

# Session I

## Considerations for Screening/Transferring Cells for Further Manufacturing

Yoshiaki Maruyama, Ph.D.  
Review Director,  
Office of Cellular and Tissue-based Products  
PMDA, Japan

**Disclaimer:**

The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

# Outline

---

- General Information:
  - ✓ Screening
  - ✓ Transferring
  
- Points to Consider

# Outline

---

- General Information:
  - ✓ Screening
  - ✓ Transferring
- Points to Consider

# Related Guidelines for Regenerative Medical Products

Standard for Biological Raw Materials  
MHLW Public Notice No.210 (2003)

General Principles for the Handling and Use of Cells/Tissue-Based Products  
PFSB/MHLW Notification No.1314 Appendix1 (2000)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

Autologous (2008)

Allogeneic (2008)

Autologous Somatic Stem Cells (2012)

Allogeneic Somatic Stem Cells (2012)

Autologous iPS-like Cells (2012)

Allogeneic iPS-like Cells (2012)

Embryonic Stem Cells (2012)

Points to Consider for the Evaluation of Specific Products

- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Articular cartilage repair (2010) ▪ Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010) ▪ Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)

# Screening

# Related Guidelines for Regenerative Medical Products

Standard for Biological Raw Materials  
MHLW Public Notice No.210 (2003)

General Principles for the Handling and Use of Cells/Tissue-Based Products  
PFSB/MHLW Notification No.1314 Appendix1 (2000)

## Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

Autologous (2008)

Allogeneic (2008)

Autologous Somatic Stem Cells (2012)

Allogeneic Somatic Stem Cells (2012)

Autologous iPS-like Cells (2012)

Allogeneic iPS-like Cells (2012)

Embryonic Stem Cells (2012)

## Points to Consider for the Evaluation of Specific Products

- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Articular cartilage repair (2010) • Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010) • Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)

# Structure of the Standard for Biological Raw Materials

## Section 1 General Rules

## Section 2 General Rules for Blood Product and Plasma Derived Products

1. General Rules on Blood Products for Transfusions
2. General Rules on Blood Plasma Fraction Products

## Section 3 General Rules for Human Derived Materials

1. Standards for Human Cells and Tissue Materials
2. Standards for Human Urine Derived Materials
3. Standards for Human Derived Materials

## Section 4 General Rules for Animal Derived Materials

1. Standards for Ruminant Animal Derived Materials
2. Standards for Animal Cells and Tissue Materials
3. Standards for Animal Derived Materials

# Standard for Human Cells and Tissue Materials (1)

- (2) Where the human cells and tissue are collected, the measures described below are required.
- a. The necessary steps to **prevent contamination from pathogenic microorganisms or other infectious agents** must be taken during the process to collect the relevant cells or tissue.
  - b. As needed, **the appropriate tests will be performed on the collected cells and/or tissue** with consideration of the latest information related to infectious disease in order to ensure that these collected cells and tissue are not contaminated by pathogenic microorganisms or other infectious agents.

# Standard for Human Cells and Tissue Materials (2)

- (3) The following criteria are applied to donors, who must be appropriately qualified to donate the cells or tissue. *If the intended recipient of the final product is the same person as the donor, a donor screening may not be necessarily required.*
- a. When the relevant cells or tissue are collected, **the interviews, examinations and tests must rule out the infection** by bacteria, fungus, virus, etc., according to the intended use of the collected source materials.
  - b. The test items and methods for step (a) above **must be appropriate in light of the latest available information** regarding infectious diseases.
  - c. Depending on the test items and methods for step (a) above there **must be re-testing performed in an appropriate timeframe with consideration made for the window periods.**

# Related Guidelines for Regenerative Medical Products

Standard for Biological Raw Materials  
MHLW Public Notice No.210 (2003)

General Principles for the Handling and Use of Cells/Tissue-Based Products  
PFSB/MHLW Notification No.1314 Appendix1 (2000)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

Autologous (2008)

