HOT TOPICS IN PV

The New PSUR/PBRER

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IFC Strategic Safety Consulting
Agenda

1. Regulation
2. Format and Content
3. The Risk Management Approach
4. PSUR is a medical document
5. Integration of all PV processes
6. Hands on : a case study
Abbreviations and acronyms (1/4)

- ADR  Adverse Drug Reaction
- AR   Assessment Report
- ATMP Advanced Therapy Medicinal Product
- B/R  Benefit –Risque balance
- CAP  Centrally Authorised Product
- CIOMS Council for International Organizations of Medical Sciences
- CHMP Committee for Medicinal Products for Human use
- DCP  Decentralised Procedure
- DDD  Defined Daily Dose
### Abbreviations and acronyms (2/4)

- **DLP**  
  Data Lock Point
- **DSUR**  
  Development Safety Update Report
- **EC**  
  European Commission
- **EMA**  
  European Medicines Agency
- **EU**  
  European Union
- **EURD**  
  European Union Reference Date
- **EV**  
  Eudravigilance
- **GVP**  
  Good Pharmacovigilance Practices
- **ICH**  
  International Conference of Harmonisation
- **ICSR**  
  Individual Case Safety Report
- **IT**  
  Information Technology
- **MA**  
  Marketing Authorisation
- **MAH**  
  Marketing Authorisation Holder
- **MCDA**  
  MultiCriteria Decision Analysis
- **MedDRA**  
  Medical Dictionary for Regulatory Activities
- **MS**  
  Member State
Abbreviations and acronyms (3/4)

- **NCA**  National Competent Authority
- **PASS**  Post Authorisation Safety Study
- **PBRER**  Periodic Benefit-Risk Evaluation report
- **PRAC**  Pharmacovigilance and Risk Assessment Committee
- **PT**  MedDRA Preferred Term
- **PSUR**  Periodic Safety Update Report
- **PV**  Pharmacovigilance
- **QA/QC**  Quality Assurance/Quality Control
Abbreviations and acronyms (4/4)

- **REMS**: Risk Evaluation and Mitigation Strategy (USA)
- **RMP**: Risk Management Plan (EU)
- **SAE**: Serious Adverse Event
- **SADR**: Serious Adverse Drug Reaction
- **SmPC**: Summary of Product Characteristics
- **SMQ**: Standard MedDRA Query
- **SOC**: System Organ Class
- **WHO**: World Health Organization
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LEGAL REQUIREMENT FOR PSUR

EU leading

- GVP Module VII Revision 1: effective 13/12/13

ICH

- ICH E2C(R2)PBRER Periodic Benefit-Risk Evaluation Report
  - adopted Dec 2012
  - applicable Jan 2013
Content of 1st revision

- Harmonisation with the ICH-E2C(R2) guideline on “Periodic Benefit- Risk Evaluation Report (PBRER))”,
- Further guidance
- Practical instructions on the EU reference date list
- Instructions on PSUR assessment process,
- Transitional arrangements
USA, Japan, other countries?

- **FDA**
  - PSUR replaces PADER under waiver
  - PBRER, draft guidance Step 2 / 1 Feb 2012

- **PMDA Japan**
  - applicable Jan 2013
  - New JP PSUR to become effective from Oct 2014

- **Other countries**
  - different flavors of the same PBRER : ie Israel
OBJECTIVE

Present a comprehensive concise critical analysis of the risk/benefit balance

ANALYSIS OF BOTH INTERVAL PERIOD CUMULATIVE

- No more for line listings
  - Summary tabulation (serious and non serious)
  - Case narratives only if relevant for analysis
Agenda

1. Regulation

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# PSUR Table of Content

- **Introduction**
- Worldwide marketing authorisation status
- Actions taken in the reporting interval for safety reasons
- Changes to reference safety information
- Estimated exposure and use patterns
- Data in summary tabulations
  - Summaries of significant findings from clinical trials
  - Findings from non-interventional studies
  - Information from other clinical trials and sources
- Non-clinical Data
  - Literature
  - Other periodic reports
  - Lack of efficacy in controlled clinical trials
  - Late-breaking information
  - Overview of signals: new, ongoing or closed
- Signal and risk evaluation
- Benefit evaluation
- Integrated benefit-risk analysis for authorised indications
- Conclusions and actions
Format and Content (1/2)

PSURs shall contain:

- Summaries of ALL data relevant to benefits and risks, incl results of all studies
- Scientific evaluation of the risk-benefit balance based on all available data, including data from clinical trials in unauthorised indications and populations
- Estimation of population exposure based on all data of sales/prescriptions volume
Format and Content (2/2)

- No more line listings
  - But may be requested during assessment.
- Summary tabulation still included (serious and non serious)
- Case narratives to be provided where relevant to the scientific analysis of a signal or safety concern
NEW : section 15
Overview of signals: new, ongoing, or closed

- significant difference in severity or frequency

- higher frequency or severity newly found in an indicated subpopulation.

