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

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

Medical Care or Clinical Research

*Ex vivo but not In vivo. Gene therapy covered by Safety Act*

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

**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
- Out of the scope of application of the Act: Yes
- Human embryonic stem cells, iPS cells, cells similar to iPS cells:
  - No
- Cells to which gene was introduced:
  - No
- Xenogeneic cells:
  - No
- Allogeneic cells:
  - No
- Stem cells are used:
  - Yes
- Purpose is reconstruction, repair or formation of human body structure of function:
  - No
- Homologous use:
  - Yes

Class I

Cell culture:
- No
  - Class II
  - Class II
- Homologous use:
  - Yes
  - Class III
  - Class II

Class II

Human embryonic stem cells, iPS cells, cells similar to iPS cells

Class III

Cells to which gene was introduced

Class I

Xenogeneic cells

Class I

Allogeneic cells

Class I

Stem cells are used

Class I

Purpose is reconstruction, repair or formation of human body structure of function

Class I

Homologous use

Class I

Cell culture

Class II

Homologous use

Class II

Class III

Cell culture

Class II

Homologous use

Class II

Class III
Rules for Hospitals and Clinics

**Safety Act**

**High Risk (class I)**
- Hospitals / Clinics Plan
- Submission
- Certified special committee for regenerative medicine
- Evaluation
- MHLW
- Health Science Council
- Opinion
- Provision (Within 90 days)
- Change order (Within 90 days)

**Middle Risk (class II)**
- Hospitals / Clinics Plan
- Submission
- Certified special committee for regenerative medicine
- Evaluation
- MHLW
- Provision

**Low Risk (class III)**
- Hospitals / Clinics Plan
- Submission
- Certified committee for regenerative medicine
- Evaluation
- MHLW
- Provision

**Plans (3,679)**
- Therapy: 102
- Research: 102

**Special committee = 48**

**Certified committee for regenerative medicine**

**Committee = 105**

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

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

PMD Act

Former Pharmaceutical Affairs Law (PAL)
- Drug
- Device

PMD Act*
(Revised PAL)

Regenerative Medical Products

*Enacted in November 2014
PMD Act

[Traditional approval system]

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

< 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

[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) → Marketing authorization or Revocation → Marketing continues

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

**HeartSheet**

- Indication: Serious heart failure due to IHD

**产品的信息**

- **Kit A**
  - Container for tissues harvested
  - Serum separation Kit A

- **Kit B**
  - Frozen myoblast cells
  - Kits for sheet preparation And Media

**HeartSheet**

- **Product Main Component**
  - Autologous skeletal myoblast HeartSheet

**Allogeneic MSC TEMCELL HS Inj.**

- **Conditional & Time-limited approval**

- **Indication:**
  - Steroid refractory acute GVHD

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)
<table>
<thead>
<tr>
<th>Round</th>
<th>Product Name</th>
<th>Target Condition/Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Round (2016)</td>
<td>STR01</td>
<td>Autologous bone marrow-derived mesenchymal stem cell, Neurological symptoms and disabilities caused by spinal cord injury</td>
</tr>
<tr>
<td></td>
<td>G47△</td>
<td>Growth-controlled oncolytic gene modified HSV-1, Malignant glioma</td>
</tr>
<tr>
<td></td>
<td>JRM-001</td>
<td>Autologous cardiac progenitor/stem cells, Pediatric congenital heart disease (single ventricle physiology)</td>
</tr>
<tr>
<td>2nd Round (2017)</td>
<td>CLS2702C/D</td>
<td>Epithelial cell sheet prepared by culturing autologous oral mucosal epithelial cell, Prevention of the formation of the esophageal stenosis after ESD</td>
</tr>
<tr>
<td></td>
<td>Allogeneic iPS derived dopaminergic neuronal cells, Amelioration of neurological symptoms of Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Somatic Stem Cell Adult bone marrow derived allogeneic stem cell, Ischemic stroke (treatment window period of 18-36 hrs after the onset)</td>
<td></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
Differences between Cells and Biological Products

Biotechnological/Biological Products

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

Regenerative Medical Products

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

- 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

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

Specification (Release Testing)

Extended Characterization
Stability Profile

Process Consistency
- Process Control
- Process Validation
Prior Knowledge
Specifications of the Final Product

Verification of suitability of the mfg. process

Method of maintaining consistency

Quality control of the raw materials & intermediate products
## 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><strong>Process-Related Impurity</strong>: Residual DNA, host cell protein, media ingredients (including feeder cells), chemical reagents, or any other process-related materials</td>
</tr>
<tr>
<td></td>
<td><strong>Product-Related Impurity</strong>: 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)

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

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

No cryopreservation
Shell-life; <72hrs
# Rapid Microbiological Methods (1)

## 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>
</tbody>
</table>
### Rapid Microbiological Methods (2)

#### 2. Indirect method (Cont.)

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Example of detection/measurement device</th>
</tr>
</thead>
<tbody>
<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 (Gas production, etc.)</td>
<td>Gas measuring instrument</td>
</tr>
<tr>
<td></td>
<td></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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>infrared spectroscope</td>
</tr>
<tr>
<td>Mass spectrometry</td>
<td>Cell component</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>Genetic fingerprinting method</td>
<td>DNA</td>
<td>Electrophoresis apparatus</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.
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</th>
<th>ATCC/NBRC Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acholeplasma laidlawii</td>
<td>ATCC 23206, NBRC 14400</td>
</tr>
<tr>
<td>Mycoplasma arginini</td>
<td>ATCC 23838</td>
</tr>
<tr>
<td>Mycoplasma fermentans</td>
<td>ATCC 19989, NBRC 14854</td>
</tr>
<tr>
<td>Mycoplasma hyorhinis</td>
<td>ATCC 17981, NBRC 14858</td>
</tr>
<tr>
<td>Mycoplasma orale</td>
<td>ATCC 23714, NBRC 14477</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>ATCC 15531, NBRC 14401</td>
</tr>
<tr>
<td>Mycoplasma salivarium</td>
<td>ATCC 23064, NBRC 14478</td>
</tr>
</tbody>
</table>
It is desirable to collect a broad range of information on quality from the early stage of development. 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.
Thank you for your attention!

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