Accelerated CMC Development of Regenerative Medical Products

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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

- Regulatory Framework for Regenerative Medicine
  - The Act on the Safety of Regenerative Medicine (Safety Act)
  - The Act on Pharmaceuticals and Medical Devices (PMD Act)
- Accelerated CMC Development
Outline

- Regulatory Framework for Regenerative Medicine
  - The Act on the Safety of Regenerative Medicine (Safety Act)
  - The Act on Pharmaceuticals and Medical Devices (PMD Act)

- Accelerated CMC Development
Regulatory Framework for Regenerative Medicine

All medical **technologies** using processed cells which safety and efficacy have not yet been established.

The Act on the Safety of Regenerative Medicine (Safety Act)

- Medical Care or Clinical Research
  - *Ex vivo but not In vivo* Gene therapy covered by Safety Act

Production and marketing of regenerative and cellular therapeutic **products** by firms.

The Act on Pharmaceuticals and Medical Devices (PMD Act)

- Commercial Product Marketing Authorization Purpose

*Enacted in November 2014*
Risk Classification Regenerative Medical Technology

Safety Act

Technology excluded by Cabinet Order
- Yes
- No

Human embryonic stem cells, iPS cells, cells similar to iPS cells
- Yes
- No

Cells to which gene was introduced
- Yes
- No

Xenogeneic cells
- Yes
- No

Allogeneic cells
- Yes
- No

Stem cells are used
- Yes
- No

Purpose is reconstruction, repair or formation of human body structure or function
- Yes
- No

Homologous use
- Yes
- No

Class I

Class II

Cell culture
- Yes
- No

Homologous use
- Yes
- No

Class III
Rules for Hospitals and Clinics

Safety Act

High Risk (class I)

- Hospitals / Clinics
- Plan
- Submission
- Evaluation
- MHLW
- Health Science Council
  - Opinion
  - Provision (Within 90 days)

Middle Risk (class II)

- Hospitals / Clinics
- Plan
- Submission
- Evaluation
- MHLW
- Provision

Low Risk (class III)

- Hospitals / Clinics
- Plan
- Submission
- Evaluation
- MHLW
- Provision

Certified special committee for regenerative medicine

Special committee = 48

Certified committee for regenerative medicine

Committee = 105

Plans (3,679)

Therapy: 102
Research: 49

Research: 17

(As of 31 May 2017)
Regenerative Medical Product in the PMD Act

**PMD Act**

- Former Pharmaceutical Affairs Law (PAL)
  - Drug
  - Device

- Regenerative Medical Products
  - PMD Act*
    (Revised PAL)

*Enacted in November 2014

### Cellular and Tissue-based Products
- The reconstruction, repair, or formation of structures or functions of the human body
- The treatment or prevention of human diseases

### Gene Therapy

- **In vivo** Therapy; Direct application of gene therapy products
  - Viral vector
  - Naked DNA (Plasmid)
  - Oncolytic virus

- **Ex vivo** Therapy; Gene-modified cell products
  - iPS-derived cells
  - CAR-T cells
Expedited Approval System under PMD Act

**PMD Act**

### [Traditional approval system]

- **Clinical study**
- Phased clinical trials (confirmation of efficacy and safety)
- **Marketing authorization**

### [New scheme] (for regenerative medical products)

- **Clinical study**
- Clinical trials (likely to predict efficacy, confirming safety)
- **Conditional/time-limited authorization**
- Marketing (Further confirmation of efficacy and safety)
- **Re-application within a period (max. 7 yrs)**
- Marketing authorization or Revocation
- Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

< Drawback of traditional approval system >

Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, such as non-uniform quality reflecting individual heterogeneity of autologous donor patients
Marketing Authorized Products

PMD Act

Autologous Culture Epidermis **JACE**

Indication:
- Serious burns treatment
- Wound after removal of giant congenital melanocytic nevus

Autologous Cultured Cartilage **JACC**

Indication:
- Traumatic cartilage defects and osteochondritis dissecans

Indication:
- Serious heart failure due to IHD

HeartSheet

Conditional & Time-limited approval

Kit A
- Container for tissues harvested
- Serum separation kit

Kit B
- Frozen myoblast cells
- Kits for sheet preparation and media

Product Main Component

Main Component

Product Subcomponent

Frozen myoblast cells

Allogeneic MSC **TEMCELL HS Inj.**

Indication:
- Steroid refractory acute GVHD

http://www.jcrpharm.co.jp/news/2015126_3991

http://www.jcrpharm.co.jp/news/2015126_3991

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

Pharmaceuticals and Medical Devices Agency
IND: Submission of the Clinical Trial Notification

PMD Act

Timing

The first notifications; **31 days before** (others; **2 weeks before**)

<table>
<thead>
<tr>
<th>Product Number</th>
<th>Cell therapy</th>
<th>Gene therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IND</td>
<td>46</td>
<td>15</td>
</tr>
<tr>
<td>Sponsor</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>Investigator</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