- An ongoing signal refers to a signal that was still under evaluation at the data lock point.
Rev 1 : changes overview
Clarification of section 15 : signals

- Signal tabulation
  - brief description
  - date when MAH became aware
  - status at the end of the reporting interval (close or ongoing)
  - date when the signal was closed, if applicable
  - source of the signal
  - brief summary of key data
  - plans for further evaluation;
  - actions taken or planned.
- Details of assessment in section 16
NEW : section 16-
Signals and Risk evaluation / summary of safety concerns

At the beginning of review period

- Important identified risks
- Important potential risks
- Missing information
16-Signals and Risk evaluation/Signal evaluation

- How did you closed your signals
  - It became a risk
  - It was refuted

- Arguments, arguments, arguments,
  - Public Health importance
  - Medical significance
  - Details +++

Ref to signal management process
16- RISKS

- Evaluation of risks and new information

  UPDATED TABLE
  - New Important identified risks
  - New Important potential risks
  - New non Important identified risks
  - New non Important potential risks
  - New Missing information

- Characterisation of risks: same table in cumulative

- Effectiveness of risk minimisation (if applicable)
Rev 1: section 16
signals & risks evaluation

- summary of the effectiveness of risk minimisation activities
  - Flow chart of the mapping of signals & risks
  - Missing information could be an important risk
NEW : section 17
Benefit evaluation sections

- **Baseline** Efficacy and Effectiveness
- **Newly Identified information** on Efficacy and Effectiveness
- **Characterisation of Benefits**
- **Enough detailed**
NEW: section 18
B/R evaluation

- Integrated Benefit/Risk Analysis for approved indications
  - *Only key risk and benefits (rev1)*
  - Discuss strengths/weaknesses of evidence
  - Used methodology: quantitative, qualitative
  - Benefit-risk Context - Medical Need and Important Alternatives
  - Benefit-risk Analysis Evaluation
Conclusion and actions

- **Is there a need for:**
  - changes of safety information
  - Updated RMP
  - New or updated risk minimisation action

**A REAL AND PROACTIVE CONCLUSION**
Conclusions and actions

- Variation type I: update of SmPC and Patient leaflet, warnings
- Communication to Healthcare professionals
  - Brochure
  - Training
  - Newsletter
  - Dear Healthcare Professional Communication
- Communication to patient:
  - Patient leaflet
  - Pictogram
  - SmPC update.
- Intensive monitoring: registries set up,
- Internal training for sales reps and medical team
Appendices

- Cumulative summary tabulations of SAE from clinical trials
- Cumulative and interval summary tabulation of SADR and non SADR from post marketing data source
- Signal tabulation *Better in the PSUR body*
- Signals evaluation *Better in the PSUR body*
- Reference information
- Listing of all PASS
- List of sources of information used (at MAH discretion)

**Proposal for changes in SmPC must be proposed in annexes**
EU Specific requirements – regional annexes

- **Proposed product information**
- **Proposed** additional PV and risk minimisation activities
- Summary of ongoing safety concerns
- Reporting of results from post-authorisation safety studies in PSURs
- **Effectiveness of risk minimisation**
To summarize ….
Medical analysis in depth (1/2)

- « Signal and risk evaluation » allow providing interpretation and critical appraisal of the new information

- « Benefit evaluation » to characterize and update
  - Characterisation of benefits
Medical analysis in depth (2/2)

- Period always compared to cumulative data
- Holistic approach with clinical trials data
- Level of detail has to reflect the medical significance
- «Integrated benefit-risk analysis» provides an overall appraisal of the benefit and risk of the medicinal product used in clinical practice
The EU RD List & submission timelines
EURD List (EU reference date)

List of more 3000 active substances marketed in EU defining

- EU Reference date
- Next DLP
- Frequency of submission
- Reference Member State
- Entered into force: April 2013
EURD List

