EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

GVP Module IX: Signal Management

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4th Stakeholders Forum

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Topics

- **Scope of Module IX**
- **Signal Management (SM) definition and steps**
- **Work sharing for data monitoring in EudraVigilance (EV)***
- **SM steps per stakeholder group**
- **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

Scope of GVP Module IX

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

- 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

  (Section IX.C)

Signal Management (SM) definition and steps

SM is defined as: 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.

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

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

- EMA will publish a list of substances (~ 3,000) 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 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.

SM steps per stakeholder group

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

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 on its way ~ 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,

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

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
  - This should include outcomes of signal validations,
- All validated signals (and confirmed) shall be entered in EPITT 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

- Transparency and clear roles and responsibilities,
- Public list of all 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.

Further reading

•CIOMS Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010)

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

•EudraVigilance access policy for medicines for human use published on 8 July 2011

http://eudravigilance.ema.europa.eu/human/docs/EV%20Access%20Policy%20for%20human%20use%20doc.pdf

Thank you