The EU Risk Management Plan: Does A Common Standard Exist?

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Risk management - external expectations

- Public: regulators should improve the protection of public health
- Regulators: companies should
  - Understand the risks associated with their products
  - Communicate identified risks more clearly
  - Implement measures that minimise risk
- Risk management plans are now a reality

ICH E2E – Pharmacovigilance Planning

- Describes method for summarising identified & potential risks, and limitations in the pre-approval safety data
- Proposes structure for pharmacovigilance plans
- Sets out principles of good practice for design and conduct of observational studies
- Does not encompass risk mitigation activities

Safety Specification & Pharmacovigilance Plan

- Safety Specification
  - Important known risks
  - Potential for important unidentified risks
  - Populations potentially at risk
  - Situations not adequately studied
- Pharmacovigilance Plan
  - Summary of ongoing safety issues
  - Description of routine pharmacovigilance practice
  - Safety action plan for specific issues and/or important missing information
  - Summary of actions to be completed, including milestones

Risk Management

- **Risk Management**: the identification and implementation of strategies to reduce risk to individuals and populations

  Risk Assessment plus Risk Minimisation

- **Risk Management Plan**: a plan identifying the risks associated with a medicinal product, methods to further clarify the safety profile of a product, and ways to minimise risk to individual patients in clinical use

Risk Management Plans

- Should address all aspects of risk management
  - **Safety Specification** - structured method for documenting the established important risks of a drug and the potential for important unidentified risks
  - **Pharmacovigilance Plan** - proposes collection of data to clarify the safety profile, to demonstrate safety as well as identify harm
  - **Risk Minimisation Activities** - activities required to reduce risk to individual patients and populations
- Each plan should be unique for the product under consideration

Risk minimisation activities

- All products require high quality pharmacovigilance & product labelling
- Some products may require specific intervention to minimise risk, e.g.:
  - Information directed at prescribers, pharmacists and/or patients
    - Patient educational programs
    - Healthcare provider education programs
    - Certification programs for prescribers and pharmacists
    - Additional education forums
  - Specialised packaging
  - Controlled access and/or product distribution channels

EU Risk Management Plans

- European Union Guideline on Risk Management Systems for Medicinal Products for Human Use [EMEA/CHMP/96268/2005]
  - Annex C: Template for EU Risk Management Plan [EMEA/192632/2006]

EU Risk Management Plans

- **Part I**
  - Safety Specification
    - To include the potential for:
      - Overdose
      - Transmission of infectious agents
      - Misuse for illegal purposes
      - Off-label use
      - Paediatric use
  - Pharmacovigilance Plan
- **Part II**
  - Evaluation of the need for risk minimisation activities
    - Potential for medication errors
  - Risk minimisation activities
  - Assessment of effectiveness of risk minimisation activities

EU Risk Management Plan Template

- One size does not fit all!
  - RMP should meet the needs of the product concerned
  - Pragmatism is advised
- Detailed set of requirements
  - Lacks explanatory text: could lead to inconsistent interpretation of requirements
  - Extensive use of tables
    - Regulators should not expect a complete dataset for every product
    - Seemingly ignores one Member State's wish for use of graphics (e.g. Kaplan-Meier curves)
  - Numeration of section headings is non-sensical
    - Practical difficulties arise when developing in-house template

EU Risk Management Plan Template cont'd

- Template requires brief description of the pharmacovigilance system, with cross-reference to the detailed description provided within the MAA submission
  - What is required for products already on the market?
- How will Annex 1 work?
  - Companies to provide identified and potential risks electronically so that they can be monitored on EudraVigilance
    - Applies to centrally authorised products only
    - Update to be provided whenever EU-RMP is revised
  - **Industry should be consulted on its development and operation**
- Unclear rationale for Annex 5 (study protocols) and Annex 6 (study reports)
  - Suggest these should be kept available upon request rather than submitted each time

Type II Variations

- Seemingly not required for amendment to EU-RMPs
- But it appears they are required for any amendment to the Detailed Description of Pharmacovigilance System
  - Does not promote the concept of 'living' documentation
- Type II variations should not be necessary for amendments to the Detailed Description
  - If a Type II variation is necessary, it should be applied to a single Master File than can then be used in support of all marketing authorisations by that company

AstraZeneca Patient Risk Management Plans

- Cross-functional SOP in effect since July 2005
- PRMPs are prepared for:
  - All investigational products (Phase I-III)
  - New marketed products
  - Existing marketed products (significant change in indication and/or formulation)
- Global PRMPs
  - AZ template based upon EU-RMP template
  - Provides basis for EU-RMP and Local RMPs
    - LRMPs adapted in accordance with local requirements

