Human and veterinary pharmaceuticals regulation

Towards EU accession: Serbia's regulatory challenges, expectations and opportunities

29-30 November 2010

Hotel Holiday Inn, Belexpo Convention Centre, Belgrade, Serbia

Republika Srbija
Ministarstvo zdravlja
Ministarstvo poljoprivrede, šumarstva i vodoprivrede,
Uprava za veterinu

Republic of Serbia
Ministry of Health
Ministry of Agriculture, Forestry and Water Management,
Veterinary Directorate

alims
Agencija za lekove i medicinska sredstva Srbije
Medicines and Medical Devices Agency of Serbia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EudraVigilance and Risk Management

Session on Pharmacovigilance

Presented by: Dr. Thomas Goedecke, European Medicines Agency (EMA)

Outline

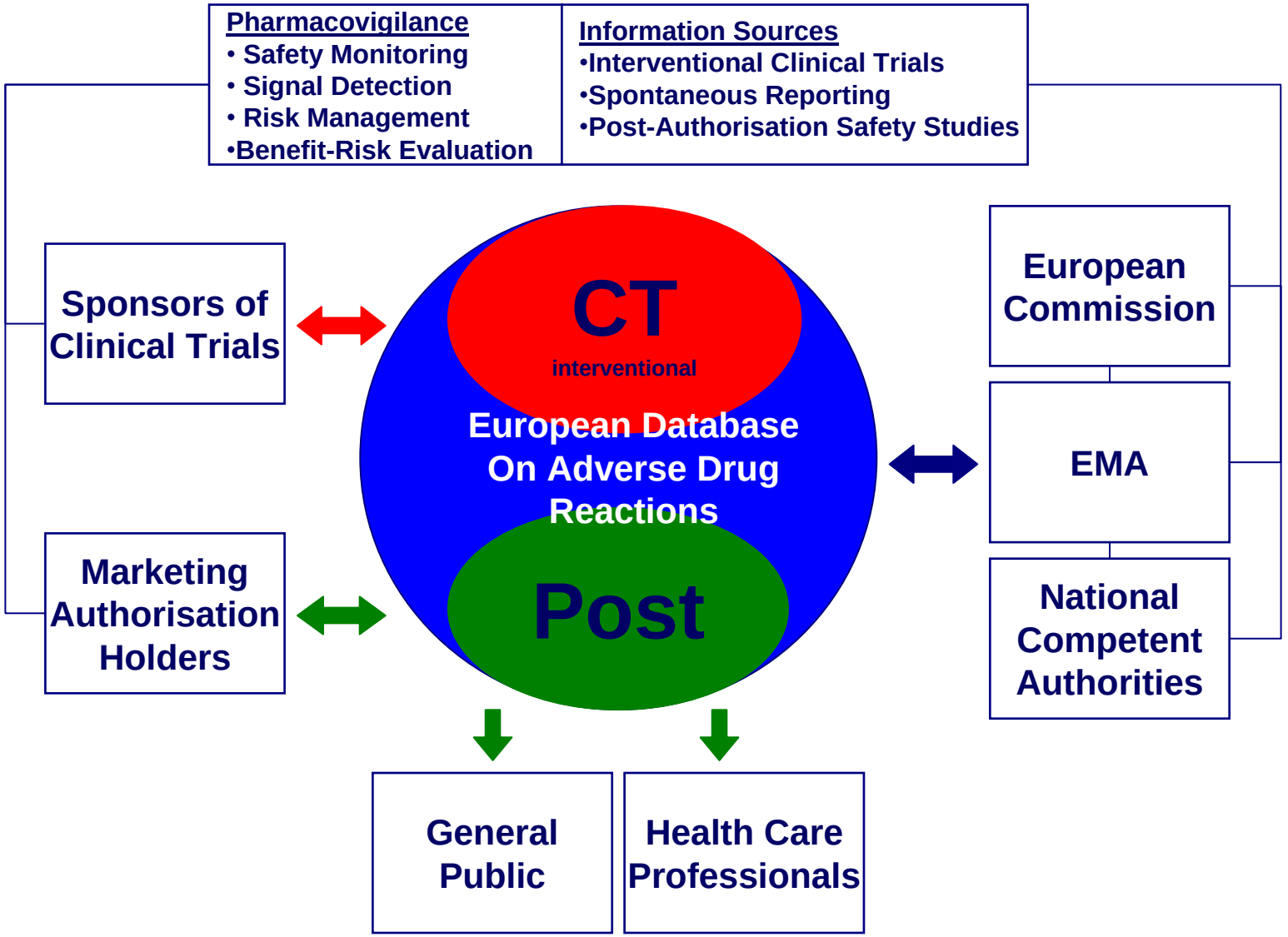
EudraVigilance

- Role in Pharmacovigilance
- System Components and Functions
- Signal Detection – Signal Evaluation

EU Risk Management

- Why needed?
- Legal basis and requirements
- EU-RMP template

Protection of Public Health



Data collected in EudraVigilance

Post Authorisation Module (EVPM)

- Suspected serious adverse reactions (ICSRs)
  - Health care professionals' spontaneous reporting
  - Post-authorisation studies (non-interventional)
  - Worldwide scientific literature (spontaneous, non-interventional)
- Suspected transmission of infectious agents

Applicable to all medicines authorised in the EEA independent of the authorisation procedure

Pre Authorisation Module (EVCTM)

- Suspected Unexpected Serious Adverse Reactions (SUSARs) reported by sponsors of clinical trials
  - Interventional clinical trials

Applicable to all investigational medicinal products for clinical trials authorised in the EEA

Reports handled in EudraVigilance

Post-Authorisation reports:

- EEA ICSRs: 968,295
- Non-EEA ICSRs: 1,283,730
- **Total: 2,252,025**

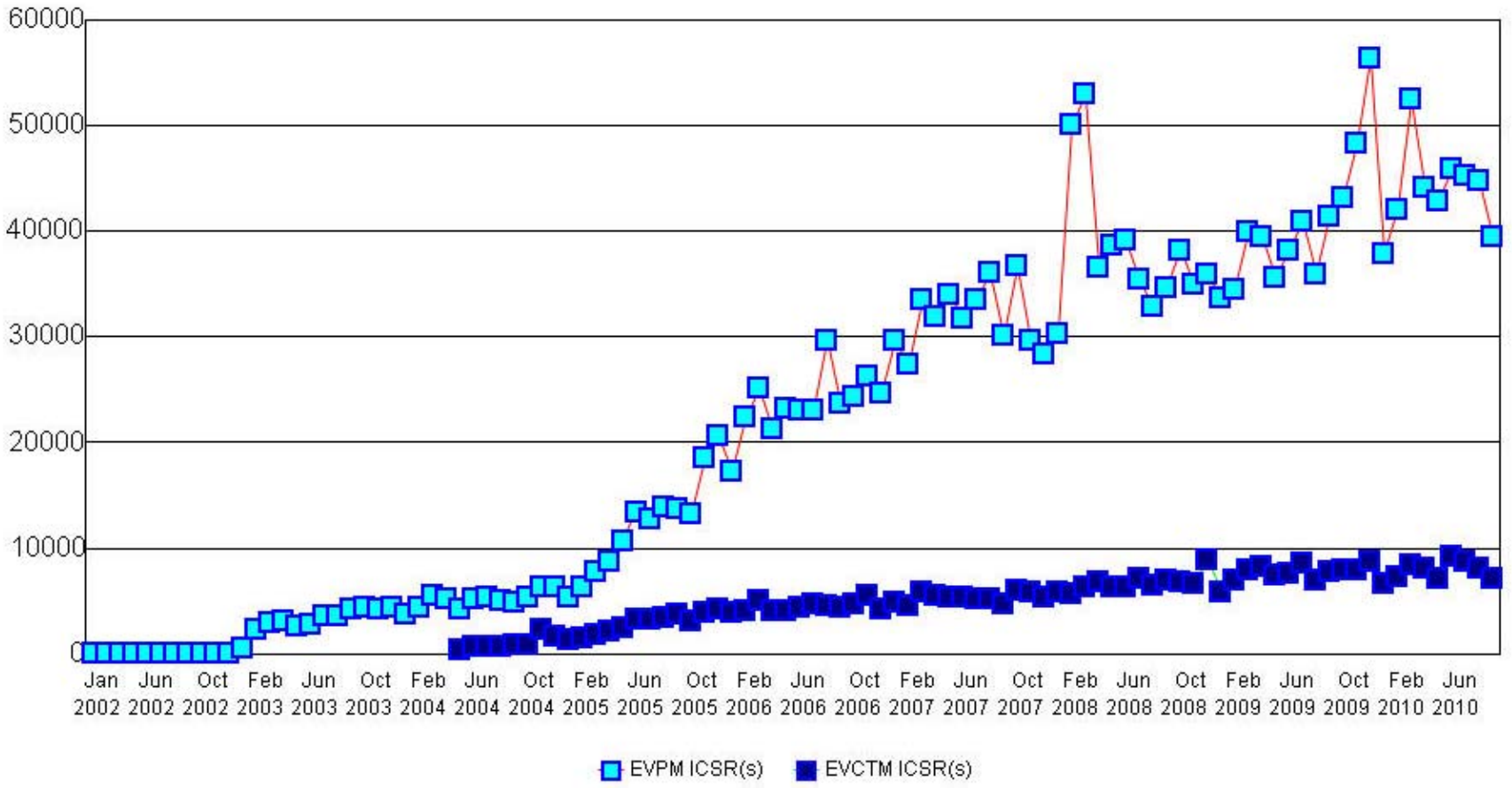
Clinical Trial reports:

- EEA ICSRs: 211,228
- Non-EEA ICSRs: 190,970
- **Total: 402,198**

All figures are between January 2002 and September 2010 (excluding backlog reports)

6

Reports (ICSRs) over time (total)

