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Risk Management Plans

Dr Stella Blackburn

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Phase I – III development

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The Past ?

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The Reality

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The Legislation

Article 8 (3)(ia) of Directive 2001/83/EC requires the MAA to submit:

"a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce."

The Pharmacovigilance System

This is company specific NOT product specific.
Description of how the company will implement the PhV requirements in Regulation (EC) No 726/2004, and Directive 2001/83/EC as amended

Details found in the Chapter "*Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections*" in Volume 9A of The Rules Governing Medicinal Products in the European Union

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The Pharmacovigilance System

- **PhV QP**
- **PhV Databases**
- **Systems for collecting adrs**
  - **SOPs**
  - **Co-licensing agreements**
- **Systems for reporting adrs**
  - **Expedited reports**
  - **PSURs**

A Pharmacovigilance System is different from a Risk Management System!

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The Risk management System

Definition:

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

Requirement for a RM System can be fulfilled by the submission of an EU RMP

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The EU Risk Management Plan

Part I

- **Safety Specification**
- **Pharmacovigilance Plan**

} **ICH E2E**

Part II

- **Evaluation of the need for risk minimisation activities,**

if a need for additional risk minimisation activities

- **Risk minimisation plan**

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Safety Specification
(According to ICH Topic E2E)

Non-clinical

- **Toxicity**
- **General pharmacology**
- **Drug interactions**

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Safety Specification

Clinical

- **Limitation of human safety database**
  - **Clinical trial population**
  - **Post-marketing exposure (if any)**
- **Populations not studied**
- **Post-marketing experience (actual use vs SPC)**
- **Adverse reactions**
  - **Risks (identified or potential)**
- **Identified and potential interactions**
- **Epidemiology**
- **Pharmacological class effects**

Safety Specification

- **EU Specific**
  - Potential for overdose
  - Potential for transmission of infectious agents
  - Potential for misuse for illegal purposes
  - Potential for off-label use
  - Potential for off-label paediatric use

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Safety Specification

Safety specification conclusions:

Important Safety concerns

- **Important identified risks**
- **Important potential risks**
- **Important missing information**

These form the basis for the PhV Plan and the evaluation of the need for risk minimisation activities

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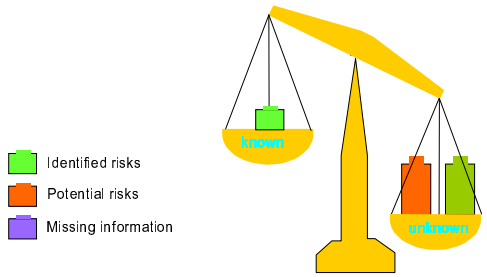
At time of the Marketing Application



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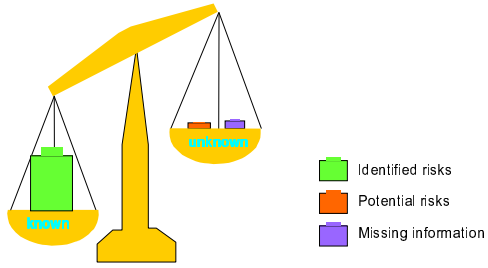
Mature Product



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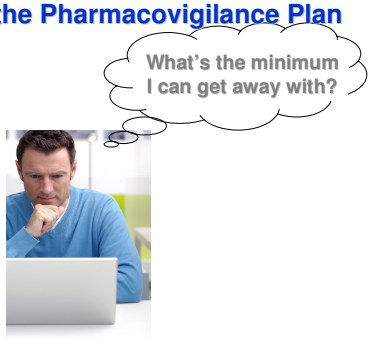
Writing the Pharmacovigilance Plan



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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

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Pharmacovigilance Plan
(According to ICH Topic E2E)

- **Actions proposed**
  - **Routine pharmacovigilance** (e.g. signal detection, adverse reaction reporting, PSURs)
  - **Additional pharmacovigilance activities** (e.g. active surveillance, intensive monitoring, PhEpi studies)

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Evaluation of the need for risk minimisation activities

Look at each important safety issue

- **Discuss whether risk minimisation actions needed**
- **Is the product literature sufficient for this purpose?**
- **If not then risk minimisation plan needed**
- **Potential for medication error**

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BBC NEWS

Doctor admits drug blunder killing

A doctor has admitted the manslaughter of a teenage cancer patient who died after a hospital drug blunder.

Wayne Jowett, 18, died after a toxic cancer drug was wrongly injected into his spine rather than a vein.

Wayne Jowett died a month after the mistake

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Risk minimisation Plan

- **Only needed if additional risk minimisation activities needed**
- **Should list safety concerns for which risk minimisation activities needed**
- **Should include both routine and additional risk minimisation activities**

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Additional Risk Minimisation Activities

- 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

Summary of activities in EU-RMP

Safety concern	PhV Plan	Risk Min Activities
1. **Hepatitis**	• Routine PhV. • Study to investigate the incidence and risk factors for hepatitis in Wonderdrug and other immuno-suppressant drugs using GPRD database	• Contraindication for patients with active viral hepatitis in section 4.3 of the SPC • Warning in section 4.4 of the SPC that LFTs should be monitored monthly • Listed as ADR in section 4.8

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Situations when EU-RMP submitted I

- **New marketing authorisation**
  - **New active substance**
  - **A similar biological medicinal product**
  - **Generic/hybrid** where safety concern requiring additional risk minimisation activities has been identified with reference medicinal product
  - **Informed consent** where safety concern requiring additional risk minimisation activities has been identified with reference medicinal product
- **Paediatric use Marketing Authorisation (PUMA)**

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Situations when EU-RMP submitted II

- **Situations where EU-RMP might be required when new authorisation via centralised procedure**
  - **"known active substances"**
  - **hybrid medicinal product where the changes compared with ref product suggest different risks**
  - **bibliographical applications**
  - **"fixed combination" applications**

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Situations when EU-RMP submitted III

- **Significant changes to MA**
  - **New pharmaceutical form**
  - **New route of administration**
  - **Significant change in an indication/patient population**

  } **Unless agreed not needed**
- **On request from the Competent Authority**
- **On company initiative e.g. safety issue with a marketed medicine**
- **Update to previous EU-RMP**

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Update to the EU-RMP

The EU-RMP is a living document

- updated throughout the lifecycle of the product
- safety specification will change over time
  - results from other clinical trials
  - results from studies in PhV Plan
  - spontaneous reports and literature
- PhV Plan and Risk Min Plan will also change over time

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Risk Management Plans

from 01/09/2005 – 31/10/2008

	Positive Opinions	RMP	Additional Risk min activities
New Marketing Authorisations	170	143	20
Post- auth. procedures		68	8

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