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 Julie Wheldon
Science Correspondent
BRITISH men have gone blind after taking Viagra, it was claimed yesterday.
Newsweek
CLINTON VS. DOLE
Ritalin
Are We Overmedicating Our Kids?
Revealed: the danger of taking Prozac
Drug maker knew 20 years ago of possible link to suicide
SIDE EFFECTS
DOLE
12 BUSINESS
300 mi
BAD MEDICINE
Glaxo Smith Kline faces legal action over claims that it withheld key data on a drug to treat depression, report Paul Durman and Dominic Rushe
Washington Times
FINAL
FRIDAY, OCTOBER 1, 2004
25 cents
Merck recalls Vioxx
Heart risk found in arthritis drug
TRENTON, N.J. (AP) —
PAINFUL
MERCK
Suicides blamed on acne drug


VIOXX®
STROKE ~ HEART ATTACK ~ DEATH
BLOOD CLOTS ~ PULMONARY EMBOLISM
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
James Rolshouse & Associates
Personal Injury Attorney
visit us online at
TOLL FREE 888

Remicade (Infliximab)
Side Effects Lawsuits
Tuberculosis, Multiple Sclerosis, Lupus, and Serious Infections


Celebrex
100 mg
GAL03


Market
BY MICKEY
Glaxo shares under fire
as $400m lawsuit loom

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

Risk Management – A Shift in Emphasis

"Old Model"

Pre-marketing Safety Analysis → **ISS** → **Approval** → **"See what happens in real world use"**

- Pre-clinical toxicology
- Clinical trial safety data
- Laboratory data
- ECGs/other data
- Targeted safety studies

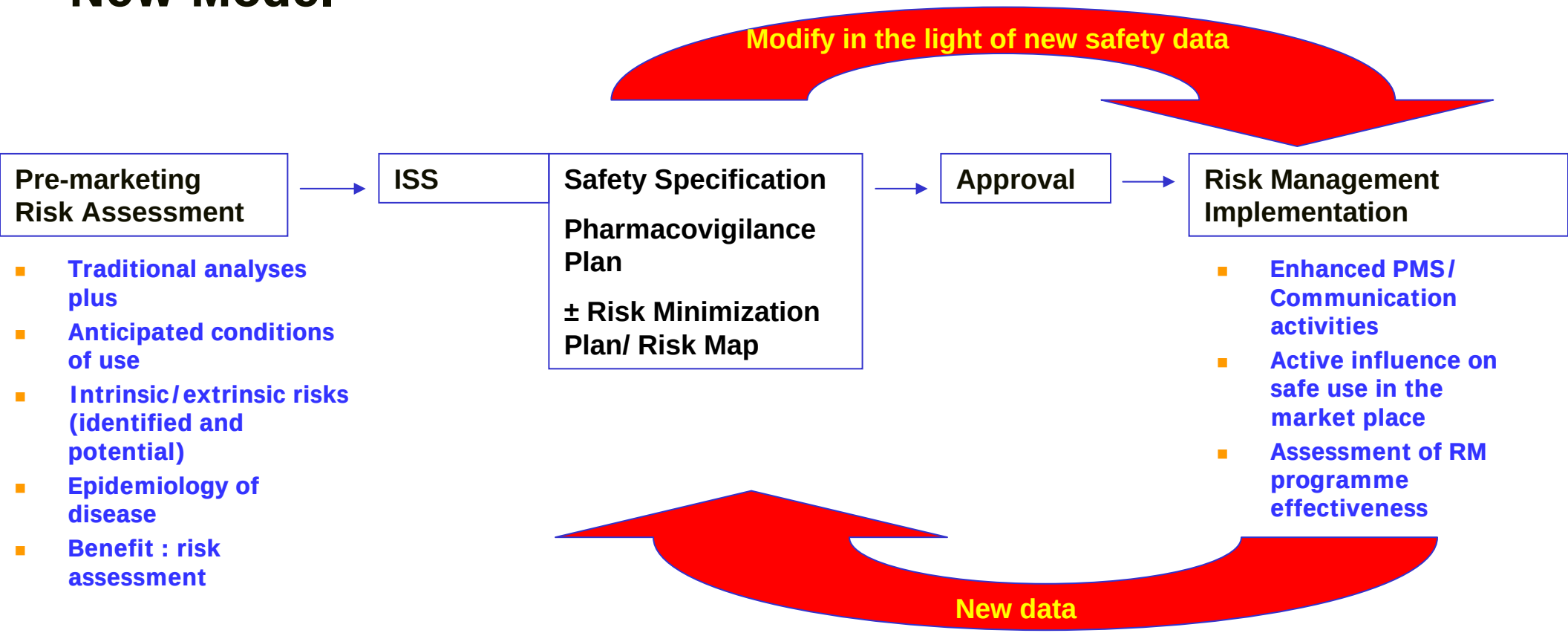
- Integrated safety analysis
- SADRs
- AEs
- Laboratory/other data

