PMDA’s perspective on regulatory science in pharmaceutical regulation

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Pharmaceuticals and Medical Devices Agency (PMDA)
Visiting Professor, Graduate School of Medicine, Chiba University
Visiting Professor, Graduate School of Medicine, Nagoya University
Circumstances surrounding drug regulation
Huge increase of costs to get a “Drug”

Improving but still unmet medical needs

Contribution of drug to medical therapy

Satisfaction of medical therapy

High unmet medical needs

Pancreatic cancer

Alzheimer’s

Fibromyalgia

Depression

Schizophrenia

Asthma

Breast Cancer

Myocardial infarction

Diabetes

Pancreatic cancer

Alzheimer’s

Fibromyalgia

Depression

Schizophrenia

Asthma

Breast Cancer

Myocardial infarction

Diabetes
More pressures to shorten the review period, but such competitiveness among regulatory agencies would not be constructive for public health
Rapid Evolution of Science
The Nobel Prize in Physiology or Medicine

All Nobel Laureates in Physiology or Medicine

The Nobel Prize in Physiology or Medicine has been awarded 107 times to 211 Nobel Laureates between 1901 and 2016. Click on the links to get more information.

The Nobel Prize in Physiology or Medicine 2016
Yoshinori Ohsumi
"for his discoveries of mechanisms for autophagy"

The Nobel Prize in Physiology or Medicine 2015
William C. Campbell and Satoshi Ōmura
"for their discoveries concerning a novel therapy against infections caused by roundworm parasites"

Youyou Tu
"for her discoveries concerning a novel therapy against Malaria"

The Nobel Prize in Physiology or Medicine 2014
John O'Keefe, May-Britt Moser and Edvard I. Moser
"for their discoveries of cells that constitute a positioning system in the brain"

The Nobel Prize in Physiology or Medicine 2013
James E. Rothman, Randy W. Schekman and Thomas C. Südhof
"for their discoveries of machinery regulating vesicle traffic: a major transport system in our cells"

The Nobel Prize in Physiology or Medicine 2012
Sir John B. Gurdon and Shinya Yamanaka
"for the discovery that mature cells can be reprogrammed to become pluripotent"
Scientific Innovation

Example: iPS cell-derived products

iPS cell-derived retinal pigment epithelial cell sheets

https://www.healios.co.jp/
What is Regulatory Science?
GAP between expectation and Reality

Concerns and Needs for medical services

New study design and analytical tool

Predictable model for efficacy/safety

Advancing Regulatory Science

Ensure Social Balance

Medical Needs

Traditional Science

Current Issues

SAE after approval, Lower success rate, Scientific uncertainty etc.

New approach on risk communication and management

New tool/methods for benefit/risk assessment

Regulatory Science

Traditional Science
PMDA’s definition of “Regulatory Science”

the science aimed at the optimal introduction into society of new products of science, such as discovered substances and new scientific tools and technologies as well as knowledge and information.

Regulatory Science Bridge

Proper introduction

Tools for data production

Data assessment

Balancing of various factors

Products of science

(Substance, Knowledge, Information)

Patients/Society

Microscopic feature of Regulatory Science

Data assessment based on clinical trials to conclude benefit/risk of a drug

- For example
  - Evaluating efficacy on the primary endpoint
  - Evaluating safety based on dose-response relationship

Microscopic observation
Real-world feature of Regulatory Science

Value to the Society in promoting the Health

Regulatory Science

Scientific, Non-bias, Objective,
Evaluation based on Regulatory Science

Truth

Positive data

Cohort Study

Placebo-controlled RCT

Article

Expert Opinion

Cohort study

Active-controlled RCT

News item

Case Report

Rumors

News item

Case Report

Article

News item

Cohort study

Active-controlled RCT

Case Report

Article

News item

Cohort study

Active-controlled RCT

Case Report

Article

News item

Cohort study

Active-controlled RCT
Multi-disciplinary team of regulatory science

Experts in various fields need to collaborate for better decision

Seeds for a drug

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Pharmaceuticals & Medical Devices Agency

CORS Univ Copenhagen, Denmark, November 2016
PMDA efforts for promoting innovative drug development and advancing regulatory science
Message from Dr Kondo, Chief Executive (PMDA)

1. More scientific contributions during development through consultation

2. Utilizing “BIG DATA” for improving quality of approval review and safety assessment

3. Promoting regulatory science
   - Developing methods and criteria for responding to advances in science and more
Special consultations on Pharmaceutical Regulatory Affairs

