EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

GVP Module IX: Signal Management

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SME Workshop "*Focus on Pharmacovigilance*"

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Topics

- Background
- Sections of GVP Module IX
- Signal Management
  - definitions
  - steps
- Work sharing for data monitoring in EudraVigilance (EV)*
- Periodicity of data monitoring in EV*
- MAHs' obligations
- Role of Pharmacovigilance Risk Assessment Committee (PRAC)
- Tracking
- Improvements

* Applicable for the European Medicines Agency and the National Competent Authorities

Background

- 5% of all hospital admissions are due to an ADR
- 5% of all hospital patients suffer an ADR
- ADRs are the 5th most common cause of hospital death.
- It is estimated that 197,000 deaths per year in the EU are caused by ADRs
- The total cost to society of ADRs in the EU is €79 billion.

Even small improvements in the pharmacovigilance system will have a major impact on public health and society

Source: Annex 2 of the Report on the impact assessment of strengthening and rationalising EU Pharmacovigilance
COMMISSION OF THE EUROPEAN COMMUNITIES Sept 2008

Sections of GVP Module IX

- Section IX.A Introduction

  Definitions of signal and signal management

- Section IX.B General guidance and requirements on structures and processes

  Data sources, methodology, the steps applicable to all organisations involved

- Section IX.C Description on how these structures and processes are applied in the EU regulatory and pharmacovigilance network to detect new or changed risks related to medicinal products

  The actors: the MAHs, the NCAs (lead/co-lead Member States), the Agency, the PRAC

  Their responsibilities, interactions

Signal Management definitions

Signal:

> "Information that arises from one or multiple sources (incl. observations and experiments), which suggest 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"

Practical Aspects of Signal Detection in Pharmacovigilance Report of CIOMS Working Group VIII, Geneva 2010,

* For the purpose of GVP Module IX only adverse reactions are followed.

Signal Management definitions

Signal Management (SM) is a set of activities to determine based on various data sources* whether there are new/changed risks associated with active substances/medicinal products:

SM steps:

- Signal detection,
- Signal validation (and confirmation),
- Prioritisation, analysis and assessment,
- Recommendation for action,
- Exchange of information.

* ICSRs (EudraVigilance, national databases, company specific), data from active surveillance system or studies, literature and other available

Signal Management steps (1)

Signal detection performed:

- by reviewing of ICSRs (applicable for small data sets),
- by statistical analyses (example from EV on next slide) in large databases (using e.g. pre-defined criteria of frequency/severity/clinical importance, novelty),
- by combination of both (as at the EMA),
- on a periodic basis.

Signal detection: example of statistical output from EV

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	0.86	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	3.18	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	0.36	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	2.36	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	193	3.74	4.30	4.93	0	0	0	0

Reference period: 01SEP2010 - 14SEP2010

Signal Management steps (2)

Signal validation

• Clinical relevance incl. strength of evidence (e.g. number of reports, temporal association, plausible mechanism, de/rechallenge, confounders), severity, novelty, possible drug-drug interactions, special populations in which the reaction occurs

• Previous awareness (whether already included in SmPC or assessed in the PSUR, RMP, discussed by scientific committee – in principle only new information is a signal unless reports of known risk but suggestive of higher severity, frequency, persistence…)