- Regulatory approval for labelled use
- Risks included in label (disclosure)

- 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

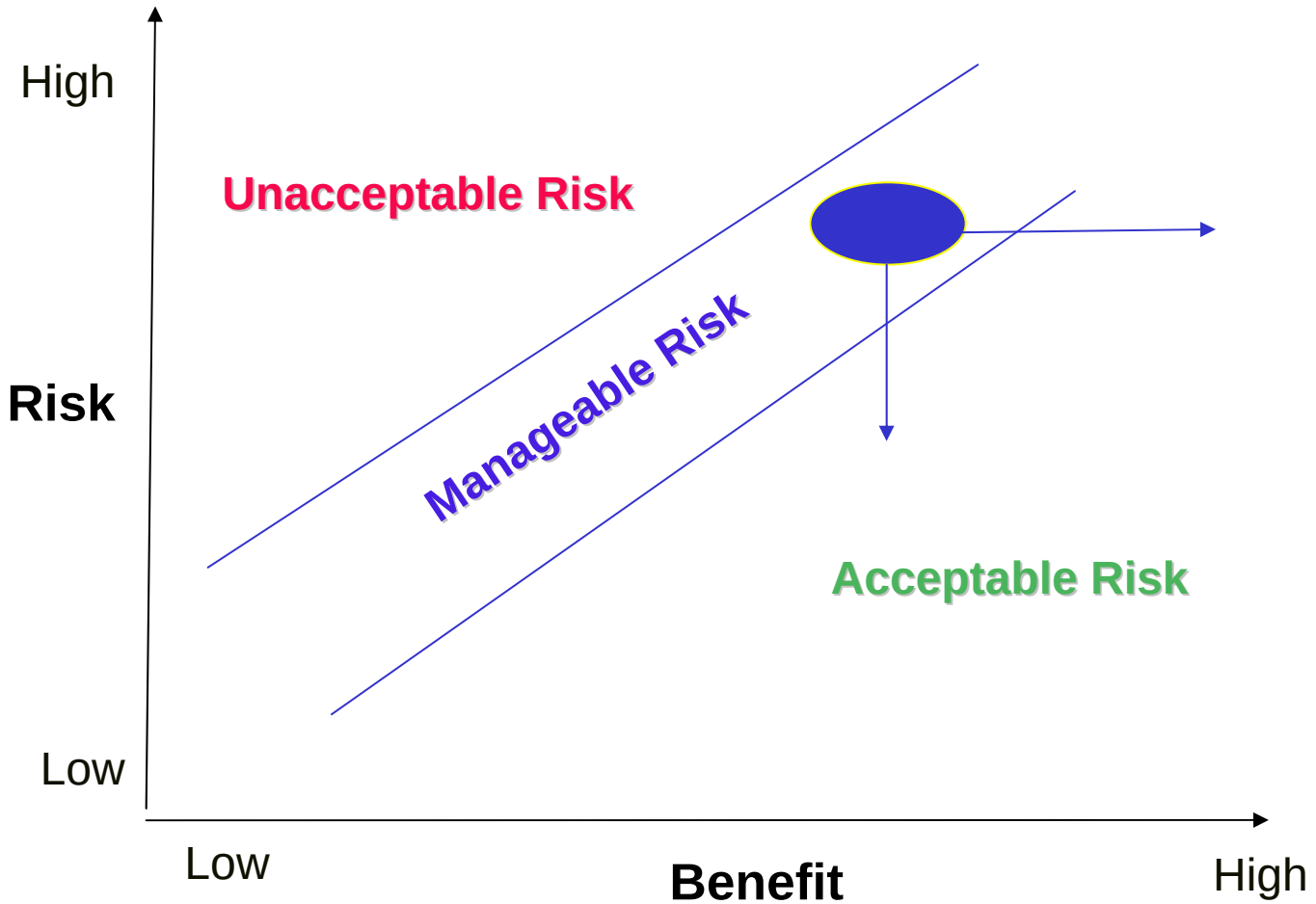
Risk Management – A Shift in Emphasis

"New Model"



Overall Objectives of Risk Management Planning
Benefit - Risk Optimization

Optimizing Benefit 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."

……..or is it ???

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.

