Pharmacovigilance Update Europe

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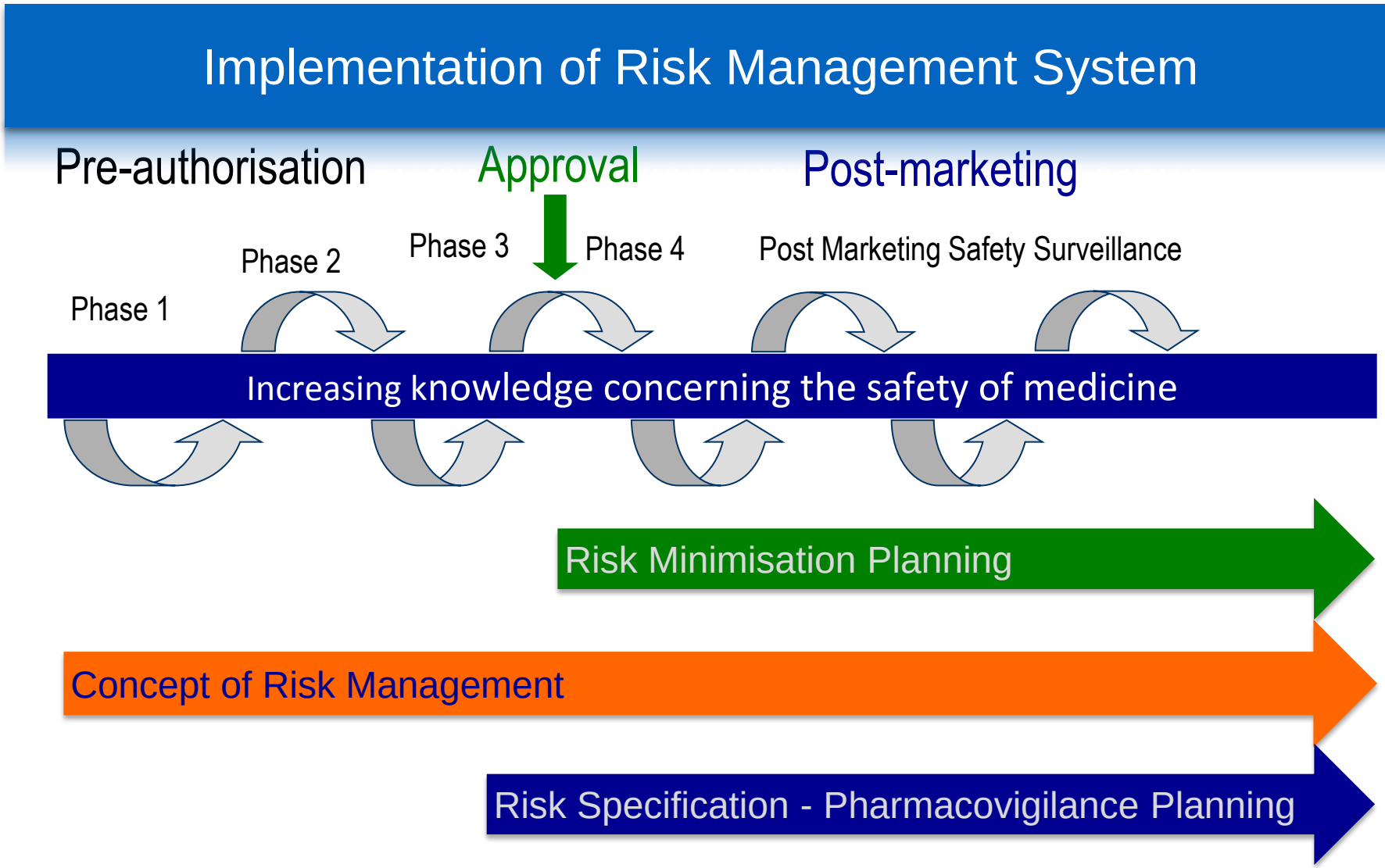
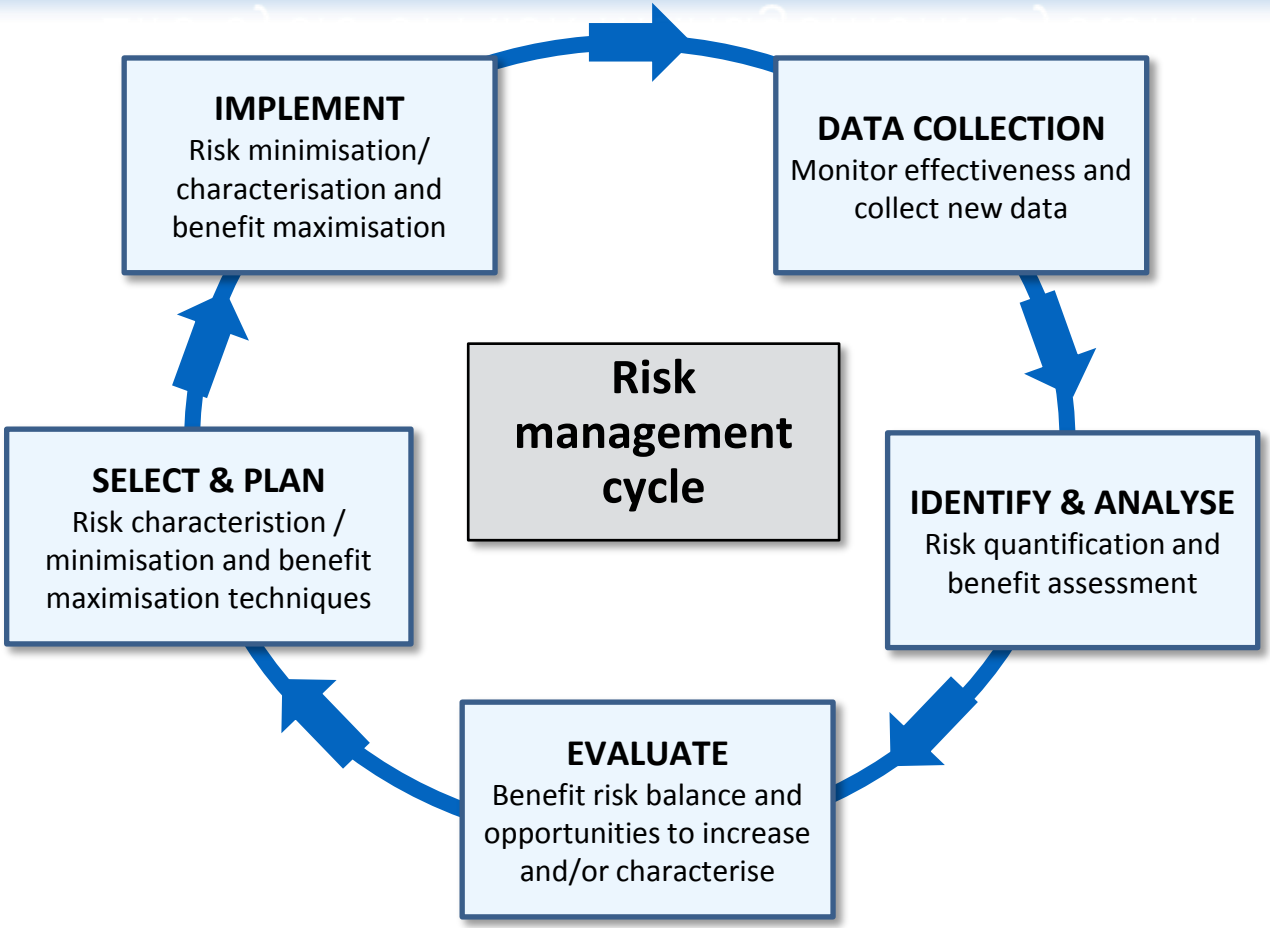
- EU Risk Management Plan (RMP)
- Risk Minimisation Measures
- PASS (Post Authorisation Safety Studies)
- Medication Errors / Off Lable Use
- Paediatric Pharmacovigilance