Allogeneic (2008)

Autologous Somatic Stem Cells (2012)

Allogeneic Somatic Stem Cells (2012)

Autologous iPS-like Cells (2012)

Allogeneic iPS-like Cells (2012)

Embryonic Stem Cells (2012)

Points to Consider for the Evaluation of Specific Products

- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Articular cartilage repair (2010) ▪ Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010) ▪ Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)

# Structure of the Q/S GLs

## Chapter 1 General Principles

1. Objective
2. Definitions

## Chapter 2 Manufacturing Methods

1. Raw Materials and Materials Used in Manufacturing
2. Manufacturing Process
3. Quality Control of Final Product

## Chapter 3 Stability

## Chapter 4 Preclinical Safety Testing

## Chapter 5 Studies to Support Potency or Efficacy

## Chapter 6 Pharmacokinetics

## Chapter 7 Referring to Clinical Trials

# Donor Selection Criteria and Eligibility (1)

## Autologous

To ensure the safety of patients, the personnel involved in manufacturing the product, and the healthcare workers who treat patients, establish test parameters by which to assess possible infection of the cells and/or tissues and provide justification for the parameters.

HBV, HCV, HIV, HTLV(-1/2)

## Allogeneic

Establish selection criteria and eligibility criteria that take into consideration age, sex, ethnic characteristics, genetic characteristics, the medical history, the health condition, test parameters related to any type of infection that may be transmitted via cell and/or tissue samples, immunological compatibility, and other characteristics and explain their appropriateness. If donor genomic or gene analysis is undertaken, it shall be performed in accordance with “Ethical Guidelines for Analytical Research on Human Genome/Gene,” by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW) and Ministry of Economy, Trade and Industry (METI).

HBV, HCV, HIV, HTLV(-1/2) and parvovirus B19  
Infection with CMV, Epstein-Barr (EB) virus, or West Nile virus shall also be ruled out, if necessary

# Donor Selection Criteria and Eligibility (2)

For allogeneic human cell-based products, further assess and determine the eligibility of donors by examining the medical history of the donor.

- Bacterial infections, such as syphilis, chlamydia, gonorrhea, and tubercle bacillus
- Sepsis or suspected sepsis
- A malignant neoplasm
- Serious metabolic or endocrine disease
- Collagen and blood diseases
- Hepatic diseases
- Confirmed or suspected TSE or other brain disorders
- A specific genetic disease or a family history of a specific genetic disease

# Records Related to the Donor

- Retain complete records related to the donor so that any information necessary to ensure the safety of cells and tissues that are used as raw materials can be verified. Concrete measures shall be described.
- For patients and donors of test samples, it is sufficient to prepare and retain only specific information that is related to the intended use of the cells.

# Collection, Storage, and Transport of Cells and Tissues (1)

## (i) Eligibility of personnel and medical institutions collecting the samples

Describe the technical requirements for personnel and medical institutions that collect the cells and tissues.

## (ii) Suitability of the sampling site and sampling method

Describe the rationale for selecting the cell and tissue sampling sites and the sampling method. State why the selected sites are scientifically and ethically appropriate. For cell and tissue sampling methods, indicate the suitability of the equipment and drugs used and the measures adopted to prevent microbial contamination, erroneous sampling (mix-up), and cross-contamination.

# Collection, Storage, and Transport of Cells and Tissues (2)

## (iii) Informed consent from donors

Describe the details of the informed consent, including the clinical application, provided by the donor of the cells or tissue.

## (iv) Protection of donor privacy

Indicate the measures adopted to ensure the protection of the donors' privacy.

## (v) Tests to ensure donor safety

If tests such as those to confirm the state of the sampling site need to be performed in order to ensure the safety of the donor at the time of cell or tissue sampling, describe the details of the tests as well as any interventions undertaken after test results indicate a problem.

