The European Perspective on Risk Management

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GUIDELINE ON RISK MANAGEMENT SYSTEMS FOR MEDICINAL PRODUCTS FOR HUMAN USE
(EMEA/CHMP/96268/2005)
Legal Basis

- **Directive 2001/83/EC:**
  
  • **Art. 8 (3) (ia) requires:** A detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce”
  
  • **Art. 70 – 72 = Title VI describes:** conditions or restrictions which should be imposed on the legal status and supply or use of the medicinal product
  
  • **Art. 103 c, d:** role of qualified person for PV
Legal Basis

- Regulation 726/2004:
  - Art. 6 referencing RMP in 2001/83/EC
  - Art. 9 (4) referencing *Title VI* in 2001/83/EC
When is a risk management plan required?

- Submission for new marketing authorisation
  - All new active ingredients
  - ATMPs (Advanced Therapy Medicinal Products), Gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered products
When is a risk management plan required?

- Significant change to existing license, e.g. pharmaceutical form, new indication …

- Changes to the production process in biotechnology Products (re: ICHQ5E transformed into CPMP/ICH/5721/03)
When is a risk management plan required?

- **... and *may* in addition**: when seeking approval via centralized procedure for products NOT falling in the afore mentioned categories:
  - Known active substance (generics) only when there are ongoing risk minimisation activities of the originator
  - Bibliographical applications
  - Fixed combination products
When is NO risk management plan required?

- Generic products

- "for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant ...."

- This means that nothing is required where such emerging safety events have not occurred
The „formalism“

The description of a risk management system should be submitted in the form of an EU-RMP.

Formal guidance:  [Annex C of RMP Guideline](#)
Major Goals in Risk Management

- Risk detection
- Risk assessment

QUESTION: Need for risk-minimizing action?

-----------------------------------------------

- *Risk minimization*
  - EDUCATION (COMMUNICATION)
  - CONTROL
  - LEGAL STATUS
EU Risk Management Plan (EU-RMP)

Translate the goals into 4 steps:

- **Part I**
  - Risk detection = **Safety Specification** = Step 1
  - Risk assessment = **Pharmacovigilance Plan** = Step 2

- **Part II**
  - Evaluation of the need for risk minimization activities = Step 3
    
    *and (only) if there is a need for additional (i.e. non-routine) risk minimization activities*

  - Risk minimization plan = Step 4
EU Risk Management Plan

(Step 1) = risk detection

- Safety specifications

- **Non-clinical**: non-clinical safety findings that have **not** been adequately addressed by clinical data

- **Clinical**: limitations of human database (n), populations not studied, identified and potential AEs and Interactions, pharmacological class effects
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– Safety Specification (Step 1) = risk detection

IDENTIFIES:

• Important identified risk
• Important potential risk
• Important missing information
EU Risk Management Plan

– **Safety Specification** (Step 1) = risk detection

**Summary of Safety Specifications (section 1.10)**

ONLY (!) risks listed in 1.10 are carried forward into:

– the PV-Plan (step 2)
– the evaluation on the need for risk minimizing activities (step 3)
– additional risk minimising activities (step 4).

Results from step 2 and 4 go into the summary of the RMP!
**EU Risk Management Plan**

**Identified risk**, examples of identified risks include:

An adverse reaction **adequately demonstrated** in non-clinical studies and confirmed by clinical data

An adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference … **suggests** a causal relationship

An adverse reaction suggested by a number of **well-documented spontaneous reports** where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.
**EU Risk Management Plan**

Important identified risk
important potential risk
important missing information

IMPORTANT means:
“An identified risk, potential risk or missing information that could impact on the risk-benefit balance of the product or have implications for public health.” (Further definition NTA Volume 9 p 199)

Only IMPORTANT risks should go into summary of safety specifications (1.10). This means that not all AEs identified as risks need to be in the summary of the safety specifications (1.10).
– **Pharmacovigilance Plan** (Step 2) = risk assessment

• Section 2.1: Provide description of **routine pharmacovigilance system**, ref to Module 1.8 (detailed description of the PV-system acc. NTA Vol. 9.

• Section 2.2: For each safety concern (from 1.10 summary of safety specifications) provide a summary table of planned **additional pharmacovigilance activities**... Where only routine PV (see above), please justify.
What are additional PV activities?

= always new studies (labelling is routine risk minimisation and comes later!)

All activities to increase the available database

= intensify signal detection, e.g. to identify:
  – incidence rates in defined populations
  – rate ratio in comparison to reference product
  – how risk varies with different doses and duration of exposure
EU Risk Management Plan

- Pharmacovigilance Plan (Step 2) re: ICH

Methods to be used to intensify signal detection are epidemiological tools:
- stimulated reporting
- active surveillance
- observational studies … see Annex A to Guideline (!)
EU Risk Management Plan

– Pharmacovigilance Plan (Step 2)

Needs to include

– study protocol
– timelines
– action plan
– decision-making process for handling of new data
## EU Risk Management Plan

