Integrating Risk Management with Clinical Development Programmes

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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.
Confidence about the safety of medicines

Launch

Postmarketing

Information

Kent Wood - MHRA
Pharmacovigilance Planning

- Safety specification
- Pharmacovigilance/risk management plan
- Risk minimisation methods
- Monitor efficacy of methods applied
When is a RMP needed

• New product (including biological products) containing a new active substance
• Significant change in a marketing authorisation e.g.
  • new dosage form
  • new route of administration
  • new manufacturing process of a biotechnologically-derived product
• significant change in indication
  • unless it has been agreed with the Competent Authority
  • that submission is not required;
• New safety issue
When is a RMP needed

• On request from a Competent Authority (both pre- and post authorisation)
• On the initiative of an Applicant/MAH when they identify a safety concern with a medicinal product at any stage of its life cycle
Epidemiology

• The epidemiology of the indication(s) should be discussed.
• Incidence
  – Prevalence
  – Mortality
  – Relevant co-morbidity

• Should take into account, whenever possible, stratification by:
  – Age
  – Sex
  – Racial and ethnic origin

• Difference in epidemiology in different regions, where feasible,
  (because the epidemiology of the indication(s) may vary across the regions),
  but the emphasis should be on epidemiology in the EU.
A systematic review of the epidemiology of gastro-oesophageal reflux disease (GORD) has been performed, applying strict criteria for quality of studies and the disease definition used. The prevalence and incidence of GORD was estimated from 15 studies which defined GORD as at least weekly heartburn and/or acid regurgitation and met criteria concerning sample size, response rate, and recall period. Data on factors associated with GORD were also evaluated. An approximate prevalence of 10-20% was identified for GORD, defined by at least weekly heartburn and/or acid regurgitation in the Western world while in Asia this was lower, at less than 5%. The incidence in the Western world was approximately 5 per 1000 person years. A number of potential risk factors (for example, an immediate family history and obesity) and comorbidities (for example, respiratory diseases and chest pain) associated with GORD were identified. Data reported in this systematic review can be interpreted with confidence as reflecting the epidemiology of "true" GORD. The disease is more common in the Western world than in Asia, and the low rate of incidence relative to prevalence reflects its chronicity. The small number of studies eligible for inclusion in this review highlights the need for global consensus on a symptom based definition of GORD.
Pharmacovigilance Plan

- The objectives differ according to the issue
- For important identified and potential risks, the objectives are:
  - Measure the incidence rate in a larger or different population
  - Measure the rate ratio or rate difference in comparison to a reference medicinal product
  - Examine how the risk varies with different doses and durations of exposure
  - Identify risk factors
  - Assess causal association
Clinical Part of the Safety Specification

• Limitation of the Human Safety Database
  – The size of the study population
  – Study inclusion/exclusion criteria

  With the implications of such limitations with respect to predicting the safety of the product in the market place

  Particular reference should be made to populations likely exposed during the intended or expected use of the product in medical practice
Clinical Part of the Safety Specification
Limitations of the database

• In terms of frequency of adverse events detectable given the size of the database
• Regarding suspected long-term adverse reactions (e.g. malignancies) when it is unlikely that exposure data is of sufficient duration and latency
Populations not studied in the pre-authorisation

- Populations which have not been studied or have only been studied to a limited degree in the pre-authorisation phase
- The implications of this with respect to predicting the postmarketing safety should be explicitly discussed
Specification in risk management plans: lessons learned from a pilot project.

CL, Evans SJ, Waller PC, Shakir S, Payvandi N, Murray AB.

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The ICH E2E guideline, risk management plans (RMP) defining the cumulative limitations in safety information are now required for marketing authorisation. In this project was conducted to gain experience with tools for presenting the information. This paper presents those tools found to be useful and the methods. Data was obtained from a successful MAA were utilised. Methods were used to evaluate the sensitivity of the clinical data and identifying safety signals from adverse event and laboratory data. RESULTS: The extent of clinical safety experience was assessed over time. Adverse event data were presented using dot plots, patients with the events of interest, the odds ratio, and 95% confidence interval plots were utilised for evaluating the sensitivity of the clinical database. Box and whisker plots were used to display laboratory data. CONCLUSIONS: New evidence-based methods for presenting and evaluating clinical safety data advance the way safety data from clinical trials can be analysed and suggests the importance of early and comprehensive planning of the safety package, especially in epidemiology data.

Related Articles

- Identification and evaluation of a possible signal of exacerbation of colitis during rofecoxib treatment, using Prescription-Event Monitoring data.
- Pharmacovigilance during the pre-approval phases: an evolving pharmaceutical industry model in response to ICH E2E.
- CIOMS VI, FD:
- Evolving paradigms in pharmacovigilance.
- Risk management strategies in the postmarketing period: safety experience with the US and European hospetan surveillance programmes.
Extent of Clinical Safety Experience: Number of Patients Exposed by Time

During development based on intended numbers to be treated
- For duration of follow-up e.g. for vaccines
Extent of Clinical Safety Experience: Number of Patients Exposed by Time by Age-Group

Exposure plot can be produced:
By sub-groups e.g. age, gender, dose, study type (open-label v double-blind)
Limitations of the premarketing database

