Federal Agency for Medicines and Health Products (FAMHP)

RISK MANAGEMENT SYSTEM

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Agenda

- Introduction
- RMP purpose
- Structure of the RMP
- PART III: Section Additional pharmacovigilance (safety) activities PASS
- Part IV: Plans for post-authorisation efficacy studies PAES
- The relationship between the RMP and the PSUR
- When a risk management plan should be submitted?
- Conclusion

INTRODUCTION

Guideline on good pharmacovigilance practices

GVP Module V Risk Management Systems (Draft)

EMA/838713/2011

Adheres to the principles in the ICH E2E on Pharmacovigilance Planning

Main RMS items in PhV legislation

- **RMP will be required for all new applications**
- **RMP should be proportionate to risks**
- **Key role of PRAC in relation to RMP**
- **PASS may be condition of MA**
- **PAES may be condition of MA**
- **Summary of the RMP to be made public**
- **Enhanced requirement to monitor the effectiveness of risk minimisation**

INTRODUCTION

Risk Management System

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions [DIR Art 1(28b)]

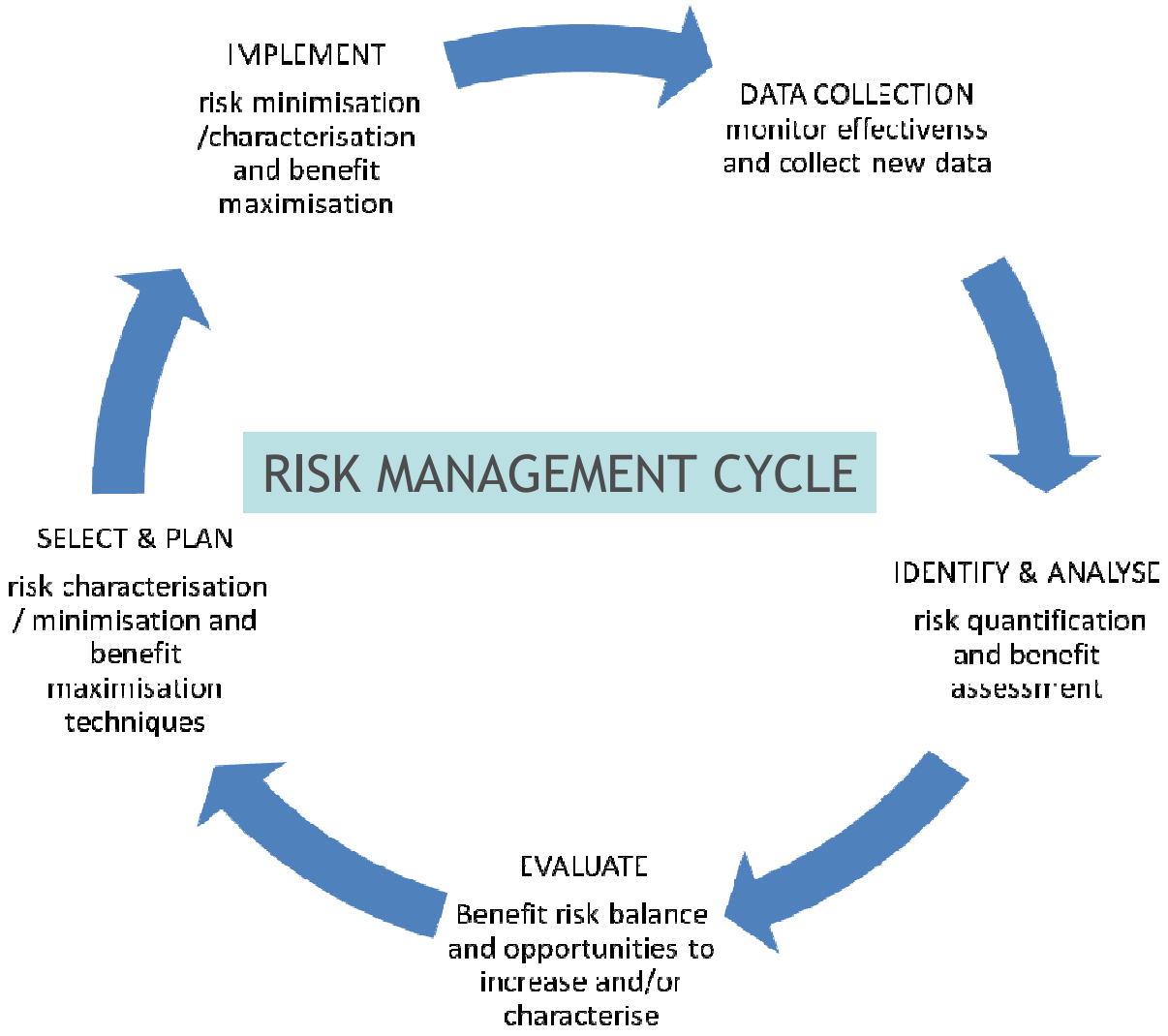
Risk Management Plan

A detailed description of the risk management system [DIR Art 1(28c)]

Risk Minimisation Activity (risk minimisation measure)

A public health intervention intended to prevent or reduce the probability of the occurrence of an adverse reaction associated with the exposure to a medicine or to reduce its severity should it occur

INTRODUCTION



RMP Purpose

The content of RMP must:

- Identify or characterise the safety profile of the medicinal product(s) concerned

- Indicate how to characterise further the safety profile of the medicinal product(s) concerned

- Document measures to prevent or minimise the risks associated with the medicinal product including an assessment of the effectiveness of those interventions