- Only the products where PSUR is required
- If product is not on the list
  - Other products → current calendar applies as specified in MA
- **Waiver**: Generics, Well established use, homeopathic and Herbal medicines
- **Rev 1 MAH could request amendment on EURD list (use of IBD for harmonization purposes)**
PSUR submission – timeline

- **within 70 calendar days** of DLP
  - for period **up to 12 months**;
- **within 90 calendar days** of DLP
  - For period in **excess of 12 months**;
- **Note: for ad hoc PSUR requested by NCA**
  - Submission timeline **specified in the request**, otherwise **within 90 days** of DLP
Role of PRAC in decision-making process

Centrally authorised medicine is involved

Assessment report by a rapporteur appointed by PRAC

PRAC: adoption and recommendations

CHMP: opinion on regulatory action, based on PRAC recommendations

$CHMP=PRAC$

Written explanation together with a decision

Decision transmitted to EC
MAH comments on assessment report and recommendations

- assessment report is due within 60 days
- MAH is entitled to answer and argument recommendations
- Answers will be evaluated before a final decision by EC
Transparency

- Publicly available on the EU webportal
  - Final assessment conclusions of the adopted assessment reports.
  - PRAC recommendations, including relevant annexes
  - CMD(h) position
  - CHMP opinion
  - European Commission Decision
Quality Management System (MAH)

- Submissions
  - Check regularly the URD list,
- Production of PSURs according to legal requirements.
- For products with no risk management plan (RMP)
  - the MAH should maintain on file a specification of important identified risk, important potential risks and important missing information in order to support the preparation of the PSURs.
PSUR Quality Management System: EUQPPV responsibilities

- Production
- Submission
- Quality
- Responses
- Awareness of conclusions
- PRAC recommendations
- CHMP opinionspositions
- Actions to be implemented.
- Record management
**Tips**

**Labelling and coding consistency**

- Rules for labelling and coding (incl. MedDRA)
  - Main ADR
  - LL/PT
  - SOC
  - Listedness/expectedness

- Template for narrative summary
  - Introduction sentence

- Template for Company statement

- Template for summaries in LL

- Intra-cases consistency, dataentry validation
Tips
If coding and labelling are not consistent …

QC on queries results mandatory before data locking for PSUR

✓ LL, ST, any tabulated presentation of PSUR cases, narratives

✓ Number of cases, ADRs, deaths, clinical trial cases, pregnancies, listedness, seriousness, ages, ...

✓ Figures consistency, MedDRA consistency, intra-cases and inter-cases consistency
Tips

eCTD submission : EMA Webinar

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3. **The Risk Management Approach**
4. PSUR is a medical document
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6. Hands on : a case study
The Risk Management Approach

PSUR is a mini-RMP
YESTERDAY

A Passive Process
Collect and analyse information
And

A Reactive Process
Actions implemented in a crisis situation
New concept!

**TODAY**

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

Safety Specifications

Clinical Research

MA

Post-Marketing

EURMP & REMS1

RMP/REMS2

R&D

PV

Risk management

Marketing

Sales

Top Management

Regulatory affairs

IT

QA/QC
Guidelines EMA

Risk Management Plan

- Safety Specifications
- PV Plan

Risk Minimisation Plan

RISK
- Identification
- Evaluation
- Minimisation and /or Prevention
- Communication

© L'Entreprise Médicale 2012
EU-RMP Mandatory

- **New products:**
  - Prepare immediate launch time

- **High risk products:**
  - ATMP, Monoclonal antibodies
  - Immuno-modulation agents...

- **Products on the market:** new safety concern

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**ALL PRODUCTS**

- Light RMP for generics, herbal, well established use

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since November 2005

since July 2012
Pharmacovigilance Plan

**Based on safety specifications**

- Description of routine Pharmacovigilance
  - (Module 1.8.1 of approval dossier)
- EU QPPV, 24/7/365
- Need for enhanced Pharmacovigilance activities
- Planned activities for each safety concern
  - Identified, potential or missing information
Safety Specifications : structure

Analysis

- Non clinical data

Clinical data

Compilation

- Identified Important Risks
- Potential Important Risks
- Missing Information
## 2 Clinical Safety 2.5 Adverse Events/ADRs

