EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# GVP Risk Management Systems

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# Risk Management - EU legal basis

Introduced with the revised EU Legislation that came in to force in 20th November 2005

- Article 6 of Regulation (EC) No 726/2004 and Article 8 (3)(ia) of Directive 2001/83/EC, as amended lay down the particulars and documents to be included in an application for the authorisation of a medicinal product for human use:

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

# ...and then in 2010

Directive 2010/84/EU of the European Parliament and of the council of 15 December 2010 *amending*, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

Regulation (EU) No 1235/2010 of the European Parliament and of the council of 15 December 2010 *amending*, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products.

**A New Gold Standard**

# Impact of EU legislative changes

- ✓ Enforced legal basis
  - ✓ RMP describing the RMS required for all new MAA
  - ✓ Operation of a RMS may be imposed in PM phase if there are concerns
- ✓ Focus is on planning – prospective, dynamic and risk proportionate
- ✓ Key role of PRAC in relation to RMP
- ✓ PASS/PAES are integrated elements and may be a condition of MA
- ✓ Summary of the RMP to be made public
- ✓ Enhanced requirement to monitor the effectiveness of risk minimisation

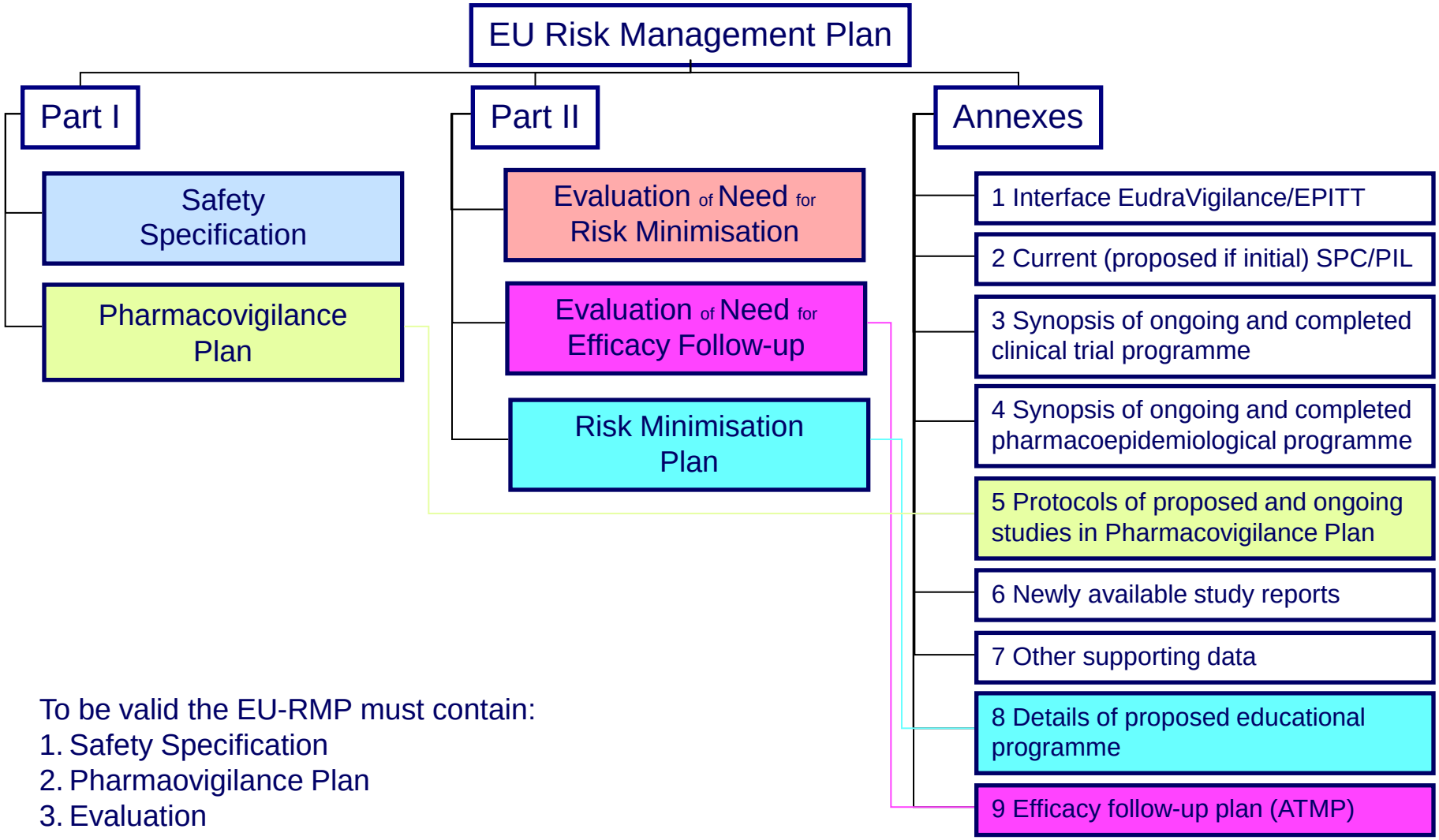
# Principles

- IM very high level
- Detail in GVP Module
- Aligned with ICH E2E
- Keep what has worked, change  the less good

# Risk Management Plan – purpose

- Describe what is known and not known about the safety profile of a medicine
- Plan how to characterise further the safety profile of the medicine
- Put in place measures to prevent or minimise risks associated with the product and assess the effectiveness of those interventions
- Document the need for efficacy studies and maximise the benefit risk balance of the product for the individual patient and for the target population as a whole and to facilitate integration of benefit risk planning.

