PMDA’s Efforts
- Regulation and Innovation

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<tr>
<th>Type of Financial Interest within last 12 months</th>
<th>Name of Commercial Interest</th>
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<tr>
<td>☐ Grants/Research Funding</td>
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<td>☐ Stock Shareholder</td>
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<td>☐ Consulting Fees</td>
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<td>☐ Employee</td>
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<td>☐ Other (Receipt of Intellectual Property Rights/Patent Holder, Speaker’s Bureau)</td>
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1. Overview of PMDA’s activity to seek Innovation
2. Pharmaceutical Affairs Consultation on R&D Strategy
3. SAKIGAKE Designation (2nd designation)
4. Enhancement of Electronic Data Submission
5. Regulatory Science
6. Future Issues
Regulatory Authorities in JAPAN

MHLW
Pharmaceutical Safety and Environmental Health Bureau, MHLW

- Final Authorization of applications
- Publishing Guidelines
- Advisory committee
- Supervising PMDA Activities

PMDA
Pharmaceuticals and Medical Devices Agency

- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials etc.
Today’s topic

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# Lead the World in Regulatory Innovation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Agendas for PMDA</th>
<th>Activity</th>
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<tbody>
<tr>
<td>Development</td>
<td>○ Support for promising seeds to forward the development</td>
<td>➔ Pharmaceutical Affairs Consultation on R&amp;D Strategy (from July 2011)</td>
</tr>
</tbody>
</table>
| Review      | ○ Approaches to cutting-edge technologies (including iPS Cells by collaboration with Academia)  
○ Support early practical use of Regenerative Medical Products  
○ Encourage Japan-first development and approvals  
○ Improve efficiency of development and review process by utilizing electric data | ➔ Science Board (from June 2012)  
 ➔ Conditional Time-limited Authorization (from November 2014)  
 ➔ SAKIGAKE Designation System (from FY 2015)  
 ➔ Advanced review system (from October 2016) |
| Post-marketing | ○ Utilize medical information database to develop more sophisticated safety measures | ➔ MIHARI project (from FY 2009)  
 ➔ MID-NET project (under development) |

Reform to rational and efficient structure based on Regulatory Science  
- to deliver more effective and safer drugs, medical devices, and regenerative medical products to clinical settings.
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Enhancement of Pharmaceutical Affairs Consultation on R&D Strategy

- Facilitate development of medical products by academia by developing more reliable ROADMAP.
- Contribute to promotion of clinical trials led by academia.

Advice on ROADMAP

Advice on protocol of each study

Quality study

Non-clinical study

Clinical study

- Exploratory trial
- Confirmatory trial

Basic Research

Promising seeds

Bridge between seeds and products

Practical Use

Innovative drugs, medical devices, and regenerative medical products

* In collaboration with the Japan Agency for Medical Research and Development (AMED), PMDA will proactively support establishment of an exit strategy via Pharmaceutical Affairs Consultation on R&D Strategy.
Enhancement of Consultation from Earlier Stage

Basic Research → Applied Research → Research with specific objectives (disease treatment, etc.) aiming at practical use → Development Research → Non-clinical trial → Clinical Trial → Application Review -> Approval

[Old Model] Consultation → LATER SATGE

[New Model] Consultation → EARLIER SATGE

Accelerate the application & approval period
Process
Pharmaceutical Affairs Consultation on R&D Strategy

Points on summary
Pre-Consultation (Free of charge)

Technical Experts mainly responsible for the consultation to organize the points to consult. Review Team also attend when necessary.

Scientific discussion (consultation record is fixed within a month)

Face to Face Consultation (charged)

Review Team and Technical Experts are mainly responsible for the consultation. When necessary, external experts join the consultation.

Technical Experts explain the procedures & contents on the Pharmaceutical Affairs Consultation on R&D Strategy prior to Pre-Consultation.
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<table>
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<tr>
<th>Establishment</th>
<th>SAKIGAKE</th>
<th>Breakthrough therapy</th>
<th>PRIority MEdicines (PRIME)</th>
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<tr>
<td>April 2015 (trial)</td>
<td>July 2012</td>
<td>March 2016</td>
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**Designation Criteria**
- New mode of action
- Life threatening or no radical treatment
- Prominent efficacy
- First NDA in the world
- Serious condition
- Substantial improvement on clinically significant endpoint(s)
- Unmet medical need
- Potential to address to unmet medical need

**Project Manager**
- Review partner (Concierge)
- Senior manager
- Cross-disciplinary project lead
- Dedicated contact point
- Appointment of rapporteur

