Regulatory updates in Japan

6th Joint Conference of Japan and Taiwan on Medical Products Regulation
11th October 2018
Regulatory Authority in JAPAN

MHLW – PSEH Bureau
Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health Labour and Welfare
- Final Authorisation of applications
- Administering laws, publishing legislations
- 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.
New active substance (NAS) median approval time for six regulatory authorities in 2008-2017 (Pharmaceuticals)
PMDA was the agency with the smallest difference between expedited review median approval time and standard review median approval time in 2017.
## Lead the World in Regulatory Innovation

Reform to rational and efficient structure based on Regulatory Science

Establishment of Regulatory Science Center (from April 2018)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Agendas for MHLW/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>→ Regulatory Science Consultation (from July 2011)</td>
</tr>
<tr>
<td></td>
<td>○ Approaches to cutting-edge technologies (including iPS Cells by collaboration with Academia)</td>
<td>→ Science Board (from June 2012)</td>
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<td></td>
<td>○ Encourage Japan-first development and approvals</td>
<td>→ SAKiGAKE Designation System (from 2015)</td>
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<td></td>
<td>○ Improve efficiency of development and review process by utilizing electric data</td>
<td>→ Conditional Early Approval System for Pharmaceuticals (from October 2017)</td>
</tr>
<tr>
<td>Review</td>
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<tr>
<td>Post-marketing</td>
<td>○ Utilize medical information database to develop more sophisticated safety measures</td>
<td>→ MIHARI project (from 2009)</td>
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<td></td>
<td>○ Predictability &amp; Transparency in post-marketing change control</td>
<td>→ MID-NET project (from April 2018)</td>
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<td>→ PACMP pilot (from April 2018)</td>
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</table>

*PACMP: Post-Approval Change Management Protocol*
# Summary of the Accelerated review system in Japan

<table>
<thead>
<tr>
<th>Type/Designation requirement</th>
<th>Outline</th>
</tr>
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<tr>
<td><strong>Basic</strong></td>
<td>Screening → Clinical trial (Exploratory · confirmatory) → Review 12 Month → Re-examination period</td>
</tr>
<tr>
<td><strong>Priority review</strong></td>
<td>Screening → Clinical trial (Exploratory · confirmatory) → Review 9 Month → Re-examination period</td>
</tr>
<tr>
<td><strong>Orphan Disease product</strong></td>
<td>Screening → Designation → Clinical trial (Exploratory · confirmatory) → Review 9 Month → Re-examination period (10 years)</td>
</tr>
<tr>
<td><strong>Conditional Early Approval</strong></td>
<td>Screening → Clinical trial (Exploratory) → Review 9 Month → Re-examination period (8-10 years)</td>
</tr>
<tr>
<td><strong>SAKIGAKE</strong> (Forerunner designation)</td>
<td>Screening → Clinical trial (Exploratory · confirmatory) → Review 6 Month → Re-examination period (8-10 years)</td>
</tr>
</tbody>
</table>

*In addition to priority review
1. No. of patients is less than 50,000 or intractable diseases designated based on a law
2. Possibility of development

*In addition to priority review
1. Confirmatory clinical trials don’t have sufficient feasibility.
2. Confirmation of a certain degree of efficacy and safety through clinical trials other than confirmatory clinical trials.

For Regenerative Medical Products, the “Conditional and Time-limited Authorization” is established based on PMD Act.

