Recent Regulatory Updates and Regulatory Progress for Promoting Cutting-Edge Technology in Japan

4th Brazil-Japan Seminar of Regulations on Pharmaceuticals and Medical Devices

3rd December 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.**

Cooperation with ANVISA

2014

- The 1st Brazil-Japan Seminar in Brazil on August 2nd
- Shinzo Abe, the Prime Minister of Japan, participated in 1st Seminar to make a special speech.

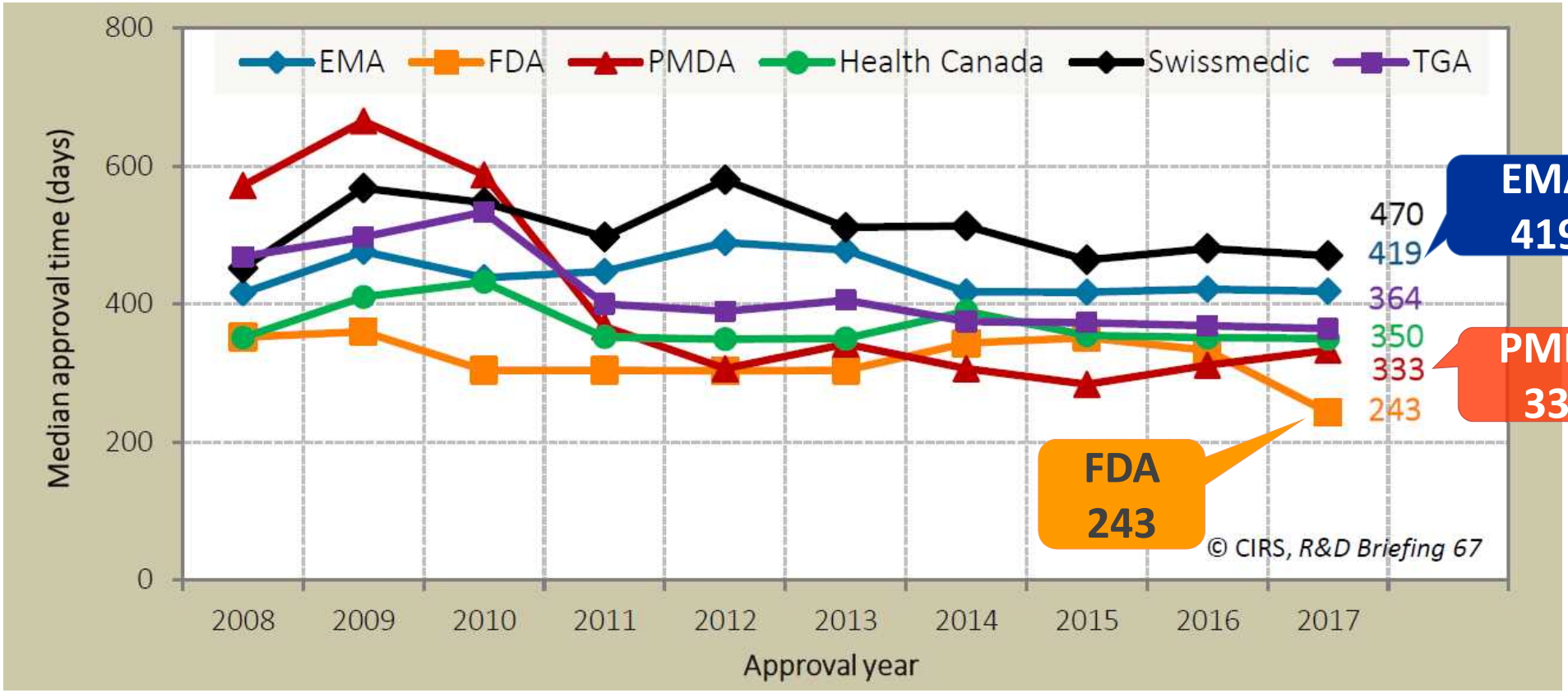
2015

- The 2nd Brazil-Japan Seminar in Japan on September 10th
- MOC regarding Pharmacopoeia signed on September 11th
- Bilateral meeting between ANIVSA and PMDA in Brazil on November 25th

