Transformation towards a New Regulatory Paradigm

Risk Management Plan (RMP) on Biologicals and NCE

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PMDA, Japan
Pharmaceuticals and Medical Devices Agency
Date of Establishment: April 2004

PMDA Homepage:

Kansai Branch
Agenda

1. Introduction of PMDA
2. Background
3. Outline of J-RMP
4. Review process of J-RMP
5. Current situation and future challenges
6. Summary
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PMDA continues to improve the public health and safety of our nation by reviewing applications for marketing approval of pharmaceuticals and medical devices, conducting safety measures, and providing relief to people who have suffered from adverse drug reactions.

We conduct our mission in accordance with the following principles:

- We pursue the development of medical science while performing our duty with greater transparency based on our mission to protect public health and the lives of our citizens.

- We will be the bridge between the patients and their wishes for faster access to safer and more effective drugs and medical devices.

- We make science-based judgments on quality, safety, and efficacy of medical products by training personnel to have the latest technical knowledge and wisdom in their field of expertise.

- We play an active role within the international community by promoting international harmonization.

- We conduct services in a way that is trusted by the public based on our experiences from the past.
As the only regulatory authority in the world which plays three roles in an integrated manner, PMDA contributes to improve the standard of medical care by delivering safer and higher quality products faster to medical practice based on regulatory science.
PMDA Third Mid-term Plan for Safety

- Enhance Collection of ADRs
- Improve the System and Process of ADRs Evaluation
- Establish the System to Utilize Electronic Healthcare Data
- Enhance Feedback of Safety Information
- Enhance Dissemination of Information to the patients
Sophistication of Safety measures

1. Medical Information for Risk Assessment Initiative (MIHARI Project)
2. Project for developing the medical information database infrastructure (MID-NET)

PMDA

Safety assessment based on conventional data sources
- ADR reports DB
- Literatures
- Presentations at Academic Conference
- Overseas Regulatory information

Safety assessment based on Electronic Health Information Databases = MIHARI Project
- Claim Data
- Health insurance societies’ claims
- Medical Records DB
- *DPC, etc. (inpatient) DB

MHLW

Safety assessment based on conventional data sources

Medical institutions

Transmit To medical institutions

Development of New DB = MID-NET
PMDA Third Mid-term Plan for Safety

► Promote Appropriate Safety Measures based on the J-RMP
► Enhance Post-marketing Safety Measures in Cooperation with Review Teams
► Improve Follow-ups of Safety Measures Conducted
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Continuous and Comprehensive B/R Evaluation through Life Cycle of Drugs

- Risks
- Benefits

Development
  (Clinical Trial Consultation)

Review

Post-Marketing
### Current Pharmacovigilance measures

<table>
<thead>
<tr>
<th>Pre-market review</th>
<th>Approval</th>
<th>Post-market</th>
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<td>Pharmcovigilance plan For NME</td>
<td>EPPV (NME 6mo.)</td>
<td>6-10 years Re-examination</td>
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<td>Post-market commitment</td>
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*3rd PMDA Training Seminar – January 21-25, 2019*
Monitoring ADRs is critical in the first 6 months after the launch of a new drug.

Early Post-market Phase Vigilance

- Visit each hospital before supply and after that periodically
- Periodical dissemination of safety information to the sites via visits, e-mails, letters, etc
EPPV was introduced in October 2001.
Number of before-EPPV is based on 30 new active ingredients launched between Apr. 2000 and Mar. 2001.
Re-Examination

- **Aim:** reconfirmation of the clinical usefulness of drugs after approval

- **Timing of re-examination:** designated by the MHLW at the time of their approval as new drugs.
  - new drug substance: 8 years (maximum 10 years)

- **Surveys and studies required for reexamination applications:** in compliance with the GPSP, GCP or GLP depending on their objective
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Risk Management Plan in Japan (J-RMP)

- Notification
  - April 11, 2012: Guidance of J-RMP
  - April 26, 2012: Format of J-RMP
  - September 7, 2012: Q&A(1) of J-RMP
  - March 4, 2013: Publication of J-RMP
  - March 6, 2013: Q&A(2) of J-RMP
  - December 25, 2013: Q&A(3) of J-RMP
  - August 26, 2014: Guidance of J-RMP for generic drugs
Notification released on April 11, 2012, applying to all new drugs and follow-on biologics for which approval applications are submitted on or after April 1, 2013.
RMP guidance has been implemented since April 1, 2013.

