Module 9: Risk Management

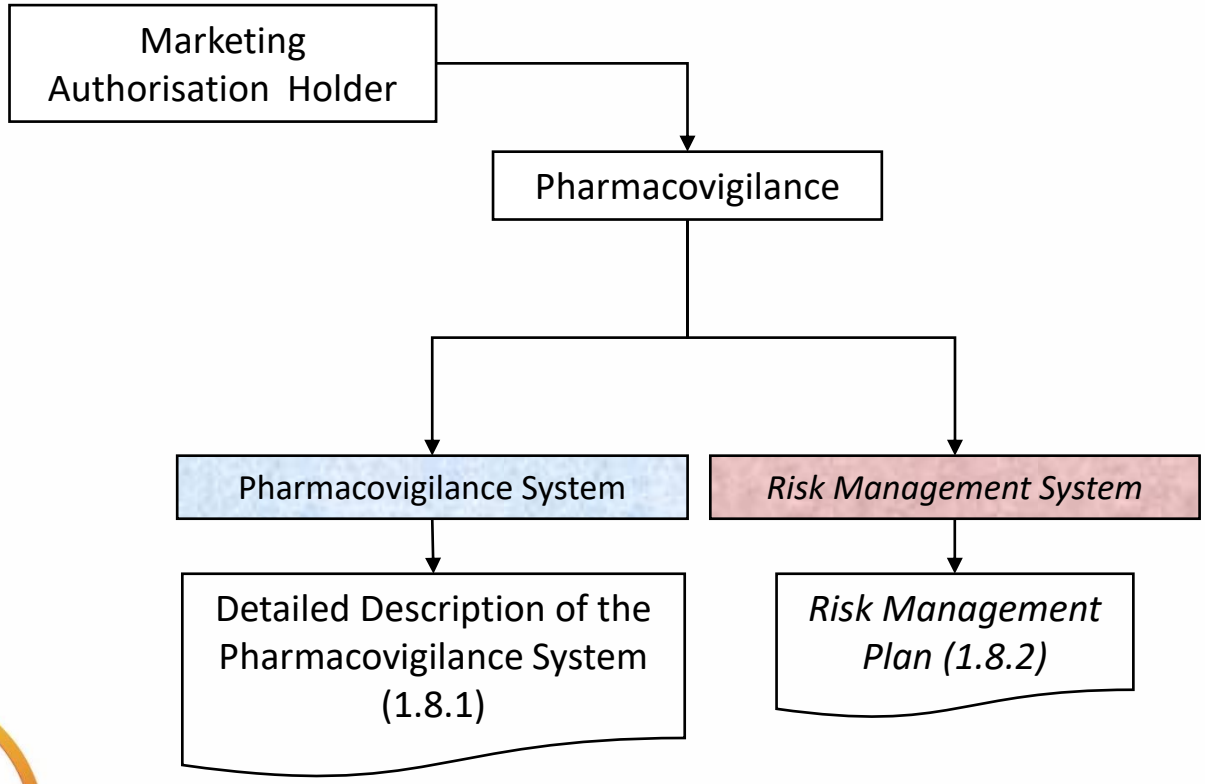
Risk Management

Risk management has three stages which are inter-related and re-iterative:

- Characterization of the safety profile
- Planning of pharmacovigilance activities to characterize risks and identify new risks
- Planning and implementation of risk minimization and mitigation and assessment of the effectiveness of these activities.

The purpose of risk identification and characterization is to allow for risk minimization or mitigation wherever possible.

MAH's post-marketing surveillance



Legislation

- Article 8 (3)(ia) of Directive 2001/83/EC requires the MAA to submit:

"a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce."

Guidelines

- ✓ Guideline on good pharmacovigilance practices (GVP) Module V: Risk management systems (Revision 2, dated February 2016)
- ✓ ICH Harmonized Tripartite Guideline: Pharmacovigilance Planning - E2E (2004)

Definition of risk

- The probable rate of occurrence of a hazard causing harm and the degree of severity of the harm.
- Harm: Physical injury and/or damage to health
- Risk can be defined in many ways:
  a. Exposure to a possibility of loss or damage.
  b. The quantitative or qualitative possibility of loss that considers both the probability that something will cause harm and the consequences of that something

Definition of Identified risk in Drug Safety

As per the GPVP Guidelines Module V

An **identified risk** *is*

- *"**An undesirable outcome** for which there is **sufficient scientific evidence** that it is caused by the medicinal product.*
- *In a clinical trial, the comparator may be placebo, active substance or non-exposure. Where an adverse event which is an identified risk for a comparator occurs at a similar (active comparator) or higher frequency with a new product, this suggests that the adverse event should also be an identified risk for the new product.*