2016

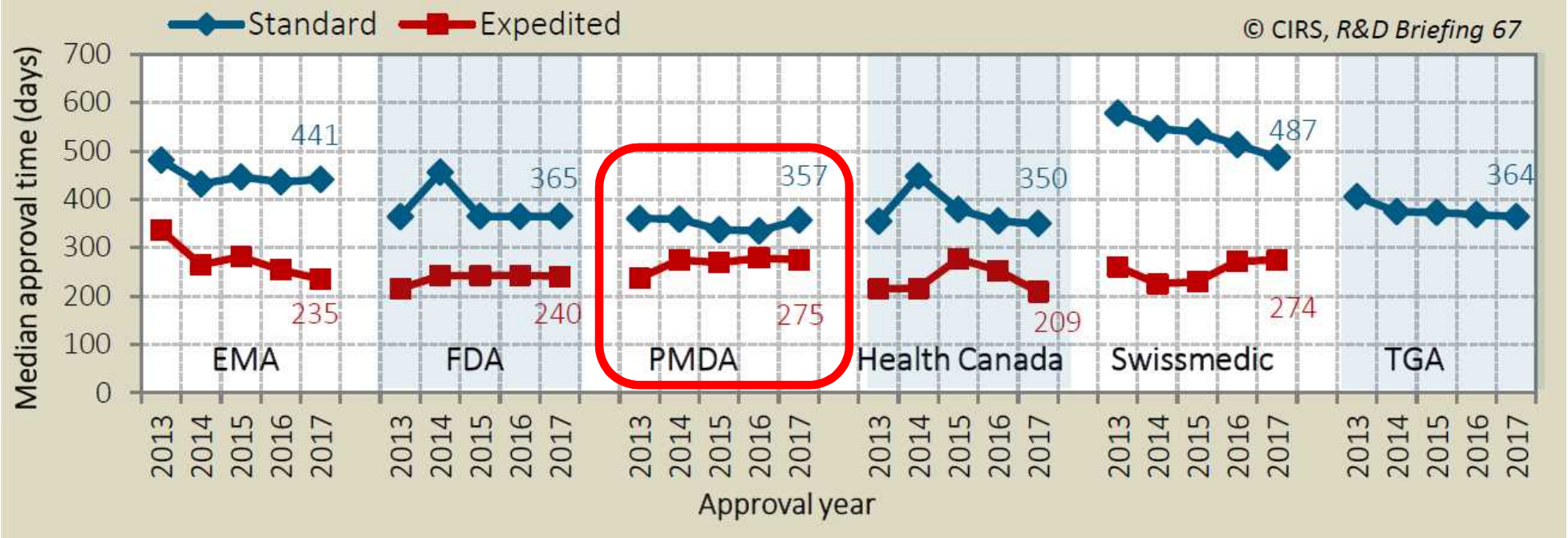
- The 3rd Brazil-Japan Seminar in Brazil on October 4th

New active substance (NAS) median approval time for six regulatory authorities in 2008-2017 (Pharmaceuticals)



Centre for Innovation in Regulatory Science (CIRS) , 2018, R&D Briefing 67

NAS median approval time by review type
for six regulatory authorities in 2013-1017



PMDA was the agency with the smallest difference between expedited review median approval time and standard review median approval time in 2017.

Centre for Innovation in Regulatory Science (CIRS) , 2018, R&D Briefing 67

Lead the World in Regulatory Innovation

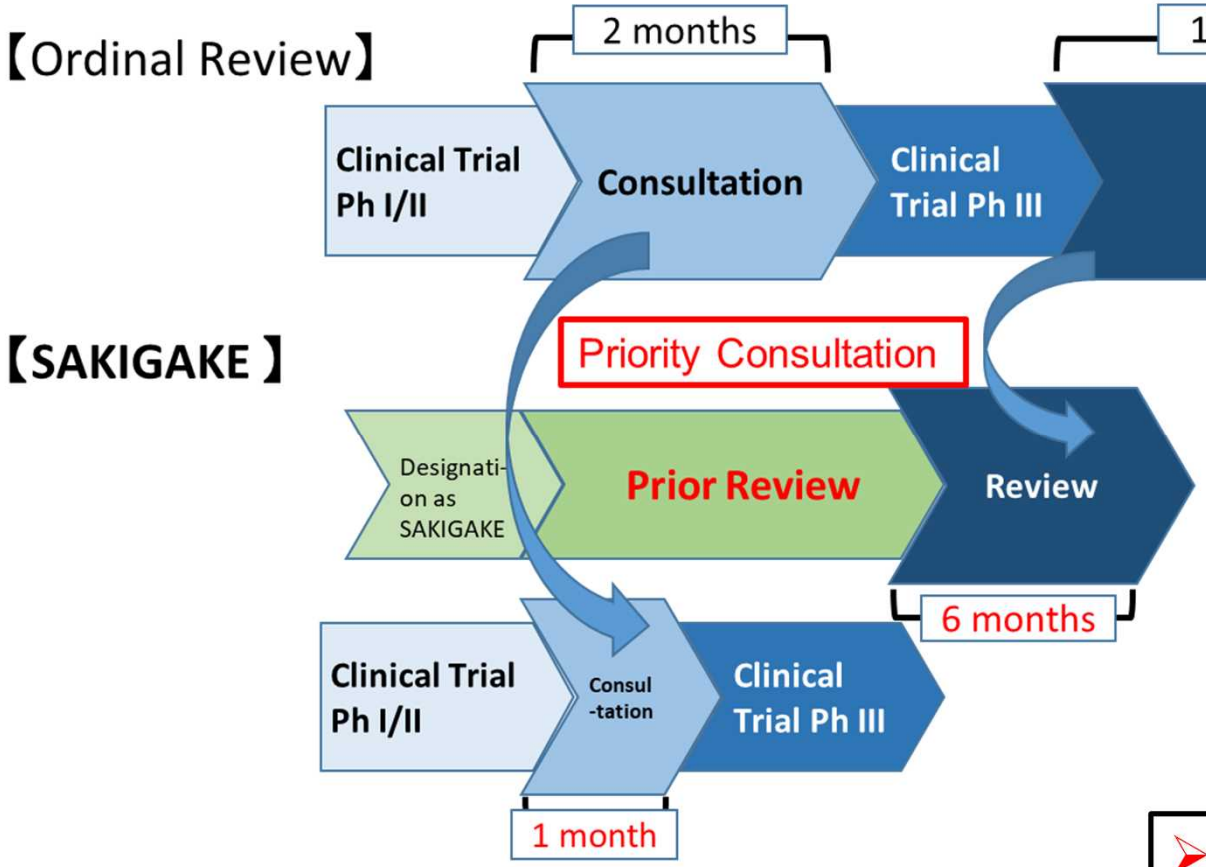
Reform to rational and efficient structure based on Regulatory Science

