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Review Article

Regulatory Practices

Non-clinical, quality and environmental impact assessments of cell and gene therapy products: Report on the 5th Asia Partnership Conference of Regenerative Medicine - April 7, 2022

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ABSTRACT

The 5th Asia Partnership Conference of Regenerative Medicine (APACRM) was held online on April 7, 2022 to promote regulatory harmonization of regenerative medicine products throughout Asia. The recognition of domestic regulatory guidelines within each country and region and the underpinning rationales are important initial steps toward the harmonization of regulations. The 5th APACRM featured open dialog regarding non-clinical, quality and environmental impact assessment settings for cell and gene therapy products through presentations from the industry and panel discussions with regulatory agencies. The latest updates on regenerative medicine fields in each country and region were also introduced. This paper summarizes the proceedings of the 5th APACRM for public dissemination to foster future discussion.

Introduction

The Asia Partnership Conference of Regenerative Medicine (APACRM) was established in 2018 with the aim of optimizing and eventually harmonizing the regulations of regenerative medicine (RM) including but not limited related to product/raw material quality control, requirement for preclinical evaluation, manufacturing and patient eligibility/safety across Asian countries and regions, with the leading industry associations for RM as contributing members of the forum (Figure 1). Although RM is usually defined as a cell therapy, therapeutic tissue-engineering product, human cell and tissue product in the narrow sense, it is expanded to include *in vivo* gene therapy products. The broader mission of the APACRM is to support the development and delivery of high-quality RM products to all patients within Asia.

The 5th APACRM meeting was held online on April 7, 2022, which assembled 50 presenters and panelists, in addition to 150 viewing

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Figure 1. Participating members of the APACRM: ABLE, Association of Biotechnology Led Enterprises (India); CMBA, China Medicinal Biotech Association (China); BPIPO, Biotechnology and Pharmaceutical Industries Promotion Office (Taiwan); SAPI, Singapore Association of Pharmaceuticals Industries (Singapore); RMAF, Regenerative Medicine Acceleration Foundation; CARM, The Council for Advanced Regenerative Medicine (Korea); and FIRM, Forum for Innovative Regenerative Medicine (Japan).

audiences from India, Singapore, China, Korea, Taiwan, Japan, Indonesia, Malaysia and the Philippines. Notably, health authority regulators from each country and region joined the discussion as panelists and commenting participants.

This proceeding paper summarizes the content of the 5th APACRM, with particular focus given to the discussion with regulators based on the survey results of three working groups (WGs): WG1 for non-clinical assessments, WG2 for quality assessments and WG3 for environmental impact assessments for genetically modified organism (GMO).

Program and Session Summaries

The 5th APACRM consisted of five sessions (supplementary Table 1).

Session 1: Update on RM from each industrial association

In the first session, "Update on regenerative medicine from each participating industry association," an array of topics pertaining to RM in each country and region was shared. Approved RM products for each country and region are listed in supplementary Table 2.

Japan

Yoshitsugu Shitaka, a presenter of the Forum for Innovative Regenerative Medicine, provided an update on the development and regulations of cell and gene therapy (CGT) products in Japan. Five products have been approved within the last year, bringing the total number up to 16 as of March 2022. Twelve of these products have been fully approved, whereas the other four products were given conditional and time-limited approvals. Since 2019, four autologous chimeric antigen receptor-T (CAR-T) cell products have been approved. The development in gene therapy, especially in the category of adeno-associated virus, has been increasing rapidly in line with the global active trend. The regulatory system related to the Cartagena Act, which requires developers to carry out the assessment of the environmental impact of the use of living modified organisms, has improved significantly through exchange of views between the regulators and the industry. One improvement is that it has become possible to apply for partial change by obtaining viral shedding data during clinical stages. Another improvement is an abolishment of the confirmation step of a draft application of the type 1 usage for the Cartagena Act by Pharmaceutical and Medical Device Agency (PMDA). With these improvements, developers are able to initiate clinical trials more easily and to optimize the measures against viral shedding at the clinical trial stages.

China

Herui Wang, a presenter from the China Medicinal Biotech Association, shared updated regulations, standards developed by the industrial association and approved RM products in China. The Biosecurity law, published in 2021, requires researchers and developers to register equipment and materials associated with biotechnology research development and application, such as gene sequences, cells and organs. Developers also need to pay attention to the new pharmacopoeia volume III and IV because these specifically stipulate biological products required throughout production. Volume IV focuses more on the general requirements for pharmaceutical excipient, drug validation and reference materials. In addition, three trial guidelines for gene therapy have been issued by the Center for Drug Evaluation, which address non-clinical study and evaluation of human gene therapy, non-clinical study and evaluation of cell therapy products with gene modifications and long-term follow-up for gene therapy products. Apart from the governmental guidelines, an industrial standard with a focus on the ethical assessment of stem cell sources has been published. Developers are required to protect the privacy of donors and conduct ethical assessment through qualified organizations. Two autologous CAR-T cell products, Yescarta and Carteyva, have been approved in 2021. Nine mesenchymal stem cell products derived from the umbilical cord, bone marrow, adipose cells or other sources are in clinical trials for the treatment of immune-associated diseases.

Korea

Bryan Choi, a presenter from the Council for Advanced Regenerative Medicine and Regenerative Medicine Acceleration Foundation, provided an update on product development and regulations in Korea. In 2021, Kymriah, Zolgensma and Luxturna were approved, and a total of 18 products had been approved for the market since the first approval in 2001. Among these products, six products, including Kymriah and Zolgensma, are covered by the National Health Insurance. Luxturna is

currently under the review process. It is estimated that >75% of Korean citizens are covered by private health insurance, but the amount of insurance coverage for expensive cell and gene therapies, such as Kymriah and Zolgensma, is very limited. All the 18 products were newly categorized as advanced biopharmaceuticals (ABPs) according to the Advanced Regenerative Bio Act enacted in August 2020. It consists of two tracks, the Advanced Regenerative Medicine track for clinical research, controlled by the Ministry of Health and Welfare, and the ABP track for commercial trials, controlled by Ministry of Food and Drug Safety (MFDS). Both tracks deal with the same categories of cell therapy, gene therapy, tissue-engineering therapy and combination therapy. The Advanced Regenerative Medicine track classifies therapies into low, middle or high group, depending on the risk level. Cell produced using advanced technologies, such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and CAR-T cells belong to the high-risk group. Only certified hospitals and clinics can submit clinical research proposal, and only those cell processing centers certified by the MFDS can provide therapeutic cells. The ABP track manages the safety during the entire product life cycle. Regarding the procurement of raw material cells, a new certification for "Management Business for Human Cells etc." is a mandatory license required to procure cells and tissues from hospitals, process down in Good Manufacturing Practice (GMP) facility, and supply as raw materials to cell therapy companies. Cell therapy companies need the license to directly procure cells from hospitals. MFDS established three special review schemes to promote ABP therapies. The tailored review adopts the rolling review process, and the priority review expedites the review process. The conditional approval allows for market approval after phase 2 trial, with a condition that the phase 3 trial will be conducted.

Singapore

Wong Kum Cheun, from the Singapore Association of Pharmaceuticals Industries, presented the current national CGT regulations and the environmental risk assessment. The cell, tissue and gene therapeutic products (CTGTPs) are regulated under the Health Products Act that was implemented from March 1, 2021. The Health Products Act covers broad areas, which include manufacturing, import, supply, presentation, registration, duties and obligations of manufacturers or importers and certification. CTGTPs are stratified into two classes. The class I products, which have lower risk, are minimally manipulated, intended for homologous use and not combined or used in conjunction with therapeutic products or medical devices. The class II products include high-risk products, such as gene-modified cells or vectors with therapeutic genes. The class II products can go through two evaluation routes: the full pathway, which is for a new product that has not been approved by any comparable overseas regulator, or the abridged pathway, which is for a product that has been approved by at least one of the comparable overseas regulators. These regulators include the Therapeutic Goods Administration of Australia, Health Canada, US Food and Drug Administration (FDA), European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency. According to the Appendix 8 of the Health Sciences Authority (HSA) guidance, CTGTPs containing GMOs, such as viral vectors, require environmental risk assessment (ERA) before clinical trials and product registrations. Applicants must submit an ERA application to the Genetic Modification Advisory Committee This procedure normally follows the EU guidelines for the ERA assessment and the regulatory requirements for Genetic Modification Advisory Committee recommendations. This forms part of the dossier submission to HSA for clinical trials or product registration applications.