Potential Risk in Drug Safety

A potential risk is defined as

*An **undesirable outcome** for which there is a **scientific basis for supposition of a causal relation** with the medicinal product (e.g. a signal, a class effect plausible also for the new product, findings from (non-) clinical studies) but where **there is insufficient support to conclude that there is a causal association***

Missing information in Drug Safety

- *Gaps in knowledge about a medicinal product, related to the anticipated utilisation patterns such as long-term use or use in particular patient populations, which could be clinically significant. For instance:*
  - *Safety profile with long-term use when there are suspected potential risks related to cumulative or long-term exposure;*
  - *Use is anticipated in populations not studied (e.g. pregnant women or patients with severe renal impairment) and the safety profile is expected to be different in these populations;*
  - *Off-label use is likely; if a markedly different safety profile than that in the target population is suspected, the specific safety concern that might be associated with off-label use should be specified rather than the global term 'off label use'."*

Safety Concerns

Safety Concerns are defined as:

Important identified risks, important potential risks and

missing information

RMP and REMS

- ✓ **Risk Management System**

A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions

- ✓ **Risk Management Plan**

A detailed description of the risk management system.

Requirement of RMP – when?

- ✓ At any time following a product's life cycle
- ✓ For all new marketing applications
- ✓ At the time of the renewal of the marketing authorization
- ✓ Significant change to an existing marketing authorization:
  - ➢ new dosage form;
  - ➢ new route of administration;
  - ➢ new manufacturing process of a biotechnologically-derived product;

When RMP: Contd

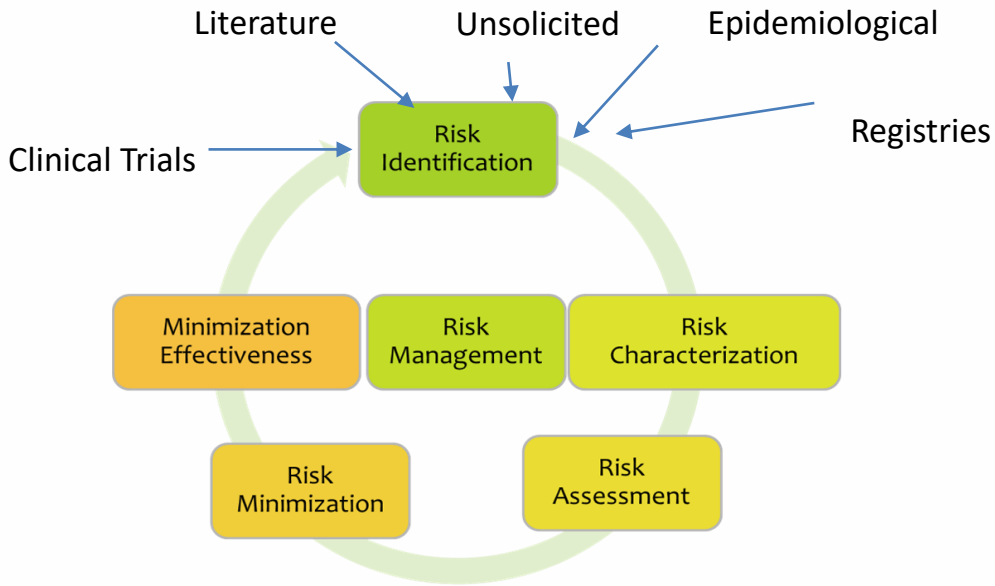
- pediatric indication;
- other significant change in indication

✓ at the request of the Agency (EMA) or national competent authority when there is a concern about a risk affecting the risk-benefit balance;

✓ with a submission of final study results impacting the RMP;

✓ with a PSUR, when the changes to the RMP are a direct result of data presented in the PSUR

Risk Management Cycle



ICH E2E Guidelines

ICH E2E guideline describes a method for:

- summarising the safety concerns,
  - including the potentially at-risk populations and
  - situations where the product is likely to be used that have not been studied pre-approval.
- It proposes:
  - A structure for a Pharmacovigilance Plan
  - sets out principles of good practice for the design and conduct of observational studies.
- It does not describe other methods to reduce risks from drugs, such as risk communication.

ICH E2E Guidelines

The guideline is divided into the following sections :

- Safety Specification;
- Pharmacovigilance Plan;
- Annex – Pharmacovigilance Methods.

- ICH-E2E defines two basic parts of a RMP : the safety specification and the pharmacovigilance plan.

