Current Topics in Japan with Respect to Evaluation and Control of Biotechnology Products

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Japanese Regulation for Cell/Tissue-based Advanced Medicinal Products

A Guideline on Subsequent-Entry Protein Products (SEPP)
3 Types of Cell/Tissue Therapies in Japan

- **Products** (PMDA/PAFSC)
  - Q/S Pre-evaluation
  - Relevant GL

- **Basic Seeds**
  - Non-clinical Study
  - SC Clinical Res. GL
  - GL on Clinical Res. Ethics
  - Advanced Medical Treatment (AMT) by MD

- **Medical Tec.**
  - (Health Science C.)
  - Highly AMT
  - AMT
  - Health insurance coverage

- **Clinical Trial**
  - Marketing Authorization, Commercial Products
  - GLP, INDGMP, GCP, GMP, GVP
  - Health insurance coverage
  - PAL

- **Entrusted at the Discretion of MD** (No health insurance coverage)

- **Medical Act**
Development of cell/tissue-based medicinal products in Japan under the PAL

- October 2007
  The first approval of a cell/tissue-based medicinal product
  autologous cell-based product for serious burn

- Q/S Pre-evaluation
- Clinical Trial
  - Skeletal myoblast autologous
  - Mesenchymal stem cell allogenic
  - Corneal epithelial cell sheet allogenic
  - Cultured skin allogenic

- MAA
  - Cartilage cell autologous

- Approval
  - Cultured skin autologous
<table>
<thead>
<tr>
<th>Target Tissue/Organ</th>
<th>Source</th>
<th>Cell Type</th>
<th>Target Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Autologous</td>
<td>bone marrow mesenchymal stem cells</td>
<td>osteonecrosis of lunate bone</td>
</tr>
<tr>
<td>Bone</td>
<td>Autologous</td>
<td>bone marrow mesenchymal stem cells</td>
<td>aseptic necrosis of the femoral head</td>
</tr>
<tr>
<td>Heart</td>
<td>Autologous</td>
<td>CD133+ bone marrow cells</td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td>Intervertebral Disc</td>
<td>Autologous</td>
<td>bone marrow mesenchymal stem cells, intervertebral disc-derived cells</td>
<td>lumbar disk herniation, etc.</td>
</tr>
<tr>
<td>Blood Vessel/Neuron</td>
<td>Autologous</td>
<td>bone marrow monocytes</td>
<td>cardiogenic cerebral thrombosis</td>
</tr>
<tr>
<td>Cornea</td>
<td>Allogenic</td>
<td>corneal stem cells, bone marrow mesenchymal stem cells</td>
<td>Stevens-Johnson syndrome, ocular pemphigoid etc.</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Autologous</td>
<td>bone marrow mesenchymal stem cells</td>
<td>osteochondritis dissecans, etc.</td>
</tr>
<tr>
<td>Bone</td>
<td>Autologous</td>
<td>bone marrow mesenchymal stem cells</td>
<td>bone cyst, intraosseous ganglion, etc.</td>
</tr>
<tr>
<td>Heart</td>
<td>Autologous</td>
<td>skeletal myoblasts</td>
<td>severe cardiomyopathy</td>
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<tr>
<td>Blood Vessel</td>
<td>Autologous</td>
<td>CD34+ peripheral blood cells</td>
<td>occlusive peripheral vascular disease</td>
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<tr>
<td>Heart</td>
<td>Autologous</td>
<td>cardiac stem cells</td>
<td>severe chronic ischemic heart failure</td>
</tr>
<tr>
<td>Bone</td>
<td>Autologous</td>
<td>bone marrow mesenchymal stem cells</td>
<td>severe bone loss in alveolar ridge</td>
</tr>
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Development of various guidelines for ensuring quality and safety of cell & tissue-based advanced medicinal products intended for MA under the PAL
General Principles for the Handling and Use of Cell/Tissue-Based Products
- PFSB/MHLW Notification No.1314 (12/12/2000) Appendix No 0330030 (Partially revised version 30/03/2007)

Guideline on Ensuring Quality and Safety of Products Derived from Engineered Autologous Human Cell/Tissue
- PFSB/MHLW Notifications No.0208003 (8/02/2008)

Guideline on Ensuring Quality and Safety of Products Derived from Engineered Allogeneic Human Cell/Tissue
- PFSB/MHLW Notifications No.0912006 (12/09/2008)
Draft Guidelines on Ensuring Quality and Safety of Products Derived from:

- **Autologous** Engineered Human Induced Pluripotent Stem Cells
- **Autologous** Engineered Human Somatic Stem Cells
- **Human** Embryonic Stem Cells
- **Allogenic** Engineered Human Induced Pluripotent Stem Cells
- **Allogenic** Engineered Human Somatic Stem Cells
Guidelines on Ensuring Quality and Safety of Products Derived from Engineered Human Cell/Tissue:

- Describe the basic technical elements to ensure the quality and safety of pharmaceuticals and medical devices derived from processing of autologous and allogeneic human cell/tissue, respectively.