India

Dr. Pawan Kumar Gupta, of the Association of Biotechnology Led Enterprises in India, presented the national regulation and approval processes for CGT products. According to the New Drugs and Clinical Trials Rules, 2019, issued by the Central Drugs Standard Control Organization (CDSCO), any stem cell–derived products, gene therapeutic products or xenografts intended for use will always remain a new drug. A new drug means any drug that is not yet approved by Central Licensing authority under Drugs and Cosmetic Act 1940. The clarification document issued by the government of India, dated February 9, 2021, states that a stem cell–derived product refers to a drug processed by means of substantial or more than minimal manipulation or manipulation by genetic engineering. The first step of the approval process for cell- or stem cell–derived products from Indian manufacturers is to get the GMP facility approval. Manufacturers have to submit applications for the manufacturing of experimental test batches to the Central Licensing Authority. Pre-clinical studies can be conducted with cells manufactured in approved facilities. Applications for clinical trials are submitted with clinical batches manufactured in the approved facility. The review processes are conducted within 30 days. For developers outside India, applications are submitted, in addition to a clinical trial form, to import finished formulations for test and analysis and these are reviewed within 90 days. For new drugs approved outside India, phase 3 studies need to be conducted to generate evidence of efficacy and safety of the drug in Indian patients. Exposure to Indian patients is required for approval of New Drugs in India. There are several approval systems for expedited patient use in unmet medical needs, and accelerated approval is considered for serious, life-threatening or rare diseases. The conditional approval is dependent on the nature of products. Orphan drugs are defined as drugs for diseases affecting not more than 500 000 patients. As of April in 2022, there are five approved cell- or stem cell–derived products in India.

Taiwan

Thai-Yen Ling, a presenter of Taiwan Association for Cellular Therapy (TACT) and a Director of Department of Pharmacology College of Medicine, National Taiwan University, spoke on the current status of cell therapy and RM in Taiwan. One of the most important regulations for cell therapy is the administrative interim measures of inspection and testing of medical instruments or use of special medical techniques, referred to as “Regulations Governing the Application of Specific Medical Technique and Medical Device,” which was established in 2018. In the regulation, six types of cells that are considered safe to use as autologous can be administered to patients for autograft therapy. These include CD34-positive hematopoietic stem cells, immune cells, adipose-derived mesenchymal stem cells, fibroblasts, bone marrow–derived mesenchymal cells and chondrocytes. According to statistics on the application and approval for cell therapy, >300 cases have been submitted for application, and 120 cases have currently received the approval. Aside from autologous cell therapy, two drugs, Zolgensma and Kymriah, have been approved for RM, whereas 80 cases for cell therapy and 28 cases for gene therapy are under clinical trials. Two RM Acts are expected to be passed by legislature in 2023: Regulations on the Implementation of Regenerative Medicine focus on medical treatment protocols, and Regulations on the Administration of Regenerative Medicinal products focus on cellular products.

Session 2: WG 1 activity

Introduction to panel discussion

WG 1 involves the non-clinical assessment of RM products and the harmonization across Asia. We kicked off our activity focusing on CAR-T products in July 2021, with 38 experts in the industry gathering from five countries/regions. The panel discussion was conducted in two parts: Aim 1: Comparing the non-clinical test packages of CAR-T product required for IND submission among Asian countries/regions and Aim 2: Discussing the non-clinical assessments required for next-generation CAR-T products. For a fruitful discussion within a

limited time, question/discussion points were shared with regulators in advance. (supplementary Table 3).

Panel Discussion Aim 1

Background

Since the approval of the world's first CAR-T product, Kymriah, in 2017, the development of CAR-T products has become active worldwide. CD19–CAR-T products are most advanced in progress with some have been launched or are in late clinical studies. There are other CAR-T products come close in development targeting hematological malignancy.

To conduct the survey for the IND submission, WG1 sets a virtual CAR-T product with a similar profile to CD19–CAR-T (supplementary Figure 1), and presented non-clinical packages following the available guideline of each country/region.

Based on these survey outcomes, we extracted discussion points and questions for regulators to elucidate their viewpoints on the non-clinical evaluation of CAR-T products. The discussion was further divided into pharmacology, cellular kinetics and biodistribution (CKBD) and safety.

Pharmacology

In the pharmacology session, three specific topics were discussed. The first topic was the selection of CAR-T cell source for *in vitro* and *in vivo* studies. CAR-T cells derived from patients are ideal, but they are not easily obtained due to limited accessibility, compared with those derived from healthy volunteers or commercially available peripheral blood mononuclear cells. In the WG1 survey, all the respondents considered that non-clinical pharmacology studies, in which CAR-T cells derived from healthy volunteers or commercially available peripheral blood mononuclear cells are used as cell sources, should be acceptable. The answers from Japanese, Korean, Taiwan and Singaporean regulators were similar to the WG1 survey results, suggesting there is no need to use CAR-T cells derived from patients. Moreover, the Indian regulator commented about the selection of cell source for CAR-T as follows:

CDSCO, India regulator.

> *"The selection of cell source for CAR-T depends on the risk factor. The patient-derived CAR-T cells may be used; however, CAR-T cells derived from healthy subjects may also be used for preclinical testing."*

The second topic was the selection of tumor model for *in vivo* studies. In the WG1 survey, all respondents suggested that *in vivo* pharmacological evaluation with xenograft tumor model would be sufficient for *in vivo* study of the conventional virtual CAR-T. With regard to this topic, all the regulators presented similar opinions to the results of WG1 survey, suggesting there is no need of assessments in other models, including the syngeneic model.

The third topic was the estimation of the clinical cell dose before the first-in-human study. In cell therapy, it is very challenging to estimate the clinical cell dose from animal data. In particular, the graft-versus-host disease (GVHD) response that occurs in animals after administration of human T cells is one of the critical issues. In WG1 survey, the respondents from Japan, China and Korea proposed that clinical studies of similar products should be used as reference to estimate clinical cell dose. The respondents from Taiwan and India emphasized on an extrapolation strategy from animal dosing. In this panel discussion, we asked if extrapolation from animal cell dose is recommended for the estimation of clinical cell dose. The Japanese, Korean, and Singaporean regulators all answered "no," whereas the Indian regulator answered "yes." The Taiwanese regulators answered "no," but they added that the extrapolation from animal dose is also possible. The rationales of the answers from Japanese and Indian regulators were as follows:

PMDA, Japan regulator.

> *"From the pharmacological point of view, non-clinical pharmacological studies can be used for clinical dose estimation. However, in terms of safety, we believe that there are limitations in considering human dosing based solely on the result of animal studies, as GVHD may occur if CAR-T cells derived from human are administered to animals. Therefore, human dosage should be established by considering the results of clinical trials of similar products."*

CDSCO, India regulator.

> *"Our answer is 'no.' Actually, it is not specifically required because the response in humans is totally different from that in animals, but it is useful in certain case as an indicator. Starting dose is mainly based on safety, and to some extent, proof-of-concept (PoC) can be obtained from an animal model. Extrapolation is usually not possible, but the results from an animal model can act as an indicator."*

Cellular kinetics and biodistribution

In WG1 industry survey for IND-enabling study packages of the virtual CAR-T product, all the countries/regions stated that *in vivo* cellular kinetics is necessary, and some similarities and differences were found in the details of the study conditions. At the panel discussion with Asian authorities, the following three topics were discussed:

The first topic was the rationale for the time points of blood and tissue sampling in CKBD study. The WG1 industry survey showed that the time points were dependent on the countries/regions, and each country/region has its own rationales, and we asked Asian authorities if they have solutions to this seemingly simple challenge. All regulators, except for the Japanese regulator, answered "Yes, we have rationales for time points of blood and tissue sampling." The comments or rationales are summarized as follows:

PMDA, Japan regulator.

> *"Several guidelines for cell therapy products in Japan describe the objective of CKBD. The guidelines state that the objective of CKBD is to estimate the survival of cells for tissues and duration of the effect of administered cells as general consideration. However, CAR-T cells are generally expected to be widely distributed after systemic administration. CKBD evaluation is not important for conventional CAR-T cells. Therefore, we do not have any rationale for the time points or tissue selection."*

HSA, Singapore regulator.

> *"We would actually ensure that the peak time and elimination phase are considered for blood collection and tissue sampling."*

CDSCO, India regulator.

> *"The purpose of CKBD is to assess the systemic exposure achieved in animals and its relationship with the dose levels and the time course of the toxicity studies because once the cells go into the blood, they basically replicate and their persistence in the blood is seen. Therefore, our response is that sampling points should be at the peak time, recovery time, and the elimination phase during monitoring, and they should be reported."*

Taiwan Center of Drug Evaluation (CDE), Taiwan regulator.

> *"The applicant should demonstrate the distribution and persistence of CAR-T cell products. Therefore, multiple time points are recommended to demonstrate these."*

The second topic was the rationale for tissue selection in CKBD study of CAR-T products. The tissue selection was also dependent on the countries/regions in the WG1 industry survey. Some are based on the properties of the cell product, some insisted that most of the tissues should be monitored, and some are based on the guidance for gene therapy products. We asked Asian authorities for their opinions. Among the five authorities, India, Singapore and Taiwan regulators had their own rationales, whereas Japan and Korea had no rationales. Key comments are summarized as follows:

PMDA, Japan regulator.

