HOT TOPICS IN PV

International Society
of Pharmacovigilance

The New PSUR/PBRER

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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 Prodedure
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

- **Regulation (EC) No 726/2004** amended by Regulation (EU) No 1235/2010 / **Directive 2001/83/EC**, amended by Directive 2010/84/EU
- **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

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PSUR Table of Content

- Introduction
- Worldwide marketing authorisation status
- Actions taken in the reporting interval for safety reasons
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- Other periodic reports
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- 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

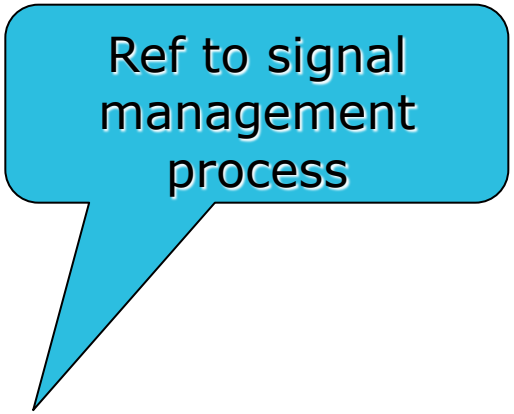
From RMP Safety specifications

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



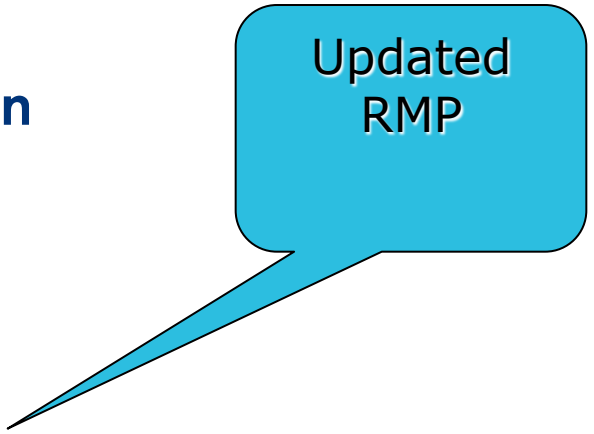
- Arguments , arguments , arguments ,
  - Public Health importance
  - Medical significance
  - Details +++

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**

Monitoring Of RMP Minimisation Actions

- *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
  - Newletter
  - Dear Healthcare Professonial 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

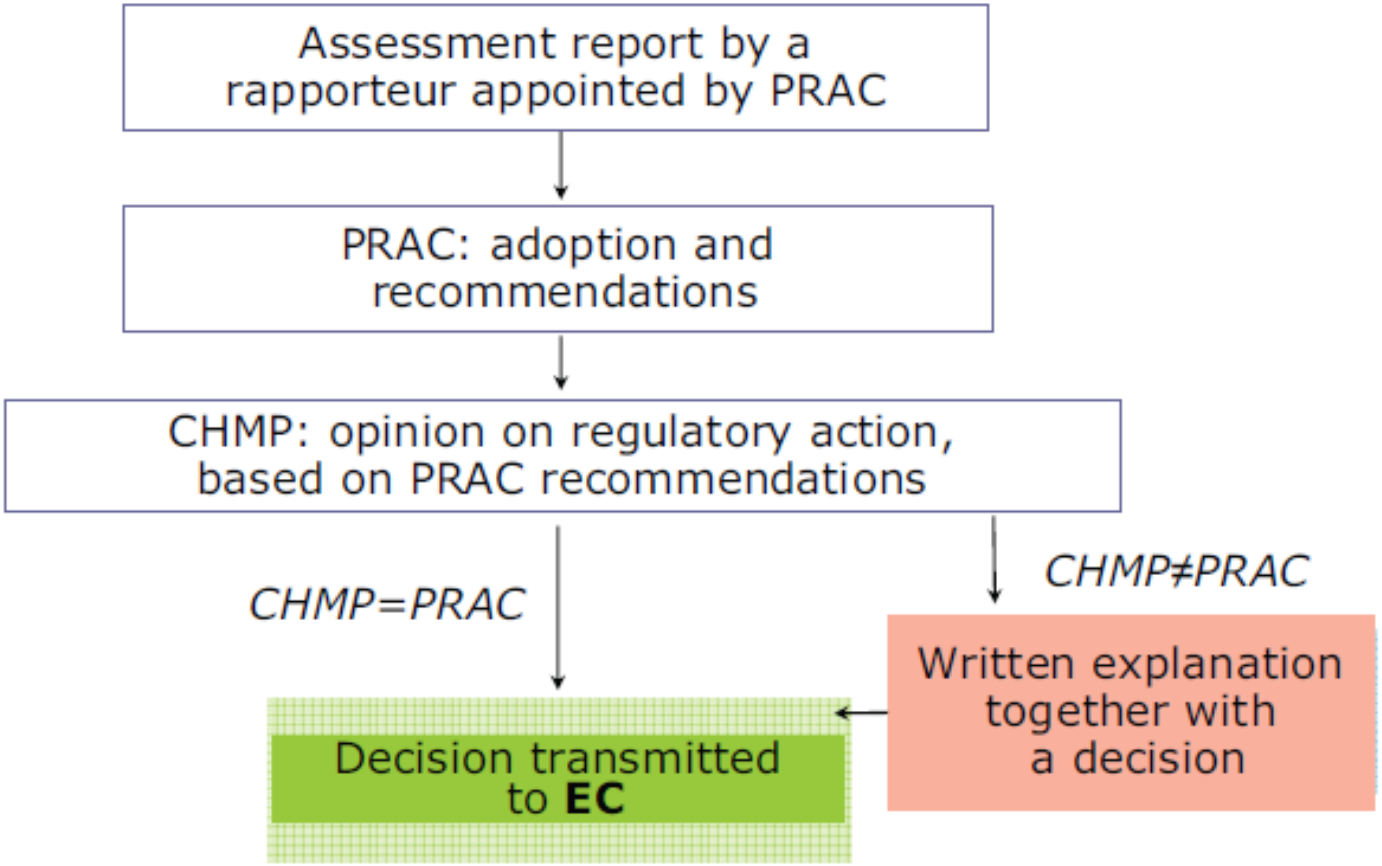
- Only the products where PSUR is required
- If product is not on the list
  - Other products → current calendar applies as specified in MA
- **Waiver** : Generics, Well established use, homeopathic and Herbal medicines
- *Rev 1 MAH could request amendment on EURD list (use of IBD for harmonization purposes)*

