Signal Detection in Pharmacovigilance

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Signal detection

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Signal detection - Objectives & principles

The overall objective of signal detection is to better **protect patients** and public health.

Signal detection and its assessment is the most important aspect of pharmacovigilance

In the EU, the principles of signal detection were initially introduced by the CIOMS VIII group in 2010 (reflected on Vol 9a).

The concepts and approach used used in current legislation (1235/2010 as amended; Directive 2010/84/EU as amended; implementing regulation 520/2012) are based on these principles and are reflected in:

- GVP Module IX – Signal management
- Module XV – Safety communication

Signal detection - Objectives & principles

With the new EU Pharmacovigilance legislation (02-Jul-2012), introduction also of the Pharmacovgilance Risk Assessment Committee (PRAC).

Signal detection is mandatory for all active substances for which there is a marketing autorisation, whether a PSUR is required or not.

Signal detection - Definitions

Signal detection

The act of looking for and/or identifiying signals using the event data from any source (CIOMS)

Signal

Information that arises from one or multiple sources, 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 of beneficial that is judged to be of sufficient likelyhood to justify verificatory actions (CIOMS VIII)

Signal detection - Definitions

Signal (2)

- Usually more than a single report is required to have a valid signal but single case may nevetheless represent a potential signal
- A signal can arise from any source (unsolicited reports, literature, studies including observational database studies, etc).
- Further information/investigation is always needed

Signal detection - Definitions

Signal management (most common definitions)

Signal management is a set of activities to determine (based on any source of data) whether there are new/changed risks associated with an active substance or a medicinal product

Emerging Safety Issue

A safety issue considered by a MAH in relation to an authorised medicinal product under its responsibility to require urgent attention of the competent authority because of the potential major impact on the risk-benefit of the product and/or on patient or public health, that could warrant prompt regulatory action and communication to patients and healthcare professionals.

Signal detection -Role of competent authorities

IN THE EU

Signal detection is performed by EMA for CAP* and by Member states for NAPs*.

Validated signals are entered in a central database

PRAC (Pharmacovigilance Risk Assessment Committee):

- Covers all aspects of risk management related to the use of medicinal products including, detection, assessment, minimisation and communication of risk to industry.

* Central Authorisation Procedure¨** National Autorisation Procedure

Signal detection -Role of competent authorities

- PRAC sends monthly signal notifications to all QPPVs registered in Eudravigilance
- Makes Recommendations for label updates including proposed wording in EU languages
- The minutes of the PRAC meetings are **public**

Signal detection -Role of competent authorities

USA - FDA

- More responsibilities on MAH and routine signal detection and quality of case reports
- FAERS: quarterly reports on potential serious side effects
- Vaccine Adverse Event Reporting System (VAERS) data mining
  - No recommendations to MAH
  - Based on drug-events pairs
  - Expected count of pairs is calculated based on the total number of vaccine reports (for the vaccine of interest) and the total number of adverse events in VAERs (for the event of interest)
  - The observed number of vaccine-adverse event pairs divided by the expected count yields the relative reporting ratio

Signal detection - Role & responsibilities of MAH

- Each MAH must develop an end-to-end process for the signal detection and management
- The process must be described in procedures
- The QPPV must have an oversight of these activities and the resulting actions
- The frequency and rationale for frequency of the signal detection activities should be determined on a risk-based approach
- The process must follow global PV quality requirements
  - Assessment, validation, prioritisation, resulting actions &exchange of information with timelines must be recorded and tracked

Signal detection - Role & responsibilities of MAH

- **Tracking** system should include all potential signals, also those that were concluded not to be valid signals (rationale for the decision)
- All decisions must be clearly **documented** and demonstrate that the system functions properly and effectively
- Staff performing signal detection must be adequately trained and **qualified**

➔ **Importance of quality assurance and quality control**

Signal detection - Role & responsibilities of MAH

- **Qualitative** methods are based on clinical evaluation for a single case or series of cases. Usually used for low case volumes
- **Quantitative** ('automated' or 'data mining') techniques usually used for large volumes and complement the medical review. Use of computational power to analyse the large volume of data. These statistical techniques provide estimates of the extent of how the number of observed cases differs from the number of expected cases. The underlying principle is to explore indicators of disproportionality that may then reveal associations of interest. *Different measures include ranking of incidence rates and risks within time periods, risk and/or rate ratios between time periods, and reasons for treatment withdrawal*. The data may also be compared with the expected frequencies (e.g. from prescribing information), or from external data sources.

Signal detection process - Methods

Statistical techniques:

4 main methods

- Proportional Reporting Ratio (PRR)
- Reporting Odds Ratio (ROR)
- Multi-item Gamma Poisson Shrinker (MGPS)
- Bayesian Confidence Propagation Neural Network (BCPNN)

All methods identify drug-event combinations that are disproportionately present in a database (observed vs expected)

Signal detection process - Methods

Considerations related to performance

Even when only one carefully characterised method of signal detection is used a major challenge is to reliably assess its performance. When a signal detection system is constructed using several different methods then these parameters should ideally be established for each method in competition with the other methods. In addition, if this performance is to be maintained in a working pharmacovigilance system, each method must be carefully standardised so that a set of rules or criteria are consistently applied. This includes not just the statistical methods, which lend themselves to standardisation, but also non-statistical methods.