Establishment of Regulatory Science Center (from April 2018)

Stage	Agendas for MHLW/PMDA	Activity
Development	○ Support for promising seeds to forward the development	→ Regulatory Sceince Consultation (from July 2011)
Review	○ Approaches to cutting-edge technologies (including iPS Cells by collaboration with Academia) ○ Encourage Japan-first development and approvals ○ Improve efficiency of development and review process by utilizing electric data	→ Science Board (from June 2012) → **SAKIGAKE Designation System** (from 2015) → **Conditional Early Approval System for Pharmaceuticals** (from October 2017)
Post -marketing	○ Utilize medical information database to develop more sophisticated safety measures ○ Predictability & Transparency in post-marketing change control	→MIHARI project (from 2009) **MID-NET project** (from April 2018) →**PACMP pilot** (from April 2018)

*PACMP: Post-Approval Change Management Protocol

Progress of SAKIGAKE Designationc



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

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

Details of the product approved with SAKIGAKE-designation

Name of product (Applicant)	Summary of product	Product indications
XOFLUZA Tablets 10mg/20mg (baloxavir marboxil) by Shionogi & Co., Ltd.	- 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)	Influenza Types A and B

< 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)

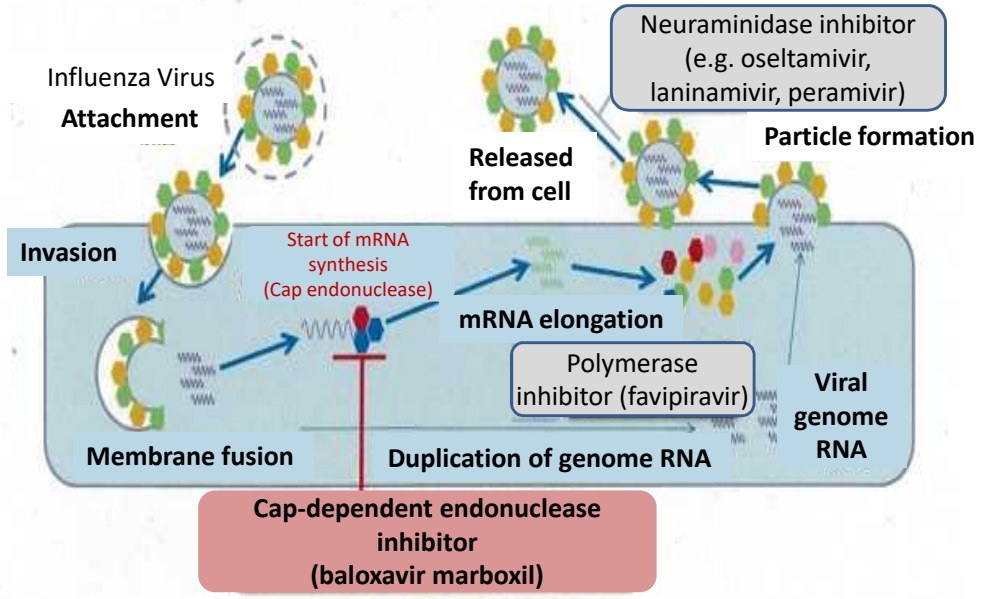


Figure Excerpted with partial revisions from Shionogi's original press release

Details of the product approved with SAKIGAKE-designation

Name of product (Applicant)	Summary of product	Product indications
TITANBRIDGE™ (device for thyroid cartilage fixation) by Nobelpharma Co., Ltd.	- 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)	Type Ⅱ thyroplasty