MAA: Marketing Authorisation Application  
MA: Marketing Authorisation
Progress of SAKIGAKE Designation

- **1st round pilot designation (Oct., 2015)**
  6 Pharmaceuticals, 2 Medical Devices, 3 Regenerative Products
- **2nd round pilot designation (Feb. & Apr., 2017)**
  5 Pharmaceuticals, 3 Medical Devices, 1 In-Vitro Diagnostic, 3 Regenerative Products
- **3rd round pilot designation (Mar., 2017)**
  6 Pharmaceuticals, 2 Medical Devices, 3 Regenerative Products

- **4th round pilot : application (Oct., 2018)**

- Xofluza (Anti-influenza drug) was approved on 23rd Feb, 2018.
- Rapalimus Gel (m-TOR inhibitor) was approved for the treatment of skin conditions such as angiofibroma in tuberous sclerosis complex on 23rd Mar, 2018.
## 3rd Round of SAKIGAKE Designated Products

(newly designated on Mar. 27, 2018)

<table>
<thead>
<tr>
<th>No.</th>
<th>Name of product</th>
<th>Applicant</th>
<th>Planned indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RTA402</td>
<td>Kyowa Hakko Kirin Co., Ltd.</td>
<td>Diabetic kidney disease</td>
</tr>
<tr>
<td>2</td>
<td>JR-141</td>
<td>JCR Pharmaceuticals Co., Ltd.</td>
<td>Mucopolysaccharidosis type II (Hunter syndrome)</td>
</tr>
<tr>
<td>3</td>
<td>Tafamidis meglumine</td>
<td>Pfizer Japan Inc.</td>
<td>Transthyretin ardiomyopathy (TTR-CM)</td>
</tr>
<tr>
<td>4</td>
<td>MSC2156119J</td>
<td>Merck Serono Co., Ltd.</td>
<td>Advanced non-small-cell lung cancers (stage IIIB/IV) with MET exon 14 skipping mutations</td>
</tr>
</tbody>
</table>
| 5   | Trastuzumab deruxtecan | DAIICHI SANKYO COMPANY, LIMITED | Unresectable advanced and/or recurrent gastric cancers  
- Exacerbated following cancer chemotherapy  
- Confirmed HER2 overexpression |
| 6   | Entrectinib    | Ignyta, Inc. | Solid tumors exhibiting local progression or distant metastasis in adults/children  
- Tumor progression observed after prior therapy(ies) or where there is no tolerable standard therapy  
- NTRK fusion gene-positive |
Details of the product approved with SAKIGAKE-designation

<table>
<thead>
<tr>
<th>Name of product (Applicant)</th>
<th>Summary of product</th>
<th>Product indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>XOFLUZA Tablets 10mg/20mg (baloxavir marboxil) by Shionogi &amp; Co., Ltd.</td>
<td>an antiviral drug indicated for influenza - novel mechanism (suppresses influenza viral replication via inhibition of cap-independent endonuclease enzymes required for viral mRNA synthesis in host cells)</td>
<td>Influenza Types A and B</td>
</tr>
</tbody>
</table>

< Timeline of SAKIGAKE-designation >

Oct. 2015: Designated for SAKIGAKE

Oct. 2017: Submission for marketing approval

4 months

Feb. 2018: Regulatory approval

- Novel mechanism of action developed in Japan (Shionogi & Co., Ltd)
- Influenza Attachment
- Neuraminidase inhibitor (e.g. oseltamivir, laninamivir, peramivir)
- Particle formation
- Released from cell
- Membrane fusion
- Duplication of genome RNA
- Viral genome RNA
- Cap-dependent endonuclease inhibitor (baloxavir marboxil)
- Start of mRNA synthesis (Cap endonuclease)

Figure: Excerpted with partial revisions from Shionogi’s original press release
## 3rd Round of SAKIGAKE Designated Products
### (newly designated on Mar. 27, 2018)

### - Medical Devices -

<table>
<thead>
<tr>
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<th>Planned indication</th>
</tr>
</thead>
</table>
| 1   | OFT-G1 Cardiac-repair patch (tentative name) | TEIJIN LIMITED. | A Cardiac-repair patch used during cardiovascular intervention  
- Comprised of bioabsorbable and non-bioabsorbable synthetic polymeric threads and a bridging gelatin membrane  
- Applied to correct blood flow, maintain hemoperfusion, and to construct/reconstruct surrounding tissues |
| 2   | CliniMACS CD34 System | Miltenyi Biotec K.K. | Product capable of facilitating synostosis  
- CD34-positive cells obtained by selective isolation  
- Administered to the site of non-union bone fracture with collagen-containing soft-tissue injection materials as a scaffold |