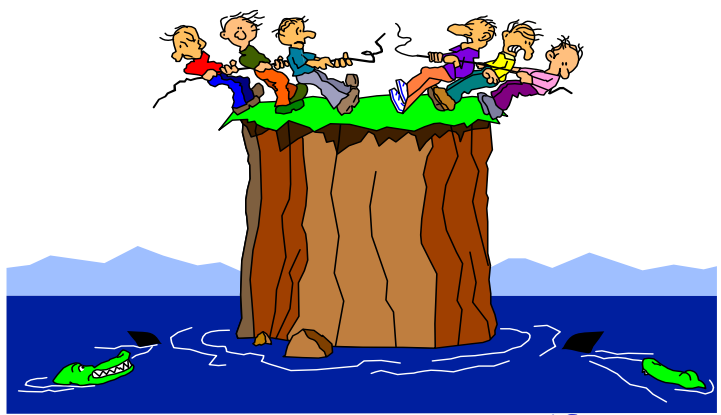
Europe : A set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions

…..but then along came REMS

Risk Management and International Harmonization

International harmonization is wonderful in theory

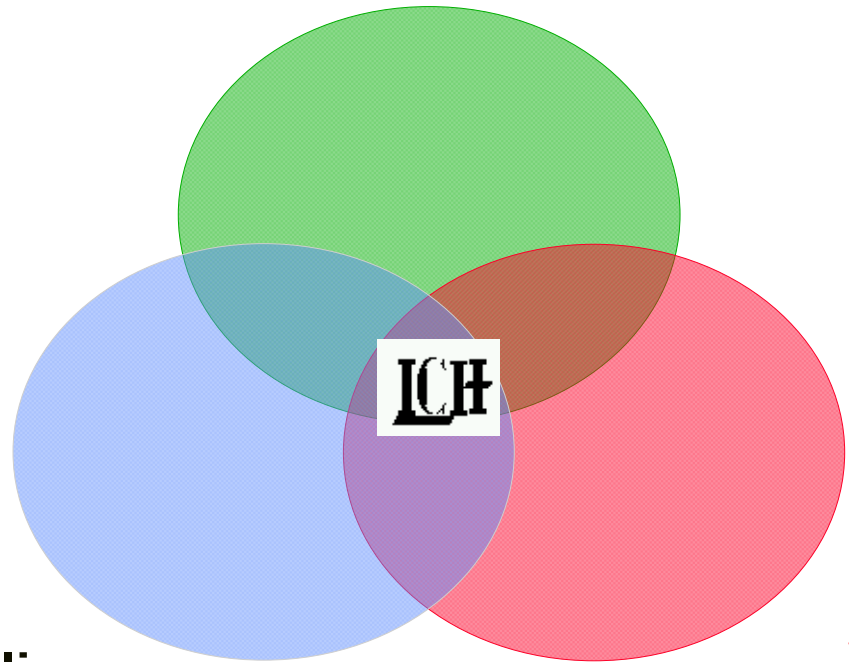
…….but everyone is harmonizing differently