- Document post-authorisation obligations that have been imposed as a condition of the marketing authorisation

RMP Purpose

- Describe what is known and not known about the safety profile of the concerned medicinal product(s)

NEW !!

- Indicate the level of certainty that efficacy shown in clinical trial populations will be seen in everyday medical practice and document the need for studies on efficacy in the post-authorisation phase

- Plan how the effectiveness of risk minimisation measures will be assessed

Structure of the RMP

The RMP is a ***dynamic***, stand alone document which should be updated throughout the life-cycle of the product

For products requiring periodic safety update reports (PSURs), certain (parts of) modules may be used for both purposes

Structure of the RMP

Current RMP structure

Part I

Safety Specification

Pharmacovigilance Plan } ICH E2E

Part II

Evaluation of the need for risk minimisation activities,

if a need for additional activities

- **Risk minimisation plan**

RMP structure in IM

Part I	Product(s) Overview
Part II	Safety Specification
Part III	Pharmacovigilance Plan
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk Minimisation Measures
Part VI	Summary of the RMP
Part VII	Annexes

Structure of the RMP

Part II: Safety specification (S.S.) 8 Modules:

Module SI: Epidemiology of the indication(s) and target population(s)

Module SII: Non-clinical part of the Safety Specification

Module SIII: Clinical trial exposure

Module SIV: Populations not studied in clinical trials

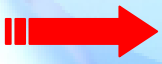
Module SV: Post-Authorisation Experience

Module SVI: Additional EU requirements for the S.S.

Module SVII: Identified and potential risks

Module SVIII: Summary of the safety concerns

Structure of the RMP



S1: Epidemiology of the indication(s) and target population(s).

