MHLW/PMDA international activities

Nobumasa NAKASHIMA, Ph.D.
Senior Director for International Programs
Pharmaceuticals and Medical Devices Agency (PMDA)
1. Multilateral Cooperation to Foster Regulatory Harmonization/Convergence

2. Initiatives toward Regulatory Harmonization/Convergence in Asia/Pacific Region

3. Next Step
MHLW/PMDA Multilateral Cooperation

WHO (1948-) is the directing and coordinating authority on international health within the United Nations’ system.

ICMRA (2012-) is a voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities.

ICH (1990 renovation 2015-) unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

IPRP (2018-) for exchange of information and regulatory cooperation for pharmaceuticals.

APEC-LSIF-RHSC (2009-) for regulatory convergence by promoting ICH and other international guidelines in the APEC region.

PIC/S (1995-) for harmonizing inspection procedures and facilitating communication.


eetc.
The International Coalition of Medicines Regulatory Authorities (ICMRA)

- ICMRA provides a global architecture to support enhanced communication, information sharing, crisis responses and address regulatory science issues.

- MHLW/PMDA lead ICMRA Innovation Work Stream 1

  <Mission>
  To identify best practices of horizon scanning (HS) through compiling and analyzing each regulator’s scanning methods and to find solutions to common difficulties faced by the regulators.

  <Members>
  AIFA, DKMA, EMA, US.FDA, HC, HPRA, MFDS, MHRA, MPA, Swissmedic
What is Horizon Scanning? ~ General Overview ~

**Without Horizon Scanning...**

**Stakeholders**:
unsure of regulations...

Report on Technology A

Regulator

**Regulators**:
cannot keep pace with accelerating innovation...

**With Horizon Scanning...**

- Proactively scan the horizon for emerging trends, technologies, etc.
- Make necessary regulatory preparations.

Emerging Technologies

Regulator
What is Horizon Scanning?
~ Illustration of Horizon Scanning ~

1. Identification
   - Identify pool of novel technologies

2. Prioritization
   - High Priority
     - Issue Guidance on Technology
     - Hire Experts on Technology
   - Medium Priority
   - Low Priority

3. Assessment
   - Assessment of High Priority Technologies

4. Dissemination/
   Regulatory Action
   - Assessments presented to management
   - Regulatory actions
     - Issue Guidance on Technology
     - Hire Experts on Technology
     - Etc...
ICMRA Innovation Project

**Work Stream 1:**
Analysis of global best practices in horizon scanning methodologies
- Survey of members to analyse existing HS methodologies and approaches
- Identification of HS best practices and development of a HS methodology framework

**Work Stream 2:**
Leveraging from outcomes of horizon scanning through critical innovation/ expertise and skills
- Compilation of three case studies to identify and review products and technologies, where regulatory science approaches are required.
- Discussions regarding future expertise requirements and potential opportunities for collaboration and capacity building to support innovation

**Work Stream 3:**
Novel Approaches to Licensing/ Early Access Schemes
- Review of various international regulatory approaches to licensing that aim to address the demand for timely access to innovative products.
- Questionnaire among ICMRA members regarding current novel regulatory pathways to licencing (NRPL) and which are implemented through legislation, regulation, and policy.

led by MHLW/PMDA

led by EMA, HPRA

led by Health Canada
Future ICMRA Activities

• On June 23, PMDA’s Chief Executive, Dr. Yasuhiro Fujiwara, was elected as ICMRA’s New Vice Chair 2019 in ICMRA meeting held in San Diego.

• Dr. Fujiwara will lead ICMRA along with Prof. Guido Raji, Executive Director of European Medicines Agency, elected as new Chair, and Prof. John Skerritt, Deputy Secretary for Health Products Regulation Department of Health, Australia, elected another Vice Chair.
ICH is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

ICH aims to achieve harmonization through the development of ICH Guidelines with regulator and industry experts.
ICH has produced over 60 Guidelines on technical requirement.
Over 20 working groups are now ongoing.

ICH was created in 1990 and 30th Anniversary in 2020.
MedDRA

- MedDRA – International standard for electronic safety data exchange, used through the entire regulatory process, from pre-marketing to post-marketing, and data entry, retrieval, evaluation and presentation.

- 2019 marks 20 years of MedDRA which was first released in 1999.

- 12 languages, Over 5,700 MedDRA Subscribing Organizations in 122 Countries
Preparation for ICH Guideline Implementation
~ Introduction of PACMP pilot program in Japan ~

- ICH Q12 will introduce PACMP (Post-Approval Change Management Protocol), a mechanism enables planning and implementation of future CMC changes in an efficient and predictable manner.
- MHLW/PMDA started the pilot program for future implementation since April 1, 2018 (before ICH Q12 reaches Step4/5).