Signal detection process - Methods

To identify safety signals of adverse events from safety reports, data mining techniques are increasingly used to supplement the traditional expert review of the reports and to rapidly analyze the large volume of accumulated data. These data mining techniques—commonly known as signal detection algorithms (SDAs)—are used to explore pharmacovigilance databases for concealed associations between drugs and reported adverse events that may evade the scrutiny of manual case assessment

Signal detection process - Methods

DPA methodologies use frequency analysis of 2×2 contingency tables (or stratified versions thereof) to quantify the degree to which a drug-event combination co-occurs disproportionally compared to what would be expected if there were no association. By virtue of being multivariate modeling techniques, approaches in this class can account for potential confounding and masking factors during the analysis of drug-event relationships

Signal detection process - Methods

SDAs are designed to compute surrogate measures of statistical association between drug-event pairs reported in a database. These measures are often interpreted as signal scores, with larger values representing stronger associations, which are assumed more likely to represent true ADEs. A signal score threshold is often used to highlight signals worthy of further review. There are two main types of SDAs: those based on disproportionality analysis (DPA), and those based on multivariate modeling techniques such as logistic regression

Signal detection process – key elements

Signal detection is linked to the MAH's global PV processes

- Data collection
  - Consider all sources of safety information
  - Robust collection system
  - Validated safety database or other ICSR recording tool
- Processing of ICSRs
  - Consistent MedDRA coding
  - Importance of drug dictionary (active substance vs proprietary name)
  - Duplicate detection
  - Expertise of processors and reviewers

Signal detection process – key elements

- Aggregate safety reports
- Procedures describing these processes

Signal detection process – key elements

Sources for signals

- Internal sources
  - Pre-Clinical studies
  - Clinical trials (pre and post marketing)
  - Safety database containing all ICSRs from all sources received by MAH
  - Manufacturing alerts/Product quality issues
  - Epidemiological studies
- Other sources
  - Health care databases
  - EudraVigilance, WHO (Vigiflow), FDA VAERS and AERS,…(MHRA, LAREB, Canada, Germany, etc)
  - Social Media
  - Medical and scientific literature

Signal detection process – key elements

- Define periodicity
- Define method
- Validation
- Assessment & priortisation
- Recommendations for actions
- Documentation and communication

Signal detection process – key elements

- **Define periodicity**

The periodicity of the signal detection is related to the business model, i.e the case volume and the methods used for signal detection. Signal detection frequency should also be based on a risk-based approach (well established used products/genericx vs new drugs with higher risk/black triangle, biologics etc)

Signal detection process – key elements

- **Define method**

The method and tools used for signal detection will depend on the business model and mainly the volume of cases by product received by the MAH.

Signal scores or weekly signal case analysis should be computed alongside number of cumulative cases

The need for large database reviews is also determined by the business model and type of product

Signal detection process – key elements

- **Validation of signal**

When a signal has been detected, an evaluation of the information supporting the signal should be performed to verify that the data is strong enough to suggest a new potentially causal association, or a new aspect of a known association, and therefore to justify further assessment of the signal

The assessment should take into account following aspects

- Clinical relevance
- New/unrecognised adverse event (not yet documented in the RSI of the product)

Signal detection process

- Frequency, severity or outcome worse than reflected in the RSI
- Occurrence of AEs known to be extremely rare in the general population
- Drug interactions (previously unrecognised)
- Identification of previously unrecognised at-risk population
- Confusion about a product's name, labeling, packaging or use
- Impact on public health and patients
- Time to onset suggestive for temporal association
- Concentrations of cases with a same lot number

Signal detection process – key elements

- Biological plausibility
- Positive dechallenge and rechallenge
- Circumstances surrounding the onset of the AE
- Clinical and laboratory manifestations and accompanying symptoms
- Quantitative SD detection i.e is there any artefact that could explain a higher incidence like cluster reporting

Signals may need to be assessed at a broader level e.g at the therapeutic or System Organ Class level. The use of SMQs (Standard MedDRA queries) or other MedDRA terms should also be evaluated

Signal detection process – key elements

- **Assessment and prioritisation**

Once a signal has been confirmed, the associated risk is evaluated. The assessment is the scientific evaluation of all the evidence available

Criteria for risk evaluation:

- Impact on patient welfare and public health
- Strenght of signal
- Likelyhood to happen (biological plausibility, causal association)
- Number of patients affected/Exposure
- Is the overall benefit-risk affected?

Signal detection process – key elements

- **Recommendations for actions**
  - Immediate actions (communication to HCPs, product recall, MA withdrawal, urgent safety restrictions, etc)
  - Update of the product information
  - Heightened surveillance/close monitoring
  - Post-Autorisation Measures (e.g PASS)
  - Additional investigations and/or risk minimisation activities (see RMP)
  - Continuous monitoring

Signal detection process

- **Documentation and Communication**
  - Document internally all potential signals with assessment, actions and timelines
  - Signals having a significant impact on the benefit-risk balance of a product should be notified as Emerging Safety Issue (EU requirement)
  - Signals should be discussed in period safety update reports

Signal detection process – key elements

Causality assessment - Relevance

- An inherent problem in pharmacovigilance is that most case reports concern *suspected* adverse drug reactions. Adverse reactions are rarely specific for a drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified.
- Few adverse reactions are 'certain' or 'unlikely' related; most are somewhere in between these extremes, i.e. 'possible' or 'probable'.
- Different systems have been developed for a structured and harmonised assessment of causality.
- Not possible to produce a precise and reliable quantitative estimation of relationship likelihood.

Nevertheless, causality assessment has become common routine procedure in pharmacovigilance

Signal detection process – key elements

Several assessment methods but MAH should select the most suitable method according to its business model

The most common methods are detailed in the presentation ‘Basic elements of a PV System’

Signal management in a nutshell