Epidemiological review for pharmacovigilance planning in new drug application

Chieko Ishiguro, MPH
Office of Medical Informatics and Epidemiology (OME)
Pharmaceuticals and Medical Devices Agency (PMDA)
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to DIA, its directors, officers, employees, volunteers, members, chapters, councils, Communities or affiliates, or any organization with which the presenter is employed or affiliated.

These PowerPoint slides are the intellectual property of the individual presenter and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. DIA and the DIA logo are registered trademarks or trademarks of Drug Information Association Inc. All other trademarks are the property of their respective owners.
Take home messages

- Each safety issues could be sorted into routine PV and additional PV based on what should be known in post-approval.
- Single cohort studies (exposure registries) may be appropriate only for special occasions.
- A study is not generally required when there is no concern about lack of efficacy.
- There may be a possible that more than one studies are conducted per each product, but “Shiyoseiseki chosa” & “DB study” are not generally conducted for same research question in parallel.
1. The time has finally come?

2. Role of epidemiologists in NDA review ream

3. Notifications from MHLW/PMDA
The time has finally come?

Paradigm shift from a uniform single cohort study to customized/strategic pharmacovigilance (PV) planning
Contents

1. It’s time to enter a new era?

2. Role of epidemiologists in NDA review ream

3. Notifications from MHLW/PMDA
PV plan review timeline

- Submission
- Initial Meeting
- Review report 1
- Expert Meeting
- Review report 2
- Committee on Drug
- Approval

Safety issues needed for further evaluation in postmarking

Outline of PvP per each issue
- Routine/Additional
- RCT/Observational
- Primary data collection/DB
PV planning/review flow

Step 1. What should be know in post-approval?

Step 2. How to know it?

Step 3. Which pharmaceutical affairs frame must be complied with?

Step 4. Protocol details
Most RMPs in the current NDA packages…

All Safety issue

Routine PV & Additional PV = “Shiyoseiseki chosa” = Single cohort

One protocol
Step 1. What should be know in post-approval?

Clarification of a concern in post marketing per each safety

– Examples

◆ Potential risks --- causality
◆ Identified risks --- unknown risk factor
◆ Missing information × Identified risk --- potential risk factor
◆ Efficacy --- lack of efficacy
Step 2. How to know it?

Decision of appropriate method to address the concerns

– Signal level of the concerns?
  • If signal detection/strengthening level
    – Spontaneous report, etc
      (or database study for signal strengthening)
  • If signal strengthening/verification level
    – Observational study with Database
    – Observational study with primary data collection
    – Interventional study with primary data collection

Create a research question per each safety issue
Step 3. Which pharmaceutical affairs frame?

Chose the frame which must be complied with

- GVP: Routine PV, EPPV
- GPSP: Studies

Study frames in GPSP

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Observation</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary data collection</td>
<td>DB</td>
<td>Primary data collection</td>
</tr>
<tr>
<td>“Post marketing clinical trial”</td>
<td>“Post marketing database study”</td>
<td>“Drug use result survey”</td>
</tr>
</tbody>
</table>

There may be a possible that more than one studies are conducted per each product, but “shiyoseiseki chosa” & “DB study” are not generally conducted for same research question in parallel.
Inquiry from PMDA: Example 1

Per each safety issue, please explain the reason why an additional study is needed or not needed.
Inquiry from PMDA: Example 2

Per each safety issue, please explain the reason why a post-marketing database study is selected as an additional PV

Per each safety issue, please explain the reason why a primary-data-collection observational study (Shiyoseiseki chosa) is selected as an additional PV
Regarding the potential risk, the applicant mentioned that an observational study with single cohort design (Shiyo-seiseki chosa) as an additional PV is required. PMDA think that comparison group is required to evaluate the association between this drug exposure and the adverse event.

Please clarify the research question and explain why a single cohort design is selected.
Inquiry from PMDA: Example 4

It is required to select the most suitable database in each post-marketing database study with consideration of the possibility of the data acquisition about drug exposure and the outcome. Please explain the reason why the database is selected per each post-marketing database study.
Inquiry from PMDA: Example 5

PMDA think validation studies are needed for some safety issues for which post-marketing database studies are planned by applicants. Please explain the need and the plan for validation study per each safety issues.
Take home messages

- Each safety issues could be sorted into routine PV and additional PV based on what should be known in post-approval.
- Single cohort studies (exposure registries) may be appropriate only for special occasions.
- A study is not generally required when there is no concern about lack of efficacy.
- There may be a possible that more than one studies are conducted per each product, but “Shiyoseiseki chosa” & “DB study” are not generally conducted for same research question in parallel.