EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Routine signal detection and statistical tools on paediatrics

Paediatric workshop – 28 April 2014

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How to improve monitoring of drugs in the paediatric population

Pharmacovigilance

→ 1) Paediatric query

→ 2) Paediatric Signal Detection

- *PhV obligations for routine monitoring of ADRs*
- *Stastical and clinical relevance*
- *e-RMR: a tool for signal detection*
- *Medication error in children*
- *Update on future developments*
- *Conclusion*

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;

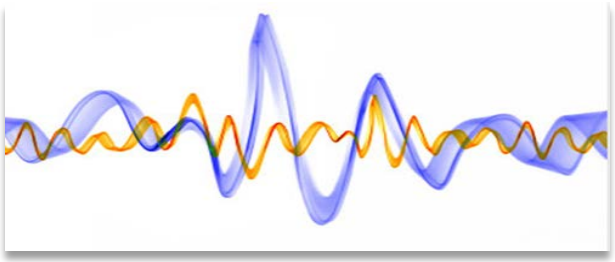
(b) customised queries supporting the evaluation of individual case safety reports and case series;

(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.

Signal definition



Signal is 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 event, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Report of the Council for International Organisations of Medical Sciences WG VIII, Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010).

Sources of information–Hypothesis Generating

Clinical trials data

Source of all signals evaluated by EMA in 2013 (n=2449)

EudraVigilance Human

Spontaneous ADR reporting systems

Pharmacovigilance

Scientific literature

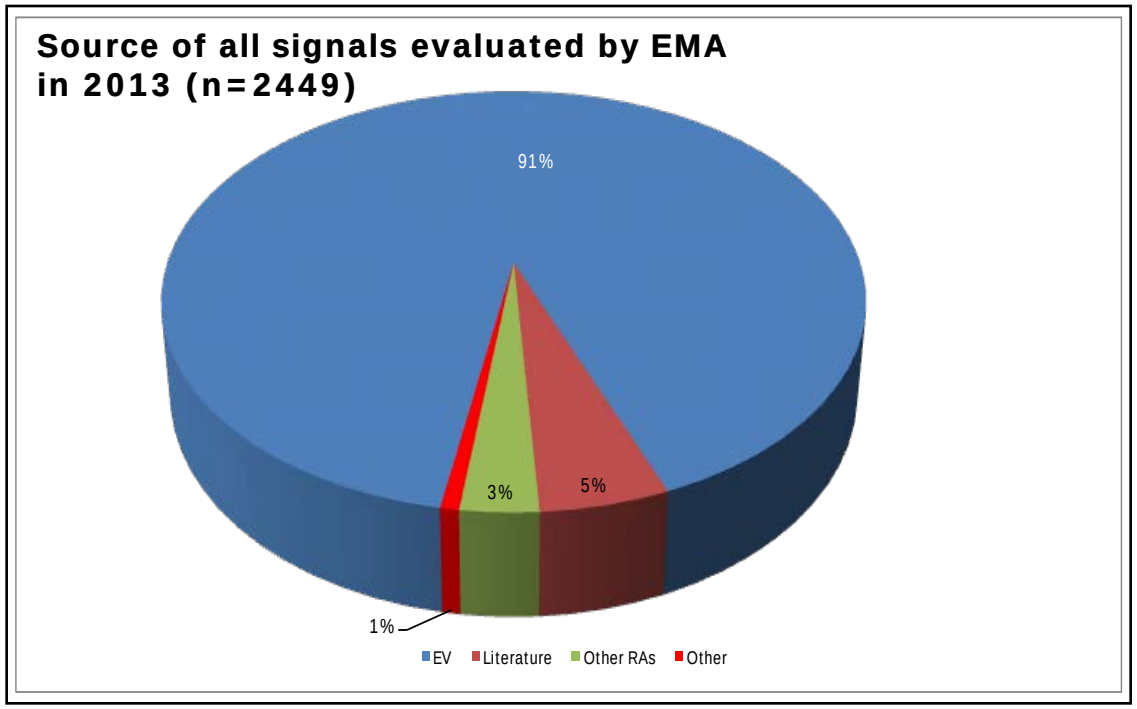
Non clinical trial data e.g non-interventional studies

Pharmacoepidemiological studies

Sources of information–Hypothesis Generating

91% of signals evaluated by EMA originate from EudraVigilance

70% of signals validated and forwarded to PRAC by EMA originate from EudraVigilance