(As of April 2017)
# Early Access Schemes; SAKIGAKE Designation System

<table>
<thead>
<tr>
<th>PMD Act</th>
<th>Forerunner review assignment (Rolling submission)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Name of regenerative medical products</strong></td>
</tr>
<tr>
<td>1st Round (2016)</td>
<td>STR01 Autologous bone marrow-derived mesenchymal stem cell</td>
</tr>
<tr>
<td></td>
<td>G47△ Growth-controlled oncolytic gene modified HSV-1</td>
</tr>
<tr>
<td></td>
<td>JRM-001 Autologous cardiac progenitor/stem cells</td>
</tr>
<tr>
<td>2nd Round (2017)</td>
<td>CLS2702C/D Epithelial cell sheet prepared by culturing autologous oral mucosal epithelial cell</td>
</tr>
<tr>
<td></td>
<td>Allogeneic iPS derived dopaminergic neuronal cells</td>
</tr>
<tr>
<td></td>
<td>Somatic Stem Cell Adult bone marrow derived allogeneic stem cell</td>
</tr>
</tbody>
</table>

(As of Feb. 28, 2017)
Outline

- Regulatory Framework for Regenerative Medicine
  - The Act on the Safety of Regenerative Medicine (Safety Act)
  - The Act on Pharmaceuticals and Medical Devices (PMD Act)
- Accelerated CMC Development
The idea of meaning and purpose of quality and the principle of the approach of quality assurance can be used in the same way as traditional biotechnological/biological products

- Process and product quality understanding
- Quality by design approach
- Quality risk management
- Control strategy
- Consistency of process and product quality throughout product life cycle
Reference guidelines for Quality of Regenerative Medical Products

- **Q5A**: Viral safety evaluation of biotechnology products derived from cell lines on human or animal origin
- **Q5B**: Analysis of the expression construct in cells used for production of R-DNA derived protein products
- **Q5C**: Stability testing of biotechnological/biological products
- **Q5D**: Derivation and characterization of cell substrates used for production of biotechnological/biological products
- **Q5E**: Comparability of biotechnological/biological products subject to changes in their manufacturing process
- **Q6B**: Specifications: Test procedures and acceptance criteria for biotechnological/biological products
Specifications

Speciation (Release Testing)

Extended Characterization
Stability Profile

Process Consistency
• Process Control
• Process Validation
Prior Knowledge

Can be established and used for:

► Quality control of the raw materials and intermediate products
► The release criteria of the final products
► Validation of the suitability of the manufacturing process
► The method of maintaining consistency
Specifications of the Final Product

- Verification of suitability of the mfg. process
- Method of maintaining consistency
- Quality control of the raw materials & intermediate products
Differences between Cells and Biological Products

Biotechnological/Biological Products

- Source Materials, Process Variability
- In-process Control
- Characterization
- Specification

Regenerative Medical Products

- Source Materials, Process Variability
- In-process Control
- Characterization
- Specification

- Difficult to cover every aspect of quality by specification
- Limited information can be obtained from characterization and specification
- Much more rely on in-process control to control quality
# Specifications of Regenerative Medical Product (Cell Therapy)

<table>
<thead>
<tr>
<th>Specifications</th>
<th>For example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Biochemical markers, immunological markers, characteristic products, and other appropriate genotypes or phenotypes of the intended target cells and tissues</td>
</tr>
<tr>
<td>Purity</td>
<td>Undifferentiated cells, cells exhibiting abnormal growth, transformed cells, contaminating cells</td>
</tr>
<tr>
<td>Impurities</td>
<td>Raw materials, non-cellular components, media ingredients (including feeder cells), chemical reagents, or any other process-related materials</td>
</tr>
<tr>
<td>Tests for cell-derived undesirable physiologically active substances</td>
<td></td>
</tr>
<tr>
<td>Sterility tests, Tests for the presence of mycoplasma, Endotoxin tests, Virus tests</td>
<td></td>
</tr>
<tr>
<td>Potency tests, Specific biological tests</td>
<td>Secretion of a specific physiologically-active substance from the cell, specific (quantitative or qualitative) biological testing that takes into account the cell type</td>
</tr>
<tr>
<td>Mechanical compatibility tests</td>
<td></td>
</tr>
<tr>
<td>Assay</td>
<td>Cell number and cell viability</td>
</tr>
</tbody>
</table>
## Specifications of Regenerative Medical Product (Gene Therapy)