**<Step 1>**

- Share draft PACMP document and schedule b/t PMDA and MAH
- Determine the need for GMP consultation
- Confirm draft PACMP (incl. draft application Form)
- Agree PACMP b/w PMDA and MAH

**<Step 2>**

- PCA: Partial Change Application
- MCN: Minor Change Notification
- GMP inspection application:
  - Pre-approval GMP compliance
  - Inspection application

If PACMP (incl. draft application Form) is changed, a follow-up meeting is used to confirm revised PACMP and agree b/w PMDA with MAH.

PACMP Quality Consultation: 4 mon.
PCA: 3mon. (median)
Preparation for ICH Guideline full-Implementation
~ Review of PMD Act.* ~

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

(1) Streamline of Approval Process for early patient access
   ① “Conditional Early Approval System” and “SAKIGAKE Review Designation” should be legislated to clarify process and raise transparency.
   ② New Approval system for Medical Devices to reflect the characteristics of medical devices (considering innovative technologies; Big Data, AI etc.,)
   ③ Clarification of Clinical Trials Process

(2) Introduction of new Quality Management System
   ① Introduction of GMP and GCTP inspection per manufactory
   ② Revision of current QMS inspection
   ③ Introduction of PACMP

(3) Strengthen Safety Measures
   ① Provide electronic information of Package Inserts
   ② Increase traceability of pharmaceuticals and medical devices
   ③ Utilize Patient Registry Data For safety measure

*: Pharmaceuticals and Medical Devices Act

MHLW will introduce PACMP in the regulation for full-implementation of ICH Q12.
Based on the outcome from the IPRP discussion, ICH will initiate new ICH guideline preparation for Non-clinical BD studies for gene therapy products.

Streamlined development of the gene therapy products with higher scientific rigor while minimizing the unnecessary use of animals.

Current guideline for Gene Therapy Products in the Founding Regions

- Scope of Guideline
- Timing and design of BD study to support early human clinical trials
- Design of BD studies and collection of BD data, etc.

*This slide is provided by Mr. Yokota, JPMA*
ICH Assembly endorsed proposed “Non-clinical Biodistribution Studies for Gene Therapy Products” as a new ICH topic at ICH Assembly in Amsterdam (5-6 June 2019).

MHLW/PMDA

IPRP Reflection Paper
Expectations for Biodistribution Assessments for Gene Therapy Products (June 2018)

12th Summit Heads of Medicines Regulatory Agencies 2017 (ICMRA Summit)

Main Theme: Innovation
Regulatory convergence on regenerative medicines
Outline

1. Multilateral Cooperation to Foster Regulatory Harmonization/Convergence

2. Initiatives toward Regulatory Harmonization/Convergence in Asia/Pacific Region

3. Next Step
2nd Asian Network Meeting in Tokyo on April 10, 2019

- Co-chaired by Japan, China, India and Singapore
- Participants; top-level executives of regulatory agencies from 10 countries (Japan, China, India, Singapore, Indonesia, Malaysia, Myanmar, Philippines, Thailand and Vietnam)

Confirmed the following points;
- The importance of the opinion exchange from a high-level perspective on the common issues across Asian region
- Fostering trusting relationships
- Sharing best practices
- Periodical meeting in the future
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 FY2018, 267 regulators from 31 countries/regions participated.**
  (Numbers are growing)

Training seminar seminars to Regulatory Authority members by PMDA

- Lectures, case studies, and on-site training
- Establishing a centralised training center for multi-regional clinical trials

