้วิจัยสังกัด เท่านั้น ไม่ต้องผ่านคณะกรรมการของแพทยสภา	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
5. การใช้ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด กรณี (ความเสี่ยงสูง) compassionate use ควรผ่านการพิจารณาจากคณะกรรมการการจริยธรรมการทำวิจัยในคนของสถาบัน ก่อนดำเนินการรักษาแก่ผู้ป่วย	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2. ข้อเสนอแนะต่อการกำกับ ดูแล ควบคุม ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) รูปแบบการรักษาเพื่อผู้ป่วยภายในสถานพยาบาล		
2.1 การกำหนดรายการโรคที่สามารถนำผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดมาใช้เพื่อการรักษา (ความเสี่ยงสูง)		
2.1.1 หน่วยงานแพทยสภา หรือ ราชวิทยาลัยที่เกี่ยวข้อง ประกาศกำหนดรายการโรค และแนวทางการรักษาว่าโรคใดที่สามารถนำเซลล์มาใช้ในการรักษากับผู้ป่วยได้ **หรือ** 2.1.2 แพทย์ผู้วิจัยทำการทดลองอย่างน้อยในมนุษย์เฟส 2 ภายในโรงพยาบาล เพื่อสนับสนุนข้อมูลประสิทธิภาพและความปลอดภัย แล้วเสนอไปยังราชวิทยาลัยที่เกี่ยวข้อง หรือ แพทยสภา เพื่อประกาศรับรองเป็นวิธีมาตรฐานการรักษา ก่อนเปิดให้บริการกับผู้ป่วย	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.1.3 กำหนดเงื่อนไขในการใช้แพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) ภายในสถานพยาบาล เช่น ไม่มีผลิตภัณฑ์ยาที่ได้รับการอนุมัติทะเบียนในประเทศ **หรือ** ไม่มีความเหมาะสมด้านประสิทธิภาพ หรือความปลอดภัย **หรือ** มีข้อห้ามใช้สำหรับผู้ป่วย	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.2 คุณสมบัติของผู้ประกอบวิชาชีพเวชกรรม		
2.2.1 ต้องมีแพทย์ผู้อำนวยการ หรือผู้ที่ได้รับมอบหมายโดยตรง เป็นผู้รับผิดชอบการกระทำทั้งหมดที่จะเกิดขึ้นภายใต้การรักษาด้วยเซลล์บำบัดภายในสถานพยาบาล	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.2.2 แพทยสภา หรือ ราชวิทยาลัยที่เกี่ยวข้องกำหนดคุณสมบัติของผู้ประกอบวิชาชีพ ที่เหมาะสมต่อการรักษาด้วยเซลล์บำบัด	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.2.3 ผู้ประกอบวิชาชีพเวชกรรมมีความเชี่ยวชาญในโรคของผู้ป่วย โดยได้รับวุฒิบัตร หรือหนังสืออนุมัติจากแพทยสภาหรือหน่วยงานที่แพทยสภารับรอง	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.2.4 ผ่านการอบรมตามหลักสูตรจากราชวิทยาลัยที่เกี่ยวข้องหรือแพทยสภากำหนด	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.2.5 มีระบบขึ้นทะเบียนแพทย์ที่สามารถให้การรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง)	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.3 คุณสมบัติของผู้ที่เกี่ยวข้องอื่นๆ นอกเหนือจากผู้ประกอบวิชาชีพเวชกรรม		
2.3.1 ผู้ที่ได้รับมอบหมายในการผลิตเซลล์จากผู้ประกอบวิชาชีพเวชกรรม และ 2. พยาบาล ดูแลผู้ป่วยต้องผ่านการอบรม หรือได้รับวุฒิบัตรที่เกี่ยวข้อง	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.4 คุณสมบัติของสถานที่หรือห้องปฏิบัติการด้านเซลล์ทางการแพทย์		
2.4.1 สถานพยาบาลต้องได้รับการขึ้นทะเบียนเป็นสถานที่ผลิตยาแผนปัจจุบัน ตาม พรบ. ยาฯ	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.4.2 สถานที่ผลิตเซลล์ผ่านการรับรองปฏิบัติตามหลักเกณฑ์วิธีการที่ดีในการผลิตยา Good Manufacturing Practice (GMP)	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.4.3 สถานที่ผลิตเซลล์ต้องปฏิบัติให้มีความสอดคล้องกับหลักเกณฑ์วิธีการที่ดีในการผลิตยา compliance with Good Manufacturing Practice (GMP)	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.4.4 มาตรฐานห้องปฏิบัติการเซลล์ทางการแพทย์ที่กรมวิทยาศาสตร์การแพทย์ได้จัดทำขึ้น สามารถนำมาใช้อ้างอิง หรือ เป็นแนวทางในการสร้างห้องปฏิบัติการเซลล์ทางการแพทย์ได้ในช่วงเริ่มต้นได้สำหรับประเทศไทย	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.4.5 ดำเนินการตามระบบคุณภาพเกี่ยวกับเซลล์ หรือเนื้อเยื่อคือ Current Good Tissue Practices (cGTP)	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.5 กระบวนเวชปฏิบัติ (medical procedure)		
