Quality Aspects of Regenerative Medical Products

Yoshiaki Maruyama, Ph.D.
Office of Cellular and Tissue-based Products
PMDA, Japan
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Contents

- Introduction of Regenerative Medical Products
- Proposal on Basic Approach to Quality Assurance of Regenerative Medical Products
  (The Cell Processing Center (CPC) Subcommittee, The Science Board, PMDA)
Regenerative Medical Products 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

Former Pharmaceutical Affairs Law (PAL)

Drug

Device

PMD Act* (Revised PAL)

Regenerative Medical Products

*Enacted in November 2014
Contents

- Introduction of Regenerative Medical Products

- Proposal on Basic Approach to Quality Assurance of Regenerative Medical Products (The Cell Processing Center (CPC) Subcommittee, The Science Board, PMDA)
### Guidelines for Regenerative Medical Products

#### Standard for Biological Ingredients
- **MHLW Public Notice No.210 (2003)**

#### General Principles for the Handling and Use of Cells/Tissue-Based Products

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

<table>
<thead>
<tr>
<th>Autologous</th>
<th>(2008)</th>
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<tbody>
<tr>
<td>Autologous Somatic Stem Cells</td>
<td>(2012)</td>
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<tr>
<td>Autologous iPS-like Cells</td>
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<tr>
<td>Allogeneic</td>
<td>(2008)</td>
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<td>Allogeneic Somatic Stem Cells</td>
<td>(2012)</td>
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<tr>
<td>Allogeneic iPS-like Cells</td>
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<tr>
<td>Embryonic Stem Cells</td>
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#### Points to Consider for the Evaluation of Specific Products
- Implant-type tissue-engineered cartilage for severe nasal deformity in orofacial cleft (2015)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Corneal endothelial cell sheet (2010)
Support for Innovation Implementation via Science Board

Universities/institutes/medical institutions
Researchers with superior knowledge, experiences in drugs/medical devices, and with superior research achievements, who are taking active part in the front line.

Collaboration with Academia
Take initiative in putting cutting-edge technologies into practical use based on regulatory science

Rotation of Personnel

Science Board
Exchange opinions between top-class researchers in Japan and PMDA reviewers on assessment methods of cutting-edge technologies
Outcome of the Science Board of PMDA

Cellular and Tissue-based Products Subcommittee

- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from iPSCs and iPSCs as Their Starting Materials
  (20 August 2013)

Pharmaceuticals Subcommittee

- Proposal on Basic Approach to Quality Assurance of Regenerative Medical Products
  (14 August 2015)
Characterization of Regenerative Medical Products

- Live cells
- Difficulty in identifying quality attributes to describe product efficacy and safety
- Heterogeneity, lot-to-lot quality consistency
- Variability of test methods
- No appropriate reference material (like potency assay)

How is the quality of a regenerative medical products assured?
The quality of the product is verified by meeting properties defined in the specifications by:

1. Controlling the variability of raw materials and manufacturing process, through in-process control and intermediate product testing.
2. Conducting characterization in advance to find the quality attributes and the variability of the product manufactured through the controlled manufacturing process.
# Specifications of Regenerative Medical Products

<table>
<thead>
<tr>
<th>Specifications</th>
<th>Details</th>
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</thead>
<tbody>
<tr>
<td><strong>Identification</strong></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><strong>Purity</strong></td>
<td>Undifferentiated cells, cells exhibiting abnormal growth, transformed cells, contaminating cells</td>
</tr>
<tr>
<td><strong>Tests for process-related impurities</strong></td>
<td>Raw materials, non-cellular components, media ingredients (including feeder cells), chemical reagents, or any other process-related materials</td>
</tr>
<tr>
<td><strong>Tests for cell-derived undesirable physiologically active substances</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sterility tests, Tests for the presence of mycoplasma, Endotoxin tests, Virus tests</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy tests, Potency tests</strong></td>
<td>Secretion of a specific physiologically-active substance from the cells</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>Cell number and cell viability</td>
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Variations in raw materials and manufacturing process are substantial in regenerative medical products, and furthermore, only limited information is available from characterization and specifications as to the complete quality attribute of the product.
Key Consideration

**Quality System** for regenerative medical products, considering the characters of these products; such as **raw materials that cannot be sterilized**

- Quality Risk Management
- Manufacturing Control (Sterility Assurance, Prevention of Cross-contamination..)
- Quality Control (Verification / Validation, Quality review)
- Facility Requirements

It is necessary to consider whether the risk is manageable, not only from the **facility** point of view, but from the effects of the manufacturing **operation**, such as the evaluation of performance.
Concept of Quality System in Manufacturing Control and Quality Control

Management & Supervision System
(Release, Deviation, Change control, Self-inspection, Training/education, Complaint management, Recall)

Product quality review

Validation / Verification

Quality Control System
(Labo. system)

Supplier Control System

Manufacturing Control System
(Operational performance of process, Sterility assurance, Product quality monitoring)

Facility & Equipment System
(Qualification, Calibration, Maintenance)

Document Management System
(Product master file, Specification, Statement, SOPs, Records)

Reflecting product marketing authorization documents

Quality Risk Management/ Knowledge Management
The quality risk of regenerative medicine products is not lower than that of biological products, and complete elimination of the quality risk is impossible by any means.

Significance and essence of QRM

QRM will **promote understanding of products and processes**, so that you will obtain stronger ability to assure quality of products manufactured, leading to **more robust quality assurance**.

- Risk cannot be eliminated
- Recognize the risk
- Predict, prevent and manage the risk
Research and development of regenerative medicine products require a developmental strategy that takes into account discrepancies in product lifecycle.

Establish a compatible quality assurance system for with its best effort for protection of patients in the study even at an early stage of the clinical study.

It is desirable to collect a broad range of information on quality from the early stage of development, and it is effective to make a plan based on the concept of knowledge management, quality risk management, and control strategy.
Validation or Verification

The purpose is to “validate” the facility and equipment and procedure at the manufacturing site are giving the expected result, or to “verify” they have given the expected result.

The documentation of validation or verification is intended to allow constant manufacturing of quality compatible products.

⇒ After identified variables, normally the sponsor validates “three lots” of manufacturing control and quality control methods give the expected results.(prospective validation)
Verification

The implementation of process validation is difficult manufacturing process

• Manufacturing experience is limited
• Quantitative limitation of the specimen due to ethical reasons,
  • technical limitations

⇒ To verify and document manufacturing procedures have given the expected results for each product for each lot number or batch number
Corresponding to the latest technology

- Steady progress is being made in the development of technology involved in the regenerative medicine products, including the development of advanced technology that could be the solutions to issues stated earlier.

- It is strongly recommended to constantly review and improve the approaches and methods of quality assurance for regenerative medicine products through actively incorporating the rapidly evolving new technologies.
Summary

The CPC Subcommittee of PMDA Science Board has summarized the basic concept for critical factors regarding the quality assurance of regenerative medical products and the basic approaches for achieving them.

Continuous efforts should be made in developing a comprehensive consensus through discussion based on the latest knowledge and collective wisdom from a scientific point of view.
Where to find information?


CPC (Cell Processing Center) Subcommittee

Past meetings

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