In the revised Good Vigilance Practice (GVP) enforced on October 1, 2014, RMP is required as a condition for approval if necessary.
Drug risk should be managed based on RMP

What is RMP?

• A set of pharmacovigilance activities designed to minimize the risks of drugs based on the identified safety issues of individual drugs.

• The activities include investigations and information collection through use-results surveys and Early Post-marketing Phase Vigilance, etc., as well as additional information provision to healthcare professionals.

• Mandatory for new drugs and biosimilars/follow-on biologics, and for some of generic drugs.
Drug risk should be managed based on RMP

**Basic Points of J-RMP**

- Pharmacovigilance activities and risk minimization activities should be performed based on Safety Specification.
- RMP should be evaluated at respective milestones and the result should be reported to the PMDA.
- RMP should be revised based on the evaluation of RMP.
Scope of J-RMP

Development of the J-RMP should be considered at the following milestones:

• At the time of submission of approval application for new drugs and biosimilars

• At the time when new concerns regarding safety have been identified in the post-marketing phase

• At the time of submission of approval application for generic drug versions of the original drugs for which additional pharmacovigilance activities or additional risk minimization activities are being performed
RMP Conceptual Diagram

Safety Specification
- Important identified risks
- Important potential risks
- Important missing information

Need Additional Actions?

Yes

Pharmacovigilance and/or Risk Minimization activities

Additional
- EPPV
- Use-Results Surveys
- Specified Use-Results Surveys
- Post Marketing Clinical Trials

Routine
- Spontaneous report
- Study report
- Report of safety measures taken in overseas

Revise, if necessary

Pharmacovigilance plan

Risk Minimization plan
- Package insert
- Drug Guide for Patients

Evaluation of the Benefit/Risk balance

Etc.

- EPPV
- Provision of information to HCP
- Provision of information to patients,
  • Access Limitation

Etc.
Identification of “Safety Specifications”

- Important identified risks
- Important potential risks
- Important missing information

Safety Specifications
Important identified risks

• DEFINITION:
  • Risks for which the association with the drug is known

• EXAMPLES:
  ✓ Adverse reactions that occurred more significantly in the drug group in clinical studies
  ✓ Adverse reactions for which causal relationship is suggested by temporal relationship derived from many spontaneous reports
Important **potential** risks

**• DEFINITION:**

Risks for which the association with the drug has been suspected but not been sufficiently confirmed

**• EXAMPLES:**

- Adverse reactions that are predicted from the pharmacological effect of the drug, etc. but have not been clinically confirmed
- Adverse reactions that have been observed in the drugs of the same class with the same indications
Important **missing** information

• DEFINITION:
  Risks for which sufficient information has not been obtained to predict the safety

• EXAMPLES:
  ✓ Safety information in patient populations (e.g. elderly patients, patients with renal impairment or hepatic dysfunction, pregnant women, and pediatric patients) that are excluded from clinical studies but are expected to frequently use the drug in clinical settings
Safety Specification
- Important identified risks
- Important potential risks
- Important missing information

Pharmacovigilance and/or Risk Minimization activities

Need Additional Actions?

Yes

Routine
- Spontaneous report
- Study report
- Report of safety measures taken in overseas

Risk Minimization plan
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- EPPV
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Revise, if necessary
RMP Conceptual Diagram

Pharmacovigilance plan

Routine

• Spontaneous report
• Study report
• Report of safety measures taken in overseas

Risk Minimization plan

• Package insert
• Drug Guide for Patients
RMP Conceptual Diagram

Pharmacovigilance plan

- EPPV
- Use-Results Surveys
- Specified Use-Results Surveys
- Post Marketing Clinical Trials
  etc.

Risk Minimization plan

- EPPV
- Provision of information to HCP
- Provision of information to patients,
- Access Limitation
  etc.

