CMC Consideration for the Development of Regenerative Medical Products

Kazunobu Oyama, PhD
Deputy Review Director, Office of Cellular and Tissue-based Products, PMDA, Japan

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Quality issues on regenerative medical products
Challenges for CMC development
SAKIGAKE Designation
Point to consider for strategy of CMC development
Regenerative Medical Products

- Live cells
- Heterogeneity, lot-to-lot quality consistency
- Variability of test methods
- Difficulty in identifying quality attributes to describe product efficacy and safety

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP
http://www.jcrpharm.co.jp/news/20151126_3991
Quality Issues for Regenerative Medical Products

- **Raw Materials** (esp. human and animal-derived materials)
  - Risk of infection/Viral contamination
  - Material variability/Donor-to-donor variability

- **Process development**
  - Knowledge management from academic field through the commercial life
  - Limited materials for process evaluation (esp. patient materials)
  - Identification of CPP and CQA
  - Comparability for process changes (e.g. scale up)
Quality Issues for Regenerative Medical Products

- Manufacturing control
  - GCTP
  - Aseptic process considerations
  - Viral safety considerations
  - Process performance consistency

- Analysis
  - Complex characteristics
  - Specification (esp. potency assay)
  - Analytical validation and procedures
  - Short shelf-life
Overall Picture of CMC Development

【Typical Development】

- Non-Clinical Study
  - Phase 1: Establishment of Design Quality and Product Quality by CMC study
  - Phase 2
  - Phase 3

- Clinical Study
- Approval

- Post-Approval
  - Process Validation
  - Control Strategy

- Target product Profile
- Control Strategy
- Control Strategy
- Control Strategy

- Quality Attributes
- Process Parameters
  - CQA
  - CPP

- Consistency
- Equivalency

- Knowledge Management／Quality Risk Management
- GMP for Investigational Product
- GMP
Expedited Approval System under PMD Act

【Traditional approval process】

Non-IND Clinical study → Phased clinical trials (confirmation of efficacy and safety) → Marketing authorization → On Market

< Drawback of traditional PAL 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)

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

Post-marketing safety measures must be taken, including informed consent of risk to patients
Overall Picture of CMC Development

【Typical Development】

Non-Clinical Study

Phase 1

Establishment of Design Quality and Product Quality by CMC study

Clinical Study

Phase 2

Early access review timeline

Approval

Post-Approval

Process Validation

Control Strategy

Target product Profile

Control Strategy

Control Strategy

Consistency

Equivalency

Knowledge Management/Quality Risk Management

Quality Attributes

CQA

Process Parameters

CPP

Equivalency

Consistency

Equivalency

Knowledge Management/Quality Risk Management

Target product Profile

Control Strategy

Control Strategy

Control Strategy

GMP for Investigational Product

GMP
Residual Risk is the Concern

Residual Risk

Control Strategy

Knowledge

Post-approval

Product Lifecycle

Conditional/Term-Limited Approval

Approval
ICH Q10 [PHARMACEUTICAL QUALITY SYSTEM ]

GLOSSARY;

- A planned set of controls, derived from current product and process understanding, that assures process performance and product quality.

- The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Table 1: Application;

- Pharmaceutical Development
- Technology Transfer
Understanding of Product Quality

- Design Quality
  - Characterization
  - Control Strategy (Specification etc.)

- Procedure
- Process
- Material
- Equipment

- Product Quality
  - Quality Management

- Quality Risk Management / Knowledge management
Quality by Design Approach

1. Identify the critical quality attributes based on the potential risks
2. Linking material attributes and process parameters to CQAs, in this case, risk assessment is useful
3. Establishment and implementation of control strategy
4. Knowledge and understanding obtained could facilitate continual improvement

QbD is useful tool for understanding quality
Control of variable factors of final product

- The release criteria of the final products depends on
- Quality control of the raw materials and intermediate products
- Verification of the suitability of the manufacturing process
- The method of maintaining consistency
Different Quality Concepts

**Bio-pharmaceuticals**
- Source materials, process variability
- In-process control
- Characterization
- Specification

**Regenerative Medical Products**
- Source materials, process variability
- In-process control
- Characterization
- Specification
Establishment of Specification

Can be established and used for:

- Specifications are one part of total control strategy designed to ensure product quality and process consistency.