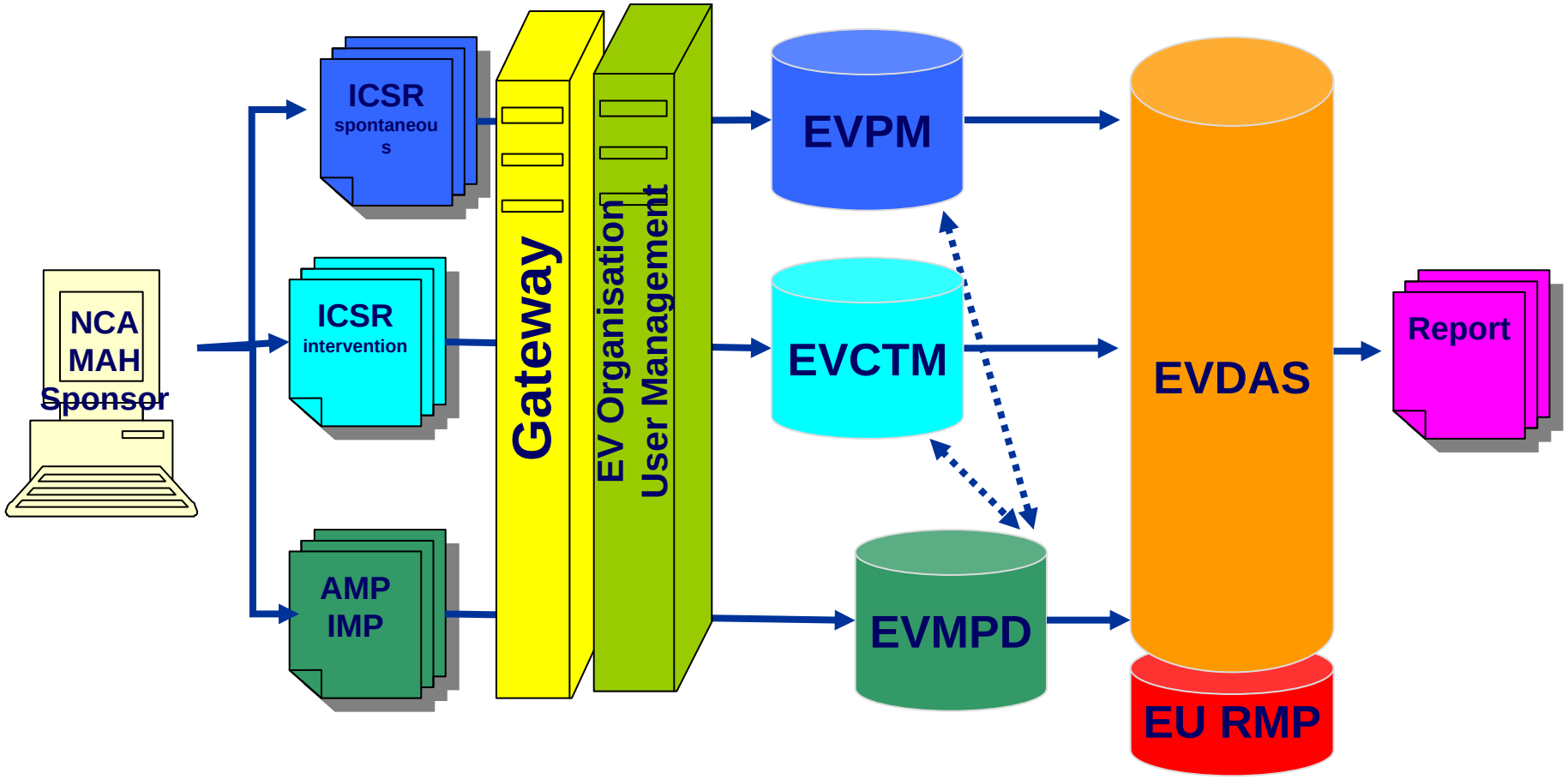


All figures are between January 2002 and September 2010 (excluding backlog reports)

EudraVigilance System - Functions

- **Data processing network** interlinking all National Competent Authorities in the EEA, the European Commission and the EMA to exchange information in pharmacovigilance
- **Electronic data exchange** of adverse drug reaction reports (ICSRs) in line with **ICH standards** (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)
- **Unique repository** of **EU and non-EU adverse drug reactions** for development and authorised medicinal products
- Incorporates the international medical terminology **Medical Dictionary for Regulatory Activities (MedDRA)**
- Monitoring of core risk profiles (identified/potential risks, missing information) defined in **EU Risk Management Plans (EU-RMP)**

EudraVigilance Data Processing



ICSR = Individual Case Safety Report
AMP = Authorised Medicinal Product
IMP = Investigational Medicinal Product

General Aspects of Signal Detection

- **Signal Detection** describes a **routine review of all ICSRs** reported to EudraVigilance:
  - For CAPs under monitoring all reactions reported within defined timeframes are listed by System Organ Class
  - Reviewed by EMA Signal Detection Team in collaboration with Rapporteur/Co-Rapporteur team
- **Signals** are based on statistical algorithms **measuring disproportionality: Proportional Reporting Ratio (PRR)**
  - an *event (R)* is relatively more often reported for a *medicinal product (P)* compared to the number of reports of this event for all other medicinal products in the database

	Event R	All other events	
MP P	a	b	a + b
All other MPs	c	d	c + d
	a + c	b + d	

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

EudraVigilance Reaction Monitoring Report

- **Reaction Monitoring Report** used for Signal Detection
- **Report criteria**:
  - All spontaneously reported ICSRs to EV Post Module
  - Generated at active substance level
  - CAPs authorsied ≤ 2 years: intensive monitoring (2-weekly), all others: routine monitoring (monthly)
- **List of reactions (MedDRA Preferred Terms)** grouped by System Organ Class (SOC) indicating
  - New cases/fatal cases associated with reaction
  - Total number of cases/fatal cases
  - Origin (EU/non-EU) of cases
  - Proportional Reporting Ratio (PRR) and 95% Confidence Interval
- **Signals of Disproportionate Reporting** are highlighted if
  - Number of ICSRs ≥ 3 and
  - Lower bound of 95% Confidence Interval of PRR ≥ 1

Example: Reaction Monitoring Report

Reaction Monitoring Report - Intensive 12:19 Wednesday, September 15, 2010 1

SOC=METABOLISM AND NUTRITION DISORDERS Active Substance(s)

