Latest Trend of Pharmaceutical and Medical Device Regulation in Japan

Yoshikazu Hayashi, PhD
Senior Executive Director, PMDA
### 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>
</tr>
</thead>
<tbody>
<tr>
<td>Development</td>
<td>- Support for promising seeds to forward the development</td>
<td>→ Regulatory Science Consultation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from July 2011)</td>
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<tr>
<td>Review</td>
<td>- Approaches to cutting-edge technologies (including iPS Cells by collaboration with Academia)</td>
<td>→ Science Board</td>
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<tr>
<td></td>
<td>- Encourage Japan-first development and approvals</td>
<td>(from June 2012)</td>
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<tr>
<td></td>
<td>- Improve efficiency of development and review process by utilizing electric data</td>
<td>→ SAKIGAKE Designation System</td>
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<tr>
<td></td>
<td></td>
<td>(from 2015)</td>
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<tr>
<td></td>
<td></td>
<td>→ Conditional Early Approval System for Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from October 2017)</td>
</tr>
<tr>
<td>Post-marketing</td>
<td>- Utilize medical information database to develop more sophisticated safety measures</td>
<td>→ MIHARI project</td>
</tr>
<tr>
<td></td>
<td>- Predictability &amp; Transparency in post-marketing change control</td>
<td>(from 2009)</td>
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<tr>
<td></td>
<td></td>
<td>→ MID-NET project</td>
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<td></td>
<td></td>
<td>(from April 2018)</td>
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<tr>
<td></td>
<td></td>
<td>→ PACMP pilot</td>
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<td>(from April 2018)</td>
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</tbody>
</table>

*PACMP: Post-Approval Change Management Protocol*
SAKIGAKE Designation System

【Ordinal Review】

Clinical Trial Ph I/II → Consultation → Clinical Trial Ph III

- 2 months

Review

- 12 months

◇ 1st round pilot designation (Oct., 2015)
◇ 2nd round pilot designation (Feb. & Apr., 2017)
◇ 3rd round pilot designation (Mar., 2017)
◇ 4th round pilot designation (Apr., 2019)

【SAKIGAKE】

Priority Consultation

Clinical Trial Ph I/II → Clinical Trial Ph III → Prior Review

- 1 month

- 6 months

Priority Review

7th Joint Conference of Taiwan and Japan on Medicinal Products Regulation
# Approved Product under SAKIGAKE Designation (1)

## Pharmaceuticals

<table>
<thead>
<tr>
<th>Designation</th>
<th>TM (generic name)</th>
<th>MAH</th>
<th>Indication</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 Oct. 2015</td>
<td>Xofluza Tablets 10mg, 20mg (Baloxavir marboxil)</td>
<td>Shionogi &amp; Co., Ltd.</td>
<td>influenza A or B virus infections</td>
<td>23 March 2018</td>
</tr>
<tr>
<td>27 Oct. 2015</td>
<td>Rapalimus Gel 0.2% (Sirolimus)</td>
<td>Nobelpharma Co., Ltd.</td>
<td>skin lesions associated with tuberous sclerosis complex.</td>
<td>23 March 2018</td>
</tr>
<tr>
<td>27 Oct. 2015</td>
<td>Xospata Tablets 40 mg (Gilteritinib fumarate)</td>
<td>Astellas Pharma Inc.</td>
<td>relapsed or refractory FLT3 mutation-positive acute myeloid leukemia.</td>
<td>21 Sep. 2019</td>
</tr>
<tr>
<td>27 March 2018</td>
<td>Vyndaqel Capsules 20mg (Tafamidis meglumine)</td>
<td>Pfizer Japan Inc.</td>
<td>transthyretin cardiac amyloidosis (wild-type and hereditary).</td>
<td>26 March 2019</td>
</tr>
<tr>
<td>27 March 2018</td>
<td>Rozlytrek Capsules 100mg, 200mg (Entrectinib)</td>
<td>Chugai Pharmaceutical Co., Ltd.</td>
<td>NTRK fusion gene positive advanced or recurrent solid tumors.</td>
<td>18 June 2019</td>
</tr>
</tbody>
</table>
## Approved Product under SAKIGAKE Designation (2)

