Signal Detection and Signal Management
An Introduction

Katharina Hartmann, PharmD
Signal – WHO (1992)

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. (*WHO defined 3 similar reports*)
Definition:

Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or a set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.
Signal management
Principles

• Proactive collection of information about vaccines to understand balance of benefit and risk to protect public health
• Fundamental part of routine pharmacovigilance
• Decisions and communication must be appropriately prompt and take into account public health impact
• Effective monitoring of process
• Documentation of decision making and communication
Signal Management
Principles for Industry

Signal management process goals:

1. Early detection of safety signals
2. Validate and evaluate any safety signals
3. Communicate safety issues appropriately
4. Manage new safety risks in a timely manner
5. Ensure effective tracking of actions in response to a new safety signal
6. Continually monitor the safety profile throughout the product lifecycle
GVP Module IX Rev 1 2017 / Addendum 1
Signal management

Guideline on good pharmacovigilance practices (GVP)
Module IX – Signal management (Rev 1)

Date of coming into effect of first version | 2 July 2012
Draft Revision 1+ finalised by the Agency in collaboration with Member States | 30 June 2016
Draft Revision 1 agreed by the European Risk Management Facilitation Group (ERMS FG) | 18 July 2016
Draft Revision 1 adopted by Executive Director | 4 August 2016
Release for public consultation | 8 August 2016
End of consultation (deadline for comments) | 14 October 2016
Revised draft Revision 1 finalised by the Agency in collaboration with Member States | 27 September 2017
Revised draft Revision 1 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG) | 4 October 2017
Revised draft Revision 1 adopted by Executive Director as final | 9 October 2017
Date for coming into effect of Revision 1* | 22 November 2017**

Note: This guidance extends and updates some of the information given in the Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System (EMEA/106464/2006 rev. 1) and supersedes the previous advice in the areas addressed by this new guidance.
GVP P I Product-specific considerations: PV for vaccines for prophylaxis against infectious disease

- Module relevant to vaccines used in pre- and post-exposure prophylaxis of infectious diseases.
- Module focuses on vaccine-specific aspects to be respected when designing and implementing PV activities for vaccines.
- Module provides guidance specific for vaccines in relation to PV processes described in the following GVP Modules:
  - Module V: Risk Management System
  - Module VII: Periodic Safety Update Report
  - Module VIII: Post-authorisation Safety Studies
  - Module IX: Signal Management
  - Module XV: Safety Communication
- Module provides guidance on „Batch recall and quarantine“ (legal basis: EMA GMP and GDP compliance)
GVP Module IX – P I: Signal management - Vaccines

• Signal in the field of vaccines may also relate to:
  – Evidence of reduced efficacy or effectiveness
  – Vaccine failures
  – Quality deviation with potential impact on safety, efficacy or effectiveness (e.g., batch related issues).

• Standard case definitions to be used (i.e. Brighton case definitions).

• Single report of serious events only to be processed as a signal in case of a causal association to the vaccine.

• Specificities of signal detection in mass vaccination programmes, incl. observed to expected analyses.

• Special considerations in vaccine signal detection when performing statistical disproportionality analyses.

• Signal validation, as described in the report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance.
Signal Management Process
GVP Module IX

- Signal detection
- Signal validation
- Signal confirmation
- Signal analysis
- Signal prioritization
- Signal assessment
- Recommendations for action
- Exchange of information

Roles and responsibilities of the MAH:
- Continuously monitor the safety of their medicinal products and inform authorities of any changes that might have an impact on MA
- Monitor the data in EudraVigilance
- Keep an audit trail of the signal detection activities
Signal detection /1
Where can we find signals?

- Reports of unexpected and serious AEFI s
- Expected AEFI s with
  - increased frequency
  - greater severity
  - long-term sequelae
  - new risk factors
- Evidence from formal studies
- Change in effectiveness
- Risks are greater than with competitor vaccines
Signal detection /2
Where can we find signals?

• Early / potential signals
  – Pre-clinical data
    • safety surveillance in pre-clinical studies
    • look for anticipated risks
    • expectation for new vaccine

• Single case signals (“striking cases“)
  – single SAEs / SUSARs / SARs from any source
    • Focused medical evaluation

• Multiple statistical signals
  – from case series, PSURs / PBRERs etc.
  – From registries and databases (VAERS, Vigibase, national / company database, etc.

