



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Key considerations in risk management plans

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Risk Management Section

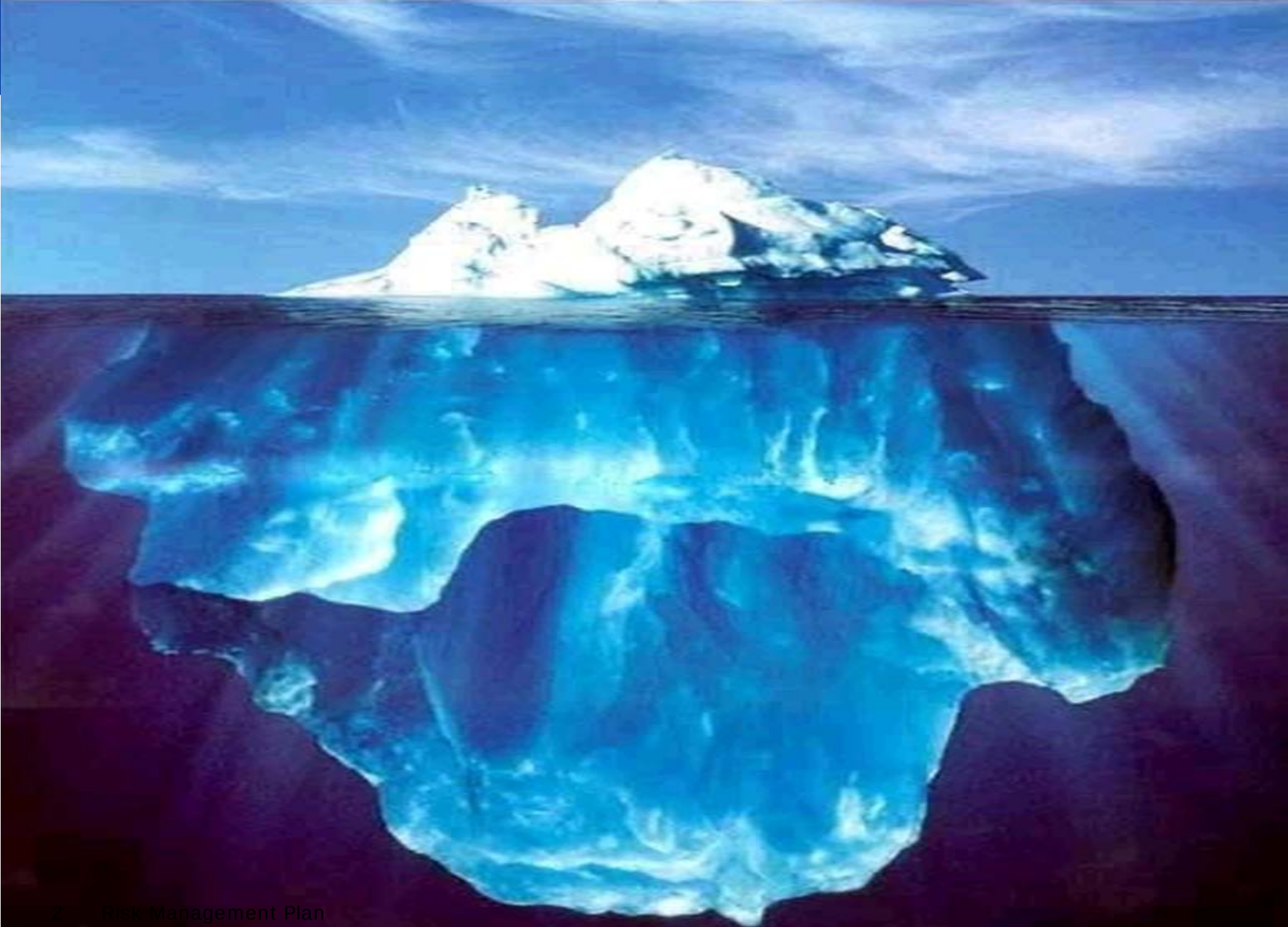
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Presentation Overview