- Promoting innovative drug development by academic institute and venture enterprises in Japan
- Focusing on early stage of drug development including quality and non-clinical as well as clinical matters

- Discovery (Identifying a candidate product)
- Manufacturing / quality assessment
- Non-clinical (Pharmacology/ADME/Toxicology etc.)
- Clinical
- Review
- Post-Market

Special consultation on Pharmaceutical Affairs

NDA
Approval
Scientific Consultations in PMDA

Modified from Figure by Ichimaru K et al, Clin Pharmacol Therapeut, 88: 454-457, 2010
“SAKIGAKE” Strategy

- MHLW launched a new system termed “Strategy of SAKIGAKE as a Package” to lead the world in the practical application of innovative medical products in 2014.

General Framework of "SAKIGAKE"

**Original Review**

<table>
<thead>
<tr>
<th>Step</th>
<th>Timeframe</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Consultation</td>
<td>1 month</td>
<td>Non-clinical research/clinical research</td>
</tr>
<tr>
<td>2. Consultation on clinical trial</td>
<td>2 months</td>
<td>Clinical trial Phase I/II</td>
</tr>
<tr>
<td>3. Clinical trial Phase III</td>
<td>12 months</td>
<td>Review</td>
</tr>
<tr>
<td>4. Covered by insurance</td>
<td></td>
<td>Commercialization in market</td>
</tr>
</tbody>
</table>

**Review under SAKIGAKE Designation System**

<table>
<thead>
<tr>
<th>Step</th>
<th>Timeframe</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Designation as SAKIGAKE</td>
<td></td>
<td>Prior Review</td>
</tr>
<tr>
<td>2. Prior Review</td>
<td>6 months</td>
<td>Review</td>
</tr>
<tr>
<td>3. Covered by insurance</td>
<td></td>
<td>Commercialization in market</td>
</tr>
<tr>
<td>4. Early Access to the innovative medical products</td>
<td></td>
<td>Prior Review</td>
</tr>
<tr>
<td>5. Review Partner</td>
<td></td>
<td>Extending re-evaluation period (post-market exclusivity)</td>
</tr>
</tbody>
</table>

*Accept the data of Phase III after the application depending on conditions*
### SAKIGAKE Designated Products

#### Drugs, as of Oct. 2015

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Proposed indication</th>
<th>Name of applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus (NPC-12G)</td>
<td>Angiofibroma associated with tuberous sclerosis</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
<tr>
<td>NS-065/NCNP-01</td>
<td>Duchenne muscular dystrophy (DMD)</td>
<td>Nippon Shinyaku Co., Ltd</td>
</tr>
<tr>
<td>S-033188</td>
<td>Influenza A or B virus infection</td>
<td>Shionogi &amp; Co., Ltd.</td>
</tr>
<tr>
<td>BCX7353</td>
<td>Management of angioedema attacks in patients with hereditary angioedema (HAE)</td>
<td>Integrated Development Associates Co., Ltd.</td>
</tr>
<tr>
<td>ASP2215</td>
<td>First-relapsed or treatment-resistant FLT3 mutation-positive acute myeloid leukaemia</td>
<td>Astellas Pharma Inc.</td>
</tr>
<tr>
<td>Pembrolizumab (genetical recombination)</td>
<td>Unresectable, advanced and recurrent gastric cancer</td>
<td>MSD K.K.</td>
</tr>
</tbody>
</table>
### SAKIGAKE Designated Products

Medical devices and Regenerative Medical Products, as of Feb. 2016

<table>
<thead>
<tr>
<th>Name of medical products</th>
<th>Proposed indication</th>
<th>Name of applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titanium Bridge (Hinge-type plate with titanium)</td>
<td>Adduction-type spasmodic dysphonia</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
<tr>
<td>STR01 (Autologous bone marrow-derived mesenchymal stem cell)</td>
<td>Nerve syndrome and dysfunction caused by spinal cord injury</td>
<td>NIPRO Medical Co., Ltd.</td>
</tr>
<tr>
<td>G47 △ (Growth-controlled oncolytic herpes simplex virus type 1)</td>
<td>Malignant glioma</td>
<td>Daiichi Sankyo Co., Ltd.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The University of Tokyo, Institute of Medical Sciences</td>
</tr>
<tr>
<td>Autologous cardiac progenitor/stem cells</td>
<td>Pediatric congenital heart disease (single ventricle physiology)</td>
<td>Japan Regenerative Medicine Co., Ltd.</td>
</tr>
</tbody>
</table>
BIG DATA utilization
for better assessment and promoting public health
CDISC data submission on NDA formally started on October 1st, 2016

- NDA Review: More effective & High quality 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 etc.