< Timeline of SAKIGAKE-designation >

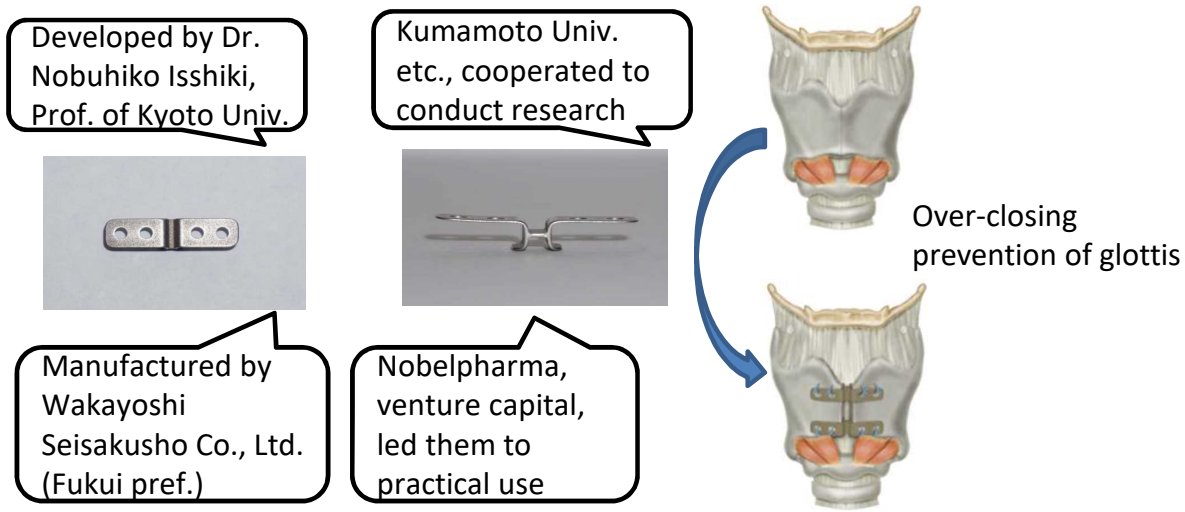
Feb. 2016: Designated for SAKIGAKE

Jun. 30, 2017: Submission for marketing approval

6 months

Dec. 15, 2017: Regulatory approval

- Novel mechanism of action developed in Japan (Nobelpharma Co., Ltd)