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 medecine is involved



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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

- http://esubmission.emea.europa.eu/gateway/eSubmissions%20of%20PSUR%20via%20EMA%20Gateway%20Webclient11.pdf

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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

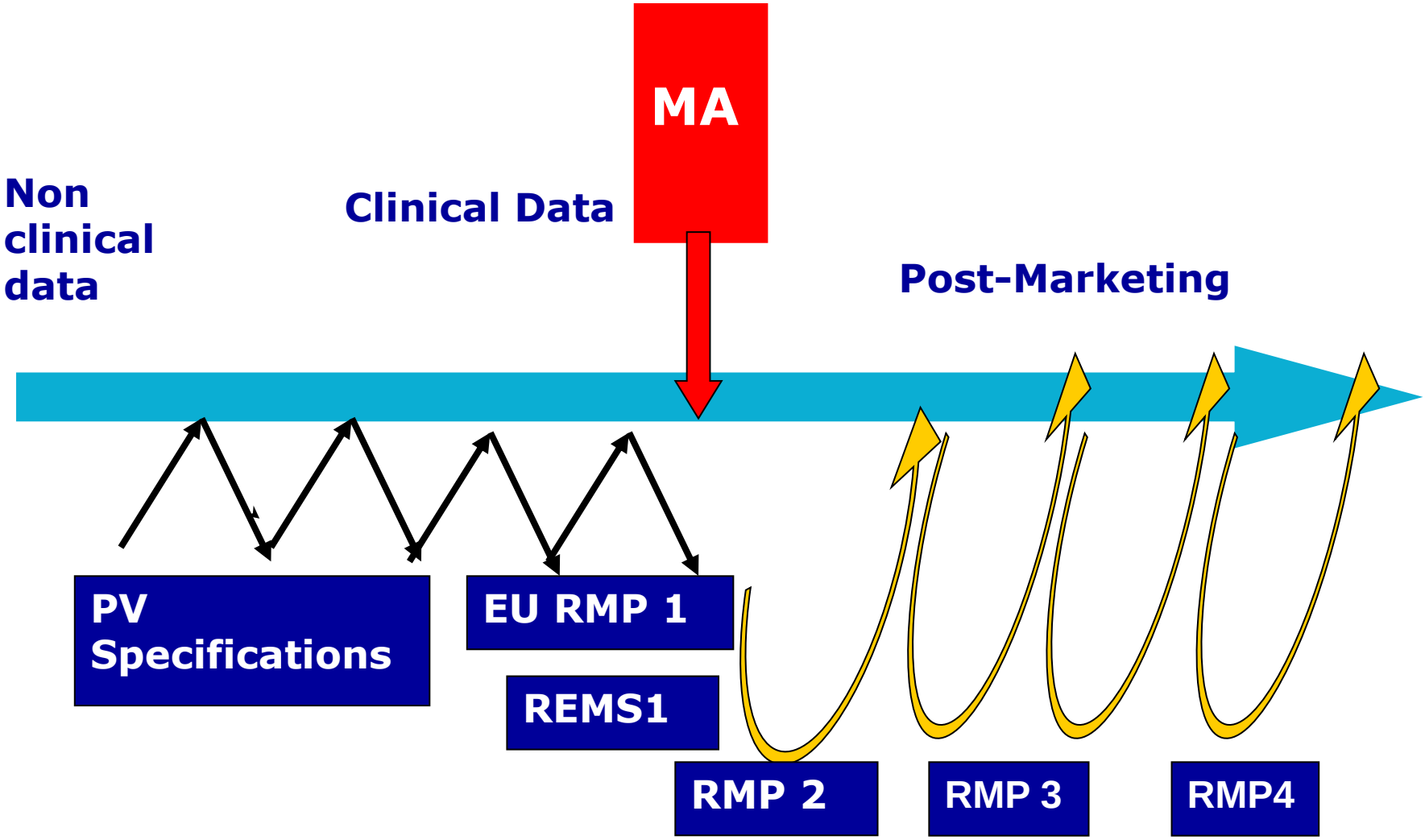
1. A Proactive Approach

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

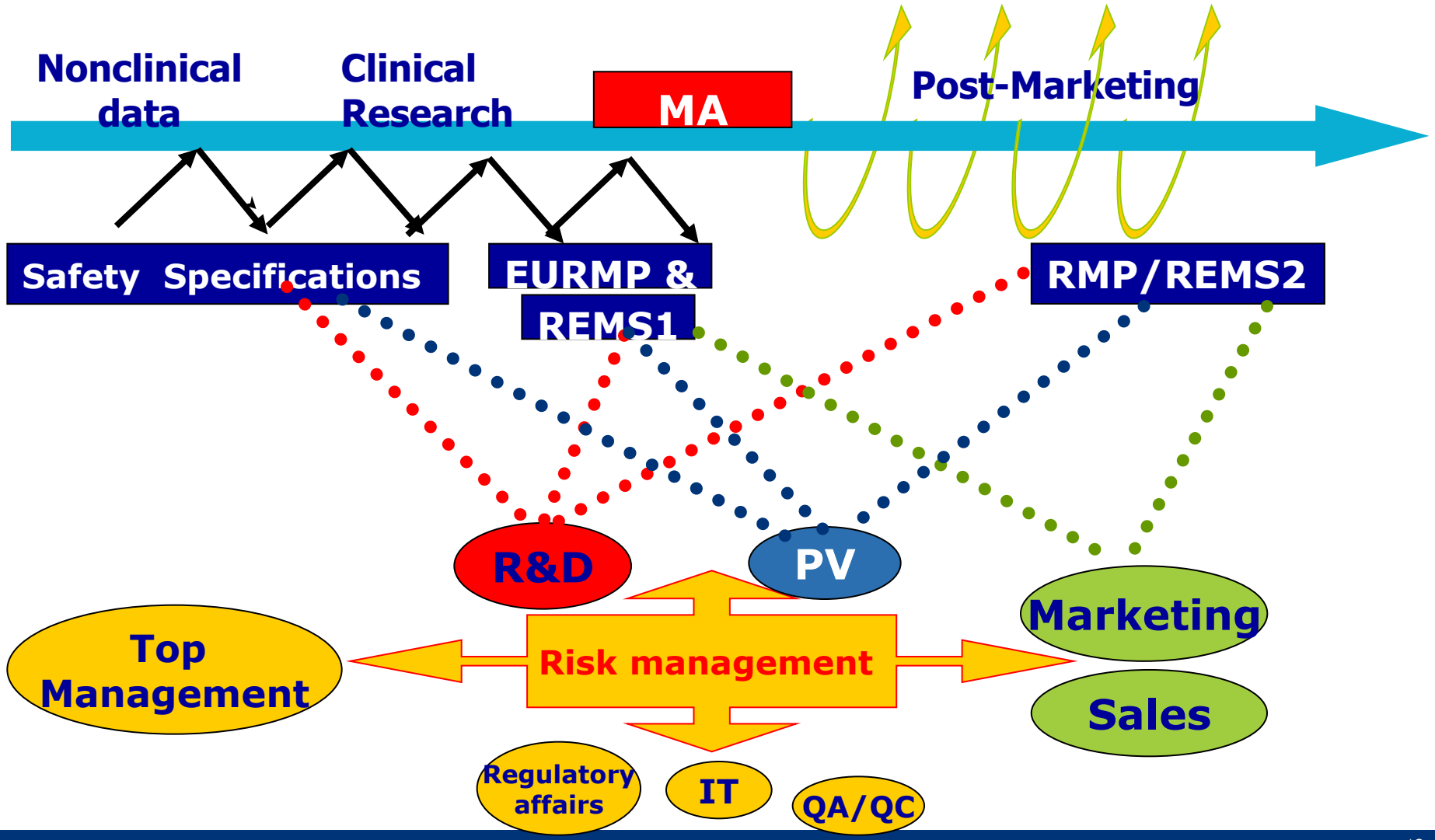
Key-word

PREVENTABILITY

2. All along the product's life cycle



3. Integrative Approach



Guidelines EMA

Risk Management Plan

- **Safety Specifications**
- **PV Plan**

Risk Minimisation Plan

RISK

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

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

since November 2005

- **ALL PRODUCTS**
  - Light RMP for generics , herbal, well establish use

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

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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

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

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
- HarmonisationPSUR/DSUR/RMP
- Method for Benefit Risk ratio

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Analysis

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 ; ie: 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
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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
  - Hepatotocity
  - Renal toxicity
- Focus on one System Organ Class

Multi-organ reaction : hypersensibility symptoms

Grade I:	**Mucocutaneous**