Additional

- Uppsala
- Danish
- EPPV
Content of J-RMP

1. Summary of Risk management plan
   1.1 Safety specification
   1.2 Concerns for efficacy
2. Summary of pharmacovigilance plan
3. Summary of plans for surveillance and studies for efficacy
4. Summary of risk minimization plan
5. Lists
   5.1 A list of pharmacovigilance plan
   5.2 A list of plans on surveillance and studies for efficacy
   5.3 A list of risk minimization plan
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<th>PDF</th>
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<td>324</td>
<td>1. Risk Management Plan</td>
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<td>(Summary)</td>
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<td>(2) technetium (99mTc) hydroxymethylene phosphonate</td>
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<td>hydroxymethylene phosphonate injection</td>
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<td>3. List of Products Subject to Early Post-marketing</td>
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<td>Phase Vigilance (as of May 31, 2015)</td>
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Japanese version issued on: July 7, 2015
Information about the J-RMP (in English)

Content
- Summary
- Outline
- Related notice
- Message to HCP

Risk Management Plan (RMP)

Summary of Risk Management Plan (RMP)

In order to ensure the safety of drugs, it is important to assess measures for appropriate management of the risks of drugs at any time from the development phase to the regulatory review and the post-marketing phase. The RMP is a document which shows the consistent risk management of drug from the development phase to the post-marketing phase. And the RMP aims to be made evaluate the risk management at regular intervals or in response to the progress of post-marketing surveillance and a set of pharmacovigilance activities to minimize the risks of drugs. Sharing the published information among medical professionals is meant to ensure further enhancements of post-marketing safety measures.

Outline of the RMP

The RMP consists of the following three elements for individual drugs. 1) Safety specification: Important adverse drug reactions, which are clarified or suspected to the association with the drug, and important missing information. 2) Pharmacovigilance activities: Activities for collecting information which are performed in post-marketing. 3) Risk minimization activities: Activities for safety measures taken to
Publication of RMP (informed via e-mail)

【PMDAメディアナビ】

医薬品リスク管理計画の掲載のお知らせ
(2014/1/8配信)

本日、「医薬品リスク管理計画（RMP）について」のページを更新しましたのでお知らせします。
http://www.info.pmda.go.jp/rmp/rmp_index.html#select0

RMP提出品目一覧に、以下の医薬品のRMPを掲載しました。

■販売名：ケアラム錠25 mg
一般名：イグラチモド
製販業者：エーザイ株式会社

■販売名：コルベット錠25 mg
一般名：イグラチモド
製販業者：富山化学工業株式会社

RMPの詳細については、医薬品・医療機器等安全性情報No.300にも解説されていますのでご参照ください。

【医薬品・医療機器等安全性情報No.300】
http://www.info.pmda.go.jp/iyaku_anzen/file/PMDSI300.pdf#page=3

医療従事者の皆様におかれましては、RMPをご覧頂き、市販後の安全対策への更なるご協力をお願い申し上げます。
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Development and revision of RMP

Consultation → Discuss with review team → Revision as necessary

- New Drug Application
- Advisory committee
- Approval
- Launch

~ 300 days
30~ 60 days

Submission of draft RMP
RMP agreed with the review team
Submission of fixed RMP (1 month before launch)
PMDA consistently monitor the safety of drugs from the clinical stage to post-marketing stage with cooperation between Review team and Safety team.

- In PMDA, Risk manager system has been started since April 2010.
Roles and duties of Risk Manager

- For the continuous and comprehensive benefit-risk evaluation
  - Through life-cycle of product
    - From development stage to review period and post-approval stage
    - Integration of information of development and post-marketing stage

- Advise to developing product
  - To clarify the safety issues
  - To make safety measure before approval
  - To identify issues to collect post-marketing data
  - To avoid misuse
  - To make user friendly information (incl. labeling)

- Liaison between clinical development and post-marketing safety measures

- 13 Risk Managers in different disease areas

- **Risk Managers will be mainly in charge of RMP**
Composition of review team

RM$\cdot\cdot\cdot$
- are on the member of Safety Team.
- spend much time as a member of a Review Team.
- involve consultations of new drug development, safety evaluations of new drugs and considerations of package inserts and RMP.

