Current situation on nonclinical safety evaluation of regenerative medical products in Japan

Takuya Nishimura
Office of Cellular and Tissue based Products
PMDA

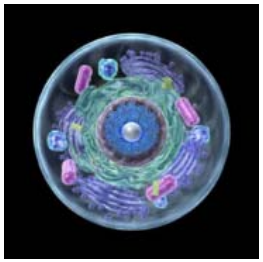
Disclaimers

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency (PMDA).

Definition of Regenerative Medical Products in Japan

In the PMD Act, regenerative medical products have been newly defined as…

- **Cellular and tissue based products**



- **Products for gene therapy**

The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act) were enacted in 2014

Classification of Regenerative Medical Products

Cellular or tissue based products

- Cell source
  - Somatic Cells
  - Somatic Stem Cells
  - Embryonic Stem Cells
  - iPS Cells
- Genetic relationship of cells to host
  - Autologous
  - Allogenic

Products for gene therapy

- Plasmid vector
- Virus vector
  - Non-proliferating virus
  - Attenuated virus

Genetically modified cellular products

References for Safety Evaluation

Cellular based products

■ **Guidlines on ensuring the Quality and Safety of Cellular based Products**

- **Autologous products, *2008***
- **Allogeneic product, *2008***

- **Autologous Somatic Stem Cells, *2012***
- **Autologous iPS-like Cells, *2012***
- **Allogeneic Somatic Stem Cells, *2012***
- **Allogeneic iPS-like Cells, *2012***
- **Embryonic Stem Cells, *2012***

PFSB Notification No. 0208003, 0912006,
PFSB Notification No. 0907-2,3,4,5,6

Products for gene therapy

■ **Guidance on ensuring the Quality and Safety of Products for Gene Therapy *2013***

PFSB/ELD Notification No.0701-4

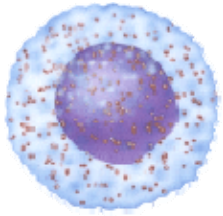
☐ ICH Considerations

- **General Principles to Address Risk of Inadvertent Germ line Integration of Gene therapy vectors, *2006***
- **General Principles to Address Virus and Vector Shedding, *2009***
- **Oncolytic Viruses, *2009***

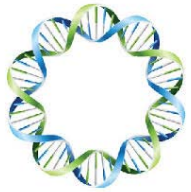
1. General considerations for non-clinical safety assessment for regenerative medical products

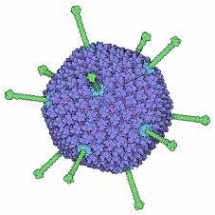
Components of Regenerative Medical Products

- ☐ Cells / Tissues

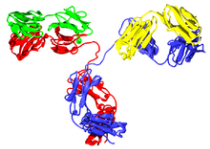


- ☐ Transgenes / Vectors





- ☐ Non-cellular Ingredients

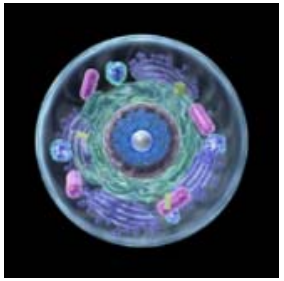


- ☐ Impurities from the manufacturing process

Points to consider for cellular or tissue based products

PFSB Notification No. 0208003, 0912006,
PFSB Notification No. 0907-2,3,4,5,6

- Inadvertent cell transformation
- Inadvertent ectopic tissue formation
- Physiologically active-substances produced by cells
- Potential effects on healthy cells or tissue
- Tumor formation
- Undesirable immunological reactions
- General toxicity



- Safety evaluation based on guidance for products for gene therapy, when the products have transgenes.

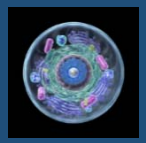
Points to consider for products for gene therapy

PFSB/ELD Notification No.0701-4

- **Emergence of proliferative virus**
- **Cytotoxicity on healthy cells or tissue**
- **Inadvertent gene integration**
- **Effect of expression of transgene**
- **Tumor formation**
- **Undesirable immunological reactions**
- **General toxicity**

Toxicity tests for regenerative medical products

Cellular or tissue based products



- **General toxicity test**
  - Systemic/Local toxicity
  - Effect on vital organs
  - Formation of ectopic tissue
- **Tumorigenicity study**

Products for gene therapy

- **General toxicity test**
  - Systemic/Local toxicity
  - Effect on vital organs
  - (Biodistribution, Germline integration)

2. General toxicity tests for regenerative medical products

General considerations for general toxicity study

Cellular or tissue based product	Products for gene therapy
✓ Species differences in biological reaction ✓ Xenogenic immune responses ✓ Inappropriateness of conventional TK/ADME study	✓ Species differences in infectivity or transduction efficiency ✓ Worst-case scenario, such as unexpected leak or proliferation of vectors
Hazard Identification	Hazard Identification Risk assessment

