PMDA perspective: Recent Trends in the Regulation of Biopharmaceuticals

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The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA
Outline

- Electronic submission of data for NDA
- Revision of ministerial ordinances on GPSP
- Strategy of SAKIGAKE
- Conditional early approval system
- Registry of Regenerative medical products
- Biopharmaceuticals
ELECTRONIC SUBMISSION OF DATA FOR NDA
Electronic Submission of Data for New Drug Applications

NDA submission
- e-Submission of data
  - Submission of electronic data from clinical and nonclinical studies
  - Storage of electronic data in the dedicated server and registration in the database

Regulatory Review
- Use of electronic data
  - Accessible, visualized electronic data for each reviewer
  - Easy to identify individual clinical case data, drilling down of data
  - Operation of various analyses—simple, subgroup analysis for the present

Utilization of Accumulated Data
- Integration of cross-products information
- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme—e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

Visualization and analysis of data, supported by browsing software

Scientific discussion and decision making on the basis of internal analysis result

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab
Electronic Submission of Data for New Drug Applications ~ Future goals

- Make proposals leading the world
- Development of guideline
- Increase of development success rate
  → Effective and Successful Development (Shortened development time, cost reduction)

Analysis by PMDA
- Additional scientific value to submitted data

A rational & effective evaluation process for regulatory decision

Regulatory science = Science of prediction and verification

- More predictable efficacy/safety after approval
- Reduction of applicant’s work load
- More scientific discussion and regulatory decision
  → Effective and High Quality Review

Cooperation with academia?

Development of Japan’s original innovative drugs and medical devices
Electronic Submission of Data for New Drug Applications

• The study that require the submission of principles are as follows
  – All Phase II and Phase III studies (including long-term study) that are considered to be the main reasons for efficacy, safety, and dosage regimen.
  – Phase I and clinical pharmacology studies, the following tests
    • Anti-cancer agent
    • Phase I (international study, bridging study)
    • QT/QTc based on ICH E14

Consultation for Electronic submission of data confirmation

Applied from 2016.10.1, Transitional period: until 2020.3.31
REVISION OF MINISTERIAL ORDINANCES ON GPSP
Revision of Ministerial Ordinances on GPSP

• Good Post-marketing study practice
• In order to make medical information database, for example MID-NET, available as reexamination application data
• Scope: Pharmaceuticals, Medical devices, Regenerative medical products

• Schedule:
  – Promulgation 2017.10.26
  – Enforcement 2018.04.01
Revision of Ministerial Ordinances on GPSP

Application

Review

Approval

Safety periodic report

Spontaneous report

Post-marketing Study

Application for Reexamination

Review

Result notification

The post-marketing study conducted by the company, Certain reliability criteria (GPSP ministerial ordinance) must be satisfied.
Revision of Ministerial Ordinances on GPSP

Post-marketing survey

Usage performance survey
- General drug use survey
- Specific drug use survey
- Drug use comparative survey

Post-marketing clinical trial

Post-marketing database survey

Either or some of these investigations Combine and make re-examination materials.

Post-marketing database survey: to collect and prepare reexamination application materials based on post-marketing surveillance using medical information database

General drug use survey: conventional drug use survey

Drug use comparative survey: to compare and evaluate information on multiple drugs

Consultation for epidemiological survey on post-marketing database survey
STRATEGY OF SAKIGAKE
SAKIGAKE DESIGNATION SYSTEM
General Timeframe of SAKIGAKE

【Standard】
- Non clinical studies, Clinical studies
- Clinical trials I/II
- Consultation on Clinical trials
- phase III study
- Review
- Reimbursement
- Post Marketing
- Priority Consultations

【SAKIGAKE】
- Prior review (Rolling submission)
- Review Partner System
- Strengthening Post-Marketing Safety

※ In some cases, may accept phase III data during review
SAKIGAKE Consultations

Consultation with Concierge

CMC

Non-Clinical

Clinical

GCP/GLP Compliance

GCTP Compliance

Prior review (Rolling submission)