> *"As mentioned previously, CAR-T cells are expected to be widely distributed following systemic administration, and hence, a CKBD evaluation is not necessary."*

HSA, Singapore regulator.

> *"The rationale depends on the product itself. Actually, it is good to collect as many tissue samples as possible for analysis. Of course, this is an autologous product, and we are talking about CAR-T for blood cancer, which is different from iPSC-derived CAR-T products."*

CDSCO, Indian regulator.

> *"With regard to New Drugs and Clinical Trial Rules 2019, we basically request all the sponsors of these studies to choose tissues similar to those used in the toxicity studies."*

Taiwan CDE, Taiwan regulator.

> *"The applicant may select the organs/tissues based on similar products approved in Taiwan or other countries/regions. This information may be obtained from the public assessment reports published by US FDA, EMA or other regulatory bodies."*

The third topic was the evaluation of CKBD for un-transduced T cells. We asked whether the evaluation of CKBD for un-transduced T cells is necessary for the autologous CAR-T cells, and the answer from all the regulators was "no." However, we also asked "what about the development of next-generation products, such as allogeneic or iPSC-derived product? In this case, do we need to evaluate CKBD?" The answers from authorities are summarized as follows:

PMDA, Japan regulator.

> *"Unless there is a specific concern that affects CKBD, CKBD evaluation is not required for next generation CAR-T cells."*

HSA, Singapore regulator.

> *"Unless the untransduced T cells have specific concerns, this is not required."*

CDSCO, India regulator.

> *"Based on current understanding, we agree that it may not be required unless the sponsor justifies its need."*

Safety

Regarding non-clinical toxicology data package for virtual CAR-T cell products, WG1 survey in the industry suggested that there are slightly different viewpoints on the data package potentially required among countries/regions. Two specific topics, human tissue cross-reactivity test (TCR) and immunogenicity, were discussed in this session.

TCR test

Traditionally, TCR has been considered as a standard assay to assess on-target/off-target and off-tumor binding potential of the binders of biological products; however, it is not clear whether this approach can be applied to CAR-T cell therapy. In addition, plasma membrane protein array (PMPA) has recently been developed for on-target and off-target binding assessment, which is a cell array that expresses >5500 human plasma membrane proteins [1]. The question to health authorities for this topic was "when it is known that the target CDxx is highly specific to B cells, based on the literature, is the human TCR study necessary to initiate a clinical trial of CDxx CAR-T cell product, in addition to PMPA that is separately conducted?" The regulators from India and Korea answered "yes," and those from Japan, Taiwan and Singapore answered "no." The importance of the reliable information of characteristic and expression patterns of target antigen was also noticed. Key comments are shown as follows:

HSA, Singapore regulator.

> *"No need for TCR because we are talking about a specific target and a specific indication on the B cells. TCR may not be necessary to initiate a clinical trial with this specific target in mind. An example is CD19 CAR-T, which is specifically expressed on B cells. There is a supplement data from PMPA, which can provide information on the off-target binding potential. Therefore, if there is any risk, we have to see if it needs to be addressed, but generally, there is no need for TCR."*

PMDA, Japan regulator.

> *"The evaluation of on-target effects by TCR is not considered mandatory if the sponsor can explain on-target effect using the information from databases and published literature on target expression. Moreover, off-target effects should be evaluated by assays, such as PMPA."*

CDSCO, India regulator.

> *"In this case, PMPA is separately conducted to assess off-target effects, but our answer is 'yes' because it is recommended to identify the off-target bindings and to identify the sites of on-target bindings, which were not previously identified. Precisely yes, if the sponsor is able to justify through supplemental tests using PMPA, which can also be added to the submissions. Precisely our answer is yes, broadly."*

Taiwan CDE, Taiwan regulator.

> *"No, but it depends on the robustness of the evidence for B-cell-specific expression of CDxx and the selectivity of the single-chain fragment variable (scFv) to the target CDxx."*

Immunogenicity

In general, immunogenicity can be assessed in clinical studies. An example of non-clinical assessment for immunogenicity that was proposed by some industry members was to measure anti-CDxx scFv antibody from mice administered mouse surrogate CAR-T cells. The question on this topic was "Do the health authorities think non-clinical immunogenicity assessment is necessary for the initiation of a clinical trial of CDxx–CAR-T cell product?" and "If necessary, what

kind of studies/assays do the authorities consider useful?" The regulator from India answered "yes," whereas other regulators from Japan, Korea, Taiwan and Singapore answered "no," recognizing that non-clinical immunogenicity studies provide limited knowledge for assessing immunogenicity potential in humans in most cases. Key comments are shown as follows:

HSA, Singapore regulator.

> *"No. it is not required. We do not think it will give any immunogenicity information in animals. As you said, it should be carried out on the clinical samples."*

PMDA, Japan regulator.

> *"We said no because we believe that it is difficult to predict immunogenicity in humans by assessing the immunogenicity in* in vivo *animal studies. If there are any specific concerns,* in vitro *study using human cells might be an option to evaluate the effects on the human immune system."*

CDSCO, India regulator.

> *"Actually, it is optional, as correctly mentioned in the Indian survey, but yes, it may be required because this non-clinical immunogenicity assessment may provide basic information about the immunogenicity response elicited by the immune system to the CAR-T cell products. However, if the sponsor is able to justify that it is not necessary, it may not be required. As per our New Drugs and Clinical Trial Rules, it is optional, depending on the nature of the product and the source of the gene of interest, which is to be introduced in the T-cell products during the preparation of CAR-T cells."*

Panel Discussion Aim 2

Background

Although some products have successfully been used in the treatment of hematological malignancy, CAR-T therapy still has some limitations. The first group of limitations includes the high cost, long production time, quality variability and production failure, which are associated with the autologous nature of the products. The second group of limitations are associated with efficacy and safety. Current CAR-T products are only effective against hematological malignancy and have several safety concerns, such as cytokine-releasing syndrome, neurotoxicity, and potential tumorigenesis. To address these limitations, several approaches have been under trial as next-generation CAR-T therapies.

This panel discussion involved non-clinical considerations for four product categories: (i) allogeneic CAR-T, (ii) iPSC-derived CAR-T for off-the-shelf CAR-T, (iii) solid tumor and (iv) other components for effective and safe CAR-T.

Allogeneic CAR-T

Allogeneic, off-the-shelf CAR-T products have the potential to address various limitations of autologous products, such as high price, long production time, quality variability and manufacturing failure. Donor-derived PBMCs and cord blood, both containing differentiated immune cells or $CD34^+$ hematopoietic stem cells, are used as cell sources. Because of the limited proliferation capacity of these cells, the batch size of donor-derived products is relatively small, and this causes batch-to-batch differences. Using pluripotent stem cells that have infinite proliferation potential, such as iPSCs and ESCs, is one of the options to reduce batch-to-batch differences.

Regardless of the cell sources, allogeneic T-cell receptors (TCRs) cause GVHD, and, thus, TCRs should be knocked out/down. Using other cell types with invariant TCRs ($\gamma\delta$T, natural killer [NK]-T, MAIT cells, etc.) or without TCRs (NK cells) is another option to avoid GVHD. Human leukocyte antigen molecules of allogeneic cells also should be knocked out/down to avoid rejection from the host immune system.

The first discussion point related to the quality control of the product was about cell viability after cryopreservation of the products. NK cells, $\gamma\delta$T cells or other innate immune cells suitable for allogeneic use are generally cryopreservation-sensitive, and low levels of post-thaw cell viability before infusing back to patients is a potential concern. We asked the regulators whether they would accept products with <70% cell viability, which is considered as a reference standard for cell therapy products, including autologous CAR-T, and all the regulators answered "no." This was a challenge from the industry, and we understood that there is no space for discussion about this topic.

The second discussion point was on the batch-to-batch differences of the product. Particularly for donor-derived allogeneic products, the batch-to-batch differences can potentially affect the results of non-clinical studies. We asked the regulators whether using three batches of the products in a study is sufficient to confirm the efficacy and safety of the product. Contrary to our concern, no regulators required more than three batches for non-clinical studies. The regulators from Japan, Korea, Singapore and Taiwan responded that the study with a single batch of the product could be accepted if the comparability between batches is assured. India responded that a study involving three batches is normally required according to the law.

The third discussion point of this topic was about GVHD risk assessment. GVHD is one of the most important safety concerns of allogeneic CAR-T products. However, as this is an immune reaction between human cells, an *in vivo* study administering human cells to immunocompetent or immunodeficient animals cannot work. We asked the regulators how we can demonstrate the reduced risk of the product for GVHD, for example, in the TCR-knockout CAR-T cells. In fact, based on past experience, knocking out TCRs can effectively reduce GVHD risk. We presented three options: A: *in vivo* study using human CAR-T cells and human target cells engrafted into immunodeficient animals; B: *in vitro* study using human CAR-T cells and human target cells and C: no experimental demonstration is required. The answers differed among countries/regions. Korea, Taiwan and Singapore stated that the *in vitro* study alone is sufficient and that there was no need for the *in vivo* study. India responded that *in vivo* study is required. Japan responded that it is not appropriate to assess the risk of GVHD in humans in a non-clinical study, and, hence, they stated that such a study is not required. The details of comments from regulators of India and Japan are shown to follow:

CDSCO, India regulator.