2.5.1 ราชวิทยาลัยที่เกี่ยวข้อง หรือ แพทยสภา รับรองเวชปฏิบัติของผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ว่ามีความปลอดภัย และมีประโยชน์ต่อผู้ป่วย	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.5.2 คณะกรรมการของสถานพยาบาล ซึ่งอาจมีผู้เชี่ยวชาญทั้งภายใน หรือภายนอกร่วมพิจารณาการอนุญาตให้เปิดบริการการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด อาจเป็นในลักษณะของ conditional approval ที่เกิดขึ้นภายในสถานพยาบาลเท่านั้น	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.6 คุณสมบัติของสถานพยาบาล		
2.6.1 ต้องเป็นสถานพยาบาลที่ขึ้นทะเบียนตาม พรบสถานพยาบาล และ .เพิ่มบริการการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง เซลล์บำบัด	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.6.2 สถานพยาบาลที่เปิดบริการการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ในระยะเริ่มต้นควรเป็นโรงพยาบาลเท่านั้น (ความเสี่ยงสูง)	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.6.3 มีการตรวจประเมิน และต่ออายุใบอนุญาตสถานพยาบาลที่เปิดบริการการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ทุกปี (ความเสี่ยงสูง)	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.7 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง)		
2.7.1 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) สามารถแบ่งออกได้เป็นสองประเภท คือ 1. ผลิตภัณฑ์ที่ขึ้นทะเบียน อย. สามารถกระจายไปยังสถานพยาบาลอื่นๆ ได้ 2. ผลิตภัณฑ์ที่ไม่ได้ขึ้นทะเบียน อย. ต้องใช้ภายในสถานพยาบาลที่มีการผลิตเท่านั้น	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.7.2 ผลิตภัณฑ์ที่ไม่ได้ขึ้นทะเบียน อย. ควรมีหน่วยงานให้การรับรองคุณภาพและการควบคุมการผลิต หรือจัดตั้งคณะกรรมการของสถานพยาบาล ซึ่งอาจมีผู้เชี่ยวชาญทั้งภายใน หรือภายนอก (อย. และราชวิทยาลัยที่เกี่ยวข้อง) เพื่อร่วมพิจารณาอนุญาตผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด อาจเป็นในลักษณะของ conditional approval ที่เกิดขึ้นภายในสถานพยาบาลเท่านั้น	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.8 กระบวนการติดตามหลังการรักษาภายในสถานพยาบาล		
2.8.1 มีกระบวนการติดตามทั้งความปลอดภัยและประสิทธิภาพภายหลังการได้รับการรักษาด้วยผลิตภัณฑ์เซลล์บำบัด โดยสองปีแรกของการรักษาต้องมีการติดตามแบบใกล้ชิด หลังจากนั้นติดตามตามความเหมาะสมของผู้ป่วย	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.8.2 ส่งรายงานอาการไม่พึงประสงค์ รายงานผลการรักษา รายงานการผลิต และผู้ป่วยที่ได้รับการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ไปยัง (ความเสี่ยงสูง) กระทรวงสาธารณสุข เพื่อรวบรวมข้อมูลการรักษาและเป็นการเก็บข้อมูลไว้ที่ส่วนกลาง	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.8.3 เจ้าพนักงานสามารถที่จะเข้าไปยังสถานพยาบาลเมื่อเกิดเหตุที่อาจจะส่งผลต่อความไม่ปลอดภัยกับผู้ป่วย หรือระงับการให้บริการเซลล์บำบัดได้ทันที	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.8.4 พิจารณาการสุ่มตรวจ หรือมีช่องทางรับรายงานเรื่องร้องเรียน	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.8.5 ควรมีหน่วยงานติดตามการรักษาด้วยเซลล์บำบัดแก่ผู้ป่วย มีหน้าที่พิจารณาผลลัพธ์จากการรักษาด้วยเซลล์บำบัด ไม่ว่าจะเป็นด้านประสิทธิภาพ ความปลอดภัย เพื่อนำข้อมูลมาเพื่อใช้ในการประเมินการให้บริการด้วยเซลล์บำบัด และถ้าหน่วยบริการแห่งใดไม่มีประสิทธิภาพในการรักษาสามารถที่จะปิดการให้บริการ	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.9 ประเด็นอื่นๆ ที่เกี่ยวข้อง		
2.9.1 ไม่ควรโฆษณาการรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด (ความเสี่ยงสูง) โดยตรงต่อประชาชน	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.9.2 กรณีเมื่อมีการนำเข้า หรือ ผลิต ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ที่ผ่านการอนุมัติทะเบียนจาก อย. แล้ว**ควรยกเลิก**การรักษาด้วยผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ที่มีการผลิตและการใช้ภายในสถานพยาบาลในข้อบ่งใช้เดียวกัน เพราะผลิตภัณฑ์ที่ผ่านการอนุมัติทะเบียนมีหลักฐานทางวิชาการที่แสดงถึงประโยชน์มากกว่าความเสี่ยงอย่างชัดเจน	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.9.3 พิจารณาระบบการเบิกจ่าย (reimbursement) สำหรับการรักษาที่มีมูลค่าสูง แต่มีผลลัพธ์ทางการรักษาที่มีประสิทธิภาพมากกว่าการรักษาที่มีในปัจจุบัน เช่น ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ข้อเสนอแนะ หรือความคิดเห็นอื่นๆ