Inquiry/Answer

I/A

MAA Submission

Review

On-site Inspection

On-site Inspection

6 month

5 Tracks as 1 package
Cost: 90,000 USD

Approval
SAKIGAKE Assignment

• 1st Round (2015)
  – Pharmaceuticals: 6
  – Medical devices: 1
  – RM*: 3

• 2nd Round (2017.4.21)
  – Pharmaceuticals: 5
  – Medical devices: 3
  – Diagnostic agent: 1
  – RM*: 3

• 3rd Round
  – 2017.10.5 public offering

http://www.pmda.go.jp/review-services/drug-reviews/0003.html

*Regenerative medical products
## SAKIGAKE Assignment (2\textsuperscript{nd} Round)

<table>
<thead>
<tr>
<th>Product name</th>
<th>Expected indication</th>
<th>company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceuticals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olipudase alfa</td>
<td>Acid sphingomyelinase deficiency</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Aducanumab</td>
<td>Suppression of Alzheimer's disease progression</td>
<td>Biogen Japan</td>
</tr>
<tr>
<td>DS-5141b</td>
<td>Duchenne muscular dystrophy</td>
<td>Daiichi Sankyo</td>
</tr>
<tr>
<td>SPM-011</td>
<td>• Recurrent malignant glioma</td>
<td>Stella Pharma</td>
</tr>
<tr>
<td></td>
<td>• Unresectable locally recurrent head and neck cancer and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>locally advanced head and neck cancer</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Biliary tract cancer</td>
<td>Ono Yakuhin Kogyo</td>
</tr>
<tr>
<td>Diagnostic Agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer related gene panel inspection system</td>
<td>Collective detection of gene abnormality in DNA in tumor tissues of solid cancer patients</td>
<td>National Cancer Center Sysmex</td>
</tr>
</tbody>
</table>
# SAKIGAKE Assignment (2nd Round)

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Expected Indication</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Devices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artificial trachea</td>
<td>Reconstruct resected trachea due to malignant tumor or stenotic disease</td>
<td>Kyoto University Daiichi Ika</td>
</tr>
<tr>
<td>Boron Neutron Capture Therapy (BNCT) System</td>
<td>Apparatus for irradiating neutron beam</td>
<td>Kyoto University Stella Pharma Sumitomo jukikaikogyo</td>
</tr>
<tr>
<td>UT-Heart</td>
<td>A medical device program for simulating the individual heart of a patient on a computer</td>
<td>UT-Heart Laboratory Fuji Film</td>
</tr>
<tr>
<td><strong>Regenerative Medical Products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLS2702C/D (Autologous oral mucosa-derived esophageal cell sheet)</td>
<td>Extensive endoscopic submucosa dissection (ESD) in esophageal cancer</td>
<td>CellSeed Tokyo Women’s Medical University Hospital</td>
</tr>
<tr>
<td>Dopamine neural precursor cell derived from allogenic iPS cell</td>
<td>Parkinson’s disease</td>
<td>Sumitomo Dainippon Pharma CiRA, Kyoto University</td>
</tr>
<tr>
<td>Pluripotent progenitor cell derived form allogeneic adult bone marrow</td>
<td>Acute brain infarction</td>
<td>Healios Athersys</td>
</tr>
</tbody>
</table>
Registry of regenerative medical products

Notification (No. 0928-1) from Director, Pharmaceutical Safety Division, dated 28 September 2017, "Enrolling patient record to National Regenerative Medicine Database (Request for cooperation)"

薬生安発 0928 第 1 号
平成 29 年 9 月 28 日

（別記１）殿

厚生労働省医薬・生活衛生局医薬安全対策課長

再生医療等製品患者登録システムへの参加等について（依頼）

平成 26 年 11 月に施行された医薬品、医療機器等の品質、有効性及び安全性の確保等に関する法律（昭和 35 年法律第 145 号。以下「法」という。）において、新たに「再生医療等製品」が定義づけられました。

https://www.pmda.go.jp/safety/info-services/ctp/0009.html
MAH utilize the patients' data collected through registry to report the malfunction (adverse events) by regenerative medical products and conduct post-marketing surveillance.
RM patient registry initiatives (with JSRM) in a product lifecycle management