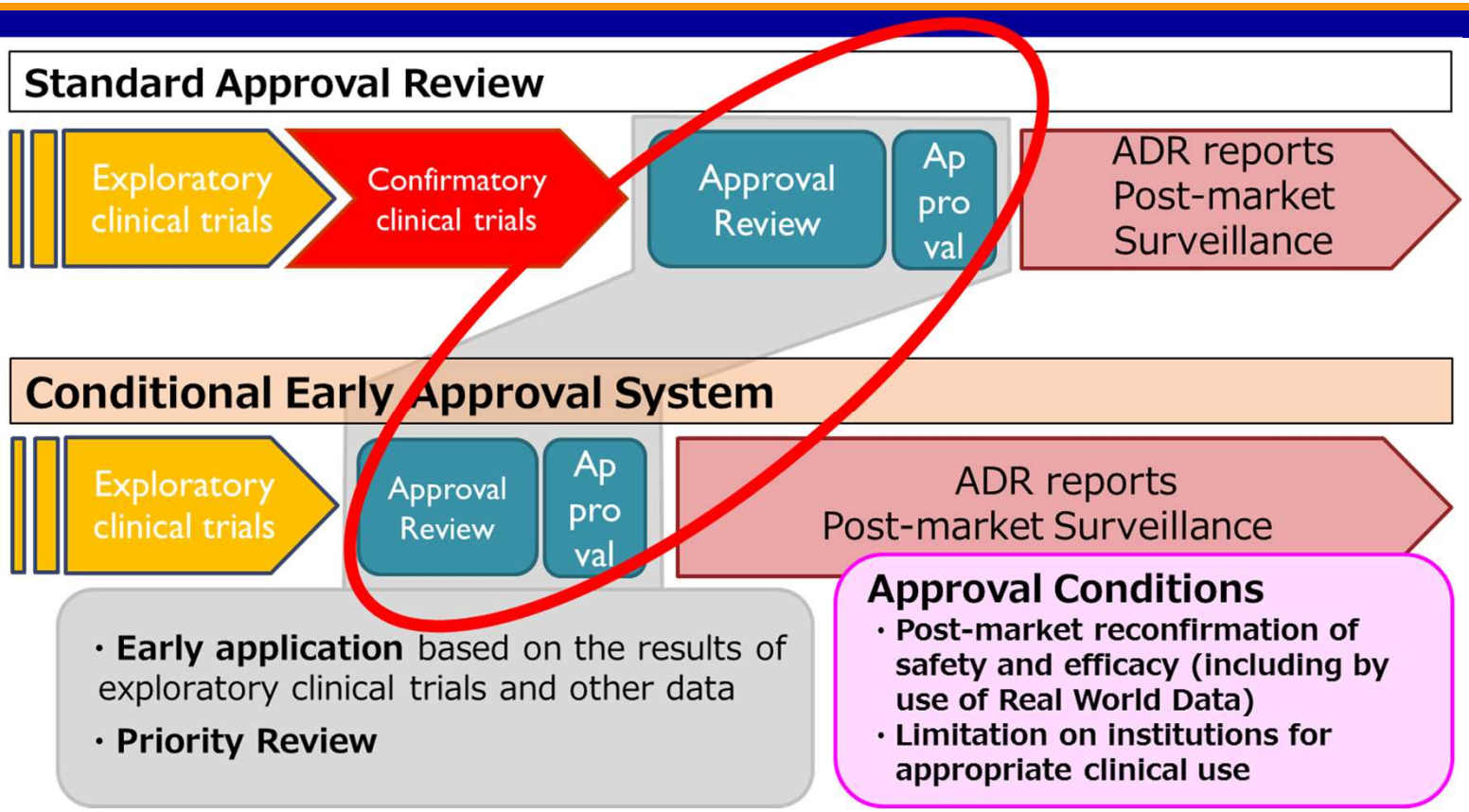


*There AMED research funding support of MHLW

Conditional Early Approval System for Pharmaceuticals

<Implemented on 20 Oct, 2017>

Pharmaceuticals and Medical Devices Agency

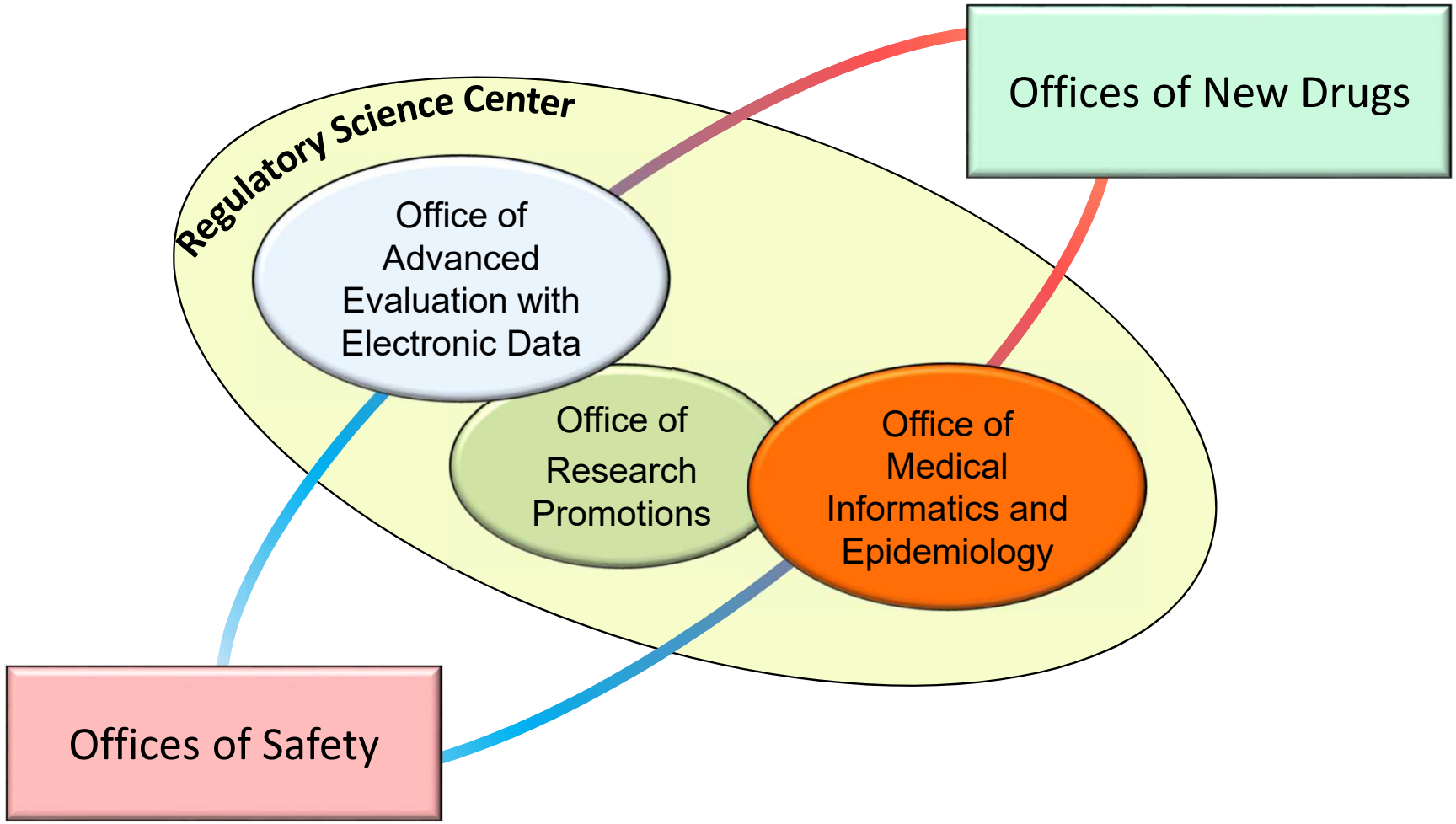


To realise early access to innovative treatments that are:

- 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

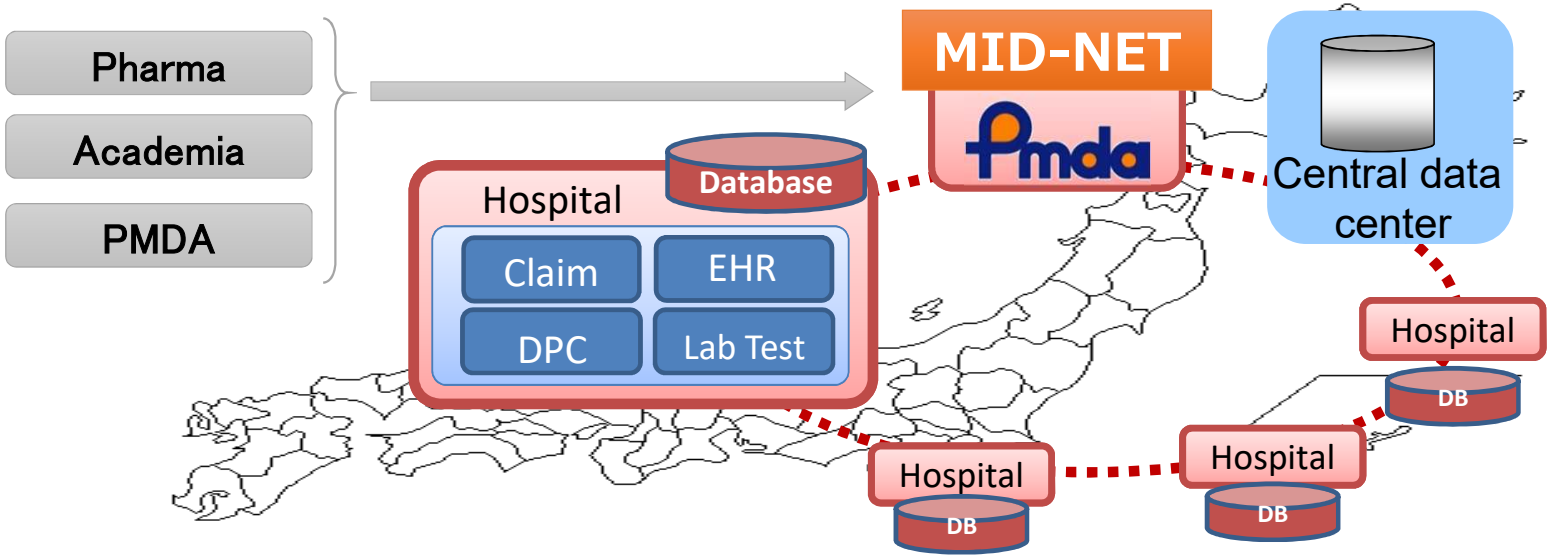
Product	Expected indication	Marketing Authorization Holder
Lorlatinib	The treatment of patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on 1 or more ALK tyrosine kinases inhibitors (TKIs).	Pfizer

Regulatory Science Center
- Collaboration with other PMDA Offices -



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

Science Board

Universities
Research Institutes

Medical institutions

Collaboration

Science Board

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

Reports of Science Board (3rd term) FY2016 – 2017

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.

Publication on the Journal

Advanced Biomedical Engineering
7: 118–123, 2018.

