PMDA’s Approaches to the Approval of Innovative Products

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<table>
<thead>
<tr>
<th>Type of Financial Interest within last 12 months</th>
<th>Name of Commercial Interest</th>
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<tbody>
<tr>
<td>☐ Grants/Research Funding</td>
<td></td>
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<tr>
<td>☐ Stock Shareholder</td>
<td></td>
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<tr>
<td>☐ Consulting Fees</td>
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<tr>
<td>☐ Employee</td>
<td></td>
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<tr>
<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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Japan’s New Regulatory Approaches

1. Balanced pre/post-market evidence requirement
   - Conditional Time-limited Authorization

2. Streamlined procedures of consultation/review
   - SAKIGAKE Designation
• Actualization of adaptive licensing
• The fittest pathway to meet the nature of the products
Conditional Time-limited Authorization of Regenerative Products

Conventional Regulatory Approval Process

Clinical research → Clinical trial (Confirmation of efficacy and safety) → Approval → Marketing

- Clinical Research
  - Clinical trial (likely to predict efficacy, confirmation of safety)

- Conditional time-limited authorization
  - Marketing Authorization or Revocation of the conditional approval

- Marketing
  - Re-Application (or Expiration) within max. 7 yrs

- Continued marketing

Further confirmation of efficacy and safety

Clinical research process:
- Clinical research
- Clinical trial
- Approval
- Marketing
- Continued marketing

Conditional time-limited authorization process:
- Clinical Research
- Conditional time-limited authorization
- Marketing Authorization or Revocation
- Marketing
- Continued marketing

Re-Application or Expiration within max. 7 yrs
Skeletal Myoblast Sheet (Conditional Time-limited Authorization)

Applications for marketing authorization: October 2014
Approval: September 2015

Target: Serious heart failure due to Ischemic Heart Disease
Product: Autologous skeletal myoblast
Manufacturing Process
- Biopsy from Quadriceps -> manufactured at company CPF -> sheet culture in hospital CPF

Conditional approval requirement (part)
I. Confirmation of efficacy (survival) with 60 HeartSheet cases vs 120 existing treatment cases
II. Time limitation of approval: 5 years

Figures quoted from the company press release docs
Related Guidelines for Regenerative Medical Products

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

- Autologous (2008)
- Allogeneic (2008)

Points to Consider for the Evaluation of Specific Products

- Cell sheet for heart failure (2010)
- Corneal epithelial cell sheet (2010)
- Corneal endothelial cell sheet (2010)
- Articular cartilage repair (2010)
- Cell sheet for periodontal tissue regeneration (2011)
- Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
- Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)

Guidelines on Ensuring the Quality and Safety of Products Derived from Processed Human Stem

- Autologous Somatic Stem Cells (2012)
- Autologous iPS-like Cells (2012)
- Allogeneic Somatic Stem Cells (2012)
- Allogeneic iPS-like Cells (2012)
- Embryonic Stem Cells (2012)

Outcomes of Science Board, PMDA

- Current perspective on evaluation of tumorigenicity of cellular and tissue-based products derived from induced pluripotent stem cells (iPSCs) and iPSCs as their starting materials (8/20/2013)
- Proposal on Basic Principle to Quality Assurance of Cell Therapy (CT) Products (8/14/2015)
PMDA’s Science Board - reflecting cutting-edge science to consultation & review

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

R&D Strategy Consultation

Exchange opinions between top-class researchers and PMDA reviewers
Consultations on Cellular and Tissue-based Products started in 2014

<table>
<thead>
<tr>
<th>Consultation Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural consultation</td>
<td>for cellular and tissue-based products</td>
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<tr>
<td>Pre-development consultation</td>
<td>for cellular and tissue-based products</td>
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<tr>
<td>Non-clinical consultation</td>
<td>for cellular and tissue-based products (effectiveness, safety)</td>
</tr>
<tr>
<td>Quality consultation</td>
<td>for cellular and tissue-based products</td>
</tr>
<tr>
<td>Consultation before therapeutic exploratory study</td>
<td>for cellular and tissue-based products</td>
</tr>
<tr>
<td>Consultation after therapeutic exploratory study</td>
<td>for cellular and tissue-based products</td>
</tr>
<tr>
<td>Prior assessment consultation</td>
<td>for cellular and tissue-based products (safety, quality, effectiveness, therapeutic exploratory study, confirmatory clinical study)</td>
</tr>
<tr>
<td>Pre-application consultation</td>
<td>for cellular and tissue-based products</td>
</tr>
<tr>
<td>Consultation on protocols of clinical trials</td>
<td>for cellular and tissue-based products after the conditional time-limited authorization</td>
</tr>
<tr>
<td>Consultation at completion of clinical trials</td>
<td>for cellular and tissue-based products after the conditional time-limited authorization</td>
</tr>
<tr>
<td>Consultation on protocols of post-marketing clinical trials</td>
<td>for cellular and tissue-based products</td>
</tr>
<tr>
<td>Consultation at completion of post-marketing clinical trials</td>
<td>for cellular and tissue-based products</td>
</tr>
<tr>
<td>Additional consultation</td>
<td>for cellular and tissue-based products</td>
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<tr>
<td>Consultation on GLP/GCP (including GCTP)</td>
<td>compliance for cellular and tissue-based products</td>
</tr>
</tbody>
</table>
1. Collection and reporting of safety information
   - Post-marketing requirements
     - Adverse reaction reporting, including Periodic infection reporting
     - Post marketing studies such as treatment outcome study
   - Post-marketing support of PMDA
     - Establishment of patient registry system for post marketing studies