For every potential and identified risks

<table>
<thead>
<tr>
<th>Identified/ Potential Risk</th>
<th>All MedDRA terms PT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seriousness/ Outcomes</td>
<td>Detailed information</td>
</tr>
<tr>
<td>Severity and nature of the risk</td>
<td>Hospitalisation duration</td>
</tr>
<tr>
<td>Frequency with 95% CI</td>
<td>In the indication but also in all exposed population</td>
</tr>
<tr>
<td>Background incidence/prevalence</td>
<td>Epidemiology search</td>
</tr>
<tr>
<td>Risk group or risk factors</td>
<td>This will improve in the future</td>
</tr>
<tr>
<td>Potential mechanism</td>
<td>Science based medicine</td>
</tr>
<tr>
<td>Preventability</td>
<td>Key point for risk minimisation</td>
</tr>
<tr>
<td>Potential Public Health Impact of</td>
<td></td>
</tr>
<tr>
<td>safety concern</td>
<td></td>
</tr>
<tr>
<td>Evidence source</td>
<td>Bibliographie, avis d’experts</td>
</tr>
</tbody>
</table>
Potential for …

- Overdose
- Misuse for illegal purposes
- Off label use / paediatrics use
- Medication errors
Summary: Ongoing safety concern

- Key element: snapshot of the security profile

Instant → progression +++

- Base of

  - PV Plan
  - Risk minimisation plan
Effectiveness of risk minimisation

- GOAL: reduce probability / severity of an ADR
- Consists of:
  - routine risk minimisation: product labelling
  - or additional minimisation activities: direct HCP communication / educational materials
- Set criteria and metrics for effectiveness of actions
- Result of evaluation which refers to an individual country → PSUR regional appendix
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PSUR is a Medical Activity

- Signal detection
- Query method
- Harmonisation PSUR/DSUR/RMP
- Method for Benefit Risk ratio
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Analysis

- Signal and risk evaluation
- Benefit evaluation
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PSUR & signal detection
Good Pharmacovigilance Practices Module IX : signal management

- CIOMS VIII : Definition of a signal

An information that *arises from one or multiple sources* (including observations and experiments), which suggests a new *potentially causal association*, or a new aspect of a known *association*, between an intervention and an event or set of related events, either adverse or beneficial, that is *judged to be of sufficient likelihood to justify verificatory action*

- In GVP : only adverse reaction is considered
Where can a signal come from?

- 1rst: increase ADR reporting
- From quality, non-clinical, clinical, PV data
- Any organised data collection centres: PV systems, poisons centres, vaccine surveillance
- EudraVigilance: essential source
- Spontaneous ICSRs, literature, **PSUR**, within regulatory procedures, ongoing process
- Interventional and non interventional studies, Registries
- NCA Webportal, Internal digital media
Methodology

- Structured method to determine evidence of signal
- According to product; i.e.: vaccine ≠ other products
- Criteria:
  - Clinical relevance
  - Quantitative strength of association
  - Consistency of data
  - Exposure-response relationship
  - Biological plausibility
  - Experimental findings
  - Possible analogies
  - Nature and quality of the data
The signal management process

- signal detection
- signal validation
- signal analysis and prioritisation;
- signal assessment
- recommendation for action
- exchange of information. (at each step)
The signal management process

- signal detection
- signal validation
- signal analysis and prioritisation
- signal assessment
- recommendation for action
- exchange of information (at each step)

Any signal in one of these steps must be presented in PSUR.
SOC or SMQ* ?
Choose the relevant query method!

*Standart MedDRA Queries
MedDRA SOC

- For ADR related to one organ: ie
  - Vomiting
  - Hepatotoxicity
  - Renal toxicity
- Focus on one System Organ Class
Multi-organ reaction : hypersensibility symptoms

<table>
<thead>
<tr>
<th>Grade I:</th>
<th>Mucocutaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade II:</td>
<td>Mucocutaneous erythema, urticaria, conjonctival oedema, angio-oedema labial, Quincke's oedema. Cardiovascular: hypotention, tachycardia Respiratory, dyspnoea,, wheezing, ..... Digestives: nausea, abdominal, pain General: chills, hypo/hyperthermia, malaise</td>
</tr>
<tr>
<td>Grade III:</td>
<td>Cardiovascular signs: cardiovascular collapse, tachycardia (sinusal), cardiac rhythm disorders, cyanosis Respiratory: laryngeal oedema, bronchospasm Digestive: diarrhea, vomiting Neurological: convulsion, syncope, consciousness disorders can include coma</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Cardiac or cardiocirculatory arrest</td>
</tr>
</tbody>
</table>