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ขอขอบคุณทุกท่านที่ให้ความร่วมมือในการตอบแบบสอบถามค่ะ

โครงการวิจัย การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดที่เหมาะสมกับประเทศไทย

<u>วัตถุประสงค์งานวิจัย</u>

เพื่อพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการขึ้นทะเบียนผลิตภัณฑ์ที่เหมาะสมสำหรับประเทศไทย

<u>คำชี้แจง</u>

1. หลังจากที่ท่านได้รับเชิญให้เข้าร่วมในโครงการวิจัยนี้เนื่องจากท่านเป็นผู้ที่มีประสบการณ์ มีความเชี่ยวชาญ และเป็นผู้ปฏิบัติงานที่เกี่ยวข้องกับผลิตภัณฑ์เซลล์บำบัดเพื่อการขึ้นทะเบียนผลิตภัณฑ์ของประเทศไทย ผู้วิจัยได้เก็บข้อมูลจากการสัมภาษณ์ท่านระหว่างเดือนมีนาคม – กรกฎาคม พ.ศ. 2564

2. ผู้วิจัยได้จัดทำบทสรุปแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์ผลิตภัณฑ์เซลล์บำบัดเพื่อการขึ้นทะเบียนผลิตภัณฑ์ที่เหมาะสมสำหรับประเทศไทย จากการสัมภาษณ์และศึกษาเอกสารที่เกี่ยวข้อง เพื่อให้ท่านลงความคิดเห็นอีกครั้ง (รายละเอียดตามเอกสารแนบ)

3. ขอความร่วมมือจากท่านในการตอบแบบสอบถามตามความเป็นจริงเพราะข้อมูลที่ท่านตอบทุกข้อมีค่าและมีประโยชน์อย่างมาก เพราะถ้าหากขาดข้อมูลข้อใดข้อหนึ่งไปจะส่งผลทำให้การที่จะนำข้อมูลไปวิเคราะห์ขาดความสมบูรณ์และไม่สามารถนำไปใช้ประโยชน์ในการวิจัยได้ ขอความกรุณาส่งคืนแบบสอบถามภายใน**สามสัปดาห์** (***ภายในวันที่ 9 กันยายน 2564***) หลังจากที่ท่านได้รับ

4. หากท่านมีข้อสงสัยหรือข้อเสนอแนะประการใดกรุณาติดต่อ ผู้วิจัย น.ส. พัชราพรรณ กิจพันธ์ โทร 082-2716421 E-mail: patcharaphun_k@yahoo.com (สามารถติดต่อได้ตลอด 24 ชั่วโมง)

ผู้วิจัยหวังว่าจะได้รับความร่วมมือในการตอบแบบสอบถามเป็นอย่างดี และใคร่ขอขอบพระคุณ ท่านมา ณ โอกาสนี้ด้วย

ขอแสดงความนับถือ
น.ส. พัชราพรรณ กิจพันธ์
(ผู้วิจัย)

รหัส .....

การพัฒนาแนวทางการกำกับ ดูแล ควบคุม ผลิตภัณฑ์เซลล์บำบัดเพื่อการขึ้นทะเบียนผลิตภัณฑ์ที่เหมาะสมสำหรับประเทศไทย

นิยามคำศัพท์

1. Autologous product; คือ ผลิตภัณฑ์เซลล์ที่เตรียมจากเซลล์ หรือเนื้อเยื่อตนเอง เพื่อใช้สำหรับตนเองเท่านั้น
2. Allogeneic products; คือ ผลิตภัณฑ์เซลล์ที่เตรียมจากเซลล์ หรือเนื้อเยื่อมนุษย์ เพื่อใช้สำหรับผู้อื่น ยกเว้นฝาแฝดไข่ใบเดียวกัน
3. Matched allogeneic product; คือ การนำเซลล์ เนื้อเยื่อจากพี่น้อง ร่วมบิดามารดาหรือญาติ (sibling หรือ related donor) โดยผู้บริจาคจะต้องมีความเข้ากันได้ของลักษณะทางหมู่เนื้อเยื่อ หรือ human leukocyte antigen (HLA) กับผู้ป่วย เป็นการผลิตยาที่เฉพาะกับผู้ป่วยเท่านั้น

คำชี้แจง โปรดใส่เครื่องหมาย / ลงในช่อง ☐ หน้าข้อความให้ตรงกับความเป็นจริงของท่านมากที่สุด หรือเติมข้อความในช่องว่างที่กำหนด