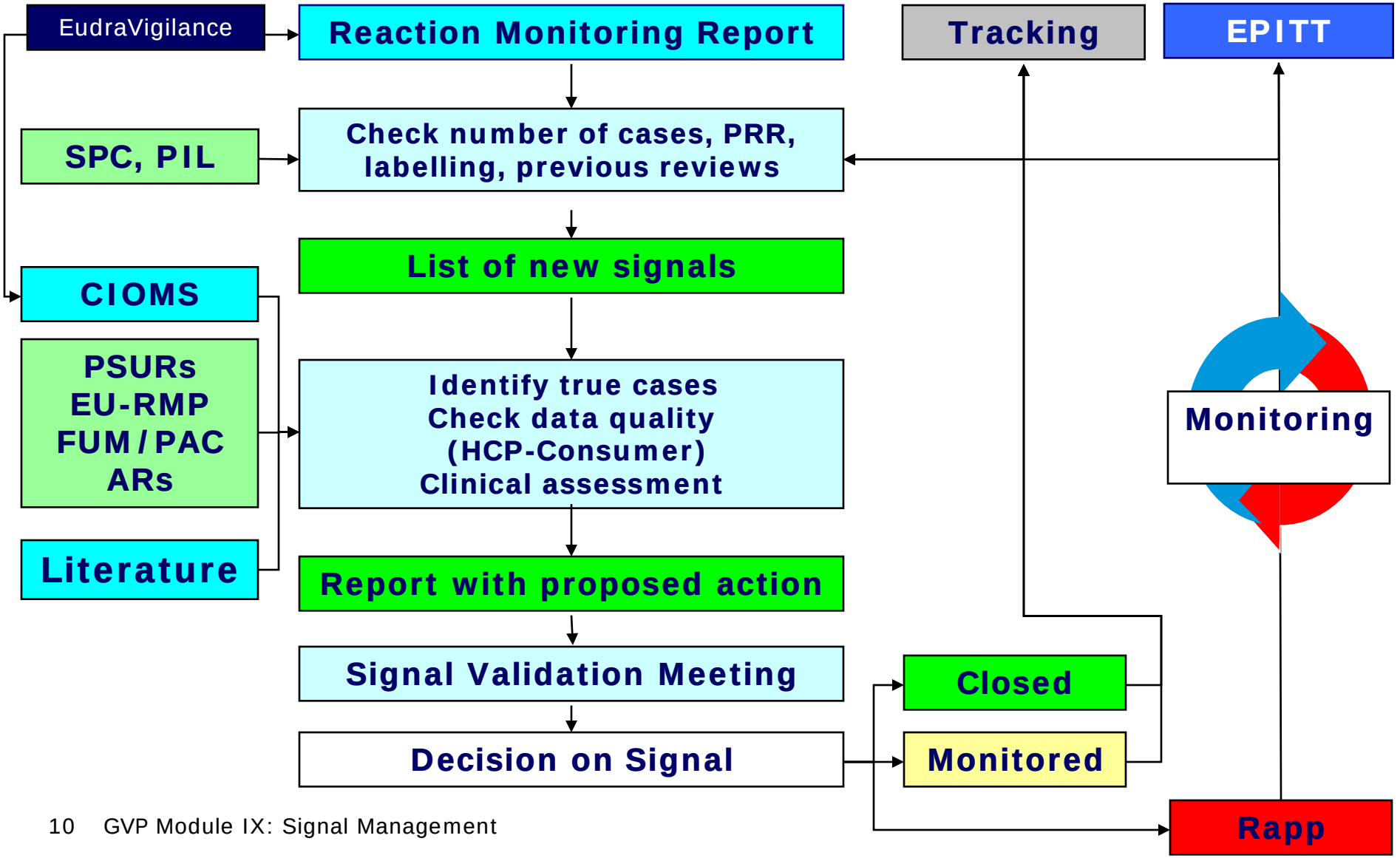
• Other relevant sources of information (e.g. literature/experimental findings, comparing with larger data sets - national vs. EV data)

Signal Management steps (3)

Signal validation

A signal becomes validated, if the verificatory process of all relevant documentation is suggestive of a new causal association, or a new aspect of known association, and therefore justifies further assessment.

Signal detection and validation at the EMA



Signal Management steps (4)

Prioritisation, analysis and assessment:

- Impact on patients (a.o. severity, reversibility, consequences of treatment…)
- Important public health impact
- Effect on benefit-risk balance
- Pharmacological, medical and epidemiological assessment
- Strengths and limitations of data used for signal generation, need for additional data
- Use of internationally agreed definitions of the concern
- Therapeutic or system organ class (higher MedDRA level or other products in class)

Signal Management steps (5)

Recommendation for action by competent authorities may include for example:

- Additional information to be provided *ad hoc* or included in routine PSUR monitoring
- Risk minimisation activities
- If conclusion based on limited evidence – a need to conduct post-authorisation safety study

Signal Management steps (6)

Exchange of information (competent authorities-MAHs-other parties)

- Share data on signals
- Collect additional data
- Further evaluate
- Facilitate decision taking