# Collection, Storage, and Transport of Cells and Tissues (3)

## (vi) A storage method and measures to prevent erroneous sampling (mix-up)

If the somatic cells that are collected must be stored for a defined period of time, set the storage conditions and storage duration and explain their appropriateness (validity). Describe in detail the measures and procedures to be followed to prevent erroneous sampling (mix-up).

## (vii) Transportation methods

If cells and/or tissues that were collected must be transported, define the containers to be used for transport and the transportation procedure (including temperature control) and provide the justification.

## (viii) Preparation of records and storage procedures

Written records for items (i) through (vii) above shall be prepared, and proper record storage procedures shall be described in detail.

# Transferring

# Related Guidelines for Regenerative Medical Products

Standard for Biological Raw Materials  
MHLW Public Notice No.210 (2003)

General Principles for the Handling and Use of Cells/Tissue-Based Products  
PFSB/MHLW Notification No.1314 Appendix1 (2000)

## Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

Autologous (2008)

Allogeneic (2008)

Autologous Somatic Stem Cells (2012)

Allogeneic Somatic Stem Cells (2012)

Autologous iPS-like Cells (2012)

Allogeneic iPS-like Cells (2012)

Embryonic Stem Cells (2012)

## Points to Consider for the Evaluation of Specific Products

- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Articular cartilage repair (2010) ▪ Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010) ▪ Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)

# Storage and Transport of Human Cells/Products

- Perform appropriate stability tests based on the viability, potency, and other characteristics of the cells, establish the storage method and validity period, and clarify their suitability, considering storage duration, distribution, and the storage form.
- In particular, when freezing and thawing, confirm that the freezing and thawing processes do not affect the stability or any other characteristic of the cells.
- When transporting cells/products, the relevant transportation vessels and transportation procedures (such as thermal management) shall be set and their appropriateness justified.

# Related Guidelines for Regenerative Medical Products

Standard for Biological Raw Materials  
MHLW Public Notice No.210 (2003)

General Principles for the Handling and Use of Cells/Tissue-Based Products  
PFSB/MHLW Notification No.1314 Appendix1 (2000)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

Autologous (2008)

Allogeneic (2008)

Autologous Somatic Stem Cells (2012)

Allogeneic Somatic Stem Cells (2012)

Autologous iPS-like Cells (2012)

Allogeneic iPS-like Cells (2012)

Embryonic Stem Cells (2012)

Points to Consider for the Evaluation of Specific Products

- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Articular cartilage repair (2010) • Cell sheet for periodontal tissue regeneration (2011)
- Cell sheet for heart failure (2010) • Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)

# Structure of the General Principles for the Handling and Use of Cells/Tissue-Based Products

---

Chapter 1 General Rules

Chapter 2 Handling of Cells and Tissue

Chapter 3 Safety Assurance Measures at the Manufacturing Stage

Chapter 4 Personal, Organisation and Management System

Chapter 5 Safety Assurance Measures at the Usage Stage

Chapter 6 Individual Data Production

Chapter 7 Reviews

# Quarantine

- Apart from exceptional circumstances **products are not to be shipped until** donor screening has been implemented for each donor and product testing and inspection is completed and the competence of the product is clarified.
- When storing products prior to shipment while waiting for completion of donor screening, product testing and inspection, the products in question are to be kept separate from not yet manufactured cells or tissue to be used as ingredients, and other products ready for shipment. This is to be ensured by proper labelling and segregation of storage areas. Measures are to be adopted to prevent inappropriate shipping or unnecessary handling of the products in question.

# Shipment and Delivery

- Shipment

When shipping the products the name of the recipient medical institution and shipment date is to be written clearly on each product.