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
1. กระบวนก่อนอนุมัติทะเบียนยา (pre marketing authorization)		
1.1 กระบวนการผลิตผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด เพื่อวางจำหน่ายต้องกระทำภายในสถานที่ผลิตยาที่เป็นไปตามแนวทางการผลิตที่ดี Good manufacturing practice: GMP ภายใต้ข้อบังคับของ พรบ. ยา พ.ศ. 2510 และที่แก้ไขเพิ่มเติม และภาคผนวกที่เกี่ยวข้อง (annex) อีกทั้งต้องนำหลักการ Good tissue practice: GTP ร่วมด้วย	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
1.2 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ถูกจัดว่าเป็นยาชีววัตถุใหม่	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
1.3 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ประเภท autologous product เป็นผลิตภัณฑ์ชนิดใหม่และแตกต่างไปจากยาชีววัตถุดั่งเดิม	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
1.4 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ประเภท allogeneic products เป็นผลิตภัณฑ์ชนิดใหม่และแตกต่างไปจากยาชีววัตถุดั่งเดิม	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2. กระบวนการอนุมัติทะเบียนยา (marketing authorization application)		
2.1 หลักการประเมินทะเบียนผลิตภัณฑ์การแพทย์ขั้นสูงชนิดเซลล์บำบัด เหมือนกับการประเมินทะเบียนยาชีววัตถุที่มีพื้นฐานหลักของ quality, safety และ efficacy	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.2 เอกสารประกอบการขออนุมัติทะเบียนผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด รูปแบบ autologous product หรือ matched allogeneic product ควรประกอบด้วย 1. ข้อมูลผลิตภัณฑ์ยาที่แสดงถึงคุณภาพ (quality) ความปลอดภัย (safety) ประสิทธิผล (efficacy) ที่จัดเรียงในรูปแบบ ACTD หรือ ICHCTD และ 2. ผลการตรวจวิเคราะห์ผลิตภัณฑ์สำเร็จรูป ทางห้องปฏิบัติการโดยหน่วยงานสถาบันชีววัตถุ กรมวิทยาศาสตร์การแพทย์	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.3 เอกสารประกอบการขออนุมัติทะเบียนผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด รูปแบบ allogeneic products ประกอบด้วย 1. ข้อมูลผลิตภัณฑ์ยาที่แสดงถึงคุณภาพ (quality) ความปลอดภัย (safety) ประสิทธิผล (efficacy) ที่จัดเรียงในรูปแบบ ACTD หรือ ICHCTD และ 2. ผลการตรวจวิเคราะห์ผลิตภัณฑ์สำเร็จรูป ทางห้องปฏิบัติการโดยหน่วยงานสถาบันชีววัตถุ กรมวิทยาศาสตร์การแพทย์	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
2.4 การพิจารณาตรวจทางห้องปฏิบัติการ โดยการวิเคราะห์ตัวอย่างผลิตภัณฑ์ยาสำเร็จรูป จากหน่วยงานภาครัฐ ควรพิจารณาองค์ประกอบ -จุดประสงค์การตรวจวิเคราะห์ -ศักยภาพของการดำเนินการตรวจวิเคราะห์ทางห้องปฏิบัติการ -ปริมาณตัวอย่างที่ใช้ -ราคาของผลิตภัณฑ์ -หลักปฏิบัติของสากล และ -ความคุ้มค่าจากการตรวจวิเคราะห์ เนื่องจากค่าใช้จ่ายที่เกิดขึ้นจากการตรวจวิเคราะห์ทางห้องปฏิบัติการจะเป็นส่วนหนึ่งของการการวิจัย พัฒนายา และการขึ้นทะเบียน มีผลต่อราคาขายในอนาคตที่สามารถส่งผลกระทบต่อผู้ป่วย	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.5 การอนุมัติทะเบียนผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ควรมีช่องทางในการอนุมัติทะเบียนในกรณีที่เร่งด่วน สำหรับผลิตภัณฑ์ยากลุ่ม life-threatening condition, unmet medical needs	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.6 ควรพิจารณาอนุมัติทะเบียนแบบมีเงื่อนไข (conditional approval) สำหรับผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.7 อนุมัติทะเบียนแบบมีเงื่อนไข (conditional approval) อย. สามารถกำหนดให้ผู้ขออนุญาตขึ้นทะเบียนผลิตภัณฑ์ทำการศึกษาเพิ่มเติม เพื่อติดตามความปลอดภัย และประสิทธิภาพ ภายหลังการอนุญาต และนำข้อมูลเหล่านั้นมาประกอบการอนุมัติทะเบียนแบบถาวร หรือ ยกเลิกทะเบียน กรณีที่ไม่สามารถพิสูจน์ให้เห็นถึงประสิทธิภาพและความปลอดภัยภายหลังการอนุมัติทะเบียนแบบมีเงื่อนไข	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.8 อนุมัติทะเบียนแบบมีเงื่อนไข (conditional approval) ต้องประกอบด้วย Risk management plan (RMP) และการแสดงข้อมูลด้านความปลอดภัย Periodic Safety Update Report (PSUR) ที่ทันสมัย	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.9 ควรมีระบบ Expedite Programs ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด เช่น 1. Fast track Designation เป็นโครงการในประเทศสหรัฐอเมริกา 2. Breakthrough Therapy Designation เป็นโครงการในประเทศสหรัฐอเมริกา 3. Priority medicine scheme เป็นโครงการในสหภาพยุโรป 4. SAKIGAKE designation เป็นโครงการในประเทศญี่ปุ่น	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.10 จากข้อกำหนดของ พรบ. ยาฯ มาตรา 25 (6) และ 27 (6) กรณีของการผลิตหรือนำสั่งต้องมีการเก็บตัวอย่างยา (retain sample) ที่นำเข้าหรือผลิตของผลิตภัณฑ์แต่ผลิตภัณฑ์รูปแบบ autologous product หรือ matched allogeneic product **ไม่**ต้องดำเนินการข้อกำหนดนี้ แต่ต้องเก็บฉลาก ภาชนะบรรจุ เอกสารทุกอย่างที่มีลักษณะเหมือนผลิตภัณฑ์ยา	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.11 จากข้อกำหนดของ พรบ. ยาฯ มาตรา 25 (6) และ 27 (6) กรณีของการผลิตหรือนำสั่งต้องมีการเก็บตัวอย่างยา (retain sample) ที่นำเข้าหรือผลิตของผลิตภัณฑ์ ผลิตภัณฑ์รูปแบบ allogeneic products ต้องดำเนินการตามข้อกำหนดนี้	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