### - Cellular and Tissue-based Products (Regenerative Medical Products) -

<table>
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<tr>
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<th>Applicant</th>
<th>Planned indication</th>
</tr>
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</table>
| 1   | TBI-1301 | Takara Bio Inc. | Product used to treat synovial sarcoma using autologous lymphocytes  
- Reintroduced to the patient after transferring receptor genes *in vitro* (these receptors specifically bind to cancer antigens) |
| 2   | CLBS12 | Caladrius Biosciences, Inc. | CD34 cell therapy used to facilitate angiogenesis to address critical limb ischemia  
- CD34 positive cells isolated from patient’s own peripheral blood |
| 3   | AVXS-101 | AveXis, Inc. | Product used to treat spinal muscular atrophy  
- SMN genes transferred to the patient  
- Facilitates SMN protein expression and normalizes neuromuscular junction function |
## Details of the product approved with SAKIGAKE-designation

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</thead>
<tbody>
<tr>
<td>TITANBRIDGE™ (device for thyroid cartilage fixation) by Nobelpharma Co., Ltd.</td>
<td>- A medical device to be used for the treatment of adductor spasmodic dysphonia novel mechanism (preventing excessively tight closure of the glottis and maintaining the glottis opening)</td>
<td>Type II thyroplasty</td>
</tr>
</tbody>
</table>

**< Timeline of SAKIGAKE-designation >**

- **Feb. 2016:** Designated for SAKIGAKE
- **Jun. 30, 2017:** Submission for marketing approval
- **Dec. 15, 2017:** Regulatory approval

- Novel mechanism of action developed in Japan (Nobelpharma Co., Ltd)
- Developed by Dr. Nobuhiko Isshiki, Prof. of Kyoto Univ.
- Kumamoto Univ. etc., cooperated to conduct research
- Manufactured by Wakayoshi Seisakusho Co., Ltd. (Fukui pref.)
- Nobelpharma, venture capital, led them to practical use

*There AMED research funding support of MHLW*
Conditional Early Approval System for Pharmaceuticals

To realise early access to innovative treatments that are:

- For severe diseases with limited choice of treatments
- Difficult to conduct confirmatory clinical trials due to small number of patients or prolonged follow-up period

<table>
<thead>
<tr>
<th>Product</th>
<th>Expected indication</th>
<th>Marketing Authorization Holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorlatinib</td>
<td>The treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on 1 or more ALK tyrosine kinases inhibitors (TKIs).</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>
Review of Pharmaceuticals and Medical Devices Act

Pharmaceuticals and Medical Devices Act*: the regulation of medical products in Japan
- Mandatory review of the Act following the 5-years implementation of the previous revision
- The review examines the results of the previous revision, trend of demography, innovation and future vision.
- The Health Sciences Council started discussion in 2017; the review will be concluded by the end of 2018.

* The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices

Three themes to be discussed:
1. Ensuring early access to innovative pharmaceuticals & medical devices, and enhancing the safety measures
2. Enhancing the systems to ensure proper manufacturing, distribution and sales of pharmaceuticals & medical devices
3. The role of community pharmacies and pharmacists, and the secure access to medicines
Review of Pharmaceuticals and Medical Devices Act

Theme 1: Ensuring early access to innovative pharmaceuticals & medical devices, and enhancing the safety measures

Issues under discussion:

(1) **Approval Process** of products with high medical needs
   - Approval System of products with high medical needs
   - Clarification of Clinical Trials Process
   - Enhancing Use of Real World Data

(2) Promotion of **innovative production methods** and productivity improvement while securing safety
   - Review of Change Process of approved products concerning Quality
   - Review of GMP inspection for international harmonization
   - Review of QMS inspection for stable supply