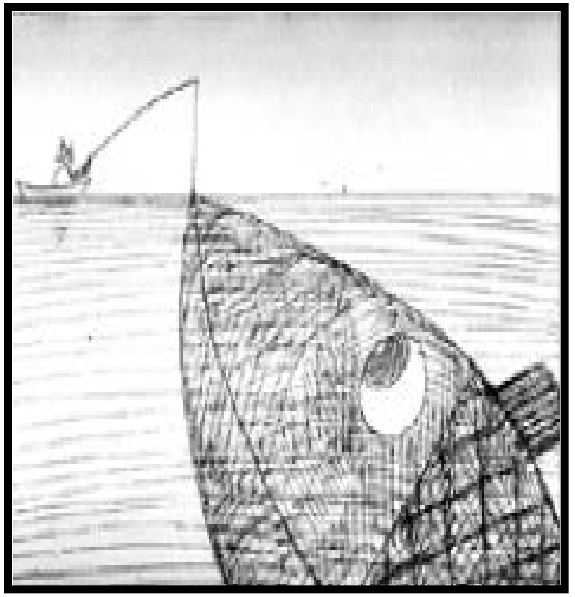
Limitations of the spontaneous reporting

- Under reporting and reporting bias
- No drug exposure data
- No adverse event natural history (prevalence, incidence)
- No indication epidemiology (prevalence, incidence)
- Data quality and missing data
- Confounders

Signal detection limitation

Fishing in the wrong place

Fishing with the wrong tool



DME = designated medical events

List of MedDRA terms with high mortality rate and high likelihood to be drug related. The list was introduced in 2012 to serve as safety net in signal detection and ensure that important events requiring review would not be missed.

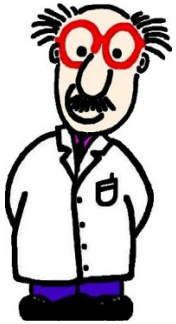
- Acute hepatic failure
- Acute respiratory distress syndrome
- Acute respiratory failure
- Agranulocytosis
- Anaemia haemolytic autoimmune
- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactoid reaction
- Anaphylactoid shock
- Angioedema
- Aplasia pure red cell
- Aplastic anemia
- Asterixis
- Autoimmune hepatitis
- Autoimmune neutropenia
- Autoimmune pancreatitis
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia
- Dermatitis exfoliative
- Dermatitis exfoliative generalised
- Disseminated intravascular coagulation
- Drug reaction with eosinophilia and systemic symptoms
- Epilepsy
- Erythema multiforme
- Febrile bone marrow aplasia
- Febrile neutropenia
- Gastrointestinal mucosal necrosis
- Gastrointestinal necrosis
- Grand mal convulsion
- Granulocytopenia
- Haemoglobinaemia
- Haemoglobinuria
- Haemolysis
- Haemolytic anaemia
- Haptoglobin decreased
- Renal failure
- Renal failure acute
- Respiratory failure
- Reye's syndrome
- Rhabdomyolysis
- Status epilepticus
- Stevens-Johnson syndrome
- Subacute hepatic failure
- Sudden cardiac death
- Sudden death
- Sudden hearing loss
- Sudden visual loss
- Suicidal behaviour
- Suicidal ideation
- Suicide attempt
- Thrombotic thrombocytopenic purpura
- Torsade de pointes
- Toxic epidermal necrolysis

Signal Management

Statistical approach:

SDRs/PRR

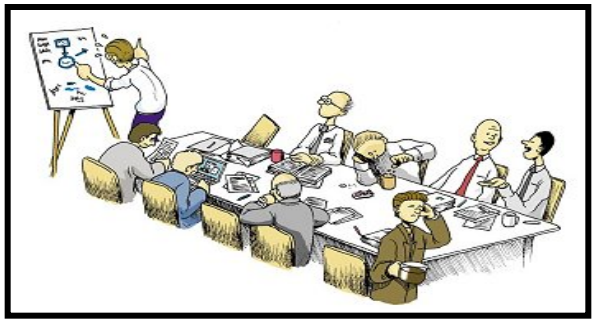
Signal Detection



Clinical approach:

- Temporal association
- Biological plausibility
- Dechall.-Rechallenge

Signal Validation

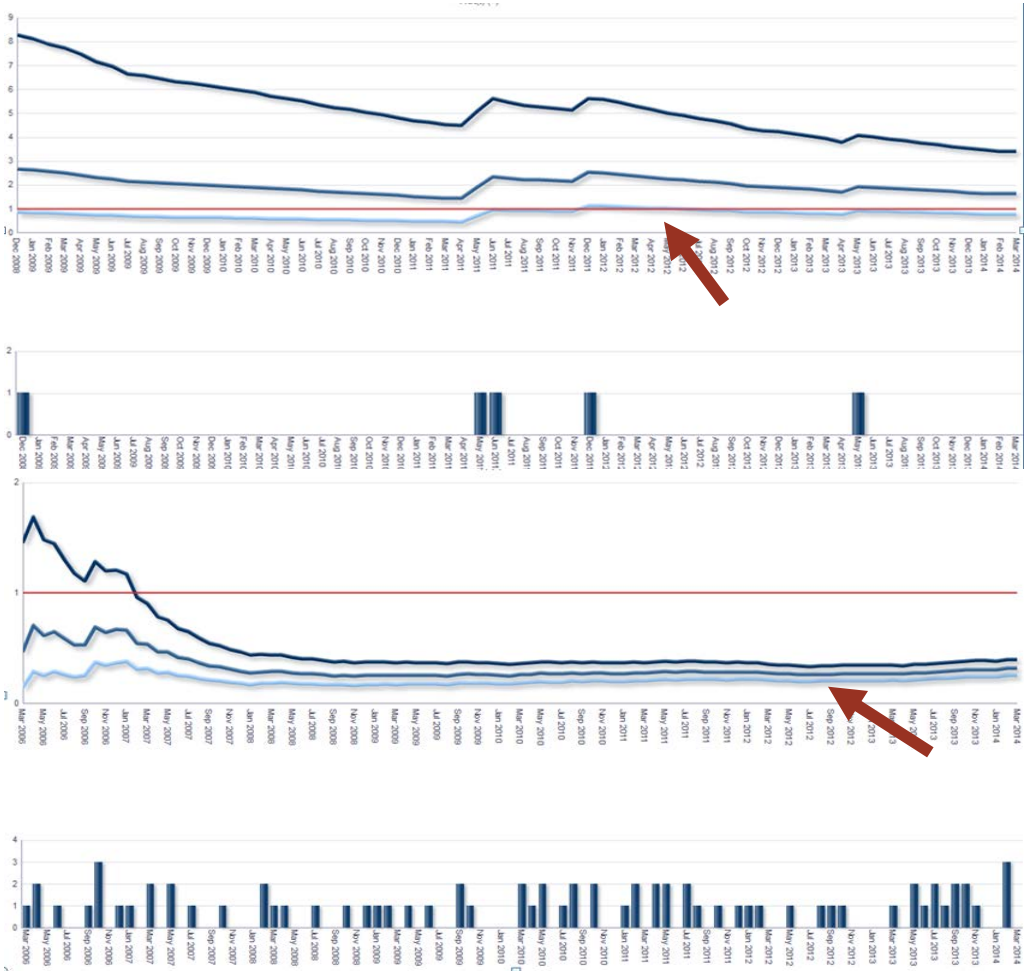


Signal confirmation

Signal Assessment /Recomm.

Hypothesis = Statistical relevance

Dynamic vs Static PRR



Disproportional Analysis

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

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

PRR

PRR(-) = 1: no reporting difference
PRR(-) > 1: there is a difference

PRR threshold in EV for a potential signal =
Lower bound of the **95% Confidence Interval** of PRR ≥ 1

Hypothesis = Clinical relevance

ICSR (CIOMS I)

- Biological plausibility
- Dechallenge / Rechallenge (+/-)
- Time to Onset: temporal association
- Confounders: co-suspected / concomitant drugs
- Underlying disease

CIOMS FORM
PAGE 1 OF 2

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1.PATIENT INITIALS (first, last)	1a.COUNTRY	2.DATE OF BIRTH Day	Month	Year	2a.AGE Years	3.SEX	4-4b.REACTION ONSET Day	Month	Year
		—	—	—	75	F	05	Oct	01

7+13.DESCRIBE REACTION(S) (including relevant tests/lab data)

ANAPHYLACTOID REACTION

A 75-year-old female patient with moderate spondylolisthesis of the 4th lumbar spine and moderate osteoarthritis of the knee started to receive on . In the evening of t, 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 , she presented to Hospital A for these symptoms. She was suspected to have allergic dermatitis and was given an I.V. injection of (20 mL) and a prescription for (cetirizine hydrochloride; 10 mg/day, p.o.). On 06Oct, she presented again to Hospital A with a persistent symptom and was given an infusion of (betamethasone sodium phosphate). During night, she developed pharyngeal swelling and became dyspneic. She presented to the emergency department of Hospital B and was admitted to the department of dermatology of the hospital. On 16Oct, she was discharged from the hospital. After discharge (date unspecified), she took a single dose of previously prescribed and developed similar symptoms. (cont.)