2.12 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ไม่ต้องมีการรับรองรุ่นการผลิต (certificate of lot release) เพราะไม่ได้อยู่ในประกาศกระทรวงสาธารณสุข เรื่อง กำหนดชนิดหรือรายการของยาชีววัตถุที่ต้องได้รับหนังสือรับรองรุ่นการผลิตก่อนออกจำหน่ายหรือส่งมอบให้ผู้ใช้ พ.ศ. 2555	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.13 การให้บริการผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ควรดำเนินการภายในสถานพยาบาลที่ถูกขึ้นทะเบียนกับกรมสนับสนุนบริการสุขภาพ (สบส.) กระทรวงสาธารณสุข	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
2.14 สถานพยาบาลที่จะดำเนินการเปิดบริการผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ควรได้รับการตรวจประเมินจากผู้ผลิต หรือ Marketing Authorization Holder ก่อน โดยเฉพาะกรณีผลิตภัณฑ์ autologous product หรือ matched allogeneic product เนื่องจากมีการเก็บเลือด หรือเซลล์ และขนส่งไปยังสถานที่ผลิต เพื่อให้เกิดมาตรฐานที่เหมาะสมระหว่างการขนส่ง และการรักษา	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
3. กระบวนการหลังอนุมัติทะเบียนยา (post- marketing authorization)		
3.1 กระบวนการติดตามหลังอนุมัติทะเบียนยามีความสำคัญ**<u>มากที่สุด</u>**ของผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
3.2 การติดตามหลังอนุมัติทะเบียนยาของผลิตภัณฑ์ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด สามารถใช้หลักการของ risk-based approach Safety Monitoring Program เหมือนยาประเภทอื่นๆ ได้	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
3.3 ควรออกหลักเกณฑ์การติดตาม**เฉพาะ**กับผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด เพราะเป็นผลิตภัณฑ์ผลิตภัณฑ์ที่มีความเสี่ยงสูงมากกว่าผลิตภัณฑ์ยาชนิดอื่น	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
3.4 หลักเกณฑ์**เฉพาะ**กับผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ควรมีองค์ประกอบเหล่านี้ -ความพร้อมด้าน**สถานที่** โดยการลงทะเบียนสถานที่ให้บริการผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด -ความพร้อมด้าน**บุคลากร**ในทีมการรักษา (medical team) เช่น แพทย์ (มีความเชี่ยวชาญในโรคของผู้ป่วย) เภสัชกร (การจัดเก็บยา รักษาคุณภาพของผลิตภัณฑ์ยา) พยาบาล (ดูแลในการให้การบริบาลผู้ป่วย) รวมถึงพนักงานขนส่ง -ความพร้อมของ**อุปกรณ์ในการเก็บรักษาคุณภาพของยา**ภายในสถานพยาบาล -ความพร้อม**ด้านยา** เมื่อเกิดอาการฉุกเฉินจากการใช้ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด -ระบบการทวนสอบ **traceability system** เพื่อมั่นใจในการทำกระบวนการผลิต การขนส่ง การเก็บรักษา และการนำไปใช้ -การรักษา**ความลับ**ข้อมูลส่วนบุคคลของผู้ป่วย การขอความยินยอม (consent form) การส่งข้อมูลที่อาจมีความเกี่ยวข้องกับพันธุกรรมของผู้ป่วย	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
3.5 Risk Management Plan (RMP) ควรเป็นเงื่อนไขในการขึ้นทะเบียนผลิตภัณฑ์ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
3.6 ควรมีการประเมิน RMP ทุก 1-2 ปี เพื่อความทันสมัยต่อการเปลี่ยนแปลงข้อมูลด้านความปลอดภัย	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
3.7 ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดต้องมีการติดตามเชิงรุกเป็นระยะเวลาอย่างน้อย 2 ปี เช่น การลงทะเบียนผู้ป่วย หรือระบบที่ทำให้สามารถติดตามผู้ป่วยได้ทุกราย	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
3.8 การติดตามผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดควรมีการติดตามทั้งด้าน**ความปลอดภัย**และ**ประสิทธิผล**	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
3.9 การติดตามหลังอนุมัติทะเบียนยาของผลิตภัณฑ์ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด ควรนำหลักการปฏิบัติของ Adverse Events Following Immunization: AEFI มาประยุกต์ใช้	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	
3.10 สร้างฐานข้อมูลกลาง เพื่อเชื่อมโยง และส่งต่อข้อมูล ให้หน่วยงานทั้งภายในอย .และภายนอกที่เกี่ยวข้อง เป็นสิ่งที่มีความสำคัญ	☐ เห็นด้วย ☐ เห็นด้วยบางส่วน ☐ ไม่เห็นด้วย	