From Lancet 1977 (Ring & Messmer classification)
Example: analysis of hypersensibility case reports

- SOC Immune system disorders
  - Urticaria, bronchospasm, anaphylactic shock
- The other symptoms of hypersensitivity in Organ SOCs
- Change in reporting rate? In symptoms? SmPC still appropriate?
- Transversal analysis: SMQs
  - SMQ Anaphylactic reaction
  - +? SMQ Angioedema
  - +? SMQ Asthma / Bronchospasm
  - +? SMQ Shock
Explain your query method: SMQs

- To be described in PSUR: chosen methods of evaluation incl data sources, & search criteria (MedDRA terms and SMQs)
- SMQ: one of the methods of signal detection and assessment
- SMQs: new tool to retrieve cases of interest
- SMQs contain terms related to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiological test data etc, that are associated with the medical condition of interest
- Medical approach by syndromes or diagnoses: tranversal rather than SOC by SOC
PSUR, DSUR & RMP

Harmonized
Same messages
PSUR / DSUR / RMP : a comprehensive overview

- One product: all indication: all formulations,
- Modular structure & Common modules
- Proportionate to risk
- Harmonised calendar
- Differences : Objectives, periodicity, end-reader
<table>
<thead>
<tr>
<th>RMP</th>
<th>PSUR</th>
<th>DSUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre &amp; post marketing</td>
<td>Post marketing</td>
<td>Pre marketing</td>
</tr>
<tr>
<td>Planned management of B/R ratio all along the life cycle</td>
<td>Evaluation of B/R ratio</td>
<td>Annual review of safety data during all development</td>
</tr>
<tr>
<td></td>
<td>Ref: SmPC of the period</td>
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<tr>
<td>Update as needed</td>
<td>Period versus cumulative</td>
<td>Annual versus previous DSUR</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>- Presentation/discussion of safety specifications</td>
<td>- Consistency of new versus cumulative data</td>
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</tr>
<tr>
<td>- Risk Minimisation Actions &amp; effectiveness</td>
<td>- Impact on patients’ safety</td>
<td></td>
</tr>
<tr>
<td>- Update if risks are changing</td>
<td>- Analysis based on identified and potential risks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Link with RMP</td>
<td></td>
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<tr>
<td>B/R: Benefit /Risk ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMP</td>
<td>PSUR</td>
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<tr>
<td>Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”</td>
<td>Section 3 – “Actions taken in the reporting interval for safety reasons”</td>
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<td>Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation exposure”</td>
<td>Sub-section 5.2 – “Cumulative and interval patient exposure from marketing experience”</td>
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<tr>
<td>Part II, Module SVII – “Identified and potential risks”</td>
<td>Sub-section 16.4 – “Characterisation of risks”</td>
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<td>Part II, module SVIII – “Summary of the safety Concerns”</td>
<td>Sub-section 16.1 – “Summary of safety concerns”</td>
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<tr>
<td>Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”</td>
<td>Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”</td>
<td></td>
</tr>
</tbody>
</table>
PSUR / DSUR Common Modules

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- Conclusions and actions
EMA Benefit-risk methodology project

- **Rational:** need for consistency, transparency and audit easiness of B-R analyses among all stakeholders
- **3-year project started early 2009**
- **To date:**
  - Among 19 methods
  - 1 winner method: *Multi-criteria decision analysis (MDCA)*
- **Good Practices in Pharmacovigilance:**
  - New Module of B/R analysis
  - expected 2014
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6. Hands on: a case study
a transverse and matrix PV system …

EU QPPV
PSMF - GVP

CASE MANAGEMENT

RISK MANAGEMENT

PERIODIC REPORTS
... with multiple input data ...

- EU QPPV
- PSMF - GVP
- CASE MANAGEMENT
- RISK MANAGEMENT
- PERIODIC REPORTS
... with many interfaces ...
... with safety specifications as a basis for each product ...
... with a continuous improvement approach ...
... and communicating and consistent processes ...
Agenda

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6. Hands on: tips & case study
WHO IS DOING WHAT?
Headquarter

- Centralize and gather all information
- Write PSUR
- Contacts with partners
- Take decisions
- Submission
- Follow up of assessment report
- Consult affiliates/partners on local use/misuse/offlabel
- Inform/train of affiliates
Affiliate

- Read the PSUR, assessment report
- Inform HQ of regional / local use
- Inform HQ of regional / local requirements
- Check submission to NCA
- Implement actions
- Give a feed back on actions

Comment is not forbidden!
FOCUS ON ....