Global Risk Management Planning
The Challenge of Reconciling the Differences

Europe

ICH E2E +/- Risk Minimization Plans



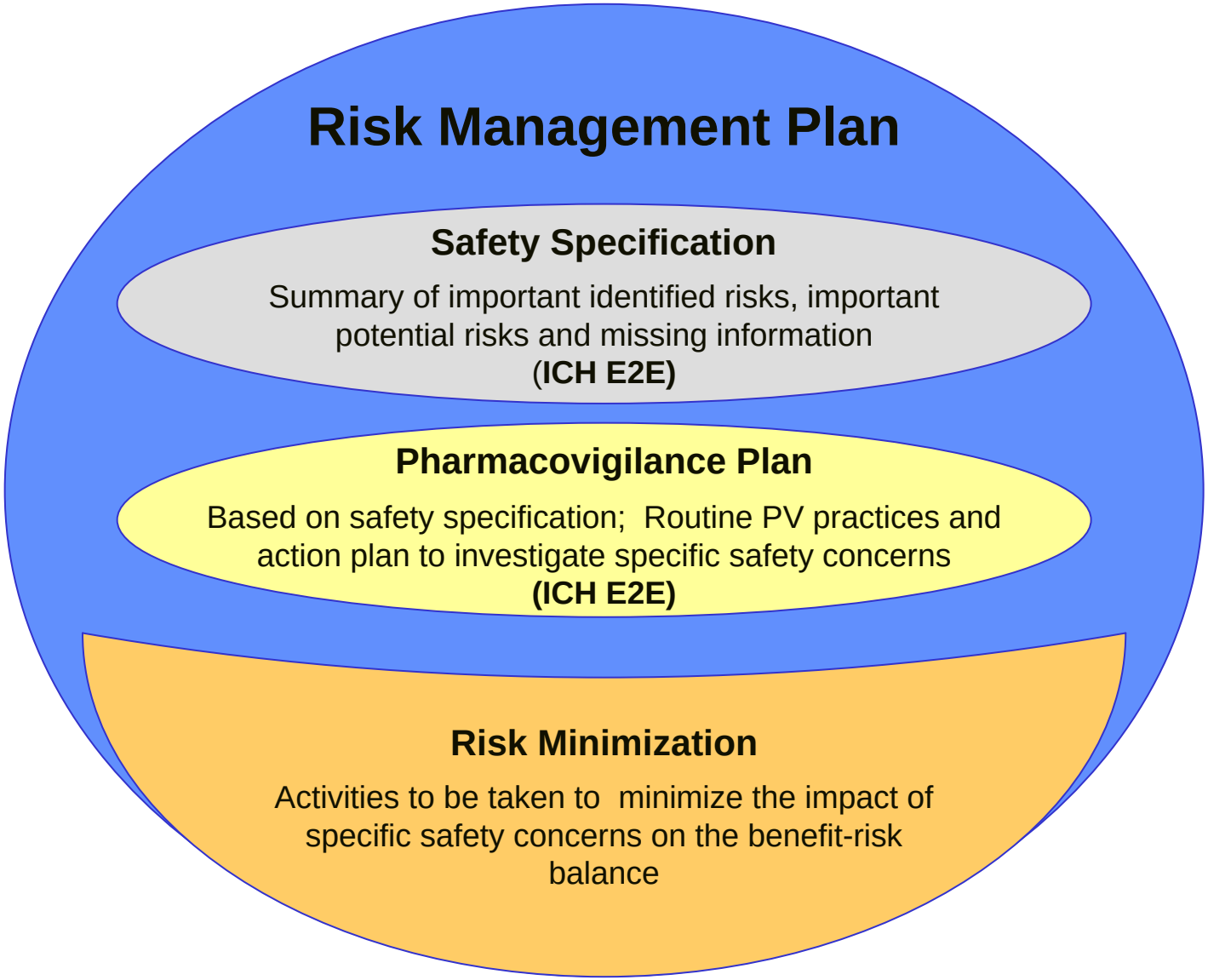
US

RM Guidelines including RiskMAP/REMs

Japan

ICH E2E + EPPV(?)

