SIGNAL DETECTION AND EUDRAVIGILANCE

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Deputy QPPV
Disclaimer

The views and statements in this presentation are the personal views of the presenter and do not necessarily represent those of Astellas in any way.

I am a physician with experience in Pharmacovigilance, including Signal Detection. However, I am not a Signal Detection expert and I am mathematically/statistically challenged.
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REGULATORY GUIDANCE

EU
Reg 520/2012
GVP Module IX, (2012, 2016 (rev.1), V
(EMA guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system)
Screening for adverse reactions in *EudraVigilance* (Dec 2016)

FDA
FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
*FAERS*

Japan
MAH has to review data in *JADER*

Other guidance
CIOMS III, VIII
ICH E2e
New EU regulations: Eudravigilance

Eudravigilance = Adverse Events Database system of the European Medicines Authority, incl. Signal Detection tools

2012 legislation/guidance:
“MAHs shall monitor the data in EudraVigilance to the extent of their accessibility” (=limited to overviews (Summary Tabulations))
PRAC will confirm, prioritise and assess signals

2016 legislation/guidance update:
“MAHs shall monitor the data in EudraVigilance to the extent of their accessibility”
+ MAH access to Eudravigilance (Signal Detection reports, download relevant ADR reports)
(Non)Validate detected signals and inform authorities within 30 days per Q4 2017
PRAC will confirm, prioritise and assess signals

Guideline on Good Pharmacovigilance Practices Module IX (2012)
draft Guideline on Good Pharmacovigilance Practices Module IX revision 1 (2016)
European Medicines Agency Policy on Access to EudraVigilance data for Medicinal Products for Human Use Regulation 520/2012
Requirement details

MAH (and EMA and Member States) should:
•  Detect signal
•  Validate (evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal)
•  Send validated signal to EMA exc. if within 30 days (from validation)
  - label change is required at validation ‘variation’
  - PSUR is due within 3 months
  - signal = Emerging Safety Issue

EMA/PRAC will:
•  Confirm (within 30 days from receipt)
•  Prioritise
•  Assess (evaluate) (on case-by-case basis, typically within 60 days)
Non-validation Variation (→EMA)

ESI (→@ema.europa.eu)

Further analysis in PSUR
Astellas Signal detection and Management

<table>
<thead>
<tr>
<th>Detection</th>
<th>Validation</th>
<th>-</th>
<th>Analysis and Prioritization</th>
<th>Evaluation</th>
<th>Risk Mngmt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max. 4 weeks</td>
<td>Max. 14 weeks</td>
<td>Max. 8 weeks</td>
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Eudravigilance Signal detection and Management

<table>
<thead>
<tr>
<th>Detection</th>
<th>Validation</th>
<th>Confirmation</th>
<th>Analysis and prioritisation</th>
<th>Assessment</th>
<th>Recommendation for action</th>
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<tbody>
<tr>
<td>30days</td>
<td></td>
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Standard timetable for the assessment of additional data from MAHs for signals

<table>
<thead>
<tr>
<th>Day</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Start of procedure</td>
</tr>
<tr>
<td>Day 30</td>
<td>Preliminary PRAC Rapporteur AR</td>
</tr>
<tr>
<td>Day 45</td>
<td>Comments from PRAC members</td>
</tr>
<tr>
<td>Day 50</td>
<td>Updated PRAC Rapporteur AR</td>
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<tr>
<td>Day 60</td>
<td>Adoption of PRAC recommendation</td>
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(draft) Module IX rev.1
EMA information day 7 Dec 2015
## Options for MAHs

<table>
<thead>
<tr>
<th>Options</th>
<th>Details</th>
<th>Advantages- disadvantages</th>
</tr>
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</table>
| 1       | Incorporate Eudravigilance into current structures and processes | **Pro:** Simple  
**Con:** Current timelines not meeting requirements  
Resources? |
| 2       | Alternative cross-functional group | **Pro:** Experience concentrated in one group  
**Con:** Accountability  
Resources? |
| 3       | Outsource the EV activity to CRO | **Pro:** Simple  
**Con:** Cost  
Lack of knowledge of company’s products and processes  
Accountability |
| ....?   | | |

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draft GVP Module IX rev.1 – finalisation due Q1 2017