ประเด็นการพิจารณา	ความคิดเห็น	เหตุผล
3.11 อย. ควรมีการตรวจสอบ (inspection) ระบบ pharmacovigilance ของผู้ผลิต หรือผู้นำสั่ง สำหรับผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	
4. ประเด็นอื่นๆ ที่เกี่ยวข้อง		
4.1 พิจารณาระบบการเบิกจ่าย (reimbursement) การรักษาที่มีราคาสูง แต่มีผลลัพธ์การรักษาที่มีประสิทธิภาพมากกว่าการรักษาที่มีอยู่ในปัจจุบัน เช่น ผลิตภัณฑ์ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัด	☐ **เห็นด้วย** ☐ **เห็นด้วยบางส่วน** ☐ **ไม่เห็นด้วย**	

ข้อเสนอแนะ หรือความคิดเห็นอื่นๆ

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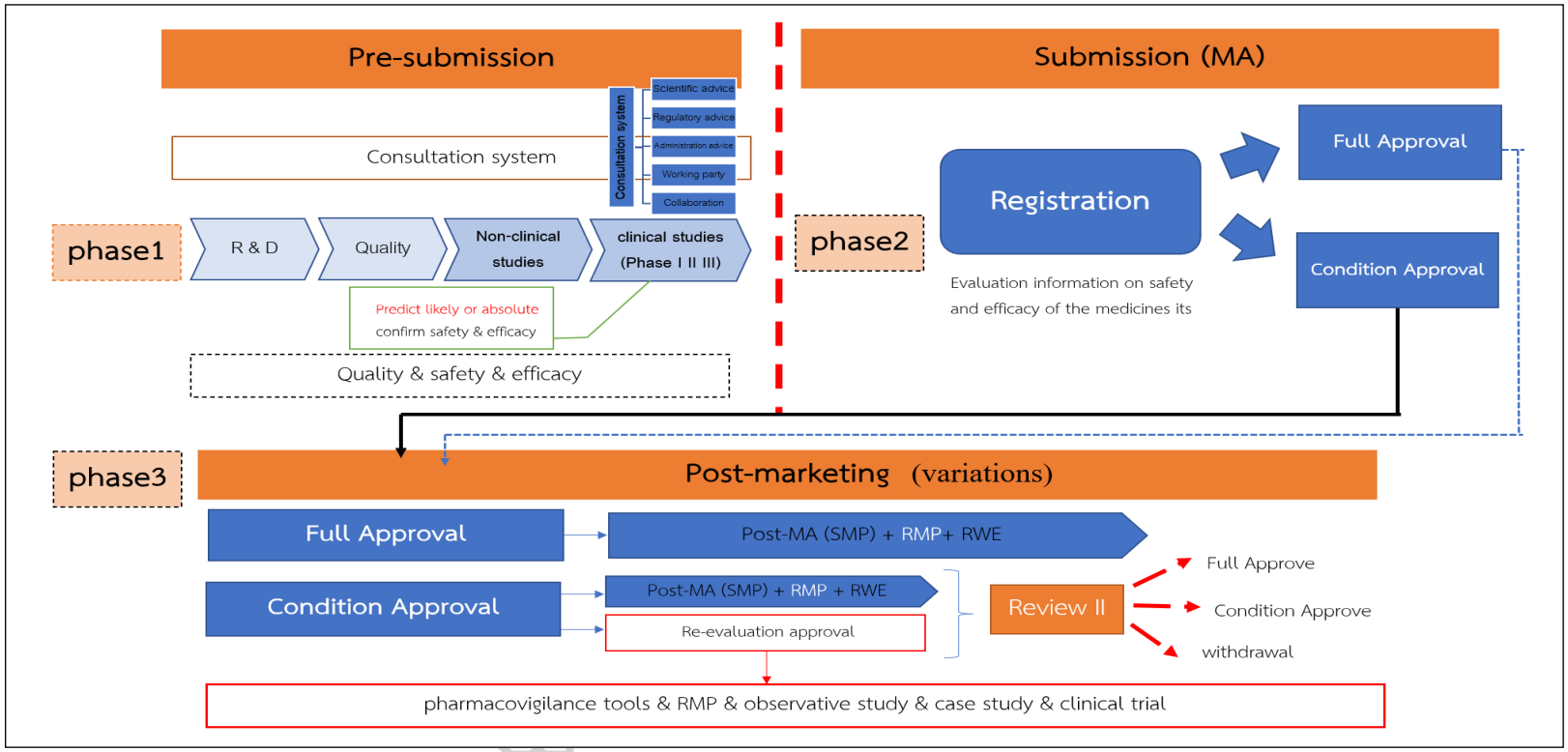
สรุปภาพรวมของการขึ้นทะเบียนผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดที่เหมาะสมสำหรับประเทศไทย