SOC Term	Preferred Term	New Fatal	Total Fatal	New EEA	Total EEA	New Non EEA	Total Non EEA	New	Total	PRR(-)	PRR	PRR (+)	New CT	Total CT	New Pediatric	Total Pediatric
Blood and lymphatic system disorders	* Anaemia	0	0	0	0	2	4	2	4	0.06	0.16	0.44	0	0	0	0
Cardiac disorders	* Cardiac disorder	0	1	0	0	1	5	1	5	0.32	0.76	1.83	0	0	0	0
	* Cardiovascular insufficiency	0	0	1	2	0	0	1	2	1.37	5.50	22.05	0	0	0	0
	* Palpitations	0	0	1	5	2	11	3	16	0.66	1.39	2.26	0	0	0	0
	* Tachyarrhythmia	0	0	1	1	0	0	1	1	0.29	2.08	14.79	0	0	0	0
	* Tachycardia	0	0	3	3	0	2	3	5	0.11	0.26	0.63	0	0	0	0
Ear and labyrinth disorders	* Vertigo	0	0	0	3	1	7	1	10	0.72	1.33	2.47	0	0	0	0
	* Vestibular disorder	0	0	0	0	1	1	1	1	0.34	2.43	17.25	0	0	0	0
	Eustachian tube disorder	0	0	0	0	1	1	1	1	5.38	39.69	292.74	0	0	0	0
Eye disorders	* Diplopia	0	0	1	1	0	3	1	4	0.40	1.05	2.80	0	0	0	0
	* Eyelid oedema	0	0	3	4	0	0	3	4	0.45	1.19	3.16	0	0	0	0
	* Visual acuity reduced	0	0	0	0	1	2	1	2	0.09	0.37	1.47	0	0	0	0
	Erythema of eyelid	0	0	1	1	0	0	1	1	0.66	4.72	33.68	0	0	0	0
	Vision blurred	0	0	0	0	4	21	4	21	1.23	1.88	2.88	0	0	0	0
Gastrointestinal disorders	* Dysphagia	0	0	2	3	1	9	3	12	0.78	1.37	2.41	0	0	0	0
	* Faeces discoloured	0	0	0	0	1	2	1	2	0.25	1.00	4.00	0	0	0	0
	* Gastrointestinal disorder	0	1	9	16	3	16	12	32	5.54	7.82	11.05	0	0	0	0
	* Gastrooesophageal reflux disease	0	0	1	2	1	4	2	6	0.53	1.19	2.65	0	0	0	0
	* Intestinal stenosis	0	0	0	0	1	1	1	1	0.78	5.54	39.54	0	0	0	0
	* Oedema mouth	0	0	0	0	1	2	1	2	0.35	1.42	5.66	0	0	0	0
	* Pancreatic mass	0	0	0	0	1	1	1	1	2.15	15.50	111.69	0	0	0	0
	* Pancreatitis	0	1	2	12	2	52	4	64	3.93	5.00	6.36	0	0	0	0
	* Pancreatitis acute	0	0	1	6	0	11	1	17	2.35	3.78	6.07	0	0	0	0
	* Reflux oesophagitis	0	1	1	1	0	1	1	2	0.88	3.51	14.04	0	0	0	0
	Abdominal discomfort	0	0	0	6	14	58	14	64	6.65	8.72	11.11	0	0	0	0
	Abdominal distension	0	0	2	5	5	19	7	24	2.46	3.67	5.46	0	0	0	0
	Abdominal pain	0	1	10	20	15	45	25	65	1.91	2.43	3.08	0	0	0	0
	Abdominal pain upper	0	0	8	23	7	41	15	64	3.77	4.80	6.11	0	0	0	0
	Constipation	0	0	4	10	3	22	7	32	1.92	2.71	3.82	0	0	0	0
	Diarrhoea	0	0	24	43	30	140	54	183	3.74	4.30	4.93	0	0	0	0

Reference period: 01SEP2010 - 14SEP2010

Example: Case Line Listing

irthdate	Sex	Serious	Serious. Death	Serious. Disabling	Serious. Hosp.	Serious. Life Threat.	Serious. Other	Parent/Child	Drug List	Reaction List	Metrics CIOMS	Metrics E2B	Metrics #ICSRs
5-DEC-920	Male	Yes	No	No	Yes	No	No	No					1
5-APR-942	Female	Yes	No	No	Yes	No	No	No		Gastric ulcer haemorrhagic			1
7-APR-930	Female	Yes	No	No	Yes	No	No	No		Gastric ulcer haemorrhagic			1
0-FEB-921	Female	Yes	Not Specified	Not Specified	Yes	Not Specified	Yes	No		Appetite lost, Reduced general condition, Stool tarry, Ulcer bleeding gastric, Vertigo, Vomiting			1
ot pecified	Female	Yes	No	No	Yes	No	No	No		Bleeding gastric ulcer, Hematemesis, Melena, Syncope			1