# The current EU-RMP template




To be valid the EU-RMP must contain:

1. Safety Specification
2. Pharmaovigilance Plan
3. Evaluation

# Proposed EU-RMP Structure

| | |
|---|---|
| Part I | **Product Overview** |
| Part II | **Safety Specification**<br>Module SI Epidemiology of indication and target population<br>Module SII Non-clinical part of Safety Specification<br>Module SIII Clinical trial exposure<br>Module SIV Populations not studied in clinical trials<br>Module SV Post-authorisation experience<br>Module SVI Additional EU requirements for Safety Specification<br>Module SVII Identified and potential risks (non-ATMPs)<br>Module SVIIa Identified and potential risks (ATMPs)<br>Module SVIII Summary of safety concerns |
| Part III | **Pharmacovigilance Plan** |
| Part IV | **Plans for studies on effectiveness and long term efficacy** |
| Part V | **Risk Minimisation Measures** |
| Part VI | **Summary of the EU-RMP** |
| Part VII | **Annexes** |

# Requirements in specific situations

- Normally all parts of an EU-RMP should be submitted.
- In certain circumstances, in line with the concept of proportionality, certain parts or modules may be omitted *unless requested otherwise by the competent authority*.
- Any safety concerns identified in a reference medicinal product should be included in the generics RMP in Module SVIII unless clearly no longer relevant.

# Part II - Safety specifications

Module SI - Epidemiology of the indications and target population (section 1.7)

Module SII: Non-clinical part of the safety specification (section 1.1)

Module SIII: Clinical trial exposure (section 1.2)

Module SIV: Populations not studied in clinical trials (section 1.3)

Module SV: Post authorisation experience (section 1.4)

Module SVI: Additional EU requirements for Safety Specification (section 1.9)

Module SVII: Identified and potential risks (section 1.5, 1.6 & 1.8)

Module SVIII: Summary of the safety concerns (section 1.10)

# Part II - Module SVII: Identified and potential risks

## Suggestion for structuring risks (if needed)

- Risks relating to active substance
- Risks related to specific formulation or route of administration
- Risks relating to specific target population
- Risks relating to switch to non prescription status

# Part III: Pharmacovigilance Plan

- Clarification of what Pharmacovigilance Plan is for:

The identification of new safety concerns
Further characterisation of known safety concerns including risk factors
Investigation of whether a potential risk is real or not
How important missing information will be sought

- Specific AR Follow up questionnaires are considered routine PhV
- Action plan for safety concerns with additional PhV
- Summary table of additional PhV activities including expected dates of milestones
- For class effects MAHs may be asked to conduct joint studies
- Include additional PhV activities requested by individual MSs

# Part IV: Plans for long term efficacy and effectiveness follow up (I)

- Long term follow up of efficacy required in legislation for paediatric medicines and ATMP

- The new PhV legislation provide the legal basis for requiring post authorisation efficacy studies for products

  - where there are concerns about efficacy in everyday medical practice or

  - when knowledge about the disease or the clinical methodology used to investigate efficacy indicate that previous efficacy evaluations may need significant revision

# Part IV: Plans for long term efficacy and effectiveness follow up (II)

- ✓ Summarise efficacy and basis of this – ie studies and endpoints (1 page maximum)

- ✓ The following areas should be discussed briefly and the need for further studies post authorisation evaluated:

    - ✓ applicability of the efficacy data to all patients in the target population
    - ✓ factors which might affect the effectiveness of the product
    - ✓ variability in benefits of treatment for sub populations

- ➢ Guidance on post authorisation efficacy studies is being draft

# Part V: Risk minimisation plan

- Needed for all products
- May need more than one
  - Multiple legal status
  - Cross therapeutic areas
  - Different risks for difference target populations
- Clarification of what is routine risk minimisation
- Justify any proposals for additional risk minimisation
- Educational materials:
  - Non promotional
  - Advice to consult communication experts, patients and HCP
  - Similar layout and content may be requested
  - Final version approved by NCA

# Part VI - Public Summary of the EU-RMP

- To be made public at European Web Portal
- Written for lay reader
- Includes information on
  - Disease epidemiology
  - Summary of risks put in context of benefits
  - Summary of safety concerns
  - Summary of risk minimisation activities
  - Plans for post-authorisation pharmacovigilance (PASS), effectiveness and long-term efficacy (PAES)
- Linked with list of medicinal products subject to additional monitoring according to Article 23(3) of Regulation 726/2004 *as amended*

# Summary of the RMP: Preliminary ideas

- One size unlikely to fit all!
- Still have “summary table” in the EPAR
- Public Summary of the RMP aimed at lay people
- Planned consultation in May with stakeholders –including patients and HCPs

# Summary of the RMP: Preliminary ideas

- Based on parts of SI, SVIII, Part IV, Part V
- Provide context of risks
  - ✓ Overview of disease epidemiology, expected benefits and where medicine fits into therapeutic armamentarium
- Summary of safety concerns in lay language
- Planned post-authorisation efficacy and pharmacovigilance studies
- Summary of safety concerns and risk minimisation activities

# Conclusions

- Substance specific
- Safety specifications organised in modules to increased flexibility
- Activities proportional to risks
- Plans for studies on effectiveness and long term efficacy follow-up
- Justification for additional risk minimisation activities
- Risk minimisation plan for all products
- Summary of the EU-RMP: Publicly available and written in lay language

Thank you