8.(a) CHECK ALL APPROPRIATE TO ADVERSE REACTION
- ☐ PATIENT DIED
- ■ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY/BIRTH DEFECT
- ☐ NONE OF THE ABOVE (IMPORTANT MEDICAL EVENTS)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (including generic name)

10.DID REACTION ABATE AFTER STOPPING DRUG? ■YES ☐NO ☐NA

15.DAILY DOSE(S): 400 mg

16. ROUTE(S) OF ADMINISTRATION: PO

11.DID REACTION REAPPEAR AFTER REINTRODUCTION? ■YES ☐NO ☐NA

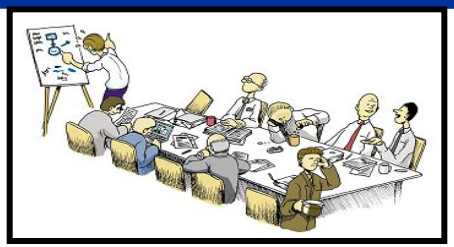
17. INDICATION(S) FOR USE: Lumbago (spondylolisthesis of the 4th lumbar spine) and knee pain (osteoarthritis of the knee)

18. THERAPY DATES (from/to): from

19. THERAPY DURATION: 10 days

III. CONCOMITANT DRUG(S) AND HISTORY

SIGNAL VALIDATION



Causality Assessment Rational

- **VERY LIKELY/CERTAIN:** plausible TTO, with no alternative explanations
- **PROBABLE:** reasonable TTO, unlikely attribute to alternative explanations
- **POSSIBLE:** reasonable TTO but it could also be attributed to alternative explanation
- **UNLIKELY:** improbable TTO also attribute to underlying disease and concomitant drugs
- **UNRELATED:** incompatible TTO and confounded by underlying disease and concomitant drugs
- **UNASSESSABLE:** insufficient information

Rational

- **ONTOLOGY =** the information in the SmPC is unable to convey the risk
- **FREQUENCY =** increasing or of concern in the subsets analysed
- **SERIOUSNESS =** outcome of the ADR is more serious than expected
- **TREATMENT =** specific action that the prescriber would not consider
- **DIAGNOSIS =** specific clinical manifestation or test that HCP would not expect causing a delay
- **PREVENTION =** monitoring the specific subset to enforce the preventability of the ADR

Signal Assessment by PRAC

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2014
EMA/PRAC/530804/2013
Pharmacovigilance Risk Assessment Committee

List of signals discussed at PRAC since September 2012

INN	Signal
Dexmedetomidine	Infantile apnoeic attack
Fentanyl, transdermal patch	**Accidental exposure**
Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed)	Complex regional pain syndrome (CRPS) linked to the process of vaccination
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Bronchospasm in patients with or without asthma
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Postural orthostatic tachycardia syndrome (POTS)
Human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)	Primary / premature ovarian failure

No action after assessment

EMA/MSs to perform additional analysis

Request of a cumulative review

Address the signal in the PSUR

PRAC Outcomes

Update of PI / RMP

PhV Inspection

Update of PI / RMP after a cumulative review

DHPC

Urgent Safety Restriction

PASS

Art. 31

eRMR (electronic Reaction Monitoring Report)

electronic tool for SD:

EV~4500 ICSRs per day

- **Save time** in screening
- **Simplify** the screening process
- **Avoid** duplication of work tracking all issue
- **Build-up** a knowledge overtime about your product
- **Improve** reliability matching different sources of information (PSUR, SPC, RMP, US_PI etc.)
- **Simplify** access to the cases

