EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Signal Management in the EU and future extended access to EudraVigilance for industry

6th Industry Stakeholder Platform Meeting, 18th December 2015

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In this presentation

- **Signal Management in the EU**
- **Update on processes, tools and guidance under development**
- **Extended access to EudraVigilance opportunities and points to consider**
- **Conclusions & Discussion**

Signal Management in the EU

Update on processes, tools and guidance under development

Extended access to EudraVigilance opportunities and points to consider

Conclusions & Discussion

Regulatory background

Updated pharmacovigilance legislation published in 2010 (amending Regulation 726/2004 and Directive 2001/83) established the principles for monitoring the data in the EudraVigilance database and the management of signals

Commission Implementing Regulation 520/2012 clarifies specific roles and responsibilities for monitoring EudraVigilance and establishes the different steps of the signal management process

GVP Module IX – Signal Management incorporates the EU legislative requirements and provides general guidance for the signal management process

Question and answer on signal management intended to provide guidance on practical aspects

Detection → Validation → Confirmation → Analysis and prioritisation → Assessment → Recommendation for action

Safety databases

Scientific literature

Communications

SIGNAL

FDA

PMDA Updates

- Spontaneous reports
- Clinical Trials
- Non-clinical data
- Observational studies
- Pharmaco-epidemiological data

Knowledge of the product
(Product Information, PSURs, RMPs, other procedures)

Potential signals detected

Signal detection and validation in EudraVigilance

CHAPTER III

Minimum requirements for the monitoring of data in the Eudravigilance database

Article 18

General requirements

1. The Agency and national competent authorities shall cooperate in the monitoring of the data available in the Eudravigilance database.

- The EMA takes the lead for monitoring EV, signal detection and validation for CAPs.
- EU National Competent Authorities take the lead for EV monitoring, signal detection & validation for NAPs according to the work sharing list for signal management.
- Signal detection is generally at substance level although product specific signals detection also applies

Signal detection and validation in EudraVigilance

Human regulatory > Pharmacovigilance > Guidance > Pharmacovigilance practices

Article 22

Worksharing for signal management

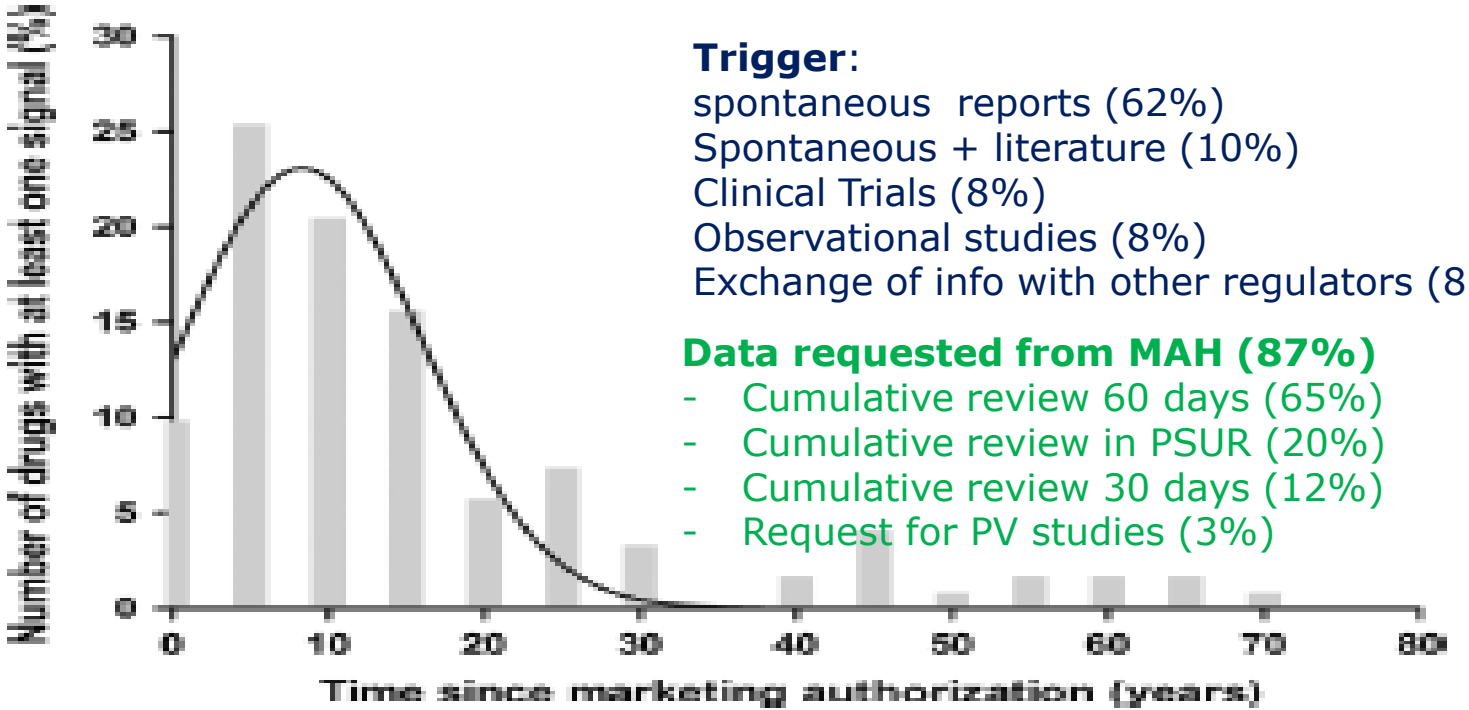
List of substances and products subject to worksharing for signal management

