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Epidemiological review for pharmacovigilance planning in new drug application

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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

Contents

1. The time has finally come?
2. Role of epidemiologists in NDA review ream
3. Notifications from MHLW/PMDA

The time has finally come?

2005

2017

ICH E2E

Matured passive surveillance system

Databases

Accelerated innovative drug development

Japanese pharmaco-Epidemiologists

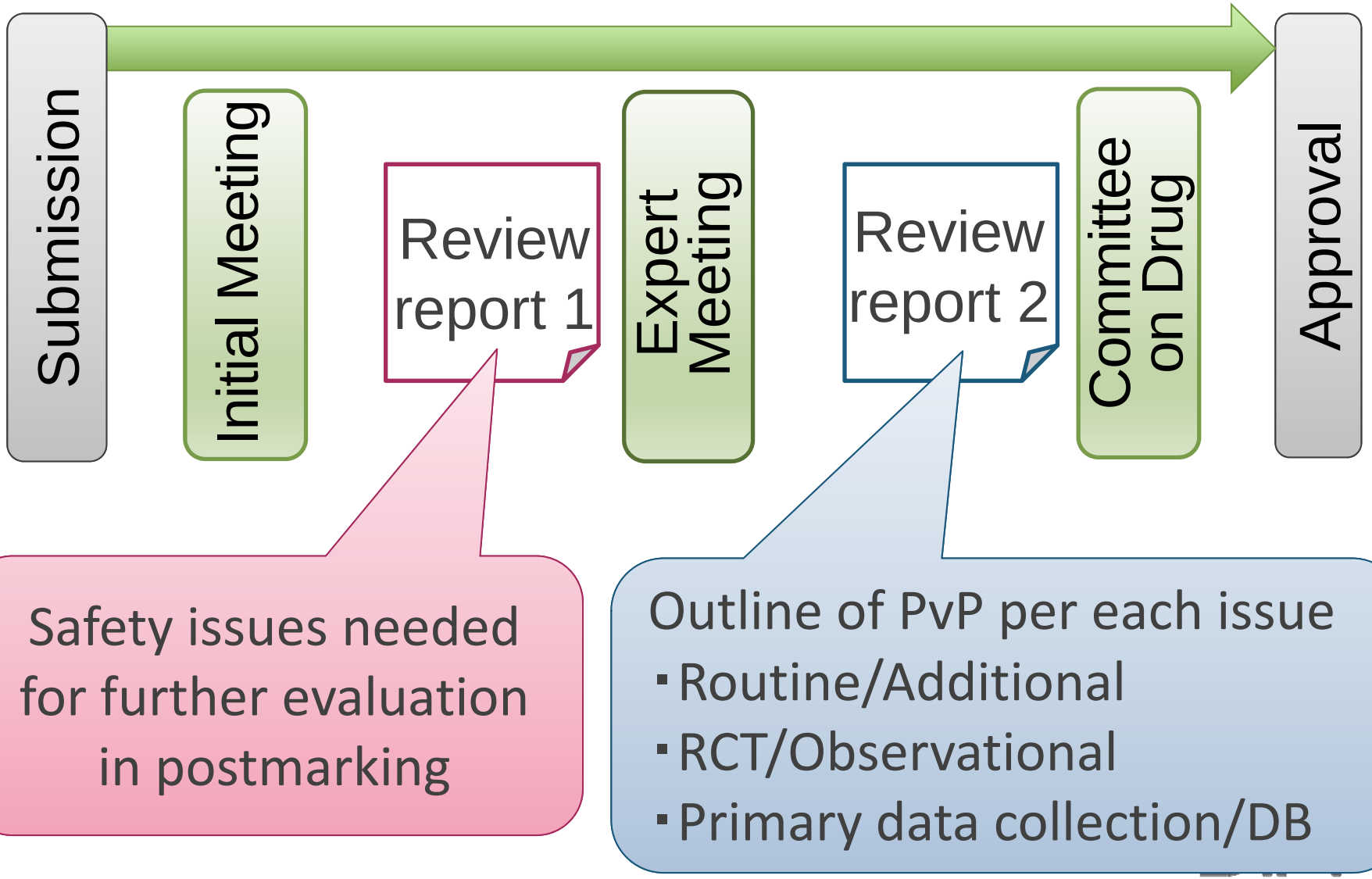
Amendment of the Ministerial Ordinance on GPSP