**Consultation**
- Priority consultation
- Intensive guidance on an efficient drug development program
- kick-off meeting about the overall development plan and regulatory strategy
- Scientific advice at key development milestones

**Rolling review**
- Eligible (SAKIGAKE comprehensive assessment Consultation)
- Eligible
- —

**Priority review**
- Review within 6 months (shorter than 9 months in ordinal priority review)
- Not automatically designated
- Eligible (Accelerated assessment)

**Other**
- Relation with drug pricing
SAKIGAKE - General Timeframe

Ordinary Review

Non-clinical | Phase I/II | Consultation 2M | Phase III | Review

SAKIGAKE

Designation | Prior Review | Review

Non-clinical | Phase I/II | Phase III

Consultation 1M

Designated in 1st round pilot (FY2015)
6 Pharmaceuticals
2 Medical Devices
3 Regenerative Products
SAKIGAKE (1st round) and Pharmaceutical Affairs Consultation on R&D Strategy (Examples)

Pharmaceuticals (October 2015)

6 SAKIGAKE Designated

2 products were supported by Pharmaceutical Affairs Consultation on R&D Strategy.

<table>
<thead>
<tr>
<th>Applicant of Consultation</th>
<th>Name of test article</th>
<th>Expected performance, intended use, indications</th>
<th>Status in Pharmaceutical Affairs Consultation on R&amp;D Strategy</th>
</tr>
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<tbody>
<tr>
<td>National Center of Neurology and Psychiatry Shinichi Takeda</td>
<td>Undecided Morpholino nucleic acid</td>
<td>Treatment of Duchenne muscular dystrophy (DMD)</td>
<td>2 Consultation in December 2011 and March 2013 (Applicant: Nippon Shinyaku Co., Ltd with Nat’ Center of Neurology and Psychiatry)</td>
</tr>
<tr>
<td>Osaka University, Mari Kaneda</td>
<td>Sirolimus (NPC-12G)</td>
<td>Angiofibroma associated with nodular sclerosis</td>
<td>1 Consultation (Applicant: Nobelpharma Co., Ltd. Seeded by Osaka University)</td>
</tr>
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Regenerative Medical Products (February 2016)

All of 3 SAKIGAKE designated products were supported by Pharmaceutical Affairs Consultation on R&D Strategy.

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<tr>
<th>Applicant of Consultation</th>
<th>Name of test article</th>
<th>Expected performance, intended use, indications</th>
<th>Status in Pharmaceutical Affairs Consultation on R&amp;D Strategy</th>
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<td>Sapporo Medical University Osamu Honmou</td>
<td>Autologous bone-marrow mesenchymal stem cell</td>
<td>Improvement for neurological symptoms, impaired daily living activities, and impaired function associated with cerebral infarction</td>
<td>5 Consultation in December 2011- November 2012 (Applicant: NIPRO Medical Co., Ltd. with Sapporo Medical University)</td>
</tr>
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</table>
SAKIGAKE (1st round) and Pharmaceutical Affairs Consultation on R&D Strategy (Concept)

Seeds

Products with Ordinary Review

SAKIGAKE Designated Products

Pharmaceutical Affairs Consultation on R&D Strategy

Preliminary Review & Evaluation
1. Innovative medical products
2. For serious diseases
3. Development & NDA in Japan being world’s first or simultaneous with other countries
4. Prominent effectiveness expected on non-clinical and early phase clinical studies

SAKIGAKE process with priorities
SAKIGAKE Designation System Pilot (2nd round)

Step 1: Announcement & application period
Announcement made on 10/3/2016, and receive applications from 10/3 – 11/22/2016

Step 2: Interview on applied products

Step 3: Evaluation and designation
Finalize designated products by designation standards in consideration with preliminary review when necessary and PMDA's evaluation.

