Risk Management Planning

Industry Experience in Implementation

Val Simmons, MD  FFPM
EU QPPV  Executive, Eli Lilly
Risk Management – A Sense of Déjà Vu?

“I am convinced that ….. the risk management issue will increase, not decrease, in importance.”
Risk Management – A Sense of Déjà Vu?

“I am convinced that ...... the risk management issue will increase, not decrease, in importance.”

W.P. Von Wartburg
1990 (RAD – AR)
Viagra blindness alert

Britons ‘lost sight after taking impotence drug’

By Julia Whiston

Doubts have been raised about the effects of Viagra, the impotence drug, after a British woman was blinded following an accident.

Residents of a town in the north of England said the woman, who had been taking the drug for several months, lost her vision in both eyes after a car accident.

The woman, who is now recovering in hospital, said she thought she was only seeing double after taking the drug.

A spokesman for the drug company said: ‘We are aware of the incident and are providing support to the woman and her family.’

The woman’s husband, who was not named, said: ‘We are totally shocked. We thought she was just suffering from mild dizziness but it got worse.’

The couple said they had been unable to use their car for several days after the accident.

United News

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Suicides blamed on acne drug

Drug maker Merck has been under pressure to withdraw its acne drug, which has been linked to deaths.

The drug, called ‘Prozac’, has been approved by the US Food and Drug Administration for use in treating depression.

However, two women who were prescribed the drug died by suicide in the UK.

Merck has been accused of not warning doctors about the risks of suicide.

The company said it was reviewing the claims and said: ‘We take the safety of our products very seriously and are committed to improving patient care.’

Washington Times

© Copyright Washington Times 1999

Merck recalls Vioxx

Merck, the pharmaceutical company, has recalled its popular anti-inflammatory drug Vioxx.

The recall comes after a study published in the New England Journal of Medicine linked the drug to an increased risk of heart attacks.

Merck said it had voluntarily recalled the drug and was waiting for further information from the Food and Drug Administration.

The company said: ‘We regret the inconvenience this may cause consumers but we remain committed to patient safety.’

US Business

© Copyright US Business 1999

Bad medicine

The British government has been criticized for allowing the drug company to sell unapproved drugs.

The government has been accused of not ensuring that the drugs were safe before allowing them to be sold.

A government official said: ‘We are investigating the issue and will take appropriate action if necessary.’

The British government has ordered an inquiry into the drug company’s sales practices.

© Copyright British Government 1999

300 ml
Merck Pharmaceutical has recalled the popular pain and arthritis medication Vioxx® (rofecoxib) from the market after studies revealed that it may increase the risk of blood clots, stroke, heart attack and death. According to acting FDA commissioner Dr. Lester M. Crawford, “Overall, patients taking the drug chronically face twice the risk of heart attack compared to patients receiving a placebo.”

YOU MAY BE ENTITLED TO MONEY DAMAGES

If you or a loved one have suffered a stroke, heart attack or death, call attorney James Rolshouse toll free at 888-VIOXX-87 (888-846-9697)

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Glaxo shares under fire as $400m lawsuit looms

Click here to contact an experienced Risperdal Attorney.
<table>
<thead>
<tr>
<th>Date</th>
<th>Regulatory Activity</th>
<th>Safety Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td></td>
<td>Seldane (terfenadine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posicor (mibefradil)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duract (bromphenac)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fen-phen</td>
</tr>
<tr>
<td>1999</td>
<td>• FDA Task Force on Risk Management report to the FDA Commissioner: “Managing the</td>
<td>Hismanal (astemizole)</td>
</tr>
<tr>
<td></td>
<td>Risks from Medical Product Use”</td>
<td>Raxar (grepafloxacin)</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td>Prepulsid (cisapride)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rezulin (troglitazone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lotronex (alosetron)</td>
</tr>
<tr>
<td>2001</td>
<td>• EPPV introduced (Japan)</td>
<td>Lipobay (cerivastatin)</td>
</tr>
<tr>
<td></td>
<td>• Eudravigilance database implemented by EMEA</td>
<td>(Baycol)</td>
</tr>
<tr>
<td>2002</td>
<td>• FDA – PDUFA III and Risk Management requirements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ICH V3 (Pharmacovigilance Planning) topic accepted</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>• FDA - Draft Risk Management guidances</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Proposed Rule (TOME)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Heads of Agencies – European RM strategy paper</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>• ICH E2E – Step 4</td>
<td>Vioxx (rofecoxib)</td>
</tr>
<tr>
<td>2005</td>
<td>• FDA RM guidances finalized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ICH E2E – Adoption by CHMP and incorporation into Volume 9</td>
<td>Tysabri (natalizumab)</td>
</tr>
<tr>
<td></td>
<td>• New Medicines Legislation implementation in Europe</td>
<td>Bextra (valdecoxib)</td>
</tr>
<tr>
<td></td>
<td>• European RM Strategy &amp; finalization of RM guidelines</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>• FDAAA passed; REMS requirement</td>
<td>Avandia (rosiglitazone)</td>
</tr>
</tbody>
</table>
Risk Management – A Shift in Emphasis