Introduction:

For medicinal products authorised through the national, mutual recognition or decentralised procedures in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation was obtained through the above-mentioned procedures, the legislation foresees that a lead Member State, and where appropriate a co-leader, may be appointed to monitor data in EudraVigilance, and to validate and confirm signals on behalf of the other Member States. The list of active substances with appointed Lead Member States was first published in October 2012 after adoption by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and was updated in May 2014.
The current version, adopted by the CMDh in September 2014, reflects the change of lead Member State for lisdexamphetamine from Denmark to United Kingdom.
The Agency provides appointed Lead Member States with reaction monitoring reports from EudraVigilance for the substances allocated to them. For substances with no Lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised.

Names of active substances or medicinal products	Lead Member State
(18f) fludeoxyglucose	France
5 fluorouracil, salicylic acid	Slovakia
abarelix	United Kingdom
abciximab	United Kingdom
acamprosate	Ireland

Signals during the first 18 months of PRAC during the first 18 months of PRAC

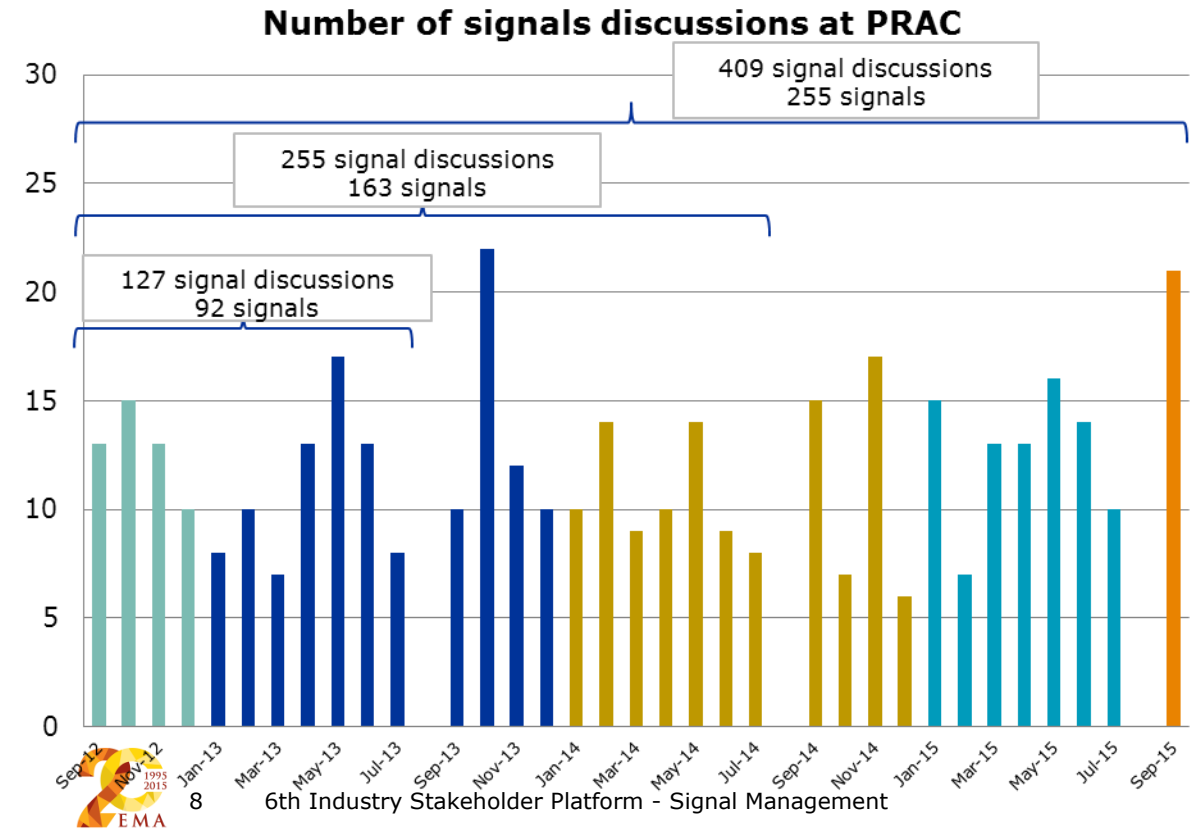


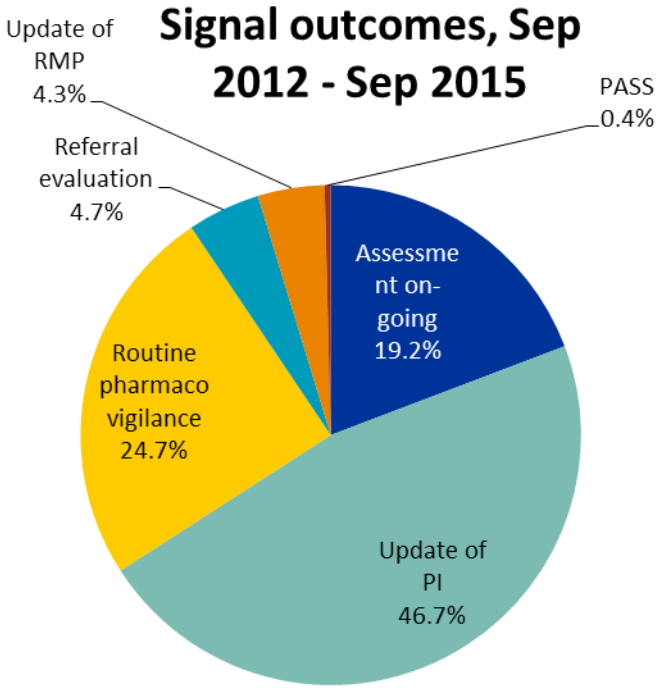
Trigger:
spontaneous reports (62%)
Spontaneous + literature (10%)
Clinical Trials (8%)
Observational studies (8%)
Exchange of info with other regulators (8%)

Data requested from MAH (87%)
- Cumulative review 60 days (65%)
- Cumulative review in PSUR (20%)
- Cumulative review 30 days (12%)
- Request for PV studies (3%)

Pacurariu et al Drug Safety 15 Nov 2014

Safety signals: faster detection and management of new and changing safety issues





EMA communication milestones for signals

Milestones	When	Target		Vehicle	
		General Public	Concerned MAHs	EMA website	Direct communication
Preliminary assessment report	Week before PRAC		✓		✓
Advanced warning to MAHs	Week before PRAC		✓		✓
PRAC agenda published	PRAC week (Monday)	✓	✓	✓	
PRAC highlights published	After PRAC (Friday)	✓		✓	
MAHs notified to submit additional data	After PRAC (Friday)		✓		✓
MAHs notified to submit variation (CAPs)	After CHMP concluded		✓		✓
