Points to consider and challenges in CMC for regenerative medical products

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Agenda

1. Regenerative medical products in Novartis
   - Tisagenlecleucel
   - Onasemnogene abeparvovec

2. Points to consider and challenges
   - Regulation for Living Modified Organisms (LMO)
   - In-country Testing
   - Change control of commercial products
Approaches for gene therapy

**Ex vivo**
- New gene is packaged inside vector
- The gene is modified or replaced in cells that have been removed from the body and that are then returned to the patient

**In vivo**
- New gene is packaged inside vector
- The gene is inserted or altered directly in the patient

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Development history of Tisagenlecleucel

2012: University of Pennsylvania and Novartis announced licensing agreement for CAR-T

- Aug. 2014: Communication with PMDA for Cartagena law
- Dec: Pre-meeting for strategic consultation
- Jun: Clinical Trial Notification
- Mar: Strategic consultation
- Novartis started clinical trials
- PMDA meetings continued
- Apr: NDA submission
- May: Launch
- Jun: Clinical Trial Notification
- Aug. 2017: Approval of Tisagenlecleucel in US
- Apr: NDA submission
- Mar: Approval
- May: Launch
- Aug. 2018: Approval of Tisagenlecleucel in EU
- Mar: Approval
- May: Launch
- Global: Change control for commercial products
- Japan: PMDA meetings continued
Development history of Onasemnogene abeparpovec

- May 2014: AveXis started clinical trial
- Apr: Novartis entered agreement to acquire AveXis
- May: Approval of Onasemnogene abeparpovec in US
- May: Conditional approval of Onasemnogene abeparpovec in EU
- Global
- Change control for commercial products
- 2018
  - Dec. 2017: pre-meeting for RS strategic consultation
- 2019
  - Nov: Approval of Cartagena type-1 use
  - Nov: Start of Clinical Trial
  - Nov: NDA submission
- 2020
  - Mar: Approval
  - May: Launch
- Japan
  - Apr: Novartis entered agreement to acquire AveXis
  - Oct: RS strategic consultation

- Global

- Japan
Regulation for LMO (Cartagena Act)
Regulation for LMO (Cartagena Act)

Cartagena Type-1 use (Usage in non containment area)

• Applicability is judged by presence of infectious vector in final product
  • in vivo gene therapy: Cartagena type-1 use
  • ex-vivo gene therapy: need to be confirmed with PMDA if final product contains infectious vector (Concept of residual non-replicating recombinant viruses used in the production of gene modified cell; December 10, 2020)
• Stipulate handling in clinical site, etc.

Cartagena Type-2 use (Usage in containment area)

• Applied to domestic manufacturing site, testing site etc.
Points to consider

Applicability of Cartagena Type-1 use for ex-vivo gene therapy

- Applicability can be confirmed at Cartagena Act related matter consultation

Lead time to start Cartagena Type-1/2 use

- Approval of Type-1 use is needed before starting clinical trial
- PMDA review for Type-2 use is necessary before clinical manufacturing

Information in environmental risk assessment

- e.g. Presence of Open Reading Frame, Homology search
Points to consider

Challenge in acquisition of vector information from third party

- Referring to Drug Master File (DMF) or Regulatory Support File (RSF) in Cartagena type-1/2 review is not allowed

Confidentiality of vector information

- Environmental risk assessment for Type-1 use will be publicly disclosed on the Web, but masking of confidential information is negotiable with MHLW
Points to consider

Application process for Type-1 use

Case 1: where not conducted pre-review consultation

- Submission of Application form & EA draft preparation
- Pre-consultation meeting
- Consultation meeting
- Finalize minutes
- Follow-up of consultation
- HAQs issued, if necessary
- Review and hold EC (respond to comments, if necessary)
- Approval issued by MHLW
- Start Type 1 Use

6 months*

Case 2: where conducted pre-review consultation (optional)

- Submission of Application form & EA draft preparation
- Pre-consultation meeting
- Consultation meeting
- Finalize minutes
- Follow-up of consultation
- HAQs issued, if necessary
- Review and hold EC (respond to comments, if necessary)
- Approval issued by MHLW
- Start Type 1 Use

Application process for Type-2 use

Case 1: where not conducted pre-review consultation

- Submission of Application form & EA draft preparation
- Pre-consultation meeting
- Consultation meeting
- Finalize minutes
- Follow-up of consultation
- HAQs issued, if necessary
- Review and hold EC (respond to comments, if necessary)
- Confirmation letter issued by MHLW
- Start Type 2 Use

3 months*

Case 2: where conducted pre-review consultation (optional)

- Submission of Application form & EA draft preparation
- Pre-consultation meeting
- Consultation meeting
- Finalize minutes
- Follow-up of consultation
- HAQs issued, if necessary
- Review and hold EC (respond to comments, if necessary)
- Confirmation letter issued by MHLW
- Start Type 2 Use

*Time for process in PMDA not including time for the applicant to deal with HAQs. EA: environmental assessment, EC: expert committee, HAQs: health authority questions, NMT: not more than...
In-country testing
In-country Testing

Current status of requirement for local release testing

- In-country test is required for regenerative medical products manufactured outside Japan in accordance with GCTP* Ordinance
- Waiver of in-country testing based on MRA/MOU is not applicable for regenerative medical products
- Test items for in-country testing to be conducted are judged on case-by-case basis considering availability of samples etc.