> *"It is a very tricky situation for such products. That is why we normally mention 'A' because it will give a very correct picture of how the product will behave as a new therapeutic product. Therefore, we recommend an* in vivo *study where human CAR-T cells can be engrafted to an immunodeficient animal."*

PMDA, Japan regulator.

> *"Given the impact of species difference on immune response, particularly MHCs, it is not appropriate to assess the risk of GVHD in humans in non-clinical studies. If the concept of reduced risk of GVHD can be explained by the literature, we believe that there is no need to conduct non-clinical studies to confirm the concept. Therefore, the risk of GVHD should be evaluated in clinical trials."*

iPSC-derived CAR-T

iPSC-derived cell therapy products are generally considered to have a high potential risk of tumorigenicity because residual undifferentiated iPSCs are naturally tumorigenic, giving rise to teratoma and genetic variations (e.g., genome instability, single nucleotide variations, copy number variation, and loss of heterozygosity). They can be introduced and accumulated from their parental cells, during the reprogramming process and during prolonged culture *in vitro*. Therefore, the evaluation of the potential risk of tumorigenicity and the characterization of the cell banks/final products from safety/quality control perspective would be the major concerns of iPSC-derived cell therapy products. From this viewpoint, the following two topics were discussed in this session.

The first discussion point was regarding the *in vivo* tumorigenicity study. Considering the high potential risk of tumorigenicity, a long-term *in vivo* tumorigenicity study is required for iPSC-derived cell therapy products. Therefore, we asked regulators what would be the appropriate study duration for the *in vivo* tumorigenicity study. The comments from the regulators were consistent; they responded that the study should be conducted through the life span of the animals (e.g., ≥12 months). However, Taiwan and Japan also mentioned that the study can be terminated when cell elimination is clearly demonstrated in CKBD study. The details of the comments from the regulators are shown to follow.

CDSCO, India regulator.

> *"As per the current understanding, the iPSC-derived cell therapy products relatively carry very high risk in terms of tumorigenicity. Therefore, the sponsor should justify the appropriate period or duration of the study, which could be ≥12 months, considering the lifespan of the animal."*

HSA, Singapore regulator.

> *"The tumorigenicity potential of iPSCs does not just come from the residual undifferentiated iPSCs that may be present in the product as an impurity. There could be other components from the manipulation of the process, including rapid demethylation associated with reprogramming that can cause genomic instability and also reactivation of pluripotency transgenes in transplanted cells. In general, we do not have much understanding yet in terms of long-term scenarios; hence, it is better to observe the products during the lifetime of the animal until we get more information on such iPSC-derived products with regard to the long-term data on tumorigenicity studies"*

Taiwan CDE, Taiwan regulator.

> *"Basically, the tumorigenicity of iPSCs needs to be observed throughout the whole lifespan; however, it is reasonable to terminate the study early when cells are entirely eliminated. CKBD studies can inform when cells are eliminated. For the tumorigenicity study designed to terminate early, the observation period should be no less than 6 months. For example, even if CKBD studies show rapid elimination of cells (e.g., 1 month), a 6-month observation period is still required because the information that CKBD studies can provide still has limitation."*

PMDA, Japan regulator.

> *"We also think observation period should be ≥12 months, considering the lifespan of the animal. However, once the cells have disappeared from the animals, there is no further need to evaluate long-term tumorigenicity, regardless of the timing of the elimination of cells."*

Once iPSCs generation is completed, a series of characterization assays should be performed, including sterility, mycoplasma, cell phenotype, pluripotent potential, chromosomal analysis and genetic stability. Genetic stability is a critical issue to be addressed for iPSCs. The presence of genetic stability can be characterized in iPSCs, including genome instability, single-nucleotide variants, copy number variation and loss of heterozygosity. These mutations can be introduced and accumulated in iPSCs from their parental cells, during the reprogramming process and during prolonged culture in vitro. G-banding karyotype assay is commonly used for iPSC-derived products. G-banding is a technique used in cytogenetics to produce a visible karyotype by staining condensed chromosomes. It is useful for the identification of structural abnormalities through the photographic representation of the entire chromosome complement. However, G-banding has only a limited resolution, which is at the level of 5–10 Mb. To detect and evaluate the abnormalities of genetic stability, additional genetic analysis should be performed, such as copy number variation and high-throughput sequencing methods, including whole-genome sequencing, comparative genomic hybridization (CGH) and single-nucleotide variant analysis.

Hence, the second discussion point was if the G-banding karyotype assay was sufficient to characterize genetic stability of iPSCs products or additional assay would be required. If not, what kind of assay would be recommended for iPSCs products? The proposed responses were (A) G-banding karyotyping is sufficient; (B) additional high-resolution genetic analysis would be recommended as a reference, but not mandatory; (C) additional genetic analysis with higher resolution is required and (D) others. Although the responses from the regulators were quite diverse, G-banding karyotyping, by itself, is definitely not adequate to address the genetic stability of iPSCs-derived products. In summary, the response from Japan and Taiwan regulators was "D," who recommended that the tumorigenicity should be fully assessed and should be determined based on the manufacturing process and chromosomal stability results. The response from Korea regulator was "C," who recommended that high-resolution assays, such as CGH and CGH assay, should be included in addition to G-banding karyotyping. The response was "B" from India and Singapore regulators, who suggested that an additional assay should be provided as a reference if safety concern cannot be fully addressed by G-banding karyotyping. Details of their comments are described to follow:

CDSCO, India regulator.

> *"The G-band karyotyping is primarily required in the official guidelines; however, this depends on the level of manipulation in manufacturing, and if there are any safety concerns related to such products, additional studies related to genome stability may be required."*

PMDA, Japan regulator.

> *"While we do not recommend any particular assay, we believe that it is important to evaluate chromosomal stability. The assay should be selected based on the complexity of the manufacturing process and chromosomal stability results. We encourage sponsors to discuss assay selection with PMDA, taking into account the individual product characteristics and manufacturing process."*

MFDS, Korea regulator.

> *"To assess chromosomal stability of iPSCs, G-banding karyotyping and CGH array should be conducted while other types of testing, such as whole-genome sequencing, are only recommended. As G-*

banding works effectively only for genetic instabilities with large structural changes, this method needs to be accompanied and complemented by high-resolution CGH array."

HSA, Singapore regulator.

"Depending on the product and the number of studies performed, if more information is required, then additional high-resolution genetic analysis would be mandatory."

Taiwan CDE, Taiwan regulator.

"The analysis of genetic stability is a part of tumorigenicity assessment. It is essential to understand whether the tumorigenicity could be fully assessed or not. If not, additional data are required."

Solid tumor

CAR T-cell therapy has accomplished considerable success in the treatment of hematological cancers. However, it has yet to achieve the same level of success in the treatment of solid tumors. As solid tumors account for >90% of all cancer types, its successful treatment represents a true breakthrough in the unmet need. The complicated tumor microenvironment of solid tumors has made the path to success filled with struggles. Many great challenges are associated with the use of CAR T-cell therapies in patients with solid tumor. These challenges (in the efficacy aspects) include the heterogeneity of solid tumors, potential on-target off-tumor toxicities associated with the targeting of T cells to tumor-associated antigens (TAAs), poor T-cell trafficking to the tumor sites, poor T-cell infiltration into the tumor mass, poor survival of T cells within the immunosuppressive tumor microenvironment (TME) due to the acidic and hypoxic conditions and the abundant immunosuppressive cells and inhibitory extracellular molecules present in the TME. Safety concerns regarding currently available CAR T-cell therapies, including those associated with cytokine release syndrome and neurotoxicity, have also remained unresolved.

In this context, armored CAR-T cells are important, as they have the potential to resolve all these challenges. In order to make CAR-T promising for solid tumor therapy, two points were discussed in the WG: (i) how to demonstrate, in the non-clinical studies, *in vivo* pharmacology results that are clinically relevant and can be extrapolated for clinical efficacy consideration, and (ii) how to evaluate the safety of a selected TAA for minimal on-target off-tumor toxicity.

In the first discussion point about the appropriate evaluation of the *in vivo* efficacy of CAR-T products, it was agreed that choosing an animal model that accurately represents the complicated tumor microenvironment is crucial. However, none of the currently available models, including cell-derived mouse model (CDX), patient-derived tumor xenograft mouse model (PDX), and syngeneic mouse models, seems ideal.