PRAC recommendations published (including translations of new product information wording)	2 weeks after CHMP	✓	✓	✓	
Minutes published	1 week after following PRAC	✓	✓	✓	

Q&A on signal management – revision 1

- Reflects improvements in SM process since 1st version (published in Oct 2013)
- Highlights:
  - Advanced notification to MAHs of signals to be discussed by PRAC
  - Publication of translations of PRAC recommendations for PI updates
  - Submission requirements for cumulative reviews
    - CAPs: EMA only
    - NAPs: EMA and all PRAC members
  - Concurrent submission of variations for both innovator and generic products
  - Updated contact points within EMA
- Planned publication: Dec 2015

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Evidence based process improvements: investment in regulatory science

- *Current methodology adequate – no major changes required*
- *Opportunities for refinement and efficiency gains*

PROTECT

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Pharmacoepidemiological Research on Outcomes of The

Selection of 20 outputs among 101 PROTECT deliverables	
Recommendations for pharmacoepidemiology	
Output 1	Inventory on drug utilisation data
Output 2	Comparison of methods to control for confounding
Output 3	Balance measures for propensity score models
Output 4	Comparison of covariate adjustment methods
Output 5	Recommendations for pharmacoepidemiological
Methods for signal detection	
Output 6	Evaluation of disproportionality analysis
Output 7	Adverse Drug Reaction Repository
Output 8	Lessons learnt from a characterisation of databases used for signal detection
Output 9	Grouping of existing adverse drug reaction terminologies
Output 10	Novel groupings for adverse drug reactions
Output 11	Subgrouping and stratification in statistical signal detection
Output 12	Statistical signal detection from clinical trials
Output 13	Statistical signal detection from electronic health records
Benefit risk integration and representation	
Output 14	Methodologies for benefit-risk evaluation
Output 15	Methodologies for graphical representation
Output 16	Final tools for graphical B:R representation
Output 17	Recommendations on methodologies for B-R integration and representation
Output 18	Development of accessible material to patients
Output 19	Repository of training material
Output 20	Enhanced ADDIS software