- Clarify differences with respect to data requirements and evaluation between MA submission and submission for verification of conducting investigational clinical trials. The latter is a Japanese specific regulatory system, i.e., Q/S pre-evaluation ("Kakunin-shinsei" in Japanese) to ascertain if there is any quality and safety problem that might pose an obstacle to initiate a clinical trial.
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 a product in question.

- Reflection of scientific progress and accumulation of experience in relevant field is always encouraged.
Guidelines also emphasize that:

- In the use of such 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 made by a patient after extensive IC should be a crucial element.
Guidelines on Ensuring Quality and Safety of Products Derived from Engineered Autologous/Allogeneic Human Cell/Tissue

Chapter 1 General Rules
Chapter 2 Method of Manufacture
  1. Raw Materials and Manufacture-Related Substances
     1. Starting Cell/Tissue for desired cells
     2. Raw materials and manufacture-related substances other than starting Cell/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
## Points to Consider on Autologous CT & Allogeneic CT

### Autologous Human Cell/Tissue
- **Infectious Status of Donor**, including infections of HBV, HCV, HIV, and HTLV.
- **Risk of Proliferation or Reactivation of virus in Manufacturing Processes**
- **Robust Process Control to Minimize Unevenness of “Custom-made” Products**
- **Limited Amount of Samples for Quality Evaluation of Products**

### Allogeneic Human Cell/Tissue
- **History, Source, Derivation**
- **Donor Screening/Testing and Donor Eligibility** (Compatibility with donor qualification criteria, including ethical and medical aspects; Freedom from the presence of HBV, HCV, HIV, HTLV and pulovirus 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**
- **Cell Banking**
- **Potential Viral Presence in Products**
- **Immunological Problems** (eg., rejection, GVHD etc.)
Points to Consider on Process & Quality

- Characterization and Grasp of Specific Profiles of Cells at Critical Steps (starting, intermediate, final) and Their Eligibility (differences in autologous/allogeneic)
- Eligibility of Other Raw Materials and Manufacture-Related Substances and Their Quality Control (especially, eligibility of biological materials, no adverse impact of non-cellular/tissue component on desired cells)
- Verification of Manufacturing Process and Constancy of Manufacture
- Product Consistency in terms of Quality Attributes such as Identity, Purity, Homogeneity and Potency
- Stability (storage conditions/expiration date, freezing & thawing processes, and shipping vessel & procedure)
- Quality Control of Final Product through Relevant Combination of Critical Quality Elements from Products & Process Aspects
Points to Consider on Non-clinical Safety (1)

- **Presence of Microorganism, especially Viruses**
- **Tumorigenicity** (Stem Cells, iPS Cells, ES Cells)
- **Ectopic Tissue Formation** (Stem Cells, iPS Cells, ES Cells)
- **Inappropriate Differentiation/Tumorigenicity** (Stem Cells, iPS Cells, ES Cells)
- **Undesired Phenotype Expression** (Stem Cells, iPS Cells, ES Cells)
- **Immunogenicity, Immunorejection or other Unanticipated Immunoresponses** (especially, allogenic cells)
Points to Consider on Non-clinical Safety (2)

- Testing in relevant animal models or in vitro to a technically possible and scientifically reasonable extent by taking into account Nature of the Product and Target Disease.
- Testing Cell/Tissue models of animal origin in relevant animal models, if such product models that can mimic those of human origin are available.
- No adverse impact of non-cellular/tissue components on starting C/T or products
- Evaluation of Risk vs Benefit
- Potential Risk Concerns on Product vs Real Risk of Patient
Points to Consider on Non-clinical Efficacy

- Examination of functional expressions, persistence of C/T action and their expected therapeutic efficacy through appropriately-designed tests using relevant animals and cells (POC)

- Examination of therapeutic effects using cell/tissue models or disease-model animals, where appropriate and possible

- Indication of far more promising efficacy or performance of the product than other medical treatments

- Evaluation of Benefit vs Risk

- Consideration on Potential Risk Concerns on Product vs Real Risk of Patient
Production & Evaluation of iPS Cell Derived Products

