Risk Management
A continuum from Clinical Trials to Post-Marketing

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Strength and Energy with Products LAVOCAT irradiated food
From Pharmacovigilance to Risk Management
Thalidomide: 1958-1961

In 50 countries as sedative and anti-nausea in pregnancy, in 1rst Q

1961: teratogenicity in 12 000 neonates with genetic transmission

10 years of law suits

Creation of Pharmacovigilance regulation and agencies in the 1960s
1998 : Thalidomide’s come back

- 1998 : new approval in USA : Leprosy, Lupus, Multiple myeloma, graft

- Risk Management Plan: STEPS

- Because of the toxicity .... THALOMID® is approved by FDA ... only under a special restricted distribution program."

- Physicians, pharmacists, and patients must be registered in the RMP

- Use of 2 type of contraceptive measures

RESULTS
80 000 patients monitored within 5 years in US

No known cases of foetal exposure
40 years later: Vioxx 1999-2004

- 1999 FDA Approval: anti-inflammatory drug
  - 2000 Myocardial infarction: risk inferior in comparator
  - 2001 Re-analysis: cardio-vascular risk: RR: 2.38
  - 2002 Change of SPC

- 2004: long term study
  - risk of cardio-vascular event: x2 vs placebo

- Sept 2004 Worldwide withdrawal

*from Xavier Kurz, EMEA ISOP Octobre 2006
“Adverse drug reactions remain a major cause of morbidity and mortality (4th cause of death in US)

Tsintis P, and coll Drug Safety, 2004; 27(8): 509-517

5% of all hospital admissions due to an adverse drug reaction (5th cause of hospital death)

197,000 deaths per year in EU; Total cost: 79 billion euros

EU Commission evaluation: 2010
From Pharmacovigilance To Risk Management

New concepts

New regulation
New concepts

Yesterday

A Passive Process
Collect and analyse information

And

A Reactive Process
Actions implemented in crisis
New concepts

1. Proactive Approach
2. All along the product lifecycle
3. Integrative organisation
4. RMP : a very part of the submission file
1. A Proactive Approach

- Assess the risk: identified, potential or missing information
- Minimise and/or prevent the risk
- Develop Post-Marketing Safety Studies
- Demonstrate the Safety

Key-word
PREVENTABILITY
2 All along the product’s life cycle
3. Integrative Approach

Nonclinical data → Clinical Research → Post-Marketing

PV Specifications → EU RMP → REMS 1 → REMS 2 → REMS 3 → REMS 4

Top Management → R&D → Risk management → Marketing → Sales

PV → IT → QA/QC

Regulat. affairs
Guidelines ICH, FDA & EMA

Risk Management

Pharmacovigilance system

Specific Risk Minimisation Activities

RISK
- Identification
- Evaluation
- Minimisation/Prevention
- Communication
ICH, FDA, EMA

Regulation


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<tr>
<td>CIOMS VI</td>
<td>ICH E2A: Clinical Safety Data Management Definitions &amp; standards for expedited reporting 1994</td>
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<td>ICH E2F: DSUR Aug 2010</td>
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<td>ICH VII</td>
<td>Eudralex: Volume 10</td>
<td>Directive 2001/20/EC under revision</td>
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<td>Draft detailed guidance on the collection, verification &amp; presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (CT-3) June 11, 2011</td>
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<td>EMA</td>
<td>Final Rule on IND Safety reporting: Federal Register, Sept 29, 2010</td>
<td>Guidance to Industry and Investigators: Safety reporting requirements for IND and BA/BE studies</td>
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## Safety in Post-Marketing

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<th>Organization</th>
<th>Reference / Document Title</th>
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<tr>
<td>CIOMS</td>
<td>CIOMS V Current Challenges in Pharmacovigilance: Pragmatic Approaches 2001</td>
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<td>CIOMS VIII Practical aspects of signal detection in Pharmacovigilance 2010</td>
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<td>Volume 9A” Guidelines on Pharmacovigilance for Medicinal Products for Human Use (September 2008) (Eudralex)</td>
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<td>21-CRF-314-80 Safety for marketed drugs</td>
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# Risk Management

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<td>RiskMAP : Risk Minimization Action Plan March 2005</td>
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<td>FDAAA Title IX, Enhanced Authorities regarding Post-marketing safety of Drugs Sept 2007</td>
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<td>Draft Guidance for Industry format &amp; content of proposed Risk evaluation and mitigation strategies (REMS) Sept 2009</td>
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The changing regulation landscape in Pharmacovigilance

- DSUR
- FDA & EMA for the reporting of SAEs in clinical trials
- EMA: Pharmacovigilance package in post-marketing
Core message!