1 / 2 eRMR – STRUCTURE & CONTENT

Use of agreed terminology

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

1 / 2 eRMR – Structure: EV data and sub-

PTs	IME / DME	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 Spontaneou	Tot Spontaneou	PRR (-)	Priority	Signal Status	Comments	New Lit	Tot Lit	Roa 1	New Roa 1	Tot Roa 1	Roa 2	New Roa 2	Tot Roa 2
Bradycardia		16	249	0	2	0	5	0	1	1	13	13	218	7.42		Listed	SmPC 4.8	0	8	Oral Use	15	237	Subcutaneous Use	0	1
Tachycardia		2	27	1	2	0	3	0	0	0	2	2	25	0.39	Pr 3	Linked	radichardia and atrio-ventricular block	0	0	Oral Use	2	25	Subcutaneous Use	0	1
Fatigue		40	603	0	5	2	24	0	3	2	22	40	591	5.92		Linked	sthenia	2	2	Oral Use	40	593	Subcutaneous Use	0	1
Malaise		14	181	2	7	0	6	0	1	0	8	14	170	1.90	Pr 3	Disease		1	11	Oral Use	13	171	Subcutaneous Use	0	1
Alanine Aminotransferase Increased		18	180	1	6	1	11	0	0	1	3	10	151	3.44	Pr 3	Listed	SmPC 4.8	0	0	Oral Use	17	170	Subcutaneous Use	0	1
Headache		37	479	0	4	2	23	0	2	0	9	34	457	3.45		Listed	SmPC 4.8	0	3	Oral Use	36	465	Subcutaneous Use	0	1
Multiple Sclerosis Relapse	Ime	36	539	0	6	2	14	1	3	0	10	31	481	65.80	Pr 2	Disease		0	8	Oral Use	35	505	Oropharingeal Use	0	1
Dizziness		30	445	0	1	2	21	0	0	0	17	29	430	3.47		Listed	SmPC 4.8	3	4	Oral Use	30	429	Subcutaneous Use	0	1
Pulmonary Hypertension	Ime / Dme	3	10	0	1	0	2	0	1	0	2	3	10	0.82	Pr 1	Check	2/10/2012. Review new cases only	3	4	Oral Use	2	7	Transplacental Use	0	1
Hypotension		3	65	1	2	0	2	0	1	0	2	3	62	0.76	Pr 3	Linked	ardiac disorders	0	0	Oral Use	3	60	Transplacental Use	0	1
Agranulocytosis	Ime / Dme	0	14	0	1	0	0	0	0	0	4	0	14	3.92		Closed	ot enough evidence	0	0	Oral Use	0	10	Intramuscular Use	0	1
Vomiting		0	12	0	3	0	1	0	1	0	0	0	12	0.41		Listed	SmPC 4.8	0	8	Intramuscular Use	0	3	Oral Use	0	3


RMP
Indication
PSUR
SmPC
Priority
Literature

eRMR – Monitoring and Tracking

Structure: interactive functionalities

PRR, SDRs, DME, IME etc.

PTs	IME / DME	Priority	Changes	SDR	Signal Status	Comments
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	

Several sources of information combined in the eRMR: SmPC, RMP, PSUR, reviews etc.