(3) Enhancement of **safety measures** based on the recent environment
Regulatory Science Center
- Collaboration with other PMDA Offices -

Offices of New Drugs

Office of Advanced Evaluation with Electronic Data

Office of Research Promotions

Office of Medical Informatics and Epidemiology

Offices of Safety
MID-NET® (Medical Information Database Network) Project

- Analyze electronic health records, insurance claim data, diagnosis procedure combination (DPC, counterpart of US’s DRG) data, lab test results, etc.
- Enables advanced pharamacoepidemiological analysis
- Covers 23 major hospitals and 4 million patients (as of Feb. 2018).
- Full operation since April 2018, MID-NET charges $430,000/Drug.
PMDA began offering “epidemiology consultations” for PV studies

PMDA provides consultation services regarding protocols of DB and similar studies done as part of PV activities based on available information.

- Consultation timing: after safety specifications are confirmed

- Consultation type
  - Prior consultation (free)
  - Consultation on epidemiological study protocols (~$23,000)
  - Additional consultation (~$11,500)

- Consultation team members
  - Epidemiologist, Risk Manager, New drug reviewers, Clinician, Biostatistician
On 24 - 25 October 2017, the 12th Summit convened in Kyoto, Japan. 86 participants from 29 countries and regions joined.

The following meeting were also held.
- International Coalition of Medicines Regulatory Authorities (ICMRA) meeting
- Bilateral meeting (Japan and 9 countries and regions)
- Asian network meeting (9 Asian countries and regions participated, the first meeting)
- Summit of Heads of Medicines Regulatory Agencies Symposium (gathered about 1500 audiences)
Summit & ICMRA 2017 Outcomes

12th Summit (2017)
- **Regenerative Medicine Products**: Promote discussion for international regulatory convergence
- **Real World Data**: Promote information exchange on the use of RWD such as through international symposium
- **AMR**: Regulators’ roles including clinical evaluation guideline
- **Counterfeit drugs**: More collaborated network by Regulators and WHO

ICMRA
- **Innovation**: Project launched, e.g., Horizon Scanning
- **Supply Chain Integrity**: Report on Track & Trace Systems
- **Pharmacovigilance**: Report on the use of Big Data
- **Crisis Management**: Network by Regulators and WHO

**Merger of Summit and ICMRA**
“ICMRA Summit” : 10th- 12th September, 2018 in the USA
# ICMRA Innovation Project

**Major focus on “Horizon Scanning”**  
Interim report will be made at DIA Japan, November 2018 in Tokyo

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<th><strong>Overall Leadership</strong></th>
<th><strong>Subgroup of the Executive Committee</strong></th>
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<td><strong>Project 1</strong></td>
<td><strong>Project 2</strong></td>
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<tr>
<td>Analysis of global best practices in horizon scanning methodologies</td>
<td>Leveraging from outcomes of horizon scanning through critical innovation/ expertise and skills</td>
</tr>
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<td><strong>Project 3</strong></td>
<td><strong>Project 3</strong></td>
</tr>
<tr>
<td>Novel Approaches to Licensing/Early Access Scheme</td>
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</table>

**Lead**  
MHLW/PMDA | EMA, HPRA | Health Canada
ICH: Expanding Memberships

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

1990~ Founding Members
- Japan
  - MHLW/PMDA
  - JPMA
- US
  - FDA
  - PhRMA
- EU
  - EC/EMA
  - EFPIA

1990~ Observers
- ANVISA, Brazil
- IGBA
- WSMI

2014~ Standing Members
- Swissmedic
- Health Canada
- BIO
- CFDA, China
- HSA, Singapore

ICH Reform: 2015
- TFDA, Chinese Taipei
- MFDS, Korea

Members
- Permanent MC Members
- Elected MC Members

Observers

ICH: International Council for Harmonisation
ICH Meeting, June 2018 in Kobe, Japan
--- Selection of New Topics ---

Five new topics are selected:

- Analytical Procedure Development and Revision of Q2 (R1) Analytical Validation: Q2(R2)/Q14 (MHLW/PMDA, FDA)
- Continuous Manufacturing: Q13 (FDA)
- Clinical electronic Structured Harmonized Protocol (CeSHarP): M11 (PhRMA)
- Drug Interaction Studies (FDA)
- Adaptive Clinical Trials (PhRMA)

First three EWGs are planned to start at ICH Charlotte meeting in Nov., 2018.
Cooperation with Taiwan

- The 5th Joint Conference of Taiwan and Japan on Medical Products Regulation in Taipei (30th Nov. – 2nd Dec. 2017)

- 2018 Joint New Drug-GBO WG Meeting of Taiwan and Japan in Taipei (8th May, 2018)

- 2018 Multi Regional Clinical Trial (MRCT) Workshop in Taipei (9th–10th May 2018)
Asia Training Center for Pharmaceuticals and Medical Devices

Regulatory Affairs

- Plan, design and coordinate training for Regulatory Authority staffs (established in 2016)
- Provide **training opportunities** including **on-site training**

- Help raise the level of Regulations in Asia and the world.
- **In FY2017, 235 regulators from 27 countries/regions participated.** (50% increase from 2016)

Training seminar seminars to Regulatory Authority members by PMDA

- Outside Japan
- APEC regions

Lectures, case studies, and on-site training

Establishing a centralised training center for multi-regional clinical trials
International Reputation of Asia Training Center

From Attendees (FY 2017)

- Nine training seminars and 235 attendees from 27 countries/regions
- More than 70% of attendees rated as “Very good” according to the questionnaire

Official approval of APEC LSIF RHSC Training “Centers of Excellence” for Regulatory Science from APEC

- Area: Multi-Regional Clinical Trials/GCP inspection, Pharmacovigilance

Stipulate utilization of ATC in the Joint Statement of ASEAN-JAPAN Health Ministers (July 15th in 2017)

PMDA contributes to mutual understanding and cooperation in Asia
## Planned Trainings: FY2018 (April 2018 - March 2019)

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<th>Contents</th>
<th>Date</th>
<th>Location</th>
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<td>1 Pediatric Review*</td>
<td>June 11-14, 2018</td>
<td>Tokyo (PMDA)</td>
</tr>
<tr>
<td>2 Pharmaceuticals Review</td>
<td>June 18-22, 2018</td>
<td>Tokyo (PMDA) and Toyama Prefecture</td>
</tr>
<tr>
<td>3 Good Registration Management (GRM)**</td>
<td>September 26-28, 2018</td>
<td>Taipei</td>
</tr>
<tr>
<td>4 Pharmaceuticals Review</td>
<td>October 15-16, 2018</td>
<td>Nay Pyi Taw, Myanmar</td>
</tr>
<tr>
<td>5 Quality Control (Herbal Medicine)</td>
<td>October 22-24, 2018</td>
<td>Toyama, Toyama Prefecture</td>
</tr>
<tr>
<td>6 Medical Devices Review</td>
<td>November 12-16, 2018</td>
<td>Tokyo (PMDA)</td>
</tr>
<tr>
<td>7 Good Manufacturing Practice (GMP) ***</td>
<td>November 26-30, 2018</td>
<td>Utsunomiya, Tochigi Prefecture</td>
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<tr>
<td>8 Multi-Regional Clinical Trial (MRCT)**</td>
<td>January 21-24, 2019</td>
<td>Tokyo (PMDA)</td>
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<tr>
<td>9 Pharmaceuticals Review</td>
<td>January 28-31, 2019</td>
<td>Jakarta, Indonesia</td>
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<tr>
<td>10 Pharmacovigilance**</td>
<td>February 4-7, 2019</td>
<td>Tokyo (PMDA)</td>
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*Joint Seminar with U.S.FDA, **APEC-LSIF-RHSC CoE Workshop, ***With the support of PIC/S
Thank you!

多謝