Signal Management steps (7)

Signal management steps	EMA, NCAs incl. lead/co-lead MSs	MAHs	PRAC	CHMP/ CMDh	EC/ NCA
Detection	X	X	-	-	-
Validation,* confirmation	X	X	-	-	-
Prioritization, analysis, assessment	-	-	X	-	-
Decision making	-	-	Recommendation**	Opinion/ Position	Decision
Regulatory action	-	X	-	-	X

* Validated signals to be tracked in EPITT (European Pharmacovigilance Issues Tracking Tool = access for regulators), ** EMA shall communicate conclusions of signal assessment to the concerned MAHs

Work sharing of data monitoring in EV (EMA, NCAs)

- EMA will publish a list of substances authorised in the EU with the authority responsible for EV data monitoring
- Principle of work sharing:
  - EMA to monitor substances with at least one MP authorised in acc with Reg. (EC) 726/2004 (in collaboration with the PRAC Rapp)
  - Member States may agree to appoint a lead Member State for substances authorised in acc with Dir. 2001/83/EC (the lead MS) and may appoint a co-lead
    - For the appointment of lead/co-lead MS consideration should be given whether the MS is responsible for the PSUR assessment or is acting as a reference MS.

Periodicity of data monitoring in EV (EMA, NCAs)

- EV baseline monitoring (generating and reviewing statistical outputs) = once monthly

- A 2 week frequency for MPs subject to additional monitoring (GVP Module X to be published in second wave) or other MPs with need for additional information

- More frequent than above only in specific situations (e.g. pandemics, targeted safety issue) by means of dedicated EVDAS* queries

* EVDAS EudraVigilance Data Analysis System

MAHs' obligations

Shall monitor:

- all available data for signals incl. emerging data and perform worldwide signal detection activities
- the data in EV to the extent of their accessibility, broader access planned ~ 2015
  - With at least once monthly frequency/proportionate to identified and potential risks or need for additional information

Shall validate signals detected,

MAHs' obligations

Shall forthwith inform EMA or relevant NCA (as per published list) about their validated signals,

Dedicated e-mail to collect validated signals on the side of the EMA or relevant NCA.

Should collaborate with the PRAC for the assessment of the signals by providing additional information upon request.

In general MAHs should have an established signal management process including steps from signal detection to validation and should communicate their validated signals to the responsible authority.

Role of PRAC

- To prioritise validated signals for further assessment,
- To nominate a Rapp for assessment of signals,
- To transmit to the CHMP or CMDh recommendations following signal assessment,
- To perform a regular review of signal management methodology and publish recommendations,
- To review the list of medical events that have to be taken into account for the detection of a signal before their publication by the EMA.

Tracking

- EMA, NCAs shall keep an audit trail of their SM activities/relevant queries and outcomes, incl. outcomes of signal validations,
- All validated signals (and confirmed) shall be entered in EPITT by EMA or NCAs administered by the Agency,
- All subsequent evaluations, timelines, decisions, actions, plans, reporting needs to be tracked in EPITT,
- MAH should keep an audit trail of their SM activities.

Improvements

- Transparent roles and responsibilities,
- Public list of EU substances with a regulator responsible for monitoring of data in EV and confirming validated signals from MAHs,
- Work/signal sharing for all EU substances:
  - Signals sharing in EU through mandatory EPITT population with validated and confirmed signals,
  - PRAC expertise for the assessment of all validated signals related to EU substances irrespective of their authorisation procedure,
- Conclusions of signal assessment in public domain.

Thank you

Questions?

European Medicines Agency

London, 26 June 2008
Doc. Ref. EMEA/106464/2006 rev. 1

EUDRAVIGILANCE EXPERT WORKING GROUP (EV-EWG)

GUIDELINE ON THE USE OF STATISTICAL SIGNAL DETECTION METHODS IN THE EUDRAVIGILANCE DATA ANALYSIS SYSTEM

The Proportional Reporting Ratio (PRR)

Collapsed in a contingency 2 x 2 table as follows:

	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 – measure of disproportionality of reporting which makes the assumption that when a SDR (involving particular AE) is identified for a MP, this AE is reported relatively more frequently in association with this MP than with other MPs

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