SII: Non-clinical part of the Safety Specification

SIII: Clinical trial exposure

SIV: Populations not studied in clinical trials

SV: Post authorisation experience

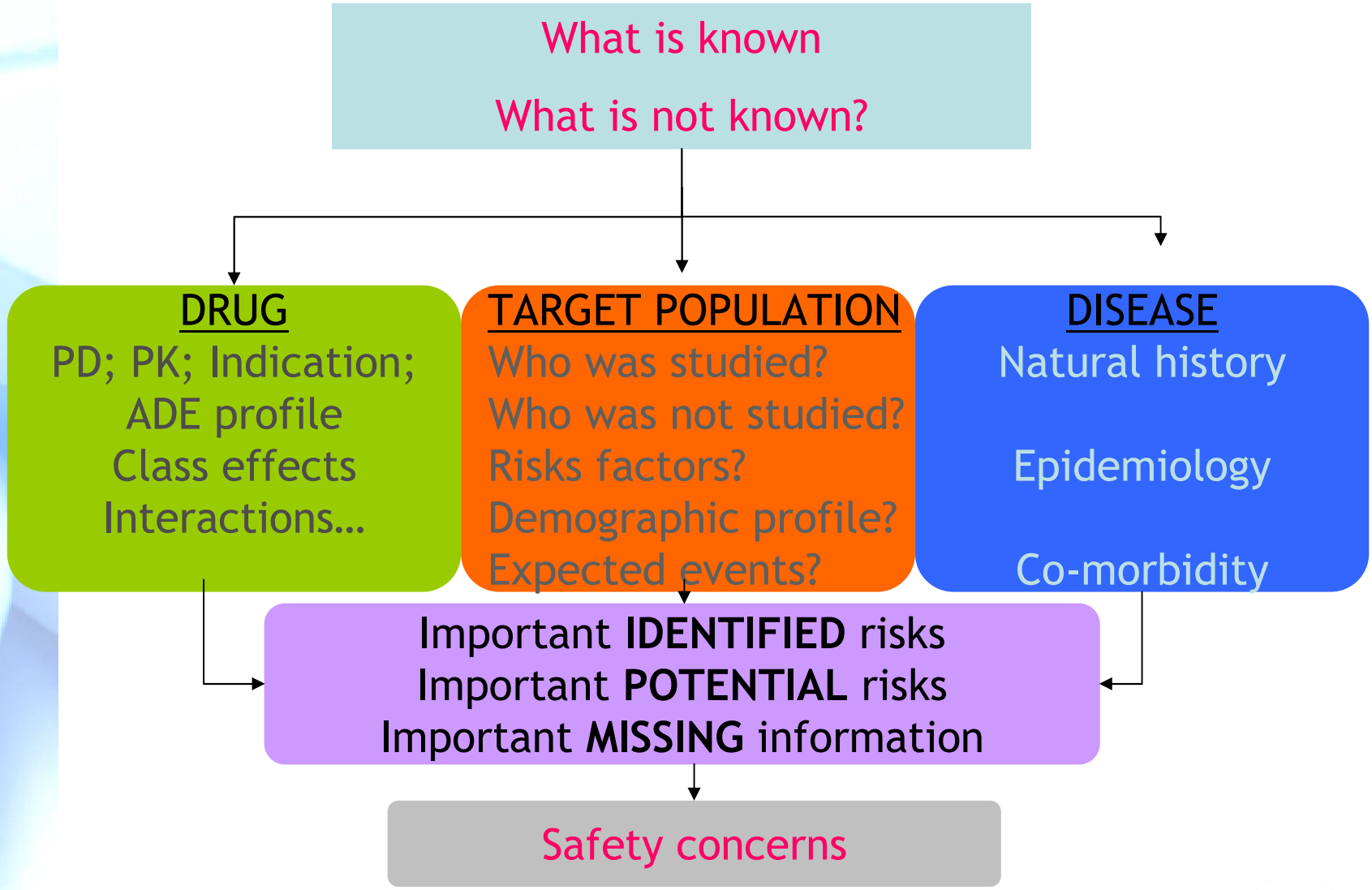
SVI: Additional EU requirements for the S.S.

SVII: Identified and potential risks

SVIII: Summary of the Safety Concerns

- Non clinical
- Limitations of the human safety database
- Populations not studied in the pre-authorisation phase
- Post marketing experience
- Adverse events/adverse reactions
- Identified and potential interactions with other medicinal products, food and other substances
- Epidemiology of the indications and important adverse events
- Pharmacological class effects
- Additional EU requirements
- Summary – ongoing safety concerns

RMP Safety specification



Adapted from Rubino & Goedecke Risk Management : Safety specification. EMA Risk Management

RMP Safety specification

SIV: Patients not studied in clinical trials

Paediatric population (<18 Y)

- Age categories : Children from birth to 18 years with consideration given to the different age categories as per ICH-E11

Elderly population (> 65 Y)

- Effect of multiple impairments and multiple medications
- ADRs of special concern in elderly – dizziness, CNS

Pregnant ; breast-feeding women

Patients with hepatic/renal impairment

Patients with other relevant co-morbidity: CV,

Immunocompromised including organ transplant patients

Specific genetic markers

Patients of different ethnic origins (implications on efficacy, safety, PK in the target population)

RMP Safety specification

SV: Post-authorisation experience

Provide information on the number of patients exposed post authorisation

How the medicinal product has been used in practice?