“Old Model”

- Pre-marketing Safety Analysis
  - Pre-clinical toxicology
  - Clinical trial safety data
  - Laboratory data
  - ECGs/other data
  - Targeted safety studies
- ISS
  - Integrated safety analysis
  - SADRs
  - AEs
  - Laboratory/other data
- Approval
  - Regulatory approval for labelled use
  - Risks included in label (disclosure)
- “See what happens in real world use”
  - Ongoing surveillance and signal assessment of serious/unexpected ADRs
  - Post-marketing safety studies
  - Update label
  - Ad hoc HCP communications (Dear Dr. letters)
  - Product restrictions/withdrawal
Risk Management – A Shift in Emphasis

“New Model”

- Pre-marketing Risk Assessment
- ISS
- Safety Specification
  - Pharmacovigilance Plan
  - ± Risk Minimization Plan/ Risk Map
- Approval
- Risk Management Implementation
  - Enhanced PMS/ Communication activities
  - Active influence on safe use in the market place
  - Assessment of RM programme effectiveness

Modify in the light of new safety data

New data

- Traditional analyses plus
- Anticipated conditions of use
- Intrinsic/extrinsic risks (identified and potential)
- Epidemiology of disease
- Benefit : risk assessment
Overall Objectives of Risk Management Planning
Benefit - Risk Optimization
Optimizing Benefit Risk

- Manageable Risk
- Unacceptable Risk
- Acceptable Risk

Risk vs. Benefit Chart:
- Low Benefit, Low Risk: Manageable Risk
- Low Benefit, High Risk: Unacceptable Risk
- High Benefit, Low Risk: Acceptable Risk
- High Benefit, High Risk: Unacceptable Risk
Risk Management Terminology

A Subject of Great Confusion
Risk Management Planning
Understand the Terminology

Risk Management = Risk Assessment + Risk Minimization
What Risk Management is Not ????

“And now at this point in the meeting I’d like to shift the blame away from me and onto someone else.”
Generally, Risk Management is the process of measuring, or assessing risk and then developing strategies to manage the risk. In general, the strategies employed include transferring the risk to another party, avoiding the risk, reducing the negative effect of the risk, and accepting some or all of the consequences of a particular risk.

*From Wikipedia, the free encyclopedia.*
Transatlantic Terminology – Risk Management

**FDA** : Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product’s benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.

**Europe** : A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions

.....but then along came REMS
Risk Management and International Harmonization

International harmonization is wonderful in theory

.........but everyone is harmonizing differently
Global Risk Management Planning
The Challenge of Reconciling the Differences

Europe
ICH E2E +/- Risk Minimization Plans

US
RM Guidelines including RiskMAP/REMs

Japan
ICH E2E + EPPV(?)

17
Basic Components of a Risk Management Plan

Risk Management Plan

Safety Specification
Summary of important identified risks, important potential risks and missing information (ICH E2E)

Pharmacovigilance Plan
Based on safety specification; Routine PV practices and action plan to investigate specific safety concerns (ICH E2E)

Risk Minimization
Activities to be taken to minimize the impact of specific safety concerns on the benefit-risk balance
Risk Management in Industry

General Considerations
Risk Management and Planning

“In preparing for battle I have always found that plans are useless, but planning is indispensable.”

Dwight D. Eisenhower
RM Planning in Industry - Critical Success Factors

- Safety governance – support from the top
- Comprehensive change management plan
- Defined process and roles/responsibilities
- Tools and skills to support the process
- Partnership, education and training
- Early planning in development
- Financial planning
RM Planning - Financial Implications

• Authorship costs
  ➢ in house staff or outsourcing

• Cost of special expertise
  ➢ Risk minimization activities …. “it is essential that appropriate specialized experts should be consulted at all stages”
  ➢ “Because of the importance of risk communication it is recommended that appropriate experts are consulted”
  ➢ Epidemiological expertise

• Cost of implementing proposed measures
  ➢ Post marketing studies, educational programmes, registries, drug utilization studies, etc.