Grade II : moderate multi-organs affection	**Mucocutaneous** erythema, urticaria, conjonctival oedema, angio-oedema labial, **Quincke's oedema.** **Cardiovascular :** hypotention, tachycardia **Respiratory**, dyspnoea,, wheezing, ….. **Digestives s**: nausea, abdominal, pain **General** : chills, hypo/hyperthermia, malaise
Grade III: serious mono or multi-organs affection	**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
Grade IV	**Cardiac or cardiocirculatory arrest**

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

RMP	PSUR	DSUR
Pre & post marketing	Post marketing	Pre marketing
Planned management of B/R ratio all along the life cycle	Evaluation of B/R ratio Ref : SmPC of the period	Annual review of safety data during all development
Update as needed	Period versus cumulative	Annual versus previous DSUR
- Presentation/discussion of safety specifications - Risk Minimisation Actions & effectiveness - Update if riisks are changing	- Consistency of new versus cumulative data - Impact on patients' safety - Analysis based on identified and potentiels risks - Link with RMP	- Consistency of new versus cumulative data - iImpact on patients' in clinical trials - Summary of identified and potential risks - Update of development plan

B/R : Benefit /Risk ratio

RMP	PSUR
Part II, module SV – "Post-authorisation experience", section "Regulatory and marketing authorisation holder action for safety reason"	Section 3 – "Actions taken in the reporting interval for safety reasons"
Part II, module SV – "Post-authorisation experience", section "Non-study post-authorisation exposure"	Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"
Part II, Module SVII – "Identified and potential risks"	Sub-section 16.4 – "Characterisation of risks"
Part II, module SVIII – "Summary of the safety Concerns"	Sub-section 16.1 – "Summary of safety concerns"
Part V – "Risk minimisation measures", section "Evaluation of the effectiveness of risk minimisation activities"	Sub-section 16.5 – "Effectiveness of risk minimisation (if applicable)"