RWE; Real World Evidence

☐ เห็นด้วย

☐ เห็นด้วยบางส่วน

☐ ไม่เห็นด้วย

เหตุผล.....

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ขอขอบคุณทุกท่านที่ให้ความร่วมมือในการตอบแบบสอบถามค่ะ

APPENDIX C

Additional recommendations for development of regulatory guideline for cell therapy medicinal products in Thailand

1. English
2. Thai

1. Additional recommendations for medical institutions' regulations regarding the use of cell therapy medicinal products that may be suitable for Thailand.

1.1 In Thailand, there is a scarcity of knowledge and expertise in the field of cell therapy medicinal products. As a result, it is vital to research and adapt lessons from other countries to Thailand's situation.

1.2 The use and production of cell therapy medicinal products in medical institutions is a novel treatment approach that is fundamentally different from other therapies. Furthermore, the production and administration processes are also complex. There is a need for new types of rules. To ensure patient access and safety, regulatory authorities such as the Thai FDA, DMSc, HSS, the Thai Medical Council, and the relevant Royal Colleges must be involved.

1.3 Cell-based therapy is not explicitly regulated in Thailand's legislation. As a result, regulatory agencies must provide the public with accurate information and communication about cell therapies. People must be aware of and sensitive of treatments that are not supported by scientific data or government bodies.

1.4 The government should financially support and reimburse the cost of undergoing cell-based therapies which is deem expensive, so that more people would have access to it. The government should also fund research at all levels (upstream, midstream, and downstream) and long-term research plan should also be set to develop this field.

2. Additional recommendations for cell therapy medicinal product regulations in terms of drug registration that may be applicable in Thailand.

2.1 As more knowledge is gained, the regulatory framework is continuing to adapt the provision or law on cell therapy medicinal products. It is not covered for new items because they are not have been registered in Thailand.

2.2 Strengthen regulations for ATMPs: cell therapy medicinal products such as by forming a disciplinary working group and reviewing and updating current standard guidelines. This type of applied regulation is appropriate for the Thai context.

2.3 Regulators such as the Thai FDA, HPVC, DMSc, and health care providers, should be provided with knowledge and skills in the development of people. Due to a lack of understanding and experience with these products.

2.4 To achieve the same level of success as Japan and Korea, the government must support the cell-based therapy eco-system through life-cycle products such as policy, funding, collaboration, and networking. Furthermore, reimbursement is required for access due to high price.

1. ข้อเสนอแนะเพิ่มเติมต่อการควบคุมการให้บริการเซลล์บำบัดเพื่อการบำบัดรักษาโรคภายในสถานพยาบาลของประเทศไทย

1.1 องค์ความรู้และผู้เชี่ยวชาญด้านการกำกับ ดูแล ผลิตภัณฑ์การแพทย์ขั้นสูง ชนิดเซลล์บำบัดในประเทศมีจำกัด

1.2 การควบคุมการรักษาด้วยผลิตภัณฑ์เซลล์บำบัดทั้งที่มีกระบวนการผลิตและการใช้ภายในสถานพยาบาลมีลักษณะเฉพาะเจาะจงกับผู้ป่วยแต่ละรายเป็นการรักษารูปแบบใหม่ซึ่งมีความแตกต่างไปจากเดิมและมีความซับซ้อนด้านกระบวนการได้มาซึ่งผลิตภัณฑ์และกระบวนการรักษา ดังนั้นรูปแบบของการควบคุมอาจจะต้องมีการเปลี่ยนแปลงไปจากเดิม หน่วยงานกำกับ ดูแลที่ต้องเข้ามามีส่วนเกี่ยวข้อง เช่น เช่น อย. กรมวิทย์ฯ สบส. แพทยสภา และราชวิทยาลัยที่เกี่ยวข้องต้องพิจารณาแนวทางการควบคุมที่เฉพาะและเหมาะสมกับผลิตภัณฑ์เซลล์บำบัดโดยที่ประชาชนสามารถเข้าถึงการรักษาที่มีประสิทธิภาพและปลอดภัย

