

Signal Detection Methods in Argus and AERS summarized and compared



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Agenda

- Introduction
- Background: Signal Detection
- Background: Signal Analysis
- Common Signal Detection Method
- Signal detection in Oracle AERS 4.6
- Signal detection in Oracle Argus
 - Overview of ARGUS Perceptive
 - Overview of ARGUS Insight
- Signal detection analysis in external tools
- Future Improvements



Introduction

- Demand for improved public health standards
- Regulatory bodies monitor drugs very closely
- Product development and pre-marketing review process - to define a risk-benefit decision for product approval and clear communication
- Post Marketing Surveillance for identification and evaluation of potential AEs information in a timely and efficient manner
- Ensures an accurate and integral safety profile of drugs.
- Pharmaceutical companies conduct **Signal detection** and **analysis**.



Background: Signal Detection

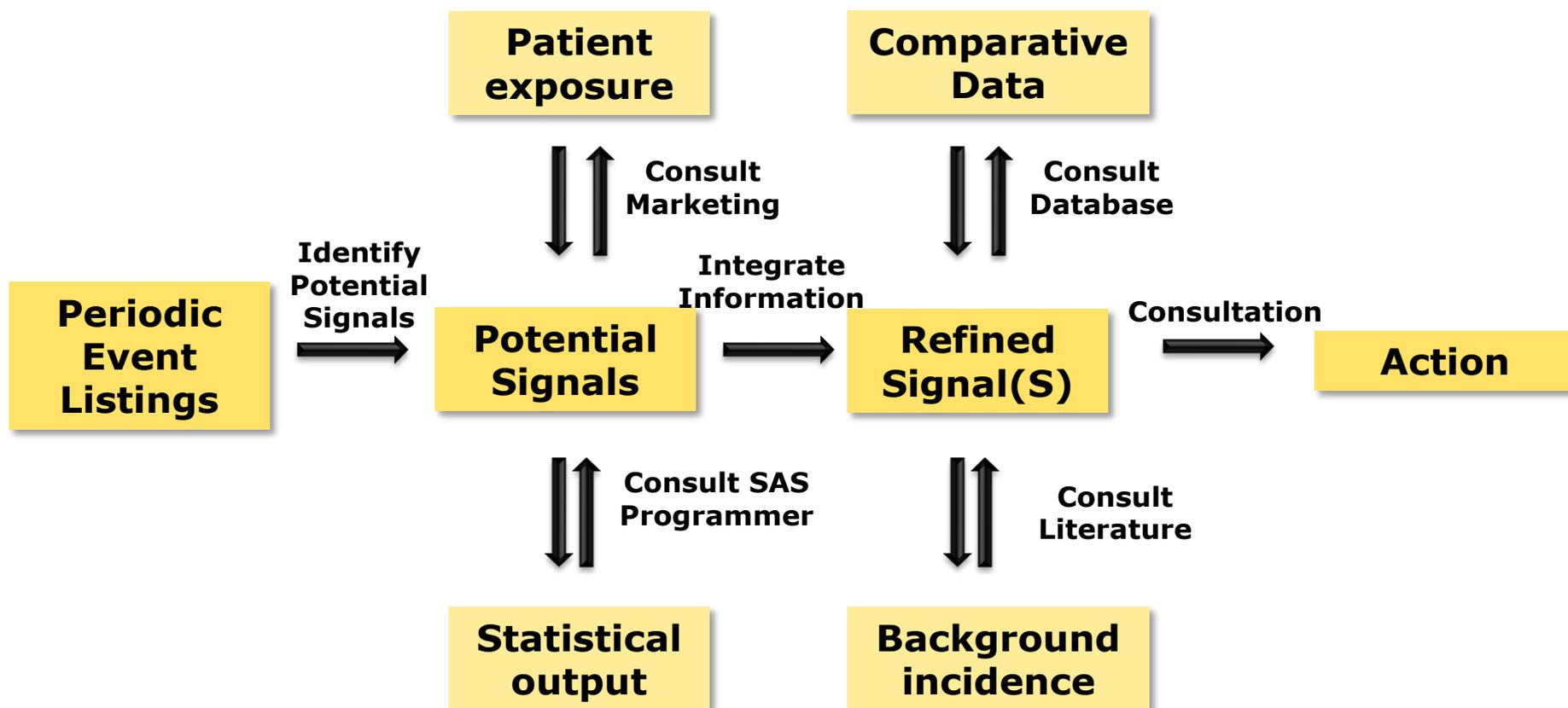
- A process for identifying trends and correlations between Adverse Events with particular drugs compared to what would be expected and compared to that for other similar drugs.

The concept is to monitor AEs which occur coincidentally and those which are actually related to the treatment or medication being provided.

- WHO defines a pharmacovigilance signal as “reported information on a possible causal association between an adverse event and a drug, the relationship being unclear or incompletely documented previously”.

Background: Signal Detection (2)

The typical process flow for Signal detection





Background: Signal Analysis

- To determine whether or not a Signal is valid, a threshold must be defined. This is a mathematical formula to determine whether or not an AE should be counted as part of a Signal.
- Confirmed Signal may require subsequent action as appropriate.
- As Signals are discovered, they must be analyzed to determine whether it represents a potential safety risk. This analysis can include:
 - Causality
 - Frequency
 - Specificity vs. Sensitivity
 - Determination of health consequences (individual outcome and societal costs)



Background: Signal Analysis

- There are many types of statistical models which are used in Signal Detection analysis, but three of the most common are:

Proportional Reporting Ratio [PRR]

- PRR is used by Eudravigilance System

Bayesian Confidence Propagation Neural Network [BCPNN]

- BCPNN is used by the WHO

Multi-item Gamma Poisson Shrinker [MGPS]

- MGPS is used by the FDA

- Due to the number of Adverse Event reports and the volume of the comparison reference data, some analytical method is required. Manual comparison is not feasible.



