Risk Management in the Pharmaceutical Industry

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Topics

Environment
Safety Risk Management Guidance
Safety RM Systems
Signal detection and evaluation
Challenges for the PV department
Moving towards integrated RM
Background

The MAH must ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility and liability for its products on the market and to ensure appropriate action can be taken, when necessary (*Volume 9*)

„Now we have more effective medicines, so the adverse event profile is becoming increasingly important. Indeed, a good safety profile can be a good selling point. The choice of drug often no longer comes down to which is the most effective – there is often little to choose between similarly efficacious products. It‘s which is the safest.“ (*Arnold Chan, Associate Professor, Harvard School of Public Health*)
Patients – have high expectations for inexpensive risk free products

Healthcare providers - want clear risk/benefit assessment

Healthcare purchasers - want value for money

Public, media and shareholders - over-react to risk surprises

Regulatory Authorities - are increasingly risk averse

Health technology assessment agencies - expect best value (risk/benefit) for money

Healthcare policy makers - ask for more control of pharmaceutical industry and increase pressure on price

Liability insurers - refuse coverage for certain products, increase premium
Regulatory Guidance on Safety Risk Management

FDA Guidance (March 2005)
- Premarket Risk Assessment
- Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
- Development and Use of Risk Minimization Action Plans (RiskMAP)

ICH E2E: Pharmacovigilance Planning (Nov 2004)
- Safety Specification
- Pharmacovigilance Plan

EU Guideline on Risk Management Systems for Medicinal Products for Human Use (Sep 2005)
Regulatory Guidance on Safety Risk Management

The Guidance suggest
- **documents** needed for future submissions, describing our
- post-approval **activities unless identified issues are resolved earlier**

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<td>&quot;How will we characterise the safety risks and close the knowledge gaps, and by when?&quot;</td>
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ICH E2E: Safety Specification

• Summary of the important identified
  • Risks
  • Potential risks
  • Missing information

• Should identify
  • Populations potentially at-risk
  • Outstanding questions which warrant further investigation to refine understanding of the benefit-risk profile

• Can be built during the pre-marketing phase
• At the time of submission, should reflect the status of issues that were being followed
ICH E2E: Safety Specification

1. Non-clinical
   > Toxicity: repeat-dose, reproductive, nephrotox., hepatotox., genotox., etc.
   > General pharmacology: CV incl. QT prolongation, nervous system etc.
   > Drug interactions
   > Other toxicity-related information or data

2. Clinical
   > Limitations of the human safety database: size, inclusion/exclusion criteria
   > Populations not studied in the pre-approval phase: children, pregnant, renal etc
   > Adverse events / adverse drug reactions
   > Identified and potential interactions: evidence, potential risks
   > Epidemiology of the indication, important adverse events (background incidence)
   > Pharmacological class effects

3. Summary
   > Important identified risks
   > Important potential risks
   > Important missing information
ICH E2E: Pharmacovigilance Plan

- Based on Safety Specification
- For any important risk, potential risk, or missing information additional actions designed to address these concerns should be considered
- Developed by sponsor and can be discussed during development, prior to approval, or when a concern arises post-marketing
- Stand-alone or part of CTD
Risk Management Systems

“A set of pharmacovigilance activities and interventions designed to proactively identify, characterize and prevent or minimize risks relating to medicinal products, including risk communication and the assessment of the effectiveness of risk minimization activities.”

Draft EMEA Guideline
Terminology in Safety Risk Management - EU

1. Risk Identification
   - Pre-marketing Risk Assessment
     - PV/Safety Specification
     - Pharmacovigilance Plan
       - (“routine” + “enhanced” PV)

2. Risk Assessment

3. Risk mitigation (action)
   - Risk Minimization Action Plan

4. Evaluation of action taken
   - Risk Management Plan
What is Risk Management?

The activities and interventions deployed to a chemical entity/group, in order to manage and mitigate known and possible risks, with the aim of protecting the individual

Continuous process to minimize a product’s risks throughout its life cycle >> optimize the benefit /risk balance

Risk management thinking should begin at the earliest stage of new drug development and continue throughout the whole life cycle. It includes proactive risk assessment and development of plans for interventions to manage patients risk.
Objectives of Safety Risk Management Planning

- Common understanding of medical safety risks within IPT and company

- Agreement on strategy and action plan(s) to systematically address all issues pre- and/or post-approval, aimed to:
  
  > Characterise risks (e.g. mechanism, background incidence, relative risk, risk groups) to protect patients and minimise impact for company

  > Continuously build robust dataset to support safety claims

  > Prepare dossier relevant regulatory documents based on matured safety profile (Safety Specification and Pharmacovigilance Plan)

  > Comply with DSMB and HA requests
Definitions

**Risk estimation** – the identification of the outcomes, the estimation of the magnitude of the associated consequences of these outcomes and the probability of these outcomes.

**Risk assessment** – the integrated analysis of the risks inherent in a product and their significance in an appropriate context.

**Risk evaluation** – the appraisal of the significance of a given quantitative (or when acceptable, qualitative) measure of risk.

**Risk management** – the process whereby decisions are made to accept a known or assessed risk and/or the implementation of actions to reduce the consequences or probability of occurrence.
Protection from Harm: Safety Risk Management
Pharmacovigilance Activities

"Routine" PV

- "good" case reports
- expedited ADR reporting
- good follow-ups
- reporting rates
- PSURs / PR
- labeling updates
- liaison with regulatory authorities
- data mining / continuous monitoring
- signal evaluation

"Enhanced" PV

- solicited reporting
- drug event monitoring
- drug / disease registry
- survey (cross-sectional study)
- case control / cohort study
- targeted clinical investigation
- large simple safety study
- descriptive study of natural history of disease
- drug utilisation study
Management of Safety Risks

Detection
Assessment
Minimization
Communication
Evaluation of Actions

Signal Detection and Evaluation
What is a signal?

A significant piece of new information detected internally or provided by regulators or by other external sources that raises concerns about the possibility of a new adverse drug reaction, passed one formal review, documented as a signal and triggers further evaluation.
1. Quantitative Safety Indicator:

A hypothesis of a causal association between a drug and an unanticipated, unfavourable safety finding, which is generated by statistical methods (e.g. PRR, specific algorithms) and has not undergone a qualitative review / plausibility check by a safety expert.
2. **Signal:**

A report or reports of an event with unknown causal relationship to treatment that is recognized as worthy of further exploration and continued surveillance. (CIOMS VI)
3. Safety Concern:

New safety information which upon initial analysis, at least to the level of a preliminary assessment report, suggests to be of such significance that a label change or more significant regulatory action may be needed.

Safety concerns may qualify for expedited reporting.
Responsibility

GMS Product Groups
- detection and investigation of medical safety signals
- preparation of a result document on signal investigation / preparation of safety statement in case of expedited reporting

GMS Safety Review Committee
- evaluation of significance of medical safety signals and decision on escalation/actions

Product Group + PSUR Coordination
- track of signals, organize review cycles, archive results
Responsibility

GMS Retrieval
- provision of specific retrievals from Safety DB

GMS Reporting Compliance
- distribution of safety statements if expedited HA notification is required

Locally
- appropriate reporting to HA
Detection of Signals

**Internal signals**: result from medical assessment activities performed by Product Groups during several GMS services

**Single case handling**
- assessment of serious unlisted single cases and SAEs

**Periodic monitoring**
- review of cumulative case information (e.g. listings, tabulations)
- review of Quantitative Safety Indicators

**Review of scientific literature**
- review of safety relevant literature

**PSUR or other periodic report**
- review of cumulative safety data during report preparation
Detection of Signals

**External signals**: detected through activities performed by external customers / parties as

**Issue handling**
- signals identified and forwarded to the company by Health Authorities, Ethics Committees or IDMBs

**A2Q**
- signals derived from medical safety related queries from external customers
Detection of Quantitative Safety Indicators

• exclusively generated by quantitative analyses (e.g. PRR) from internal or external databases

• independent of medical judgment

• require review and plausibility check by Safety Product Expert to decide:
  → not a signal (e.g. known ADR, underlying disease)
  → signal
Investigation of Signals

- Product Expert reviews relevant information to assess a causal association between the event and the product(s), (e.g. retrievals from ADR database, external databases, scientific literature, clinical trial data, preclinical data, patient exposure data)

- Investigation of safety signal results in the conclusion:
  • a causal association between signal and product is accepted
  • a causal association between signal and product is rejected
  • no clear conclusions as to causality can be drawn and the signal is further monitored
Documentation of Signal Investigation

Depending on nature and source of the signal, the responsible Product Expert provides a written documentation of the signal investigation in

- a separate signal investigation result document
- Chapter 9 of the PSUR
- safety statement for submission to Authorities
- answer to a query from a customer

Medical safety signals which are detected from any source are documented on a signal tracking sheet with the result signal investigation and resulting action.
Evaluation of Safety Signals

- Signal detection, investigation and evaluation is performed on a continuous basis in the GMS Product Groups.

- Identified signals are discussed with **Product Group Head**.

- If a causal association between signal and product is **accepted**, the **Head of Assessment** is informed to discuss main facts.

*All relevant safety signals (as well as safety issues and medically relevant product complaints) are presented in the GMS Safety Review Committee.*
Drug Safety - Vision of the Future

Drivers for Change
- Drug Withdrawals
- Regulations
- Public Expectations

2006

2010
Challenges for the PV Department

- Need for highly trained and qualified staff
- Pharmaco-epidemiological know-how is essential
- Interface with other functions (internal & external)
- Resources often inadequate
- Process changes
- Requires a mind set change to realize the value adding aspect
- Impact on market potential
Interfaces

Most of the MDs:
- do not read the SPC text or further amendments
- not willing to report ADRs

Most of the patients:
- do not read the PIs
- do not get a real understanding of the safety risks

Patient organizations request access to safety data

Media reports based on individual cases may lead to confusion and to unnecessary actions
Interfaces

Communication difficulties between Marketing/Sales and Drug Safety

Reasons:

- not understanding the need for communication
  >> marketing/sales reps may receive more information on safety issues as reported to Drug Safety

- attitude of both parties
Interfaces

*Improve Communication within the Company*

- full support from top management is essential!
- forums for sharing information >> collaboration
- two-way communication
Benefits

• Protects patients, physicians, long term commercial viability of the products

• Enhances trust and reputation

• Improved value

• Foster non interventional studies

• Generic defense
Integrated Risk Management

Goal
- Ensure recognition and effective management of events that could damage product profile and business success

Scope
- Covers all business risks of a developmental project
- Involves multiple functions
- Planned from Phase II onwards

Deliverables
- Risk Landscape
- Risk Response Plan
"There are risks and costs to a program of action. But they are far less than the long-range risks and costs of comfortable inaction."

_John F. Kennedy (1917 - 1963)_