Syngeneic mouse models are established by implanting mouse tumor cells in immunocompetent mice sharing the same genetic background. These models would be the most suitable model for murine TME; however, the biology of the murine model does not accurately recapitulate human biology and mechanism of action of human CAR-T. PDX mouse models are established by implanting patient-derived tumors in immunodeficient mice. Although these models more accurately recapitulate human TME (than syngeneic mouse models), they do not include an (human host's) immune system. Nevertheless, it is considered more clinically relevant than CDX models. However, both the reliability and reproducibility of currently available PDX models are still relatively low. CDX mouse models are established by implanting human tumor cell line into immunodeficient mice. Although the nature of cell line–derived tumor is different from that of human tumor in several aspects, it has long been used in the oncology field for screening and as an evaluating platform of anti-tumor therapeutics. Two directions have been proposed for further discussion with the regulatory bodies.

Regulators from Japan considered the CDX model to be acceptable because neither syngeneic mouse model nor PDX model can accurately recapitulate the tumor microenvironment found in human patients. The regulators from India, Taiwan, Korea and Singapore recommended that additional *in vitro* pharmacodynamic data should be added as a requirement, in addition to the use of the CDX model, for efficacy evaluation.

The second discussion point focused on the safety aspect of TAA evaluation, more specifically with respect to evaluation of the on-target off-tumor or off-target toxicities. It was agreed that the binder(s) selection of the gene of interest design is the key for successful targeting with reduced safety risks. Most target molecules are not tumor-specific and TAA will not only be overexpressed in tumor cells but also in some healthy tissues (albeit often at lower levels). As such, there is a high chance of inducing "on-target off-tumor" toxicities resulting from the cross-reactive binding of CAR-T to normal tissues that also expressed the targeted TAA. Therefore, the binder(s) will be selected based on the sufficient affinity to the target TAA overexpressed on tumors but with lower levels of binding (unwanted recognition) to healthy tissues. We carried out in depth discussions regarding the studies that may be suitable for the evaluation of on-target off-tumor or off-target toxicities for the first IND. We also sought the opinions from the regulatory bodies.

The regulators from Korea and Taiwan accepted the evaluation protocol, which involves conducting (sequentially) the risk assessment to understand the expression level of the targeted TAA in major organs/tissues, followed by the evaluation of the *in vitro* cytotoxicity of the targeting CAR-T cells against cell lines without the expression of the targeted TAA(s) and monitoring the release of cytokines in *in vivo* pharmacological and toxicological studies. The regulators also mentioned that the level of target antigen expression in each tissue should be identified. If the cytotoxicity or binding activity has been observed in certain tissues and attributed to the CAR-T cells or scFv, respectively, the *in vitro* and *in vivo* cytotoxicity data on these relevant tissues or organs should be required for further analysis. The regulators from Taiwan also recommended the analysis of TAA expression patterns, including the level, timing and location of the targeted TAA in patient samples or made it a requirement that other additional data be provided for the evaluation of the potential toxicities. The regulators from India agreed with the aforementioned evaluation procedure but recommended to additionally require evaluation of cytotoxicity against healthy cell types (primary cells or iPSC-derived cells), such as those found in the central nervous system, heart, liver, lung, skin, vascular, blood and bone marrow.

Other components

CAR-T cell therapies are evolving to improve T-cell activation and persistence, overcome immunosuppression and mitigate toxicities. Several new approaches are extensively explored to enhance the therapeutic outcome of CAR-T cell therapy. In this "other component" part, the challenges against a successful safety and CKBD evaluation of a novel CAR-T product expressing other molecules, in addition to CAR molecule, were discussed. For this purpose, a model product 1928z CAR-T was established. 1928z CAR-T cells are genetically manipulated to express 4-1BBL on their surface to enhance antitumor activity and persistence of the cells. Expressed 4-1BBLs act on neighboring activated CAR-T cells by engaging 4-1BB receptors expressed on their cell surface. These 4-1BBL is membrane-bound and not secreted. It is reported that IgG-based 4-1BB agonistic monoclonal antibodies can cause liver toxicity, suggesting the potential safety risk of this approach. Since human 4-1BBL does not cross-react with

mouse 4-1bb receptor, potential toxicity of 4-1BBL cannot be evaluated when using mice in non-clinical tests.

The first point discussed was about the requirement of *in vivo* toxicity study. The query to regulators was "Is there a need for a separate *in vivo* toxicity study to evaluate these CAR-T cells expressing costimulatory molecules that do not cross-react with the murine counterpart?" and the following three options were discussed: (A) toxicity study for conventional CAR-T is acceptable and no additional toxicity study is required; (B) use of non-human primates that can react with human costimulatory molecules required instead of using mouse model and (C) use of CAR-T cells expressing mouse model of costimulatory molecules is required for toxicity study in an appropriate mouse model. Inputs from the regulators are presented to follow:

HSA, Singapore regulator.

> *"It really depends. There is no fixed answer, as we can choose A, B, or C for this particular aspect. A combination of experiments is required to show the in vivo toxicity of these CAR-T cells, especially because it depends on the co-stimulatory molecule that is being used and how it is going to impact the production of these cytokines."*

Taiwan CDE, Taiwan regulator.

> *"The first time we saw this case, we thought there was not enough information to answer this question. After our request, the information was updated, but it is still not sufficient. For example, we don't know whether the liver toxicity triggered by the 4-1BBL was manageable or not, and how the CAR-T cells were generated. This hypothetical case is too simplified, and more detailed background information should be provided."*

PMDA, Japan regulator.

> *"If the co-stimulating molecule is essential for pharmacological action, it will be difficult to evaluate how on-target toxicity occurs in animals. Again, we believe that there are limitations in safety evaluation in animal studies, as GVHD may occur when CAR-T cells is administered to animals. Therefore, we believe that safety evaluation in the pharmacological study, with limited safety endpoints, is acceptable."*

CDSCO, India regulator.

> *"Yes, considering the potential safety risks of human CAR-T cells and as per the understanding that CAR-T cells expressing the mouse version of the costimulatory molecules can be used in xenogeneic models to do the toxicity studies, and because we also understand these are going to increase the persistence of T cells. Of course, the sponsor has to justify all these while making the submissions. As per the current understanding, we will go with option C."*

The second point discussed was about CKBD evaluation. The regulators were asked to share their comments on the need to conduct CKBD evaluation of costimulatory molecules expressed on CAR-T cells in addition to that of CAR-T itself, and three options were provided: (A) CKBD study for conventional CAR-T is acceptable and no additional information is needed; (B) separate CKBD study is needed to detect the levels of costimulatory molecules in potential target organs and (C) CKBD of costimulatory molecules can be indirectly determined by combining CKBD data of CAR-T cells with information on the expression level of costimulatory molecules on CAR-T surface quantified *in vitro*. Inputs from the regulators are as follows:

HSA, Singapore regulator.

> *"It depends on the overall CKBD study that was provided as a package with regard to the co-stimulatory molecule that is being used for the CAR-T product. Again, as I said, the co-stimulatory molecule is very important because it can impact the in vivo cell expansion, the persistence of the CAR-T cells and the activation of other immune cell types within the system. Therefore, it can be B, but again, it depends on the dataset that the sponsor provides."*

PMDA, Japan regulator.

> *"If there is a specific concern that can affect CKBD, it should be evaluated."*

CDSCO, India regulator.

> *"We agree with option C because we understand that the co-stimulatory molecules may modulate the action of the CAR-T cells."*

WG 2: Quality panel discussion

Introduction to panel discussion

Comparison of guidelines of biological ancillary materials used for the manufacturing process of gene and cellular therapy products in Asia.
WG2 have investigated the guidelines for biological ancillary materials (AMs) defined in United States Pharmacopeia (USP) 1043 as materials used in manufacturing process but not intended to be present in the final products in Asia (China, India, Japan, Korea and Taiwan), the United States and the European Union. This investigation has been published [2]. Supplementary Table 4 shows the direct guidelines about AMs in each country or region surveyed. The guidelines can be classified into two types based on whether specific AMs are scoped: (i) general guidelines for risk assessment of AMs and (ii) guidelines for specific AMs. However, because the available guidelines are limited to only a few AMs and countries/regions, there are no common regulations for specific AMs across Asian countries and regions. Therefore, we sought the requirements and thoughts of regulators from each country and region in the panel discussion.

Regulatory agency panel discussion

In the panel discussion, four topics were on the agenda: (i) overview of regulations in each country and region, (ii) how we can perform risk assessment associated with biological AMs, (iii) risk of approved commercial drug products in other counties and regions used as AMs and (iv) points to consider for specific AMs, particularly for bovine serum and trypsin. Although regulatory agencies from Korea and Malaysia could not take part in this panel discussion, the written responses on each topic were provided after the 5th APACRM. Their responses are also described side by side with the comments from the panelists.

Discussion 1: Overview of regulations in each country and region

Our first discussion topic includes four dimensions: (i) what are the most critical considerations in your regulation? (ii) Do you accept certifications from other countries/regions? (iii) How should manufacturers using biological raw materials balance between overall risk assessment based on the risk factors and the specific regulations on certain materials? (iv) Share with us from actual review experiences about the common problems and best practices that have been encountered on the use and control of biological raw materials.

