Drug Safety  Risk Identification, Analysis and Mitigation:

- The EU Risk Management Plan -

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Overview

- Risk Management System (EU-RMP)
- Risk Management during clinical development
  - Key Elements of Risk Management
  - Operating Model of Risk Management (SMTs)
  - Structure of the EU-RMP
  - Example: how to address an important identified risk into the EU-RMP
- Summary and Conclusions
Risk Management System (EU-RMP)

GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL PRODUCTS FOR HUMAN USE

may need to be submitted at any time of a product’s life-cycle (ie during both the preauthorisation and post-authorisation phases)

- mandatory for a new marketing authorisation and updates to previous EU-RMPs
- In case of significant changes to MA (new formulation, new route of administration, significant change in indication /patient population
- On request from CA or on company initiative e.g. in case of a safety issue with a marketed medicine

NOTE: complete list and description when an RMP is needed refer to EMEA/CHMP/96268/2005
Risk Management System (EU-RMP)

- aim is to ensure that the benefits of a medicine exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.
- This can be done either by increasing the benefits or by reducing the risks.

By its definition, risk management focuses upon the risk reduction approach.
Risk Management System (EU-RMP)

- A risk management system is 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 interventions.
- This requirement can be met by the submission of an EU-Risk Management Plan (EU-RMP)

(Doc.Ref. EMEA/192632/2006; Annex C: Template for EU-RMP)
Key Elements of Risk-Mgt

1. View on risk topics
   - Output from signal detection process
   - AE listings
   - Literature

2. Identify risks
   - Characterize the risk
   - Evaluate probability and impact (indication/ population)
   - Categorize the risk
     - Risk requires action
     - Risk requires no action beyond established procedures
     - Analyse revealed that risk topic is no risk
Key Elements of Risk-Mgt

1. Identify
2. Analyse
3. Increase knowledge about the risk and if needed:
   - influence behaviour to change the risk
   - restrict access to the medicinal product
4. Implement necessary actions
   - ensure completion and follow up of agreed actions
5. Measure effectiveness of actions to avoid/reduce risks

WCI GRMP Model
The purpose of establishing a SMT is

- to minimise the risk of patients in clinical studies and post approval
- to provide medical safety expertise and guidance for clinical projects
- to develop an RMP and to update this document during the clinical development phases to have a submission-ready RMP (at DP8)

The SMT plans and conducts risk management by thoroughly and routinely assessing all safety information.
Operating Model of Risk-Mgt

Safety Council

SMT MEMBERS
- Pharmacovigilance (lead)
- Medical Scientific Strategy & Medical Marketing
- Exploratory Clinical Development
- Toxicology
- Clinical Operations
- Regulatory
- Biometry/Pharmacov epidemiology

Independent reporting and escalation line

Safety Management Team

Regulatory SubTeam

Core Project Team
- Operations
- Non-clinical
- Clinical trial oper.
- Int'l marketing

MSS & MM

IP & MA

Other expertise will be invited as required
Operating Model of Risk-Mgt

Part I:
- Roles & Responsibilities
- Meeting schedule, Agenda, Minutes

Part II:
- Medicinal Product
  - Pharmacological Class Effects
- Indication
  - Aetiology, Epidemiology, symptoms, Treatments
- Development stage & relevant safety findings
  - Clinical Trials, Patient Exposure, ARs
- Critical Safety Parameters
  - AEs of Interest, AEs caused by background disease, other potential safety issues, potential and identified risks

Development of SMT Project Specific Guideline including a DRMP

Regular SMT Meetings

Ad Hoc SMT Meetings

SMT Lead
 Operating Model of Risk-Mgt

- Non Clinical findings
- AEs from CTs
- Post-Marketing Safety Data
- New safety information (literature/ epidemiological)
- Questions/ activities from Reg. Authorities
- Signal/ alerts from internal/external sources

SMT Meeting Conduct

Development of Recommendations on actions/ follow-up

Meeting Minutes

Information of Head of Pharmacovigilance and/or QP-PV in case of urgent recommendations

May lead to SMT GL (DRMP) update
Documention about ongoing Risk Mgt activities and rationales about decisions (inspection relevant)
Standard list of regulatory mandated risk factors considered at the SMT meetings

Potential Risks / knowledge gaps always to be considered:

- Hepatotoxicity
- Nephrotoxicity
- Immunogenicity (biologics)
- Bone marrow toxicity
- Effects on cardiac conduction / QTc prolongation
- Potential for reactive metabolite formation and hypersensitivity reactions
- Long-term toxicity
- Genotoxicity, carcinogenicity
- Reproductive and Developmental Toxicity
- Local tolerance
- Overdose
- Transmission of infectious agents
- Misuse for illegal purposes
- Off-label use
- Off-label-paediatric use
- Medication errors

Populations at risk / with knowledge gaps always to be considered:

- Paediatric patients
- Elderly patients
- Women of child-bearing potential
- Patients with renal impairment
- Patients with hepatic impairment
- Other potential high-risk populations or circumstances
Operating Model of Risk-Mgt

Recommendations and actions of the SMT during clinical development may include:

- No action
- Further investigations, targeted follow up (AE of special interest, Topic of special interest)
  - Non-interventional studies
  - Additional clinical trials
  - Additional nonclinical studies
- Update to core reference documents like IB
- Trial protocol/PI/ICF amendments (e.g. add specific inclusion/exclusion criteria)
- Additional training/communication/ Dear Doctor letters
- Establishment of ad hoc group for review of unblinded data
- Limitations to or discontinuation of Clinical Trials
- Project withdrawal
The EU-RMP