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- Announcement made on 10/3/2016, and receive applications from 10/3 – 11/22/2016
- Finalize designated products by designation standards in consideration with preliminary review when necessary and PMDA's evaluation.
### 2nd Round of SAKIGAKE Designated Products
- **Regenerative Medical Products**

<table>
<thead>
<tr>
<th>Name of product</th>
<th>Summary of product</th>
<th>Name of applicant</th>
</tr>
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<tbody>
<tr>
<td><strong>CLS2702C/D</strong>&lt;br&gt;(Oral mucosa-derived esophageal cell sheet)</td>
<td>Shorter re-epithelialization period after extensive endoscopic submucosa dissection (ESD) in esophageal cancer.</td>
<td>CellSeed&lt;br&gt;(Seeds: Tokyo Women’s Medical University Hospital)</td>
</tr>
<tr>
<td><strong>Dopamine neural precursor cell derived from non-autologous iPSC cell</strong>&lt;br&gt;(Therapeutic stem cell for Parkinson’s disease)</td>
<td>Novel therapy by inducing dopamine discharge to mitigate neural symptoms of patients with Parkinson’s disease.</td>
<td>Sumitomo Dainippon Pharma Co., Ltd.&lt;br&gt;(Seeds: Center for iPS Cell Research and Application, Kyoto University)</td>
</tr>
<tr>
<td><strong>Pluripotent progenitor cell derived from human (allogeneic) adult bone marrow</strong>&lt;br&gt;(Stem cell suspension derived from adult marrow)</td>
<td>Novel therapy for improving functional impairment caused by acute brain infarction.</td>
<td>Healios K.K. in Japan&lt;br&gt;Athersys (US company) outside of Japan</td>
</tr>
<tr>
<td>Name of product</td>
<td>Summary of product</td>
<td>Name of applicant</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
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<tr>
<td>Artificial tracheal (made of polypropylene mesh and collagen sponge)</td>
<td>Aiding reconstruction of tracheal while maintaining intratracheal structure after partial removal.</td>
<td>Daiichi Medical (Seeds: Kyoto University, etc.)</td>
</tr>
<tr>
<td>Boron neutron capture therapy (BNCT) system (Neutron irradiation system for BNCT)</td>
<td>Selective destruction of tumor cells marked by boron agents, without damaging normal cells.</td>
<td>Stella Pharma Corporation Sumitomo Heavy Industries, Ltd. (Seeds: Kyoto University, etc.)</td>
</tr>
<tr>
<td>UT-Heart (Software program to aid prediction of effectiveness of cardiac resynchronization therapy)</td>
<td>Higher accuracy of prediction of effectiveness of cardiac resynchronization therapy for patients with serious heart failure.</td>
<td>Fujifilm Corporation UT-Heart Inc. (A venture company by The University of Tokyo)</td>
</tr>
<tr>
<td>Cancer-related gene panel examination system (Diagnostic system for DNA sequencer)</td>
<td>Collective examination of cancer-related genes to aid decisions on cancer treatment strategies</td>
<td>Sysmex Corporation (Seeds: National Cancer Center)</td>
</tr>
</tbody>
</table>
Boron Neutron Capture Therapy

Figures from Tanaka, H. 2015
http://www.rri.kyoto-u.ac.jp/neutron/optics/workshop/20150116/20150116_02.pdf
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CDISC Data Submission [NDA]

- **NDA Review**
  - More effective & High level review
  - B/R evaluation with raw data analysis

- **Scientific Consultation**
  - More efficient & Successful development
  - Scientific advices based on the information obtained from analyses including M&S

- **Cross-Products Analysis**
  - More evidences & Advancing Regulatory Science
  - Establish disease models
  - Identifying common risk factors among different drugs

Modeling & Simulation: Concentration-Response
Model PBPK: Physiologically-based Pharmacokinetic Model, etc.
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Science Board

Established in May 2012; to discuss how PMDA can better cope with products with advanced science & technology in each developmental stage (basic research, development support, product review, and PMS).

Board members

Academia (Knowledge of the Latest Innovative Technologies)

Communication
Major Outcome Reports

1st term (FY2012 - 2013)
- 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 (2013)

2nd term (FY2014 - 2015)
- Report on the use of non-clinical studies in the regulatory evaluation of oncology drugs (2016)
1. Clinical evaluation of rare cancer
- Discuss current situation of clinical evaluation and possible evaluation methods of disease areas in which efficacy of drug by comparative studies is difficult, such as in rare cancers, due to the number of patients is specifically limited among rare diseases (no more than 50,000 patients).

2. Facilitating R&D of Academia-originated Pharmaceuticals
- Sort out problems of bottleneck of drug discovery in academia, and discuss their solutions

3. Artificial Intelligence and its application in medical field
- Discuss “totally new elements of AI” by overviewing new technologies using AI and facilitate them into future medical device review and consultations.

Outcome documents will be published in March, 2018
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Innovative Product/Regulation from Japan to World

- Facilitating Innovation
- Faster Access of Patient to Innovative Products in Global Scale

Seeds of New Medical Products in Japan
Ask

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