EMA Statistical Signal Detection in practice

PROTECT symposium 18 February 2015

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Signal Management
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Presentation contents

- Signal management (EMA perspective)
- Legal requirements
- eRMR
- Priorities
The EU signal management process at a glance...

Detection

Validation

Confirmation

Analysis & prioritisation

Assessment

Recommendation for action

PRAC Rapp, Lead MS

PRAC

30 days

30/60 days

EMM, MSs, MAHs
Signal Management

Statistical approach: SDRs/PRR

Clinical approach:
- Temporal association
- Biological plausibility
- De-Rechallenge

Disproportional Analysis

\[
\text{PRR} = \frac{a(a+b)}{c(c+d)}
\]

Signal Detection

Signal Validation

Causality assess:
- Very likely/certain
- Probable/possible
- Unlikely
- Unrelated
- Unassessable...
Sources of information

- Clinical trials
- Scientific literature
- Spontaneous ADR reporting systems
- Non-interventional studies
- PE studies

91% Literature
5% Other RAs
3% Other
LEGAL BACKGROUND

COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012
of 19 June 2012


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.
Why an electronic tool for Signal detection?

- More products authorised
  ~800 CAPs
  ~4500 ICSRs per day

- Several Sources of information
  (SmPC, RMP, PSUR, EPITT etc.)

**eRMR = electronic Reaction Report**

**Monitoring**
- MedDra Built-in dictionary
- Historical of ADRs
- Reminder for SDR

**Tracking**
- Signal Status
- Comment field
## eRMR structure

### Use of agreed terminology

<table>
<thead>
<tr>
<th>Active substances</th>
<th>eRMR structure</th>
<th>Legal Requir</th>
<th>Priorities</th>
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<tbody>
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<td>Blood</td>
<td>Haematologic Disorders</td>
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<td>Agranulocytosis, Haematopoietic Cytopenias</td>
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<td>Anaemias nonhaemolytic and marrow depression</td>
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<td>Noninfectious Myocarditis</td>
<td>Ventricular Hypertrophy</td>
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</table>

**Notations:**
- **SOCs**: System Organ Classes
- **HLGTs**: High-Level Generic Terms
- **HLTs**: High-Level Terms
- **SMQs (narrow)**: Specific Medicinal Qualities, Narrow
- **PTs**: Preferred Terms

**Legend:**
- **C** = Blood
- **D** = Card

**Table:**

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<th>D</th>
<th>E</th>
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## eRMR structure

### EV data and different categories

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<th>Tot Geriat</th>
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<th>Tot EEA</th>
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<th>Tot HCP</th>
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<th>Tot Spontaneous</th>
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</table>
Criteria for prioritisation in Screening the eRMR:

Use of statistical and clinical principles

Pr1 = Designated Medical Events

Pr2 = Important Medical Events with a Signal Of Disproportionate Reporting

Pr3 = Important and non Important Medical Events with a Fatal outcome or Paediatric Cases
**eRMR – Operational Functionalities**

<table>
<thead>
<tr>
<th>PTs</th>
<th>IME / DME</th>
<th>Priority</th>
<th>Changes</th>
<th>SDR</th>
<th>Signal Status</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Haemolysis</td>
<td>Dme</td>
<td>Pr1</td>
<td>Increased</td>
<td>Sdr (27)</td>
<td>Listed</td>
<td>SPC 4.8</td>
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<td>Retinopathy Haemorrhagic</td>
<td>Ime</td>
<td>Pr 2</td>
<td>Increased</td>
<td>Sdr (3)</td>
<td>Disease</td>
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<td>Palpitations</td>
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<td>Pr 2</td>
<td>Increased</td>
<td>Sdr (27)</td>
<td>Ongoing</td>
<td>Review of the cases</td>
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<td>Increased</td>
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<td>Ime/ Dme</td>
<td>Pr1</td>
<td>Increased</td>
<td>Sdr (27)</td>
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**Monitoring**

**Tracking**
Assigning the Signal Status

<table>
<thead>
<tr>
<th>PTs</th>
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<th>Comments</th>
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<td>Closed</td>
<td>6 cases, 2 valid not related to CAPs and in the context of TEN</td>
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<tr>
<td>Corneal Disorder</td>
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<td>Closed</td>
<td>18/10/2011. 5 unique cases in eudravigilance, all cases occurred with dexamethasone intravitreal injection in the</td>
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<td>Identified risk. Proposed to be included in 4.4 - 4.8</td>
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<td>Ocular Hypertension</td>
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</table>

Signal Status:
- Listed
- Linked
- Check
- Closed
- Monitor
- PSUR
- RMP
- Disease

- SmPC 4.8/4.4
- Synonymous or more severe medical concept
- Review cases
- Cases reviewed
- PT under monitoring
- Rapporteur’s conclusion
- Potential/Identified Risk
- Indication/Symptoms
Message to take home

1 - Read EV data
   eRMR

2 - Prioritise ICSRs
   priority column (DME, SDR, fatal etc.)

3 - Differentiate ICSRs
   assigning signal status

4 - Assess EV data
   check previous awareness (PSUR, RMP), review cases, review literature
RMP

PSUR

Indication

SmPC

e-RMR GOAL

Literature
Thank You