- Introduction
- Risk Management Plan
- Points to consider





Introduction

Approval Decision

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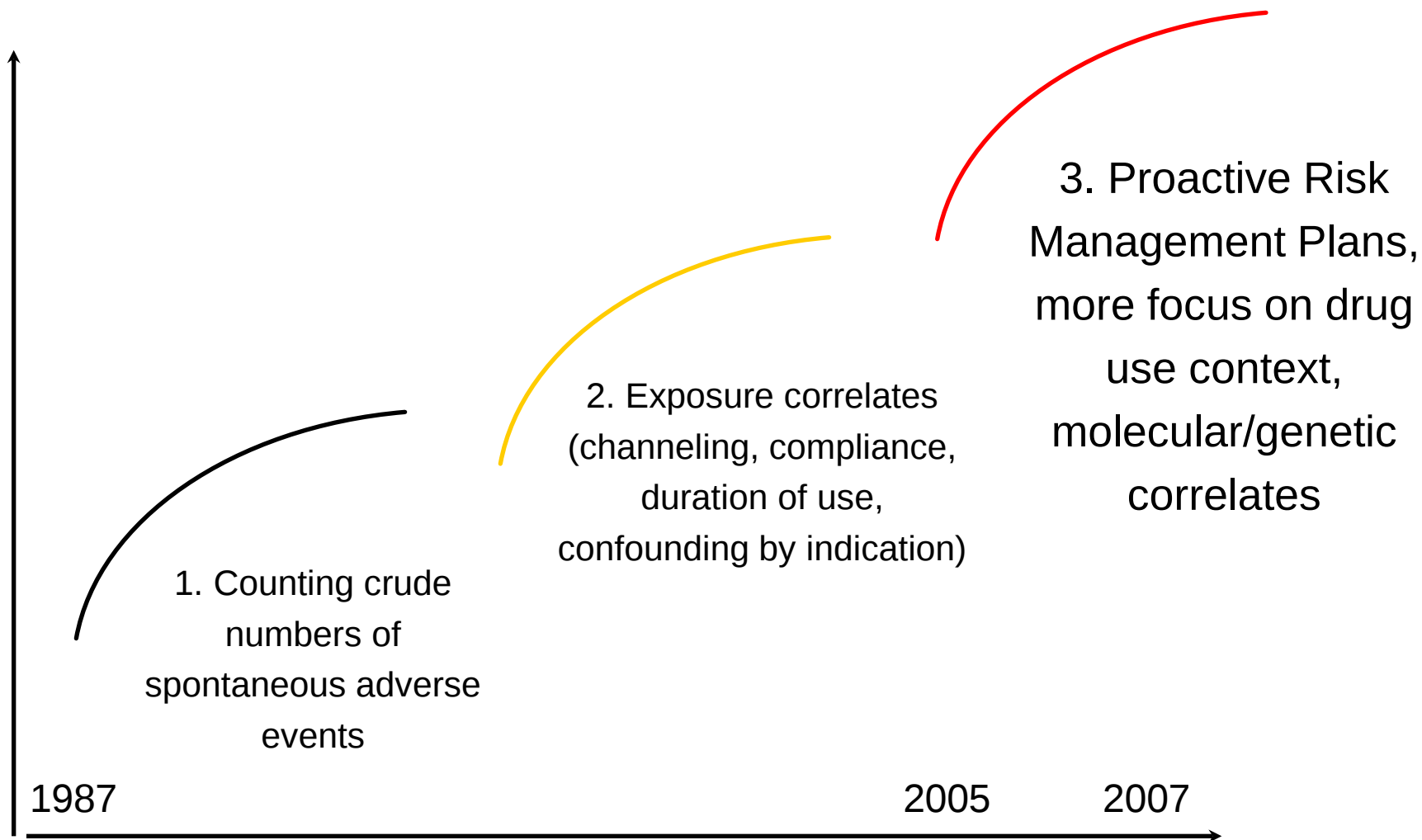
Critical Juncture

Beginning of lifecycle

pursue and manage **emerging** knowledge about

risk–benefit

uncertainty



Courtesy professor H Leufkens
University of Utrecht/MEB the Hague



Introduction

2005

New pharmacovigilance legislation

- Introduction of Risk Management Plan (RMP)
- Pharmacovigilance activities and interventions designed to identify, characterise, prevent, or minimise risks relating to medicinal products