Safety Specifications

The Safety Specification is:

- A summary of the safety concerns.
- It should also address the populations potentially at-risk (where the product is likely to be used),

and

- Outstanding safety questions which warrant further investigation to refine understanding of the benefit-risk profile during the post-approval period

Elements of Safety Specifications

Elements of Safety Specification: Non-Clinical

In this section, non-clinical safety findings that have not been adequately addressed by clinical data should be presented, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.);
- General pharmacology (cardiovascular, including QT/QTc interval prolongation; nervous system; etc.);
- Drug interactions;
- Other toxicity-related information or data.

Elements of Safety Specifications: Clinical

In This section, following information should be presented:

- Limitation of the human safety database
- The worldwide experience, including the extent of the worldwide exposure,
- Any new or different safety issues identified,
- Any regulatory actions related to safety, and
- Populations not studied in the preapproval phase

Elements SS: Identified Risks that required further evaluation

- In this section, detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product.
- This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available.
- Risk factors and potential mechanisms should be discussed.
- These AEs/ADRs should usually call for further evaluation as part of the PV Plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups, etc.).

Elements of SS: Potential Risks that required further evaluation

- Important potential risks should be described and the evidence that led to the conclusion that there was a potential risk should be presented.
- Identified and potential interactions, including food–drug and drug–drug interactions should be discussed with consideration of the evidence, and potential health risks posed for the different indications and in the different populations should be discussed.

Elements of SS: Epidemiology

- The epidemiology of the indication(s) should be discussed including incidence, prevalence, mortality and relevant co morbidity and should take into account whenever possible stratification by age, sex, and racial or ethnic origin.

- Differences in the epidemiology in different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), if this information is available.

- For important AEs that may require further investigation, it is useful to review the incidence rates of these events among patients in whom the drug is indicated (i.e., the background incidence rates).

Elements of SS: Pharmacological Class Effects

To identify risks believed to be common to the pharmacological class.

Pharmacovigilance Plan: I

The pharmacovigilance plan:

• Should be based on the safety specification and developed by the sponsor.

•It can be discussed with regulators

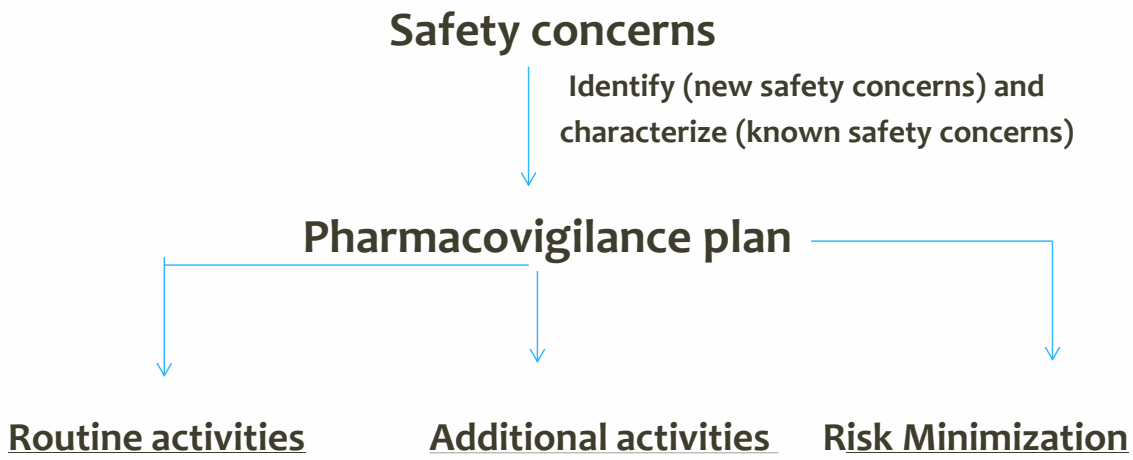
- During product development,
- Before approval of a new product (i.e., when the marketing application is submitted), or
- When a safety concern arises post-marketing.

- It can be a stand-alone document.

Pharmacovigilance Plan: II

- For products for which no special concerns have arisen:
  - Routine pharmacovigilance should be sufficient for post approval safety monitoring, without the need for additional actions (e.g., safety studies).
- For products with important identified risks, important potential risks, or important missing information:
  - Additional actions designed to address these concerns should be considered.

Pharmacovigilance Plan



Risk Minimization Measures

Summary of the Activities in the RMP

- Overview of disease epidemiology
- Summary of benefits/efficacy and uncertainties
- Summary of safety concerns (including preventability)
- Summary of risk minimization measures by safety concern – Routine & additional measures
- Planned post-authorization development plan
  - Studies which are a condition of MA
- Summary of major changes to RMP over time
- Written in lay scientific language

Updates to a RMP

- ✓ Significant change to the benefit-risk balance
- ✓ At the request of the Agency or a national competent authority
- ✓ Whenever the risk management system is modified
- ✓ When submitting a PSUR

Any Questions?

Thanks