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

Contents

NDA review team member

PV plan review time line



PV planning/review flow

NDA review

After approval

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

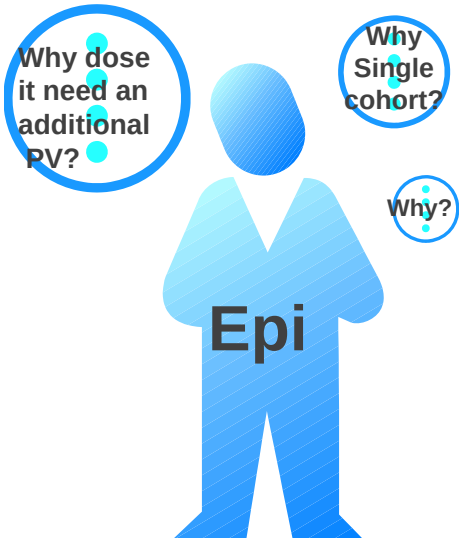
Step 2. How to know it?

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?

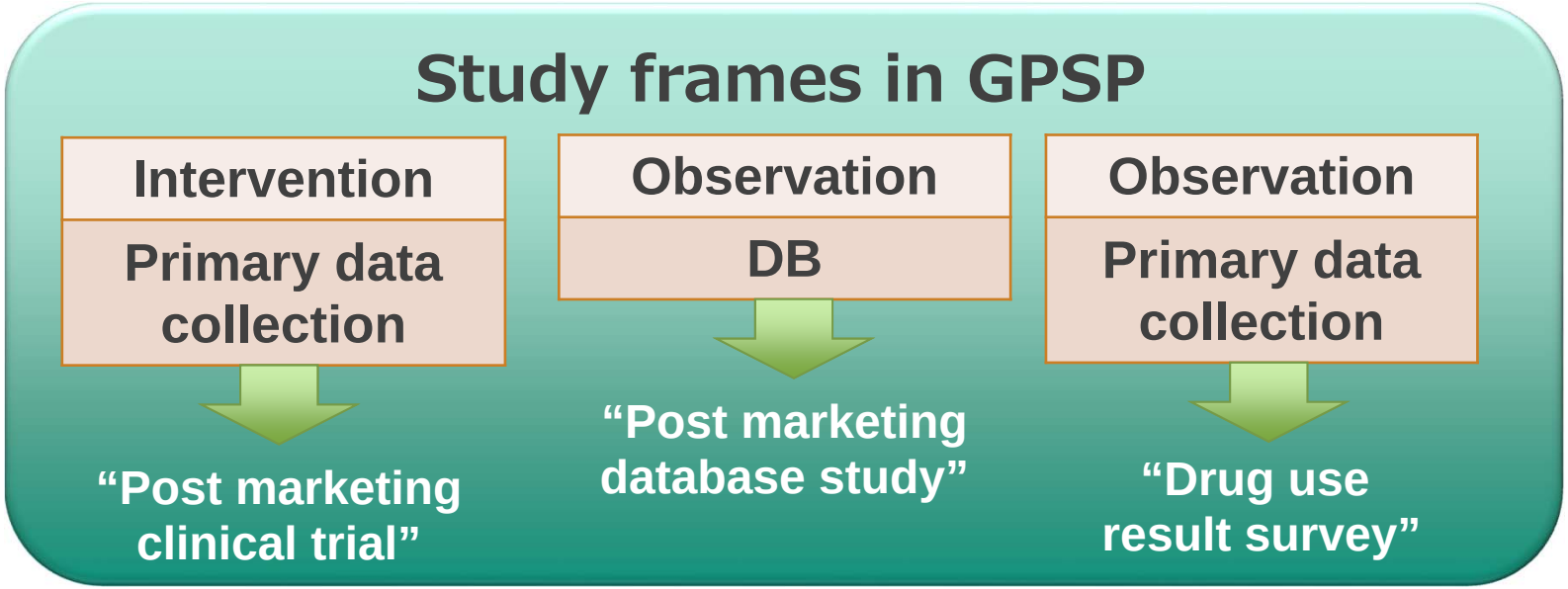
- Decision of appropriate method to address the concerns
  - Signal level of the concerns?
    - If signal detection/strengthening level
      - Spontaneous report, etc

      (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



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

Inquiry from PMDA: Example 3

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.

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Ask