- Start early
- Apply same tools and methods for PV
- Use medical approach
  - Individual cases
  - Aggregated data
- Look for real life safety profile
- Set up signal detection procedures
- Comply to International Harmonization
- Set up multidisciplinary team
CIOMS VI : the basis of new regulation in Clinical trials

- Set up a PV system asap
- Involve Pharmacovigilance experts in development plan
- Set up a Development Risk Management plan
- Simplify the causality assessment : YES/NO
- Periodic review of data +++
- Medical approach vs regulatory one
DSUR

- Applicable in all regions: September 2011
- Same principle that PSUR (in post marketing)
- Harmonization in format, content and calendar worldwide!
- Focused on one investigational product rather than a clinical trial
- Gather all safety experience for risk analysis; studies, post-market, epidemiology…..
- Use a safety database
- Start thinking in «potential and identified risk» category
FDA Final rule & EMA : reporting of SAEs in clinical trials

- Set up a PV system
- Harmonization of definitions and procedures → ICH
- Causality assessment : YES/NO
- Medical relevance is paramount
- No interest in high morbi-mortality events ie oncology : Exceptions for collecting and reporting of SAEs
REMS and RMP

- **Start early**
  - Early termination of a CT if needed
  - Identification of risk factors to target the population with the higher benefit /risk

- **Pharmaco-epidemiology : THE MUST**

- Risk Communication is a key element toward HCP and patients

- **EMA & FDA : Authorities counselling on the best mitigation/prevention/minimization tools**

- **Efficiency of actions must be evaluated periodically**

- **EMA : Mandatory for any MA application**

- **FDA may require a REMS for any NDA or BLA**
Steps to implement Developmental Risk Management Plan

- Set up Risk Management Team
- Starts writing safety specifications at phase I
- Set up risk minimization actions
- Update safety specifications in each DSUR
- Recurrent process all along the product life cycle
Prepare the early post-marketing period

- Set up the PV system ASAP
  - SOPs
  - Quality Plan
  - Training plan
- Nominate Qualified Person for Pharmacovigilance (EUQPPV)
- Set up the PV System Master File (EU)
Pharmacovigilance system

The tool for inspection readiness
PHARMACOVIGILANCE & RISK MANAGEMENT SYSTEM

Pharmacovigilance system

Risk Management Specific Activities

Resource and Structures

Role of the EU QPPV and the local QPs

Quality Assurance System/Quality controls

Pharmacovigilance Training Filing/Archiving Organization

Data protection

Safety agreements Assessment of expedited reporting criteria

Technology

Safety Data base

Internal Communication: workflows

External Communication And Eudravigilance

PSURs

Risk Communication

Risk Minimization Actions

Development

Post-authorisation Safety Studies

Safety Crisis management

Answers to queries from Competent Authorities

Pharmacovigilance Interface With other departments

Specific Activities
Case study

Soliris® Risk Management
Risk identification

- Eculizumab: monoclonal Ab, anti C9 complement, 1rst in class
- Indication in Paroxystic Nocturnal Hemoglobinuria: orphan disease
- Genetic deficiency in C9:
  - infections to encapsulated bacteria: meningococcus, pneumococcus,
  - other infections: herpes..
- Infections: POTENTIAL RISK
Risk assessment

- 1rst meningitis in clinical trials
- Patient went too late to hospital
- Severity +++
- Sequellae +++
- Jeopardized
  - the product
  - the whole trial
  - the company
Risk minimisation during clinical trial

- Meningococcus vaccination before treatment
- Patient Safety card:
  - Identify early symptoms
  - Go to emergency
  - Call trial phone number
- Investigators training
- Results: 2 patients with meningitis
  - Complete recovery in few days
RMP US & EU

- 2007: Marketing authorization granted in US & EU
- Risk minimization plan:
  - Restricted distribution: performance linked with vaccination
  - Educational material
    - Medical guide
    - Patient guide
    - Patient safety card
    - Vaccination reminders
  - Registry
- RiskMAP converted in REMS

*In 2010, Soliris was the most expansive drug on the market*
Risk Management is expansive

But will prevent...
Analysts' estimates on Vioxx's liability from 20 to 55 billion $.

- Sept 2005: 7500 plaintiffs
- 1st Trial: 26 millions $

Source: Washington Post

October 2005
Within 1 year, decrease of shares >46%
From Business Week
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Thank you for your attention

For any question

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