Pharmacovigilance
- Regulatory perspective -

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Agenda

- Concept of Pharmacovigilance
- Current Regulation & Challenge in Japan
- Summary
  - What should we do?
Concept of Pharmacovigilance

Pharmacovigilance

- Not only post-approval …
  - Traditionally it focused on detection and evaluation of signals in post-approval
  - But now, it is defined to cover from pre-approval to post-approval by CIOMS VI
- Necessity from first in human until withdrawal through the lifecycle of drugs
  - Seamless transition from development stage to the post-approval period
Purpose of PhV

- To secure early detection of new adverse reactions or patients subgroups of exceptional sensitivity
- To introduce measures to manage those risks

Pharmacovigilance and Risk Management

- Post-approval phase is inseparable from development
  - Necessity of cooperation between development Div. and Pharmacovigilance Div.
- Approval is just ‘passing point’ of drug lifecycle
- Continuous Safety Specification from early development phase to post-approval is important.
- To consider how to manage the risks if they are identified.
- Don’t forget the possibility that more effective dosage might exist.
- The concept of CIOMSVI and DSUR must be useful tools on pharmacovigilance and risk management
What is lifecycle?

- Sales amount transition from launch until withdrawal

Sales amount transition from launch until withdrawal

Lifecycle Management in Medicinal Products

Execution and implementation of Strategy that maximizes sales,

To bring out a latent faculties,
To minimize risks,
To activate role of the drug in medical treatment, and to continue it
Lifecycle Management

- Concept of LM was occurred in marketing area
- To prolong lifecycle, it is important to keep share and to boost sales
- For the purpose, industry have to make efforts continuously

For well control of Lifecycle

- More effective
- Safer
- More convenient style to use
- To avoid misuse
proactive & preventive measurement

To measure after safety problems

Identify significant safety issues by clinical studies etc.
- Management of ADRs
- early detection of ADRs

Current Regulation & Challenge in Japan
Re-examination

- The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS, through collecting information on the efficacy and safety of the drug during a specified period of time after approval.

- The surveillance and studies required for reexamination applications must be performed in compliance with the GPMSP (GPSP), GCP or GLP depending on their objective.

- The timing when these drugs should be reexamined is designated by the MHLW at the time of their approval as new drugs.
  - Reexamination period of drugs containing new active ingredients: 8 years (maximum 10 years)

Early Post-Marketing Phase Vigilance: EPPV

Enforced on Oct 1, 2001

1. To ensure necessary information for appropriate use (contraindication, careful administration etc) is explained to the medical institutions 2 weeks before delivery.

2. To request medical institutions to use the drugs carefully and report serious ADRs, if occurred, immediately to pharmaceutical companies.

3. To request appropriate use and ADR reporting repeatedly to medical institutions for 6 months after delivery.
Number of reported ADRs of New Active Ingredients before and after the introduction of EPPV (average per month)

<table>
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<th>Months elapsed since launching</th>
<th>No. of reports before and after the introduction of EPPV</th>
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<td>Before (EPPV not introduced)</td>
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EPPV was introduced in October 2001.
Number of before-EPPV is based on 30 new active ingredients launched between Apr. 2000 and Mar. 2001.

PhV Plan and J-NDA

- Pharmacovigilance plan is a component of CTD (if the plan has been prepared)
  - PMDA recommend to prepare PhV plan until NDA submission through consultation

- PhV is an important discussion point under review
  - Description on review report

- Monitor and review the data
  - Submission of a local periodic report with PSUR
Risk management on review

- Brand name
  - To avoid misuse
- Package
  - To avoid misuse
- Risk communication tool
  - For healthcare professionals & patients
  - Package insert, leaflet, website … etc.

What do we consider in review?

- We hope for drugs which don’t have any ADRs, but all drugs have ADRs.
- We do not review the drug is dangerous or not.
- It is important that all stakeholders comprehend the character of the drug, including ADRs

Benefit / risk balance is key in review!
Appropriate measures in Japan

- Some situations are different between Japan and other regions
  - Medical practice
  - Medical Representatives (MR, sales and information distributor)

- What is appropriate measure for the drug in Japan?

What do we expect PMS?

- The concept is described in ICH-E2E
  - What is potential risk?
  - What is missing data? etc.

- We recommend the MAH to conduct meaningful PMS, but …
Zenrei-chosa

- Observational study of all cases
- A kind of Drug Use Investigation
- All cases of use over some period of time
- Number of cases and time period designed at the discussion with PMDA

New Initiative on the RMP in PMDA

- PMDA’s Office of Safety has launched a pilot program to establish a new drug safety measures
  - To monitor safety issues throughout the life-cycle of a drug
  - To accelerate PhV
  - To detect safety signal earlier
  - Prospect & Pre-avoid measurement
Expectations for new initiative

- Assessment of safety profile of drugs at development stage
  - Safety for subjects/patients
  - Preparation of post-marketing studies

- Assessment of safety profile of drugs NDA review stage
  - Agreement between PMDA and industry on details of post-approval surveys and clinical studies prior to the approval

Introduction of Risk Management System - Product Management -

- Purpose of RM System
  - PMDA will collect, compile, evaluate and manage all the safety information on new drugs from development to post approval stages to give guidance and advice to companies on PMS at early stage and in a timely manner.

- PMDA RM System will help the life cycle management of drugs in safety aspect
  - Identification safety specification from development stage
  - Guidance and advice on designing post-approval surveys, studies and other activities at review stage
  - Evaluation and advice on outcome and problems of post-approval surveys, studies and other activities etc

Tentatively called ‘Product Management’
Possible benefits of new risk management system

- Efficient preparation of effective PMS plan
- Consistent safety management throughout lifecycle both in PMDA and companies
- Preventing withdrawal of new drugs (at early stage)
- Completion of lifecycle of a drug
- Protection of patients especially at early stage of marketing

What should we do?
We should consider…

- What data are needed for more effective, safer and optimal use of the drug?
  - At each milestone of the development
  - Revised at that time, if necessary

- Which data should be collected early post-approval stage?

Minimize risk
Maximize benefit to patients

What should we do?
What can we do?

Integration • share • continuation!