- Populations considered for discussion should include (but not limited to):
  - Children
  - The elderly
  - Pregnant and lactating women
  - Patients with relevant co-morbidity, such as hepatic or renal disorders
  - Patients with disease severity different from that studied in clinical trials
  - Sub-populations carrying known and relevant genetic polymorphism
  - Patients of different racial and/or ethnic origins
RMP

• More closely based on
  – product specific issues identified in pre- or post-authorisation data
  – pharmacological principles
The incidence of identified or potential ADRs in the underlying population
Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data
Hennesy et al. BMJ.2002;325:1070

- Cohort of patients with schizophrenia treated with antipsychotic drugs, a control group with glaucoma and a control group with psoriasis
- Outcome measure diagnosis with cardiac arrest or ventricular arrhythmia

Patients with schizophrenia had higher rates of cardiovascular death than controls ranging from 1.7 to 3.2
Identified risks that require further evaluation

• Most important identified ADRs
  – Serious or frequent ADRs that might have an impact on the benefit/risk balance

Information on the evidence bearing on:
  – causal relationship
  – Severity
  – Seriousness
  – Frequency
  – Reversibility
  – At risk groups
Potential risks that require further evaluation

• Important risks should be described with the evidence that led to the conclusion that there was a potential risk

• For important potential risk, there should be a further evaluation that characterises the evaluation further
Presentation of safety concerns

• Classification of the safety concern by:
  – Dose
  – Time
  – Risk factors

• Analysis of susceptible patients possibly by from analysis of cases
Identified Risk

• An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include:
  – an ADR adequately demonstrated in non-clinical studies and confirmed by clinical data
  – an ADR in well designed clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest suggest a causal relationship
  – an ADR suggested by a number of well documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic site reactions.
Important Identified Risk, Important Potential Risk or Important Missing Information

• 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
Missing Information

• Information about the safety of a medicinal product which is not available at the time of submission of the EU-RMP and which represent limitations of the safety data with respect to predicting the safety of the product in the marketplace
Potential Risk

- An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples of potential risks include:
  - Non-clinical safety concerns that have not been observed or resolved in clinical studies.
  - Adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on the parameter of interest raises suspicion of, but is not large enough to suggest a causal relationship.
  - A signal arising from the spontaneous adverse reaction reporting system
  - An event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product
Pharmacological Class Effects

• Risks believed to be common to the pharmacological class
• If a risk thought to be common to the pharmacological class is not thought to be of safety concern with the medicinal product, this should be justified
Additional Requirements
(if the potential risk is considered to be significant)
Significant means that there is a reasonable likelihood that it will occur

• Potential for overdose, special attention in particular cases, e.g.
  – narrow therapeutic margin
  – significant toxicity and/or there is an increased risk of overdose in the target population
Potential for misuse for illegal purposes

• The Potential for misuse should be considered
• If appropriate, the means for limiting this, e.g. by use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the RM plan. (Evaluation of the Need for Risk Minimisation Activities)
Potential for off-label paediatric use

- If the disease being treated or prevented is found in the paediatric population, the potential for off-label paediatric use should be discussed
Summary

- Important identified risks
- Important potential risks
- Important missing information
Pharmacovigilance Plan

• Routine pharmacovigilance for products with no specific safety concerns
• Additional pharmacovigilance activities, for products with
  - Important identified risks
  - Important potential risks
  - Important missing information

Example Routine pharmacovigilance is likely to be inadequate when a potential risk has a significant background incidence in the target population(s)
Pharmacovigilance Plan

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Pharmacovigilance Plan

• For important missing information the objective is to investigate the possibility of a risk or provide reassurance about absence of a risk
Threshold for investigating further depends on the indication, target population and the likely impact on public health.

For example a safety concern with a vaccine will have a different threshold for investigation than the same issue in a medicine used in the palliative treatment of metastatic cancer.
• Write as many parts as possible of the desired SmPC
• Develop SS and RMP as early as possible – end of phase 2/beginning of phase 3
Early writing of RMP

Based on dynamic assessment of
Potential risks
Identified risks
Missing information

The efficient approach is to develop a RMP:
• Modify pre-marketing studies, when necessary
• Or conduct additional study (studies) to ensure that the licence is granted or not delayed
• Sometimes, for example, when there is insufficient data on long term usage, it may sufficient to prolong the monitoring of safety in an open extension of large trials
Safety Specification, Pharmacovigilance Planning and Risk Minimisation

• Safety specification – defines systematically what is known and what is not known about the safety of the product
• Pharmacovigilance planning – builds on the Safety Specification to enrich the evidence base
• Risk Minimisation – applies measures based on the best possible evidence
• Monitor effectiveness of actions
Known knows
Known unknowns
Unknown Unknowns

Unknown unknowns which could have been known unknowns or known knowns!!
Assessing and responding to the effectiveness of the RMP

- Assessment of the effectiveness of the interventions
- Alternative methods need to adopted if a particular risk minimisation strategy is ineffective.
- Surrogate measures while waiting for risk minimisation measurements, for example:
  - Surveys to assess whether the information is being effectively communicated
  - Drug utilisation studies to assess how uniformly advice is being adhered to, e.g. reviewing concomitant medications or lab tests.
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