- **Introduction** is already a summary
  - Indications, exposure, signals, risks, B/R evaluation, actions

- All new sections,

- **Signals table**
  - compare to what you have in Israel

- **Signals and risks evaluation**
  - Define your events of interest in ongoing routine
  - and your own signal detection
FOCUS ON ....

- Actions taken in the reporting interval for safety reasons
- Changes to reference safety information
- B/R assessment

CONCLUSION AND ACTIONS

- WHAT DO YOU HAVE TO DO ?
- NOW AND HERE
PSUR ROADMAP

Where and when to start?
PSUR/PBRER : ROADMAP
1- Prepare your data input with your contributors

Meet with all stakeholders

Explain Why? What? When?

Set up internal procedure

D0 = DLP
Data Lock Point

FEW MONTHS BEFORE
PSUR/PBRER: ROADMAP
2- Prepare the PV team

**Few months before**

- Write your SOP *(asap)*
- Set up the PSUR calendar and distribute it
- Check data Quality (Coding)
- If no RMP: write your safety specifications → risks table
- For each product: choose SMQ or SOC or both?
- Triage of your periodic literature review
  - cases reports
  - Relevant articles for PSUR

**Few weeks before**

- Reminder to your interfaces
- Read your reference documents: previous PSUR, RMP, DSUR
PSUR/PBRER : ROADMAP
3- Follow-up your PSUR

Inform all contributors

Decide Communication actions

Set up Workplan
Who? When?

FEW WEEKS AFTER
# Gather all documents : Reference Information

<table>
<thead>
<tr>
<th>Document</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective &amp; - Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCSI</td>
<td>D-25</td>
<td>D-15</td>
<td>Indications versus Off label use Expectedness Need for update</td>
</tr>
<tr>
<td>Labelling</td>
<td>D-25</td>
<td>D-15</td>
<td></td>
</tr>
<tr>
<td>National SmPC</td>
<td>D-25</td>
<td>D-15</td>
<td></td>
</tr>
<tr>
<td>Signal detection reports</td>
<td>D-25</td>
<td></td>
<td>• Signal table</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Signal evaluation &amp; actions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• New &amp; potential risks ?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Missing info</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Minimisation actions effectiveness ?</td>
</tr>
<tr>
<td>Previous PSUR</td>
<td>D-25</td>
<td>D-15</td>
<td>Comparison of frequency New signals ? New risks</td>
</tr>
<tr>
<td>Previous DSUR</td>
<td>D-25</td>
<td>D-15</td>
<td>Common sections Data from Studies</td>
</tr>
</tbody>
</table>
## Data Input: Regulatory Affairs

<table>
<thead>
<tr>
<th>Document</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statuts of the Marketing Authorisations</td>
<td>D-15</td>
<td>D7</td>
<td>Obtention date, n° MA, procedure type</td>
</tr>
<tr>
<td>Update of regulatory status</td>
<td>D-15</td>
<td>D7</td>
<td>During the period</td>
</tr>
<tr>
<td>Regulatory actions taken for safety reasons</td>
<td>D-15</td>
<td>D7</td>
<td>MA Refusal, suspension or withdrawal, restrictions, change in dosage or formulation, change in target population or indication.</td>
</tr>
</tbody>
</table>
## Data Input: Clinical Development

<table>
<thead>
<tr>
<th>Data from studies during period N</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of all ongoing and closed studies</td>
<td></td>
<td></td>
<td>Interventional / non interventionalal studies</td>
</tr>
<tr>
<td>Status and data from started or ongoing studies</td>
<td>D-15</td>
<td>D7</td>
<td>Summary of clinically important efficacy and safety findings.</td>
</tr>
<tr>
<td>Data from completed studies during period N</td>
<td>D-15</td>
<td>D7</td>
<td></td>
</tr>
<tr>
<td>End of study report</td>
<td>D-15</td>
<td>D7</td>
<td></td>
</tr>
</tbody>
</table>
### Data Input: marketing & sales