• Information from other sources
  – Scientific literature, authorities, media, internet, claims databases, competitive intelligence, etc.
Qualitative Signal Detection

Case-by-case analysis:

- Early potential signals from pre-clinical studies
- Signals from individual case safety reports (ICSRs), e.g.,
  - the striking case
  - a priori suspect case
  - newly arisen suspicion
- Signals from case series
- Signals from aggregate data sets (e.g., DSURs, CSRs, PSURs / PBRERs, RMPs)
- Signals from other sources, e.g.,
  - literature, health authorities, media, internet, social media, competitors
Qualitative Signal Detection
Limitations

- Data quality often questionable
- Missing and / or inaccurate data
- Underreporting and / or selective reporting
- Causality assessment difficult
- Confounding: disease linked with outcome
- Diagnostic bias
- Channeling: susceptible patients switched to a new drug
- Not suited for the detection of
  - delayed reactions
  - ADRs with high disease background incidence

no denominator - cannot calculate:
  incidence / prevalence
  relative risk
Quantitative Signal Detection
Disproportionality analysis

• “Is what we observe different from what we expect?”
• Identification of statistically prominent reporting associations between pairs of drugs / vaccines and events
  – Screening (data mining) of large databases composed of spontaneous reports for disproportionate associations or dependencies between variables, i.e., drug/event combination compared with a control, i.e., observed / expected probability of occurrence
• Data mining has enhanced signal detection performance and possibly replaced some traditional approaches
• Data mining results are highly situation dependent, e.g.:
  – reporting sources / collection methods,
  – type of medicinal products in the database, medicinal terminology / coding
  – date of creation of database
"Data Mining" for Signal Detection

2 x 2 Contingency Table:

<table>
<thead>
<tr>
<th></th>
<th>Event of interest</th>
<th>All other events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine of interest</td>
<td>A</td>
<td>B</td>
<td>A+B</td>
</tr>
<tr>
<td>All other drugs</td>
<td>C</td>
<td>D</td>
<td>C+D</td>
</tr>
<tr>
<td>Total</td>
<td>A+C</td>
<td>B+D</td>
<td>A+B+C+D</td>
</tr>
</tbody>
</table>

PRRs = $\frac{A}{(A + B)} \div \frac{C}{(C + D)}$

Reporting Ratio RR : $\frac{A}{(A + B)} / \frac{(A+C)}{(A+B+C+D)}$

Reporting Odds Ratio ROR: $(A/C) / (B/D)$
Signal of Disproportionate Reporting SDR

• No gold standard for establishing threshold for “statistical signals”
• SDR applied in queries of EudraVigilance Data Analysis:
  – PRR with 95% CI: lower bound of 95% CI ≥ 1; number of individual cases: ≥ 3
  – PRR displayed with Chi-square statistics: PRR ≥ 2; Χ² ≥ 4
• All SDRs must be evaluated in their clinical context.

GVP Modul IX Signal detection:

“Use of statistical tools may not be appropriate in all situations....”

“The method should be appropriate for the data set; ... the use of complex statistical tools may not be appropriate for smaller data sets....”
Bayesian Statistics / Mathematical Modelling

- Bayesian method:
  - Without including prior knowledge we are over-sensitive to data
    - leads to false signals
  - Uses „probability“ to express subjective belief in a specific outcome
  - Current probability based on
    - prior belief (a priori)
    - data consistently updated on addition of new data

- Mathematical modeling of disproportionality methods using Bayesian methods
  - Empiric Bayesian Screening (EBS):
    - Multi-item Gamma Poisson Shrinker (MGPS): FDA
    - Used by a number of pharmaceutical companies
  - Bayesian Confidence Propagation Neural Network (BCPNN):
    - WHO Uppsala Monitoring Centre (UMC): WHO-ADR Coding
Quantitative Signal Detection Limitations

- Frequentist signal detection methods support the analysis of AEFI reporting rates
- Quantitative methods highly support traditional signal detection methods, but they cannot replace the medical and scientific signal evaluation
- Data mining results generate hypotheses, these must be analyzed within the context of relevant clinical data
- New EU PV legislation requires signal detection - GVP Module IX Signal Management provides Guidance and Requirements on structures
- None of the data mining methods are validated, there is no gold standard.
Signal Detection Systems
Safety databases