PSUR / DSUR Common Modules

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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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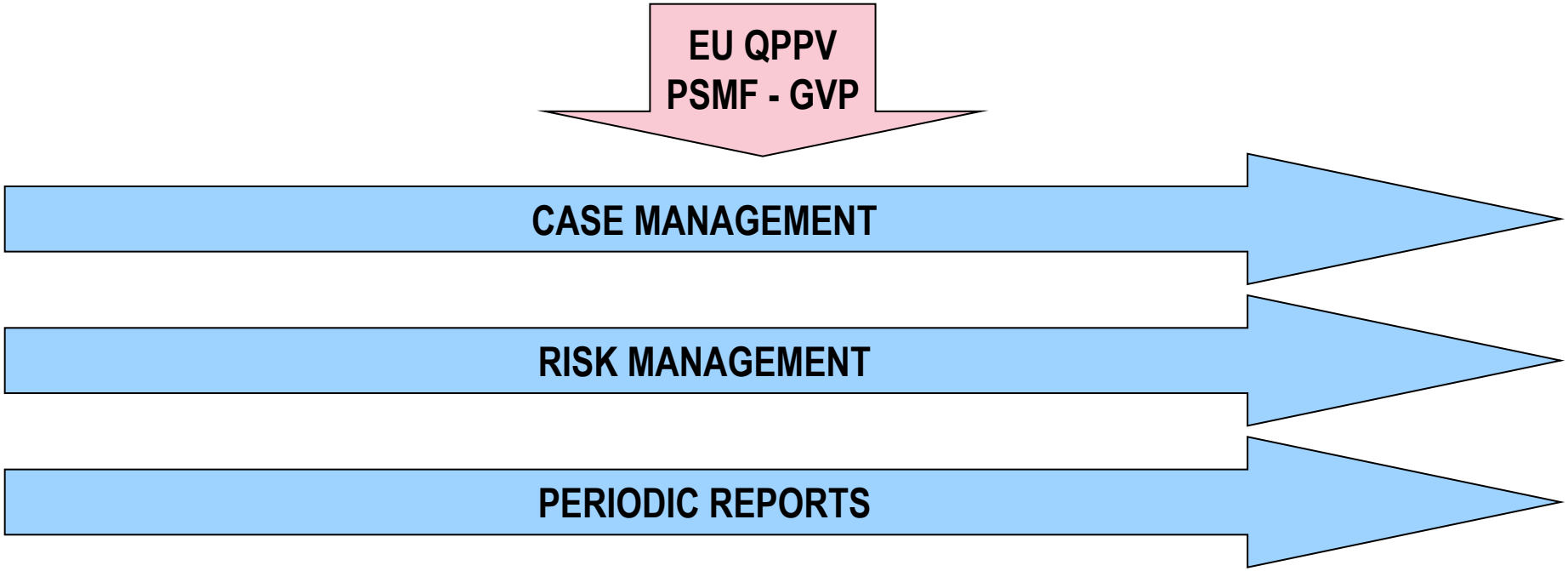
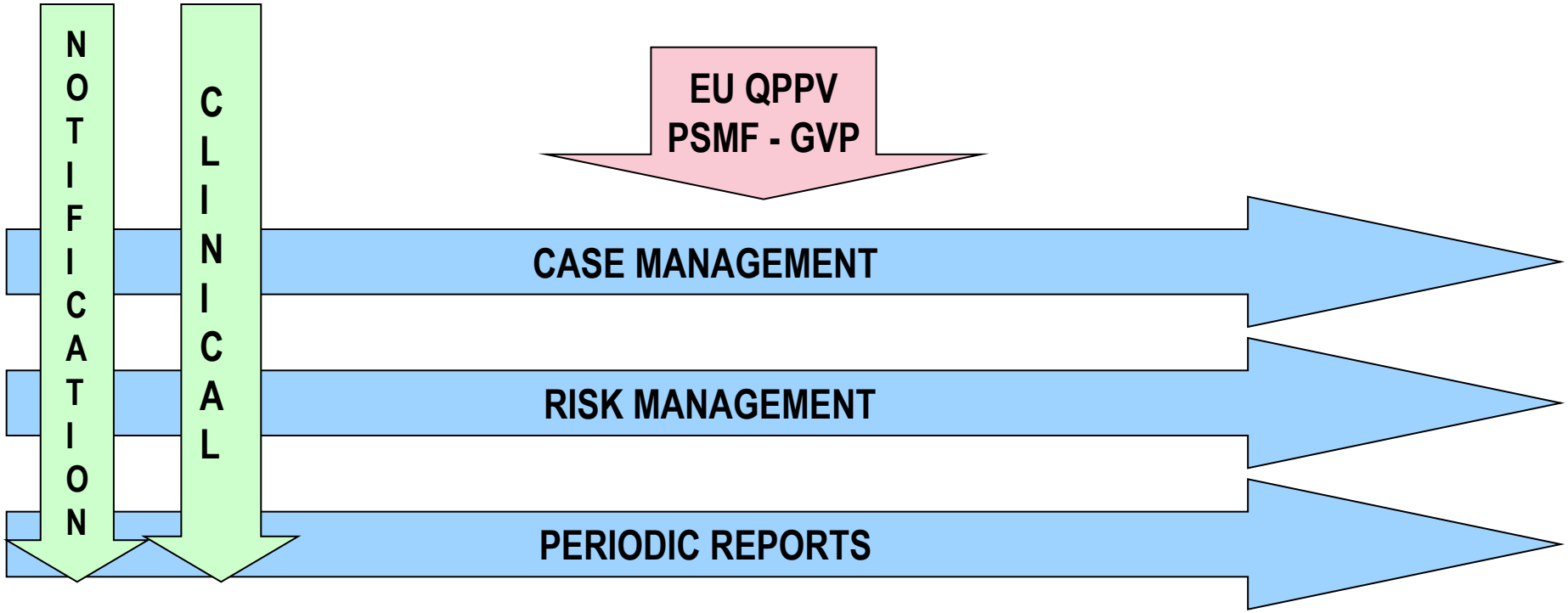
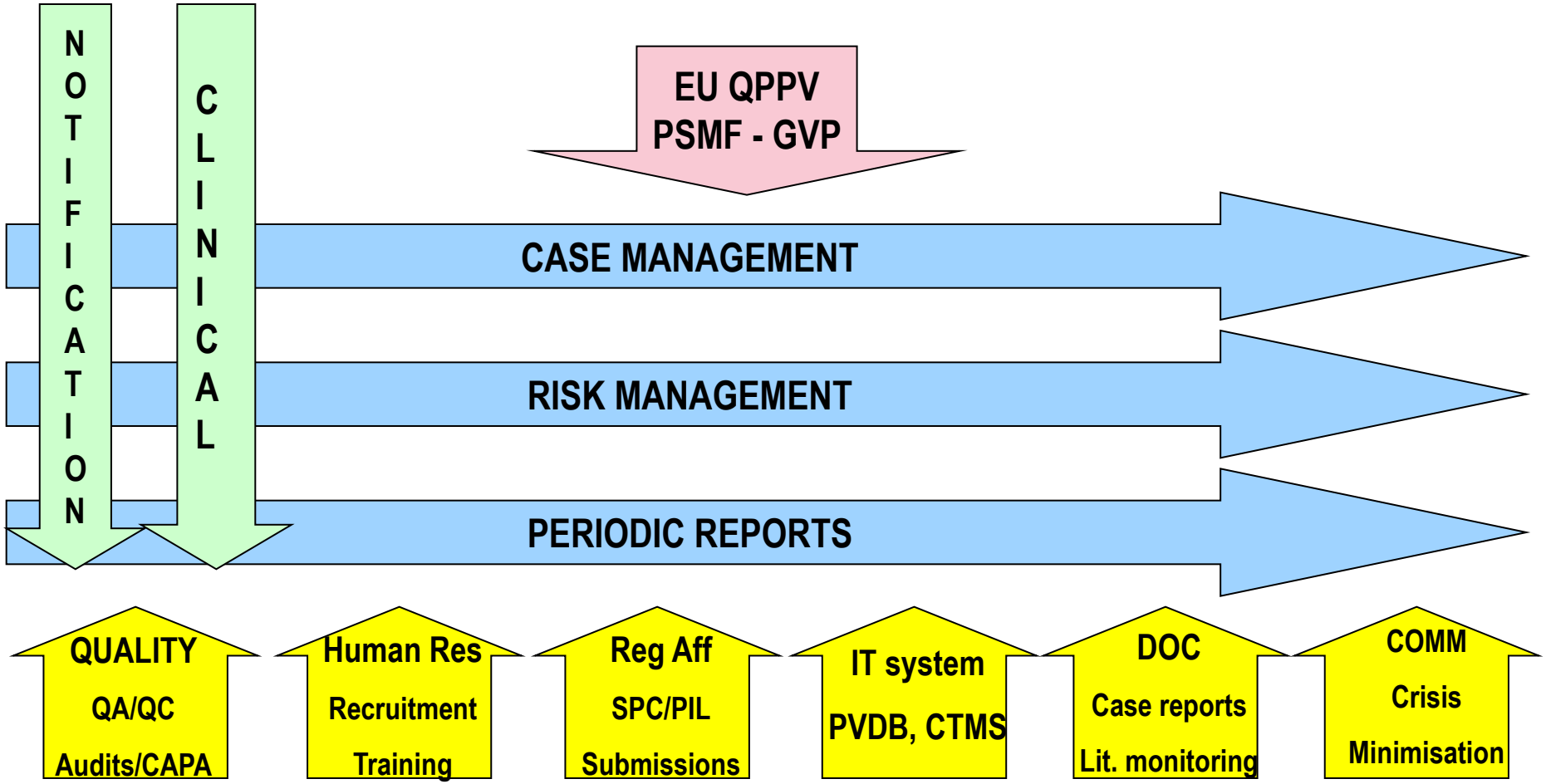
a transverse and matrix PV system …