Pharmacovigilance Update Europe



Life cycle of Risk Management System



Changes to Risk Management System

NEW! applicable for **all medicinal products** independent of authorisation status (centralised, decentralised, mutual recognition, national)

NEW! Focus on **Risk-benefit balance** and Risk Management

NEW! **Post-authorisation safety studies** and post-authorisation efficacy studies as a commitment for authorisation layed down in the RMP

NEW! **Signal detection** and intensified monitoring list as on going risk minimisation measure

NEW! Assessment by **PRAC** and recommendation to CHMP/CMDh

NEW! PRAC Rapporteur **is independent of** CHMP Rapporteur

NEW! RMP has to be a **„Stand alone“** document including a summary which has to be published in lay language

NEW! **Modular structure of RMP** template to make changes easier to apply to the approved RMP

Basic steps of Risk Management System

Risk Management covers three basic steps

1. **Safety profile characterisation of the medicinal product**
   - „Safety specification“
   - potential and identified risks

2. **Pharmacovigilance Planning**
   - Characterisation of risks
   - Identification of new risks
   - Optimising information regards safety profile

3. **Planning and implementation of Risk Minimisation**
   - routine or additional risk minimisation measures
   - Assessing effectiveness of implemented measures

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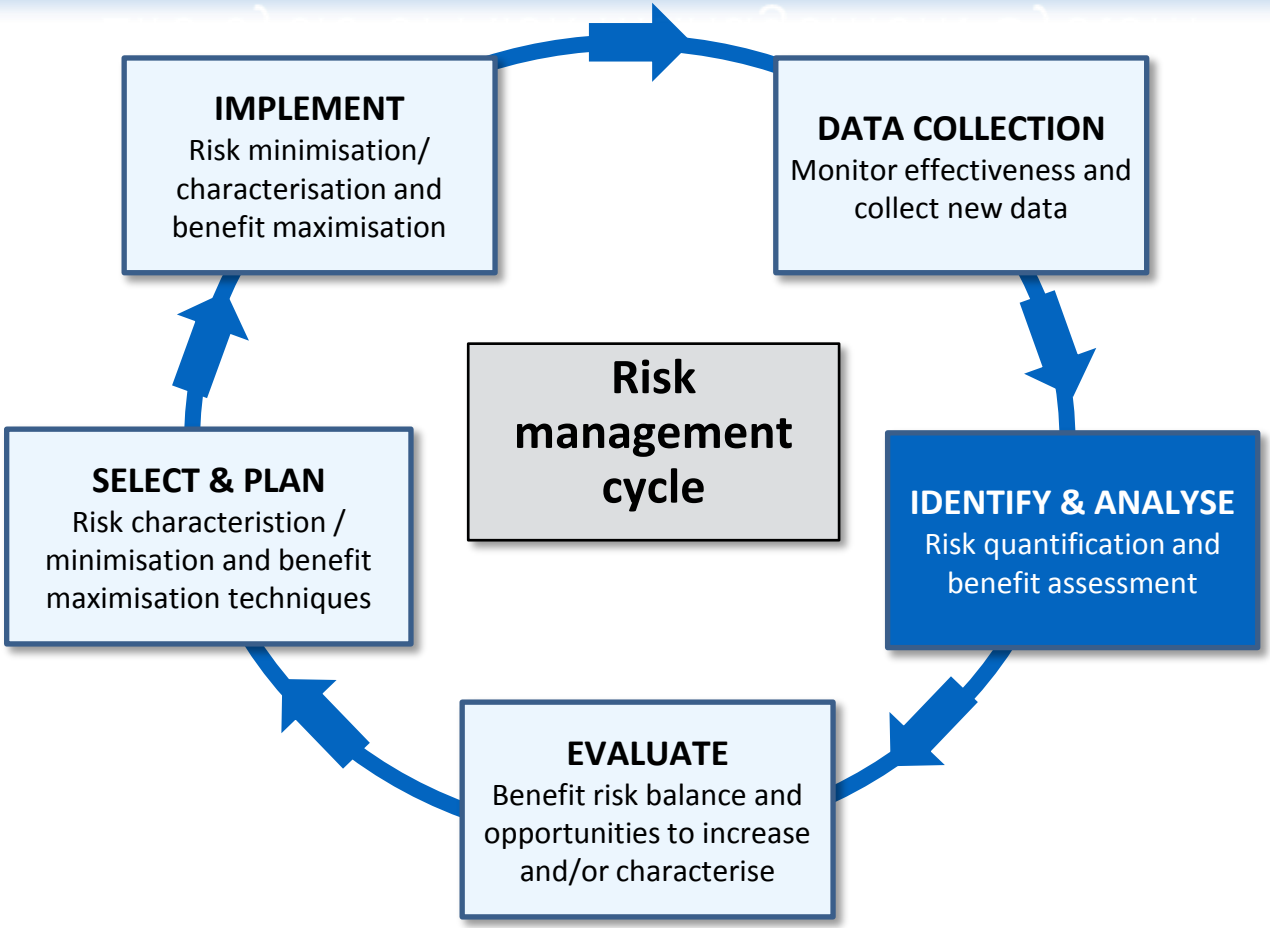