- Special populations mentioned in RMP module SIV
- The number of patients included in observational studies
- Regulatory action taken to update information on the safety of the medicinal product

RMP module SV section "Indicated use versus actual use"

For updates to the safety specification:

How the actual pattern of exposure has differed from that predicted in RMP module SVII (identified/potential risks), and from the indication(s) and CI in the SmPC (off-label use);

Information from drug utilisation studies (or other observational studies where indication is included) should be included here including drug utilisation studies which have been requested by national competent authorities for purposes other than risk management;

Off-label use, includes, amongst others, use in non-authorised paediatric age categories, and use in other (non EU-authorised) indications outside of the clinical trial setting;

When there has been a concern raised by the competent authorities regarding off-label use, marketing authorisation holders should attempt to quantify such use along with a description of the methods used to arrive at these figures.

RMP Safety specification

SVI: Additional EU requirements for the safety specification

Some safety issues were not included in ICH-E2E but are thought to be of particular interest due to either EU legislation or prior experience of a safety issue

Potential for harm from overdose
Potential for transmission of infectious agents
Potential for misuse for illegal purposes
Potential for medication errors
Specific paediatric issues
- Issues identified in Paediatric Investigation Plans
- Potential for paediatric off label use

Projected post-authorisation use
Potential for off label use

PART III: Section Additional pharmacovigilance safety activities PASS

Particular situations with post authorisation safety studies PASS

- Drug utilisation studies
- Joint studies
- Registries

PART III: Section Additional pharmacovigilance safety activities PASS

Particular situations with post authorisation safety studies PASS

Drug utilisation studies

May be requested by NCA to monitor drug usage in their country (often in relation to reimbursement discussions)

However, although they may not collect safety data, they can provide useful information on whether risk minimisation activities are effective and on the demographics of target populations

Theses studies:

- should be identified to the Rapporteur/RMS pre-opinion and included in the pharmacovigilance plan
- If requested post-authorisation by authorities not involved in medicinal product licensing ⇨ the studies should be included in the next update to the RMP

PART III: Section Additional pharmacovigilance safety activities PASS

Particular situations with post authorisation safety studies PASS

Joint studies

- If safety concerns apply to more than one medicinal product;
- Limited patients (rare diseases);
- Rare adverse reaction

In some circumstances, the requirement to do joint studies may relate to a single active substance where there are multiple marketing authorisation holders for the same active substance

PART III: Section Additional pharmacovigilance safety activities PASS

Joint studies

NCA or the EMA shall, following consultation with the PRAC, encourage the MAHs concerned to conduct a joint PASS [DIR Art 22a(1), REG Art 10a(1)]

The NCA or the EMA should facilitate the agreement of the concerned MAHs in developing a single protocol for the study and conducting the study

The NCA/EMA will propose a core protocol if failure by MAHs to agree joint study

PART III: Section Additional pharmacovigilance safety activities PASS

Particular situations with post authorisation safety studies PASS

Registries

Registries : non-interventional cohort studies

Disease registry will usually be more suitable than a registry confined to a specific product

However, if, as part of an agreed RMP, the MAH institutes a registry, the protocol for the registry will allow all patients who are prescribed the active substance or who have the same disease, as appropriate, to be entered in the registry

Entry to the registry should not be conditional on being prescribed a product with a particular invented name or marketing authorisation holder unless there are clear scientific reasons for this.