HSA, Singapore regulator

"Generally, when we talk about AMs used in the manufacturing of cell therapy or tissue-engineered products, it varies from the source itself whether it can be serum or if it is tissue engineered products, then you use some of the scaffold that can be used for seeding of the cells. In general, from Singapore, we do not have any specific regulatory guidelines on the use of AMs. We use international guidelines, and where possible, we encourage the use of non-animal–derived products in the manufacturing process. However, if that is not possible and they want to use an animal-derived product, such as albumin, we will require the certificate of suitability (CEP) issued by the European Directorate of the Quality of Medicines & HealthCare (EDQM). We will assess the overall use of these materials in the manufacturing process, including evaluating the residual limit present in the final product and see how it affects and impact on the final product.

To your last question on common pitfalls, I cannot recall anything, but the best practice is to avoid, as much as possible, the use of animal-derived materials, even for iPSCs and ESCs. People are now adopting non-feeder, layer-based and non-animal–based manufacturing of these products."

Taiwan CDE, Taiwan regulator

"In Taiwan, besides the Pharmacopeia updated last year, we also have the Points of Consideration for the industry: The raw material of the biological origin for production of biopharmaceutical product. However, they are only in Chinese version for now. The Points of Consideration also includes the concepts from other countries' pharmacopeia or guidelines. The major risk for AMs derived from biological products is the adventitious agents, which are our primary concern. Therefore, the risk assessment for AMs is the species of the source, potential contamination of adventitious agents, how adventitious agents can be removed or controlled in the manufacturing process and certificates of analysis. All of which are included in the suitability assessment of AMs. With regard to the second question, we recognize other countries' guidelines, such as those listed in supplementary Table 2. When reviewing the materials, we evaluate them from the science point of view. When the sponsor refers to those guidelines of pharmacopeia, they still need to provide relevant data and reasonable justifications.

For the third question, generally speaking, guidelines or pharmacopeia should be followed. For example, for bovine serum, the requirements of pharmacopeia for bovine serum should be complied. Applicants or the manufacturers need to be aware if there are certain regulations on specific biological materials that are intended for use. For the fourth question, the best control strategy is to control the origin or source of materials. Therefore, we recommend that the use of materials from animal or human origin should be avoided."

PMDA, Japan regulator

"In Japan, there is a Standard for Biological Materials as a general guideline, and it covers all requirements for animal-derived materials. We cannot accept other countries' certification, and we do not have specific guidelines, such as for bovine serum or porcine-derived trypsin. If the raw materials cannot fulfill the requirements by the Standard for Biological Materials, the materials should generally be replaced with appropriate materials. However, it is possible that biological safety might be kept by total manufacturing process of not only materials but also the final product. If you believe you can show us the appropriate reason and viral safety strategy, please use PMDA's consultation on a case-by-case discussion. For question iv, to be on the safe side, it is important to get confirmatory proofs from suppliers of raw materials on viral inactivation test report at the early developmental stage. Accessing some information on raw materials is sometimes time-consuming. The worst case is that there is no information concerning the requirement. It is good to be proactive in getting access to the necessary information."

CDSCO, India regulator

"With regard to the first question, in India, as per drug rules 1945, the sponsor shall furnish to the licensing authority the data justifying that the product is safe for use in the context of the vehicles' excipients, additives or formulation aids used in the formulation under the concentration in which the formulation for administration and use are recommended. In principle, the biological AMs are covered through these regulations. The sponsor has to justify the source from where the AM will be procured, of course with the certificate of analysis, and the vendor should be qualified. We discourage procuring AM specifically from those geographical areas that have the high potential of contamination from TSE and BSE. This is the answer to the first question. Concerning the second question, with respect to the certificate complying with the other country's guidelines, yes, we do accept the certificate complying with the other countries, provided that it has been issued by authentic source. We recommend that it should have been issued by a government agency, and further been tested as appropriate may also be required to be conducted by the sponsor. With regard to the question number 3, we recommend as per our guidance document that this AM should be tested for bovine and/or porcine infectious organisms and these materials should be tested to ensure that these are Transmissible spongiform encephalopathies (TSE) or bovine spongiform encephalopathy (BSE) free. Like if fetal calf serum is used, BSE estimation is to be carried out and if trypsin is used, it should be estimated further for the presence of any residue like host cell DNA. And regarding the last question about the common pitfalls and best practices, what I replied also covers that, but finally the presence or absence of adventitious agents like bacteria, human viruses, and porcine viruses in the AM is very critical, which needs to be assessed."

Dr. Yoji Sato

"Regarding the third point, in the balance of Japan's own requirements and the power for the enforceability of the Standard document, in general the overall risk assessment of CGT product should be more important compared with the simple compliance with domestic regulation for biological raw materials. But the enforceability of guideline document depends on its legal or administrative status in the country. For example, in Japan, the Standards for Biological Raw Materials are classified in a document called ministerial notice, which has quite strong enforceability, but in other countries, other standards may be less enforceable. That's when I said to balance on the level of compliance. Regarding the fourth question, you need to ensure the quality of each AMs or raw material for your products by taking its future international marketing into consideration. Quality requirements for AM or biological raw materials in different countries vary depending on the circumstances in each country. For example, quality standards of blood-derived materials could be different between countries where blood selling is legal and illegal. It's not reasonable to ignore these differences and force one country to adapt its

standards to those of others. It's important for industry associations to share resources that make it easy to understand regulatory differences between countries, which APACRM is now conducting."

Written response from MFDS, Korea regulator

"Regarding the first point, in Korea, regulations on the review and authorization of ABPs prescribe that information on the origin, source and specifications of all the materials used in manufacturing ABPs should be submitted. For animal-derived materials, in particular, data demonstrating their safety should be submitted and this requirement is also applied for IND approval. Korea doesn't have any source material-specific guidelines, but frequently asked Q&A guides have been published instead, when necessary, to provide information on assays to be performed for the use of animal-derived materials. Regarding the second point, certificates complying with other National Regulatory Agency guidelines can be acceptable when MFDS determines that these documents present appropriate evidentiary criteria and if the issuing organization is found to be recognizable. For example, EDQM certificate on TSE safety is currently considered to be reliable. Regarding the third point, in principle, safety of each animal-derived material should be ensured at the incoming material level. When source material-level safety data are omitted, safety of these AMs may be evaluated in other time points if justified (e.g., in case where a material is used in the manufacture of Master cell bank [MCB] but with incomplete viral safety data, this MCB can still be used if safety is subsequently confirmed in MCB). Regarding the fourth point, suggestions to developer, if a material of animal origin is selected for use, is recommended using one for which TSE (for ruminants) and virus safety is already confirmed."

Written response from National Pharmaceutical Regulatory Agency (NPRA), Malaysia regulator

"Regarding the first point, Malaysia does not have any specific AM guidelines. We refer to guidelines from reference countries such as from United Kingdom, Medicines and Healthcare products Regulatory Agency; Europe, EMA; Sweden, Medical Products Agency; France, French National Agency for Medicines and health products safety; United States of America, FDA; Australia, Therapeutic Goods Administration; Canada, Health Canada; Japan, PMDA; and Switzerland, Swissmedic. Regarding the second point, we recognize certificates from reference countries as listed in the first point. Regarding the third point, if specific guidelines are available, to follow specific guidelines. If specific guidelines are not available, the general guidelines should be followed. Regarding the fourth point, some of the points for best practice are (i) preference for non-TSE materials, (ii) testing on safety aspects of the AM, (iii) to provide certificate of suitability and certificate of analysis of AM and (iv) declaration on compliance to relevant guidelines."

Discussion 2: How we can perform risk assessment associated with biological AM

When we look at the different levels of risk exposures of human/animal sourced or animal-derived raw materials, what can you suggest to the developers or producers in the audience with regard to conducting risk assessment given the different risk classes of the materials? And the second question is how far upstream should we make such an assessment?

Taiwan CDE, Taiwan regulator

"For this question, our opinion is as described in the Points of Consideration for the industry: The raw material of the biological origin for production of biopharmaceutical product. It defines the risk category for the AMs. The highest risk involves the AMs for industrial or research use, where it may contain harmful impurities and animal- or human-derived components harboring adventitious agents. Next, the high risk involves the AMs either intended for research use locally produced under laboratory condition or not intended for use in CGT product manufacturing. The next tier, a well-characterized material produced under established quality systems, but AM is not licensed or an approved medicinal product. The low risk is the highly qualified material, such as a licensed biological or drug or medicinal device. Therefore, the risk assessment will be helpful for the sponsor to understand the risk level of materials used in the manufacturing process. For the second question, making an example, monoclonal antibodies are intended for use as AMs and animal-derived cells are used as host cells to produce the antibodies. If fetal bovine serum is used in the upstream process of antibody production, the bovine viral contamination and TSE/BSE risk should be considered."

CDSCO, India regulator

"For the first question, with regard to the AMs of human origin, there is a risk of the presence of adventitious agents, such as human immunodeficiency virus and bacteria. The sponsor is required to test for the presence of all these organisms, especially human immunodeficiency virus, syphilis and gonorrhea. With regard to AMs of animal origin, they should be free from TSE and BSEs. Substances of human and animal origin should be tested for the transmissible pathogens and/or any immunogenic responses. For the second question, the risk assessment of the AM used during the upstream production should be carried out in consideration of the source of the AM. For example, AM of a pharmaceutical quality and pharmacopeial grade that are well-tolerated or safe is considered a low-risk material, and materials that are derived from human or animal origins or tissues are considered relatively of high-risk potential."

HSA, Singapore regulator

"A lot has been said on these two parts. Of course, we must take reference from USP 1043 and USP 92; for example, with regard to the growth factors and the cytokines used for cell therapy manufacturing of these products. These are the things that need to be considered in the development of cell therapy products and in the use of these AMs of human or animal origin. How upstream risks assessment analysis depends on the manufacturing process and how much of these products are going to be present in the final product, and the risk assessment should come all the way from where these materials are being used in the manufacturing process."

PMDA, Japan regulator

"First answer, there are several standards of human-derived materials, human cell/tissue materials and human materials. And blood products require specific standards. The standard focuses on each specific risk; for example, the standard for human cell/tissue materials focuses on the screening of donors. Second, in Japan, primary and secondary materials are required to comply with the standard for

biological materials. Of course, information about tertiary or more upstream materials should be collected, if applicable. But they do not need to comply with the standard for biological materials. This information is not mandatory but can be used in the development of total risk assessment strategy in the manufacturing process."

Dr. Yoji Sato

"The answer for the second question depends on how much the risk is mitigated by inactivation or purification. The risk-based approach should be adopted for decision making, regardless of research use only or clinical, GMP grade or something. The sponsors and reviewers should assess the safety of the raw materials from such a viewpoint."

Written response from MFDS, Korea regulator

"For the first point, although the manufacturing process of each material should be considered, in general, the risks of contamination of each source material with animal-derived virus/TSE are deemed higher in materials directly sourced from humans/animals than those incurred by materials manufactured using human/animal-derived materials. For the second point, evaluation should go upstream to cover substances used in the manufacturing of source materials, that is, secondary AMs."

Written response from NPRA, Malaysia regulator

"Regarding the first point, the required testing and control for (i) AM of human or animal origin and (ii) AM produced using substances of human or animal origin are the same. Regarding the second point, the declaration of all materials used should be from the beginning to the end of the manufacturing process. The manufacturer should indicate at which point AMs from human/animal origin were used."

Discussion 3: Risk of approved commercial drug product in other counties and regions used as AMs

It is generally considered that approved commercial drug products have lower risk as AMs for CGT production because commercial products are manufactured under appropriate GMP controls and approved for their safety and quality by regulatory agencies. The discussion point was whether commercial products from other counties and regions are acceptable to be used as AMs in each Asian country or region under survey.

CDSCO, India regulator

"As per new drugs and clinical trial rules, there is a detailed provision mentioned in the rules. We consider that this specifically has a low risk, particularly if these products fulfill the criteria as prescribed under the new drugs and clinical trial rules for marketing in the country."

Taiwan CDE, Taiwan regulator

"Approved commercial therapeutic products in A10 reference countries used as AMs are considered as low risk. If the product is not approved in those A10 countries, the risk category of the product will be evaluated. However, even for the low-risk AMs, the sponsor still needs to provide relevant data and overall risk assessment considering the intended use."

HSA, Singapore regulator

"If it is a product that is registered for commercial supply, then of course, we would consider that as a low-risk product because the quality, safety, and the efficacy of the product has already been reviewed for its intended use."

PMDA, Japan regulator

"It is not considered as a low-risk product. There are two points of concerns. One is that there are differences in the requirement of raw materials across countries, and Japan is one of the strictest countries in terms of the regulation of raw materials. The other point is that pharmaceuticals must be approved, considering the balance of risk and benefit. However, we cannot access the detailed information about approval in other countries and cannot recognize whether the specific risk imposed by raw materials exists or not."

Dr. Yoji Sato

"Japanese regulatory authorities usually regard products approved for marketing in Japan as safe products. However, we need some evidence with adequate data to confirm the safety or to make our scientific decisions on drugs approved in other countries, regardless of marketing authorizations by any country."

Written response from MFDS, Korea regulator

"As drug products approved by other National Regulatory Agencies must have been appropriately reviewed for safety through relevant regulatory review processes, these products are generally considered to be of low risk."

Written response from NPRA, Malaysia regulator

"The products registered in Malaysia or reference countries are regarded as low-risk products."

Discussion 4: Points to consider for specific AMs, particularly for bovine serum and trypsin

Bovine serum and trypsin are very common animal-derived AMs. We asked whether there are specific points to consider for these two AMs, in addition to the general consideration from risk assessment perspective in Discussion 2.

HSA, Singapore regulator

"We have guidelines on the use of animal-derived products for humans, which stimulate the requirements that need to be provided. For cell therapy products, we will ask for the TSE and BSE certification

of these products. They need to provide, as I earlier mentioned, the certificate of suitability issued by EDQM. As much as possible, we advise sponsors or manufacturers not to use animal-derived materials, whether it is serum or some of the enzymes, such as trypsin. But where it is not possible, we ask for justifications, such as knowing how much of the material remains in the final product and the studies that have been conducted."

Taiwan CDE, Taiwan regulator

"As mentioned just before, we have the pharmacopeia and the Points of Consideration for the industry to deal with the question. The risk assessment for the bovine serum or trypsin should take consideration of animal source, potential contamination of adventitious agents, how adventitious agents be removed or controlled in the manufacturing process, certificates of analysis and so on. For risk evaluation of TSE/BSE, we recognize the certificate from EDQM. If the material is bovine serum, the sponsor needs to provide the serum certificate to demonstrate the origin of the bovine and ensure it does not come from a TSE-contaminated country."

CDSCO, India regulator

"As per the guidance document for the industry, we normally recommend using materials of human origin, and in case of animal origin, we ask for the certification with respect to TSE and BSE. With regard to EDQM, we do recognize EDQM certificates for the purpose."

PMDA, Japan regulator

"Certification by EDQM could be used as information in the certification for Japanese regulation. However, this certification may not contain all the information that is necessary for certification in Japan and that is why only EDQM certification cannot be acceptable. Regarding bovine serum and trypsin, Japan's regulation is a bit strict, and although it is not mandatory, we would strongly recommend animal-free materials."

Dr. Yoji Sato

"At least in Japan, the risk of infectious diseases, including TSE, is considered to be reduced quite a lot as long as the raw materials are compliant with the standards for biological raw materials. Even in cases that do not comply with the criteria of standard, their eligibility may be determined flexibly based on the amount used, the method used, the severity of the target disease and availability of alternative treatment. Please use the PMDA consultations. The standards for biological raw materials have a chapter called standard for ruminant materials, which describe the requirements strictly for general and TSE safety of ruminant materials."

Written response from MFDS, Korea regulator

"To ensure the safety of animal-derived materials, information related to AM safety, measures taken to confirm AM safety during manufacturing, virus test results, etc. are reviewed. For bovine serum, virus safety data (culture-based assays (cytopathic effects, hemadsorption) and tests for bovine adenovirus, bovine parvovirus, bovine respiratory syncytial virus, bovine viral diarrhea virus, bluetongue virus, rabies virus, reovirus) are required alongside with TSE safety information. In addition, AMs should be confirmed as sterile and mycoplasma-negative. For porcine trypsin, tissues of origin harvested from pigs fit for human consumption and with porcine parvovirus-negative test results should be used. In addition, they should be confirmed sterile and mycoplasma-negative. For ruminant-derived materials, Korea has regulations that pose restrictions on the country of origin. Depending on the types of tissues/materials of origin, etc., the applicability of these restrictions varies. For bovine serum, the submission of information showing negligible risk of TSE is required for its use. Risk assessment of BSE is conducted considering BSE risk status of country of origin of source animals, tissues of origin to be used, and treatment processes to be applied. TSE-Certificate of Suitability issued by EDQM is recognized as evidence for TSE safety of ruminant-derived materials."

Written response from NPRA, Malaysia regulator

"The current policy is that any use of animal source in the product has to be declared on the label. However, we understand that animal-derived materials are commonly used in the manufacture of biologics (including CGT products) and frequently, it is only used in the early stages of manufacture. As per Drug Registration Guidance Document (DRGD) Appendix 4: Guideline on Registration of Biologics, a confirmation on the presence/absence of the animal materials in the final product should be provided. Hence, a laboratory analysis (i.e., DNA analysis) would be a form of confirmation on the presence/absence of the animal materials. It is agreed that in the event that the applicant can demonstrate the absence of animal source through DNA testing in the final product, declaration of the animal source on the label can be omitted. The checklist that the applicant has to complete for TSE-relevant materials is provided in supplementary Table 5. The certificate of suitability issued by EDQM is acceptable as a proof of controlled TSE risk."

Key differences and considerations among the regulatory agencies with respect to discussion outlined in WG2 session are summarized in supplementary Table 6.

WG3: Environmental impact assessment of GMO for CGT panel discussion

Introduction to panel discussion

Innovative gene therapy products of GMO generally have more complex regulatory framework in non-clinical and clinical development than in conventional drug development. It is necessary to carefully consider the risk of transmission of living modified organisms to others than patients, animals or the entire environment, and hence, the environmental impact assessment (EIA) will be required. Careful measures, such as safe handling of GMO and method of administration to patients and disposal, are adopted to prevent GMO from spreading outside.

WG3 of APACRM was established in 2022 to discuss if there is room to harmonize the regulation related to EIA in clinical and/or regulatory perspective(s). In the first approach, WG3 compared the regulation regarding the Cartagena or EIA in APAC region.

Comparative Survey

A survey with four questions were performed in advance for each Asian country/region: if they are member of Cartagena protocol (Question 1), if there are general guidelines on EIA including the one for gene therapy (Question 2), and if there are any regulations on the

control of viral shedding (Question 3) and special regulatory reviews for gene therapy development (Question 4). The survey result enabled us to identify common points, similarities, and differences in the regulations/guidelines on EIA particularly regarding gene therapies in participating Asian countries/regions.

At the meeting, the survey results of Questions 1 to 4, as shown in Table 1, were discussed.

Question 1: Out of the six Asian countries/regions, China, India, Japan and Korea are members of the Cartagena protocol. Japan and Korea incorporated the Cartagena protocol into domestic regulation.

Question 2: Almost all the countries/regions have some sort of domestic regulation related to gene therapy development from non-clinical, clinical and biodiversity risk assessment to prevent exposure. When initiating gene therapy product development in the future, it is necessary to compare each item of the guidelines in each country/region in order to deepen the understanding of requirement of non-clinical data package, and preparation for clinical studies is required.

Question 3: Some countries/regions referred to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) considerations for virus shedding. The ICH guideline provides requirements in clinical trial protocol regarding the sampling time for measuring viral shedding and preclinical studies to assess the safety of viral vectors used for gene therapies.

Question 4: Almost all countries/regions have special review systems focusing on the evaluation of GMO, which is different from scientific review in clinical trial application (Table 1). It is necessary to understand the regulatory review systems in each country/region for the simultaneous conduct of clinical trials. Further investigation into the details and comparison of the review systems among Asia countries/regions is needed.

Table 1
Responses to the questionnaire (Cartagena Protocol and Guidelines related to gene therapy products).

		China	India	Japan	Korea	Singapore	Taiwan
A member of Cartagena Protocol							
Q1	Is your country/ region a member of the Cartagena Protocol?	Yes	Yes	Yes	Yes	No	No
Guidelines related to gene therapy products: adeno associated virus, adenovirus and lentivirus etc.							
Q2	Are there any domestic regulations (including guidelines) related to the environmental impact assessment?	No.	No	No,	Yes	Yes	Yes
Viral shedding control							
Q3	Are there any reference national regulations regarding the control of human viral shedding in clinical studies?	No	No	Yes[a]	Yes[a]	No[b]	Yes[c]
GMO review system for gene therapy product including GMO							
Q4-1	When developing or marketing a gene therapy product containing genetically modified organisms, is there any special review by health authorities concerning GMO other than the review of the clinical trial notification?	Yes	Yes	Yes	Yes	Yes	Yes
Q4-2	When will the regulatory authority review it? 1. Before the start of the study (before clinical trial application) 2. Stage of product registration (after new drug application)	1. Before clinical study	1. Before the start of the study	1. Before CTN or in parallel with CTN	1. Before clinical trial[d]	1. Before the start of the study[e] (before clinical trial application)	2. Stage of product registration (after new drug application)

CMC, chemistry manufacturing and controls; CTA, clinical trial application; ERA, environmental risk assessment; GMAC, Genetic Modification Advisory Committee; GMO, genetically modified organism; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; NDA, New Drug Approval.

[a] ICH consideration (*ICH Considerations: General Principles to Address Virus and Vector Shedding).

[b] Not specific. However, viral shedding details need to be submitted during CTA as part of CMC dossier under 3.2.S.3.1.

[c] Please refer to "Guidance on NDA for Gene Therapy Medicinal Products."

[d] GMO review is a part of CTA review.

[e] 1. in parallel with CTA submission. GMAC ERA approval as a pre-requisite to CTA approval. 2. Before NDA. GMAC ERA approval required for NDA submission.

[f] The GMO-related review is specified in regulation for clinical trial and product registration. However, it is unclear in the regulatory practice (reality) when related information should be ready. Therefore, it would not be surprised if the regulator would request related information prior to approval of clinical trial.

Regulatory agency panel discussion

After the presentation, the following discussions and comments relating to EIA were made by the regulators that participated in this meeting.

CDSCO, India regulator

> *"With regard to the biodiversity risk assessment in India, there is biological diversity rules 2004, whereby the central government regulates, manages, or controls the risks associated with the release of living modified organisms.*
>
> *Regarding this topic, we do not have any specific comments, but we really appreciate the establishment of WG3 for deliberations on the environmental impact assessment of cell and gene therapeutic products. I think this discussion would help to harmonize the guidelines across the regions."*

PMDA, Japan regulator

> *"It may be the first time to compare the requirement of the environmental risk assessment of GMOs across the Asian countries. It is a good way to clarify the gap in the requirements of GMOs in Asian countries, and it may provide good information to industries that want to develop GMO-related pharmaceuticals internationally.*
>
> *However, it would be hard to harmonize environmental risk assessment regulated by domestic (Japanese) laws in each country, and sometimes the rules are not pharmaceutical rules but environmental specific rules. In Japan, the specific act that regulates GMO is known as the Cartagena act. The Cartagena act is literally based on Cartagena protocol but there are some complicated points. The Cartagena act covers all GMOs, including their use for research, medical, and agriculture. Some countries regulate GMOs for pharmaceuticals by using pharmaceutical-specific rules, some guidelines, or a sort of lower-level notification.*
>
> *The point is that environmental risk regulation in each country is extremely different from the aspects of the rule system. Therefore, harmonization of the environmental risk regulation is a huge and challenging project. Of course, it is agreeable to collect the information of each regulation, as this can be very useful for industries and regulators."*

HSA, Singapore regulator

> *"For Singapore, EIA review is not done by the regulators of pharmaceuticals. It is done by another agency. Therefore, the timeline for EIA review is not known. WG3 is a good effort, but as pointed out by PMDA, Japan, it would be very challenging because they are very country-specific, and the scope of the environmental risk and the GMO are very wide. The expertise is also quite different, as the expertise required for the review of GMO food is different from that required to review gene therapy products containing GMO."*

Taiwan CDE, Taiwan regulator

> *"The environmental risk assessment of GMOs is evaluated by the Ministry of Science and Technology, Council of Agriculture and Ministry of Health and Welfare. In Taiwan, the CDE is not involved in the evaluation of GMOs. There is no comment in the section."*

CDSCO, India regulator

> *"It is good that you have made a comparative chart and it is good that you have made known to everybody that there is a requirement of clearance from the environmental authorities. However, what are the specifics of the requirements and how much timeline is required in each region of Asia? These are the most important goals so that available information can be appropriately used in the developmental process. The environmental risk associated with the GMOs or LMOs should be considered in the development of gene therapeutic product. Of course, there are some expectations when it comes to recombinant DNA-derived medical products or the vaccines. Making the information, specifics and timelines available should be prioritized, as this will probably facilitate the developmental process and timeline."*

In conclusion, the comments from the different regulators in APAC countries/regions indicate that it is difficult to harmonize the regulations and/or procedures regarding EIA review because of various country-specific reasons and situations. However, we can seek more concise and effective evaluation of EIA in the future by referring to the scheme/perspective in each country/region.

Conclusions

This is a report of the discussion of regulatory agencies and industries from participating Asian countries/regions at the 5th APACRM meeting. Through the WG discussions, regulatory differences and the underlying rationales were clearly defined among the countries and regions. Knowledge-sharing, exchange of opinions on regulatory guidelines and collation of data based on a dialog between industry and regulatory agencies are the key steps toward the harmonization of regulatory viewpoints surrounding CGTs in Asian countries and regions.

Proactive efforts on regulatory innovation (e.g., the necessity of new guidelines) can facilitate regulatory harmonization and optimization across Asia, enabling the rapid delivery of CGT products to many patients in need.

Declaration of Competing Interest

The views and opinions expressed in this article represent the personal ideas of the participants and are not necessarily the official positions of the agency. All authors, except for BHC are employees of companies developing cellular therapies, providing testing or enabling technologies for the manufacturing of cellular therapies.

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Supplementary materials

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