PMDA Office

Outside Japan

APEC regions
## PMDA-ATC Training Seminars held in FY 2018

<table>
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<tr>
<th>Contents</th>
<th>Date</th>
<th>Location</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pediatric Review*1</td>
<td>Jun. 11-14, 2018</td>
<td>Tokyo (PMDA)</td>
<td>24 (12 countries/regions)</td>
</tr>
<tr>
<td>2 Pharmaceuticals Review</td>
<td>Jun. 18-22, 2018</td>
<td>Tokyo (PMDA) and Toyama Prefecture</td>
<td>30 (16 countries/regions)</td>
</tr>
<tr>
<td>3 Good Registration Management</td>
<td>Sep. 26-28, 2018</td>
<td>Taipei</td>
<td>29 (11 countries/regions)</td>
</tr>
<tr>
<td>4 Pharmaceuticals Review</td>
<td>Oct. 15-16, 2018</td>
<td>Nay Pyi Taw, Myanmar</td>
<td>32 (Myanmar)</td>
</tr>
<tr>
<td>5 Quality Control (Herbal Medicine)</td>
<td>Oct. 22-24, 2018</td>
<td>Toyama, Toyama Prefecture</td>
<td>15 (14 countries/regions)</td>
</tr>
<tr>
<td>6 Medical Devices Review</td>
<td>Nov. 12-16, 2018</td>
<td>Tokyo (PMDA)</td>
<td>25 (17 countries/regions)</td>
</tr>
<tr>
<td>7 Good Manufacturing Practice (GMP) *2</td>
<td>Nov. 26-30, 2018</td>
<td>Utsunomiya, Tochigi Prefecture</td>
<td>14 (14 countries/regions)</td>
</tr>
<tr>
<td>8 Multi-Regional Clinical Trial (MRCT)*3</td>
<td>Jan. 21-24, 2019</td>
<td>Tokyo (PMDA)</td>
<td>21 (13 countries/regions)</td>
</tr>
<tr>
<td>9 Pharmaceuticals Review</td>
<td>Jan. 28-31, 2019</td>
<td>Jakarta, Indonesia</td>
<td>48 (Indonesia)</td>
</tr>
<tr>
<td>10 Pharmacovigilance*3</td>
<td>Feb. 4-7, 2019</td>
<td>Tokyo (PMDA)</td>
<td>29 (15 countries/regions)</td>
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*1 Joint Seminar with U.S.FDA, *2 With the support of PIC/S, *3 APEC-LSIF-RHSC CoE Workshop
## PMDA-ATC Training Seminars held/planned in FY 2019

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<th>Contents</th>
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</tr>
</thead>
<tbody>
<tr>
<td>1 Pediatric Review*¹</td>
<td>Jul. 8-11, 2019</td>
<td>Tokyo (PMDA)</td>
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<tr>
<td>2 Pharmaceuticals Review*²</td>
<td>Jul. 22-26, 2019</td>
<td>Tokyo (PMDA) and Toyama Prefecture</td>
</tr>
<tr>
<td>3 Good Registration Management (GRM)</td>
<td>Sep. 2019</td>
<td>Taipei</td>
</tr>
<tr>
<td>4 Good Manufacturing Practice (GMP) *³</td>
<td>Nov. 11-15, 2019</td>
<td>Toyama Prefecture</td>
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<tr>
<td>5 Medical Devices Review *⁴</td>
<td>Nov. 25-29, 2019</td>
<td>Tokyo (PMDA)</td>
</tr>
<tr>
<td>6 Quality Control (Herbal Medicine)</td>
<td>Dec. 10-12, 2019</td>
<td>Toyama, Toyama Prefecture</td>
</tr>
<tr>
<td>7 Multi-Regional Clinical Trial (MRCT)*⁵</td>
<td>Jan. 20-23, 2020</td>
<td>Tokyo (PMDA)</td>
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<tr>
<td>8 Pharmacovigilance*⁵</td>
<td>Feb. 3-6, 2020</td>
<td>Tokyo (PMDA)</td>
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- PMDA contributes to the capacity building for partner regulatory agencies through these training seminars.
22. We commit to improve and harmonize the national regulatory system of pharmaceutical products and medical devices in ASEAN Member States through fostering collaboration and advancing regulatory science platforms such as the ASEAN harmonization systems and "Asian Training Center for Pharmaceutical and Medical Devices" by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan with technical assistance by the WHO.
APEC-LSIF-RHSC
(Asia-Pacific Economic Cooperation – Life Sciences Innovation Forum – Regulatory Harmonization Steering Committee)

- APEC-LSIF-RHSC aims to promote a more strategic, effective and sustainable approach to pharmaceuticals and medical devices regulatory harmonization.
- Japan serves as co-Chair of APEC-LSIF-RHSC with the United States.

<table>
<thead>
<tr>
<th>PWAs</th>
<th>Champion Economies</th>
</tr>
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<tbody>
<tr>
<td>MRCT/GCP inspection</td>
<td>Japan, Thailand</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Republic of Korea</td>
</tr>
<tr>
<td>Biotherapeutics</td>
<td>Republic of Korea</td>
</tr>
<tr>
<td>Advanced Therapies</td>
<td>Singapore</td>
</tr>
<tr>
<td>Good Registration Management</td>
<td>Chinese Taipei, Japan</td>
</tr>
<tr>
<td>Global Supply Chain Integrity</td>
<td>the United States</td>
</tr>
<tr>
<td>Medical Devices</td>
<td>Japan, the United States,</td>
</tr>
<tr>
<td></td>
<td>Republic of Korea</td>
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</table>
Center of Excellences (CoEs) provide the training seminars for promoting regulatory convergence, capacity and cooperation in PWAs.