AstraZeneca Patient Risk Management Plans

- Product A (new product)
  - Extensive pharmacoepidemiology programme & enhanced pharmacovigilance, to clarify safety profile
  - Prescriber education: "*10mg is the start dose*"
  - Specialist prescription of highest dose in some countries
- Product B (new product)
  - Post-marketing safety studies & enhanced pharmacovigilance
  - Hospital prescription only
- Product C (established product)
  - Patient, prescriber & healthcare provider education programmes, for new treatment paradigm

AstraZeneca Patient Risk Management Plans

- Products D, E & F (established products)
  - New indications or formulation
  - Routine safety surveillance & product labelling should suffice
    - Deemed insufficient for one product: revision in progress (addition of pharmacoepidemiology studies)
- Product G (withdrawn from market)
  - Hepatic surveillance program proposed, to clarify risk of liver toxicity
    - 'No blood/No drug' & use of registry considered

Other Companies

- **Accutane** (Roche & others): birth defects
  - Strengthened distribution programme
- **Exubera** (Pfizer/Sanofi-Aventis): immune responses, cancer risk
  - Clinical trials (incl. 5-year extensions), epidemiology studies, mechanistic studies, 'real-world' surveillance
- **Orencia** (BMS): infection and cancer risk
  - Long-term follow up (clinical trials), enhanced pharmacovigilance, epidemiology studies, pregnancy registry
- **Pargluva** (BMS & Merck): cardiovascular events
  - Clinical trials (incl. sub-populations), epidemiology studies, post-marketing surveillance, physician education
- **Prexige** (Novartis): cardiovascular risk
  - Enhanced pharmacovigilance, epidemiology studies, special packaging (high dose), prescriber education
  - **Published on MHRA web-site**

Challenges (Internal)

- Limited experience to learn from; shared learning is essential
- Risks need to be managed in diverse settings
  - Global risk management strategy cascaded into specific local operational activities
- Monitoring the effectiveness of risk management strategies: how do we do it?
- Getting ‘buy in’ from all parts of the business, to encourage a proactive risk management culture

Challenges (External)

- Limited experience to learn from; shared learning is essential
- EU-RMPs must conform with the CHMP guideline
  - **Regulatory agencies should not be dogmatic in their application of the template**
- Description of the Pharmacovigilance System
  - Core component of any risk management strategy
  - **Member State authorities should accept a single description submitted on a pan-EU basis, covering the entire product portfolio, based upon guidance within Volume 9A**
- It should not be necessary to submit an EU-RMP with every PSUR, if no revisions have been made

Challenges (External) cont'd

- Inconsistent/uncertain regulatory expectations
  - When are post-marketing safety studies required?
  - When are additional risk minimisation activities required?
  - When can registries be established as a means of assessing/managing risk?
  - What is the process for review and discussion of draft RMPs?
- Some regulatory authorities seem reluctant to accept data from other countries when assessing risk to national health
- National RMPs should be required by exception and only if justified by differences in medical practice etc
- Need early collaboration with key regulators to define and manage expectations

Future Expectations

- Regulatory authorities will request more safety-oriented clinical studies that previously
- Sales forces provide an excellent opportunity for effective delivery of safety information
- Monitoring of prescribing practices will increase
  - Will real time use of electronic medical records be feasible?
  - Will authorities seek active minimisation of off-label use?
    - **Role of regulators and MAHs will need to be defined**
- Methods need to be developed that enable consistent measurement of effectiveness of risk management activities

Recommendations

- **A common standard is essential**: RMPs should be discussed and agreed without the need for multiple strategies and duplicative negotiations with individual Member States
  - Should not be a need for greater variation than that justified by differences in population characteristics, disease epidemiology, medical practice or legal/cultural factors
- RMPs should focus on issues which have appreciable scientific evidence and public health impact
  - Safety Specification should only have to detail important risks
  - Need clear thresholds/criteria for when additional risk assessment and minimisation activities are necessary
  - Good pharmacovigilance and product labelling should suffice for most products, particularly those with no special safety concerns

Recommendations cont'd

- Risk assessment data from all sources should be acceptable without the need to duplicate activities across countries
- Summary information may be more appropriate for public display than unrestricted access to full RMPs
- Further consideration should be given to the presentation and assessment of benefits to patients

Conclusions

- Risk management plans are a reality
- Regulatory expectations are high
- A single EU standard for risk management should exist but will Member States facilitate or hinder this?