Pharmacovigilance

Key considerations for Risk Management Plans

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Key considerations for Risk Management Plans

Outline of the presentation

1. Introduction
   - Background
   - Evolution of pharmacovigilance
2. Risk Management Plan
   - Content
   - Considerations
3. Conclusions

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Introduction

Who am I?

- Deputy European Union Qualified Person for Pharmacovigilance (EU QPPV) at MSD
- Based in the Netherlands
- Over 18 years in Pharmacovigilance
  - Medicines Evaluation Board (CBG-MEB)
  - European Medicines Agency (EMA)

Providing an EU perspective

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Introduction

What is Pharmacovigilance?

WHO definition: *The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems*

Objectives of pharmacovigilance are (per EU GVP Annex I – Definitions):

- *preventing harm from adverse reactions of authorised medicinal products; and*
- *promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public*

Monitoring of the Benefit/Risk profile of medicinal products throughout their lifecycle

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Introduction

Why is Pharmacovigilance important?

At start of medicinal product lifecylce:

- Limitations around knowledge of safety profile
  - Inclusion/exclusion criteria
  - Study population different
  - Study population limited

Need for continuous monitoring after authorisation to ensure patient safety
Very rare ADRs are identified still for ‘old’ medicinal products too

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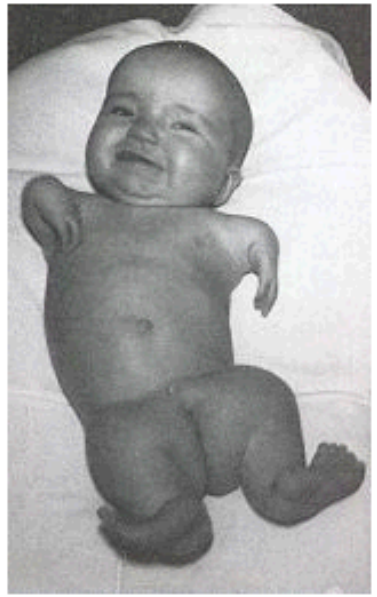
Introduction

It all started with AE collection



- Softenon / thalidomide
- Example of serious ADR detected through spontaneous reporting of cases
- Sparked organisations to formally collect AEs

Followed by Periodic Safety Update Reports (PSUR)

- Mandatory in Europe since 1997
- Summary of available safety information

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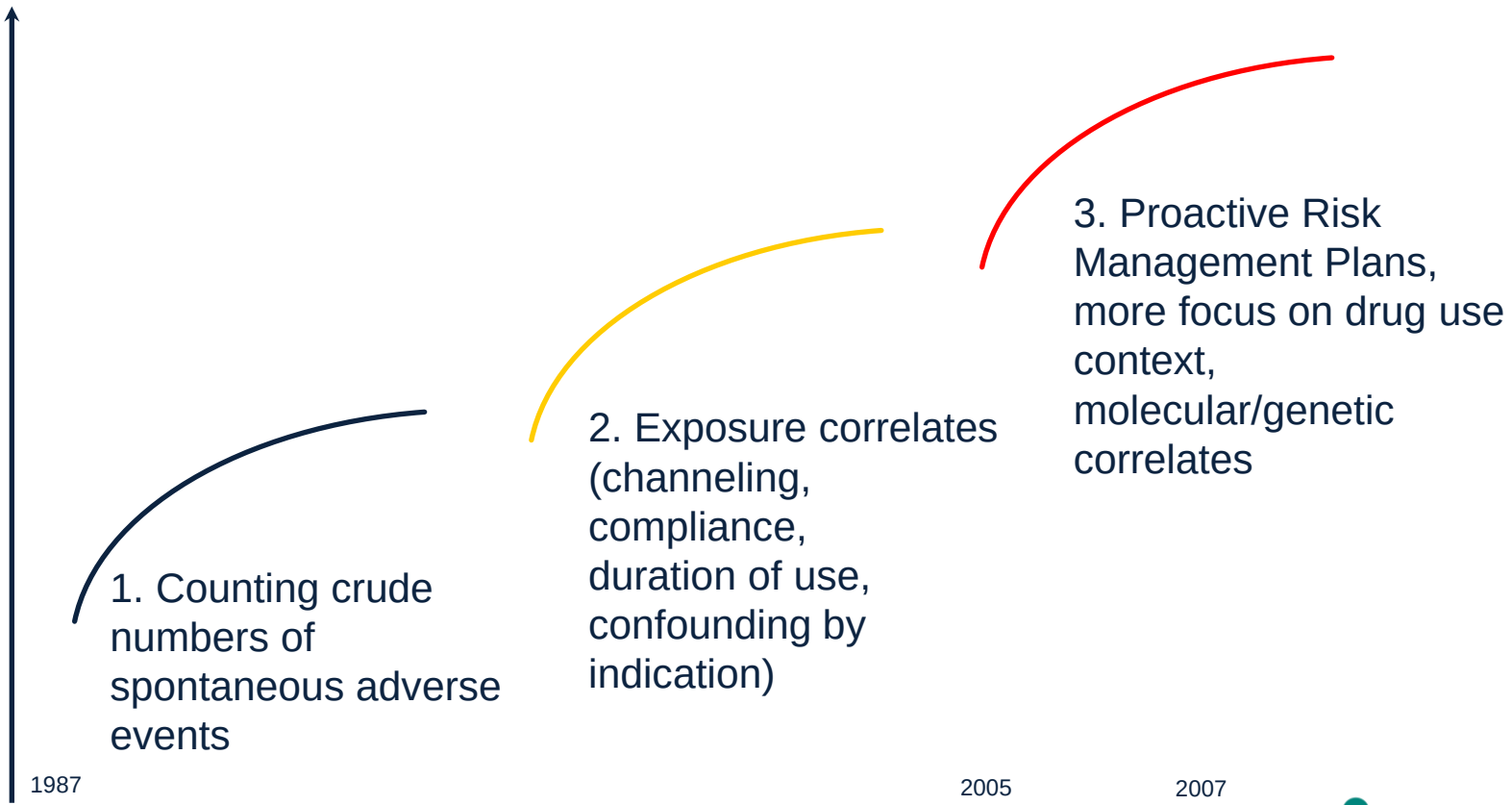
Introduction