• Cost of delays to marketing approval
  ➢ If the RMP is considered inadequate
Risk Management in Industry
General Considerations

Communicating Change

An Essential Foundation to Implementing Risk Management Planning Activities
Risk Management in Industry - Stakeholder Groups

- Corporate Senior Management
- GRA Senior Management
- Regional Medical and Regulatory
- Global Product Teams/Medical
- Central and Affiliate Product Safety
- Licensing partners
- Legal
- Financial and marketing
**Risk Management in Industry**

**Key Messages**

- Good Risk Management Planning = Good Business; the advantages of getting it right
- Trade-off between investment and delay in authorization or future product withdrawal.....the risks of getting it wrong
- Risk Management is not just a RiskMAP or REMS….or a bureaucratic box to be ticked !
- Global standards are critical
- Additional PM studies are likely to be the rule, not the exception
- Need to think beyond routine practice and the label
- Risk Management is not going to go away........
Risk Management Planning in Industry

Other Practical Considerations
When to start RM Planning – CIOMS VI Principles

- Early in development; based on non clinical data & information on closely related compounds
- Establish a procedure & Multi Disciplinary Team; advisory bodies
- Determine background data
- Ready accessibility of all safety data
- Develop a proactive approach
- Establish time frames and milestones
- Decision making: focus on safety reviews
**Generic Life-cycle Risk Management Planning Model**

Development Risk Management Plan created First Time in Humans

- Candidate selection - FTIH
- FTIH - PoC
- PoC - Commit to Ph3
- Phase 3
- File and launch
- Lifecycle

**DRMP updated** with significant new data at least annually and before key development milestones

Evolves into the Risk Management Plan submitted with the Marketing Application

**RMP continues to be updated** at agreed milestones; coordination with PSUR, labelling etc.
Figure 1. Overview of RMP Preparation

Planning for final document preparation is coordinated with other documentation.

Analyze safety data using updated plan.

Develop safety.

Define types of post-launch risk interventions.

Specify compound.

Specify benefit/...
RM Planning - Practical Considerations

The Role of Epidemiology

• Important early in development and throughout the RM process
• Critical for the Safety Specification and PV Plan……bridging the knowledge gap

- Defines demographics & expected characteristics of the target patient population
  - co morbidities
  - anticipated AE profile in usual clinical practice
- Design of post marketing safety studies/registries
- Identification of existing databases
- Design of drug utilization studies
- Assess effectiveness of risk minimization measures
RM Planning - Practical Considerations

What format to use

- European template now in use since October 2006; why reinvent the wheel???
- Aim for a globalized document; concept of a “Core RMP” based on ICH E2E and the European template with adaptation as required to meet local needs e.g. EPPV in Japan (risk assessment)
- Getting the safety specification right is critical
  - Use tabulations and graphical presentation of data vs extensive verbiage
- Strategic risk minimization plan should be the same globally; implementation can be tailored to local medical practice
- Regulatory feedback and early discussion are useful to optimize content
Pharmacovigilance Plan

When *is* routine pharmacovigilance practice sufficient?

- Probably not often and unlikely for NCEs (in Europe at least)
- Initial experience indicates that US and Europe may request different risk assessment activities; regionally focussed
- Need to focus additional risk assessment activities on:
  - issues according to level of evidence & public health impact vs theoretical considerations
  - clinically important risks
  - those which are practical, feasible and likely to yield meaningful, timely results
- Need for coordinated activities and consistent standards (globally and across Europe)
- Importance of well defined milestones
Risk Minimization Plan

When is a specific Risk Minimization Plan needed?

