PMDA’s perspective on regulatory science in pharmaceutical regulation

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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

Depression

Schizophrenia

Fibromyalgia

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. Sudhof
"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 cells are created from somatic cells by transfecting Yamanaka factors.

Differentiation induction

Nerve cells
Cardiomyocytes

Hepatocytes
Pancreatic cells

iPS cell-derived retinal pigment epithelial cell sheets

Innovation/uncertainty

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

Concerns and Needs for medical services

Traditional Science
- SAE after approval, Lower success rate, Scientific uncertainty etc.

Current Issues

New approach on risk communication and management

New tool/methods for benefit/risk assessment

Medical Needs

Predictable model for efficacy/safety

New study design and analytical tool

Advancing Regulatory Science

Ensure Social Balance

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

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

Expert Opinion

Article

News item

Cohort study

Case Report

Expert Opinion

Article

News item

Case Report

Rumors

Active-controlled RCT

News item
Multi-disciplinary team of regulatory science

Experts in various fields need to collaborate for better decision

Practical Drug Use

Sociology

Veterinary Medicine

Agricultural Science

Biostatistics

Medical Science

Technology Science

Business Administration

Pharmaceutical Science

Seeds for a drug

and More
PMDA efforts for promoting innovative drug development and advancing regulatory science
Message from Dr Kondo, Chief Executive (PMDA)

Nature Reviews Drug Discovery 13, 490 (2014)

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
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
Modified from Figure by Ichimaru K et al, *Clin Pharmacol Therapeut*, 88: 454-457, 2010
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】

1. Priority Consultation
2. Prior Review
3. Priority Review

【Review under SAKIGAKE Designation System】

1. Priority Consultation
2. Prior Review
3. Priority Review

- Designation as SAKIGAKE
- Early Access to the innovative medical products

*Accept the data of Phase III after the application depending on conditions

- Covered by insurance
- Commercialization in market
<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</td>
<td>Adduction-type spasmodic dysphonia</td>
<td>Nobelpharma Co., Ltd.</td>
</tr>
<tr>
<td>(Hinge-type plate with titanium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioresorbable adhesion barrier</td>
<td>Postoperative adhesion prevention</td>
<td>Otsuka Pharmaceutical Factory, Inc.</td>
</tr>
<tr>
<td>(THN-01: Trehalose solution)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STR01</td>
<td>Nerve syndrome and dysfunction caused by spinal cord injury</td>
<td>NIPRO Medical Co., Ltd.</td>
</tr>
<tr>
<td>(Autologous bone marrow-derived mesenchymal stem cell)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G47 △</td>
<td>Malignant glioma</td>
<td>Daiichi Sankyo Co., Ltd.</td>
</tr>
<tr>
<td>(Growth-controlled oncolytic herpes simplex virus type 1)</td>
<td></td>
<td></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

- 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.

NDA Review
- B/R evaluation with raw data analysis

Scientific Consultation
- Scientific advices based on the information obtained from analyses including M&S

Cross-Products Analysis
- More evidences & Advancing Regulatory Science
- More efficient & Successful development
- More effective & High quality review
MIHARI PROJECT
(PEpi Assessment based on EHR)

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

Electronic Healthcare Data utilization
- Claims DB
- MID-NET (EMR DB)
- DPC DB

MHLW
- Safety measure
- Risk Management/communication

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Hospital/Medical institutes

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

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)

- Database
  - HIS data
  - Claims data
  - DPC data

- 23 hospitals
- In closed network

PMDA

Pharmaceuticals & Medical Devices Agency
Example: MID-NET Data Utilization
-Prazaxa-induced GI bleeding-

Compare risk of GI bleeding between Prazaxa and Warfarin

<table>
<thead>
<tr>
<th>Number of Prescription</th>
<th>Number of Patients</th>
<th>GI Bleeding</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patient number</td>
</tr>
<tr>
<td>Prazaxa</td>
<td>779</td>
<td>164</td>
</tr>
<tr>
<td>warfarin</td>
<td>14,534</td>
<td>1,204</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>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>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>prazaxa</td>
<td>164</td>
<td></td>
<td>41</td>
<td>25.0%</td>
<td>7</td>
</tr>
<tr>
<td>warfarin</td>
<td>1,204</td>
<td></td>
<td>304</td>
<td>25.2%</td>
<td>148</td>
</tr>
</tbody>
</table>
Utilization of e-data for better regulatory decision in:
- Development
- Pre-Approval
- Pharmacovigilance

“BIG DATA”-utilized Assessment & Regulation

- Better Prediction
- Better B/R balance
- More Successful Development
- Promoting Precision Medicine
- Accelerating Innovation
Advancing Regulatory Science & PMDA RS Center

FY2014-FY2015

- Start routine PEpi analysis for safety assessment
- Pilot studies in using CDISC data

FY2016-FY2017

- Reinforcement of collaboration among PMDA Offices (New Drug Review, Safety, M&S Group, PEpi Group)

FY2018-FY2019

- Start cross-product analysis (M&S)
- Launch MID-NET for PEpi analysis
- 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
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

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Thank you for your kind attention