One registry regardless of which brand of drug prescribed

Part IV: Plans for post-authorisation efficacy studies

Efficacy in legislation for paediatric medicines and ATMP:

- *applications for a MA that include a paediatric indication;*
- *applications to include a paediatric indication in an existing marketing authorisation;*
- *application for a paediatric use MA;*
- *advanced therapy medicinal products (ATMP).*

Ability to require post-authorisation efficacy studies in new PhV legislation

Logical extension of pharmacovigilance planning

PAES for products where there are concerns about efficacy which can only be resolved after the product has been marketed, 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 post-authorisation efficacy studies

The following areas should be discussed:

- Applicability of the efficacy data to all patients in the target population;
- Factors which might affect the efficacy of the product in everyday medical practice;
- Variability in benefits of treatment for sub-populations.

Updates RMP: data which impacts on efficacy should be mentioned

Summary table showing an overview of the planned studies together with timelines and milestones; draft protocols for these studies (annex 7)

The relationship between the RMP and the PSUR

PSUR : post-authorisation risk benefit assessment
RMP: pre-and post-authorisation risk-benefit management and planning
=> the two documents are complementary

When a PSUR and a RMP are to be submitted together, the RMP should reflect the conclusions of the accompanying PSUR

For example if a new signal is discussed in the PSUR and the PSUR concludes that this is an important identified or important potential risk, this risk should be included as a safety concern in the updated RMP submitted with the PSUR. The pharmacovigilance plan and the risk minimisation plan should be updated to reflect the marketing authorisation holder's proposals to further investigate the safety concern and minimise the risk.

The relationship between the RMP and the PSUR

RMP section	PSUR section
Sub-section of part I – "Product overview"	Section 2 – "Worldwide marketing approval status" and EU marketing approval status included in the EU Regional Appendix
Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason"	Section 3 – "Actions taken in the reporting interval for safety reasons"
Part II, module SV – "Post-authorisation experience", section "Non-study post-authorisation exposure"	Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"
Part II, module SVIII – "Summary of the safety concerns" (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)	Sub-section 16.1 – "Summary of safety concerns"
Part II, Module SVII – "Identified and potential risks"	Sub-section 16.4 – "Characterisation of risks"
Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"	Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"

When a risk management plan should be submitted?

An RMP or an update, as applicable, may need to be submitted at any time during a product's life cycle, i.e. during both the pre- and post-authorisation phases

RMP for all new marketing applications Article 8(3)(iaa)

RMP should be proportionate to risks

When a risk management plan should be submitted

Applications for innovative products where an RMP or RMP update will normally be expected include:

- With an application involving a significant change to an existing MA:
  - new dosage form;
  - new route of administration;
  - new manufacturing process of a biotechnologically-derived product;
  - paediatric indication;
  - other significant change in indication;

- At the request of the EMA or NCA when there is a concern about a risk affecting the risk-benefit balance

when a risk management plan should be submitted

Normally all parts of an RMP should be submitted. However, in ce… pr… ot… …ess

Type of new application	Part I	Part II, Module SI	Part II, Module SII	Part II, Module SIII	Part II, Module SIV	Part II, Module SV	Part II, Module SVI	Part II, Module SVIa	Part II, Module SVII	Part II, Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent [1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓						✓	✓	✓	✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	Λ	Λ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	Λ	Λ	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Well established use ”	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
“Same active substance”	✓	✓	*	*		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] Application under Article 10(c) of Directive 2001/83 as amended

[2] Application under Article 58 of Regulation 726/2004 as amended

Λ May be omitted under certain circumstances

* Modified requirement

Transparency

EMA and MS shall make publically available public assessment reports and summaries of risk management plans [REG Art 26(1), DIR Art 106].

For centrally authorised products the EMA will:

- make public a summary of the RMP;
- include tables relating to the RMP in the EPAR including the product information and any conditions of the marketing authorisation.

To promote public health, the EMA will make available (either on request or via its web portal):

- any questionnaires included in RMPs for centrally authorised products which are used to collect information on specified adverse reactions;
- details, which may include copies, of educational material or other additional risk minimisation activities required as a condition of the marketing authorisation;
- details of disease or substance registries requested as part of the pharmacovigilance plan for centrally authorised products.

Conclusion

RMP guidance overhauled to reflect new legislation and experience since 2005

Change to modular structure to make it easier to satisfy different regulatory needs

Important new areas include:

- a new Public Summary which will be written for lay people
- A new part IV on plans for post-authorisation efficacy studies (PAES)

Thank you