Database of Clinical Trial Results

Analysis

Modeling & Simulation:
- Concentration-Response Model,
- PBPK: Physiologically-based Pharmacokinetic Model etc.
MIHARI PROJECT
(PEpi Assessment based on EHR)

Conventional information sources

- Spontaneous ADR report DB
- Overseas regulatory actions
- Literatures
- Presentations in Academic Meetings
- etc.

Electronic Healthcare Data utilization

- Claims DB
- MID-NET (EMR DB)
- DPC DB

PMDA

MHLW

Hospital/Medical institutes

Risk Management/communication

Safety measure

- a new database of medical information of Japanese patients

Overseas regulatory actions

Presentations in Academic Meetings

Conventional information sources

- Spontaneous ADR report DB
- Overseas regulatory actions
- Literatures
- Presentations in Academic Meetings
- etc.

Electronic Healthcare Data utilization

- Claims DB
- MID-NET (EMR DB)
- DPC DB

PMDA

MHLW

Hospital/Medical institutes

Risk Management/communication

Safety measure

- a new database of medical information of Japanese patients
The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients)
Example: MID-NET Data Utilization
-Prazaxa-induced GI bleeding-

Compare risk of GI bleeding between Prazaxa and Warfarin

Results from 1 cooperative hospital of MID-NET

<table>
<thead>
<tr>
<th></th>
<th>Number of Prescription</th>
<th>Number of Patients</th>
<th>GI Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient number</td>
</tr>
<tr>
<td>Prazaxa</td>
<td>779</td>
<td>164</td>
<td>3</td>
</tr>
<tr>
<td>Warfarin</td>
<td>14,534</td>
<td>1,204</td>
<td>28</td>
</tr>
</tbody>
</table>

Patients distribution based on Cr at the time of first prescription

Results from 1 cooperative hospital of MID-NET

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Normal -0.9mg/dL</th>
<th>Mild 0.9-1.35mg/dL</th>
<th>Moderate 1.35-2.7mg/dL</th>
<th>Severe 2.7-mg/dL</th>
<th>No Lab-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Prazaxa</td>
<td>164</td>
<td>57</td>
<td>34.8%</td>
<td>41</td>
<td>25.0%</td>
<td>7</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1,204</td>
<td>373</td>
<td>31.0%</td>
<td>304</td>
<td>25.2%</td>
<td>148</td>
</tr>
</tbody>
</table>
Archives of e-data

CDISC Data

EMR Data

Utilization of e-data for better regulatory decision in
- Development
- Pre-Approval
- Pharmacovigilance

Regulatory Science Center

Active Utilization

"BIG DATA"-utilized Assessment & Regulation

Accelerating Innovation

Better Prediction

Better B/R balance

More Successful Development

Promoting Precision Medicine
Advancing Regulatory Science & PMDA RS Center

FY2014-FY2015

- Start e-data (CDISC) submission for NDA (Oct 2016)
- More PEpi studies including MID-NET pilot studies
- Start routine PEpi analysis for safety assessment
- Pilot studies in using CDISC data

FY2016-FY2017

- Start cross-product analysis (M&S)
- Launch MID-NET for PEpi analysis
- Reinforcement of collaboration among PMDA Offices (New Drug Review, Safety, M&S Group, PEpi Group)

FY2018-FY2019

- Launch PEpi consultation

FY2020-FY2021

- Full scale cross-product analysis
- Full scale PEpi analysis
- Publish more guidelines
- Strengthening international collaboration on utilization of BIG-DATA

FY2022-FY2023

- Collaboration with academia/industries on BIG-DATA analysis
- Routine regulatory measure based on BIG DATA analysis

Tentative
Products of science
(Substance, Knowledge, Information)

Drug A

Proper introduction

Tools for data production

Data assessment

Balancing of various factors

Regulatory Science Bridge

Patients/Society

Stronger & More Complete Regulatory Science Bridge will help us in the future drug developments

Information

- PMDA web site

- E-mail:
  uyama-yoshiaki@pmda.go.jp

Bilateral Cooperation between PMDA and Foreign Regulatory Authorities

Thank you for your kind attention