### Regenerative Medical Products

<table>
<thead>
<tr>
<th>Designation</th>
<th>TM (generic name)</th>
<th>MAH</th>
<th>Indication</th>
<th>Approval</th>
<th>Addendum</th>
</tr>
</thead>
</table>

### Medical Devices

<table>
<thead>
<tr>
<th>Designation</th>
<th>TM (generic name)</th>
<th>MAH</th>
<th>Indication</th>
<th>Approval</th>
<th>Addendum</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Feb. 2016</td>
<td>TITANBRIDGE (Fixture for thyroid cartilage)</td>
<td>Nobelpharma Co., Ltd.</td>
<td>fix the thyroid cartilage with the incision gap made during type II thyroplasty to improve symptoms of adductor spasmodic dysphonia.</td>
<td>15 Dec. 2017</td>
<td></td>
</tr>
</tbody>
</table>

### IVDs

<table>
<thead>
<tr>
<th>Designation</th>
<th>TM (generic name)</th>
<th>MAH</th>
<th>Indication</th>
<th>Approval</th>
<th>Addendum</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 Feb. 2016</td>
<td>OncoGuide NCC OncoPanel System</td>
<td>Sysmex Corporation</td>
<td>A template DNA preparation reagent and analysis program to acquire comprehensive genomic profiling pertaining to 114 cancer-related genes obtained from patients with solid tumors</td>
<td>25 Dec. 2018</td>
<td>Combination with program medical device</td>
</tr>
</tbody>
</table>
Details of the Product Approved with SAKIGAKE-Designation

OncoGuide NCC Oncopanel System

- Approved product name: OncoGuide NCC Oncopanel System
- Approved Marketing Authorization Holder: Sysmex Co. Ltd. (Head Office: Kobe-city, Hyogo)
- Indications: Obtaining comprehensive profiles pertaining to cancer-related genes from patients’ tumor

【Gene testing with NCC Oncopanel and Decision of treatment policy】

1. Informed consent by physician
2. Specimen Sampling
3. Testing with NCC Oncopanel
4. Analysis by next generation sequencer
5. Analysis by cicCall
   (A-to-T mutation is observed at the regular site of “A” chains)
6. Significance of analysis results by expert panels
7. Explanation of the diagnostic result, treatment choice


7th Joint Conference of Taiwan and Japan on Medicinal Products Regulation
<table>
<thead>
<tr>
<th>System/Designation requirement</th>
<th>Outline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard review</strong> <em>At present, no incentive is provided to determine the dosage for pediatric use.</em></td>
<td>Screening → Clinical trial (Exploratory/Confirmatory) → Review 12 months → Approval → Re-examination period</td>
</tr>
<tr>
<td><strong>Priority review</strong></td>
<td>Screening → Clinical trial (Exploratory/Confirmatory) → Review → Approval → Re-examination period</td>
</tr>
<tr>
<td><strong>Orphan drugs</strong> 1. No. of patients is less than 50,000 or designated intractable diseases 2. Possibility of development</td>
<td>Screening → Nonclinical study → Clinical trial (Exploratory/Confirmatory) → Review 9 months → Approval → Re-examination period (10 years)</td>
</tr>
<tr>
<td><strong>Sakigake designation</strong> 1. Innovativeness 2. Serious diseases 3. Prominent effectiveness 4. Approved first in Japan</td>
<td>Screening → Nonclinical study → Clinical trial (Exploratory/Confirmatory) → Review 6 months → Approval → Re-examination period (8 – 10 years)</td>
</tr>
<tr>
<td><strong>Conditional early approval</strong> In addition to requirements for priority review: 1. Confirmatory clinical trials are not feasible. 2. A certain degree of efficacy/safety is confirmed through other types of studies.</td>
<td>Screening → Nonclinical study → Clinical trial (Exploratory) → Review 9 months → Approval → Re-examination period → Post-marketing surveillance according to the approval conditions</td>
</tr>
</tbody>
</table>
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

### Product Information

<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>
<tr>
<td>Pembrolizumab</td>
<td>The treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) Cancer</td>
<td>MSD</td>
</tr>
</tbody>
</table>
Regulatory Science Center
- Collaboration with Other PMDA Offices -

**Functions:**

1. Command center on regulatory science

2. Actively utilizes clinical trial data and EHR

3. Promotes innovative approaches to advanced therapies and technologies
   - Science Board
   - Horizon Scanning
- The Medical Information Database Network in Japan for a real-time assessment of drug safety
  - currently >4.7M patients
- PMDA has led the project for establishing an integrated real-time EMRs database with high quality