General Toxicity: Design

<table>
<tr><th></th><th>Cellular or tissue based products</th><th>Products for gene therapy</th></tr>
<tr><td>Test product</td><td colspan="2">Final product</td></tr>
<tr><td>Dose</td><td colspan="2">• Maximum dose: As high as possible (MTD, MFD, …)</td></tr>
<tr><td></td><td>–</td><td>Depending on target disease,
• include the pharmacologically effective dose range
• establish NOAEL</td></tr>
<tr><td>Dosing regimen</td><td colspan="2">• In principle, dosing regimen should reflect the clinical dosing regimen</td></tr>
<tr><td></td><td><table><tr><th>Clinical trial</th><th>Toxicity test</th></tr><tr><td>Single</td><td>Single</td></tr><tr><td>Repeated</td><td>Repeated or Single when not accumulative</td></tr></table></td><td>• ICHS6, S9 guidelines may be referred</td></tr>
</table>

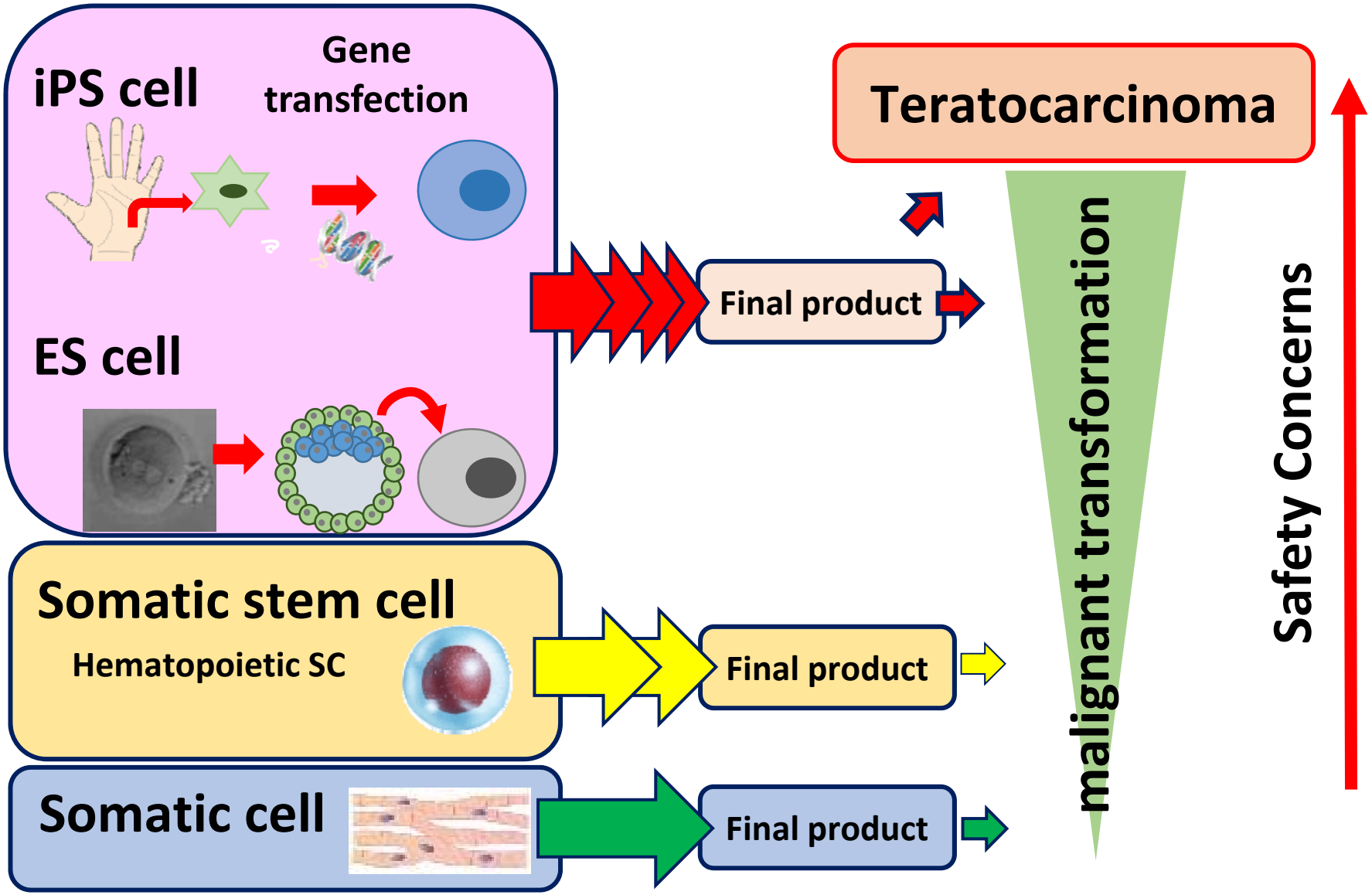
General Toxicity: Design

	Cellular or tissue based products	Products for gene therapy
Animal	Animals expressing pharmacological effect are desirable. 1. Mechanism of action 2. Xenogenic immune response 3. Anatomical feature  	1. Infectivity, Viral tropism 2. Transduction efficiency 
Route	Therapeutic route-available animals If not, animals available alternative routes	
Species	One species is possible, when warranted.	
Observation	Refer to Toxicity test method guidelines (ICHS4 guidelines)	

The designs are modifiable depending on the properties of the product.