Case Report in CIOMS format

Reaction MedDRA PT terms

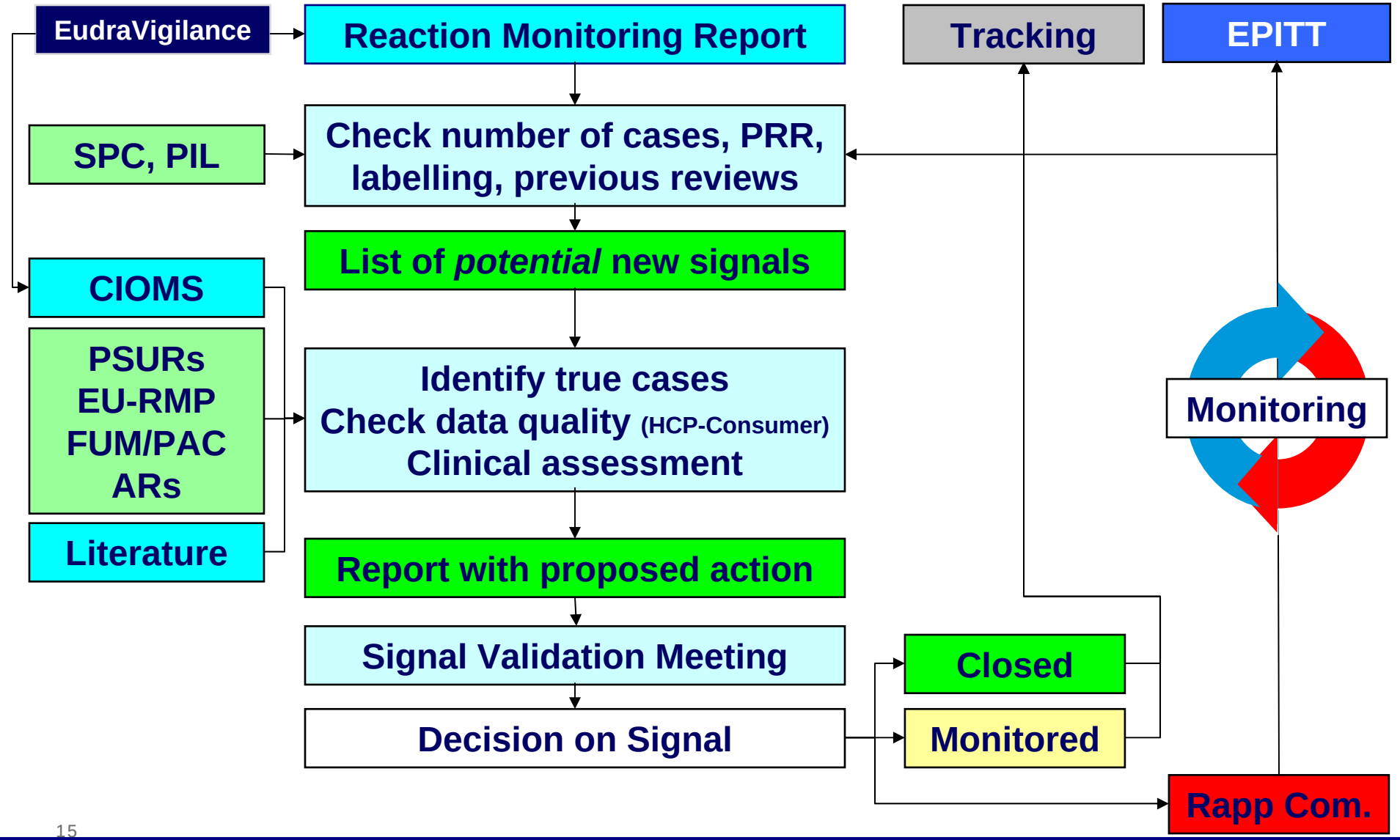
Interpretation of SDRs

Statistical Signal ≠ Drug Safety Issue

- **No implication of causal relationship** → each drug-event pair requires **medical evaluation** based on case report details
- **Artificial thresholds** for Signals of Disproportionate Reporting
- **Nature and quality of data** in database on which PRR is calculated needs to be considered → influence on PRR
- **Various sources of bias** (e.g. underlying disease, statistical artefacts, etc.)
- **Criteria for prioritisation** (e.g. labelledness, impact on public health, change of frequency or seriousness, subgroup analysis etc.)

Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System, Doc. Ref. EMEA/106464/2006 rev. 1

EMA Signal Detection Process



Outline

EudraVigilance

- Role in Pharmacovigilance
- System Components and Functions
- Signal Detection – Interpretation of SDRs

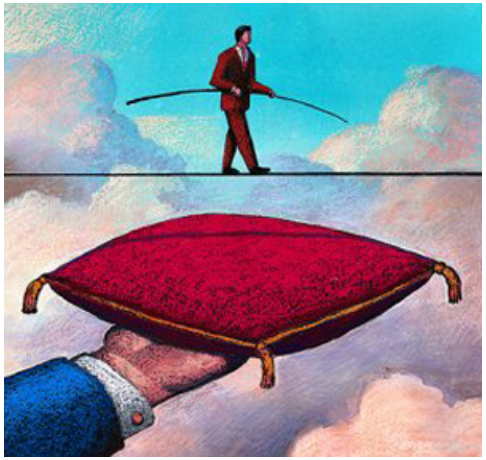
EU Risk Management

- Why needed?
- Legal basis and requirements
- EU-RMP template

Authorising medicines: What we know…

At the time of authorisation:

- Dossier of evidence submitted by the companies on quality, safety and efficacy
- Full assessment by the regulators
- Benefits must outweigh risks based on evidence from clinical trial program



What we know:

- Usually good evidence from clinical trials demonstrating efficacy in the specific indication and populations studied
- Good evidence from clinical trials on the most common adverse reactions

…and what we don't know

- Effectiveness of the product in normal clinical practice: compliance, resistance, populations not included in trials
- Full safety profile including adverse drug reactions which are:
  - Rare
  - Delayed
  - From chronic exposure
  - From interactions
  - Medication errors
  - Off-label use
  - Associated with abuse/misuse
  - Associated with populations not studied in trials (children, very elderly, pregnancy, lactation, co-morbidity)

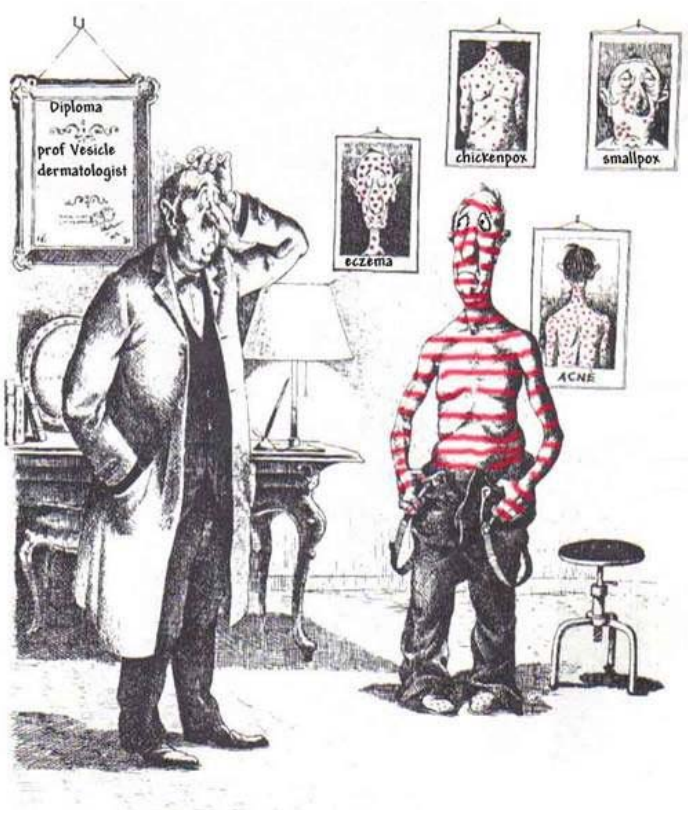
Table 1 — Chance that a very rare side-effect (0.01%) will not be observed

Number of patients treated	Chance of missing (%)
500	95.1
1000	90.5
2500	77.9
5000	60.7
7500	47.2
10000	36.8
15000	22.3
20000	13.5
25000	8.2
30000	5.0

Amery K Pharmacoepidemiology and Drug Safety, 8: 61±64 (1999)

Why the Concept of Risk Management?