Basic Components of a Risk Management Plan



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

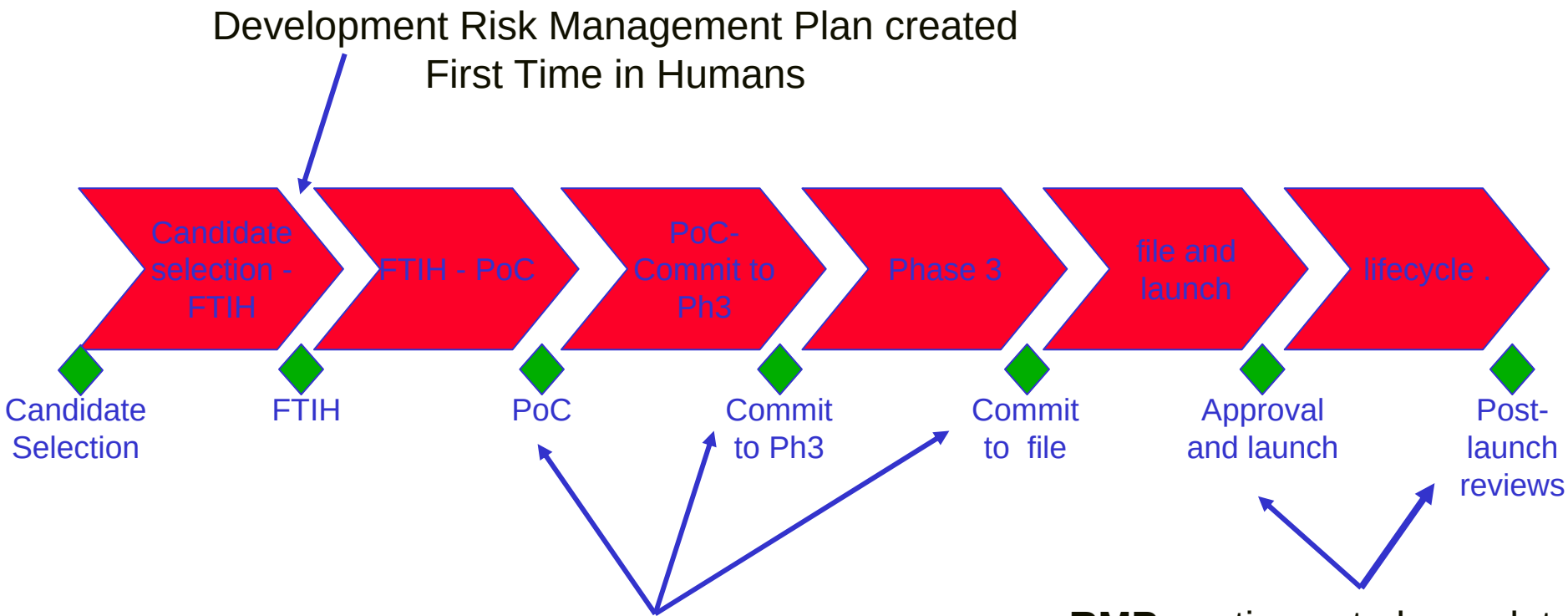
Other Practical Considerations

RM Planning - 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

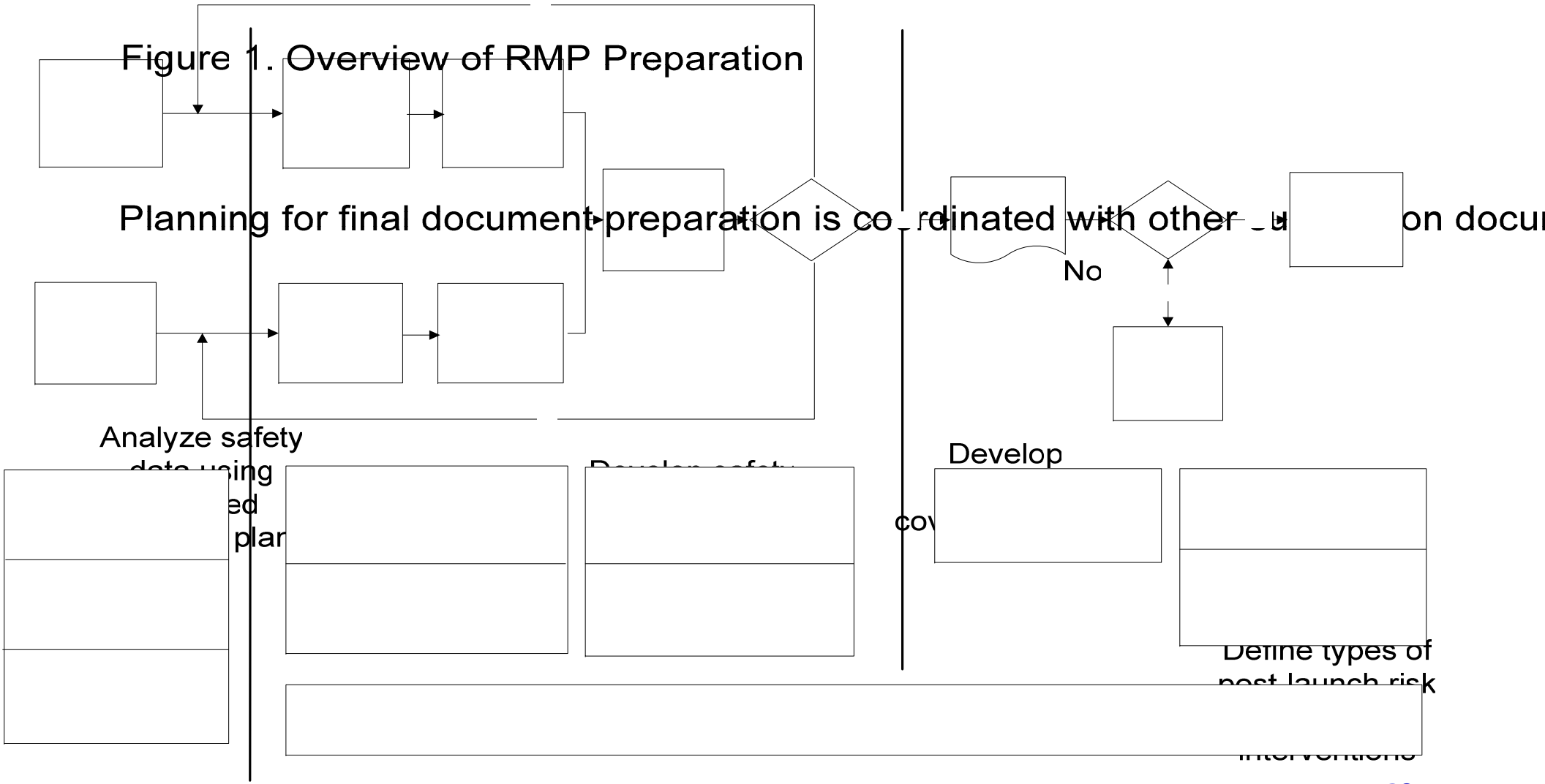


DRMP updated with significant new data at least annually and before key development milestones

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



RM Planning - Practical Considerations

The Role of Epidemiology

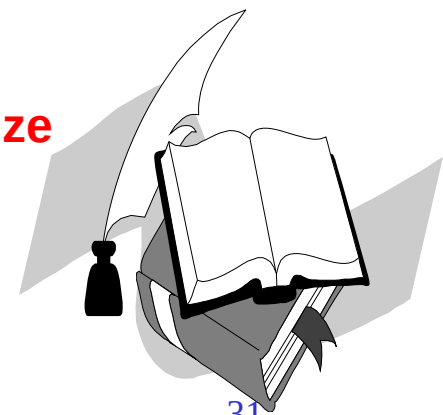
- Important early in development and throughout the RM process
- Critical for the Safety Specification and PV Plan……bridging the knowledge gap