Part I (ICH E2E)
- Safety Specification
- Pharmacovigilance Plan

Part II
- Evaluation of the need for risk minimisation activities

If a need for additional activities
- Risk Minimisation Plan
The EU-RMP

Safety Specification

- Non-clinical safety concerns that have not been resolved by clinical data
- Limitations of the human safety database
- Populations not studied in the pre-approval phase
- Potential risks that require further evaluation
- Most important identified ADRs
- Identified and potential interactions
- Epidemiology of the indication(s) and important adverse events
- Pharmacological class effects

- summary of safety concerns
  - important identified risks
  - important potential risks
  - important missing information (populations potentially at-risk and situations that have not been studied)

- forms the basis of the evaluation of the need for risk minimisation activities and, where appropriate, the risk minimisation plan.
The EU-RMP

Pharmacovigilance Plan

– Routine Pharmacovigilance Practices (as described in the PV System: e.g. PSURS, ADR reports, signal detection)

– Summary of safety concerns and planned pharmacovigilance actions for each important identified and potential risk or important missing information

  • List of routine and additional pharmacovigilance activities (e.g. observational study, active surveillance, additional clinical trials) with description of

    – Objectives and rationale for proposed actions(s)
    – Description on how the safety concern and proposed actions is monitored by the MAA/MAH
    – Milestones for evaluation and reporting
The EU-RMP

• Evaluation of the need for risk minimisation activities
  – Evaluation of routine risk minimisation activities i.e. labelling and packaging is sufficient or if additional risk minimisation activities beyond routine activities are needed
  – The evaluation should also address the potential for medication error and if there is a need for additional (ie non-routine) risk minimisation activities:

• A risk minimisation plan
  – Risk minimisation activities:
    • Label and packaging (routine activities)
    • Education and training (e.g. Prescribing/Dispersion guide, Patient Cards)
    • Restricted distribution (e.g. restricted access programs)
How to address an important identified risk into the EU-RMP

1. **Risk Identification:**

   During phase III trials higher frequencies of AEs “Weight Decrease” on NEW DRUG occurred compared to PBO. “Weight decrease” was identified as ADR and safety topic of interest.

2. **Risk Analysis:**

   in further trials regular body weight measurements (prior to, during and after the treatment phase) and bioimpedance measurements were established. Investigators and study personnel were specifically trained to observe and document weight changes.

   - increased reporting of weight decreased in later studies reflects the developing of awareness of this ADR.
   - Specific subgroup analysis were performed to further characterize the safety profile of NEW DRUG (e.g. Indication severity subgroups, subgroups acc. to BMI classes, other AEs in parallel etc.).
   - Weight Decrease was evaluated as identified important risk and incorporated into the EU-RMP with appropriate risk minimisation activities.
From Safety Concern to Risk Minimisation activities

EU-RMP structure

<table>
<thead>
<tr>
<th>Safety Specification:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing safety concerns for the use of NEW DRUG</td>
</tr>
<tr>
<td>Important identified risk: WEIGHT DECREASE</td>
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</table>

| Pharmacovigilance Plan: |

| Evaluation of Risk minimisation activities: |

| Risk Minimisation Plan: |
From Safety Concern to Risk Minimisation activities

**Safety Specification:**
Important identified risk: WEIGHT DECREASE

**Pharmacovigilance Plan:**

**Planned action(s)**
- Routine PV
- Close follow-up of reported cases and special section in PSUR
- Long-term comparative observational post-marketing study

Evaluation of Risk minimisation activities:

Risk Minimisation Plan:
### From Safety Concern to Risk Minimisation activities

#### EU-RMP structure

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#### Evaluation of Risk minimisation activities:

<table>
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<th>Routine risk minimisation activities sufficient?</th>
<th>No</th>
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<td>Educational material for prescribers and patients will be distributed</td>
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#### Risk Minimisation Plan:
Risk Minimisation Plan for the Important identified risk WEIGHT DECREASE:

**Routine risk minimisation activities (i.e. product information, labelling and packaging):**

Section of the SmPC XX: … Body weight of underweight patients should be checked at each visit. Patients should be advised to check their body weight on a regular basis. In the event of an unexplained and clinically concerning weight decrease, the intake of NEW DRUG should be stopped and body weight should be further followed-up.

SmPC section XX: Weight decreased is included as common adverse reaction.

**Additional risk minimisation activity i.e. educational material:**

Objective and rationale:
To prevent any risk associated with substantial weight loss due to NEW DRUG treatment.

Proposed actions:
Educational material will be provided to prescribers at the time of market introduction and repeatedly at visits of company representatives to practices or hospitals. Patient cards will be provided to the patients with every prescription of NEW DRUG.

Criteria to be used to verify the success of proposed risk minimisation activity:
Negligible numbers of adverse reaction reports concerning serious cases of weight loss as reported with each PSUR.

Proposed review period:
Reports of serious cases of weight loss will be summarised with each PSUR.
Summary and Conclusions

- Risk-Mgt. is a systematic approach to identify and to handle risks (Identification, Analysis, Priorisation & Planning, Controlling & Reporting, Monitoring).

- EU-RMP may need to be submitted at any time of product’s lifecycle. It consists of a safety specification, a Pharmacovigilance Plan, an Evaluation of the need for risk minimisation activities and if needed a Risk Minimisation Plan.

- Risk-Mgt is a complex process, which needs a governance structure.
  - SMTs are an operating model to ensure patient safety and to document permanent safety evaluation of an medicinal product
  - SMTs should be established in a early stage of a clinical development and starting to develop an RMP to meet the regulatory requirements
Thank you for your attention

Questions?