- In the past high profile safety issues warranted urgent regulatory actions (suspension, withdrawal)
- Pro-active monitoring of drug safety to evaluate changes in benefits and risks
- Changing environment of drug safety
  - More information with better access
  - Increased expectations from health authorities, public and media



Legal Basis: ICH E2E (2004)

ICH E2E guideline on pharmacovigilance planning

- To support pharmaceutical industry and regulators in planning of pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug
- Basis for documenting risks: **Safety Specification**
- Structure for a **Pharmacovigilance Plan** (pre- or post-authorisation)

EU Legislation on Risk Management

- Article 8 (3)(ia) of Directive 2001/83/EC as amended by Directive 2004/27/EC → Risk Management System required where appropriate
- Article 9(4)(c) of Regulation (EC) No 726/2004 → lays down Conditions & Restrictions for supply and safe and effective use
- CHMP Guideline on Risk Management Systems (EMEA/CHMP/96268/2005)

  http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf
- EU Risk Management Template (EU-RMP) (EMEA/192632/2006)

  http://eudravigilance.ema.europa.eu/human/docs/19263206en.pdf

} Vol 9A

Risk Management Definition

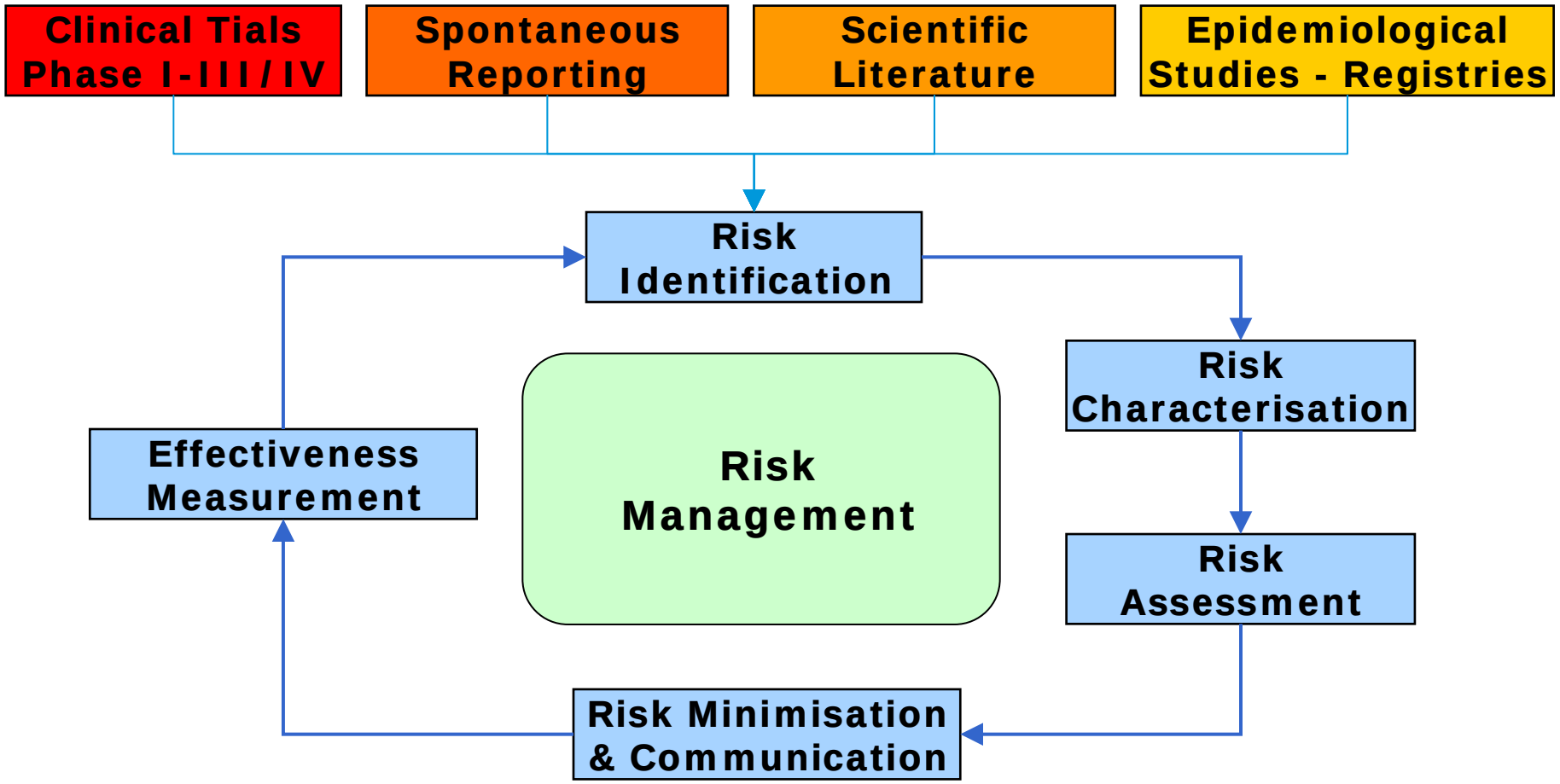
- CHMP Guidance on Risk Management Systems

  «... a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions»