  - **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

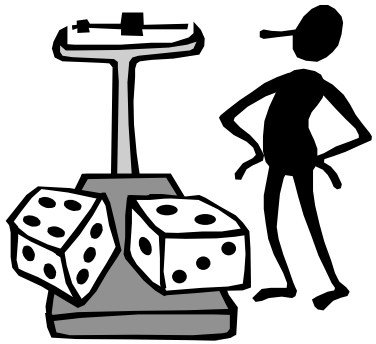


Pharmacovigilance Plan

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

	Positive Opinions	RMP	Additional Risk Minimization Activities
New Marketing Authorisations	134	113	20
Post-authorisation Procedures		80	6

European Regulatory Experience with RMPs Review & Learning Project - Phase 1

RMP Assessment	Number(%) N=12
Satisfactory quality	**3 (25%)**
Non-compliance with EU RMP guidelines	**9 (75%)**
Missing parts ▪**Specification, PhV Plan, Risk Minimization Plan, Summary etc** ▪**Protocol/outline** ▪**SPC not attached**	**8 (67%)** **"Several"**
Deviating Structure	**5 (41%)**
Non-relevance/redundancy (Safety Specification)	**5 (41%)**

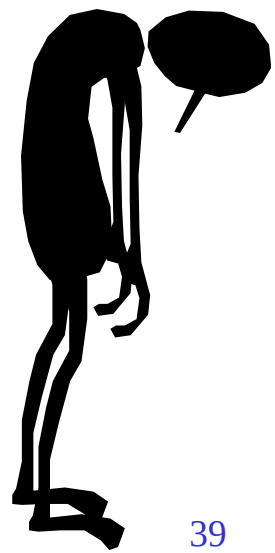
Following the structure and contents of the EU guidelines and template was considered sufficient to address most issues

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."

Dose	10 mg	20 mg	40 mg
Shape	Round	Round	Round
Size mm	6.2 x 2.8	7.9 x 3.3	9.8 x 4.3
Colour	Pink	Light beige	Beige

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

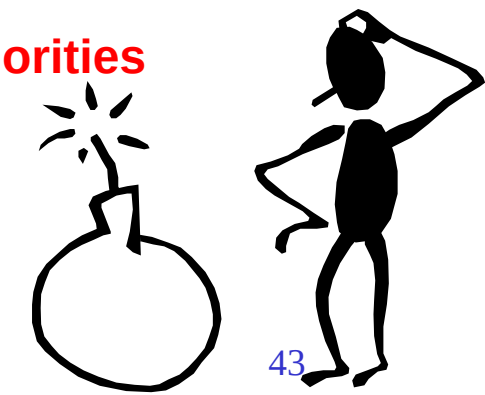
	No of patients Total (male/female)
Diabetic nephropathy	65 (39/26)
Hypertensive nephropathy	71 (47/24)
Glomerulonephritis	207 (143/64)
Other	246 (140/106)

Table y: Special population exposure

Population	Number of patients
Children (<12 years)	None
Elderly (>75 years)	14
Pregnant or lactating women	None
Relevant co-morbidities •Hepatic impairment •Cardiac disease	 57 243 ....
Genetic polymorphism	Not applicable
Ethnic origin •Caucasian •other	 584 5