Ensure that the benefits outweigh the risks in the largest possible way



Introduction

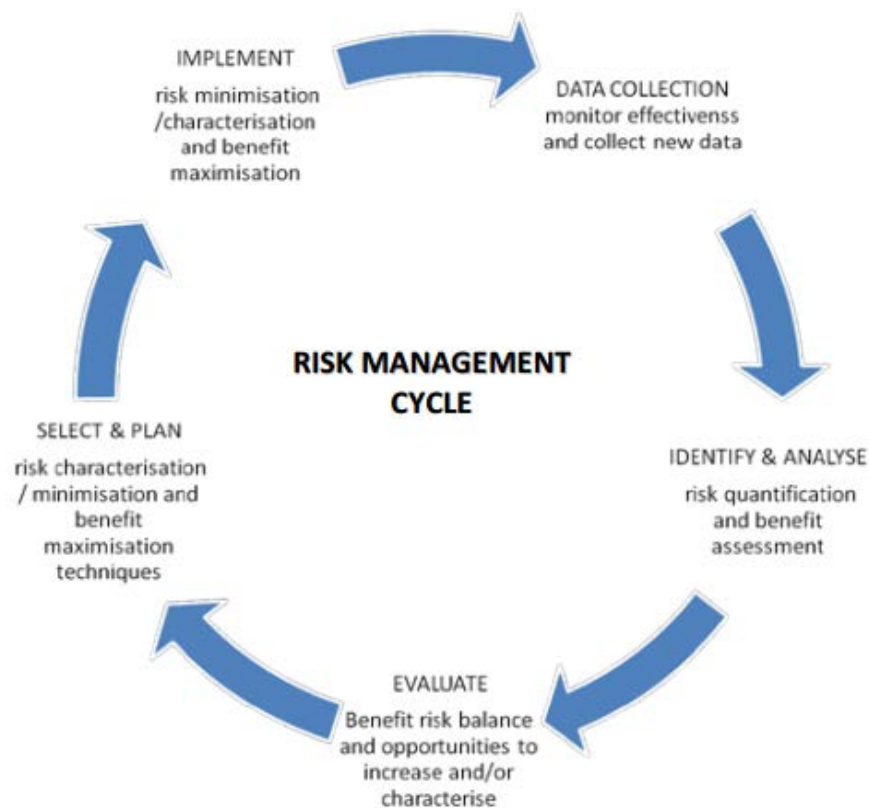
2012

New pharmacovigilance legislation

- New format of the RMP
- Assessment by PRAC
- GVP Module V
 - Module VIII – Post-authorisation safety studies
 - Module XVI - Risk-minimisation measures: selection of tools and effectiveness indicators



Introduction





Risk Management Plan

Objectives of the RMP

- Identify or characterise safety profile
- How to characterise further
- Measures to prevent or minimise risks including assessment of the effectiveness of those measures
- Document post-authorisation obligations



Risk Management Plan

Part I	Product(s) overview
Part II	Safety specification
	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 safety specification
	Module SVII Identified and potential risks
	Module SVIII Summary of the safety concerns
Part III	Pharmacovigilance plan
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
Part VI	Summary of the risk management plan
Part VII	Annexes



Risk Management Plan

Part II leads to Safety Specifications:

Important Identified Risks

Risk for which there is adequate evidence of an association

Important Potential Risks

Risk for which there is suspicion of an association but no confirmation

Important Missing Information

Information about a risk is not available and represents a limitation of the safety data



Risk Management Plan

‘IMPORTANT’??

- Impact on the risk-benefit balance of the product
 - Impact on individual
 - Seriousness of the risk
 - Impact on public health
- Risks to be included in the ‘contraindications’ or ‘warnings and precautions’ section of SmPC



Risk Management Plan

Part III leads to Pharmacovigilance Plan:

- For each of the safety concerns the planned pharmacovigilance activities should be provided
- Routine pharmacovigilance (PSUR, ADR collection and analysis) or additional pharmacovigilance (PASS, measurement of effectiveness of Risk Minimisation Activity)
- A single safety concern can have no, one, or multiple additional pharmacovigilance activities
- Protocols of the studies should be submitted as part of the RMP with clear milestones



Risk Management Plan

Part IV leads to plans for post-authorisation efficacy studies:

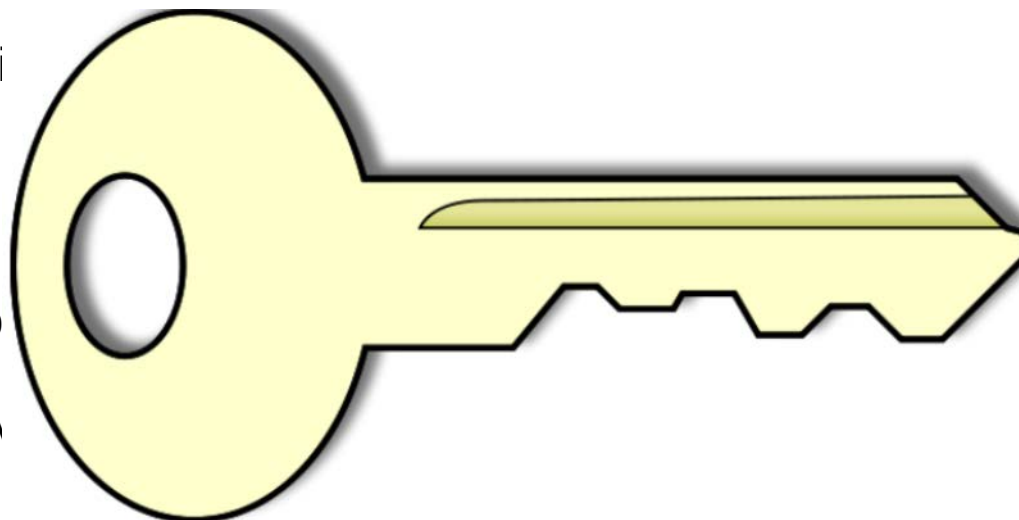
- For many medicines there will not be a need for post-authorisation efficacy studies (PAES)
- Long term follow-up of efficacy will be potentially needed for certain medicinal products:
 - Marketing authorisation applications that include a paediatric indication / or will only seek a paediatric indication
 - Applications to add a paediatric indication to an existing marketing authorisation
 - Advanced therapy medicinal products
- The PAES refers only to the current indication and **not** to studies investigating a new indication



Risk Management Plan

Part V of the RMP handles Risk Minimisation Measures

- Routine Ri
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KEY MESSAGE

- The Risk Minimisation Measures should not be promotional in nature, and should not be a repetition of information that is already clearly stated in the SmPC



Risk Management Plan

Part VI provides a Summary of the Risk Management Plan

- Overview of epidemiology
- Summary of efficacy data
- Summary of safety concerns
- Summary of risk minimisation measures
- Summary of pharmacovigilance plan
- Major changes to the RMP over time



Points to consider

When to submit an RMP?

An RMP should be submitted at initial marketing authorisation application for new products.

For already existing marketing authorisations an RMP should be submitted at the time of a significant change to the marketing authorisation, or at the request of the Agency.



Points to consider

How will the PRAC be involved in the review of RMPs?

The regulatory oversight of RMPs lies with the PRAC. The PRAC is involved in procedural and scientific matters regarding RMPs as of its meeting in September 2012. The RMP will be assessed by the PRAC Rapporteur. The PRAC provides 'Advice' to CHMP.



Points to consider

RMP is living document – will be updated throughout the life cycle of the product

Each update will be assessed by the PRAC

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.



Points to consider

How do the EMA expect to receive the RMP

The revised RMP should be provided in CTD section 1.8.2, using the document structure as provided in the guidance. For updates of existing RMPs: Until further notice companies have to send in all parts of the RMP so that a complete RMP is provided to the Agency.



Points to consider

Different types application, different types of submission

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 SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓								✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
"Well established use"	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
"Same active substance"	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

¹ Application under Article 10(c) of Directive 2001/83/EC

^ May be omitted under certain circumstances

* Modified requirement



Points to consider

How is the assessment of an educational program as additional risk minimisation handled?

The outlines of the educational program (i.e. the key elements) are part of Annex II of the marketing authorisation. Assessment of the educational program incorporating these key elements is done at the Member State level since GVP Module V chapter V.C.7 states that Member States have the responsibility for ensuring that the key elements described in the conditions and/or restrictions are implemented by the marketing authorisation holder in their territory.



Points to consider

Will a summary of the RMP be published, and is an RMP summary required for already existing RMPs?

An RMP summary is required for all medicines authorised. The current approach is that subsequent updates could be used to ensure all medicines have an RMP summary. The summary of the RMP for each medicinal product shall be made publically available.



Points to consider

If there is no RMP in place for a reference medicinal product, how should module SVIII 'summary of the safety concerns' be populated for a generic medicinal product?

The company of the generic medicinal product should use the (E)PAR and the SPC of the reference medicinal product to obtain the safety concerns to be included in module SVIII of the RMP. Companies may also discuss with the relevant competent authority what safety concerns should be included.



In summary

- Proactive approach
- Characterise safety profile
- Prevent or minimise the risks
- PRAC oversight
- Living document



Questions?