Safety specification

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

- Discussion of Epidemiology of the Indication
- Aspects of benefit and position of medicinal product: Prophylaxis, Protection, treatment of disease

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

Safety specification

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

Module SII: Non-clinical part of the Safety Specification

- Summary of important non-clinical safety findings, z.B. Toxicity, Pharmakology, Interaction, …

Module SIII: Clinical trial exposure

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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

- Information from clinical trials: Number of subjects treated with medicinal product, patient-year of exposure, duration of treatment
- Specific information (age, sex, Indication, ethnic group)
- In/- exclusion criteria in clinical trials („Population not studied“)

Module SIV: Populations not studied in clinical trials

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Module SIII: Clinical trial exposure

Module SIV: Populations not studied in clinical trials

- Target group and safety database
- Evidence of data collected in relation to the detection of ADRs
  - number of subjects studied, patient-year-exposure
- Discussion of data from special population, z.B. Children, elderly, pregnant woman, multi morbidity, …

Module SV: Post-authorisation Experience

Module SVI: Additional EU requirements for the Safety Specification

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Module SV: Post-authorisation Experience

- Regulatory and MAH action for safety reasons
- Indicated use vs. actual use (Off-label use, …)
- Reports form use in pharmaco-epidemiological Studies

Module SVI: Additional EU requirements for the Safety Specification

Module SVII: Identified and potential risks

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Module SVI: Additional EU requirements for the Safety Specification

- Risk by overdosing, Misuse (z.B. Doping), „Medication Error“, special aspects for paediatrics (PIP, Off-Label-Use)
- Potential for transmission of infection

Module SVII: Identified and potential risks

Module SVIII: Summary of the safety concerns

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

- Information on identified and potential Risks
- identified and potential Interaction (food-drug, drug-drug)
- Pharmacological class effect
- New safety-aspect since latest approved RMP

Module SVIII: Summary of the safety concerns

Safety specification

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

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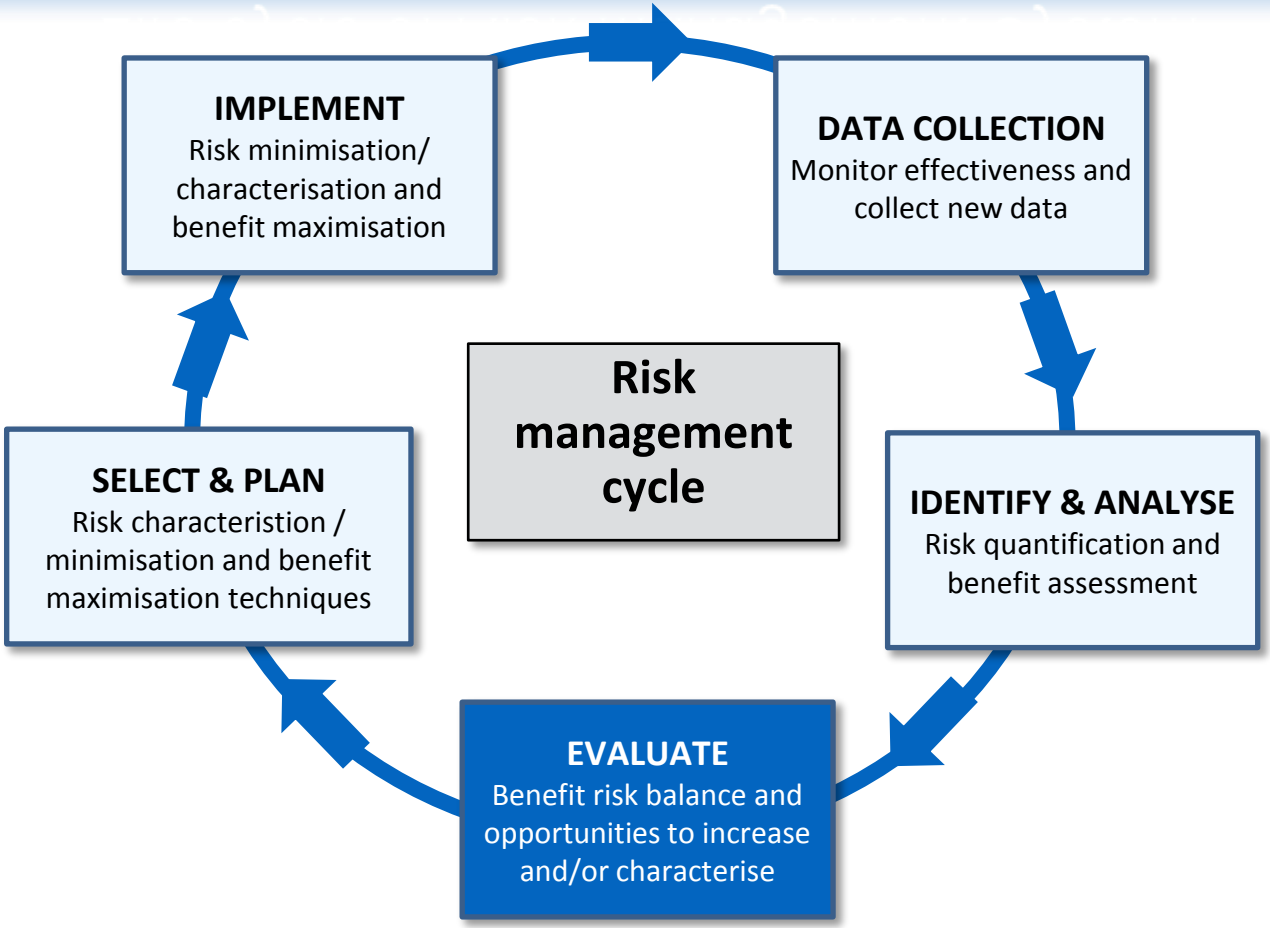
Module SVI: Additional EU requirements for the Safety Specification

