PMDA’s Perspective on Quality and non-Clinical Evaluation of Cell/tissue-based Products

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<table>
<thead>
<tr>
<th>Purpose</th>
<th>Clinical Trial</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>Application for Marketing Authorization</td>
<td><strong>Not</strong> for Marketing Authorization (publication of research papers, medical treatment)</td>
</tr>
</tbody>
</table>
| **Regulatory Framework** | Pharmaceutical Affairs Law | • Medicinal Practitioners Act  
• Ministerial Notification of MHLW No.425 |
| **GCP compliance** | Required | **Not** Required |
| **IND-Review** | PMDA/MHLW | • IRB  
• MHLW (for **stem cell-based products** and **gene therapy products**) |
Development of Cell/Tissue-based Products

Pharmaceuticals/Medical devices

Quality

Non-clinical

Clinical trial

Review of clinical trial protocol (30days-IND review)

Application for Marketing Authorization

Development

ADD-ON for cell/tissue-based products

Evaluate quality and safety of cell/tissue-based products

Application for confirmation “Kakunin-Shinsei”

Confirmation “Kakunin”
Clinical Studies of Human Cell/Tissue-based Products in Japan

Clinical trial (Kakunin)

<table>
<thead>
<tr>
<th>Target Disease</th>
<th>Autologous</th>
<th>Allogeneic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target Disease</td>
<td>Cell/Tissue</td>
</tr>
<tr>
<td></td>
<td>Prostate cancer</td>
<td>Dendritic Cell</td>
</tr>
<tr>
<td></td>
<td>Myeloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe burn</td>
<td>1. Epidermal cell</td>
</tr>
<tr>
<td></td>
<td>(2 products)</td>
<td>2. Epidermal cell and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibroblast</td>
</tr>
<tr>
<td></td>
<td>Cartilage injury</td>
<td>Cartilage cell</td>
</tr>
<tr>
<td></td>
<td>Coronary Infraction</td>
<td>Skeletal Myoblast</td>
</tr>
</tbody>
</table>

Clinical research (Stem cell-derived)

<table>
<thead>
<tr>
<th>Target organ</th>
<th>Number</th>
<th>Target organ</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>48</td>
<td>Nerve</td>
<td>4</td>
</tr>
<tr>
<td>Blood vessel / Heart</td>
<td>38 (4)</td>
<td>Adipose tissue</td>
<td>4</td>
</tr>
<tr>
<td>Born / Cartilage</td>
<td>31 (6)</td>
<td>Liver</td>
<td>3</td>
</tr>
<tr>
<td>Eye</td>
<td>13 (1)</td>
<td>Other</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>
Guidelines for Cell/Tissue-based Products

- General Principles for the Handling and Use of Cell/Tissue-Based Products
  Notification No.1314 (26 Dec. 2000)

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

- Autologous
  No.0208003 (8 Feb. 2008)

- Allogeneic
  No.0912006 (12 Sep. 2008)

- Q&A for the Guidelines
  No.0327025 (27 Mar. 2008)

- How to complete the Kakunin-shinsei application form
  No.0420-2 (20 Apr. 2010)

- Under Development;
  Guidelines on Q and S of Products derived from Human Somatic Stem Cells, iPS and ES

- Points to Consider on Manufacturing and Quality Control
  - Cells sheet for heart failure
  - Corneal epithelial cells sheet
  - Corneal endothelial cells sheet
  - Chondrocytes

- Points to consider
  - Cells sheet for heart failure
  - Corneal epithelial cells sheet
  - Corneal endothelial cells sheet
  - Chondrocytes

Under Development;
Guidelines on Q and S of Products derived from Human Somatic Stem Cells, iPS and ES
Outline of “Guidelines on Ensuring Quality and Safety of Products Derived from Processed Autologous Human Cell/Tissue”

Chapter 1 General Rules
Article 1. Purpose
Article 2. Definitions

Chapter 2 Method of Manufacture
Article 1. Raw Materials and Manufacture-Related Substances
  1. Desired cells/tissue
  2. Raw materials other than desired cells/tissue
Article 2. Manufacturing Process
  1. (Non) formation of lot and provisions concerning lots
  2. Method of manufacture
  3. Characterization of processed cells
  4. Form and packaging of final products
  5. Constancy of the manufacture
  6. Changes in the method of manufacture

Article 3. Quality Control of Final Products
  1. General statement
  2. Method of controlling the quality 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 Internal Behavior of Products

Chapter 7 Clinical Study
Preface

- Flexible approaches are necessary on a case-by-case basis according to:
  - types, characteristics and expected clinical indication of the product
  - the scientific progress and experience in this field

- “Kakunin-shinsei”
  - Confirmation of the absence of quality or safety problems which obstruct starting clinical trials of the product.
  - Appropriate data/information to meet the purpose should be submitted.
  - The scope and degree of data/information required depend on the product characteristics, target disease, patient populations and route of administration.