<table>
<thead>
<tr>
<th>Data</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sales : period N</td>
<td>D-15</td>
<td>D7</td>
<td>Patient exposure; evaluation of frequency and incidence: period N</td>
</tr>
<tr>
<td>Sales : cumulative</td>
<td>D-15</td>
<td>D7</td>
<td>Patient exposure; evaluation of frequency and incidence: cumulative</td>
</tr>
</tbody>
</table>
## Data from literature

<table>
<thead>
<tr>
<th>Data</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant abstracts</td>
<td>D-15</td>
<td>D15</td>
<td>Either ongoing literature survey or at the time of the PSUR</td>
</tr>
<tr>
<td>Full articles order</td>
<td>D-15</td>
<td>D15</td>
<td>Relevant = Therapeutic class, meta-analysis, disease environment....</td>
</tr>
<tr>
<td>Analysis</td>
<td>D-15</td>
<td>D15</td>
<td></td>
</tr>
</tbody>
</table>
Safety database: requests

Format?
By whom?
when?
Methodology: SOC or SMQ?

SOC: System Organ Class
SMQ: Standard MedDRA Query
## Safety database requests
**During the period (N)**

<table>
<thead>
<tr>
<th>Data</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of cases+ List of ADRs in period N</td>
<td>D-15</td>
<td>D7</td>
<td>Excel : case number, Event Term (PT), SOC, seriousness, expectedness, outcome, causality, country, source.</td>
</tr>
<tr>
<td>List of pregancy cases</td>
<td>D-15</td>
<td>D7</td>
<td>Excel : same + narratives</td>
</tr>
<tr>
<td>Age &amp; Sex</td>
<td>D-15</td>
<td>D7</td>
<td>Liste Excel : specific Populations</td>
</tr>
</tbody>
</table>
## Safety database requests During the period (N)

<table>
<thead>
<tr>
<th>Data</th>
<th>Request</th>
<th>Deadline</th>
<th>Objective Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>D-15</td>
<td>D7</td>
<td>Excel + narratives</td>
</tr>
<tr>
<td>Narratives + company comment</td>
<td>D-15</td>
<td>D7</td>
<td>All serious ; all non serious &amp; unexpected</td>
</tr>
<tr>
<td>Line listings</td>
<td>D-15</td>
<td>D7</td>
<td>Medically confirmed and Not med. confirmed</td>
</tr>
<tr>
<td>Summary tabulation on N + cumulative</td>
<td>D-15</td>
<td>D7</td>
<td>Medically confirmed and Not med. confirmed</td>
</tr>
<tr>
<td>Late breaking information</td>
<td>D0</td>
<td>D70/90</td>
<td></td>
</tr>
</tbody>
</table>
# Data from SMQs

<table>
<thead>
<tr>
<th>Document</th>
<th>Date de demande</th>
<th>Deadline</th>
<th>Objectif - Recommandation</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of SMQs</td>
<td></td>
<td>D-15</td>
<td>1st : Identify relevant SMQs Provide to Safety Data Manager</td>
</tr>
<tr>
<td>Results of requests : N + cumulative</td>
<td>D-15</td>
<td>D7</td>
<td>4 Excel tables by SMQ: • ADRs in SMQ • All ADRs in one case, incl associated ADRs Concomitant drugs • Medical history • Age &amp; Sex</td>
</tr>
</tbody>
</table>
Results analysis: SOC or SMQ

- Calculation of ADRs frequency
- Comparison N versus cumulative
- Seriousness
- Labelling
- Outcome
- Age & sex
- Medical History & risk factors
- Concomitant drugs
- Selection of relevant cases
- Special populations
Case Study 1
Risk Table for a contrast media product
Identified risks

- Anaphylaxis
  - Anaphylaxis expression: cutaenous? Respiratory?
  - Severity? Shock?
  - Risk factors?
  - Target population?
  - Medical history?
  - Prevention?

- Renal toxicity
  - Date of onset?
  - Is it a direct or indirect toxicity ie within anaphylactic reaction?
  - Alone or within Multiorgan failure?
Potential risks

- Cardiotoxicity?
  - Isolated cardiac event?
  - Within Multiorgan failure?
  - Risk factors?

