



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# EMA Statistical Signal Detection in practice

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An agency of the European Union



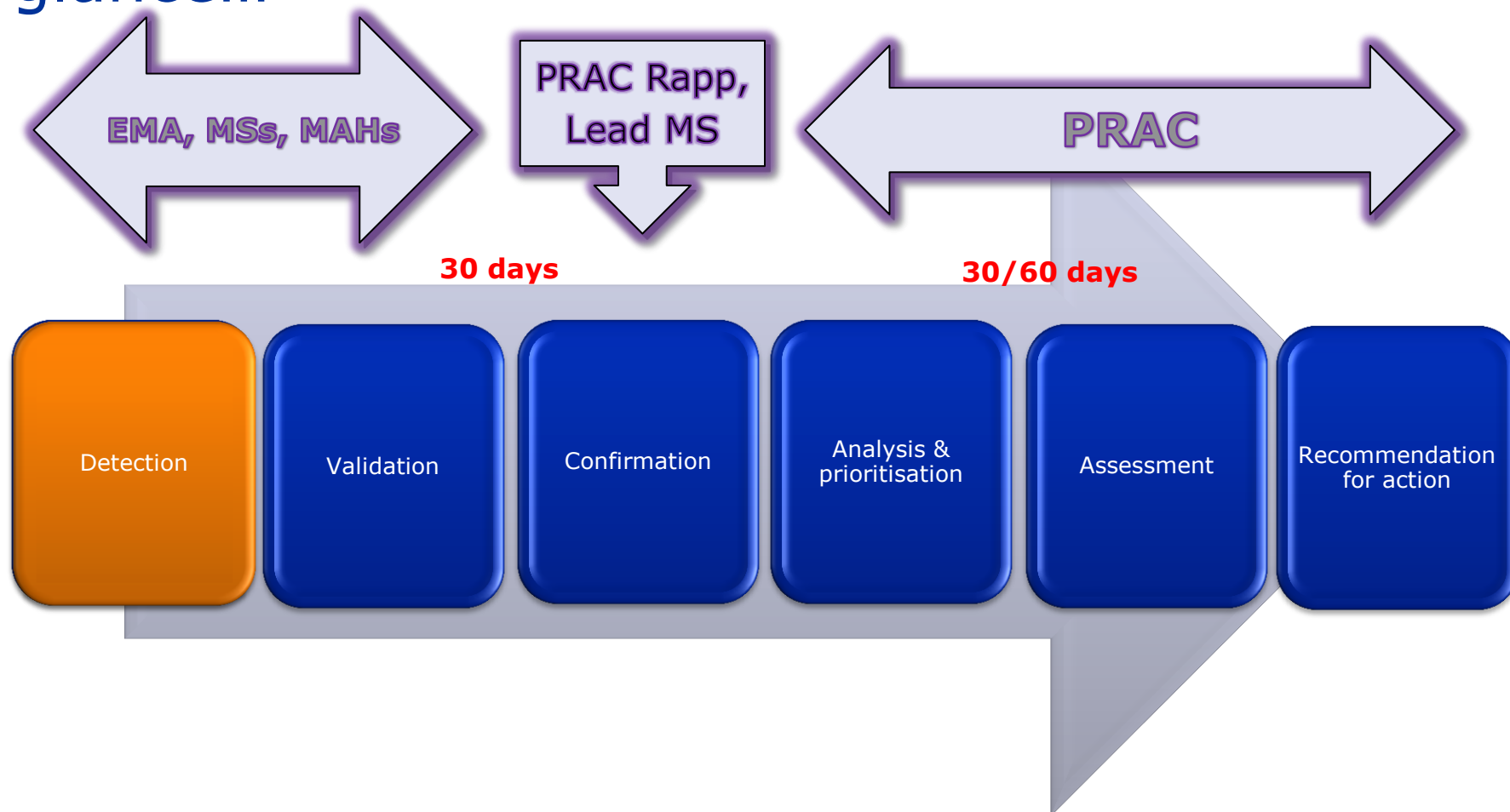


# Presentation contents

- Signal management (EMA perspective)
- Legal requirements
- eRMR
- Priorities



# The EU signal management process at a glance...





# Signal Management

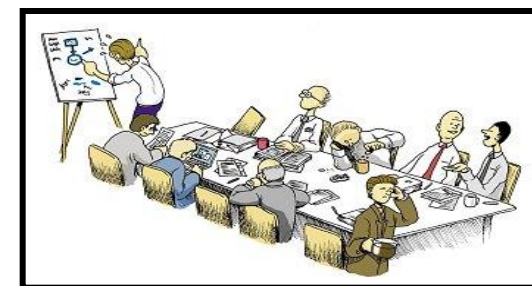


**Statistical approach:**  
SDRs/PRR

## Disproportional Analysis

	Event (R)	All other events	Total
Medicinal Product (P)	a	b	a + b
All other medicinal products	c	d	c + d
Total	a + c	b + d	n = a+b+c+d