The patient registry database has been in place for facilitating regenerative medicine studies (pre- and post-marketing)

Pre-marketing

Historical control arm for rare diseases CTs

National Regenerative Medicine Database (JSRM patient registry)

Academic Clinical Registry Database

enroll

NRMD/C R

NRMD/P MS

Transferred from PMDA

Case control matching studies for PMS

enroll

Post-marketing

Survey Case Reports

MAH

Post-marketing
The implementation plan is developed in working group collaboration with MAH, academic societies, and MHLW/PMDA.
Steps for Post-market data-collection

Step 1: Before MAA submission
- MAH plans the Post-market data-collection.
- PMDA conduct a briefing of the registry system with MAH and academic societies to prepare the registry.

Step 2: After MAA Submission
- Establish the WG.
- Determination of the implementation plan.
- Prepare for data-collection.

Step 3: Marketing Authorization
- Start data-collection.
CONDITIONAL EARLY APPROVAL SYSTEM
Conditional Approval

• Regenerative Medical Products
  – Conditional/time limited approval system (2014.11.25～)

• Medical devices
  – Conditional early approval system (2017.7.31～)

• Pharmaceuticals
  – Conditional early approval system (2017.10.20～)
Conditional Early Approval System

• For drugs with a disease that is severe and poor in effective treatment and for which it is difficult to conduct verification clinical trials because of a small number of patients and those requiring a long period of time

• Confirm certain degree of effectiveness and safety in clinical trials other than verification clinical trials at the time of application

• Organize and clarify the handling to be given under approval conditions, such as conducting surveys and the like necessary for reconfirmation of effectiveness and safety after approval, so that medical usefulness for serious diseases

• To put into practical use with high medical usefulness for serious diseases at an early stage
Conditional Early Approval System

【Standard】

Non clinical studies, Clinical studies → Clinical trials I/II → phase III study → Review → Approval → Post Marketing

【Conditional Approval】

Non clinical studies, Clinical studies → Clinical trials I/II → Review → Approval → Post Marketing

- Verify certain degree of effectiveness and safety in clinical trials other than verification clinical trials, and apply early.
- Shorten the total review period as priority review item

Approval condition
For example...
- Reaffirmed validity and safety (Including real world data)
- Set facility requirements, if necessary for proper use
Conditional Early Approval System

• Anything that falls under any of 1 to 4 below

1. Severity
   - Lethal disease
   - Irreversible, Significant impact on daily life

2. Usefulness for medical
   - No existing treatment, prevention, diagnosis
   - Superior to existing treatment, prevention, diagnosis

3. difficult to conduct verification clinical trials because of a small number of patients and those requiring a long period of time

4. Those judged to show certain efficacy and safety due to results of clinical trials etc. other than verification clinical trials

Match with the requirements of priority review
Consultation for Biosimilars

Fiscal year (from April 1 to March 31)
Current Status of Biosimilar Products

• Approved
  – Somatropin BS1
  – Epoetin alpha BS1
  – Filgrastim BS1, BS2, BS3
  – Insulin glargine BS1, BS2
  – Infliximab BS1, BS2
  – Rituximab BS1

• Addition of indication or usage
  – Infliximab BS1
BIOPHARMACEUTICALS
CHANGE OF APPLICATION CATEGORY
Change of application category of biopharmaceuticals

- **Notification 1988.6.6** Yakushin No.1-10
  drugs manufactured using cell culture technology

- **Notification 1984.3.30** Yakushin No.243
  drugs manufactured using recombinant DNA technology

Among the change in manufacturing method, when MCB is changed, it corresponds to New drug

If they are comparable, it is possible to respond by Partial change

- **Notification 2017.7.5** Yakuseiyakushinhatsu No.0705-7
  Regarding the classification of application for approval of biotechnology-applied medicines and how to prepare attached documents necessary for approval application

ICH Q5E