- Many comments (incl. Astellas’ ) – “feedback appreciated”
- EMA/PRAC flooded by signals from MAHs? - “Business as usual”
- If Signals leads (directly) to variation, “PRAC does not need to know”
  Julie Durand (EMA) (EMA - author Module IX rev. 1)
- “Validated signals that will be refuted do not need to be submitted”
- Validation* includes ‘preliminary evaluation’
  - “It took EMA two years to understand that some NCAs interpreted validation to include ‘preliminary evaluation’”
- Inspection findings because of MAH invalidating signals?
  - “PRAC has a liaison with EMA inspectorate”
  Sabine Straus (EMA - CBG-MEB)

*Validation: The process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal [IR Art 21(1)]. This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association. (draft GVP Module IX rev.1)
EMA advise to MAH:

Eudravigilance (EV) Users will have to be trained (certified*)
- advise EMA: latest from March 2017
- Several Signal Detection Training Modules available (slides/webinar)
- All training modules (incl. face-to-face meetings) in 2017

EV Users can be requested (by QPPV) per June 2017
- Number unknown yet

Audit result (awaited)
Test version Eudravigilance incl. Signal Detection tools per June 2017

Final release Eudravigilance per November 2017
- Start date new requirements

Rodrigo Postigo, Cosimo Zaccaria, Irina Caplanusi (EMA)
My impressions:

- Author Module IX rev.1 taking a theoretical approach (practical implications?)
- EMA considers PRAC’s 5 years experience sufficient to have covered all eventualities, also for MAHs
- EMA underestimates the independent (…) interpretations by e.g. Inspectorate

Module IX rev.1 to be published in Q1 2017: 28 days to go....

PM: EMA Information day on Signal Management – 27 Oct 2017 (London)
Quantitative vs. Qualitative Signal detection
A Signal Detection system – current practices

**Qualitative**
- Single case review
- Line Listing review (periodically)

**Quantitative**
- Various statistical methods to find Signal of Disproportionate Reporting (SDR)
  - frequentist
  - Bayesian
  - In ‘own’ proprietary database
  - In large non-company databases
  - FAERS, Vigibase
  - Health Claims/Insurance Database

**Resources**
- Single (product responsible) person(s)
- Dedicated group
- Supportive (system, procedures)
- Executing
A Signal Detection system – current practices

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Companies</th>
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<tr>
<td>Single case review</td>
<td>1</td>
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<tr>
<td>Line Listing review (periodically)</td>
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<table>
<thead>
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<th>Quantitative</th>
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<tbody>
<tr>
<td>SDR</td>
<td>3</td>
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<tr>
<td>frequentist</td>
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<td>Bayesian</td>
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<td>single (product responsible) person(s)</td>
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<tr>
<td>Dedicated group</td>
<td>2</td>
</tr>
<tr>
<td>Supportive (system, procedures)</td>
<td>3</td>
</tr>
<tr>
<td>Executing</td>
<td>4</td>
</tr>
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A Signal Detection system – current practices

Qualitative
• Single case review
• Line Listing review (periodically)

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  • frequentist
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  • In ‘own’ proprietary database
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Issues
• Outsourcing, documentation
• paper vs. electronic, documentation

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Issues
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• PRR, ROR
• EBGM, IC
Methods quantitative SD

Frequentist
PRR = Proportional Reporting Rate, Reporting Odds Ration (ROR)
• Sensitive (finds ‘enough’ signals, incl. ‘false positives’)
• Specific?
• High scores at low numbers of reports
• Increased reliability with combination with chi-sq.

Bayesian
EBGM, IC
• EBGM most ‘conservative’ (i.e. finding least nr. of signals, incl. least false positives)

SDRs should be processed similar to other signals, in context
A Signal Detection system – current practices

Qualitative
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- PRR, ROR
- EBGM, IC
- cloaking
- duplicates, delay
- bias
A Signal Detection system – current practices

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• Outsourcing
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• PRR, ROR
• EBGM, IC

• cloaking
• duplicates, delay
• bias

• Attention, timing
• Expensive
• Academic
• Contact product specialists
Quantitative vs. Qualitative Signal detection - Results

Quantitative
• Unexpected results
• Evaluation unknown territory
• Comparable
• Simple

Qualitative
• Largely known results
• Validation-Analysis-Evaluation
• Subjective
• Requires expert knowledge