*: Good Gene, Cellular, and Tissue-based Products Manufacturing Practice
## Challenges in in-country testing

### ex-vivo gene therapy
- Since most of ex-vivo gene therapies are derived from autologous cells, only limited sample is available for release test
- In-country testing may delay patient access to products although many of patients in target population of product need early treatment

### in-vivo gene therapy
- Since target of gene therapy is specific gene and patient number is limited in general, manufacturing scale is much smaller than biologics such as antibodies. In-country testing may consume significant part of a batch and impact on costs considerably

### Common
- Some of biological tests are complex and difficult to transfer to in-country testing site
- Huge cost and effort for in-country testing may make products unprofitable
- Since necessary in-country testing is judged on case-by-case basis, lack of clear requirements causes unpredictability
Points to consider and proposals

Preparation for in-country testing

- Early discussion with manufacturer and PMDA is recommended
- Justification should be explained why in-country testing is difficult to conduct

Proposal to Japanese health authorities

- Waiver of in-country testing for regenerative medical products manufactured at GCTP certified site based on CoA issued by the site
- Sharing examples in approved products after accumulating cases to improve predictability (e.g. issue notification or Q&A)
Change control for Cell Therapy product: Utilization of PACMP and future perspective

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¹Novartis Pharma K.K., ²EFPIA Japan, Biological Product Sub committee
Disclaimer

• This presentation contains current and future expectations. Therefore, the contents and future results may differ from the current forecast due to uncertain factors, unforeseeable risks, etc.

• This presentation may contain the views and opinions of the presenter.
Manufacturing process of Cell Therapy product

1. Apheresis (Cell Collection)
2. Transduction
3. Cell expansion
4. Quality check
5. Chemotherapy
6. Administration
7. Cell therapy

- Adhesion to cancer cell
- Cancer cell death
- T cell
- Viral vector
Characteristics of Cell Therapy product

- Drug substance
  - Bio-product
  - Drug product

- Cell Therapy product
  - Viral vector
  - Product

Characteristics

- Shelf-life extension requires Partial Change Application (PCA).
- Technically developing in both manufacturing process and testing procedure.
- Vendor’s kit is used for specification test.
- There is a test method with no experience in bio-product.

- Product is manufactured individually.
- Unable to accumulate inventory.
- Multiple sites may be used due to the large number of manufacturing lots.
## Issues in change control of Cell Therapy product

<table>
<thead>
<tr>
<th>Case</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelf-life extension</td>
<td>Partial Change Application (PCA) is required.</td>
</tr>
<tr>
<td>PCA, e.g., addition of manufacturing site and process changes</td>
<td>Review period for PCA is long (standard: 12 months). There is a possibility that Japan may become a bottleneck compared to EU and US.</td>
</tr>
<tr>
<td>Change (Relaxation) of specification criteria</td>
<td>There is a possibility that criteria may be reconsidered due to limited manufacturing experience. If criteria are not met, remanufacture is difficult. It is required to find appropriate criteria and make changes in a timely manner.</td>
</tr>
<tr>
<td>Change of analytical procedure</td>
<td>If vendor’s kit is updated and the test method is changed, time is required for the change. There is an expiry date for the original kit, which limits when testing can continue.</td>
</tr>
</tbody>
</table>
## Standard review period in Japan

<table>
<thead>
<tr>
<th></th>
<th>Chemical product</th>
<th>Bio-product</th>
<th>Regenerative medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notification of Minor Change (NMC) (Do&amp;Tell)</td>
<td>No review</td>
<td>No review</td>
<td>No review</td>
</tr>
<tr>
<td>PCA</td>
<td>6M</td>
<td>12M</td>
<td>12M</td>
</tr>
<tr>
<td>Accelerated PCA (General)</td>
<td>3～5M (For addition of manufacturing site)</td>
<td>Not Applicable</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Accelerated PCA (Request to MHLW)</td>
<td>No regulatory system</td>
<td>No regulatory system</td>
<td>No regulatory system</td>
</tr>
<tr>
<td>PACMP</td>
<td>6M</td>
<td>12M</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

Assessed whether the existing system could solve the issues to smoothly carry out change control (PACMP usability assessment).
PACMP usability assessment

- **Scoring according to:**
  - Period from protocol preparation to study:
    - If the period is short, PACMP is not useful.
  - Potential protocol changes:
    - If the frequency of changes is high, the regulatory procedure will be complicated.
  - Potential deviation from the acceptance criteria:
    - If the acceptance criteria are not met, it takes time to explain the validity.