Module SVII: Identified and potential risks

Module SVIII: Summary of the safety concerns

- Continous up-date and summary of discussed safety aspects
- Use of tabulation presentation of safety aspects

Life cycle of Risk Management System



Periodic Safety Update Report (PSUR)

- „Stand alone“-Document, but has common modules with RMP
- Actualisation of RMP with reference in on-going PSUR if:
  - Significant changes of current authorisation (Indication/ Renewal)
  - On request of competent authorities in relation to new risks
  - Actualising single parts/ modules if possible and not otherwise expected
    - New authorisation (in case of generics
    - Hybrid-medicinal products or Hybridapplication of medicinal products
    - New Indication, new population
- Summary and conclusion in PSUR and RMP should be harmonised
- Defined (suspected) adverse reactions of interest should be discussed in the PSUR
- Link important identified/ potential risks which have been described in the „Safety specification“ in the RMP

Adverse reaction (ADR) collecting and reporting

Definition

ADR is a response to a medicinal product which is noxious and unintended independent from the marketing authorisation indication

- including overdose, misuse, abuse and medication errors
- off-label use

Primary reporting source

- Health care professionals, Pharmacists, nurses, intoxications centers....
- Non-medically qualified persons like consumers, lawyers...
- MAH should regularly screen internet or digital media under their responsibility

Reporting of non-serious ADRs within 90 days to NCA/ EudravigilnceEudravigilnce

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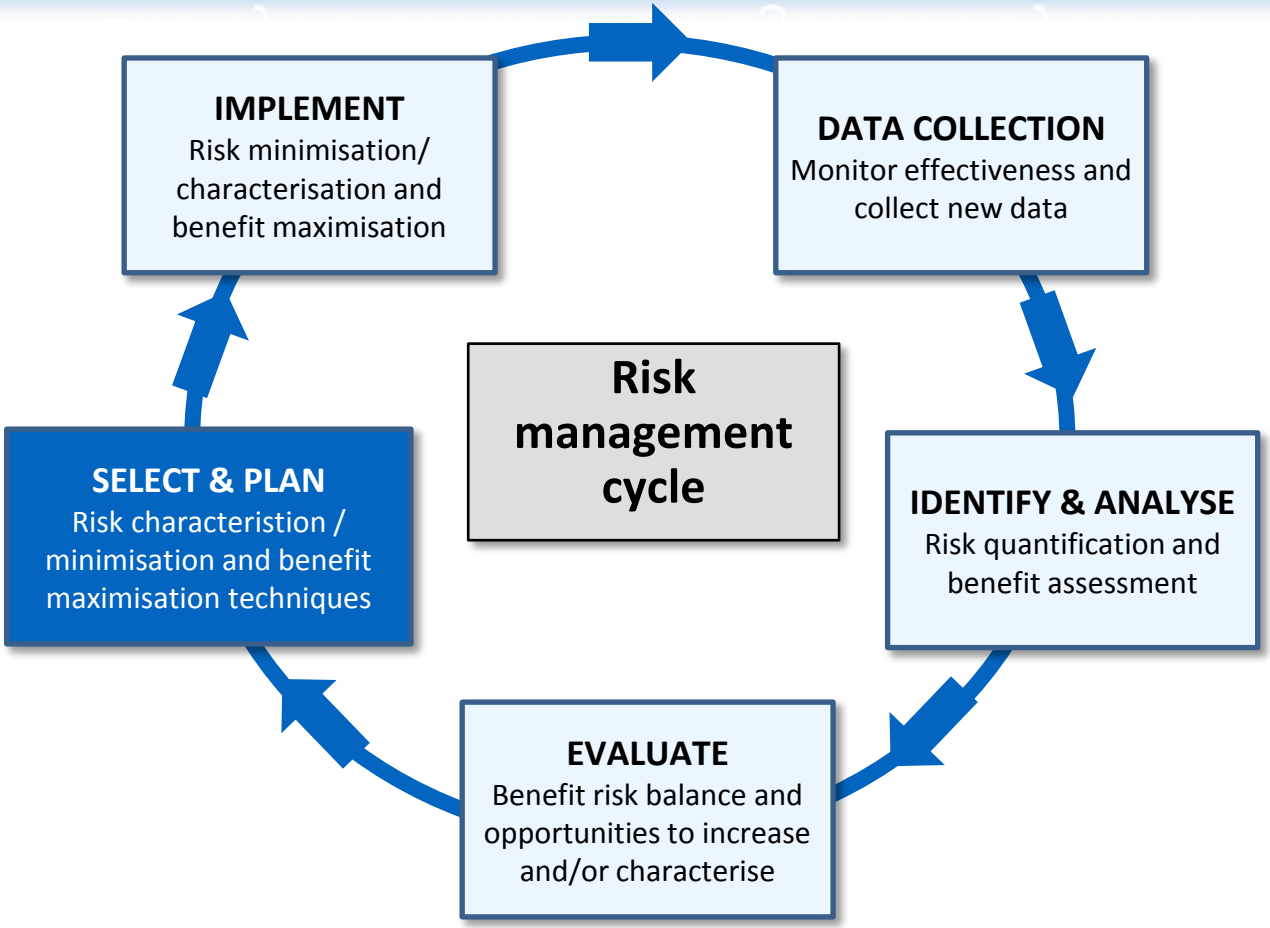