*case-by-case consultation with PMDA is encouraged.*
1. Desired cells/tissues
   - Characteristics of biological structures/functions
   - Infectious status of donors
     Appropriate tests in particular for HBV, HCV, HIV, HTLV.
   - Collection/preservation/transportation of cells/tissue
     confidentiality of donors’ information, written IC from donors,
     prevention of mixing-up, etc.

2. Raw Materials other than desired cells/tissue
   - Eligibility of raw materials including serum, growth factors,
     antibiotics etc. in culture medium
   - Attention to xenogeneic feeder cells
   - No adverse impact of non-cellular/tissue components on
     desired C/T or products
Raw Materials Labile to Virus Elimination/Inactivation Treatments

- Donor screenings
- Virus detection test with the raw materials, and appropriate intermediate and/or final product if necessary.
- Demonstrate expected benefit of the product overcomes the risk
Chapter 2 Manufacture

Article 2. Manufacturing Process

1. (Non) formation of lot and provisions concerning lots
2. Method of manufacture
3. Characterization of processed cells
4. Form and packaging of final products
5. Constancy of manufacture
6. Changes in the manufacturing process during the development
Chapter 2 Manufacture
Article 3. Quality Control

Overall QC strategy

- Raw materials
- Intermediate
- Final product

Manufacturing process

Constancy of manufacture;
- **GMP** (Pharmaceuticals)
- **QMS** (Medical Devices)

Temporary specifications except for sterility and mycoplasma may be acceptable for “Kakunin-shinsei”. QC strategies including specifications should be improved along with the development.
Chapter 2 Manufacture
Article 3. Quality Control

Quality control of final products

- Number, viability, purity and identification of cells
- Undesirable cell-derived active substances, process-related impurities
- Sterility, mycoplasma, endotoxin, viruses
- Biological activity, Potency test
- Mechanical compatibility if necessary
Guidance for Evaluation of Cultured Cornea Epithelial Cells Sheet

<Examples>

1. Morphology
   • size, hole, defect, etc.
   • layer formation

2. Characterization and selection of specification tests
   • Morphological characteristics (epithelial-like cell)
   • Proliferation and viability
   • Cell population and distribution in the sheet assessed by specific markers
   • Feeder cell-derived impurities

3. Barrier function
   • Expression of appropriate markers correlate with barrier function
   • Thickness of cell layer
   • Trans-epithelial electrical resistance
Chapter 3  Stability

• Stability tests for final products and critical intermediates define storage conditions and shelf-life

• Frozen storage
effect of freezing and thawing on the stability and specifications of the products

• The container and procedure of transportation thermal management
Non-Clinical Safety Test

Scientifically reasonable tests *in vitro* or in appropriate animal should be performed if necessary and technically possible

- Non-cell/tissue components and impurities should be assessed by physico-chemical analytical procedures where possible.

- For example,
  - absence of unintended cellular transformation
  - systemic effect of product-derived active substances, (e.g. by quantifying cytokines)
  - effects on patients’ normal cells/tissue
  - undesired Immunoreaction
  - safety of transgenes and transgene products
  - reasonably-designed general toxicity test where possible and useful safety information is expected

- Appropriate tests should be performed in consideration of the characteristics and the clinical use of the product
Tumorigenicity

Transformation of cells might be induced during the manufacturing process.

- Tumorigenicity evaluation of the product and cells cultured beyond the production cell age if appropriate.
- Examples of test method:
  - Colony formation in soft agar
  - Karyotype analysis
  - Immunocompromised animals
- For ES/iPS cell-derived products, high risk of tumorigenicity of undifferentiated cells in the product is concerned.
Non-clinical Tests to Support the Effect or Performance of the Product

- Functional expressions, persistence of the action and expected efficacy of the product should be examined to a technically possible and scientifically reasonable.

- For transgenic cells, the efficacy and expression period of the transgene products should be examined.

- For “Kakunin-shinsei”, detailed experimental examination is not necessarily required if expected benefit of the product is reasonably demonstrated to overcome the risk by literatures.
Points to consider for Selection of Animals

- Physiological mechanism of target disease is comparable with human
- Size and anatomical feature if necessary
- Established model animals for target disease if available
- If not available, try to make the model when technically possible and scientifically reasonable
- Use of homologue product derived from animal
Human-derived Product and Animal-derived Homologous Product

**Human-derived products**
- Direct evaluation of the product
- Concerns:
  - Reduced or no efficacy
  - Elimination by host immune systems

**Animal-derived homologue**
- No species difference
- Concerns:
  - Comparable with human-derived product?
  - Comparable mechanism of action?
  - Unsuitable for quantitative assessment
• Clarify to a possible and reasonable extent that the effect is sufficiently expected by
  ➢ Biodistribution of cell/tissue component
  ➢ Transgene expression products
• When cells/tissue exert their actions at specific site, localization of cells/tissue should be demonstrated.
  desired site ➞ Support efficacy and duration of action
  undesired sites ➞ Possible risk
• It is desired to observe as long as the cells/tissue can be detected.
• Data/information required for “Kakunin-Shinsei” and Marketing Authorization depends on case-by-case assessment of risk/benefit according to the product characteristics, target disease, patient populations, etc.

• Consultation with PMDA is strongly recommended.

Thank you for your attention.