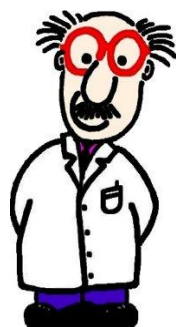
$$PRR = \frac{a/(a+b)}{c/(c+d)}$$



## Signal Detection



## Signal Validation



## Clinical approach:

- Temporal association
- Biological plausibility
- De-Rechallenge

COMS FORM  
PART 1 (UPP)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

DATE OF ONSET	DATE OF REPORT	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION
2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01

ANAPHYLACTOID REACTION

A 70-year-old female patient with moderate hypertension of the 4<sup>th</sup> lumbar spine and moderate osteoarthritis of the knee started to receive ... on 27/04/2011. In the evening of 04/05, she developed red itchy rash primarily in the neck. The rash then extended to the entire body. During night, she developed a feeling of pharyngeal discomfort and swelling. On 05/05, she presented to Hospital A for these symptoms. She was suspected to have allergic dermatitis and was given an IV injection of ... (30 ml) and a prescription for ... (10 mg/day). On 06/05, she presented again to Hospital A with ... persistent symptoms and was given an infusion of ... (100 mg/day). During night, she developed pharyngeal swelling and became dyspnoeic. She presented to the emergency department of Hospital B and was admitted to the department of dermatology of the hospital. On 10/05, she was discharged from the hospital. After discharge (date unspecified), she took a single dose of ... previously prescribed and developed similar symptoms. (date)

II. SUSPECT DRUG(S) INFORMATION

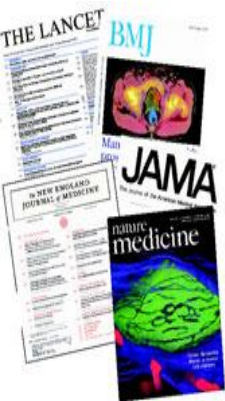
IN SUSPECT DRUG(S) INCLUDING PRODUCT NAME	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION	DATE OF REACTION
ALACETAMOL	400 mg	PO	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01	2011-01-01

III. CONCOMITANT DRUG(S) AND REPORT

## Causality assess:

- Very likely/certain
- probable/possible
- unlikely
- Unrelated
- Unassessable...

# Sources of information



Scientific literature

Spontaneous ADR reporting systems

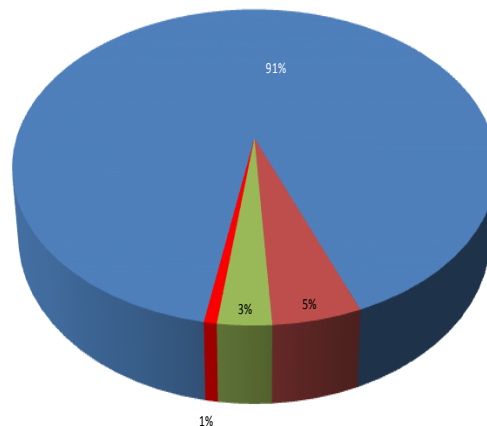
Non-interventional studies

**EudraVigilance**  
**H u m a n**



Clinical trials

PE studies



■ EV ■ Literature ■ Other RAS ■ Other



# LEGAL BACKGROUND

COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012

of 19 June 2012

on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

## Article 23

### Signal detection support

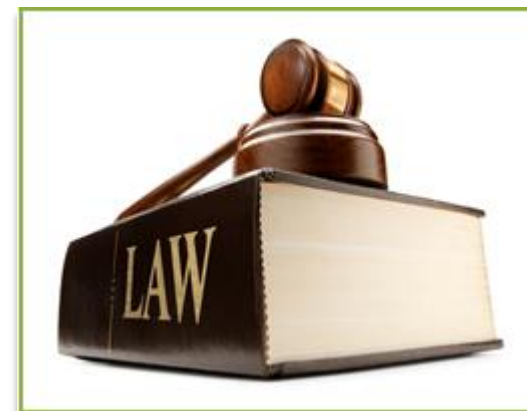
The Agency shall support the monitoring of the Eudravigilance database by providing national competent authorities with access to the following information:

- (a) data outputs and statistical reports allowing a review of all adverse reactions reported to the Eudravigilance database in relation to an active substance or a medicinal product;
- (b) customised queries supporting the evaluation of individual case safety reports and case series;

- (c) customised grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction;

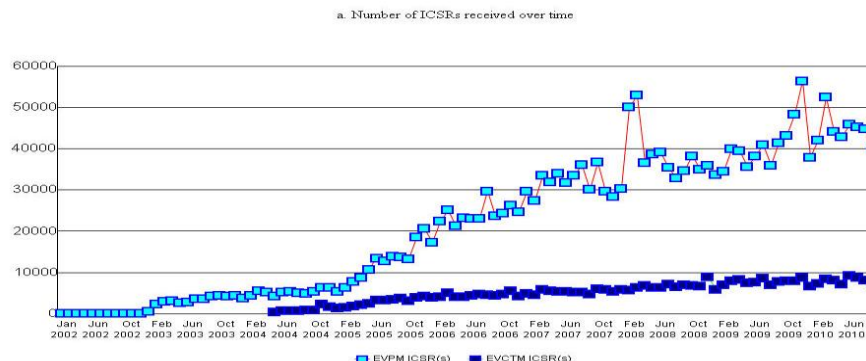
- (d) statistical signal detection methods.

The Agency shall also ensure appropriate support for the monitoring of the Eudravigilance database by marketing authorisation holders.



# Why an electronic tool for Signal detection?

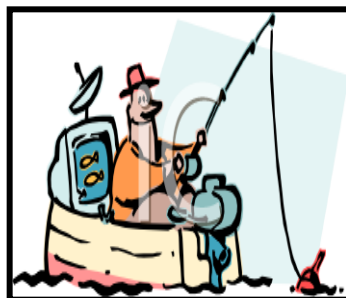
- **More products authorised**  
~800 CAPs  
~4500 ICSRs per day
- **Several Sources of information**  
(SmPC, RMP, PSUR, EPITT etc.)



**eRMR = electronic Reaction Report**

## Monitoring

- MedDra Built-in dictionary
- Historical of ADRs
- Reminder for SDR



## Tracking

- Signal Status
- Comment field





# eRMR structure

## Use of agreed terminology

### Active substances

C	D	E	F	G
SOCs	HLGTs	HLTs	SMQ Narrow	PTs
Blood	Haematologic al Disorders	Haematologic al Disorders		Haemoconcentration
Blood	Anaemias nonhaemolytic and marrow depression	Marrow Depression And Hypoplastic Anaemias	Agranulocytosis, Haematopoietic Cytopenias	Aplastic Anaemia
Blood	White blood cell disorders	Neutropenias	Haematopoietic Cytopenias	Neutropenia
Blood	Platelet disorders	Thrombocytopenias		Idiopathic Thrombocytopenic Purpura
Card	Heart failures	Heart Failures Nec	Cardiac Failure	Cardiac Failure
Card	Heart failures	Heart Failures Nec	Cardiac Failure	Cardiac Failure Congestive
Card	Myocardial disorders	Myocardial Disorders Nec		Ventricular Hypertrophy
Card	Myocardial disorders	Noninfectious Myocarditis		Myocarditis