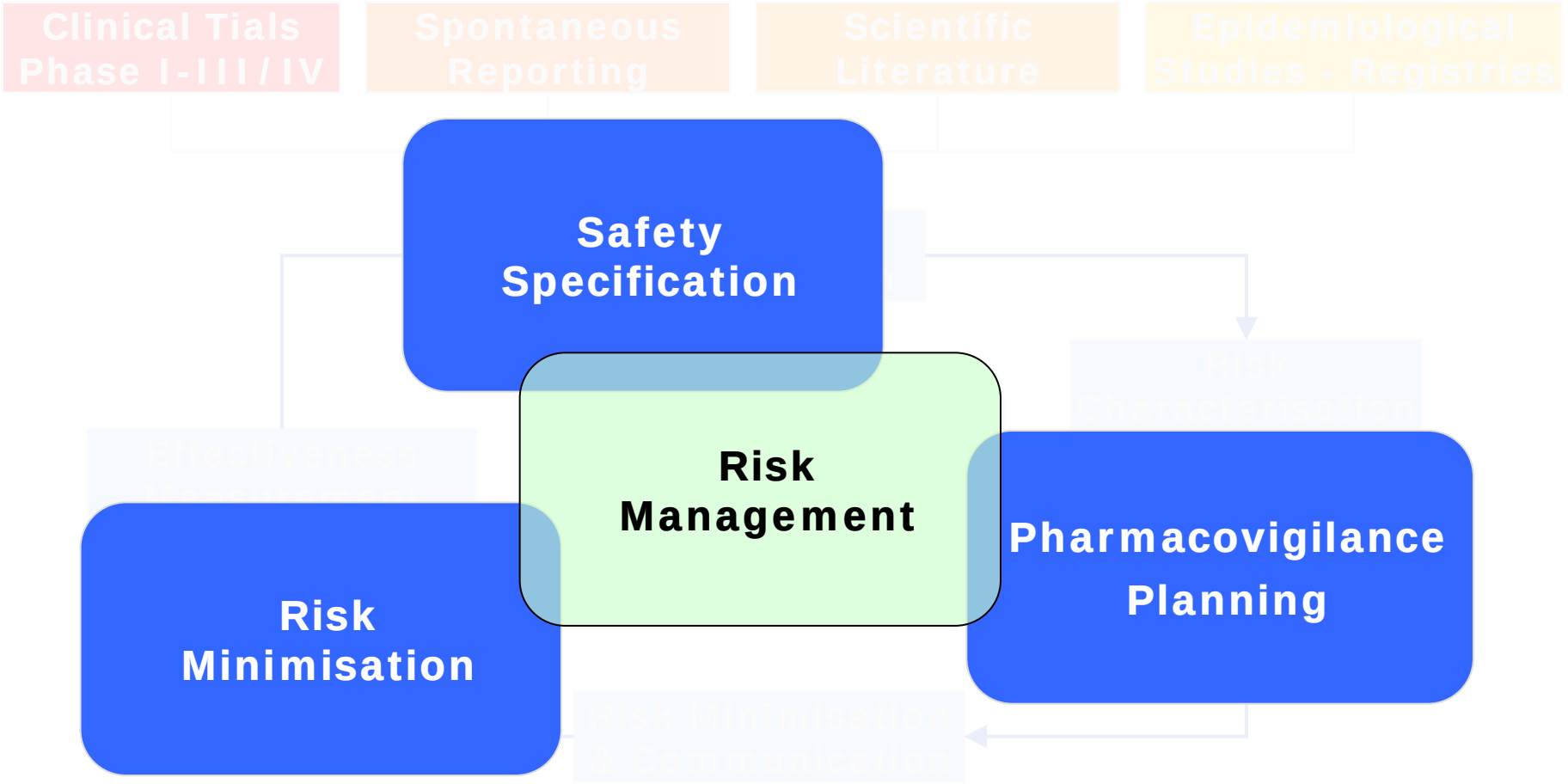
- Obligations can be fulfilled by submitting a **Risk Management Plan (RMP)**, in the format of the **EU-RMP Template**

- EU-RMP is a binding contract between EU regulators and MAH

The Risk Management Cycle



The Risk Management Cycle



When is an EU-RMP required? (1)

a) New marketing authorisation

- New active substance
- A similar biological medicinal product
- Generic/hybrid* where safety concern requiring additional risk minimisation has been identified with reference product

b) Significant Changes to Marketing Authorisation

- New pharmaceutical form
- New route of administration
- Significant change to indication/ patient population

} Unless agreed not needed

When is an EU-RMP required? (2)

c) On request from the Competent Authority

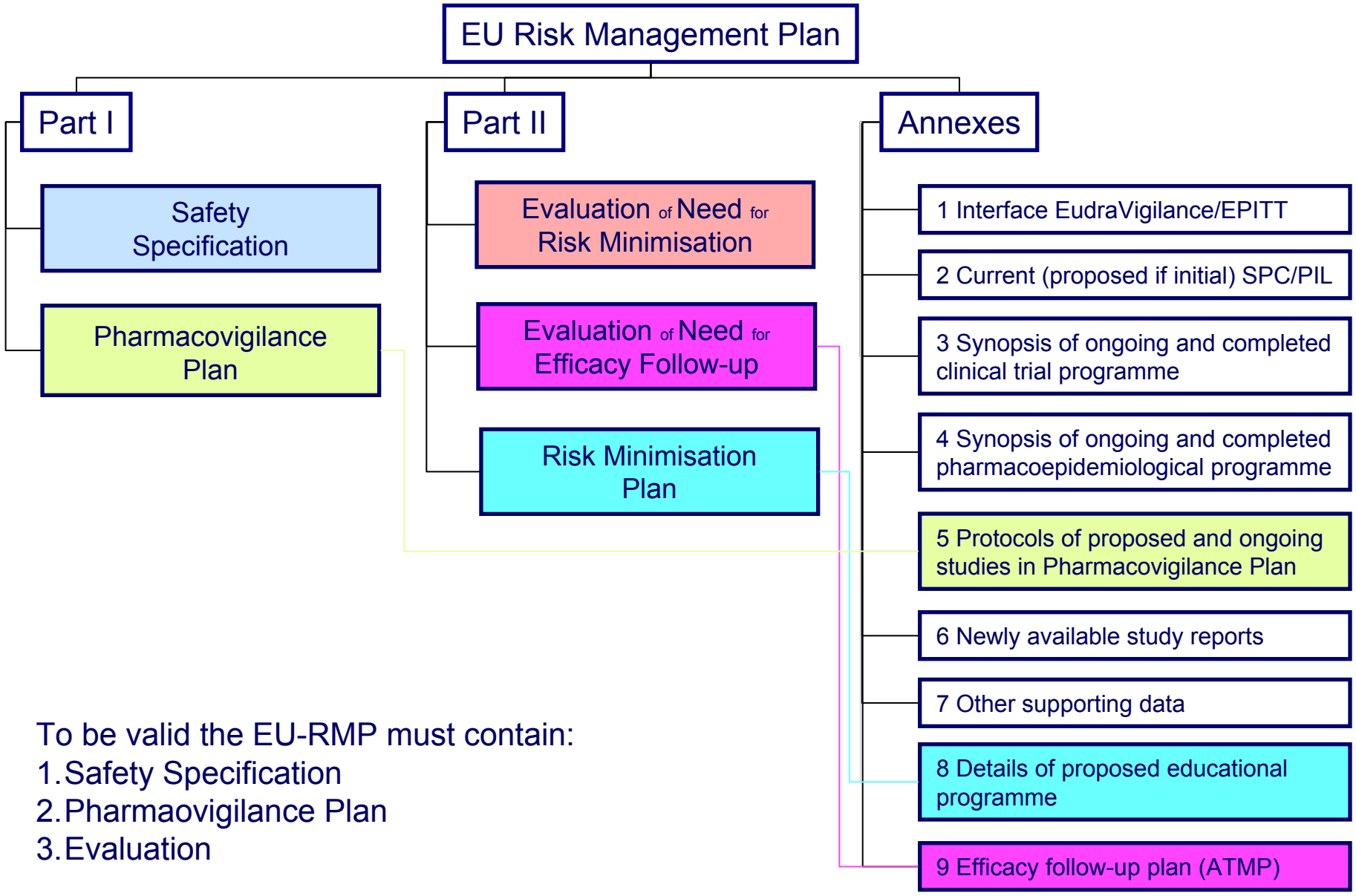
d) On company initiative e.g., safety issue with a marketed medicine