Risk Management Plans in Europe
Industry Experience

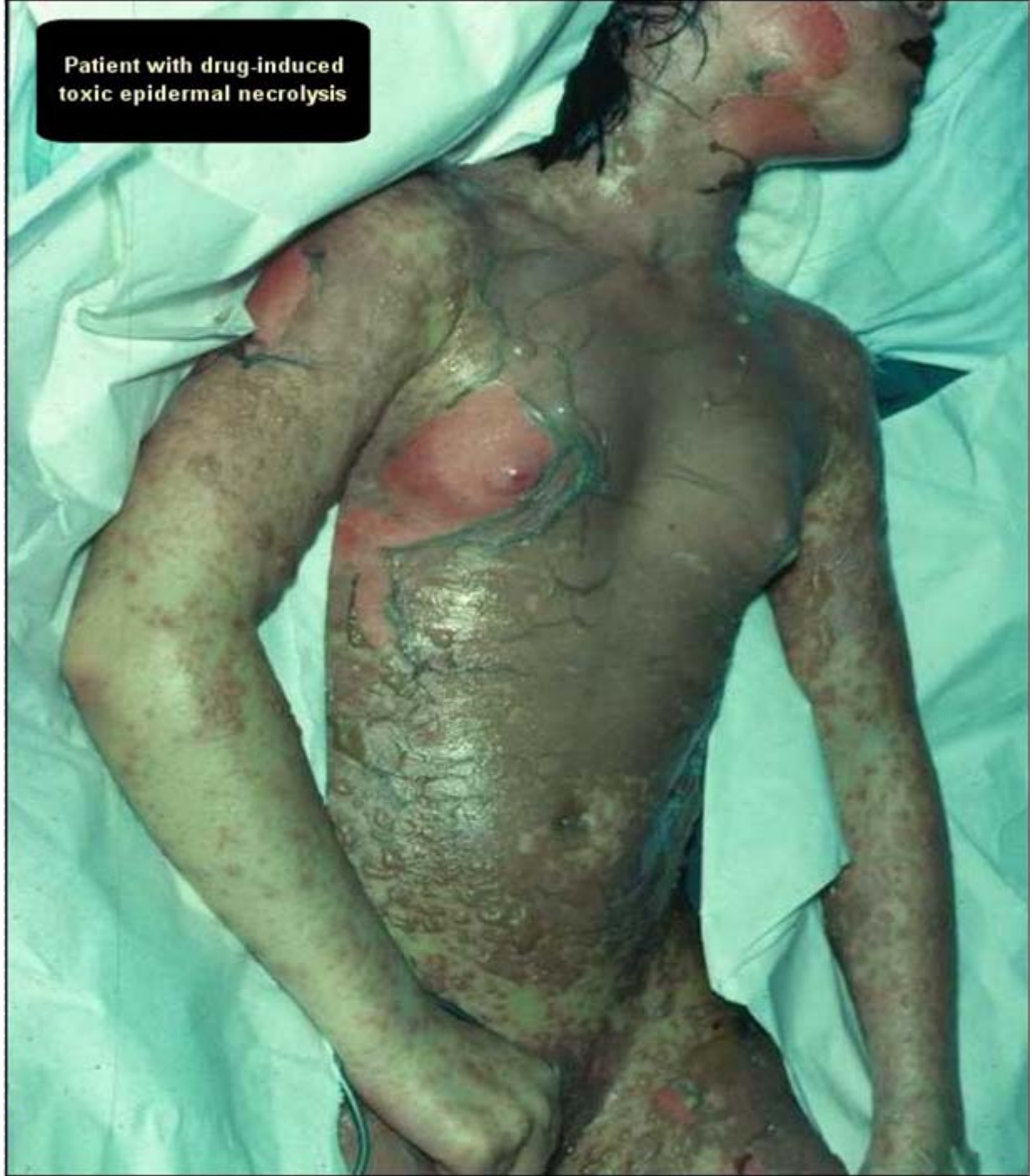
- Increasing trend to request EU specific RMP vs global document
  - **e.g.wish to see specific reference to SPC sections vs generic statements relating to the CCSI**
- For submissions of a new indication/formulation with a mature product, need to produce an RMP for the whole molecule
- Strong emphasis 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

Adverse Event Term	Yes	No
Total blindness for 30 minutes	70%	30%
Suicide threat	17%	83%
“Mild” anaphylaxis	61%	39%
Spontaneous abortion	95%	5%

Most discrepancies related to disability, life-threatening condition or medical significance



Toxic Epidermal Necrolysis (TEN)

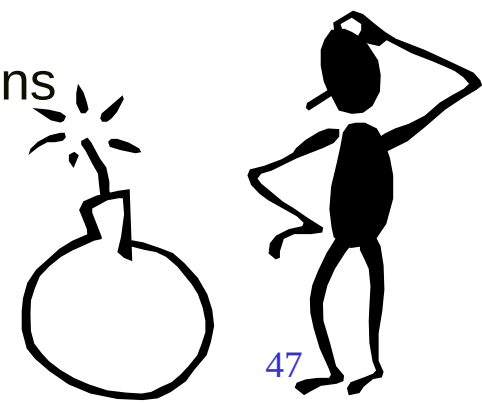
Clearly a serious and important risk

Flatulence

An important risk????

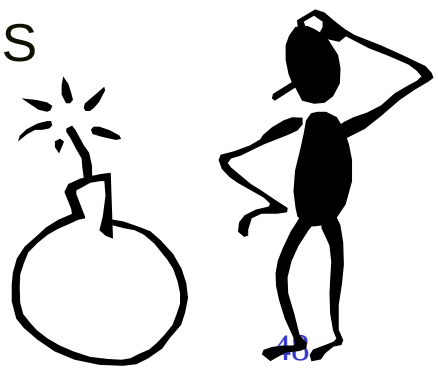
Risk Management Plans in Europe
Industry Experience