Focusing on certain ADRs

Screening the eRMR

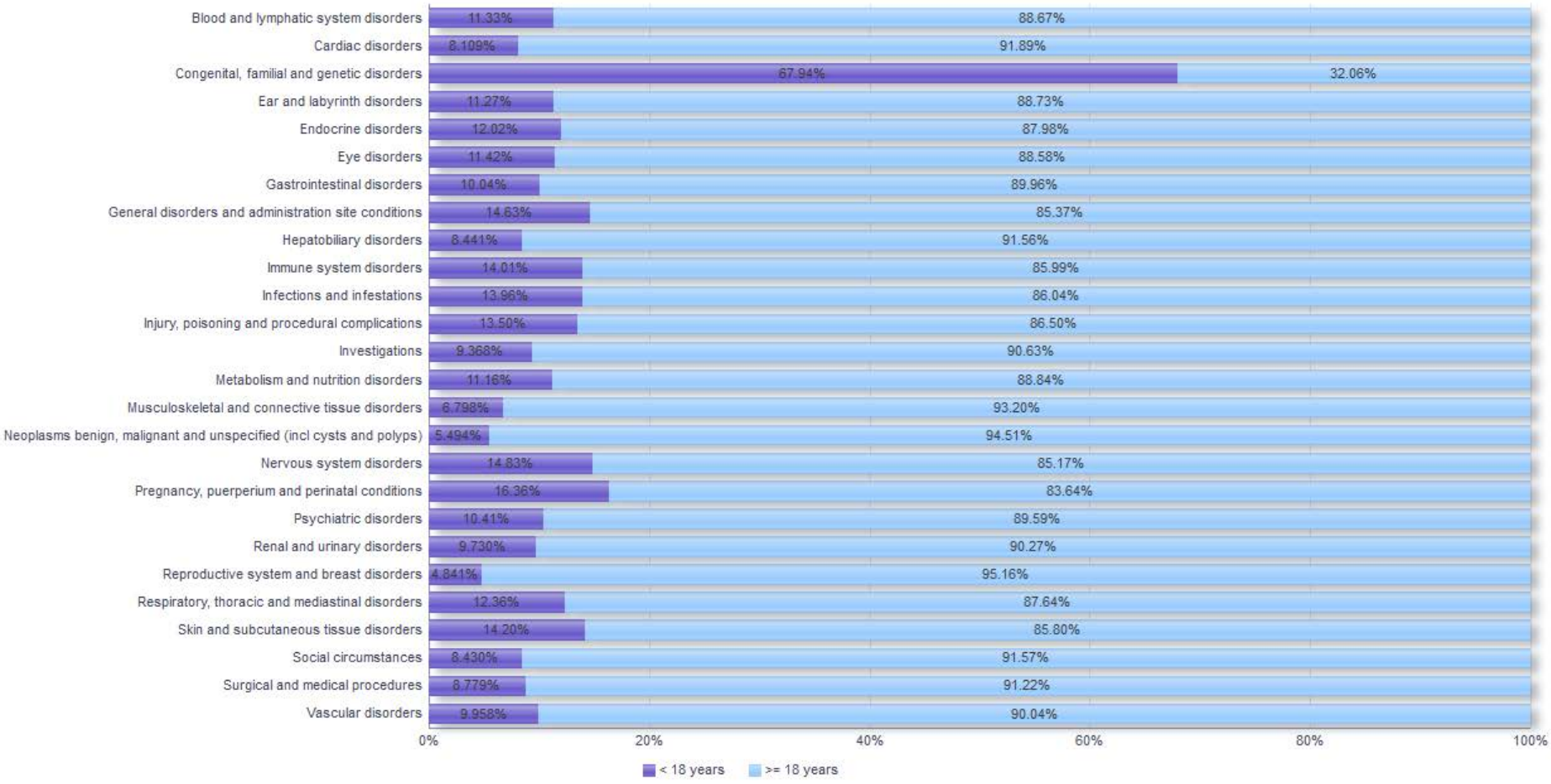
Prioritisation of ADRs

Pr1 = **D**esignated **M**edical **E**vents

Pr2 = **I**mportant **M**edical **E**vents with a **S**ignal Of **D**isproportionate **R**eporting

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

Type of ADRs in EV: Paediatrics Vs Adults



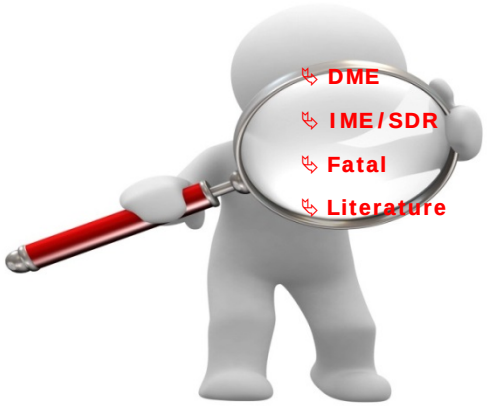
Main differences …
Child vs Adult

- **PhD and PhK** ⇨ increased vulnerability and different drug interaction profile;
- **Eccipients** ⇨ increased susceptibility;
- **Drug induced growth and develp. Disorders** ⇨ drug exposure at a sensitive point in development (critical window)
- **Paediatric ADRs** ⇨ specific only to children. In utero exposure is an additional risk factor
- **Chronic disease** ⇨ increased risk for life-long exposure
- **Unable to communicate ADRs clearly**