# eRMR structure

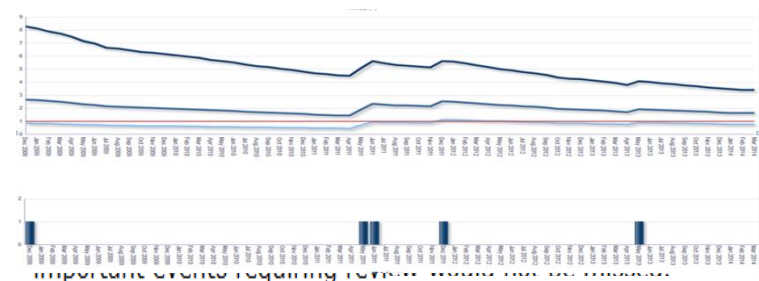
## EV data and different categories

New EV	Tot EV	New Fatal	Tot Fatal	New Med Err/Abus	Tot Med Err/Abus	New Paed	Tot Paed	New Geriatr	Tot Geriatr	New EEA	Tot EEA	New HCP	Tot HCP	New Serious	Tot Serious	New Spontaneou	Tot Spontaneou	PRR (-)	New Lit	Tot Lit	New Obs	Tot Obs	New CT	Tot CT
2	24	0	2	0	2	0	0	1	2	0	1	2	22	2	21	2	24	3.01	0	0	0	0	0	0
1	2	0	0	0	0	0	0	1	1	0	0	1	2	1	2	1	2	0.50	0	0	0	0	0	0
6	119	0	7	0	3	0	1	1	10	3	27	2	106	6	115	6	102	1.73	0	1	0	4	0	13
1	113	0	1	0	2	0	0	1	38	1	27	1	71	1	87	1	102	0.14	0	2	0	11	0	0
1	8	0	2	0	0	0	0	1	4	0	0	0	2	1	8	1	6	0.12	0	0	0	2	0	0
1	253	0	22	0	7	0	0	1	144	0	132	1	233	1	248	1	244	0.83	1	25	0	8	0	1
2	188	0	46	0	4	0	0	1	57	0	39	1	111	2	188	2	150	0.19	0	0	0	33	0	5
2	104	0	1	0	3	0	0	2	32	0	61	1	71	2	81	2	102	0.42	0	0	0	2	0	0
2	58	0	0	0	4	0	2	1	20	0	9	1	43	2	57	2	53	0.53	0	0	0	5	0	0
2	207	0	2	1	4	0	0	1	50	0	67	1	104	2	89	1	200	1.51	0	0	1	7	0	0
2	103	0	0	1	3	0	0	2	31	0	24	0	56	2	103	2	80	0.71	0	0	0	23	0	0



# Criteria for prioritisation in Screening the eRMR:

## Use of statistical and clinical principles



**Pr1 = Designated Medical Events**

**Pr2 = Important Medical Events with a Signal Of Disproportionate Reporting**

**Pr3 = Important and non Important Medical Events with a Fatal outcome or Paediatric Cases**

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

**Signal of Disproportionate Reporting (SDR) in EV:**

• **spontaneous cases:**  
N ≥ 3 (AM) or ≥ 5 (RM)

**AND**

• **PRR(-) ≥ 1**

Anaphylactoid shock	Febrile neutropenia
Angioedema	Gastrointestinal mucosa
Aplasia pure red cell	Gastrointestinal necrosis
Aplastic anemia	Grand mal convulsion
Asterobis	Granulocytopenia
Autoimmune hepatitis	Haemoglobinuria

Thrombotic thrombocytopenic



# eRMR – Operational Functionalities

PTs	IME / DMF	Priority	Changes	SDR	Signal Status	Comments
0	0	0	0	1	2	0
Haemolysis	Dme	Pr1	Increased		Listed	SPC 4.8
Retinopathy Haemorrhagic	Ime	Pr 2	Increased	Sdr (27)	Disease	
Palpitations			Increased	Sdr (3)	Closed	
Intracardiac Thrombus	Ime	Pr 2	Increased	Sdr (27)	Ongoing	review of the cases
Scleral Discolouration		Pr 3	Increased (fatal)		Linked	Intestinal Perforation
Deposit Eye			Increased	Sdr (27)	PSUR	
Pancreatitis Acute	Ime/ Dme	Pr1	Increased	Sdr (27)	Monitor	

## Monitoring



## Tracking





# Assigning the Signal Status



PTs	Tot Cases	Signal Status	Comments
Conjunctival Oedema	5	Listed	SmPC 4.8
Symblepharon	6	Closed	6 cases, 2 valid not related to CAPs and in the context of TEN
Corneal Disorder	13	Closed	18/10/2011. 5 unique cases in eudravigilance, all cases occurred with dexamethasone intravitreal injection in the
Corneal Oedema	24	Disease	
Ulcerative Keratitis	16	Monitor	09/03/2011. 12 cases, 0 valid, no cases related to CAP
Angle Closure Glaucoma	6	Linked	glaucoma
Glaucoma	48	RMP	Identified risk. Proposed to be included in 4.4 - 4.8
Ocular Hypertension	18	Listed	SmPC 4.8

Signal Status
• <u>Listed</u>
• <u>Linked</u>
• <u>Check</u>
• <u>Closed</u>
• <u>Monitor</u>
• <u>PSUR</u>
• <u>RMP</u>
• <u>Disease</u>

*SmPC 4.8/4.4*

*Synonymous or more severe medical concept*

*Review cases*

*Cases reviewed*

*PT under monitoring*

*Rapporteur's conclusion*

*Potential/Identified Risk*

*Indication/Symptoms*

# Message to take home

## 1 - Read EV data

**eRMR**

## 2 - Prioritise ICSRs

**priority column (DME, SDR, fatal etc.)**

## 3 - Differentiate ICSRs

**assigning signal status**

## 4 - Assess EV data

**check previous awareness (PSUR, RMP),  
review cases, review literature**



RMP

Indication

PSUR

SmPC

**e-RMR  
GOAL**

Literature