<table>
<thead>
<tr>
<th>Items</th>
<th>Scoring (Example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period</td>
<td>(\leq 1) Month : 1 (\leq 1) Year : 2 (\geq 1) Year : 3</td>
</tr>
<tr>
<td>Protocol changes</td>
<td>(\geq 2) times : 1 1 time : 2 No : 3</td>
</tr>
<tr>
<td>Deviation</td>
<td>(\geq 10%) : 1 (\leq 10%) : 2 No : 3</td>
</tr>
</tbody>
</table>

- **Multiply each item by the score and assess usability for each change.**
  - \(\leq 9\): Not useful
  - \(\geq 10\): Useful
## PACMP usability assessment

<table>
<thead>
<tr>
<th>Change items</th>
<th>Period</th>
<th>Protocol changes</th>
<th>Deviation</th>
<th>Total Score</th>
<th>Usability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of manufacturing site</td>
<td>Before PPQ (including comparability evaluation)</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>After PPQ protocol preparation</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Process changes</td>
<td>Before PPQ (including comparability evaluation)</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>After PPQ protocol preparation</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Analytical procedure changes</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>Not useful</td>
</tr>
<tr>
<td>Release Specification changes</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>Not useful</td>
</tr>
<tr>
<td>Shelf-life extension</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>27</td>
<td>Useful</td>
</tr>
<tr>
<td>Shelf-life specification change (EU and US)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>27</td>
<td>Useful</td>
</tr>
</tbody>
</table>

**PACMP would be useful in:**

- addition of manufacturing sites
- process changes
- shelf-life extension
- shelf-life specification change.
Case study of PACMP

- Shelf-life extension of viral vector

<table>
<thead>
<tr>
<th></th>
<th>20XX 1Q</th>
<th>2Q</th>
<th>3Q</th>
<th>4Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission of protocol</td>
<td></td>
<td>😊</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtaining stability data</td>
<td></td>
<td></td>
<td>🐐</td>
<td>🐐</td>
</tr>
<tr>
<td>Submission of Notification of minor change</td>
<td></td>
<td>🐐</td>
<td>🐐</td>
<td></td>
</tr>
<tr>
<td>Shelf-life extension</td>
<td></td>
<td></td>
<td></td>
<td>🌟</td>
</tr>
</tbody>
</table>

- The review period was shorter than standard review period of PCA.
- Shelf-life extension was achieved earlier than PCA.
How can we leverage PACMP?

- Retrospective evaluation of a request for accelerated review to MHLW
  - Potency ELISA kit update (Analytical procedure change)

PACMP was not useful for this analytical procedure change.
How can we leverage PACMP?

- Process change (Example of future change control)

<table>
<thead>
<tr>
<th>Manufacturing site</th>
<th>Activity</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site A</td>
<td>Comparability exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPQ</td>
<td></td>
</tr>
<tr>
<td>Alternative site B</td>
<td>Technical transfer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPQ</td>
<td></td>
</tr>
<tr>
<td>Alternative site C</td>
<td>Technical transfer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPQ</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Submission</td>
<td></td>
</tr>
</tbody>
</table>

😊 PCA after completion of PPQ at each manufacturing site
😊 PACMP→Change can be implemented earlier than PCA.
# Issues in change control of Cell Therapy product.

<table>
<thead>
<tr>
<th>Case</th>
<th>Issues</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shelf-life extension</td>
<td>Partial Change Application (PCA) is required.</td>
<td>Using PACMP</td>
</tr>
<tr>
<td>PCA, e.g., addition of manufacturing site and process changes</td>
<td>Review period for PCA is long (standard: 12 months). There is a possibility that Japan may become a bottleneck compared to EU and US.</td>
<td>Some resolution possible with PACMP</td>
</tr>
<tr>
<td>Change (Relaxation) of specification criteria</td>
<td>There is a possibility that criteria may be reconsidered due to limited manufacturing experience.</td>
<td>No resolution</td>
</tr>
<tr>
<td>Change of analytical procedure</td>
<td>If vendor’s kit is updated and the test method is changed, time is required for the change.</td>
<td>No resolution</td>
</tr>
</tbody>
</table>

Shortening of PCA review period may be required in some case, especially in specification and analytical procedure changes.
Summary and future perspective

- Cell Therapy products have different characteristics from bio product, therefore change control should be carried out smoothly.

- PACMP would be a useful option to carry out change control smoothly.

- There is room for improvement in PCA review period in some case, especially in specification and analytical procedure changes that are difficult to use PACMP. There is also a gap in the review period with EU and US.

Further improvement is expected for CMC change control on Cell Therapy products
Thank you