- Delivery

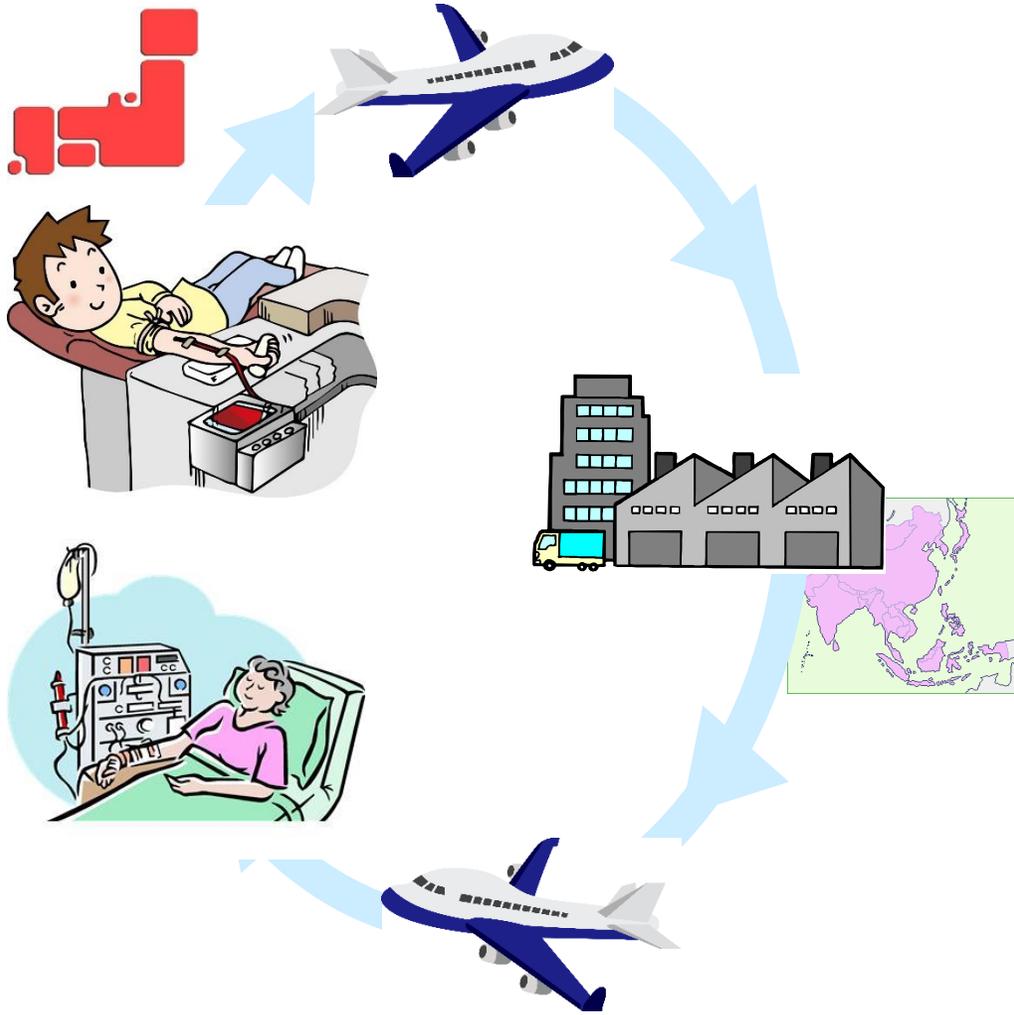
When delivering the products the necessary quality assurance measures are to be adopted, including temperature control.

# Outline

---

- General Information:
  - ✓ Screening
  - ✓ Transferring
- Points to Consider

# Point to Consider; Screening/Transferring Cells



- **Screening (for allogeneic material)**
- ✓ Donor re-testing performed in an appropriate timeframe with consideration made for the window periods.
- **Test upon receipt**
- ✓ Establish a battery of tests and acceptance criteria to assess appropriateness of the cells and tissues that will serve as the raw materials, taking into account the nature of the cells and their intended use.
- ✓ At the stage of initiation of clinical trials, provide the actual measured values obtained using test samples, and propose a provisional set of acceptance criteria based on these values.

Thank you for  
your attention!

Please visit the PMDA website

<http://www.pmda.go.jp>

<http://www.pmda.go.jp/english/index.html>