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Regulatory Trends in Regenerative Medicine in Japan

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Background for New Legislations (came into effect on 25 November 2014)

• The Act on the Safety of Regenerative Medicine
  New legislation was needed to put regenerative medicine practices (e.g. cancer immunotherapies, cosmetic surgeries) (other than product) under regulatory control to enhance their safety.

• The Pharmaceuticals, Medical Devices Act (PMD. Act)
  Revision of the Pharmaceutical Affaires Law (name changed) to accommodate cellular product characteristics.

The goal is to benefit the patients with unmet medical needs
Landscape of Regenerative Medicine in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine.

Pharmaceuticals and Medical Devices Act. (PMD Act.)

Academic Research Purpose

Clinical Research using human stem cells

108 protocols approved
(as of November 2014 - before new legislation)

Under the new legislation, as of 31 January 2016:
79 new clinical research plans, 2634 medical care plans have been notified to MHLW

Commercial Product Marketing Authorization Purpose

Cellular/Tissue based Products

4 approved marketed products

22 clinical trials initiated (including 8 gene therapy products) (~February 2016)

Covered by MHLW

Covered by MHLW and PMDA
Pharmaceutical Affairs Consultation on R&D Strategy (face to face)

No. of Consultations of R&D Strategy

Consultations given to academia / biotech companies account for 75%

<table>
<thead>
<tr>
<th>Year</th>
<th>DRUG</th>
<th>MEDICAL DEVICE</th>
<th>REGENERATIVE MEDICINE</th>
</tr>
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<tbody>
<tr>
<td>FY2011</td>
<td>19</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>FY2012</td>
<td>26</td>
<td>5</td>
<td>15</td>
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<td>FY2013</td>
<td>58</td>
<td>33</td>
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<tr>
<td>FY2014</td>
<td>45</td>
<td>13</td>
<td>53</td>
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<tr>
<td>FY2015(-Dec.)</td>
<td>33</td>
<td>9</td>
<td>40</td>
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</table>
Two acts regulating regenerative medicine & cell therapy

MHLW process

Regenerative Medicine

PMDA process

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

The Act on the Safety of Regenerative Medicine

40 contract cell processing facilities (CPF) have been licensed.

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

It may be similar to researcher initiated IND or hospital exemption of EU

Commercial IND and product approval system

* Two laws will be enacted in November 2014
Regenerative Medical Products in the PMD Act

Former Pharmaceutical Affairs Law (PAL)

PMD Act (Revised PAL)

◆ **Additions for Regenerative Medical Products**
  - Definition and independent chapter for Regenerative Medical Products
  - Introduction of conditional/time limited approval system
How to expedite R&D and review for cellular and tissue based product

- Designed for unmet needs under the present treatment: limited number of patients available for CT
- Difficult to conduct controlled study to demonstrate clinical benefit
- Heterogeneity of Quality affected by source materials

Would it take long time for CTs and review if regulator pursues the conventional drug guidelines too much?
Back ground of conditional and time-limited authorization

To what extent probability of effectiveness is to be pursued before Marketing authorization?

• A new product for life threatening disease, which is affected by the timing of access
• Breakthrough therapeutics for present unmet medical needs, longing for treatment, while paying particular attentions to the safety
• Based on regulatory sciences in terms of social responsibility for public health
Pharmaceuticals and Medical Devices Agency

Expedited approval system under PMD Act

[Traditional approval process]

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

< 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]

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

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

Pharmaceuticals and Medical Devices Agency
Two of the new product approvals under the new regulation (Update)

• In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
• They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD (normal approval)

1. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease (conditional and time-limited authorization – 5 years, conducting post-marketing efficacy studies)

Review Time less than 12 months
• Target: Steroid refractory acute GVHD
  • Fatal and Rare disease (approx. 1000-2000/y)
• Product: Allogeneic MSC
• Manufacturer JCR Pharmaceuticals Co., Ltd
• Resources and technology transferred from Mesoblast, Ltd. (Osiris Therapeutics, Inc.)
  • Prochymal® (Brand Name)
  • Conditional approval in Canada and New Zealand

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

• Target: Serious heart failure due to IHD
  • Chronic and Poor prognosis

• Product: Autologous skeletal myoblast

• Manufacturer: Terumo Corporation

• Manufacturing
  • Biopsy from Quadriceps
  • Final products are cryopreserved vials to be processed sheets using temperature responding culture plates at CPF in hospital

Note: Figures quoted from the company press release docs
Different Quality Concepts in Review process

Bio-pharmaceuticals

- Source materials, process variability
- In-process control
- Characterization
- Specification

hCTPs

- 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 → Control Strategy
Further facilitation and acceleration ………
### SAKIGAKE Assignment System

**To put innovative products into practice in Japan first in the world**

#### Assignment 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

#### Assignment Advantage

<table>
<thead>
<tr>
<th>1. Prioritized Consultation</th>
<th>2. Substantialized Pre-application Consultation</th>
<th>3. Prioritized Review</th>
</tr>
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<tbody>
<tr>
<td>[Waiting time: 2 months→1 month]</td>
<td>[de facto review before application]</td>
<td>[12 months → 6 months]</td>
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<th>4. Review Partner</th>
<th>5. Substantial Post-Marketing Safety Measures</th>
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<tbody>
<tr>
<td>[PMDA manager as a concierge]</td>
<td>[Extension of re-examination period]</td>
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#### Procedure

1. Initiation by applicant
2. Initiation by the MHLW
General Timeframe of Forerunner Review Assignment

【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
  - Prior review (rolling submission)
  - Review

① Priority Consultations
② Prior-review
③ Priority Review
④ Review Partner System
⑤ Strengthening Post-Marketing Safety

※ In some cases, may accept phase III data during review

Practical application of Innovative medical products
**Assignment on 10 February 2016**

**regenerative medical products**

<table>
<thead>
<tr>
<th>Name of medical products</th>
<th>Proposed indication</th>
<th>Name of applicant</th>
</tr>
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<tbody>
<tr>
<td>STR01 (Autologous bone marrow-derived mesenchymal stem cell)</td>
<td>Nerve syndrome and dysfunction caused by spinal cord injury</td>
<td>NIPRO Medical Co., Ltd.</td>
</tr>
<tr>
<td>G47Δ (Growth-controlled oncolytic herpes simplex virus type 1)</td>
<td>Malignant glioma</td>
<td>Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo</td>
</tr>
<tr>
<td>autologous cardiac progenitor/stem cells</td>
<td>Pediatric congenital heart disease (single ventricle physiology)</td>
<td>Japan Regenerative Medicine Co., Ltd.</td>
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Challenges of Accelerated Process in general

• Clinical study in post-marketing: RCT may be difficult for confirmation in some cases (single arm study with pre-agreed threshold or observational case / control study) in the postmarketing settings
  • monitoring, collection and use of real-world data, post-authorisation, as a complement to RCT data (like Adaptive pathway of EU)

• Reimbursement: Question on consistency with regulatory approval and on acceptance of clinical data for HTA payers

• CMC and quality assurance: limited qualification in early stage and quality control under GMP/GCTP (validation, scalability, comparability)
Sharing of Information, Experience and Knowledge is Valuable!!

...Others
Thank You for your attention!

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Thanks to my colleagues of Office of Cellular and Tissue-based Products