The Risk Management Plan

EMA Good Pharmacovigilance Practice
Module V: Risk Management Systems

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Guideline on good pharmacovigilance practices (GVP)

Module V – Risk management systems (Rev 1)

Definition

- A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, and the assessment of the effectiveness of those interventions
- RMPS are required for:
  - All new active substances
  - Significant changes to marketing authorisations
  - When an unexpected new hazard is identified
  - When requested by the Regulatory Authority

Identified Risk

- An untoward occurrence for which there is adequate evidence of an association with the vaccine of interest..
  - An AE demonstrated in non-clinical studies and confirmed by clinical data
  - An AE associated with clinical studies or epidemiological studies for which the magnitude of the difference with a comparator group suggests a causal relationship
  - An AE suggested by spontaneous reports for which the evidence suggests a causal relationship.- eg anaphylactic reaction or site reactions

Potential risk

An untoward occurrence for which there is a basis for suspicion of an association with the vaccine of interest but this association has not been confirmed

- Toxicological findings seen in non-clinical safety studies which have not been observed in clinical studies
- AEs observed in clinical trials where the magnitude of difference between the comparator group raises suspicion of an association but is not significant enough to suggest a causal relationship
- A population that has had no or limited exposure to the vaccine due to exclusion criteria in the clinical trial (eg pregnant women, patients with underlying defined conditions excluded from the trial)
- AEs arising from spontaneous reporting

Objectives of the RMP

- To specify what is known and not known about the safety of the product at the time of authorisation
- To make a plan with milestones indicating how safety knowledge will be extended post-authorisation
- To define the necessary measures to minimise known risks and monitor the success of these measures
- To document post authorisation obligations

Content of the RMP (EU)

- The RMP is in 7 parts:
  - Part I - Product Overview
  - Part II - Safety specification
  - Part III - Pharmacovigilance plan
  - Part IV - Plans for post authorisation efficacy studies
  - Part V - Risk Minimisation measures
    - including an assessment of effectiveness
  - Part VI - Summary of the RMP
  - Part VII - Annexes

Content of the RMP

- Safety Specification summarises:
  - Known safety profile of the product including exposure data from clinical trials and post authorisation use
  - Epidemiology section on the target population and relevant co-morbidities in this population
  - Populations not studied in clinical trials
  - Identified and potential risks
  - A summary of the safety concerns

Content of the RMP (EU)

- Pharmacovigilance plan documents product specific PV measures that relate
  - to potential risks outlined in the safety section
  - to extending the safety profile of the product

This should cover for example
- methods used to monitor specific risks
- studies designed to extend safety knowledge
- epidemiological studies and pre-clinical studies if appropriate

Content of the RMP (EU)

- Risk Minimisation
  - Describes measures taken to reduce risks mentioned in the safety section
  - If no risk minimisation activities are intended then justification that they are adequately covered in routine elements is required..eg
    - Summary of Product Characteristics
    - Product Information leaflet
    - Routine PV

What is included in the Safety Specification?

- The initial RMP should contain
  - Expected usage patterns
  - Projected population exposure
  - Projected markets
- Updates to RMP should contain
  - actual post authorisation data
  - Any regulatory actions taken (worldwide)
  - Any new safety issues

What is included in the product specific Pharmacovigilance Plan?

- Summaries of completed studies since the last RMP update (as defined in the Safety section)
- Summary ongoing studies should include relevant:
  - protocols and protocol amendments
  - contracts with external organisations
  - Interim reports that have been provided to relavnt authority(s)
  - Procedures are in place for notification of Adverse Events

What is included in the Risk Minimisation plan?

- Should contain:
  - Criteria for verifying the success of proposed risk minimisation measures
  - Proposed review periods of the measures
  - A summary of any relevant reports that have been generated (which should be provided on request to inspectors)

Common issues with RMPs (MHRA)

- Tend to focus more on what is known rather than identifying areas where information is lacking
- The relevance of the epidemiology to the target population is often not sufficiently considered
- The PV plan often emphasises routine PV rather than focusing on product specific measures
- Insufficient time is allowed to develop study protocols
- Justification is often not provided by MAH when it considered that extra measures were not required in the risk-minimisation section
- Plans for monitoring success of RMPs is often lacking

In Summary a Risk Management Plan…….

Outlines the risk management system for a medicine once it is available for use

Comprises:

- Known safety profile
- Identified and potential safety concerns and where appropriate how they will be mitigated
- Missing safety information where this is known or can be predicted and how this will be managed

Focuses on:

- Monitoring – Pharmacovigilance Plan
- Minimising risks associated with the use of the product – Risk Minimisation Activities

Provides:

- Coverage of the life cycle of the product
- Assurance that all risks related to the use of a medicine have been considered and acted upon