- Specification items are chosen to confirm the quality ensuring safety and efficacy, focus on biological characteristics.
Key elements of Potency

- Physiological function
- Mechanical/Structural function
- Immune response

\[ \cdots \text{etc} \]

- Physiological response/modulation
- Immune response/modulation
- Differentiation

\[ \cdots \text{etc} \]
SAKIGAKE Designation

**Designation Criteria**
- Medical products for **diseases in dire need** of innovative therapy
- Applied for approval firstly or simultaneously in Japan
- Prominent effectiveness can be expected based on non-clinical study and early phase of clinical trials

**Designation Advantage**
1. Prioritized Consultation
   [Waiting time: 2 months → 1 month]
2. Substantialized Pre-application Consultation
   [de facto review before application]
3. Prioritized Review
   [12 months → 6 months]
4. Review Partner
   [PMDA manager as a concierge]
5. Substantial Post-Marketing Safety Measures
   [Extension of re-examination period]
General Timeframe

【Standard】
- Pharmaceutical affairs consultation for R&D strategy
- Non clinical studies, Clinical studies
  - Clinical trials I/II
  - Consultation on Clinical trials
  - phase III study
  - Review
  - Reimbursement
  - Post Marketing

【Forerunner】
- Pharmaceutical affairs consultation for R&D strategy
- Non clinical studies, Clinical studies
  - Clinical trials I/II
  - Consultation on Clinical trials
  - phase III study
  - Review
  - Reimbursement
  - Post Marketing

① Priority Consultations
② Prior-Review (rolling submission)
③ Priority Review
④ Review Partner System
⑤ Strengthening Post-Marketing Safety

※ In some cases, may accept phase III data during review
Quality Issues of SAKIGAKE

- **Data & Experience (Industry)**
  - Manufacturing experience (esp. commercial products data)
  - Process Validation/Evaluation
  - Characterization data
  - Batch analysis data (incl. analytical procedures)
  - Stability data (esp. long-term stability data)
  - Technology transfer/Comparability
  - License for manufacturer and GCTP

- **Review Time (Regulatory Agency)**
Approaches for Quality Issues

Understanding particular quality issues of regenerative medical products

• Difficulty of identifying quality attributes that determine efficacy and safety of products
• High heterogeneity and lot-to-lot consistency
• Robustness of assay method and appropriate reference (especially, potency assay)
• Limitation and feasibility from technological and ethical aspect
The idea of meaning and purpose of quality and the principle of quality assurance approach can be used in the same way as pharmaceuticals

- Quality by design approach
- Process and product quality understanding
- Quality risk management
- Quality control strategy
- Consistency of process and product quality throughout product life cycle
Approaches for Quality Issues

Considering science and risk-based approaches more appropriate for the characteristics of products and the regulation of regenerative medical products
Strategy for CMC Development

Development Stage

Required Assurance Level

Product Assurance

Investigational product Verification

GCTP inspection

Investigational product Verification

Validation

GCTP inspection

Commercial Product Verification

GCTP inspection

Need for increasing knowledge

Exploratory Trial

Confirmatory Trial
Re-establishment of Control Strategy

Conditional/Term-Limited Approval

QTPP

pCQAs/pCPPs

Risk Management

Control Strategy

Continual improvement

Approval

QTPP

CQAs/CPP

Risk Management

Control Strategy

Continual improvement

Knowledge/Experience from CMC and GCTP
Summary

Key Enablers

- Knowledge of product quality and process robustness
- Quality control strategy
- Case-by-case basis for each product

- Science and risk-based approaches
- Flexible approaches to current requirement
- Earlier & more frequent communication between industry and regulatory authority during development
Thank you for your attention!

Kazunobu Oyama, Ph.D.
Office of Cellular and Tissue based Products
Pharmaceuticals and Medical Devices Agency
kazunobu-oyama@pmda.go.jp
1. 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.

2. Verification

– Implementation of process validation is difficult where;
  • Manufacturing experience is limited
  • Quantitative limitation of the specimen due to ethical reasons,
  • technical limitations

– To verify the document to demonstrate the manufacturing procedures have given the expected results for each product of each lot /batch
Consistency of Process and Product Quality

Establishment of Commercial Manufacturing

<table>
<thead>
<tr>
<th>Stage</th>
<th>Research and Development</th>
<th>Transfer</th>
<th>Commercial Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knowledge management and Tech. Transfer</td>
<td>Knowledge Management in Research &amp;/or Development Div.</td>
<td>Technical Transfer</td>
<td>Knowledge Management in Mfg. Plant</td>
</tr>
<tr>
<td>Activity</td>
<td>Investigational products’ Production (Pilot &amp;/or Commercial Scale)</td>
<td>PV</td>
<td>Commercial Batches Manufacturing</td>
</tr>
<tr>
<td></td>
<td>Verification Process of Investigational product</td>
<td>Validation Analytical method, Computer Systems, Sterility assurance, etc.</td>
<td>Validation Qualification of Equipment, Process Validation/Verification Change Control Revalidation</td>
</tr>
</tbody>
</table>

- Control Strategy
- Knowledge

- Validation
- Control Strategy