1.3 ปัจจุบันยังไม่มีกฎหมายที่เป็นรูปธรรม ชัดเจน ในการกำกับ ดูแล การใช้ผลิตภัณฑ์เซลล์บำบัดในประเทศไทย ดังนั้นหน่วยงานที่มีหน้าที่กำกับ ดูแล ควบคุม ต้องให้ความรู้และสื่อสารข้อมูลให้แก่ประชาชน รวมถึงประชาชนต้องมีความตระหนักรู้และเท่าทันต่อการรักษาที่ไม่สามารถพิสูจน์ได้จากหลักฐานทางวิทยาศาสตร์

1.4 ภาครัฐให้การสนับสนุนอนุมัติเบิกจ่ายค่ารักษาพยาบาลจากหน่วยงานหลักประกันสุขภาพ หรือหน่วยงานที่เกี่ยวข้อง เพื่อก่อให้เกิดการเข้าถึงการรักษาของผู้ป่วยด้วยนวัตกรรมการรักษาด้วยเซลล์บำบัด ซึ่งมีค่าใช้จ่ายที่สูง และสนับสนุนทุนวิจัยในการพัฒนาทั้งในระดับต้นน้ำ กลางน้ำ และปลายน้ำเพื่อต่อยอดทางอุตสาหกรรมที่มีมูลค่าและสามารถแข่งขันในระดับนานาชาติ นอกจากนั้นจำเป็นต้องมีแผนการวิจัย พัฒนาในระยะยาวของประเทศเพื่อเกิดความต่อเนื่องในการพัฒนา

2. ข้อเสนอแนะเพิ่มเติมต่อการกำกับ ดูแล ควบคุม ATMPs ชนิดเซลล์บำบัดเพื่อการขึ้นทะเบียนของประเทศไทย

2.1 การปรับปรุง เปลี่ยนแปลง หรือเพิ่มกฎหมายที่เกี่ยวข้องกับ ATMPs ชนิดเซลล์บำบัด เนื่องจากกฎหมายที่มีอยู่ในปัจจุบันไม่ครอบคลุมผลิตภัณฑ์รูปแบบใหม่ โดยเฉพาะลักษณะ autologous product ที่ไม่เคยขึ้นทะเบียนตำรับยาในประเทศไทยมาก่อน

2.2 พิจารณาสร้างความเข้มแข็งภายในระบบการควบคุม ATMPs ชนิดเซลล์บำบัด เช่น จัดตั้งคณะทำงานเฉพาะโดยมีผู้เชี่ยวชาญสาขาที่เกี่ยวข้อง ทบทวนแนวทางของสากลและปรับปรุงให้ทันสมัยรวมถึงพิจารณาบริบทของประเทศร่วมด้วย

2.3 พัฒนาบุคลากรด้านการกำกับ ดูแล ควบคุม ATMPs ชนิดเซลล์บำบัด เช่น ผู้ที่เกี่ยวข้องกับการประเมินทะเบียน การติดตามหลังวางจำหน่าย หน่วยงานศูนย์เฝ้าระวังความปลอดภัยด้านผลิตภัณฑ์สุขภาพ การตรวจวิเคราะห์ทางห้องปฏิบัติการ รวมถึงบุคลากรทางการแพทย์ที่ดูแลผู้ป่วยที่ใช้ ATMPs ชนิดเซลล์บำบัดภายในสถานพยาบาล เนื่องจากประเทศไทยยังมีองค์ความรู้จำกัด

2.4 ภาครัฐควรให้การส่งเสริมและสนับสนุน เช่น นโยบาย ทุนวิจัย การสร้างความเชื่อมโยงระหว่างนักวิจัยและภาคอุตสาหกรรม เพื่อสร้างระบบนิเวศน์ในการพัฒนาผลิตภัณฑ์ยาอย่างครบวงจร และสร้างแผนที่นำทาง (road map) เพื่อให้เกิดการทำงานที่ต่อเนื่องเหมือนในประเทศเกาหลี และญี่ปุ่น นอกจากนั้นควรมีระบบรองรับการเข้าถึงผลิตภัณฑ์ยาของผู้ป่วยเนื่องจากยามีราคาสูง

VITA

NAME	Miss. Patcharaphun Kidpun
DATE OF BIRTH	5 November 1986
PLACE OF BIRTH	Bangkok, Thailand
INSTITUTIONS ATTENDED	Thai Food and Drug Administration, Ministry of public health
HOME ADDRESS	29/51 Kanchanaphisek 005/1 Lane, Kanchanaphisek Road, Lak Song Sub-district, Bang Khae District Bangkok, 10160, Thailand