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Japanese Regulatory Principles for Ensuring Quality and Safety of Cell/Tissue-Processed Products

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Guidelines for Cell/Tissue-Processed Products

Good Tissue Practice

Standard for Biological Ingredients
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)

Basic Technical Requirements

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human (Autologous) Cells/Tissue
PFSB/MHLW Notification No.0208003 (2008)

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human (Allogenic) Cells/Tissue
PFSB/MHLW Notification No.0912006 (2008)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed :

- Human (Autologous) Somatic Stem Cells
- Human (Autologous) iPS-like Cells

PFSB/MHLW Notification No.0907-2 & 4 (2012)

Guidelines on Ensuring Quality and Safety of Products Derived from Processed :

- Human (Allogenic) Somatic Stem Cells
- Human (Allogenic) iPS-like Cells
- Human Embryonic Stem Cells

PFSB/MHLW Notification No. 0907-3, 5 & 6 (2008)

General Principle of the Use of Cell/Tissue-Based Products

The use of cell/tissue-based products should be confined to medical treatments,

where **a clinical advantage over other products/treatments** is expected, because

the potential risk of the transmission of infectious agents or of other unknown factors derived from them is not completely ruled out.

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Human Cells/Tissues or Stem Cells

- Describe the **basic technical elements** to ensure the quality and safety of pharmaceuticals and medical devices derived from processing of **autologous** and **allogeneic** human somatic cells, tissues or stem cells.

- Clarify differences with respect to data requirements and evaluation between **marketing authorization applications** and **clinical trial applications**. For the latter, it is necessary to ascertain if there is any quality and safety problem that might pose an obstacle to initiate a clinical trial.

The Q/S Guidelines emphasize that:

- When conducting or evaluating tests on individual product, it is necessary to take flexible approaches **on a case-by-case basis** in line with the concept of the guideline and on the basis of type, characteristics and intended clinical use of the product in question.

- Reflection of scientific progress and accumulation of experience in relevant field is always encouraged.

- In the use of such an advanced therapeutic product for treating patients (**First-in-Man**) with severe and life threatening diseases or injuries, the **risk/risk balance with/without the advanced treatment** should be also taken into account, rather than just discussing unknown potential risk of a product.

- Decision making by a patient after extensive IC should be a crucial element.

Contents of the Q/S GLs

Chapter 1General Rules

Chapter 2 Method of Manufacture

- 1. Raw Materials and Manufacture-Related Substances
  - 1. Starting cells/tissue for desired cells
  - 2. Raw materials and manufacture-related substances other than starting cells/tissue of desired cells
- 2. Manufacturing Process
- 3. Quality Control of Final Products

Chapter 3 Stability of Products

Chapter 4 Non-Clinical Safety Study of Products

Chapter 5 Studies to Support the Effect/Performance of Products

Chapter 6 Disposition of Products in the Body

Chapter 7 Clinical Study

Autologous *vs.* Allogeneic

Autologous Human Cells/Tissues

- **Infectious status of donor**, including infections of HBV, HCV, HIV, and HTLV.
- **Risk of proliferation or re-activation of virus in manufacturing processes**
- **Robust process control to minimize unevenness of "Custom-Made" products**
- **Limited amount of samples for quality evaluation of products**

Allogenic Human Cells/Tissues

- **History, source, derivation**
- **Donor screening/testing and donor eigibility** (compatibility with donor qualification criteria, including ethical and medical aspects; freedom from the presence of HBV, HCV, HIV, HTLV and pulvovirus B19 by screening and testing; exclusion of potential infection of CMV, EBV and WNV by testing; clinical history; experience of blood transfusion or implanting;genetic etc.)
- **Records of donor**
- **Derivation of cell strain**
- **Cell banking**
- **Potential Viral Presence in Products (Viral assay at the final product level)**
- **Immunological problems** (eg., rejection, GVHD etc.)

Specific Points to Consider on Human iPS/ES Cell-Derived Products

- hiPSCs or hESC with **pluripotency** *per se* **may NOT always be the most suitable starting material** to differentiate into a specific desired cell product.
- Significance of derivation of **hiPS-like Cells** as a starting materials in addition to hiPS Cells
- Significance of derivation of **hESC-derived differentiated Cells** as a starting material in addition to hES Cells
- Significance of establishment of **well characterized stable cell banks** and/or relevant intermediate cell products
- Elimination/inactivation of **residual undifferentiated cells** during production process be critical.

iPS cells *vs.* "iPS-like cells"

Human iPS cells

- …are cells that originate from human somatic cells
- …have been reprogrammed by forced introduction of genes, proteins or chemicals
- …have pluripotency to differentiate into all cell types of endoderm, mesoderm and ectoderm
- …have an ability or potential of self-renewal

Human iPS-like cells

- …are cells that originate from human somatic cells
- …have been dedifferentiated by forced introduction of genes, proteins or chemicals
- …have ability to differentiate into some cell type(s) of endoderm, mesoderm or ectoderm
- … have an ability or potential of self-renewal

Thank you for your attention

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