<table>
<thead>
<tr>
<th>Specifications</th>
<th>For example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>Genomic construct, Introduced plasmids (DNA sequencing, restriction enzyme mapping), Protein expression</td>
</tr>
<tr>
<td>Purity</td>
<td>Total DNA, Total RNA, Size, Structure, Particle size,</td>
</tr>
<tr>
<td>Impurity</td>
<td>Process-Related Impurity: Residual DNA, host cell protein, media ingredients (including feeder cells), chemical reagents, or any other process-related materials</td>
</tr>
<tr>
<td></td>
<td>Product-Related Impurity: Non-functional vectors, Empty particle number and aggregates</td>
</tr>
<tr>
<td>Adventitious agent safety evaluation</td>
<td>Sterility tests (JP), Tests for the presence of mycoplasma (JP GI), Virus tests (ICH Q5A), Replication competent virus, Endotoxin tests (JP)</td>
</tr>
<tr>
<td>Potency</td>
<td>Infectivity, Transduction efficiency, Delivery efficiency, Biological activity</td>
</tr>
<tr>
<td>Assay</td>
<td>Number of particle, Concentration of infectious particle, Concentration of DNA/Plasmid</td>
</tr>
</tbody>
</table>
Sterility Test and Mycoplasma Test (Cell Therapy)

Cell Collection
↓
Isolation
↓
Culture (<5 days)
↓
Final Product

- Limitations
  - Short shell-life
  - Short manufacturing process
  - Products loss (Autologous)

- No cryopreservation
- Shell-life; <72hrs
### 1. Direct method

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Example of detection/measurement device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid phase cytometry</td>
<td>Microorganism</td>
<td>Fluorescence microscope, Laser scanning cytometer, etc.</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>Microorganism</td>
<td>Flow cytometer, etc.</td>
</tr>
</tbody>
</table>

### 2. Indirect method

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Example of detection/measurement device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological methods</td>
<td>Antigen</td>
<td>Immunochromatography, Micro plate reader, etc.</td>
</tr>
<tr>
<td>Nucleic acid amplification</td>
<td>Nucleic acid</td>
<td>Electrophoresis apparatus, Quantitative PCR</td>
</tr>
<tr>
<td>Name</td>
<td>Target</td>
<td>Example of detection/measurement device</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bioluminescence</td>
<td>ATP, etc.</td>
<td>Luminescence detector, Fluorescence detector, etc.</td>
</tr>
<tr>
<td>Micro colony method</td>
<td>Growth (Micro colony)</td>
<td>Fluorescence microscopy etc.</td>
</tr>
<tr>
<td>Impedance method</td>
<td>Growth (Electrical characteristic)</td>
<td>Electrodes</td>
</tr>
<tr>
<td>Gas measuring method</td>
<td>Growth</td>
<td>Gas measuring instrument</td>
</tr>
<tr>
<td></td>
<td>(Gas production, etc.)</td>
<td>Color change of medium</td>
</tr>
<tr>
<td>Fatty acid profiles</td>
<td>Fatty acid</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>Infrared spectroscopy</td>
<td>Cell component</td>
<td>Fourier transformation infrared spectroscopic</td>
</tr>
<tr>
<td>Mass spectrometry</td>
<td>Cell component</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>Genetic fingerprinting</td>
<td>DNA</td>
<td>Electrophoresis apparatus</td>
</tr>
<tr>
<td>method</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High throughput sequencing</td>
<td>Nucleic acid</td>
<td>Sequencer, etc.</td>
</tr>
</tbody>
</table>
Validation

- To qualify introduced equipment, a standard component or strain, which represents the target of each method, should be utilized.
  - Direct measurement; standard strains
  - Indirect measurement; target bacteria
- To validate a protocol/procedure, it is required to demonstrate that the detection target is a suitable index/indicator for bacterial number or quantity.
Sterility Test

- If the test results can be obtained only after administration to the patient, the decision to administer the product will be based on the most recent data.

- In such cases,
  - Demonstrate by testing that the intermediate products are sterile and that sterility has been strictly maintained in all processes leading to the final product.
  - Methods for dealing with the lack of sterility detected after administration should be established beforehand.
A. Culture methods
B. Indicator cell culture methods
C. Nucleic Acid Amplification test (NAT)

Validation of NAT for the detection of mycoplasma

- Specificity
- Robustness
- Limit of detection

<table>
<thead>
<tr>
<th>Mycoplasma species</th>
<th>ATCC/NBRC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acholeplasma laidlawii</td>
<td>23206, NBRC 14400</td>
</tr>
<tr>
<td>Mycoplasma arginini</td>
<td>23838</td>
</tr>
<tr>
<td>Mycoplasma fermentans</td>
<td>19989, NBRC 14854</td>
</tr>
<tr>
<td>Mycoplasma hyorhinis</td>
<td>17981, NBRC 14858</td>
</tr>
<tr>
<td>Mycoplasma orale</td>
<td>23714, NBRC 14477</td>
</tr>
<tr>
<td>Mycoplasma pneumonieae</td>
<td>15531, NBRC 14401</td>
</tr>
<tr>
<td>Mycoplasma salivarium</td>
<td>23064, NBRC 14478</td>
</tr>
</tbody>
</table>
Changes in manufacturing process after the late stage of clinical study is usually associated with a high development risk from the viewpoint of ensuring equality/ equivalency of the quality.

It is desirable to collect a broad range of information on quality from the early stage of development.
Thank you for your attention!

Please visit the PMDA website
http://www.pmda.go.jp