- WHO: Vigibase - WHO Bayesian confidence propagation neural network (BCPNN)
- EU: EudraVigilance – within their data warehouse activities PRR
- FDA: VAERS - Screening algorithms, e.g., Multi-Item Gamma Poisson Shrinker (MGPS) program
- National Authority databases
- ....
- Company databases
  - little or no competitor data
  - more cases on specific drugs
  - smaller overall data set size
  - link to sales data and look at reporting rates
  - comparison to background of an international database (with caveats)
Approaches to signal detection
Example from industry

**Quantitative**

- Statistical methods used to identify signals in databases such as VAERS and VigiBase using Empirica Signal (Oracle based software)
- Threshold approach to identify Vaccine-Event combinations to review – cases ≥ 3, EB05 ≥ 2

**Qualitative**

- Other sources of data
- Including company safety database as product profile of database means background is ‘skewed’ and may mask signals
Signal evaluation
Strength of evidence

Signal evaluation strategy:

• Data gathering:
  – Generate case series, literature reviews, clinical and pre-clinical data review
  – Additional sources of information

• Methodology including search strategy (qualitative / quantitative methods)

• Data analysis:
  – SMQSs used
  – Case series analysis (descriptive narratives of the cases)
    • are all relevant facts present
    • other risk factors present
    • Clinical relevance
  – Conclusion regarding signal confirmation
  – Ad hoc report

SNIP criteria:
• Strength of association
• Newness of event
• Clinical importance at event
• Potential for preventive measures
Signal evaluation
Generic process (GVP Module IX)
**Signal Tracking Workflow**

**Example from Industry**

<table>
<thead>
<tr>
<th>DETECTION</th>
<th>TRIAGE</th>
<th>VALIDATION</th>
<th>EVALUATION</th>
<th>FINAL ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply signal detection methods &amp; thresholds to screen for unexpected findings.</td>
<td>SIGNAL TRIAGE: Application of clinical context &amp; medical judgment through medical review to determine whether the Safety Observation merits further verificatory action</td>
<td>A preliminary analysis of the data supporting the unvalidated Safety Signal with the goal of verify that the available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, &amp; therefore to justify further assessment of the signal</td>
<td>An in-depth analysis of a validated Safety Signal, which may entail the collection of additional data &amp; analyses of additional data sources.</td>
<td>The outcome of Signal Evaluation is a final assessment determining whether a signal represents an Adverse Reaction (e.g. the drug is causally associated with the event)</td>
</tr>
</tbody>
</table>

**Diagram**

Enter New Signal into Tracker

- **xx days**

Validation

- No

  - Closed - Not Supported

- **yyy days**

  - Negative
  - Insufficient Information

  - Ongoing Monitor

- Positive

  - Closed: Safety Issue

Final Assessment

- Closed: not Supported Safety Issue
Signal Management process aligned with Empirica Topics

- Process aligned with CIOMS VIII and GVP IX
- Changes regarding recording of non-validated signals

**Signal Management process**

- Collation of data for Signal detection and validation
- Signal detection and prioritisation
- Signal evaluation
- Outcome of evaluation
- Review by SMT
- SMT endorsement
- Rec’nds for action

**Empirica Topic workflow**

- Initial entry of signal
- Evaluation
- Evaluated signal
- SMT endorsement of initial evaluation
- Closed
- Further evaluation ongoing
- Closed

• Process aligned with CIOMS VIII and GVP IX
• Changes regarding recording of non-validated signals
Signal priorities and timelines

High
- Signal with important impact on public health / patient health for very serious events
- Highest level of urgency - immediate attention
- **1 month** – to evaluation & endorsement

Medium
- Potentially important impact on public health
- Medium level of urgency – attention in short term
- **3 months** – to evaluation & endorsement

Low
- Moderate/low impact on public health
- **6 months** – to evaluation & endorsement
Signal evaluation outcome
Communication / Escalation / Recommendation

- Completion of the signal evaluation within defined timeline
- Safety meeting to determine overall outcome
- Determination if identified or potential risk is important (i.e., of public health significance or likely to adversely alter benefit-risk profile)
- Recommendation on potential actions

**Identified risk**
- Vaccine reaction supported by sufficient evidence

**Potential risk**
- Inconclusive / lacking information
- Map to indeterminate signal

**Unsubstantiated risk**
- No risk attributable to vaccine / other etiologies
- Map to refuted signal*

*CIOMS VIII Chapter II.c Definition and taxonomy of drug safety signals
### Signal Detection Toolkit