Common Signal Detection Method in AERS and Argus

■ PRR (Proportional Reporting Ratio)

This is automated detection method which involves the calculation of a very simple disproportionality method

Adverse Event: A [defined by code or groups of codes within MedDRA (Ω_A)]

Treatment: T [defined by code or groups of codes within medicinal products dictionary (Ω_T)]

ICSR : i, so AE on ICSR: A_i and Treatments: T_i

$X(A, T) = |\{i: A \cap A_i \neq \Phi \text{ and } T \cap T_i \neq \Phi\}|$

So, Number of ICSRs containing an element of A and of T

$$PRR(A, T) = [X(A, T)/X(\Omega_A, T)]/[X(A, \Omega_T)/X(\Omega_A, \Omega_T)]^*$$

The ordering of pairs (A, T) based on the PRR values gives a baseline against which to compare other methods of signal detection (i.e. other ordering of (A, T)).



Current State of Signal Detection in AERS 4.6

- AERS 4.6 Built in functionality for Signal detection and reporting
 - Built in Folder Queries Under Pharmacovigilance Folders.
 - Built in reports such as Signal Identification report

- According to AERS 4.6.1 Users Guide, pg 9-4, “the Signal Identification Report is designed to compare safety profiles between date periods to help identify potential changes in a product's safety profile.”
 - Implication that there is not a comparative method against other external data sources.

- According to the AERS 4.6.1 Release Content Document, pg 15, “AERS 4.6 has been integrated with the Druglogic’s Qscan. You are now able to pass a set of cases into Qscan for further analysis and visualization, then identify and review the cases of interest within AERS.”



Possible Integration Strategies for Oracle BI and AERS

- Oracle BI has ability to scale and process large amounts of data through daily processing cycles, called ETLs (Extract Transform-Load)
- The ETL can perform a direct extraction from an Oracle AERS instance, using the same queries which drive the Signal Identification Report
- Additionally, external source data can be loaded from XML files from FDA, WHO or EU
- Mapping the analysis method directly into the Oracle BI (Siebel Analytics) engine can be done for Signal detection analysis
- BI Dashboard can be developed with the actual threshold parameters as well as specificity and sensitivity percentages
- Each analysis can be stored and replayed in scenarios. This makes longer-term signal detection possible with very little efforts.



Signal Detection with Oracle Argus

Oracle Argus Perceptive when integrated with Argus Insight, builds on a comprehensive safety knowledge base can provide a proactive approach to risk management.





Oracle Argus Perceptive

Key Features:

- Dynamic Workflow
 - Flexible enough to fit any risk management business process
 - Assessor's workflow separate from case processing
- Enhanced algorithms- more choice for alerting
 - PRR, Chi square, Case Scoring
 - Work lists
 - Easier differentiation of active/archive & watchlisted alert
- Automated Signal Detection
- Analytical tools for signaling, hypothesis testing & strengthening.

Ref: Presentation of Argus Perceptive by Oracle



Oracle Argus Perceptive

Key Features (Contd.)

- Searchable knowledgebase & repository
- Multiple levels of escalation & notifications
- Management monitoring tools & reports
- Insight Linkage :Passing the event level details to Insight in preparation for more event driven reporting & querying
- Primary / Secondary separation
- Monitored / Ad hoc vs. mined
- Linked alerts
- Support for Signal Workup Document- regulatory reporting

Ref: Presentation of Argus Perceptive by Oracle



Oracle Argus Perceptive

Two Types of Alerts....

- **Primary** alerts based on-
 - Designated Medical Events (DME)
 - Product Important Event (PIE)
 - Always Expeditable Events (EXP)
 - Serious Unlisted Events (SUL)
 - User Defined Alert type
- The Role of Secondary Alerts
 - Directed Research and Hypothesis Generation
 - Data Mining
 - Generate a Case Series to process in Argus Perceptive
 - Generate Output (reports, Charts) for signal workups



Oracle Argus Insight

Key Features:

- Query Capabilities (QBE, Filters, Advance queries, Query libraries)
- Case Series

Reports output:

- Standard Reports
- Report Writer
- Dashboard Indicators
- Cubes

Ref: Presentation of Argus Insight by Oracle



Signal Detection: SAS with AERS/Argus

- SAS Signal detection framework can be used as component to generate Safety Signals using data migration from AERS or Argus database to SAS Platform
- This can be further analyzed using the SAS BI Suite.



Signal Detection: SAS with AERS/Argus

- Source Data from AERS, ARGUS, Regulatory can be extracted using SAS ETL.
- Processing data can be further cleaned, organized in the staging area.
- Data will be stored in the Data Warehouse.
- By applying transformation rules incremental data from data warehouse can be populated in customized outbound area.
- Signal definition criteria (defined threshold) can be applied



Signal Detection: SAS with AERS/Argus

Contd ..

- Signal can be detected on basis of Signal criteria defined by users
- Analysis of signals generated by system can be done in form of report output, trend charts etc.

Ref: Published paper AD06



Future Suggestions

- AERS:

Direct integration between AERS and Oracle BI is possible if a pre-loaded ETL is made available. This is relatively straightforward since both the analysis methods and the current reporting queries are known.



Disclaimer

- Information disseminated in this presentation should in no way be construed as a recommendation to use or not use any particular software or hardware product and is presented solely for informational purposes.



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Bio:

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Questions?

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Thank you!!