Pharmacovigilance planning

Structured plan to cover

- Identification of new risks and characterisation of risk factors
- Further Investigation of identified potential risks including the planned approach how to collect these information

Routine pharmacovigilance (safety) activities

- description of Pharmacovigilance System Master File
- references to PSMF, SmPC, spontaneous reporting

Additional pharmacovigilance (safety) activities

- Discussion of necessity for further action and measures
- Requirements set by PRAC, CHMP, CMDh
- Description of planned actions/ measures for each safety concern
- like Post-authorisation safety/ efficacy studies (PASS/ PAES)

Post Marketing Safety Studies (PASS)

Investigation with the authorised medicinal product

- identifying, characterising or quantifying a safety hazard
- confirming the safety profile of the medicinal product
- measuring the effectiveness of risk management measures
- PASS could be clinical trials or non-interventional studies
- Initiation voluntarily by MAH or imposed as an obligation by NCA/ PRAC

The type of study design is not constraining a PASS, e.g. a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.

Non-interventionell (PASS)

Non-interventional studies are defined by the methodological approach used and not by its scientific objectives.

Requirements to be fulfilled cumulatively

- the medicinal product is prescribed in the usual manner according to the marketing authorisation
- the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Post Marketing Safety Studies (PASS)

Assessment by PRAC or NCA depending on authorisation status

- Submission of study report 12 months after the end of data collection

Potential grounds for conducting a PASS (PAES)

- Enhancing safety data base due to small populations in clinical trials
- Support of Benefit/ Risk balance
- Evaluation of safety in populations not studied
- Supportive data to evaluate potential risks
- Investigation of potential long-term effects
- Effectiveness studies (vaccines)
- Missing robust evidence of efficacy to be investigated post-marketing

Post Marketing Safety Studies (PASS)

Potential designs for PASS

Active surveillance

- Intensive monitoring schemes
- Prescription event monitoring
- Registries

Observational studies

- Cross-sectional study (survey)
- Cohort Study
- Case-control-studies
- self-controlled case-series
- case-crossover study

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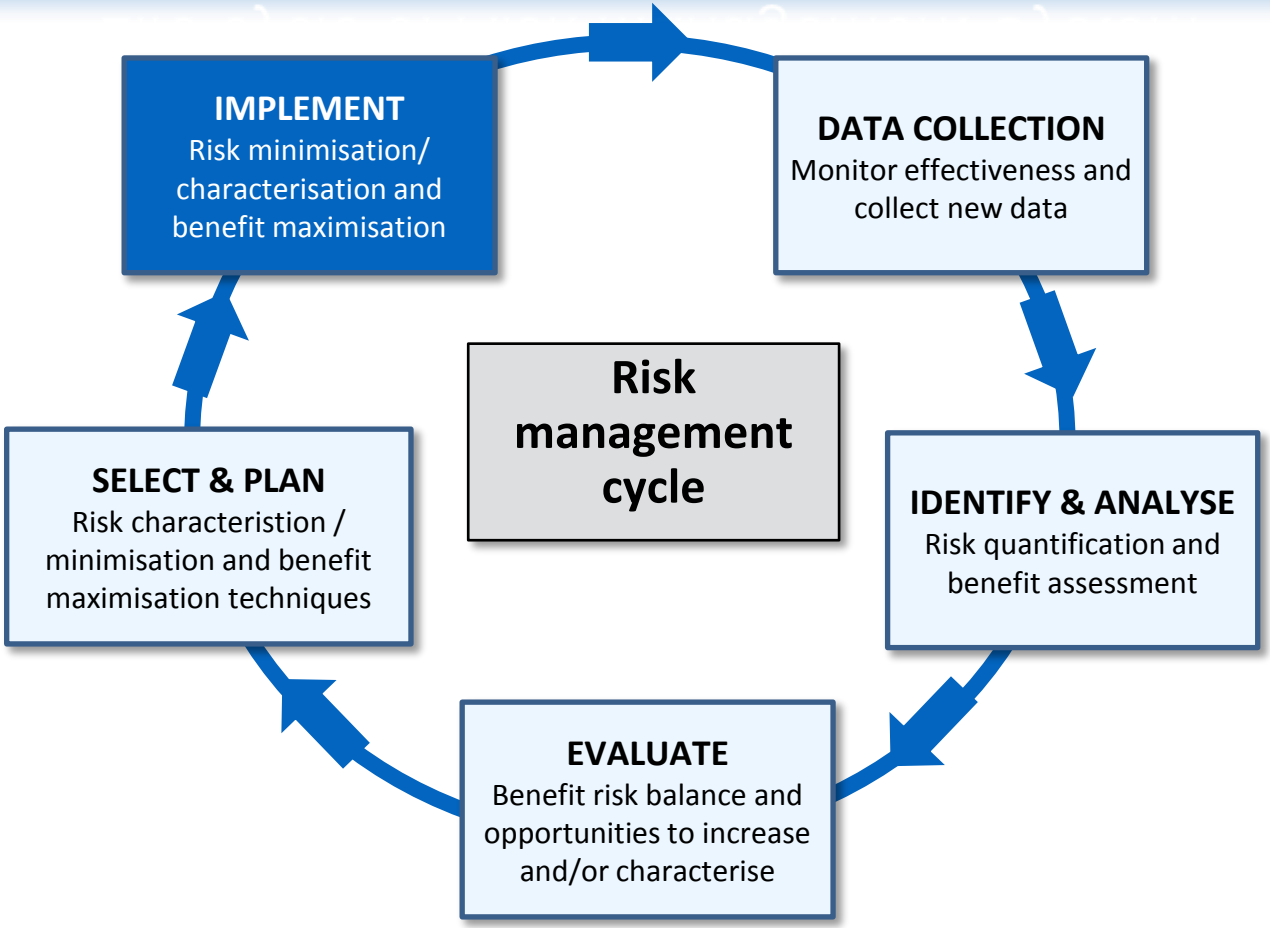