Scientific Guidance on Signal Detection Publications

1. GVP Addendum (*general principles statistical and clinical principles of routine signal detection*)
2. User manual in signal detection *(tools)*

Planned timeframe

1. Addendum
    1. Draft under development
    2. PRAC endorsement - end Q1 2016
    3. Public Consultation - end Q2 2016
2. User manual
    1. Draft under development
    2. PRAC endorsement end Q2 2016

GVP module IX - revision 1

- Highlights:
  - Guidance on MAH-validated signals:
    - MAH signals from EV and/or other sources to feed into general EU SM process
    - Template for validated signals + central mailbox accessible to EMA and Member States
    - Handling of some signals in PSURs or variations depending on seriousness, evidence and timing
    - 'Emerging safety issues' for urgent safety concerns only
    - Minimum requirements for access to EV case narratives
  - Frequency of EV monitoring (risk-based)
  - Clarifications on definitions and responsibilities throughout process

- Timing:
  - Public consultation on draft agreed by EMA and MSs: Q2 2016
  - Final publication: Q4 2016

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Commission Implementing Regulation, art 18 and 21

Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database.

Strengthen the safety monitoring

Level of access determined by the revision of the EudraVigilance Access policy

Where a marketing authorisation holder detects a new signal when monitoring the Eudravigilance database, it shall validate it and shall forthwith inform the Agency and national competent authorities.

Signals validated by MAHs

Detection → Validation → Confirmation → Analysis and prioritisation → Assessment → Recommendation for action

Opportunities and points to consider

- EMA to ensure appropriate support for monitoring of EudraVigilance data by MAHs
- Data outputs and statistical reports (electronic Reaction Monitoring Reports) to be provided to MAH have been used extensively by EMA and EU network (as of July 2012) continuously improved (including based on PROTECT outcomes)
- Published in October 2015 EudraVigilance Stakeholder Change Management Plan. The plan details the technical changes as well as business process changes in relation to reporting, managing and analysing individual case safety reports (ICSRs) from medicines in clinical use and from clinical trials.
- The revised EudraVigilance Access Policy is being finalised and will be considered by EMA Management Board in December 2015.
- User manuals and training plan under preparation

Guiding principles

- Engage with industry to ensure legislative requirements of continuous monitoring of EudraVigilance data by EMA, NCA and MAHs are implemented in complementary and risk proportionate manner
- Frequency of EudraVigilance monitoring should be risk proportionate (time since authorisation, products under additional monitoring, exposure…)
- Prioritise urgent and important issues
- Consider work-sharing and possibility for MAH to delegate through written agreement

Potential approach to communication of validated signals to EMA/NCAs

- Direct variation (if evidence sufficient to update the product information)
- Through PSURs:
  - PSUR under preparation at the time of validation
  - Validated signal does not suggest important risk
- EU signal management Process (i.e. MS confirmation, PRAC evaluation…):
  - Not enough evidence to update PI, no PSUR…
- Exception: emerging safety issues (i.e. requiring immediate attention)

Opportunities and points to consider

- In Mid 2017 Marketing Authorisation Holders will have access to all the post authorisation safety reports contained in the EudraVigilance database.
- For some products this will bring with it a substantial increase in the numbers of reports available.
- For almost all MAHs it will also mean that the products can be viewed against a different background distribution of adverse events.
- Positive effect that access to EudraVigilance data can have on signal detection within individual companies will need to be supported with open discussion to build adding value streamlined processes and provision of appropriate guidance and training.

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Conclusions and discussion

- The current EU Signal Management process is fully implemented and delivering for EU public health
- Extended EudraVigilance access offers opportunities to further strengthen safety monitoring
- Continuous improvement of processes tools and science (including regulatory science results such as PROTECT)
- Guidance, user guides and training pan under development
- Collaboration between regulators and industry is crucial to support building complementary and risk proportionate approach

Discussion

Few questions to start the discussion:

- Views on use of EudraVigilance (EV) data and tools to strengthen safety monitoring and complement methodologies currently used in companies databases
- Experience with using other regulator's data (e.g. AERS)
- Suggestions and points to consider for EV data use depending on type of company (large/medium/small, innovator/generics)
- Views on worksharing between companies
- Other views/proposals…

Thank you for your attention

Further information

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