Complementary

EMA: Eudravigilance

ROR
IME
individ. remarks
New initiatives

In signal detection
‘New’ initiatives

**Social media**
- Twitter, Facebook, dedicated sites/communities
- Example: MedWatcher Social™:
  - mixed algorithm and human system
  - 6 weeks: 28,000 reports of drugs and events – 47 “proto-AEs”
  - “Proto-AEs” show large overlap with clin. Trial AEs
- Difference: Clin. Trials: more specific (e.g. lab data) AEs
- Proto-AEs: more “nuisance AEs

**Web RADR**
- Twitter
  - Big data, low number of (proto)AEs
  - No additional value to traditional data (spontaneous reports)
- AE Reporting app (UK, NL, Croatia)
  - Easy way to report
  - New reporters (no age difference to ‘traditional’ reporters!)
New initiatives

Electronic Health Records (EHR, RWI)

- Big data
- Population based
- Potential bias (insurance)
- Source for signals or for studies
- Astellas: pilot (US) – comparison to ‘traditional Signal Detection’, ongoing
New initiatives

Eudravigilance access for MAHs

• Access to Big Data (EV 6.5 million cases; FAERS 9 million, VigiBase 8 million)
• Quantitative Signal Detection
  • Small companies, CROs
  • Diverse range of products (less risk of cloaking)
• Qualitative Signal Detection
  • PRAC assessors (subjective)
New initiatives
In signal detection

• Potentially, additional tools
• No ‘new tool to replace the old ones’
Language and definitions EU

Companies have processes, documented in procedures with fixed terminology (validation defined, prioritization detailed categories, Signal Evaluation Report) and they comply with regulatory requirements.

PRAC assessors use all kind of terms, different terms for the same purpose, the same term for different purposes – INCONSISTENTLY:

‘Cumulative review/analysis’:
- A list of all terms with numbers and a few lines of text
- A full list of cases (line listing) and evaluation text – request: all narratives

‘Validation’ to verify that the available documentation contains sufficient evidence to justify further analysis of the signal’ [IR Art 21(1)]. OR
‘Preliminary evaluation’ (EMA info Day)

*Validation*: The process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify further analysis of the signal [IR Art 21(1)]. This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association. (draft GVP Module IX rev.1)
Astellas Signal detection and Management

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Confusion

- AR: "This signal should be considered as ongoing" (after evaluations was completed) violates MAH procedure and Module VII requirements
- MAH evaluation based on global data
- PRAC rapporteur EU data (or ‘intuition’)

- Are requests for ‘cumulative evaluation’ signals?
  - Some questions are based on issues with competitor products (with different MoA)

- Appendix 4 of PSUR (tabular summary of safety signals) compliant with Module VII, criticized by PRAC PSUR Assessor for not including “numbers of reports, numbers of serious reports”, while quoting GVP Module VII (wrongly)
Global implications

Should Eudravigilance replace Vigibase for MAH?

While there is a push for big data and consolidation of efforts, there seems to be a parallel move towards national/regional requirements that do not always serve a global purpose

Globalising: PBRER
Back to region: JADER, Eudravigilance

‘Required’ frequency of monitoring Eudravigilance (“The Agency will …”)
• Every 2 weeks – 6 month
  • Duplicative efforts
  • Products with low number of reports – every 6 months: same results
  • Productive? Efficient?

Cross-regional acceptance?
• Global data contradicting Eudravigilance results…?
CONCLUSIONS, FOR NOW

Eudravigilance looks like a good system, technically
• Clear reports
• Level playing field
• Nr of MAHs accessing the system – capacity?
  • Over 800 MAHs submitted reports to Eudravigilance

Weak spot may be the people working with the system (PRAC, MAHs)

We will know more….in 3/8 months time
Thank you
Back-up
## Experience Eudravigilance signal management (PRAC)

<table>
<thead>
<tr>
<th></th>
<th>Number of signals</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signals detected by EMA 2011- 2015:</td>
<td>10650</td>
<td></td>
</tr>
<tr>
<td>Signals detected in 2015</td>
<td>2372</td>
<td>88% from Eudravigilance</td>
</tr>
<tr>
<td>Signals prioritized 2015</td>
<td>102</td>
<td><strong>End of 2015:</strong> 30% SmPC update 1 further evaluation/referral 5 other action (e.g. RMP update) 30% still under review 25% no action</td>
</tr>
<tr>
<td>Signals evaluated by PRAC since Sep 2012</td>
<td>556</td>
<td></td>
</tr>
<tr>
<td>Signals evaluated by PRAC - Astellas products</td>
<td>11</td>
<td></td>
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