**Example**

<table>
<thead>
<tr>
<th>Local AEFIs</th>
<th>Reviewed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Frequency</td>
</tr>
<tr>
<td></td>
<td>• Severity</td>
</tr>
<tr>
<td></td>
<td>• Prolonged duration</td>
</tr>
<tr>
<td></td>
<td>• Unusual pattern or trends</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic AEFIs</th>
<th>Reviewed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Frequency</td>
</tr>
<tr>
<td></td>
<td>• Severity</td>
</tr>
<tr>
<td></td>
<td>• Prolonged duration</td>
</tr>
<tr>
<td></td>
<td>• Unusual pattern or trends</td>
</tr>
<tr>
<td></td>
<td>• Events relevant in context of vaccine safety (see list of designated medical events DME)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAEs</th>
<th>Reviewed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Events relevant in context of vaccine safety (see list of DMEs)</td>
</tr>
<tr>
<td></td>
<td>• Risk factors / interactions</td>
</tr>
<tr>
<td></td>
<td>• Biological plausibility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Reviewed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Adverse outcome in mother</td>
</tr>
<tr>
<td></td>
<td>• Adverse outcome in offspring</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Known and potential risks with vaccines</th>
<th>Reviewed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>• Anxiety related responses incl. syncope</td>
</tr>
<tr>
<td></td>
<td>• Evidence of transmission of infectious agents</td>
</tr>
<tr>
<td></td>
<td>• Live attenuated vaccines: symptoms resembling wild-type disease</td>
</tr>
<tr>
<td></td>
<td>• Vaccination errors</td>
</tr>
<tr>
<td></td>
<td>• Vaccination failure (lack of efficacy)</td>
</tr>
<tr>
<td></td>
<td>• Lot-related AEFIs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Designated Medical Events (Brighton case definitions)</th>
<th>Reviewed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Abscess</td>
</tr>
<tr>
<td></td>
<td>• Anaphylaxis</td>
</tr>
<tr>
<td></td>
<td>• Cellulitis at Injection Site</td>
</tr>
<tr>
<td></td>
<td>• Chronic fatigue</td>
</tr>
<tr>
<td></td>
<td>• Convulsion / seizures</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea</td>
</tr>
<tr>
<td></td>
<td>• Encephalitis / Myelitis / ADEM</td>
</tr>
<tr>
<td></td>
<td>• Guillain Barré syndrome/ Fisher syndrome</td>
</tr>
<tr>
<td></td>
<td>• Hypotonic hyporesponsive episodes (HHE)</td>
</tr>
<tr>
<td></td>
<td>• Intussusception</td>
</tr>
<tr>
<td></td>
<td>• Meningitis, aseptic</td>
</tr>
<tr>
<td></td>
<td>• Narcolepsy</td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia / ITP / evidence of bleeding</td>
</tr>
<tr>
<td></td>
<td>• Immune mediated disorders</td>
</tr>
</tbody>
</table>
## Signal detection checklist

### DATA SOURCE(S)

<table>
<thead>
<tr>
<th>Product</th>
<th>Data source</th>
<th>Study ID(s)</th>
<th>Cut-off date</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ AAAA</td>
<td>□ Clinical Trial Database</td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ BBBB</td>
<td>□ Global Safety Database</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Other - please specify</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### ITEMS REVIEWED

<table>
<thead>
<tr>
<th>Safety Observation?</th>
<th>Solicited AEFIs</th>
<th>Unsolicited AEFIs</th>
<th>SAEs</th>
<th>Pregnancies</th>
<th>AESI / DMEs</th>
<th>Other (specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (see below)</td>
<td>□ Yes (see below)</td>
<td>□ No</td>
<td>□ N/A</td>
<td>□ Not reviewed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>□ Yes (see below)</td>
<td>□ No</td>
<td>□ N/A</td>
<td>□ Not reviewed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>□ Yes (see below)</td>
<td>□ No</td>
<td>□ N/A</td>
<td>□ Not reviewed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not reviewed</td>
<td>□ Yes (see below)</td>
<td>□ No</td>
<td>□ N/A</td>
<td>□ Not reviewed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes (see below)</td>
<td>□ No</td>
<td>□ N/A</td>
<td>□ Not reviewed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SAFETY OBSERVATION(S)

**Description:**

### ACTIONS/SIGNATURE

- □ No safety observation (no action required)
- □ Safety Observation: SMT Chair notified
- □ Emergent Safety Issue: Head Vaccine PV notified

---

Date:  
Signature: 