Risk Minimisation measures

- Aim to facilitate informed decision making to support risk minimisation
- Routine measures are applied to every medicinal product
- Additional activities to be introduced to support the safe and effective use of medicinal products
- Minimising the risk of medication error
- Ensuring appropriate administration where it is not feasible to achieve this through the product information and labelling alone
- Measuring the effectiveness of risk minimisation measures
- Burden of risk minimisation to balanced against the benefit
- **Safe and effective use of the medicinal product in all population**

Routine Risk Minimisation

Safety concerns

- Identified Risks
- Potential Risks
- Population not studied (off-label-use)

Tools

- SmPC (indication, warning, adverse effects)
- Age appropriate formulation and excipients
- Patient information/ educational programme
- Patient alert card
- Controlled distribution/ access programme

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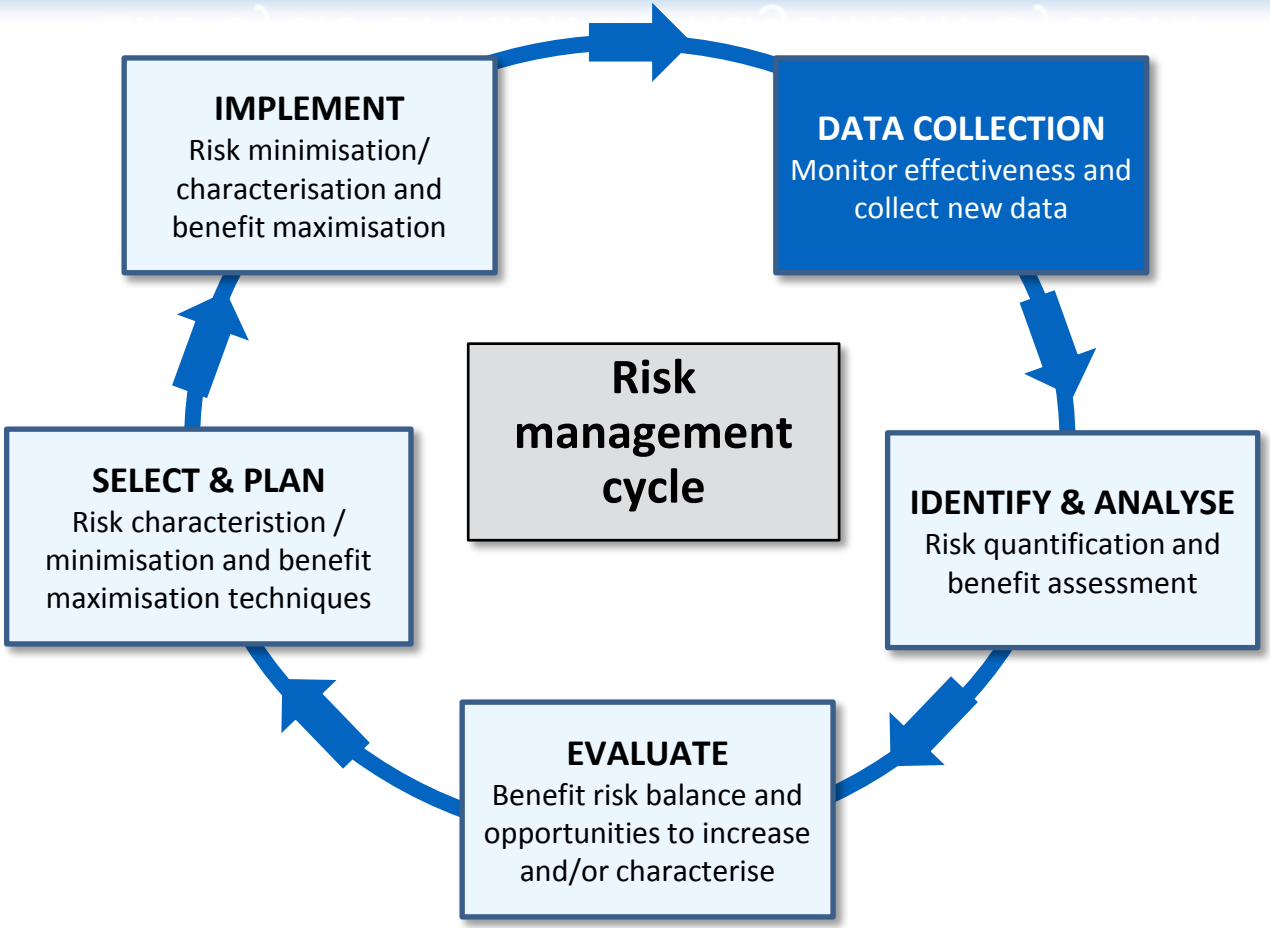
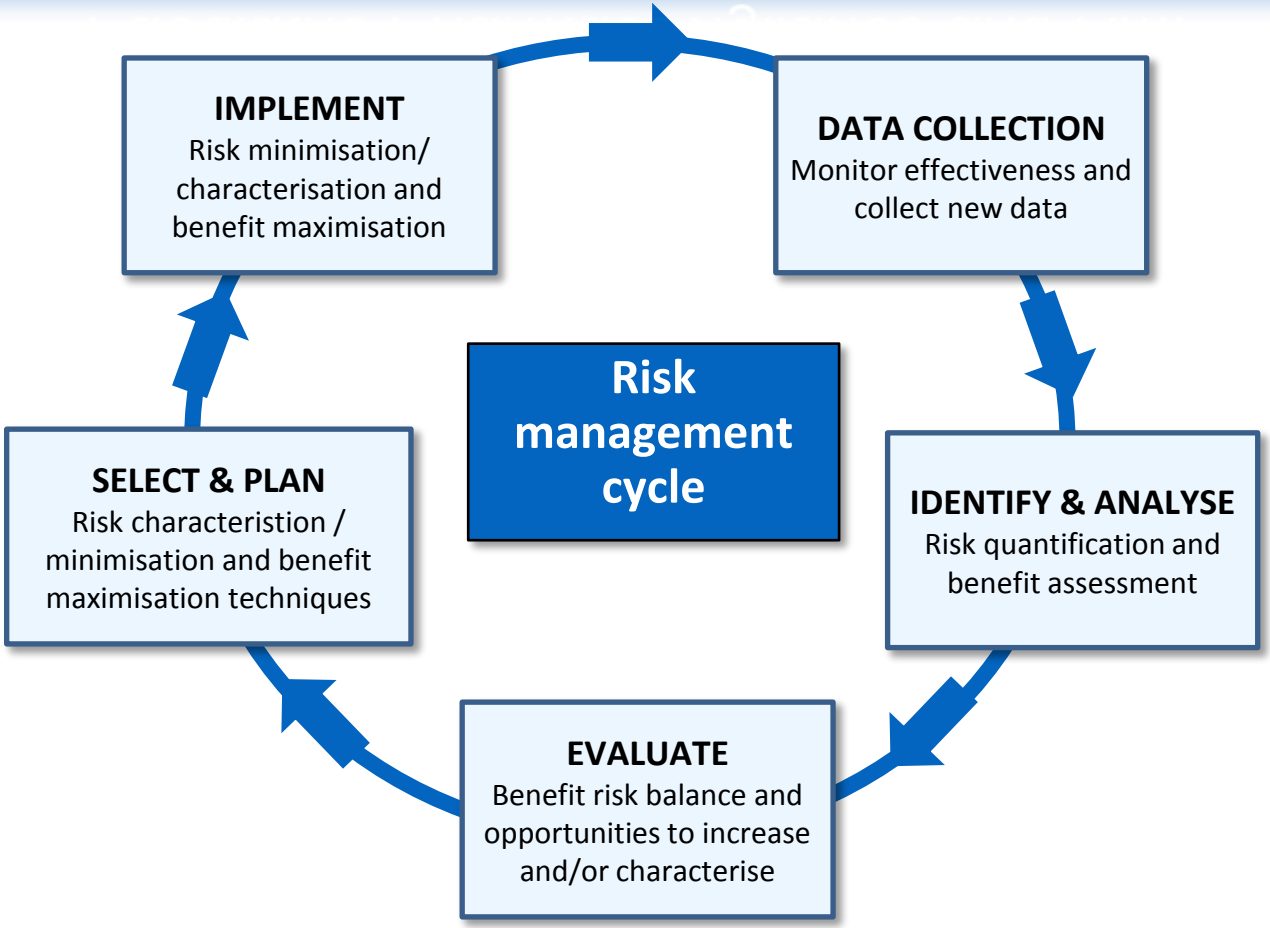