Diagram:
- Director
- Review Director
- Team Head
- Risk Manager
- Quality
- Pharmacology
- Non-clinical
- Pharmacokinetics
- clinical
- Biostatistics
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Types of drugs requiring J-RMP

- Metabolic agents (Antidiabetic agents etc.) 22%
- Antineoplastic agents 20%
- Cardiovascular agents 8%
- Central nervous system agents 8%
- Biological agents 9%
- Others 15%
- Chemotherapeutics 9%

N = 64 (As of Nov 2014)
# Additional Risk minimisation measures

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<td>Communication to HCPs</td>
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<tr>
<td>Early Post-marketing Phase Vigilance</td>
<td>79%</td>
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<tr>
<td>Educational material</td>
<td>60%</td>
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<tr>
<td>Rapid release of information</td>
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<tr>
<td>Communication to Patients</td>
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<td>Educational material</td>
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<td>Restricted access</td>
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<td>Others</td>
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As of Mar 2015
### Additional Pharmacovigilance activities

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<tr>
<th>Additional Pharmacovigilance activities</th>
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<tr>
<td>Early Post-marketing Phase Vigilance</td>
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<tr>
<td>Use-results survey</td>
<td>56%</td>
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<td>Specified use-results survey</td>
<td>52%</td>
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<tr>
<td>Post-marketing clinical study</td>
<td>39%</td>
</tr>
<tr>
<td>Others*</td>
<td>4%</td>
</tr>
</tbody>
</table>

*PK/PD studies, Patient Registry etc.  

As of Mar 2015
Discussion point about Safety Specification

Examples:

- What is the difference between identified risks and potential risks?
- What is “important”?
- Are all patient population excluded from clinical study defined in “Important Missing Information”? 
Drug X is an oral glucose-lowering agent. Pregnant women were excluded from clinical trials.

- Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013 (published by the Japan Diabetes Society)
  “Insulin therapy should be given in pregnant women in whom the glycemic goals cannot be achieved with diet therapy alone. As the use of glucose-lowering agents is not recommended, they should be switched to insulin therapy. (grade A; consensus)”

- “Drug X” Package insert in Japan
  “Pregnancy: As the use of “Drug X” is not recommended in pregnant or possibly pregnant women, Insulin therapy should be given to them.”
Future Challenges in Pharmacovigilance activities

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We need to look for more efficient and meaningful Pharmacovigilance activities!
Future Challenges in Risk minimisation measures

We need to develop methodologies to evaluate effectiveness of risk minimization!
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Characteristics of J-RMP

- Optimal risk management and data collection
- Start to discuss at the submission of NDA
- Set up milestones
  - Obvious goal of surveillance
  - Revision of RMP by new information, if necessary
- Transparency among stakeholders
  - Overview of each RMP is published on PMDA website
- Information about the product is summarized briefly
Expected effects by RMP

- Regular evaluation of RMP
- Revision of contents of risk management
  - Comprehensive risk management through life-cycle of the product
    → Effective safety operations are expected!

- Sharing contents of risk management among the relative parties
  - MHLW/PMDA, MAHs, Healthcare professionals and patients
    → Effective risk communications are expected!
PMDA Website on safety information

Safety Alert & Recalls/ Review Reports/ Package Insert

The informations, such as Package Inserts(in Japanese), Review Reports etc., are available. Please click the following links and search button. Search system is provided in Japanese only.

- **Prescription Drugs**
  - The Yellow Letter / Blue Letter
  - Recalls(in Japanese)
  - PMDA Alert for Proper Use of Drugs
  - Revisions of PRECAUTIONS
  - Safety information announced by MHLW
  - PMDA Risk Communications

- **Medical Devices**
  - The Yellow Letter / Blue Letter(in Japanese)
  - Recalls(in Japanese)
  - Revisions of PRECAUTIONS(in Japanese)
  - Notification on Self-Check(in Japanese)
  - Safety information announced by MHLW(in Japanese)
  - MHLW Pharmaceuticals and Medical Devices Safety Information

- **Over The Counter/ Behind The Counter**
  - The Yellow Letter / Blue Letter
  - Review Reports(in Japanese)

- **In vitro diagnostics**
  - The Yellow Letter / Blue Letter(in Japanese)

- **Regenerative Medical Products(Cell and Tissue based Products)**
  - Package Inserts(in Japanese)
  - Review Reports
PMDA English Website


CLICK HERE!
Thank you!
E-mail: sato-junko@pmda.go.jp

For additional questions please click on “Contact us” on our English website.