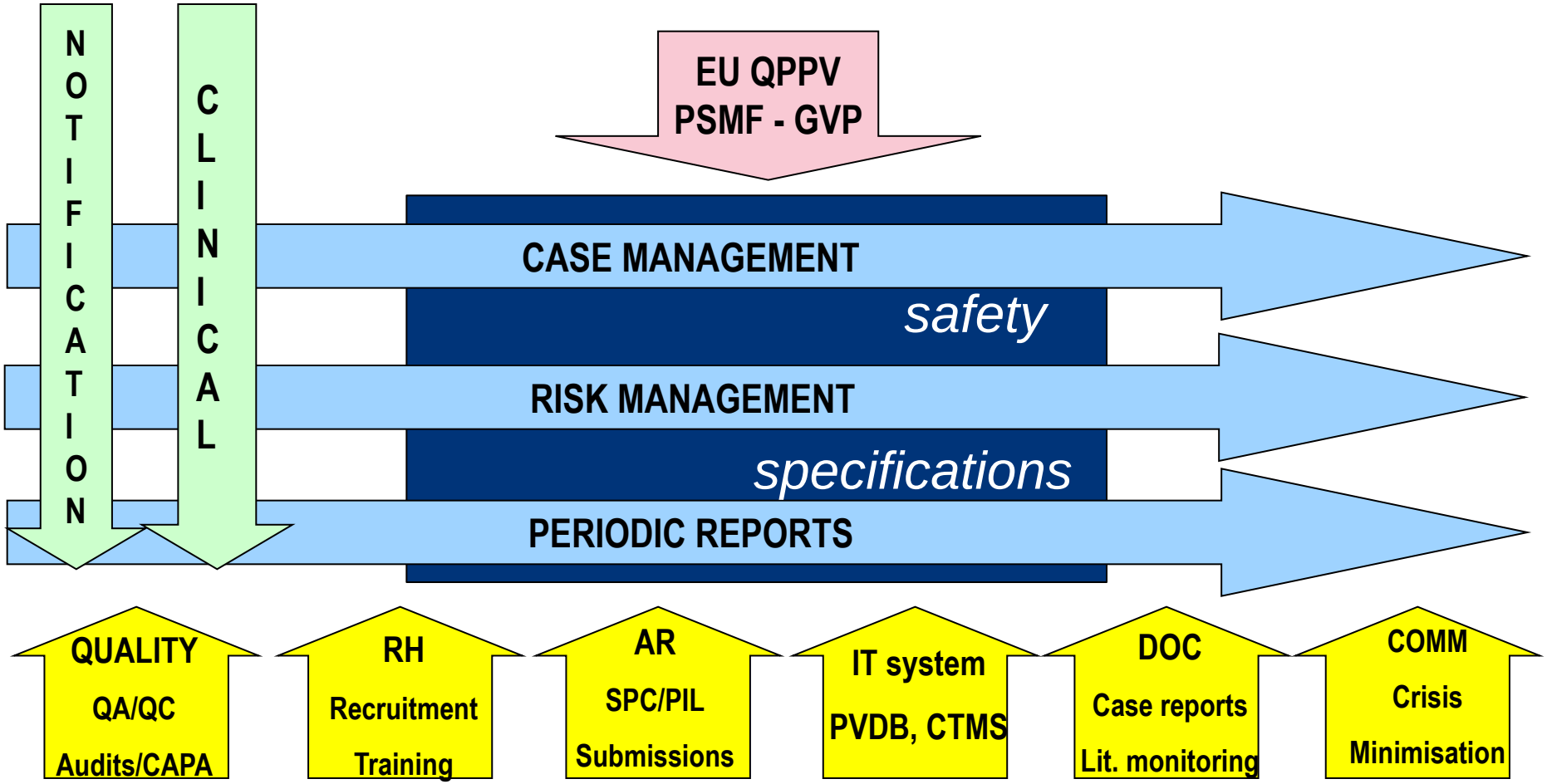
… with multiple input data …



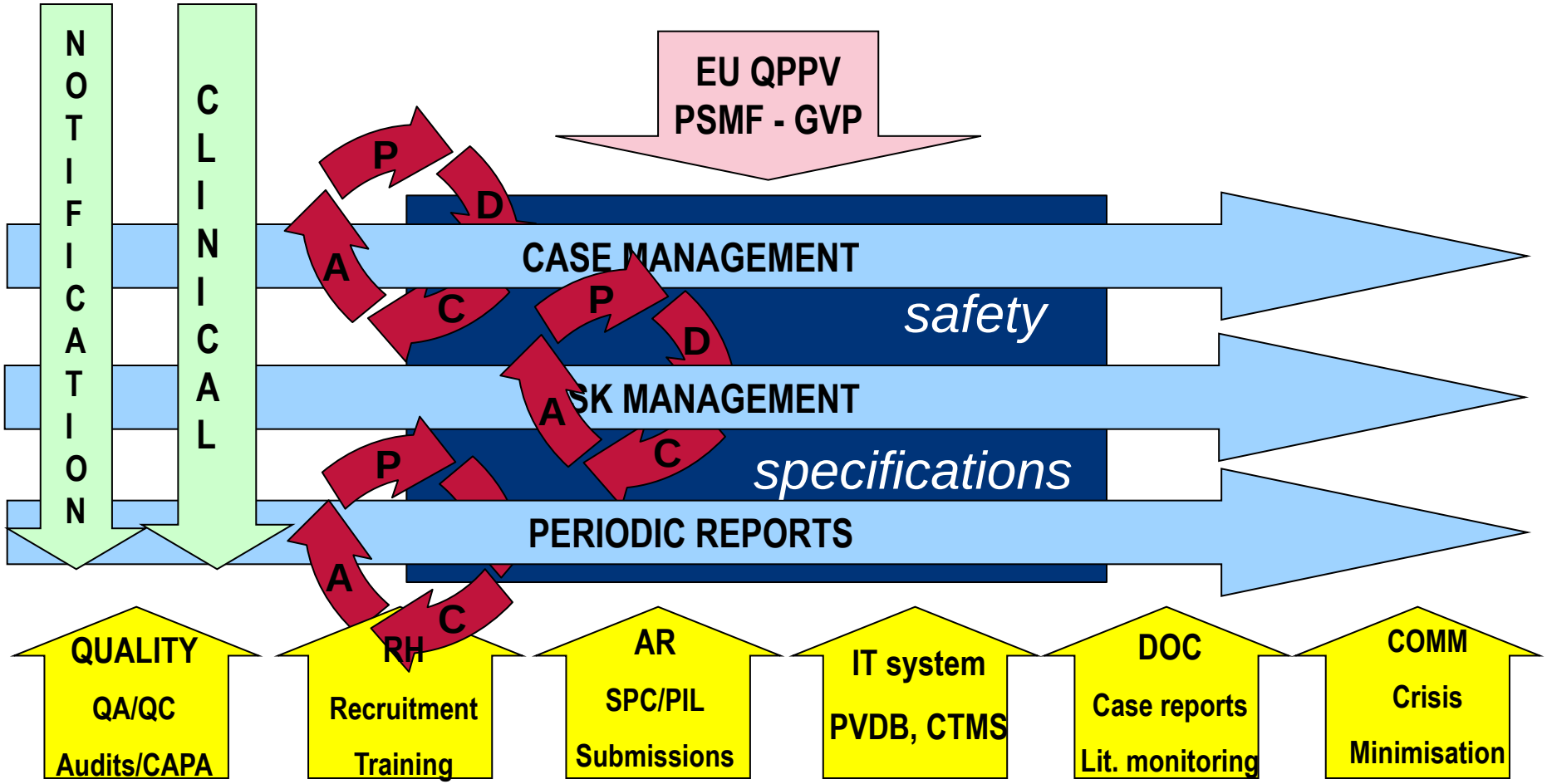
… with many interfaces …



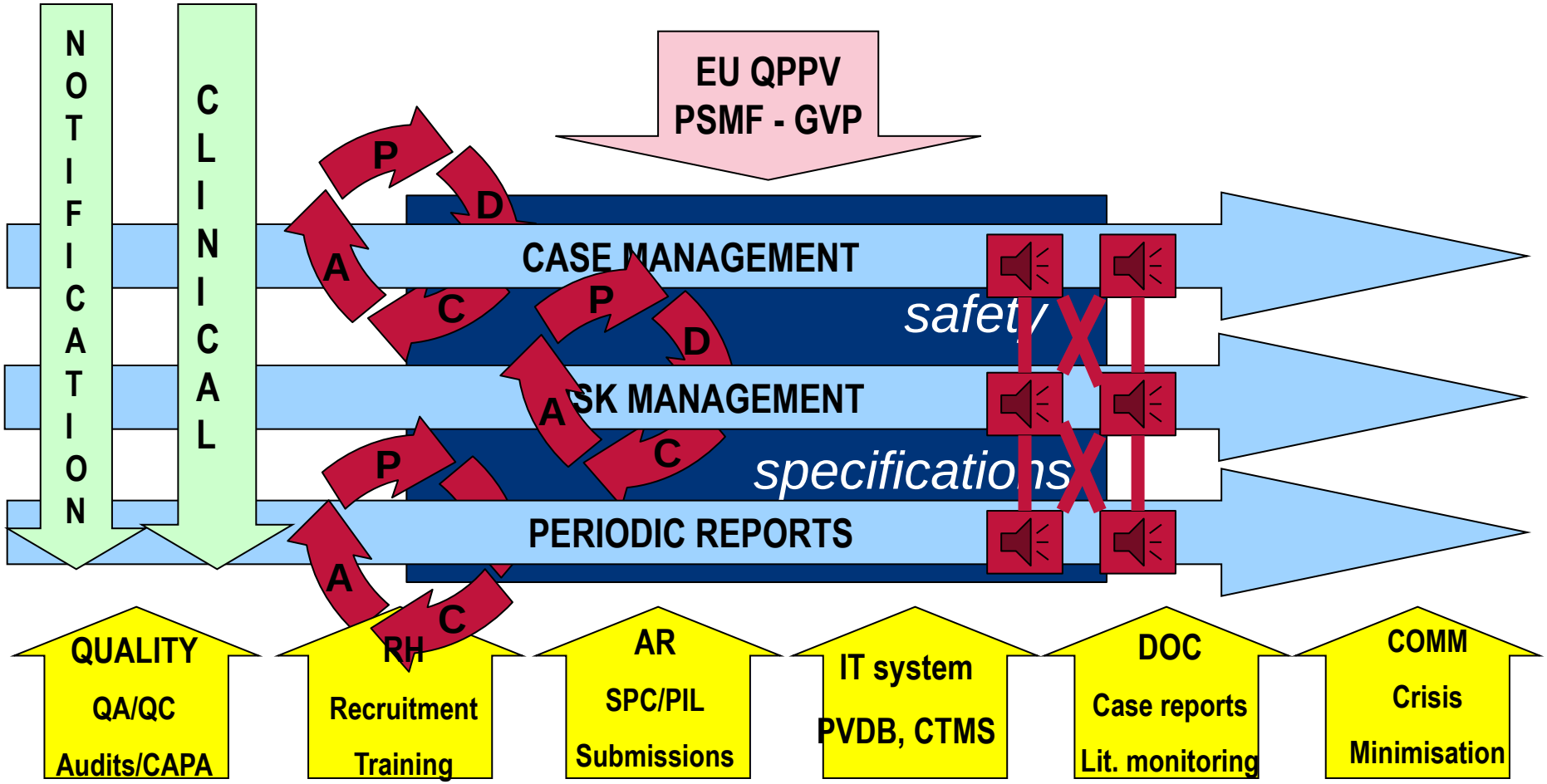
… with safety specifications as a basis for each product …



… with a continuous improvement approach …



… and communicating and consistent processes …



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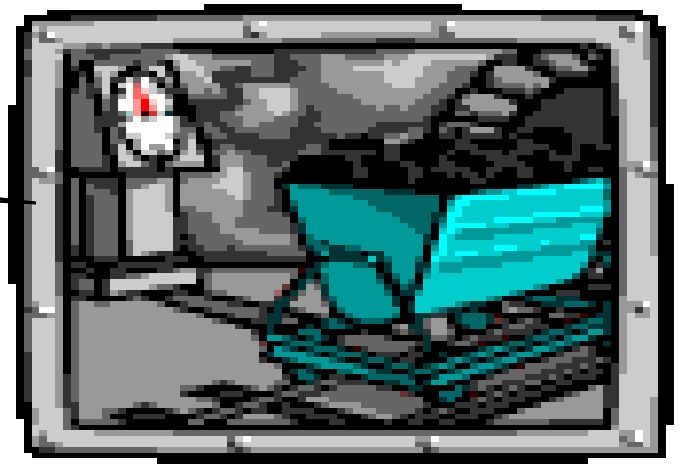
Hands on