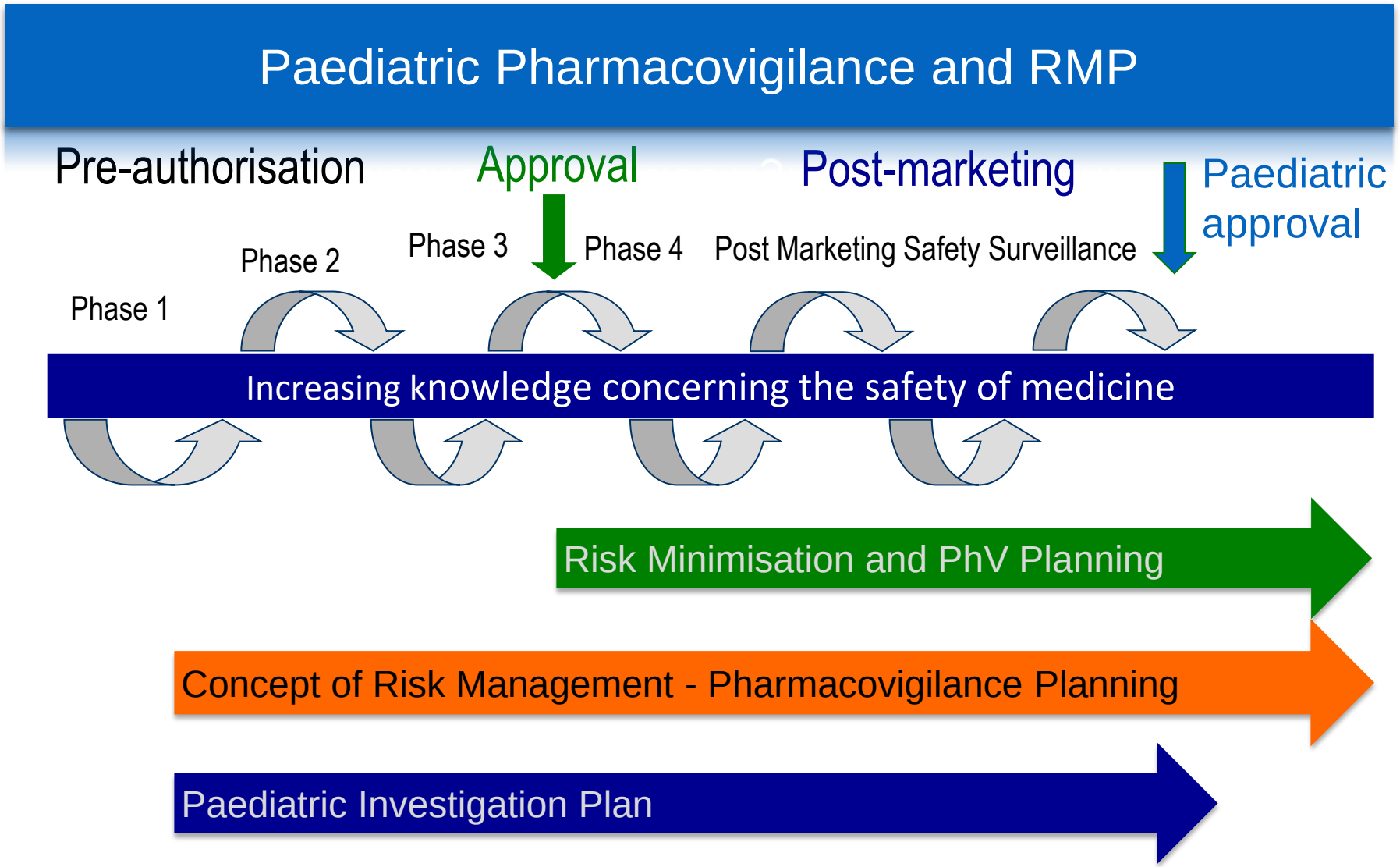
Effectifness of risk minimisation measures

- Establishing whether an intervention has been effective
- Evaluation whether further corrective actions are necessary
- Performing this for the additional risk minimisation tools individually and as a whole
- Timing should be appropriate accounting the time to launch the measures
- Timing should reflect the circumstances related to healthcare systems to introduce the measures
- Evaluating the impact on knowledge and behavioral changes in the target population
- Process and outcome indicators should be considered for evaluation of effectiveness

Paediatric Pharmacovigilance and RMP



Pharmacovigilance Update Europe



Paediatric Pharmacovigilance and RMP

RMP Tool box

- Safety specification
- registries
- PASS
- PAES
- medication error
- ADR reporting
- Signal detection

“PIP” Tool box

- pre-clinical trials
- Waiver
- Long-term follow-up
- efficacy trials
- Formulation
- Dosing
- PK/ PD trials

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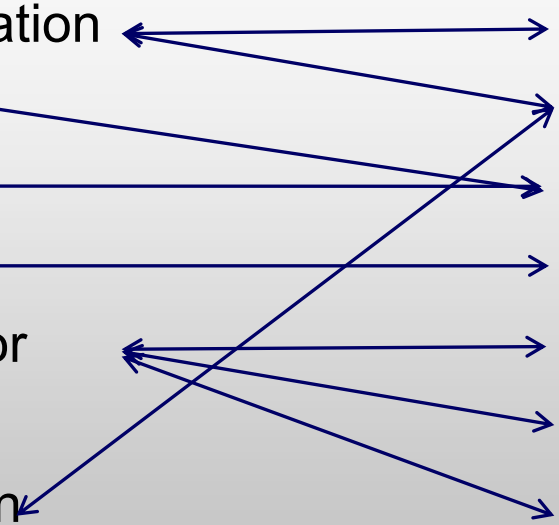

Paediatric Pharmacovigilance and RMP

Justification for waiver based on:

- Lack of significant therapeutic benefit over existing treatments
- Condition occurring only in adult populations
- Lack of efficacy in relation to likelihood of harm

Justification for deferrals:

- Scientific/ technical grounds or grounds related to public health
- delay of paediatric studies due to safety concerns in adult trials
- Request for additional non-clinical data (toxicology, carcinogenicity)
- Issues with development age appropriate formulation(s)
- Recruitment into paediatric trials will cause major delays of MAA in adults

Summary of Risk management Plan

- RMP summary according to template in lay language
- Overview of disease and its epidemiology
- Treatment options and reference of standard of care
- Conclusion on benefit / efficacy and on risks
- Summary of risk minimisation activities and related measures pre risk identified
- Planned PASS /PAES including activities related to commitment to authorisation
- Overview of changes in the RMP in chronological order

Thanks for your attention

Any Questions?