2. Relief Services to cover adverse reactions/infections related to regenerative medical products
• Streamlining the process, collapsing into multiple tracks.

• Japanese are generally good at processes, so continuous Kaizen is in store(?).
Outline of SAKIGAKE Designation System

Designation Criteria
- Innovative medical products for serious diseases
- Development & NDA in Japan being world’s first or simultaneous with other countries
- Prominent effectiveness expected on non-clinical and early phase clinical studies

Advantage for Designated Products (Drugs)

- Prioritized Consultation
  [Waiting time: 2 → 1 month]

- Prior-Review Consult. (Rolling Review)

- Prioritized Review
  [12 → 6 months]

- Review Partner
  [PMDA manager as concierge]

- Post Market Measures
  [Extension of re-examination period]
SAKIGAKE General Timeframe

Ordinary Review

Non-clinical | Phase I/II | Phase III | Review

Consultation 2M | 12M |

Prior Review

Designation | Non-clinical | Phase I/II | Phase III |

Consultation 1M | 6M |

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<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Proposed indication</th>
<th>Name of applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus (NPC-12G)</td>
<td>Angiofibroma associated with tuberous sclerosis</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
<tr>
<td>NS-065/NCNP-01</td>
<td>Duchenne muscular dystrophy (DMD)</td>
<td>Nippon Shinyaku Co., Ltd.</td>
</tr>
<tr>
<td>S-033188</td>
<td>Influenza A or B virus infection</td>
<td>Shionogi &amp; Co., Ltd.</td>
</tr>
<tr>
<td>BCX7353</td>
<td>Management of angioedema attacks in patients with hereditary angioedema (HAE)</td>
<td>Integrated Development Associates Co., Ltd.</td>
</tr>
<tr>
<td>ASP2215</td>
<td>First-relapsed or treatment-resistant FLT3 mutation-positive acute myeloid leukaemia</td>
<td>Astellas Pharma Inc.</td>
</tr>
<tr>
<td>Pembrolizumab (genetical recombination)</td>
<td>Unresectable, advanced and recurrent gastric cancer</td>
<td>MSD K.K.</td>
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</table>
## SAKIGAKE Designated Products
(Medical Devices and Regenerative Medical Products, as of Feb. 2016)

<table>
<thead>
<tr>
<th>Name of medical products</th>
<th>Proposed indication</th>
<th>Name of applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium Bridge</td>
<td>Adduction-type spasmodic dysphonia</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
<tr>
<td>(Hinge-type plate with titanium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioresorbable adhesion barrier</td>
<td>Postoperative adhesion prevention</td>
<td>Otsuka Pharmaceutical Factory, Inc.</td>
</tr>
<tr>
<td>(THN-01: Trehalose solution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STR01</td>
<td>Nerve syndrome and dysfunction caused by spinal cord injury</td>
<td>NIPRO Medical Co., Ltd.</td>
</tr>
<tr>
<td>(Autologous bone marrow-derived mesenchymal stem cell)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G47Δ</td>
<td>Malignant glioma</td>
<td>Daiichi Sankyo Co., Ltd.</td>
</tr>
<tr>
<td>(Growth-controlled oncolytic herpes simplex virus type 1)</td>
<td></td>
<td>The University of Tokyo, Institute of Medical Sciences</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>
</tr>
</tbody>
</table>
SAKIGAKE Comprehensive Evaluation Consultation (drug) (example)

Pre-Consultation Meeting

- Data Submission
- C.E. Consultation
- Quality
- Non-clinical
- Clinical
- GLP/GCP
- GMP

Application

Inquiry/Response

Inquiry/Response

Desk-top Inspections

GMP Consultation

Review

Compliance Assessment

GMP Inspection

Ca. 4 months

6 months

Approval

Consultation Complete
Thank you for your attention!
Danke für Ihre Aufmerksamkeit!

Ask