Overview of Risk Management

Risk Management Plans- An Industry Perspective

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(adapted from an RMP training by Dr Judith Sills, Global Head, Medical Safety Operations, DS&E, Novartis)

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

New Paradigm for Pharmacovigilance:

The Emergence of Risk Management

A few years ago	*Today*
1. Safety divided into pre- and post-marketing	1. HAs view safety as a life-cycle discipline
2. Reactive management through passive observation	2. Prevention is focus of earlier and better risk management
3. Reliance on SR databases	3. New databases and technologies emerging
4. Burden on HAs to detect risks	4. HA and sponsor share risk detection responsibilities
5. Risk management plans rare, drug specific	5. Risk management plans with most new dossiers
6. Routine pharmaco-vigilance is the standard	6. Drug-specific PV often requested
7. Risk activities generally not disclosed to public	7. Risk activities made public by HA

Adapted fr aining by Dr. Judith Sills, G Medical Safety Operat Novartis

Safety Risk Management – What is it?

PROCESS

DOCUMENT

SET OF INTERVENTIONS

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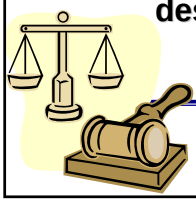
The Safety Risk Management Plan (RMP)

- **Is a regulatory document submitted to Health Authorities**
  - **With an application for a new marketing authorization, with Periodic Safety Update Reports (PSUR), as a stand alone document**
- **Document which is legally binding**
  - **Once the RMP is accepted by the Health Authorities, the Market Authorization Holder (MAH) has a legal obligation to perform the activities described in the RMP**



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What are the objectives of a Safety RMP?

The specific objectives of RMPs are three-fold:

- **To specify what is and is not known about safety of a drug at the time of submission (Safety Specification)**
- **To further characterize the safety risks post authorization (Pharmacovigilance Plan)**
- **Where necessary, to define appropriate measures to minimize known risks to patients and to monitor the success of those measures (Risk Minimization Plan and Evaluation of Effectiveness)**

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RMP allows pro-active handling of safety issues

- **Business gains for proactive handling of safety issues**
  - **No/fewer delays of approval due to safety issues (fewer safety questions by Health Authorities during approval review and shorter time required to answer those questions)**
  - **Better control of which safety risk management activities are required if risk identified internally and risk management activities proposed by MAH rather than mandated by Health Authorities**
  - **Decreased risk of marketing restrictions, unfavorable label changes and product withdrawals from market**
  - **Improved reputation and trust with Health Authorities and public resulting from proactive, responsible, and transparent handling of safety issues**
  - **Internal consistency around communication and knowledge of safety information of projects/products**

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Regulatory Requirements for Safety RMPs

- Required for all EU Submissions
- Australia adopted the EU Guidelines on Risk Management Systems, as described in Volume 9A, on 13 Nov 2008
- FDA Risk Evaluation and Mitigation Strategies (REMS) effective March 2008
  - REMS provided to FDA in addition to Global RMP

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Regulatory Basis for Safety Risk Management

European Union

- Volume 9A serves as legal basis
- Detailed EMEA Guideline for mandatory RMPs issued late 2005
- Detailed template released in 2006
  - Safety Specification summarizing risks
  - Pharmacovigilance plan
  - Evaluation of need for risk minimization activities
  - Risk minimization plan (if appropriate)
- Revised template based on 2-year experience expected in 2008
- EMEA approach focuses more on process - FDA approach focuses more on assessments

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Regulatory Basis for Safety Risk Management

United States

- FDA Risk Management Guidances issued Mar 2005
  - Pre-marketing risk assessment
  - Good pharmacovigilance practices and assessment (case series, safety signals, pharmacovigilance plans)
  - Risk minimisation action plan (RiskMAP)
- Safety risk management plans requested by FDA for most NDAs
- Risk Evaluation and Mitigation Strategies (REMS) effective Mar 2008
  - To gradually replace RiskMAPs
  - "Evaluation of need for REMS" and/or actual REMS plan mandatory for all new NDAs
  - Significant focus on risk minimization metrics

Canada and Australia

- Draft legal requirements similar to EU recently proposed

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When do we prepare a safety RMP?

- At the time of a request for approval of a new drug, new indication, new patient population, etc.
  - RMP to be submitted with submission dossier

- Upon identifying a significant new safety concern

- At the request of health authorities

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When do we update an existing safety RMP

According to Volume 9A of the Rules Governing Medicinal Products in the European Union (version dated March 2007), Risk Management Plans should be updated:

- **When new information is available that may impact the current Safety Specification, Pharmacovigilance Plan or Risk Minimization activities**
- **Within 60 days of an important milestone (pharmacovigilance or risk minimization activity) being reached or the results of a study becoming available**
- **At the request of a Health Authority**

Consider whether new risk minimisation activities are needed:

- **New safety concern**
- **Existing safety concern but data suggests that current strategy not effective**

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Risk management continuum

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Different parties involved in risk management

- **Patients:**
  - effectiveness at no risk
  - freedom to choose
- **Health care professionals:**
  - good effectiveness at low risk
  - litigation fear
- **Regulators, payers, politicians:**
  - good effectiveness, acceptable risk
  - fear of litigation and fear of the media
  - resource constraints
- **Pharmaceutical companies:**
  - enough effectiveness, acceptable risk
  - fear of litigation and fear of the media
  - resource constraints
  - return maximization: shareholders

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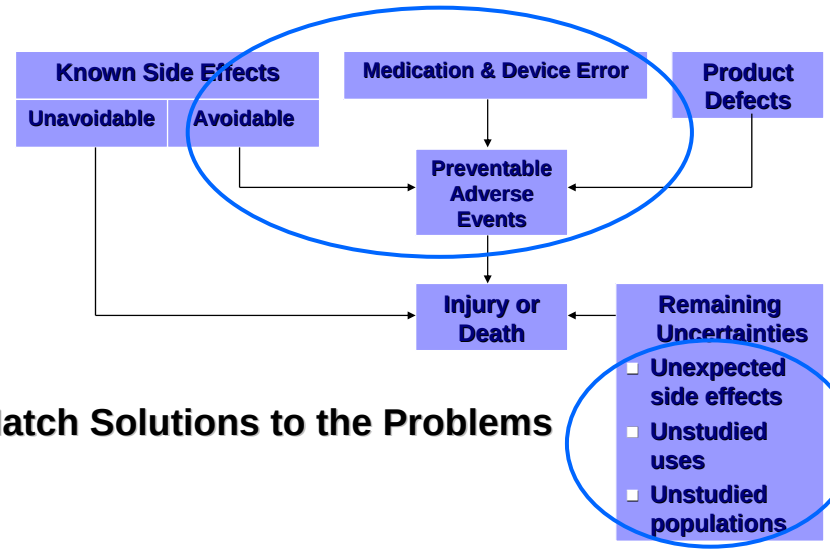
Sources of Risk from Medical Products



Match Solutions to the Problems

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Examples of RMP Goals and Objectives

Drug	Goal	Objective
Clozapine	No agranulocytosis	WBC monitoring
Thalidomide	No fetal exposure	Pregnancy prevention and monitoring for pregnancy
Lindane	Minimize CNS toxicity and death	No misuse (overdose or extended use)
Dofetilide	Minimize arrhythmia (torsade de pointes)	Dose adjustment in renal impaired, hospitalize pts while initiating therapy

- Adapted from C.Karwoski, FDA – presentation at DIA Annual Mtg, June 2006

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- **Thank you for your attention !**
- **Questions ????**

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