Gene Transfer or Other Relevant Methods for Reprogramming
Cultivation with Growth Factor etc., Mass Production
Cell Line Establishment, Cell Banking, QC, Maintenance, Constant Supply, Mass Production
Characteristics (identity, purity, potency) of iPSCells, Stability, Safety etc.
Differentiation to Desired Cell  Inducer, Culture conditions for consistent differentiation etc.
Characterization of Desired Differentiated Cell (including Heterogeniety, Tumorigenicity etc.)
Formulation of Desired Cell, Combination with Non-Cellular Materials
Characterization of Final Product, Stability, Evaluation of Safety and Efficacy by relevant Non-Clinical & Clinical Studies. Safety concerns may include: ectopic tissue formation, inappropriate differentiation/tumorigenicity, undesired phenotype expression, immunorejection or other unanticipated immunoresponses
Quality Control after MAA, PMS etc.
Specific Point to Consider on Human iPS Cells or ES Cells-Derived Products

- hiPSCs or hESCs with pluripotency per se may not always be a most suitable starting material to differentiate into a specific desired cell product
- Significance of derivation of hiPS-like Cells (hiPSLCs) as a starting materials in addition to hiPS Cells to minimize unwanted cells
- Significance of derivation of hESC-derived differentiated Cells (hESCDs) as a starting material in addition to hES Cells to minimize unwanted 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 (hiPSCs)
• ...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 (hiPSLCs)
• ...originate from human somatic cells
• ...have been de-differentiated by forced introduction of genes, proteins or chemicals
• ...have an ability to differentiate into some cell type(s) of endoderm, mesoderm or ectoderm
• ... have an ability or potential of self-renewal
Point to Consider on Clinical Study: FIM

- FIM for Promotion of New Advanced Therapy vs Assurance of Scientific Validity, Ethical Validity, Public Understanding/Recognition, and Economic Validity
- Implication of far more promising efficacy or performance of the product than any other medical treatments
- Scientific justification of conducting clinical study based on data from CMC study to non-clinical study and current knowledge
- Decision made by Patients after thoroughly disclosed written IC including unknown factors
- Evaluation of Benefit vs Risk
- Potential Risk concerns on Product/Therapy vs Real Risk of Patient
MHLW GL on SEPP (PFSB/MHLW Notifications No. 0304007, 3/04/2009)

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8. Clinical studies
9. Post-marketing surveillance
10. Names
Some Key Points (1)

1. Whatever the product is, ensuring its Quality, Safety and Efficacy is an essential element for a product intended for therapeutic use.

2. Whatever the product is, establishing a process with its associated process control is one of the critical elements for assurance of consistent drug production.

3. A new MA application category different from the existing generic approach is established.

4. The guideline applies to recombinant protein products.
Some Key Points (2)

5. If the host cell line of the innovator’s product is disclosed, it is desirable to use the same cell line.

6. It is recommended to adopt the manufacturing processes which potentially improve the safety of the product.

7. SEPP should be thoroughly characterized, and then it is not always necessary to conduct comparability testing for assessing SEPP with respect to quality attributes or to use several lots of reference DS obtained from innovator’s DP.

8. The innovator’s DS/DP (the comparator product) must be already approved in Japan.
9. It is not always necessary to conduct comparability exercises in setting specifications of SEPP DS/DP and to use several lots of the innovator’s DS/DP.

10. For product- and process-related impurities, it may be more rational to assess safety on the basis of an established manufacturing process per se and characteristics of impurities than simply to compare impurities of SEPP with those of innovator’s product.
Some Key Points (4)

11. Since identical storage conditions and storage periods to the innovator’s product are not prerequisite, a comparison of stability with the reference product therewith will not necessarily be required.

12. Provided that safety and efficacy are not affected, it is not essential for the SEPP to have the same formulation as the innovator’s product.
13. Both “comparability assessment” and “individual assessment” are applicable, depending on the purpose of the study. For example, comparability assessment may be conducted for pharmacological activity studies, whereas individual assessment is made to address the safety issues on impurities.

14. Literature information from other products with same active ingredients may be used to support the assessment of safety.
Some Key Points (6)

15. The results of repeat dose toxicity studies and accumulated knowledge of API characteristics may negate the need to perform other toxicity studies (i.e. repro tox, geno tox, carcinogenicity etc).

16. Where the data sufficient to assure the comparability in clinical endpoint have been obtained through the clinical pharmacokinetic (PK), pharmacodynamic (PD) or PK/PD studies, further clinical studies could be reduced in some cases.

17. Where the mechanism of action is known to be the same, one clinical trial may be sufficient to cover multiple indications.
Some Key Points (7)

18. A risk management plan including post marketing surveillance will be required.

19. Improvement of product Quality, Safety and/or Efficacy is always desirable and encouraged. If the results of the relevant studies on “Subsequent-Entry Protein Products” indicate an improved Q/S/E, and even though there is less comparability or similarity, the product should be acceptable.
Thank you very much for your attention!