Moving towards a more pro-active approach:

- Signal detection/management
- Post-authorisation Studies
- Risk Management Plans



Courtesy professor H Leufkens
University of Utrecht/MEB Utrecht

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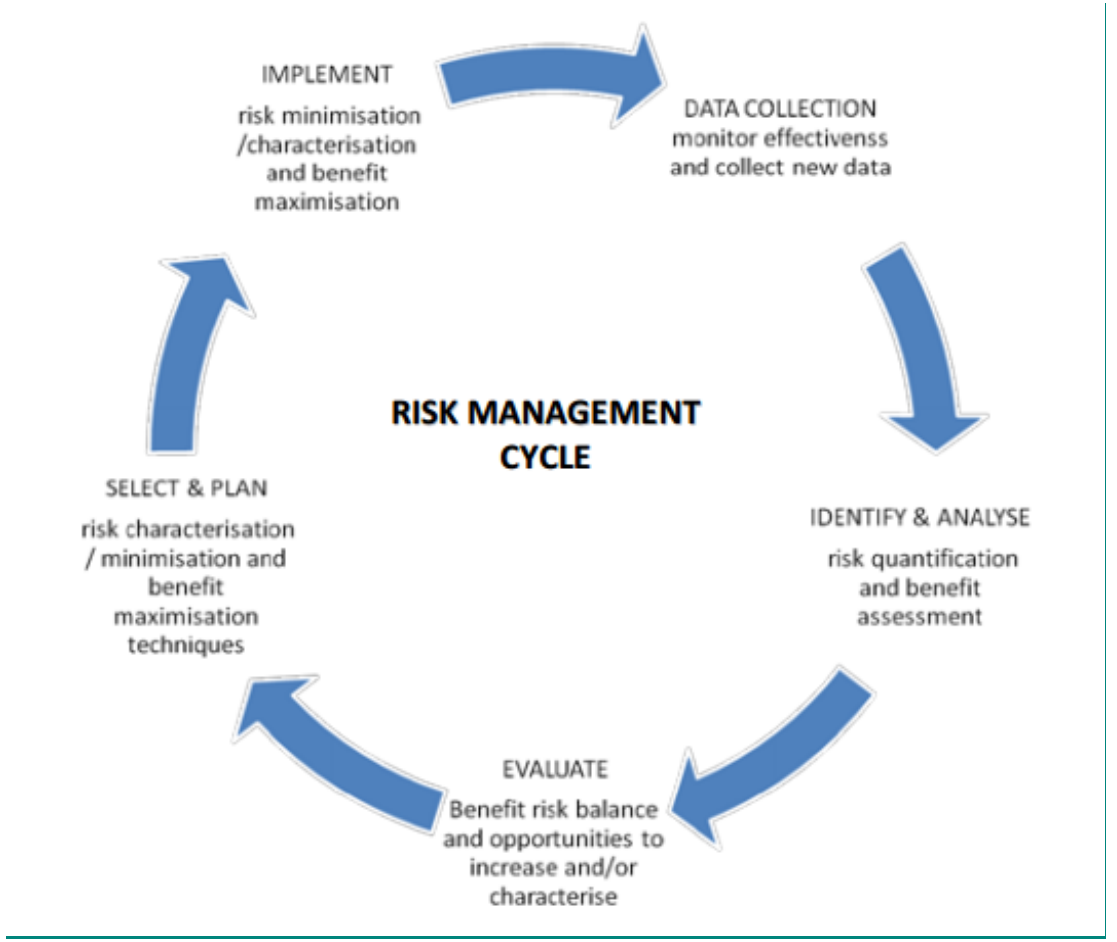
Risk Management Plan