- Not invariably but requires justification in the EU (approx 18% of RMPs)
- Likely to be the most significant divergence between EU and US RMPs
- Additional measures to mitigate known risks need to be:
  - Appropriate to the level of risk
  - Feasible in practice
  - Effectively communicated
  - Principles set at a global level but implementation according to local regulations/medical culture etc
  - Multi functional input and close coordination with affiliates important
- Current toolkit is limited
  - Need to be able to provide example(s) of proposed tools etc
  - Need to propose how effectiveness will be monitored; impact on spontaneous reporting unlikely to be acceptable
Risk Management Planning - Implementation Experience

.......from both sides of the fence
EU Regulatory Authority Experience

Important Note:

• The following slides from the EU authorities have been obtained from the original author and with their permission
• The points made were from a previous external presentation
EMEA Experience with RMPs
01 September 2005 – 31 March 2008

<table>
<thead>
<tr>
<th></th>
<th>Positive Opinions</th>
<th>RMP</th>
<th>Additional Risk Minimization Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Marketing Authorisations</td>
<td>134</td>
<td>113</td>
<td>20</td>
</tr>
<tr>
<td>Post-authorisation Procedures</td>
<td></td>
<td>80</td>
<td>6</td>
</tr>
</tbody>
</table>
## European Regulatory Experience with RMPs
### Review & Learning Project - Phase 1

<table>
<thead>
<tr>
<th>RMP Assessment</th>
<th>Number(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory quality</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Non-compliance with EU RMP guidelines</td>
<td>9 (75%)</td>
</tr>
<tr>
<td>Missing parts</td>
<td></td>
</tr>
<tr>
<td>- Specification, PhV Plan, Risk Minimization Plan, Summary etc</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>- Protocol/outline</td>
<td>“Several”</td>
</tr>
<tr>
<td>- SPC not attached</td>
<td></td>
</tr>
<tr>
<td>Deviating Structure</td>
<td>5 (41%)</td>
</tr>
<tr>
<td>Non-relevance/redundancy (Safety Specification)</td>
<td>5 (41%)</td>
</tr>
</tbody>
</table>

Following the structure and contents of the EU guidelines and template was considered sufficient to address most issues.
European Regulatory Experience with RMPs

“Overall, XXX offers significant advantage in overall survival and is an alternative to YYY for patients with (Z disease) that prolongs survival and has a positive benefit-risk profile”
Evaluation of the Need for Risk Minimization Activities

“none of the safety concerns was serious and they can be managed by the means of the proposals in the pharmacovigilance plan. Therefore there is no need for a risk minimisation plan.”
Potential for Medication Errors

“There were medication errors identified in clinical trials presumably due to misunderstanding of, or non-compliance with, drug administration instructions.”

<table>
<thead>
<tr>
<th>Dose</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Round</td>
<td>Round</td>
<td>Round</td>
</tr>
<tr>
<td>Size mm</td>
<td>6.2 x 2.8</td>
<td>7.9 x 3.3</td>
<td>9.8 x 4.3</td>
</tr>
<tr>
<td>Colour</td>
<td>Pink</td>
<td>Light beige</td>
<td>Beige</td>
</tr>
</tbody>
</table>
European Regulatory Experience with RMPs

“There are no safety concerns with XXX, therefore there is no need for a pharmacovigilance plan or risk minimization activities.”
Limitations of human safety database

Table x: Exposure by baseline disease

<table>
<thead>
<tr>
<th>Disease / Condition</th>
<th>No of patients Total (male/female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>65 (39/26)</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>71 (47/24)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>207 (143/64)</td>
</tr>
<tr>
<td>Other</td>
<td>246 (140/106)</td>
</tr>
</tbody>
</table>

Table y: Special population exposure

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (&lt;12 years)</td>
<td>None</td>
</tr>
<tr>
<td>Elderly (&gt;75 years)</td>
<td>14</td>
</tr>
<tr>
<td>Pregnant or lactating women</td>
<td>None</td>
</tr>
<tr>
<td>Relevant co-morbidities</td>
<td></td>
</tr>
<tr>
<td>• Hepatic impairment</td>
<td>57</td>
</tr>
<tr>
<td>• Cardiac disease</td>
<td>243</td>
</tr>
<tr>
<td>Genetic polymorphism</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
</tr>
<tr>
<td>• Caucasian</td>
<td>584</td>
</tr>
<tr>
<td>• other</td>
<td>5</td>
</tr>
</tbody>
</table>
Risk Management Plans in Europe
Industry Experience

• Increasing trend to request EU specific RMP vs global document
  ➢ e.g. wish to see specific reference to SPC sections vs generic statements relating to the CCSI

• For submissions of a new indication/formulation with a mature product, need to produce an RMP for the whole molecule

• Strong emphasis on paediatric use
  ➢ May require a paediatric RMP if evidence of significant off label use