CoEs (As March 22, 2019)*

- Duke-NUS Singapore (MRCT/GCP)
- Korea Institute of Drug Safety & Risk Management (Pharmacovigilance)
- MRCT Center of Brigham and Woman’s Hospital and Harvard (MRCT/GCP)
- Northeastern University (Biotherapeutics)
- Peking University (MRCT/GCP)
- PMDA (MRCT/GCP), (Pharmacovigilance)
- RAPS in cooperation with TFDA (GRM)
- University of Tennessee HSC (Supply Chain)
- USP (Supply Chain)

*12 institutes were endorsed as Pilot CoEs by APEC-LSIF-RHSC.

- Thai FDA (GRM PWA)  <CoE Pilot program : Oct. 2019>
- PMDA (Medical Device PWA)  <CoE Pilot program : Nov. 2019>
MHLW/PMDA Bilateral Cooperation

Confidentiality Agreement signed

Joint symposium held

- PMDA staff stationed at the agency
- Cooperative Arrangement on cooperation of pharmacopoeia signed
- Cooperative Arrangement signed
## Example. The history of Thailand-Japan cooperation for pharmaceuticals and medical devices regulation

<table>
<thead>
<tr>
<th>Year</th>
<th>Cooperation</th>
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| 2013 | The First Thailand-Japan Symposium and the bilateral-meeting (24th-25th Oct.)  
- The symposium takes place every year since 2013. This is the 6th symposium.  
- The bilateral-meeting between Thailand and Japan takes place almost twice every year since 2013 |
| 2014 | The PMDA training programs for staff members in Thai FDA starts  
- The PMDA training programs take place every year since 2014.  
  Total numbers of conducted programs: 9  
  - Pharmaceuticals × 7 (Japanese Pharmacopeia × 2, clinical evaluation, etc × 5)  
  - Medical devices × 2 |
| 2015 | The abridged evaluation of New drug in Thailand was issued.  
- PMDA was regarded as one of “benchmark / reference agencies” in “Priority review” which was the one of channels for new drugs registration. |
| 2016 | PMDA-ATC seminar was conducted for the first time in Thailand. |
| 2017 | An expert from JICA was dispatched to Thai FDA. |
| 2018 | Thai FDA and MHLW signed the MOC between Thailand and Japan. |
| 2019 | Thai FDA was endorsed becoming a Pilot CoE of APEC-LSIF-RHAC GRM PWA by APEC-LSIF-RHSC (Champion economies; Japan and Taiwan) in Feb. 2019. |

...what kind of cooperation we will be able to do...
Outline

1. Multilateral Cooperation to Foster Regulatory Harmonization/Convergence

2. Initiatives toward Regulatory Harmonization/Convergence in Asia/Pacific Region

3. Next Step
The Future of PMDA

Patient First

Safety First

Asia First

Access First
Views on Reliance and Recognition in WHO

1. Confidence building
   - Harmonization/Convergence
   - Information sharing
   - "Foundation" Equivalence of requirements

2. Reliance/Work sharing
   - Benefit for regulators; sharing of workload, but independent decisions

3. Recognition
   - Based on treaties; "maximal benefit" but partial loss of sovereignty with regard to decision-making

Asian Network Meeting, Tokyo, 11 April, 2019
Essential points of the Grand Design

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.

1. Promote regulatory harmonization

• Capacity building including PMDA Asia Training Center
• Reliance
• Support to embrace international standards and to participate in international activity

2. Establish high quality clinical trial systems

• The use of highly innovative pharmaceuticals and medical devices in the post-market phase is spread from clinical trial sites to other facilities.
• Establishing clinical trial sites for pharmaceuticals/medical devices result not only in accumulating useful evidence based on clinical trials, but also in improving access to post-market pharmaceuticals/medical devices.
• To build the necessary infrastructure, Japanese government examine the options available for financing other Asian partners.
Publicity Papers on PMDA International Activity

PMDA Updates

News

1. **Asia-Pacific Economic Cooperation, Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) Meeting**

Asia-Pacific Economic Cooperation, Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC) Meeting was held in Brisbane, Australia from August 22 to 24. Key participants from Japan included Dr. Nobumasa Nakashima (Senior Director for International Programs, PMDA), Dr. Erho Fukuda (Office Director, Office of International Cooperation, PMDA) and Mr. Fumihito Takanashi (Deputy director, Office of International Regulatory Affairs, MHLW). RHSC meeting aims for "Promotion of the strategic framework for the convergence of medical products regulation". Regulators from 9 APEC economies, representatives from industry (pharmaceuticals, biotechnology, etc.) participated.

Dr. Michelle Limoli, U.S. FDA (left) and Dr. Nobumasa Nakashima, Senior Director for International Programs (right), PMDA on handshake at the meeting.


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News

1. **キモノクセイ (Osmanthus fragrans)**

キモノクセイ (Osmanthus fragrans)
Work Together for patients!!

All the players in good harmony

Thank you for your attention!