Pro-active approach to pharmacovigilance

Risk Management Plan - *A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product*

For a new chemical entity or new biological, the uncertainty is highest:

But process of identifying, evaluating, planning and executing continues throughout the lifecycle for all medicinal products



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Risk Management Plan

EU RMP is structured according to GVP Module V, rev. 2

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 (including post-authorisation safety studies)
Part IV	Plans for post-authorisation efficacy studies
Part V	Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)
Part VI	Summary of the risk management plan
Part VII	Annexes

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Risk Management Plan

Safety Specification (Part II) description (in line with ICH E2E) leads to:

- Important Identified Risks
- Important Potential Risks
- Missing Information

} Summary of the safety concerns

Identified risk – there is adequate evidence of an association with the medicinal product of interest (ICH)

Potential risk – there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed (ICH)

Missing Information – gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant (GVP)

"*Important*"?

- Risk that could have an impact on the risk-benefit balance of the product or have implications for public health (ICH)
- <<we'll come back to this later >>

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Risk Management Plan

Pharmacovigilance Plan (Part III)

- Description of pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product
- Closely linked to GVP Module VIII on Post-authorisation safety studies (PASS)

- Routine pharmacovigilance activities:
  - Continous activities required for **all** authorised medicinal products, like AE collection and analysis, signal detection, PSURs
  - Not tied specifically to a safety concern in the RMP

- Additional pharmacovigilance activities:
  - Post-authorisation safety studies (non-clinical studies, clinical trials or non-interventional studies)
  - Linked to a specific safety concern in the RMP with details/milestones/protocols included in the RMP

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Risk Management Plan

Risk Minimisation Measures (Part V)

- Interventions intended to prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur
- Closely linked to GVP Module XVI on Risk minimisation measures and effectiveness indicators

- Routine risk minimisation activities:
  - Apply to every authorised medicinal products, and include the summary of product characteristics; the package leaflet; the pack size

- Additional risk minimisation activities:
  - Only when needed for the safe and effective use of the medicinal product, with details and justification provided in the RMP – should not be a repetition of the routine
  - Examples are, educational programmes; controlled access programmes; anything other than routine – details on how the effectiveness of these activities will be measured should be provided

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Considerations

‘Important’ risks to be included in the RMP

What is ‘Important’?

- Impact on the risk-benefit balance / implications for public health
  - not all safety information, not all ADRs
- Include those risks for which additional activities are planned to further characterise or minimise
- Rule of thumb: Consider to include what is planned to be reflected in the ‘Contraindications’ and ‘Warnings&Precautions’
- Difference between completely new products and more mature/older products:
  - More uncertainty around the safety profile versus more well-established safety profile
  - Modified requirements for RMPs for generics, fixed combinations

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Considerations

Evolution of the RMP over time

- Expectation that the RMP changes over time –
  - Risks are removed, new ones introduced, activities completed, new ones started, due dates amended, etc.
  - New indications are added, or use in a new population is introduced, or changes in handling of the medicinal product
  - Safety profile becomes more well-established over time – less risks and activities expected in the RMP
  - Sometimes, even ‘empty’ – no important risks, missing information or additional activities

- Harmonisation of the RMP –
  - Different MAHs with medicinal products that contain the same active substance (generics)
  - In Europe, project (HaRP) where Health Authority publishes which risks and additional activities that can be used to keep RMPs aligned (limited to old products)
  - Alignment with RMP of innovator product (if possible)

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Considerations

Risk communication in risk minimisation activities

- For HCPs and/or patients and caregivers? What is the correct target audience?
- What is the best tool? How to ensure the message gets across?

Effectiveness measurement of risk minimisation activities

- Discussion on what and how in RMP – sometimes a study
- Not always easy to do in practice -

RMM: Prescription restriction	Indicator to assess effectiveness
Contraindication in patients with certain medical condition	% patients prescribed the drug with the contraindicated medical condition (EHR)
Restricted treatment period	% patients who were prescribed longer than recommended (EHR and PR)
Dose adjustment for concomitant medication	% patients with adjusted concomitant medication (EHR and PR)

Example:
Measurements in Electronic Health Records (EHR) or in Pharmacy Records (PR)

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Conclusions

- RMP describes the risks that need further characterisation or minimisation
- RMP is a ‘living document’ – it changes over time
- Routine activities are in place by default – RMP focus is on the additional activities
- Details of additional PV activities and additional risk minimisation should be in the RMP
- Measurement of effectiveness of additional risk minimisation measures can be challenging

Thank you

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