Invited Review Paper

DOI:10.14326/abe.7.118

Regulatory Science on AI-based Medical Devices and Systems

Kiyoyuki CHINZEI,[1] Akinobu SHIMIZU,[2] Kensaku MORI,[3] Kanako HARADA,[4] Hideaki TAKEDA,[5] Makoto HASHIZUME,[6] Mayumi ISHIZUKA,[7] Nobumasa KATO,[8] Ryuzo KAWAMORI,[9] Shunei KYO,[10] Kyosuke NAGATA,[11] Takashi YAMANE,[12] Ichiro SAKUMA,[4] Kazuhiko OHE,[13] Mamoru MITSUISHI[14,#]

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 unknown inputs due to the black box characteristics precluding deductive output prediction; and 3) need of assuring 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.

Adv Biomed Eng. 7: pp. 118–123, 2018.

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

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

Received: 20 February 2018 | Revised: 2 March 2018 | Accepted: 7 March 2018
DOI: 10.1111/cas.13568

REPORT

WILEY Cancer Science

Current state of therapeutic development for rare cancers in Japan, and proposals for improvement

Akira Kawai[1,2] | Toshio Goto[1,3] | Tatsuhiro Shibata[1,4] | Kenzaburo Tani[1,5] | Shuki Mizutani[1,6] | Akiyoshi Nishikawa[1,7] | Taro Shibata[1,8] | Seiichi Matsumoto[1,9] | Kyosuke Nagata[1,10] | Mamoru Narukawa[1,11] | Shigeyuki Matsui[1,12] | Masashi Ando[1,13] | Junya Toguchida[1,14] | Morito Monden[1,15] | Toshio Heike[1,16] | Shinya Kimura[1,17] | Ryuzo Ueda[1,18]

[1]Subcommittee on Rare Cancers, The Science Board to the Pharmaceuticals and Medical Devices Agency, Tokyo, Japan
[2]Department of Musculoskeletal Oncology and Rehabilitation, Rare Cancer Center, National Cancer Center Hospital, Tokyo, Japan
[3]Program for Drug Discovery and Medical Technology Platforms, RIKEN, Tsukuba, Japan
[4]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[5]Project Division of ALA Advanced Medical Research, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan
[6]Tokyo Medical and Dental University, Tokyo, Japan
[7]Biological Safety Research Center, National Institute of Health Sciences, Tokyo, Japan
[8]Biostatistics Division, Center for Research Administration and Support, National Cancer Center, Tokyo, Japan
[9]Sarcoma Center, The Cancer Institute Hospital of JFCR, Tokyo, Japan
[10]University of Tsukuba, Tsukuba, Japan
[11]Department of Clinical Medicine (Pharmaceutical Medicine), School of Pharmacy, Kitasato University, Sagamihara, Japan
[12]Department of Biostatistics, Nagoya University Graduate School of Medicine, Nagoya, Japan
[13]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagakute, Japan
[14]Institute for Frontier Life and Medical Sciences/Center for iPS Cell Research and Application, Kyoto University, Tokyo, Japan
[15]Sakai City Hospital Organization, Sakai, Japan
[16]Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Japan
[17]Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan
[18]Department of Tumor Immunology, Aichi Medical University School of Medicine, Nagakute, Japan

Correspondence
Ryuzo Ueda, Department of Tumor Immunology, Aichi Medical University School of Medicine, Nagakute, Japan.

This article discusses current obstacles to the rapid development of safe and effective treatments for rare cancers, and considers measures required to overcome

Themes of Science Board (4th term)

Clinical evaluation of antimicrobial agents for AMR

Risk assessment of products utilizing genome editing technology

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. **<u>Ensuring early access to innovative pharmaceuticals & medical devices, and enhancing the safety measures</u>**
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

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

International Partnerships

ICH
harmonisation for better health

IMDRF

IPRP
International Pharmaceutical Regulators Programme

pmda

MDSAP

PIC/S

APEC
Asia-Pacific Economic Cooperation

RHSC

ICMRA

OECD/GLP
BETTER POLICIES FOR BETTER LIVES

What is Horizon Scanning?

Without Horizon Scanning…

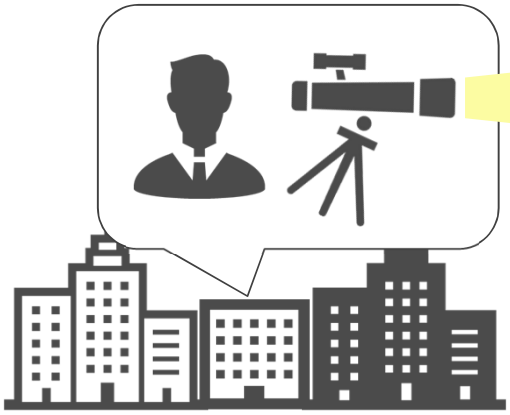
Stakeholders **:**
unsure of regulations…