• Requests for:
  ➢ studies in individual countries based on theoretical concerns
  ➢ country specific PV activities/local RMPs where an EU RMP has been agreed with CHMP
  ➢ country specific drug utilization studies by pricing authorities

• Variable interpretation of what constitutes an important risk.........
## Is the Event Serious – CIOMS V Survey

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blindness for 30 minutes</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>Suicide threat</td>
<td>17%</td>
<td>83%</td>
</tr>
<tr>
<td>“Mild” anaphylaxis</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>95%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Most discrepancies related to disability, life-threatening condition or medical significance
Toxic Epidermal Necrolysis (TEN)

Clearly a serious and important risk
Flatulence

An important risk???
Risk Management Plans in Europe
Industry Experience

• Previous advice to produce one RMP per active chemical entity now superceded by one RMP per “medicinal product” i.e by licence
  ➢ May receive requests to split existing RMPs into multiple documents

• Level of detail required for PASS protocols may be unrealistic at submission

• EU template very duplicative and unsuited to mature products
  ➢ Overly long and repetitious document (industry view)
  ➢ Based on EMEA experience: currently undergoing revision

• Public access to RMPs is happening and will be
  ➢ A key focus of future legislation

• Adherence to milestone commitments a focus in PV inspections
Risk Management Plans in the US Early Industry Experience

- Too early to determine practical impact of FDAAA and REMS
- Circa 25% RMPs submitted to FDA are in the EU Template format and accepted
- Initial experience indicates that a very conservative approach is being taken
  - E.g. an extensive REMS requested for a product on the market for over 10 years in a new indication based on preclinical toxicology findings thus far not substantiated in clinical use
- Clear that the tools for risk minimization are still being thought through
- Recent FDA inspections have focussed very strongly on compliance with RMP commitments
- Clear indication that FDA have specific expectations for REMS i.e. the risk minimization section of the RMP
Global Plan and US RMP Relationships

Global Risk Management Plan

Safety Specification
ICH E2E

Pharmacovigilance Plan
ICH E2E

Global Risk Minimization Strategy

Determine if risk minimization beyond label is warranted

US Risk Minimization Activities (RiskMap = Risk Minimization Action Plan)

REMS (Risk Evaluation & Mitigation Strategies)
Global Plan and EU RMP Relationships

Global Risk Management Plan

Safety Specification
ICH E2E

Pharmacovigilance Plan
ICH E2E

Global Risk Minimization Strategy

Determine if risk minimization beyond label is warranted

EU Risk Minimization Activities
RMP Regional Variations

Global Risk Management Plan

Safety Specification
ICH E2E

Pharmacovigilance Plan
ICH E2E

Determine if risk minimization beyond label is warranted

Global Risk Minimization Strategy

Regional Risk Minimization Activities

Regional Safety Specification Req
Regional PV Requirements
Risk Management Planning - Some Outstanding Issues

- Intelligent risk management planning is clearly the right way forward; the “devil will be in the detail”
- Global RMPs are feasible at the time of submission......maintaining the global status of the document is likely to be a challenge
- Everyone is still on the steep part of the learning curve!
- RMPs are and will continue to be an increasing focus in PV inspections.....but do not forget that much of the content involves medical judgement
- Public access to RMPS is a reality ...we have to deal with it!
- Need to investigate more effective risk minimization( including communication) methods ....... and how to assess their impact
- Need to develop more transparent and objective benefit risk models; emphasis on benefit risk and not just risk!
- Need for involvement and intelligent communication with patients/public...what do the public actually wish to see?
Better Patient Focus
“Wonder Pills”

Sir, My wife has been prescribed pills. According to the accompanying leaflet, possible side-effects are: sickness, diarrhoea, indigestion, loss of appetite, belching, vertigo, abdominal cramps, dizziness, stomach ulcers, bleeding from intestine or blood diarrhoea, ulcerative colitis, sore mouth and tongue, constipation, back pains, inflammation of pancreas, mouth ulcers, skin rashes, hair loss, sensitivity to sunlight, drowsiness, tiredness, impaired hearing, difficulty with sleeping, seizures, irritability, anxiety, depression, mood changes, tremor, memory disturbances, disorientation, changes in vision, ringing in ears, bad dreams, taste alteration, allergic reactions, swelling due to water retention, palpitations, impotence or tightness of the chest.

Should she take them?

Yours faithfully,

Letter to the Editor,1996
“It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change.”

Charles Darwin, 1859