Focusing on certain ADRs

Screening the eRMR

Prioritisation of ADRs



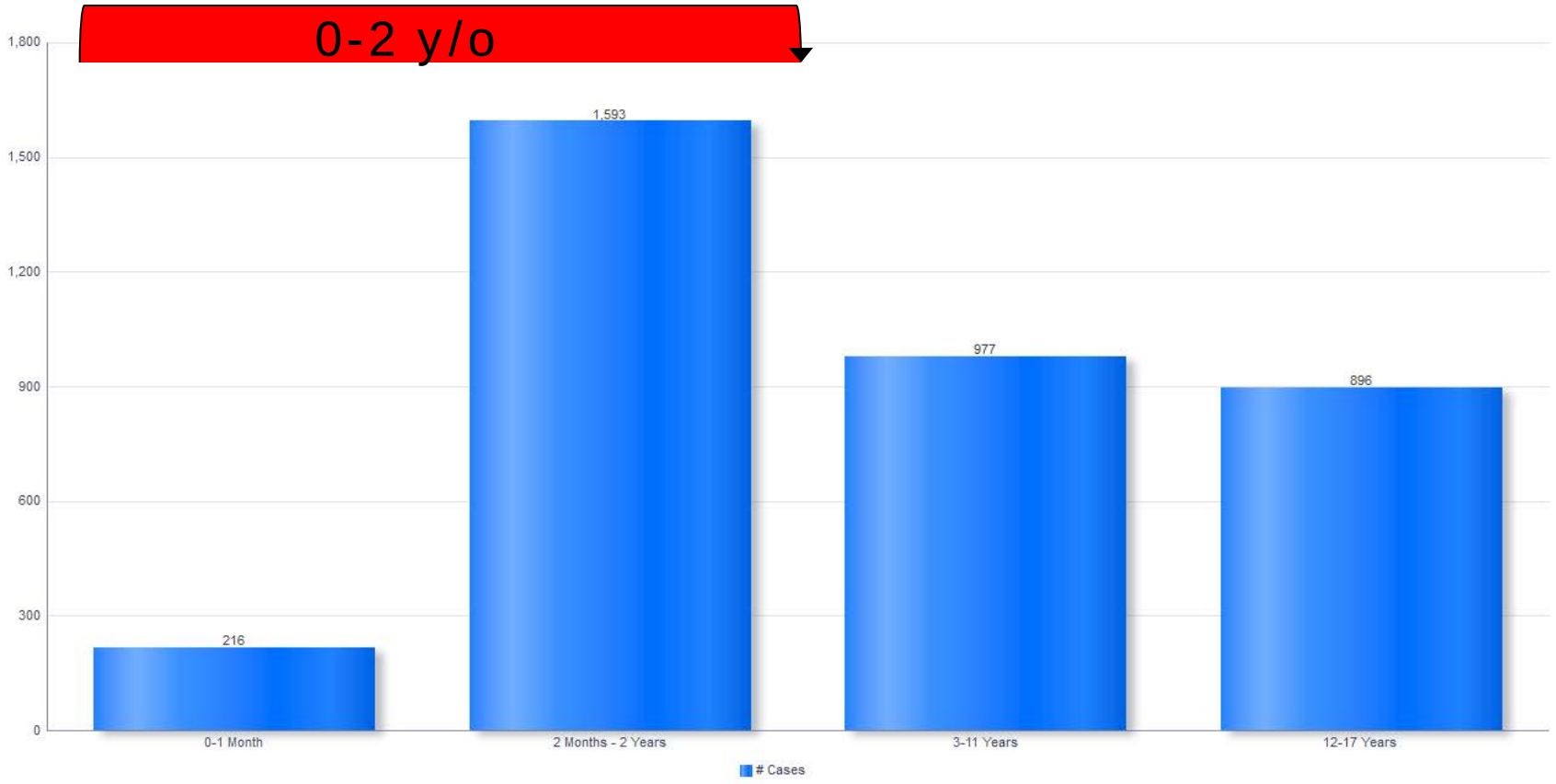
Pr1 = Designated **M**edical **E**vents

Pr2 = Important **M**edical **E**vents with a **S**ignal Of **D**isproportionate **R**eporting

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

PrPaed = Paediatric safety net;
- All IMEs in paediatrics
- All paed congenital disorder
- All Fatal paed cases
- All paed medication error and accidental exposure

Distribution of Medication Error cases (HLT) by Age group in EV = 1% of the total Paed. Cases



Medication Error…

… can occur as a combination of unfavorable, yet preventable circumstances. GVP: ME refers to any unintended error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

The Agency also has a role in facilitating coordination between Member States, national pharmacovigilance centres and national patient-safety authorities to enable the mutual exchange of information on ADRs resulting from ME and effective reporting to EudraVigilance.