Report on
Technology A

Regulator

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

With Horizon Scanning…



Regulator

Emerging
Technologies

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

ICMRA Innovation Project

ICMRA Innovation Face to Face meeting was held at DIA Japan, November 2018 in Tokyo

Overall Leadership

Subgroup of the Executive Committee

Project 1	Project 2	Project 3
Analysis of global best practices in horizon scanning methodologies	Leveraging from outcomes of horizon scanning through critical innovation/ expertise and skills	Novel Approaches to Licensing/Early Access Scheme
Lead: MHLW/PMDA	Lead: EMA, HPRA	Lead: Health Canada

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

Lectures, case studies, and on-site training

Establishing a centralised training center for multi-regional clinical trials

International Reputation of Asia Training Center

- Attendees (FY 2017)

✓ Nine training seminars and 235 attendees from 27countries/regions

✓ More than 70% of attendees rated as “Very good” according to the questionnaire

- Official certificate 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

2019 PIC/S Annual Seminar to be held in Japan

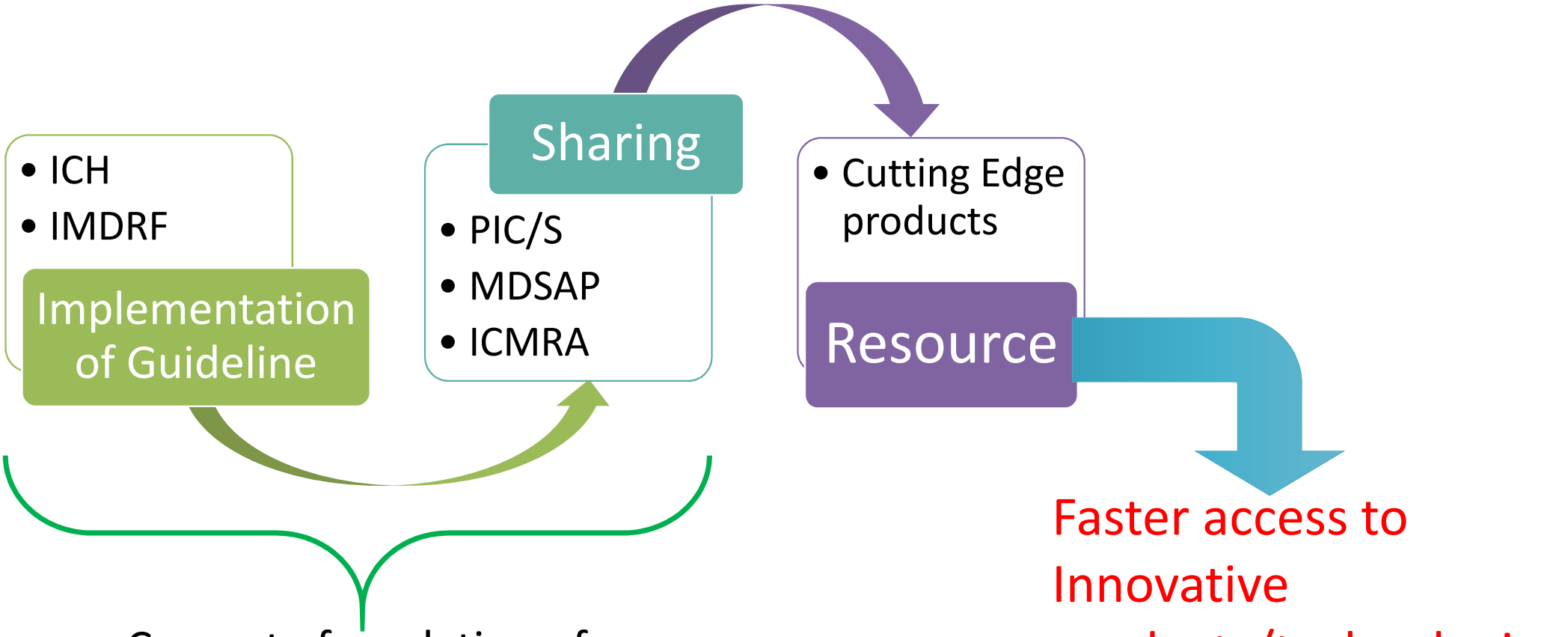
Date: 11-15 November 2019
Venue: Toyama city, Japan

Theme: “Quality Assurance of Sterile Medicinal Products -Annex1-”

Objectives:

1. To explain and discuss content of revised Annex 1 and issues which were raised during revision.
2. Through the case study of sterility assurance, to learn how to consider risk based validity.
3. To introduce advanced technologies for sterility assurance and the way of control

The importance of Work Sharing



Thank you!

Muito Obrigado
&
Muito Obrigada