### Pharmacovigilance Plan

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>&lt;&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action(s) proposed</td>
<td>&lt;&gt;</td>
</tr>
<tr>
<td>Objective of proposed action(s)</td>
<td>&lt;&gt;</td>
</tr>
<tr>
<td>Rationale for proposed action(s)</td>
<td>&lt;&gt;</td>
</tr>
<tr>
<td>Detail further measures which may be adopted on the basis of the results of this action and the decision criteria for initiating such measures</td>
<td>&lt;&gt;</td>
</tr>
<tr>
<td>Milestones for evaluation and reporting including justification for choice of milestones</td>
<td>&lt;&gt;</td>
</tr>
<tr>
<td>Titles of protocols (Annex full study protocols and provide cross reference to position an annex 5)</td>
<td>&lt;&gt;</td>
</tr>
</tbody>
</table>
— Now it comes to RISK MINIMISATION
EU Risk Management Plan

— Evaluation of the need for risk minimization activities (Step 3):

- For each safety concern (from summary of safety specifications 1.10) provide a summary table and evaluate and justify whether routine risk minimisation activities (product information, labelling and packaging) will be sufficient …
– Evaluation of the need for risk minimization activities (Step 3):

- … or whether additional risk minimisation activities (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes) will be required.
EU Risk Management Plan

- Evaluation of the need for risk minimization activities (Step 3):

  The guidance document says:
  
  - “It is possible that the risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by the careful use of labelling and packaging, which are considered as routine risk minimisation activities.”
  
  - If only routine risk minimisation activities are required there is no need to submit a risk minimisation plan.
  
  - If additional risk minimisation activities are necessary a risk minimisation plan should be provided (see section 4).
### EU Risk Management Plan

**Part II: concerns = list from safety specifications**

**Evaluation of the need for risk minimization activities (section 3)**

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimization activities sufficient?</th>
<th>If yes, provide description of routine activity and justification</th>
</tr>
</thead>
</table>
| Concern 1      | Yes                                             | § Section 4.2 provides specific guidance on the method of administration  
|                |                                                 | § Warning in section 4.4 of the SPC                     
|                |                                                 | § Listed as ADR in section 4.8                             |
| Concern 2      | No                                              | Refer to Risk Minimisation Plan (section 4) for additional risk minimising activities  
|                |                                                 | For routine measures refer to Risk Minimisation Plan as well  |
EU Risk Management Plan

- If „routine“ risk minimisation is not sufficient and additional risk minimisation activities are thought necessary, the Applicant should provide a Risk Minimisation Plan within Part II of the EU-RMP = go to step 4
EU Risk Management Plan

— **Risk minimization plan (Step 4)**

**Includes:**

For each of the safety concerns form safety specification:

— routine risk minimisation (SPC, Label)

— PLUS additional risk-minimizing action
  
  • and how effectiveness of proposed actions will be evaluated

  • and timelines & proposed review period
WHAT IS ADDITIONAL RISK MINIMISATION?

- Education
- Control
- Legal status of the medicine

- Different from PV-Plan (step 2) as these tools should have immediate effect on benefit/risk
- Annex B: detailed guidance
Risk-Minimization and Communication

- **Education**
  - **Patient**
    - Educational material, handout like “patient alert card” (the SPC is “education” but belonging to “routine risk minimisation)
  - **Physician/Pharmacist**
    - HC professional letters (“Dear doctor” letters)
    - Physicians/Pharmacists guide to prescribing/dispensing (e.g. GLIOLAN)
    - Sales force training, promotional material
Risk-Minimization and Communication

- **Control of the Medicine**
  - Control at pharmacy level (pharmacist to educate)
  - Prescription validity and prescription size limitations
  - Restricted access programs (patients have agreed to specific surveillance program)
Risk-Minimization and Communication

- **Legal Status of the Medicine**
  - Reserved for treatment in hospital environment
  - Outpatients supervised by specialists
  - Approval to be renewed after 1 year (relevant for conditional approval)
### EU Risk Management Plan

**4. Risk Minimisation Plan**
For each important identified or potential risk for which **additional** risk minimisation measures are planned, provide the following:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine risk minimisation activities</strong> (i.e. product information, labelling and packaging)</td>
<td>&lt; Short description of what will be put in the SPC, labelling etc. to minimise risk, e.g. warning in 4.4 that caution should be used in patients with cardiac failure&gt;</td>
</tr>
<tr>
<td><strong>Additional risk minimisation activity 1</strong> (e.g. educational material or training programmes for prescribers, pharmacists and patients, restricted access programmes)</td>
<td><strong>Objective and rationale</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Proposed actions</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Criteria to be used to verify the success of proposed risk minimisation activity</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Proposed review period</strong></td>
</tr>
</tbody>
</table>
Recap ...

- **Routine pharmacovigilance** = Pharmacovigilance activities as specified in Regulation (EC) No 726/2004 and Directive 2001/83/EC that should be conducted for all medicinal products.