- 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



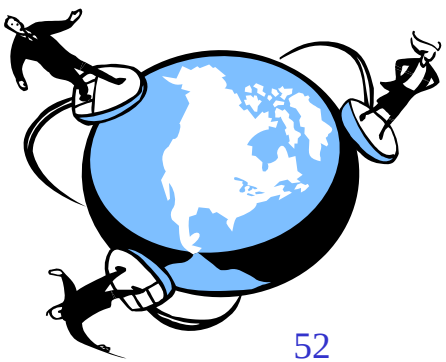
Global Plan and US RMP Relationships

Global Plan and EU RMP Relationships

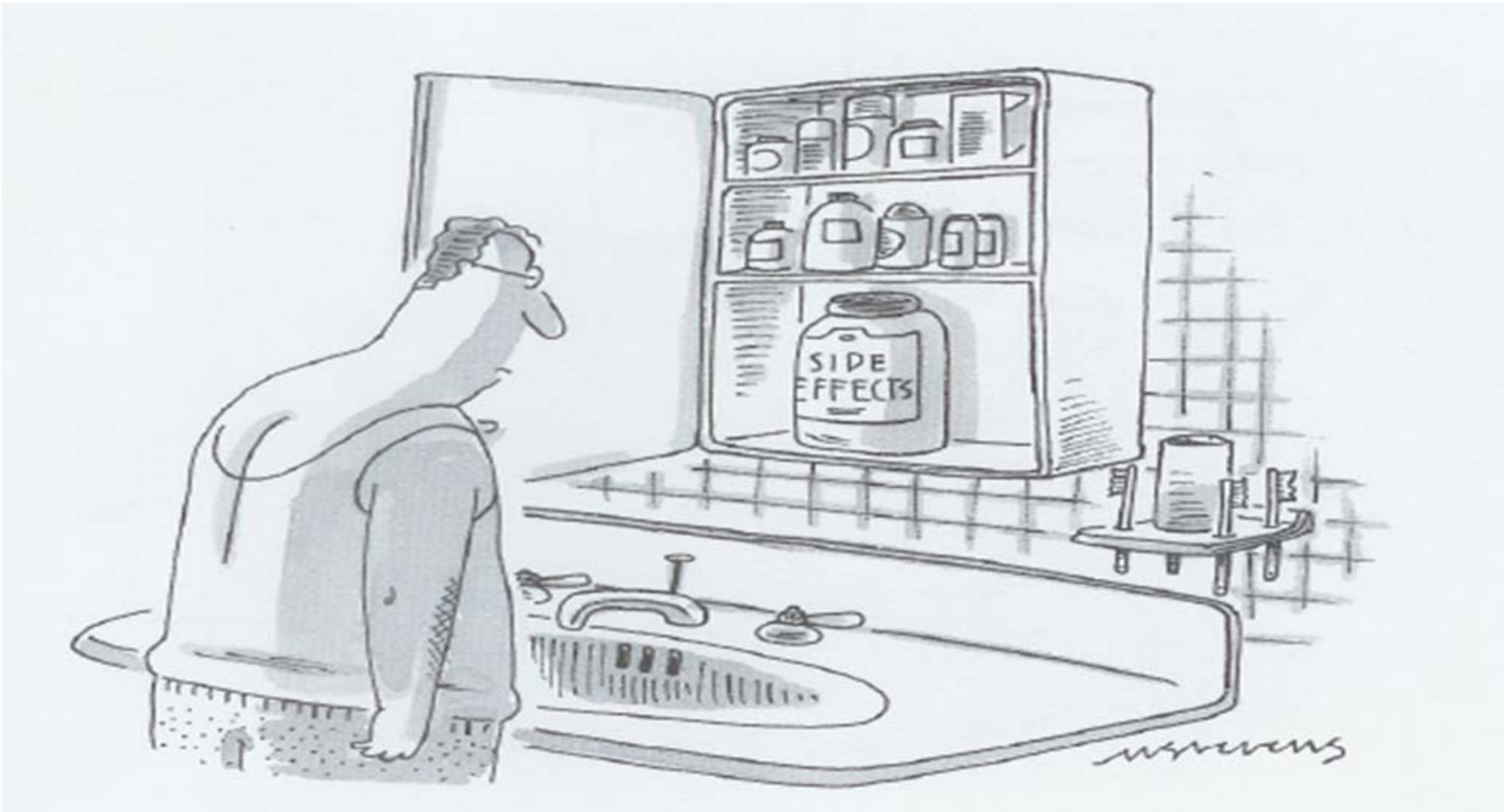
RMP Regional Variations

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 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



Safety Communications - A Patient Perspective

THE TIMES

"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.

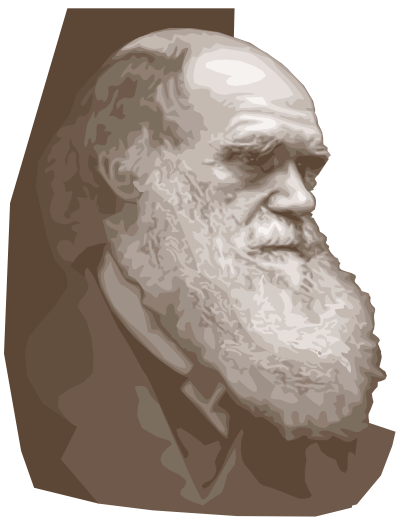
Should she take them?

Yours faithfully,

Letter to the Editor,1996

Risk Management - Conclusion
Embracing Change

"It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change."



Charles Darwin, 1859