- Pulmonary toxicity?
  - Any event not associated anaphylaxis?
Case study 2
Risk minimisation actions

Allopurinol
French Agency (ANSM) inquiry

Severe Toxidermias related to allopurinol

27 March 2012

A. GOURAUD
T. VIAL
CRPV de Lyon
Summary of ANSM report

- Allopurinol, xanthine oxydase inhibitor, marketing since 40 years
- Allopurinol is the 1st cause of severe bullous toxidermia in Europe as well as DRESS syndrom in the world
- Analysis of 3 years spontaneous data

**DRESS : Drug Rash with Eosinophilia and Systemic Symptoms**
Results

- 123 identified cases; 86 confirmed by expert dermatologists
- 65 DRESS & 21 severe bullous toxidermias bulleuses graves
- Incidence rate: 1,75 et 2,25 cases/10,000 new treatments
- Hypothesis of under notification rate of 65%, (literature)
- Estimated incidence 1 case for 1400 to 2200 new treatments
Results

Statistically significant

- Female > male
- Higher dosage (230.6 mg/d vs. 167.2)
- Dosage adaptation to renal function was less respected (47% vs. 66.3%, p<0.05)
- Indications analysis: «non indication» in 56.8%

Conclusion

- Incidence remains high despite recommendations of posology adaptation
- Misuse is frequent
Proposals

Misuse prevention
Do not prescribe for asymptomatic hyper-uricemia

Overdose prevention
Progressive dose increase whatever the renal function

Early detection of toxidermia
Inform patient to stop treatment IMMEDIATELY at 1st symptoms, even before seeking medical consultation
COMMUNICATION TOOLS

1. SmPC
2. Patient Leaflet
3. Dear Healthcare Professionals Communication (DHCPC)
Our proposals for prevention/minimisation actions

For company XXX: generics, pharmacist group
Set up of warnings on prescription & dispensation softwares

- Inform patients on 1st symptoms
- Ask patient to STOP IMMEDIATELY and consult a physician
- Warn physician:
  - asymptomatic hyperuricemia is not an indication
  - Dose must be increased progressively
  - Check renal function
COMMUNICATION INTERNAL

- Train sales reps
- Article in the monthly journal
- Presentation in the annual meeting of toxidermias
- Distribute a list of drugs associated with toxidermias
- E-mailing to all members
- Intensive monitoring
CONCLUSION
The 1st one, the most painful!

- Cumulative Analysis:
  - Characterisation of target population
- Retroplanning
- Set up risk table
- Set up risk management approach
- 1st time of benefit evaluation
- Look at environment: disease management & alternative therapeutics
- THINK ACTION

It's a long document
plan resources and time
Writing a PSUR, it’s

- A comprehensive safety database: pre and post marketing
- Many stakeholders and contributors
  - Regulatory data
  - Clinical data
  - Sales data
  - Partners
  - Providers: PV, regulatory...
Writing a PSUR, it’s:

- A calendar
- Prepare
- Organise
- Read RMP, previous PSUR/DSUR
- Read a
- Review signals
- Communicate results
- Follow up assessments recommendations
- Set up and follow up actions
Next HOT TOPICS IN PV : save the date

**TOPIC**

Safety database, electronic transmission (E2B), Eudravigilance

**WHO**

Delphine Bertram, PharmD
Head Pharmacovigilance Hospices Civils de Lyon
Expert in PhV group, EMA

**WHERE AND WHEN**

5 May 2014, Tel Aviv area

**HOSTED BY**
eVedrug
Thank you to

- The Pharmacist Association
- Bioforum
  - Yehudit for her constant support
  - Shifra for her logistics support
  - the website soon on line with presentations
News from ISOP ISRAEL
What we have done

- Set up the vision and the program
- Organise HOT TOPICS in PV : program for 1 year
- Write and publish Website
- Make ISOP ISRAEL free
- Create LinkedIn group
- Present ISOP ISRAEL to ISOP Executive Committee
- Tel Aviv University :
  - Intensive Summer Course in Epidemiology and Pharmacovigilance : joint program with John Hopkins University, July 2014, set up of a collaboration with Paris XII University, ISOP President invited
  - Certification course with Paris XII under discussion
ISOP ISRAEL

What can YOU do ?

1- Register to ISOP
- We need 10 registrations ! 210 € incl Drug safety subscription
- ISOP ISRAEL Project announced and endorsed by Executive Committee in ISOP Annual congress, Pisa 2013
- Official creation October 2014, in Annual Congress, China
- Drug Safety :
  - Part of your training Plan
  - Part of you signal detection

2- Host a meeting

3- Register on ISOP ISRAEL LinkedIn group
Thank you and good luck!

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fermont.irene@gmail.com
+972 58 40 20 688