23 hospitals
Over 4.7 million patients in Japan
MID-NET® Pilot Studies

The utilization and challenges of Japan's MID-NET® medical information database network in postmarketing drug safety assessments: A summary of pilot pharmacoepidemiological studies

Kaori Yamada¹ | Maori Itoh¹ | Yoshiaki Fujimura² | Michio Kimura³ | Koichiro Murata⁴ | Naoki Nakashima⁵ | Masaharu Nakayama⁶ | Kazuhiro Ohe⁷ | Takao Orii⁸ | Eizaburo Sueoka⁹ | Takahiro Suzuki¹⁰ | Hideto Yoko¹¹ | Chieko Ishiguro¹ | Yoshiaki Uyama¹ on behalf of MID-NET® project group

DOI: 10.1002/pds.4777

Hypocalcemia risk associated with denosumab

Liver dysfunction during antiarrhythmic drug administration
Status of the Utilization

- Approved studies for MID-NET use
  - **Utilization for safety assessment by PMDA**: 35 studies
    - Influence of hepatitis C therapeutics on blood coagulation in patients taking warfarin (12 studies)
    - Risk of thrombocytopenia in patients with prescription of G-CSF (granulocyte colony-stimulating factor) formulations (4 studies)
    - Detection for the abnormal value on renal functional test in patients taking direct-acting antivirals for hepatitis C (11 studies)
    - Methodological consideration for the risk assessment of drug-induced hepatic impairment (6 studies).
    - Implementation status of laboratory tests relate to the granulocytopenia associated with thiamazole (1 study)
    - Risk factors for the granulocytopenia associated with thiamazole (1 study)
  - **Post-marketing DB study by MAH**: 3 products
    - IBRANCE Capsules
    - PRALIA Subcutaneous Injection 60 mg Syringe
    - ATOZET Combination Tablet
  - **Other**: 2 studies
    - Characterization of MID-NET data focusing on patients using oral anticoagulant.
    - Implementation status of the test on hepatitis B virus infection prior to prescribing drugs for chronic hepatitis C, including ERELSA Tablets 50mg and GRAZYNA Tablets 50mg (EBR + GZR)
PMDA's Efforts Toward Utilization of Real-World Data (RWD)

1. New Consultation Category for Registry Utilization (piloted in FY2019)
   - Multiple consultation categories for registry holders and product developers
     - For registry holders
       - General considerations to ensuring reliability of registry data for regulatory approval
     - For product developers
       - Advice on the development plan using registry and the reliability of the registry data for individual product

2. Preparation of Guideline for Product Development utilizing RWD
   - Notification issued
     - Amended GPSP Ordinance
     - Basic Principle for Utilization of Medical Information Database in Post-Marketing Pharmacovigilance (2017.6.9)
     - Points to Consider for Ensuring the Data Reliability on Post-Marketing Database Study for Drugs (2018.2.21)
     - Points to Consider for Ensuring the Data reliability on Post-Marketing Database Study for Medical Devices (2018.12.19)
   - Basic principle for utilization of registry data for regulatory submission and points to consider for ensuring the data reliability are being developed, considering experience from consultations and global circumstance.
     - Drafts will be developed in FY2019, and their finalization/publication is planned in FY2020 after discussion with experts.

Finalization/publication is planned in FY2020
Science Board

- Exchange opinions
- Between top-class researchers in Japan and PMDA reviewers
- Assess cutting-edge technologies

Universities
Research Institutes

Medical institutions

Collaboration
Subcommittee on Rare Cancers

- Consider methodologies to evaluate drugs for rare diseases, including rare cancers, with very small patient populations (no more than 50,000 patients), which makes conduct of comparative studies difficult.

Subcommittee on Drug Development

- Sort out bottlenecks for drug discoveries by academia and discuss solutions.