e) Update to previous EU-RMP

Situations where an EU-RMP might be required:

- "Known active substances"
- Hybrid medicinal product where the changes compared with reference product suggest different risks
- Bibliographical applications
- "Fixed combination" applications

EU-RMP template



To be valid the EU-RMP must contain:

1. Safety Specification
2. Pharmaovigilance Plan
3. Evaluation

Safety Specification

Aim & purpose:

- Summary of what is known/not known at authorisation
  - Identified risks
  - Potential risks
  - Important missing information
- To identify need for specific data collection in post-authorisation phase and to construct the **pharmacovigilance plan**
- To evaluate the need of additional risk minimisation activities and to construct the **risk minimisation plan**
- To evaluate the need of efficacy follow-up and to construct the **efficacy follow-up plan** (for ATMPs only)

Probably the most important bit!

Pharmacovigilance Plan

Aim & purpose:

- To identify and characterise known and unknown risks
- To set up an action plan for each safety concern
- For products with no special concerns **routine pharmacovigilance** may be sufficient (i.e. ADR reporting, signal detection, PSURs,...)
- For products with safety concerns **additional pharmacovigilance activities** should be considered

Why Pharmacovigilance Planning?

- Are there unanswered pre-clinical or clinical questions?
- Are there safety concerns specific to a particular part of the target population?
- Is the medicine intended for long-term use?
- Is there a potential of medication error and/or off-label use?
- Are there safety concerns specific to special populations (e.g. paediatric, elderly)?

→ *Conduct of Post-Authorisation Safety Studies to answer these questions!*

Evaluation of the need for a Risk Minimisation Plan

EU-RMP Part II

For each safety concern evaluate if:

- Additional risk minimisation actions are needed?
- Is the product literature (SPC/PIL) sufficient for this purpose?
- If not, then a Risk Minimisation Plan is needed
- Potential for medical error?

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

Risk Minimisation Plan

- Only needed if additional risk minimisation activities are required for at least one safety concern
- Should include both routine and additional activities for all safety concerns with risk minimisation
- Criteria to assess the effectiveness of each (additional) activity to reduce risk(s)
  - Health outcome measures that indicate the success or failure of the process implemented based on agreed standards
- Similar structure to Pharmacovigilance Plan
  - Objective and rationale
  - Proposed actions
  - Proposed review period

Summary of the EU-RMP

- Table of routine and additional pharmacovigilance and risk minimisation activities for each safety concern
- Key information, e.g. SPC labelling, study type and objective, type of education and key message

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Identified Risks		
Increased intraocular pressure (IOP), glaucoma and ocular hypertension	Routine pharmacovigilance Additional pharmacovigilance • Added to the Sentinel Event List • Phase III two-year clinical studies 12345-67 and 12345-89 to assess safety and efficacy of X • Conduct of an observational study to gain experience with repeat administration (2nd or subsequent implant) to collect long term safety data.	Included in section 4.4 of the SPC: • As expected with intravitreal injections, increases in intraocular pressure (IOP) may be seen..... Therefore, regular monitoring of IOP is required and any elevation should be managed appropriately post injection as needed. • Increased IOP is included as "very common" adverse reaction in Section 4.8 (Undesirable effects). Educational material to instruct prescribers on the recommended injection technique and important risks associated with X, including increased intraocular pressure and ocular hypertension.

Maintenance of the EU-RMP

- Updated throughout the product lifecycle
  - With each PSUR
  - With type II variations (extension of indication) and line extensions
  - When a milestone is reached
- Safety specification changes as new information gets available:
  - Results from ongoing/finalised clinical trials
  - Results from studies in the Pharmacovigilance Plan
  - Spontaneous reports and literature
  - Results from effectiveness measurements (health outcomes)
- Continuous update of Pharmacovigilance and Risk Minimisation Plans

→ *EU-RMP is a planning tool to build up knowledge*

→ *PSUR is a periodic benefit/risk assessment tool*

Acronyms

AR	Annual (Study) Report
CAP	Centrally authorised product
CHMP	Committee for Human Medicinal Products
CIOMS	Council for International Organisations of Medical Sciences
EMA	European Medicines Agency
EU-RMP	EU Risk Management Plan
EVCTM	EudraVigilance Clinical Trial Module
EVDAS	EudraVigilance Data Warehouse and Analysis System
EVMPD	EudraVigilance Medicinal Product Dictionary
EVPM	EudraVigilance Post Authorisation Module
FUM	Follow-up measure
MAH	Marketing Authorisation Holder
MedDRA	Medicinal Dictionary for Regulatory Activities
NCA	National Competent Authority
PAC	Post-authorisation commitment
PIL	Patient Information Leaflet
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
SDR	Signal of Disproportionate Reporting
SPC	Summary of Product Characteristics

Hvala!
Thank you!

Dr. Thomas Goedecke

thomas.goedecke@ema.europa.eu

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH