Risk Management

PIPA Conference 2014

Dr Stella Blackburn
VP, Global Head of Risk Management
Real-World & Late Phase Research
Disclaimer

The views expressed are those of the speaker and should not be taken to represent the views of Quintiles or its related companies.

The views expressed should not be taken to represent the views of my former employer: the European Medicines Agency.

Quintiles provides services to multiple pharmaceutical companies.
“Levels of evidence”

But evidence of what?

Adapted from the sciencedog.wordpress.com
UK Crowd 2012
Knowledge at the time of authorisation

What we know:
- Efficacy in the clinical trial population
- Some of the adverse reactions

What we don’t know:
- Effectiveness
- Effectiveness in sub-populations
- Long term efficacy
- The real safety profile of the medicine
- How the drug will be used in practice
At the time the medicine is authorised, the benefits outweigh the risks for the average patient in the approved indication provided they are like the ones studied.
The Evolution of Risk management

2000/2001
High profile drug withdrawals

2001 Waller & Evans publish paper suggesting new form of PhV needed

ICH E2E step 2 Nov 2003

ICH E2E step 4 Nov 2004

Safety Specification
Pharmacovigilance Plan

EU RMP
USA REMS
Japan RMP
Canada RMP
Australia RMP
China RCP

Korea
Hong Kong
Taiwan
Singapore
Latin America
........
Main RMS items in PhV legislation

• RMP will be required for all new applications
• RMP should be proportionate to risks
• Key role of PRAC in relation to RMP
• PASS may be condition of MA
• PAES may be condition of MA
• Summary of the RMP to be made public
• Requirement to monitor the effectiveness of risk minimisation
• New definition of a RMP
Legislation definitions

**Risk Management system:**

A set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.

**Risk management Plan:**

A detailed description of the risk management system.
Risk Management Plan

- Identify or characterise the safety profile of the medicinal product(s) concerned;
- Indicate how to characterise further the safety profile of the medicinal product;
- Document measures to prevent or minimise the risks associated with the product including an assessment of the effectiveness of those interventions;
- Document post-authorisation obligations that have been imposed as a condition of the marketing authorisation.
Possible requirements post-authorisation

Article 22a of Directive 2001/83 /EC and Article 10a of Regulation (EC) No 726/2004 as amended ...... After the granting of a marketing authorisation,.......may impose an obligation on the marketing authorisation holder to .......

to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product

to conduct a post-authorisation efficacy study where the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly........
Structure of a (benefit)risk management plan

ICH PhV Planning 2004

Safety Specification

Pharmacovigilance Plan

New EU RMP structure 2012

Part I  Product(s) Overview

Part II  Safety Specification

Part III  Pharmacovigilance Plan

Part IV  Plans for studies on effectiveness and long term efficacy

Part V  Risk Minimisation Measures

Part VI  Summary of the RMP

Part VII  Annexes

1) Identify what is known and not known about the drug

2) Plan a research programme to identify new risks and characterise known ones

3) Take steps to protect patients from known or suspected risks

4) Investigate effectiveness in the real world setting
Part II: Safety specification

**Purpose to Identify:**

**Drug**
- Pre-clinical Tox
- Pharmacodynamics
- Pharmacokinetics
- How will it be used?
- Adverse event profile
- Class effects?
- Interactions?
- Level of confidence?

**Target population**
- Who was studied?
- Who wasn’t studied?
- Risk factors?
- What events can we expect in this population?

**Disease**
- Natural history
- Epidemiology
- What events occur as part of disease?

**Important identified risks**
- Important potential risks
- Missing information

**Safety concerns**

Purpose to Identify: what is known what is not known
Modules in safety specification

Module S1: Epidemiology of the indication(s) and target population(s).
Module SII: Non-clinical part of the Safety Specification
Module SIII: Clinical trial exposure
Module SIV: Populations not studied in clinical trials
Module SV: Post authorisation experience
Module SVI: Additional EU requirements for the S.S.
Module SVII: Identified and potential risks (non ATMPs)
Module SVIIa: Identified and potential risks (ATMPs)
Module SVIII: Summary of the Safety Concerns
Part II: Safety specification

Data in safety specification modules

Other risks

Safety concerns

SVIII
Part III: Pharmacovigilance Plan

Safety concerns

Activities to identify and characterise

Effectiveness of Risk Min Measures

Additional PhV activities
- active surveillance
- case control studies
- cohort studies
- record linkage (eHR)
- drug utilisation
- clinical trials
- Pre-clinical studies

Routine PhV activities

Measure effectiveness
Part III: Pharmacovigilance Plan

Are there unanswered pre-clinical questions?

Are there unanswered clinical questions?

Are there safety concerns specific to a particular part of the target population?

Is the medicine intended for long term use?

Are there safety concerns specific to the paediatric population?

- Growth
- Development
- Sexual maturity
- Long term use
Examples of types of PASS included in RMPs

- **Vast majority of PASS are pharmacoepidemiological (real-world) studies but...**
  - Pharmacokinetic studies in particular populations
  - Further animal studies
  - Development of an assay to measure a biomarker

- **Real world studies on particular safety concerns**
  - To confirm incidence seen in clinical trials
  - To confirm whether a potential risk is real or not
  - To identify risk factors

- **Drug Utilisation Studies (DUS)**
  - To assess real-world use of the drug (often national)
  - To assess the effectiveness of risk minimisation measures when there is concern about off-label use or medication errors

- **Registries**
  - Long term safety and/or effectiveness
  - Pregnancy registries following a product exposure
Part IV: Plans for effectiveness and long term efficacy follow up

Applicability of efficacy studies to all patients in target population

Factors which might affect efficacy in everyday medical practice

Long term efficacy

Evidence of variability in benefits in sub populations
Part V: Risk Minimisation Measures
Prevent or minimise

Risk minimisation Measures

Routine risk minimisation
- Legal status
- Pack size
- SPC
- Package leaflet
- Labelling

Additional Risk Minimisation measures
- Controlled distribution
- Educational material
- Patient alert card
- Patient monitoring card
- Training programmes
Additional Risk Minimisation Measures

Controlled distribution

Educational information for physicians
  • Particular serious risks associated with medicine
  • Existence of surveillance programme
  • Pregnancy prevention plans

Patient information

Patient alert card

Patient monitoring card

Training programme
Part VI: Summary of the RMP
RMP Summary - challenges

Who are the public?
- Different stakeholders
- Within stakeholders, different needs?

3 options
1. (E)par summary
2. Tables in (E)PAR
3. Stand alone summary
Measuring effectiveness of risk minimisation measures
Risk

RMP

Risk Minimisation Measures (RMM)

Attainment of RMM objectives

Implementation of RMM

Final outcome indicators

Process indicators

Modified from Prieto et al : Evaluation of the effectiveness of risk minimisation measures PDS DOI: 10.1002/pds.3305
Examples of possible assessment tools

- Physician surveys
- Pharmacist surveys
- Patient surveys
- Courier records
- Audits of pharmacies
- Counting of adrs
- Drug utilisation studies
- Electronic health record studies
What am I measuring?
What is the measure of success?

Teratogenic drug

No children with congenital abnormalities born

No women on the drug becoming pregnant
Epoetins and Pure Red Cell Aplasia

Figure 1. Cases of Antibody-Positive, Eprex-Associated Pure Red-Cell Aplasia Identified in the Database of the Adverse Event Reporting System of the Food and Drug Administration between January 1998 and April 2004. In Germany and Italy there were the same number of case reports within each year.

Bennet CL, Luminari S, et al
NEJM 2004:351:1 1403-9

SC route major risk factor in chronic kidney disease patients

Risk Minimisation Objective
• Ensure IV route used for chronic kidney disease patients

Risk Minimisation Measure
• Educate physicians to prescribe IV route for chronic kidney disease
What is the measure of success?

<table>
<thead>
<tr>
<th>Final outcome Indicator</th>
<th>No reported cases of red cell aplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk minimisation Objective</td>
<td>Ensure IV route used for chronic kidney disease patients</td>
</tr>
</tbody>
</table>
Implementation of Risk Min Measure

Did the educational material arrive?

Did the physician read it?

Did the physician understand it?
Implementation of Risk Min. Measures

Did it change behaviour?
What is the question?

Are patients with CKD being prescribed epoetin by the s.c. route?

Has the educational material affected doctors’ behaviour?

Drug utilisation study

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time
Summary

SAFETY (Risks)

- Safety Specification
- Safety Concerns

Part II

Pharmacovigilance Plan

- Identify & Characterise Risks
- Measure Effectiveness of Risk Minimization Measures
- Routine & Additional Pharmacovigilance
- Spontaneous Reports

Part III

Risk Minimization Measures

Part V

EFFICACY (Benefits)

- Efficacy (Benefit) Considerations
- Plans for effectiveness & long term efficacy
- Observational Studies on (comparative) effectiveness

Part IV

Clinical Trials

Pre-Clinical Studies

Literature Reports

Observational Studies
Thank you!