Subcommittee of Artificial Intelligence

- Overview new technologies using AI and discuss their totally new characteristics in order to facilitate the future review and consultations on the products.
Regulatory Science on AI-based Medical Devices and Systems

Kiyoyuki Chinni, Akinoi Shizuki, Kensaku Moro, Kanako Harada, Hideaki Takeda, Makoto Hashizume, Mayumi Ishizuka, Nobumasa Kato, Ryuho Kawamura, Shinya Kyo, Kyosuke Nagata, Takashi Yamane, Ichiro Sakuma, Kazuhiko Ohe, Mamoru Mitsushih #

Abstract
AI-based medical and healthcare devices and systems have unique characteristics including 1) plasticity causing changes in system performance through learning, and need of creating new concepts about the timing of learning and assignment of responsibilities for risk management; 2) unpredictability of system behavior in response to system inputs due to the black-box characteristics precluding deductive output prediction; and 3) need of ensuring the characteristics of datasets to be used for learning and evaluation. The Subcommittee on Artificial Intelligence and its Applications in Medical Field of the Science Board, the Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan, examined “new elements specific to AI” not included in conventional technologies, thereby clarifying the characteristics and risks of AI-based technologies. This paper summarizes the characteristics and clinical positioning of AI medical systems and their applications from the viewpoint of regulatory science, and presents the issues related to the characteristics and reliability of data sets in machine learning.

Keywords: artificial intelligence, medical devices, medical systems, autonomy, regulatory science.


1. Introduction
The applications of artificial intelligence (AI)-based new technologies have been actively investigated in various fields including medical care. However, there have been limited applications of AI-based technologies, and would also involve the users, not only the manufacturers. The Pharmaceuticals and Medical Devices Agency (PMDA; Japanese regulatory agency) organized a Subcommittee on Artificial Intelligence and its Applications in Medical Field of the Science Board, Tokyo, Japan.
Themes of Science Board (4th term)

- Clinical evaluation of antimicrobial agents for AMR
- Risk assessment of products utilizing genome editing technology
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
Issues under discussion:

(1) **Approval Process** of products with high medical needs
   ① **Approval System** of products with high medical needs
   ② Clarification of **Clinical Trials Process**
   ③ Enhancing Use of **Real World Data**

(2) Promotion of **innovative production methods** and productivity improvement while securing safety
   ① Review of **Change Process of approved products concerning Quality**
   ② Review of **GMP inspection** for international harmonization
   ③ Review of **QMS inspection** for stable supply

(3) Enhancement of **safety measures** based on the recent environment
Promoting Regulatory Harmonization in Asia

Basic Policy for Asian Human Well-Being Initiative (determined by Headquarters for Healthcare Policy in July 2016, revised in July 2018)

- In order to contribute to the elimination of drug lags between Japan and Asia, **harmonization will be promoted so that the pharmaceutical approval and safety regulations in Asia will become more effective and reasonable**, such as securing the interoperability of data used for drug approval in Asian countries.

Circumstances surrounding Asia

- Economic growth
- Population growth
- Aging

  - Increasing public interest in high-quality drugs/medical devices
  - Expansion of drug/medical device market

Issues of access to drugs/medical devices

- Access to innovative drugs/medical devices is secured in Asian countries insufficiently.
- Access to drugs/medical devices is a complex issue comprised of research and development, regulation, securing of intellectual property, etc.
- Globalization and diversification of drugs/medical devices increase the importance of international regulatory cooperation.

- Necessary to specify the Asian Human Well-Being Initiative
- Work together to harmonize regulations/related matters with related ministries and agencies.

- Establish “Grand Design for Asian Pharmaceutical and Medical Device Regulatory Harmonization” at the HQ for Healthcare Policy of Japan on 20/06/2019.
Attendees (FY 2018)

- Ten training seminars and 267 attendees from 31 countries/regions
- More than 70% of attendees rated as “Very good” according to the questionnaire

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

- Official: Multi-Regional Clinical Trials/GCP inspection, Pharmacovigilance
- Pilot: Medical Devices
- GRM: Collaboration with TFDA

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


ATC Seminars
GRM
In Taipei
(Sep 26-28, 2018, 17-19, Sep, 2019)

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)
Dr. Fujiwara’s Priorities

< 4Fs >

◆ Patient First
◆ Access First
◆ Safety First
◆ Asia First

by Fujiwara

“Rational Medicine” Initiative
by Kondo

Benefit
Risk

7th Joint Conference of Taiwan and Japan on Medicinal Products Regulation
Let’s work together for patients in Taiwan/Japan and also in the world!

多謝

Thank you!