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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

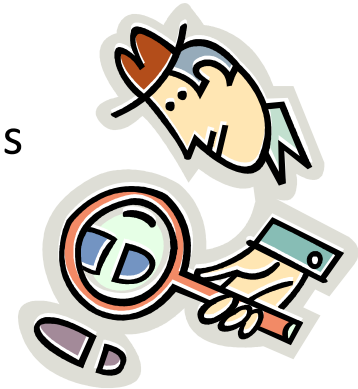
- Read the PSUR, assessment report
- Inform HQ of regional / local use
- Inform HQ of regional / local requirements
- Check submission to NCA
- Implement actions
- Give a feed back on actions

Comment is not forbidden !

Israeli PSUR summary : procedure 6

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



Israeli PSUR summary : procedure 6

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

FEW MONTHS BEFORE

Meet with all stakeholders

Explain
Why ?
What?
When?

Set up internal procedure

D0 = DLP
Data Lock Point

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

FEW WEEKS AFTER

Inform all contributors → **Decide Communication actions** → **Set up Workplan Who? When ?**

Gather all documents : Reference Information

Document	Request	Deadline	Objective & - Recommendation
CCSI	D-25	D-15	Indications versus Off label use Expectedness Need for update
Labelling	D-25	D-15	
National SmPC	D-25	D-15	
Signal detection reports	D-25		• Signal table • Signal evaluation & actions
Risk Management Plan	D-25	D-15	Common sections (16 &18) Risk table • New & potential risks ? • Missing info • Minimisation actions effectiveness ?
Previous PSUR	D-25	D-15	Comparison of frequency New signals ? New risks
Previous DSUR	D-25	D-15	Common sections Data from Studies

Data Input : Regulatory Affairs

Document	Request	Deadline	Objective Recommendation
Statuts of the Marketing Authorisations	D-15	D7	Obtention date , n° MA, procedure type
Update of regulatory status	D-15	D7	During the period
Regulatory actions taken for safety reasons	D-15	D7	MA Refusal, suspension or withdrawal, restrictions, change in dosage ou formulation, change in target population or indication.

Data Input : Clinical Development

Data from studies during period N	Request	Deadline	Objective Recommendation
Table of all ongoing and closed studies			Interventional /non interventional studies
Status and data from **started** or **ongoing** studies	D-15	D7	Summary of clinically important efficacy and safety findings.
Data from **completed** studies during period **N**	D-15	D7	
End of study report	D-15	D7	

Data Input : marketing & sales

Data	Request	Deadline	Objective Recommendation
Sales : period N	D-15	D7	Patient exposure ; evaluation of frequency and incidence : period N
Sales : cumulative	D-15	D7	Patient exposure ; evaluation of frequency and incidence : cumulative
Use of the product	D-15	D30	Off-label use? Misuse ? Alternative new therapeutics , consensus

Data from literature

Data	Request	Deadline	Objective Recommendation
Relevant abstracts	D-15	D15	Either ongoing literature survey or at the time of the PSUR
Full articles order	D-15	D15	
Analysis	D-15	D15	Relevant = Therapeutic class, meta-analysis, disease environment….

Safety database : requests

Format?

By whom?

when?

Methodology : SOC or SMQ?

SOC : System Organ Class
SMQ : Standart MedDRA Query

Safety database requests
During the period (N)

Data	Request	Deadline	Objective Recommendation
List of cases+ List of ADRs in period N	D-15	D7	Excel : case number, Event Term (PT), SOC, seriousness, expectedness, outcome, causality, country, source.
List of pregancy cases	D-15	D7	Excel : same + narratives
Age & Sex	D-15	D7	Liste Excel : specific Populations

Safety database requests
During the period (N)

Data	Request	Deadline	Objective Recommendation
Follow-up	D-15	D7	Excel + narratives
Narratives + company comment	D-15	D7	All serious ; all non seriouos & unpected
Line listings	D-15	D7	Medically confirmed and Not med. confirmed
Summary tabulation on N + cumulative	D-15	D7	Medically confirmed and Not med. confirmed
Late breaking information	D0	D70/90	

Data from SMQs

Document	Date de demande	Deadline	Objectif - Recommandation
List of SMQs		D-15	1st : Identify relevant SMQs Provide to Safety Data Manager
Results of requests : N + cumulative	D-15	D7	4 Excel tables by SMQ: • ADRs in SMQ • All ADRs in one case , incl associated ADRs Concomitant drugs • Medical history • Age & Sex

Results analysis : SOC or SMQ

- Calculation of ADRs fequency
- Comparison N versus cumulative
- Seriouness
- Labelling
- Outcome
- Age & sex
- Medical History & risk factors
- Concomitant drugs
- Selection of relevant cases
- Special populations
- Conclusion : Actions to be taken ? Labelling update ? Minimisation actions ? Communication ? Risk Management Plan update ?

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 for1400 to 2200 new treatments**

Results

Stastistically significant

- Female > male
- Higher dosage (230,6 mg/d vs. 167,2)
- Dosage adapation 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

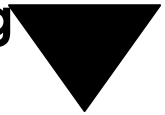
For company XXX : generics, pharmacist group

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 environnement : disease managment & 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

Safetydatabase, 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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