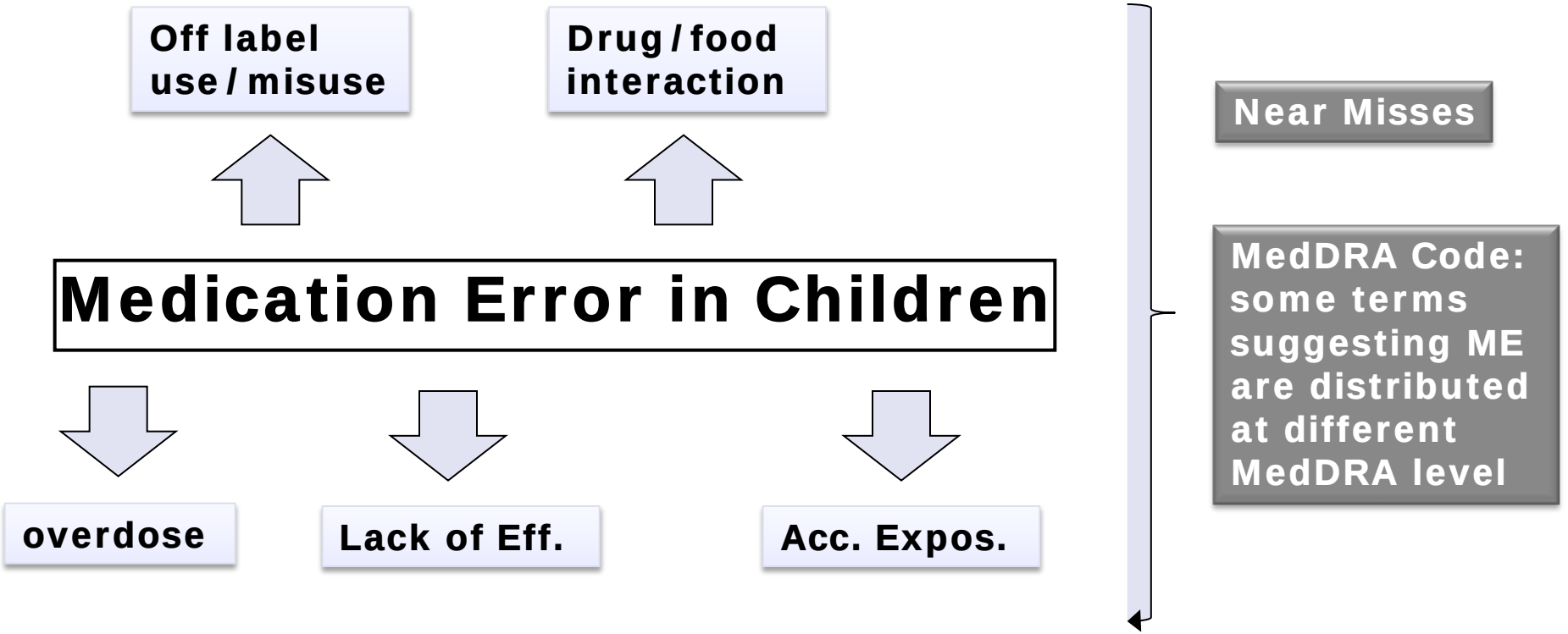
Hence, the **EudraVigilance** is a potentially useful tool for the evaluation of safety concerns due to medication error issues once its constraints are considered and accounted for.

Changes in the Legislation

The PhV Legislation has introduced a number of changes related to ME:

1. *The term adverse reaction now covers **noxious and unintended effects also resulting from medication errors** and uses outside the terms of the marketing authorisation;*
2. *EU Member States (**MSs) to collect information** on suspected ADRs also arising **from use outside the terms of the marketing authorisation** which includes: misuse, abuse, medication error as well as occupational exposure;*
3. *MSs should **ensure** that reports arising from an error associated with the use of a medicine are made **available to EV**.*

Understand the cause…



1. Higher risk from **0-2 years** old
2. drugs with **low therapeutic index** (*analgesics, anticonvulsants etc.*)
3. Drugs with **high risk formulation** (*IV, adults formulations etc.*)

Future Steps

1. PROTECT WP3.8 = sub-group and stratification analysis currently under study to investigate Routine Signal detection using PRR designed for vulnerable population (i.e. Paediatrics/Elderly etc.).

To evaluate any increase performance in detecting more **TRUE POSITIVE** and/or less **FALSE NEGATIVE**

2. PRAC–SMART = workstream focus on writing the methodological guidance for signal detection

Describe how to monitor vulnerable population:i.e. **Paediatrics**/elderly etc.

In Summary and Conclusions

1. **Paediatric Priority** **-** List for paediatric ADRs *(congenital disorders, ME, LoE etc.) and* ***Paed PRR****;*

2. Need to **enhance PhV** for premature babies at much higher risk

3. Need for **complementary data sources** to advance knowledge of benefit-risk of medicines in paediatrics;

4. **Link between PIP and RMP** to closely monitor potential risks for children in the eRMR; improve interaction PRAC/PCO)

5. Development of a new **MedDRA SMQ for ME**

6. **Encourage reporting** for HCP reluctant to report ME/off label

7. **Understand the cause** of the paediatric ADR (i.e. dose, interactions etc.) and reflect in risk minimisation measures: *(DHPC, PI updates, educational material, change in packaging design);*


Thank You