INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

ISSCR Holds First Regulatory Agency Meeting with Japan's Pharmaceuticals and Medical Devices Agency and Korea's Ministry of Food and Drug Safety

On 7 November 2024, the ISSCR held its first meeting with Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Korea's Ministry of Food and Drug Safety (MFDS). The International Society for Stem Cell Research's (ISSCR) regulatory advocacy aims to give its members a voice to help understand and educate policymakers about scientific findings and considerations that will help regulators make scientifically informed policy decisions and facilitate the development of advanced stem cell-based therapies and applications.

In this inaugural meeting with regulatory authorities from Asia, participants convened to discuss key topics related to the 1) manufacture of human Pluripotent Stem Cell (hPSC) banks as starting materials for allogeneic, PSC-based therapies, 2) genetic assessment of hPSCs, 3) jurisdictional differences in guidelines for biological Ancillary Materials (AM). The participants also had the opportunity to gain insights into the regulatory approaches of the PMDA and MFDS regarding PSC-based products.

Overview of ISSCR's Regulatory Advocacy
Presenter: Hideyuki Okano, PhD

Dr. Hideyuki Okano provided an overview of the ISSCR and its diverse international membership. He also shared an update on the forthcoming ISSCR publication on Best Practices for the Development of Pluripotent Stem Cells (PSC)-Derived Cellular Therapies. The Best Practices document will provide recommendations to facilitate and streamline the development of PSC-based cellular therapies regardless of regulatory jurisdiction. It will also provide detailed guidance at key product development pain points. Dr. Okano extended an invitation to PMDA attendees to participate in the review process of the document.

Since 2019, the ISSCR's Manufacturing, Clinical Translation, and Regulatory (MCTR) committee has held annual meetings with the U.S.'s Food and Drug Administration (FDA) on advancements in the field and challenges to commercialization. This meeting represents ISSCR's first outreach to regulators in Asia, following inaugural meetings with the UK's Medicines and Healthcare products Regulatory Agency (MHRA) last year and the European Medicines Agency (EMA) earlier this year.

Manufacture of PSC Banks as Starting Materials for Allogeneic, PSC-based Therapies
Presenters: Tenneille Ludwig, PhD
Setsuko Hashimoto, PhD

The first presentation provided perspectives on the manufacture of PSC banks as starting materials for allogeneic, PSC-based therapies. Dr. Ludwig outlined PSC line generation and cell product manufacturing processes highlighting reprogramming, expansion, and cryopreservation for Master Cell Banks (MCB) and Working Cell Banks (WCB), and differentiation of the PSCs to Drug Substance and Drug Product. Several PSC-based products undergo genome editing at the Seed Bank stage, requiring the development of risk assessment strategies to evaluate the safety and quality of the reagents and processes involved.

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Dr. Ludwig noted that among the regulatory agencies consulted, there was a consensus that high-quality non-Good Manufacturing Practices (GMP)/Good Cell Therapy Practices (GCTP) reagents can be used for seed bank manufacturing, as long as they are high quality and fit for purpose, appropriate risk mitigation measures are implemented, and laboratory controls are in place. Additionally, it is essential to maintain complete traceability, thorough documentation and well controlled research settings.

Dr. Hashimoto offered a Japanese perspective on the manufacture of cell banks as starting materials for allogenic chondrocyte products, drawing from their experience at CellSeed, Inc. She discussed establishing a stable supply of starting materials and constructing allogeneic cell banks from polydactyly-derived chondrocytes. Additionally, Dr. Hashimoto detailed the process for manufacturing allogeneic chondrocyte sheets. Other efforts highlighted include informed consent, donor testing, safety, and efficacy.

Questions:

- What is the Agency's opinion regarding the acceptability of the use of high-quality non-GMP/GCTP reagents in the production of GMP/GCTP seed banks?

The PMDA will consider traceability, but proper documentation and explanation are required.

The MFDS generally agrees with PMDA's response. The agency elaborated that it is essential that sufficient documentation is in place regarding the origin and source of the cells used to establish the seed bank—that is, the donor. Comprehensive traceability, including information on donor screening criteria and donor eligibility test results, is considered critical for ensuring the integrity and quality of the seed bank.

- What is the Agency's opinion about the acceptability of PSC Seed Banks produced in non-GMP/GCTP laboratories according to the principles of GMP/GCTP as starting materials to produce MCBs and WCBs under GMP/GCTP? Will PSC-products manufactured from these materials be suitable for clinical trials and ultimate commercialization?

PMDA confirmed that GMP/GCTP is not required for the generation of material prior to master cell banks, and non-GMP is acceptable for upstream process as long as complete documentation and traceability is obtained and preserved.

In South Korea, cell processing must be conducted at facilities designated as "Cell Management Business" sites approved by the MFDS, prior to manufacturing in a GMP-compliant facility. If a therapeutic product is to be approved for clinical trials and/or marketing authorization based on a cell bank initially established in a non-GMP/GCP facility, further discussion may be needed to address legal and regulatory compliance.

- Likewise, what is the Agency's opinion about the acceptability of gene edited PSC Seed Banks produced in non-GMP/GCTP laboratories according to the principles of GMP/GCTP as starting materials to produce MCBs and WCBs in GMP/GCTP? Will PSC-products manufactured from these materials be suitable for clinical trials and ultimate commercialization?

Everything prior to the generation of the Master Cell Bank (which must be done under GMP) is research and could be performed in well controlled laboratories with complete traceability and thorough documentation.

Genetic Assessment of Human Pluripotent Stem Cells
Presenters: Jung Hyun Kim, PhD
Akitsu Hotta, PhD
Yoji Sato, PhD

ISSCR presented on the topic of genetic assessment of hPSCs in three parts. First, they discussed the risk assessment of genomic integrity in hPSCs. Second, they addressed the manufacturing of Human Leukocyte Antigen (HLA) genome-edited Induced Pluripotent Stem Cells (iPSCs). Lastly, they compared the perspectives of ISSCR's Standards for Human Stem Cell Use in Research with the Japanese regulatory perspective.

In the discussion on the risk assessment of genomic integrity in hPSCs, Dr. Kim provided an overview of the various genetic safety tests and summarized the current understanding of genomic integrity in hPSC cultures. The presentation highlighted the repetitive nature of the common genetic variants found in hPSCs, noting that specific genetic variants may become predominant during cell culture. Additionally, certain genomic integrations are associated with tumorigenicity and some genomic integrations relate to residual hPSCs in Cellular Therapy Products (CTPs). Dr. Kim also pointed out that there is currently no consensus on the best methods for assessing risks.

Dr. Hotta presented on the manufacturing of HLA genome-edited induced pluripotent stem cells (iPSCs), discussing how the retention of HLA-C helps prevent attacks from T cells and natural killer (NK) cells. He then outlined the procedures for clinical-grade HLA genome editing of iPSCs at a cell-processing facility. The presentation also highlighted the quality tests that were conducted for evaluation of HLA-edited iPSCs at CiRA Foundation.

Dr. Sato presented the quality standards and core principles recommended by ISSCR for research on PSCs, including non-clinical studies of PSC-derived products. Stem cells are characterized by their pluripotency and undifferentiated state, with genetic changes in culture impacting their phenotype and behavior. Stocks and cultures of stem cells should be monitored for culture-acquired genetic changes. Evaluations of master and working cell banks for their genetic status are recommended, covering the entire span of experiments, including before starting, during, and after major culture bottlenecks.

New cell lines or derivatives generated by modifying culture conditions should be assessed for genetic changes post-intervention. ISSCR's standards were then compared with the Japanese regulatory perspective, discussing the consistency of PMDA's approach to quality assessment of PSCs. Questions regarding the acceptability of certain mutations and the control value of contamination rates in cell products are raised.

Overall, understanding the methodology for the genomic integrity assessment of hPSCs and hPSC-derived products is emphasized, highlighting the importance of monitoring genetic changes to ensure reproducibility and reliability in stem cell research.

Questions:

- Is PMDA's approach to quality assessment of PSCs or PSC-derived products based on genome assessment consistent with the ISSCR's Standards for Human Stem Cell Use in Research?

PMDA's concept is aligned with that of the ISSCR. As the sensitivity of instruments has increased, detecting mutations in vitro has become easier, making appropriate assessment all the more important. PMDA believes that it is inappropriate to conclude that a product cannot be used in humans based solely on the confirmation of mutations in vitro tests. While detecting mutations in vivo remains challenging, PMDA will make a comprehensive decision based on all the results.

- May a nonsignificant Cosmic Shibata mutation be acceptable case-by-case?

The MFDS stated that the appropriateness of the proposed assessment criteria may depend on factors such as the intended indication of the product. They further noted that if a favorable risk–benefit profile can be demonstrated, showing that the product is expected to provide therapeutic benefit to patients, and if the proposed assessments are supported by valid and well-controlled test results, clinical application may be considered acceptable.

- Undifferentiated iPSC stocks are shipped only when no mutation is found in the Cosmic Shibata list by WGS. If a de novo Cosmic Shibata mutation is found in differentiated cell products, would it be possible to use the cell product for clinical application if appropriate assessments are made?

Use in clinical applications may still be possible provided that a comprehensive risk assessment is conducted. In addition to the following conditions:

  - The gene is not expressed in the final cell product
  - No tumorigenicity sign by in vitro and in vivo test
  - No detectable change in protein functionality (i.e., enzymatic activity)

- Is a control value of the contamination rate of cells with mutations acceptable?

It is difficult to define a uniform acceptance criterion for residual mutant cells, as it should be evaluated based on the manufacturing process, intended indication, and product characteristics. MFDS recommended using highly sensitive assays with the lowest possible detection limits and to test a statistically adequate number of samples. Mutant cells should be considered product-related impurities and controlled through release testing.

Jurisdictional Differences in Guidelines for Biological Ancillary Materials
Presenter: Toshimitsu Tanaka, PhD

ISSCR's fourth presentation was on the region-specific issue of jurisdictional differences in guidelines for biological ancillary materials. Dr. Tanaka outlined the existing direct regulations and guidelines for ancillary materials between the US and Japan, emphasizing the comprehensive guidelines for human, animal, and ruminant animal-derived materials. There are no significant practical gaps between the US and Japanese guidelines for human-

derived materials. However, Japan's standards require the incorporation of validated viral inactivation or removal processes for animal- and ruminant animal-derived materials.

Questions:

Ancillary Materials
Processing of AM is almost out of control from cell product sponsors.

- Can cell product sponsor mitigate the risk by adding viral testing on AM, MCB and/or final product to compensate for lack of viral inactivation/removal process?

PMDA requires that if viral testing is not conducted for ancillary materials, it must be performed on the downstream process (intermedia or final product).

MFDS requires viral testing of cell banks as a basic requirement. In cases where sufficient viral safety data for raw materials are not available, additional viral testing must be performed on drug substances and drug products.

- Can viral contamination risk be considered different between animal-derived AM and recombinant AM (USP 1043)? Is different levels of risk mitigation plans reasonable?

PMDA suggests avoiding using animal-derived ancillary materials, if it is available.

Starting cells

- Rather than testing the donor at two separate timepoints, would testing the donor at time of harvest and directly testing MCB be acceptable to demonstrate viral status?

It was discussed that, with the increasing sensitivity of viral detection methods, direct testing of cell material may eventually be sufficient. While no definitive conclusions were reached, there was general consensus that the capability to assess cell lines for viral contamination is improving and may represent a viable approach in the future.

The MFDS does not specify a window period for donor suitability testing. Donor eligibility testing is performed within 7 days before or after sample collection. At the MCB stage, various viral tests, including those for human-specific viruses, are conducted depending on the manufacturing scale and product development stage. While it is not acceptable to rely solely on testing of the cell bank and/or drug substance without donor testing, it is likewise not acceptable to omit viral testing at the cell or cell bank stages based solely on donor eligibility testing.

- What are the agency’s concerns, if any, regarding this strategy?

The MFDS noted that, although the sensitivity of viral detection methods has improved, the use of NGS and similar techniques to detect unknown viruses in human-derived cells is still considered insufficiently validated as a testing approach.

PMDA Presentation: Conditional Approval
Presenter: Yoshiaki Maruyama, PhD

Accelerating Approval Pathways for regenerative medical products under the "Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act'" (PMD Act) in Japan are discussed.

The PMD Act provides the option of a new scheme for obtaining conditional and time-limited approval for regenerative medical products. To obtain conditional and time-limited approval, exploratory clinical trials are required that are expected to have certain level of efficacy (for example, by using a surrogate endpoint). Under the conditional and time-limited approval scheme, regenerative medical products are granted marketing authorization when efficacy can be presumed; however, in order to demonstrate efficacy within the granted time period (maximum period of seven years), the sponsors are subject to strict post-marketing surveillance (PMS) study as a condition for approval. To ensure that products with unconfirmed effectiveness do not remain in the market, the PMD Act provides the option of withdrawal of approval after the re-application review process within the granted time period. If the PMS study demonstrates efficacy and safety, the product will be approved; however, the conditional and time-limited approval will expire if it is not.

As of October 2024, 21 CGT products, including 5 *ex vivo* and 4 *in vivo* gene therapy products, have been approved. Five of 21 CGT products have been approved through conditional and time-limited approval scheme, however, 2 products—HeartSheet and Collategen Intramuscular Injection 4mg—have taken off the market due to withdrawn/expired. To enhance approval predictability, the guidance related to conditional and time-limited approval have been prepared.

- Guidance on Conditional and Time-Limited Approval of Regenerative Medical Products and Subsequent Effectiveness Evaluation Plans, PSEHB/MDED Notification No. 0329-3, 2024.
  Japanese: https://www.pmda.go.jp/files/000267914.pdf
  English: https://www.pmda.go.jp/files/000274350.pdf

- Guidance on Conditional and Time-limited Approval and Protocol for Post Marketing Study of Stem Cell Therapy Products, PSEHB/MDED Notification No. 0329-4, 2024.
  Japanese: https://www.pmda.go.jp/files/000267915.pdf
  English: https://www.pmda.go.jp/files/000274351.pdf

The key challenge remains the appropriate utilization of this system to swiftly deliver safe and effective regenerative medical products to patients.

MFDS Presentation: Regulations on PSC-based Products in South Korea
Presenters: Jounghee Baek, PhD
Nanyoung Ahn, MS

Regulations on PSC-Based Products in South Korea are discussed, including the Act on the Safety of and Support for Advanced Regenerative Medicine and Advanced Biological Products (ARM and ABP Act). This act, which was introduced in August 2020, aims to strengthen safety management by establishing cell management businesses, cell processing facility businesses, and long-term follow-up procedures. It also supports the development

and approval of advanced biological products through expedited processing designation and conditional approval.

Clinical research and clinical trials for regenerative medicine and advanced biopharmaceuticals differ in purpose and regulatory framework. Clinical research focuses on expanding disease treatment opportunities, whereas clinical trials aim to prove drug safety and efficacy. Both processes involve different stakeholders, laws, and require separate sets of submission materials.

The clinical research review process under ARM is outlined based on a risk-based classification system. Management and oversight vary according to the level of risk involved.

- Low-risk research involves autologous cells with minimal manipulation.
- Medium-risk research includes autologous cells excluding minimal manipulation and allogeneic cells with minimal manipulation
- High-risk research covers allogeneic cells excluding minimal manipulation, xenogeneic cells, gene therapy, and artificial tissues or organs.

As of June 2024, South Korea has approved twelve cell therapy products, with 380 clinical trials currently underway. As of September 2024, five gene therapy products have been approved, alongside 127 ongoing clinical trials for gene therapy products.

MFDS provided reference guidelines for developing Advanced Biological Products (ABPs), including guidelines on biodistribution assessment of gene therapy products, quality assessment for stem cell therapy products, and considerations for developing personalized neoantigen coded therapy products.

MFDS also outlined new Guidelines for cell bank evaluation of cell therapy products which covers test items, methods, and acceptance criteria for various types of cell banks such as Master Cell Bank (MCB), Working Cell Bank (WCB), and End-of-Production Cell (EPOC). Tests include cell characterization, stability, growth characteristics, genetic stability, sterility, and adventitious agent testing.

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