- **Routine risk minimisation activities** = The warnings and information contained within the Summary of Product Characteristics and Patient Leaflet, and the careful use of labelling and packaging, which aim to reduce the probability of an adverse reaction occurring or its severity should it occur.
## Summary of the EU-RMP

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance Activities (routine and additional)</th>
<th>Proposed risk minimisation Activities (routine and additional)</th>
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<tr>
<td>Safety concern 1</td>
<td>E.g.</td>
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<tr>
<td></td>
<td>• routine Pharmacovigilance</td>
<td>• contraindication in section 4.3 of the SPC</td>
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<tr>
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<td>• Drug utilisation study to investigate …….</td>
<td>• Warning in section 4.4 of the SPC that …….</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Education material</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Controlled distribution</td>
</tr>
<tr>
<td>Safety concern 2 etc</td>
<td></td>
<td></td>
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### Summary of the EU-RMP

#### Signal Detection

**PV-Plan**

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#### Risk Management

**Risk-Minimisation Plan**

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Annex C "EU-RMP Template" requires a contact person signature

- **Responsible:** QPPV (content)
- **Signature:** no formal requirements (e.g. QPPV, Contact Person)
Meaning for the Company

- No RMP = no approval!
- Standard for new applications in new therapeutic areas
Define Your “stakeholders” for RMP

- Need for RMP to be discussed / addressed well in advance:
  - **Company**
    - Bring together all parties involved
    - Suggest “ownership” for RMP documentation
  - **Agency**
    - New element to consider for early SA meetings
    - Gain common understanding on content
    - Agree on long-term strategy (timelines, milestones, updates, submission strategy)
RMP Submission Strategy

- The RMP is part of the CTD
- Located in Module 1.8.2
- Discussed in Clinical Overview (2.5)
- Updates should be submitted at the same time as the next Periodic Safety Update Report
- or ... unless other requirements have been laid down as a condition of the marketing authorization (Vol 9A NTA, p 48)
European Particularities in 724/2006

• „conditional“ approval (Art. 14, 7) and approval under „exceptional“ circumstances (Art. 14, 8)

... and the role of the RMP
Regulation 726/2004, Article 14, 7

- “… authorisation may be granted subject to certain specific obligations to be renewed annually by the Agency

- … The provisions for granting such authorisation shall be laid down in a Commission Regulation adopted in accordance with the procedure referred to in Article 87(2)”

  • … and this Commission Regulation is: EC 507/2006
EC 507/2006 : Conditional Approval

Scope (507/2006 Art 2) :

1. seriously debilitating or life-threatening diseases
2. emergency situations in response to public health threats
3. orphan medicinal products
EC 507/2006: Conditional Approval

- Valid for 1 year
- Renewable, to be switched to a regular MA

E.g. Sutent (PFIZER), Velcade (JANNSEN)
Exceptional Circumstances

Regulation 726/2004, Article 14, 8.

- ... applicable when, in respect of particular therapeutic indications, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use
Exceptional Circumstances

- Authorization must be based on one of the following grounds (set in Annex I to Directive 2001/83/EC):
  - Rarity of disease (e.g. orphans)
  - If it would be contrary to generally accepted principles of medical ethics to collect such information (e.g. pandemics, war, terrorist attacks) e.g. develop vaccine against anthrax

Annual re-assessment of these conditions is foreseen
Conclusion: the formal requirements of the RMP may increase the chances to make use of the conditions offered by conditional or exceptional approval
RMP: THREAT or OPPORTUNITY ?
The RMP formalism forces you to structure and to direct your thinking to an appropriate risk management.
RMP: THREAT or OPPORTUNITY?

The obligation to submit an RMP may create an internal mandate to discuss in a cross-functional manner all results, from pre-clinical to clinical.
RMP provides a platform to discuss potential risks at a very early stage with the Agency.
RMP may allow for an earlier submission as it provides a structured approach to handle data gaps (e.g. conditional approval).
RMP may make a product approvable and consequently availability to patients. This is true for risks that would not even go away with the conduct of new studies.
Recent European Agency Feedback on RMP

EXAMPLE 2

TYSABRI
TYSABRI (Natalizumab)

Natalizumab is a recombinant monoclonal antibody to prevent migration of defined leucocyte populations into inflamed tissue. FDA approval withdrawn following 3 cases of progressive multifocal leukoencephalopathy (PML)

- FDA approved Nov 23, 2004
- Withdrawn Feb 2005
- FDA re-approved June 5, 2006
- EMEA approved 2006
EMEA approval was only possible by strictly applying the rules of a RISK MANAGEMENT PLAN!

Same was taken by FDA
The Member states shall assure that: The Marketing Authorisation Holder will implement nationally…that all physicians who intend to prescribe Tysabri are provided with a physician pack containing the following information:

1. **Product information**
2. **Physician information about Tysabri**
3. **Patient alert card**

*See EPAR for Tysabri*
The Member states shall assure that the Marketing Authorisation Holder will implement nationally, and as agreed with the Competent Authorities in the Member States, that all physicians who intend to prescribe Tysabri are provided with a physician pack containing the following information:

1. Product information
2. Physician information about Tysabri
3. Patient alert card
The applicant has designed a Pharmacovigillance Plan, including **risk mitigation activities**, using a number of different approaches to further **clarify and characterize** unresolved safety issues…
EMEA EPAR from 2006 cont.:

…and at the same time allow ongoing safe use of the drug …”


= MISSION COMPLETED !
THANK YOU !