3. Tumorigenicity for cellular or tissue based products

Risk of tumorigenicity

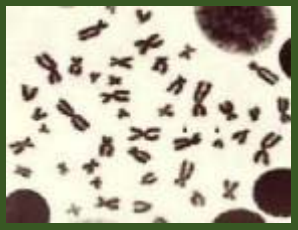


Tests for tumorigenicity assessments

***in vitro* Testing**

- Karyotype

  → Genetic stability



- Soft agar colony formation assay

  → Proliferation independent on adhesion

***in vivo* Testing**

- Testing using immuno-deficient animals

  → Tumorigenicity in vivo

The necessity should be considered on a case-by-case basis, depending on the product characteristics.

In vivo Tumorigenicity Test: Design

Test product	Final product
Route	Therapeutic route (The alternatives when warranted)
Dosage	As high as possible (MTD, MFD), Single dose
Dose range	At least 2 groups（control and product）
Number	10 animals/group
Period	High Concerns on risk • Until the implanted cells are not detectable • The period for which spontaneous lesions or aging-related lesions in test animals are not detected Low Concerns on risk • The period for which transformation or proliferation of cells are not observed in histological examination • 4-16 weeks（Ref. WHO TRS 978）

4. Assessments on impurities from manufacturing process

Safety assessments on impurities from manufacturing process

In principle

- To identify the impurities in the process, that could remain in final product
- To remove them from the final product as far as possible

Step1: Measurement or estimation of residue level in product

- To Measure the amount of impurities wherever possible
- To Estimate from the dilution rate

Step2: Estimation of human exposure level

- To estimate from the residue level of impurities in the final product and therapeutic dosage of product

Step3: Safety evaluation using existing information

Safety evaluations using existing information for impurities

Property of Impurities	Existing information
in vivo substance	• Experience as a drugs or excipients on market • Normal serum level in human • Acceptable daily intake (ADI) • NOAEL or MABEL
Chemicals	• Experience as a drugs or excipients on market • Threshold of Toxicological concerns (TTC, ICH-M7) • NOAEL or MABEL
Elemental impurities	• ICH-Q3D(Guidelines for elemental impurities)

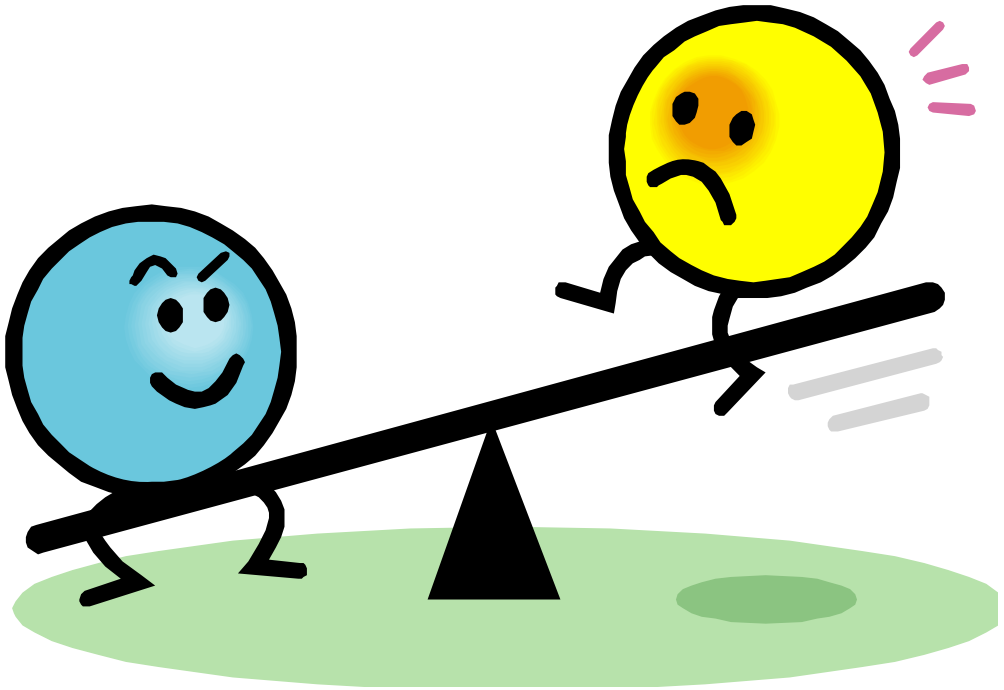
If the existing information is not available, the conduct of non-clinical safety studies should be taken into consideration.

Summary

To conduct clinical studies for regenerative medical products,

- **Understand what the products are composed of and evaluate the safety of each component properly, including the impurities from the manufacturing process**
- **Conduct nonclinical safety studies to explain the points to consider in the MHLW guidelines**
- **Plan the general toxicity studies or tumorigenicity studies, depending on the properties of the product**

Thank you for your time and kind attention!



Pharmaceuticals and Medical Devices Agency