Module VIII: Signals in Drug Safety

Contents

1. INTRODUCTION

1.1 Definition

WHO Definition of Signal Detection – Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously

According to WHO, signal is defined as:

- Previously unrecognized safety issue
- Change in severity
- Change in frequency
- Identification of at risk group

Council for International Organizations of Medical Sciences (CIOMS) VIII Definition of Signal Detection – 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 invention and an event or set of related events, either adverse or beneficial, that is judged to be sufficient likelihood to justify verificatory action.

New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the adverse reaction. A signal often relates to all medicinal products containing the same active substance, including combination products. Certain signals may only be relevant for a medicinal product or in a specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of medicinal products. **The United States (US) Food and Drug Administration (FDA) Definition GVPV Guidance –** A concern about an excess or adverse events (AE) compared to what would be expected to be associated with a product's use. Signals can arise from post marketing data and other sources, such as pre-clinical data and events associated with other products in the same pharmacological class. It s possible that even a single well-documented case report can be viewed as a signal, particularly if the

report describes a positive challenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation which may or may not need to the conclusion that the product caused the event. After a single is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

Signal management process: A set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

The European Union (EU) signal management process includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritization, signal assessment and recommendation for action.

Signal prioritization: The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay.

Signal Detection: The process of looking for and/or identifying signals using data from any source Signal detection (SD) involves a range of techniques (CIOMS VIII). The WHO defines a safety signal as: "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 event and quality of the information available.

Data mining pharmacovigilance databases is one approach that has become increasingly popular with the availability of extensive data sources and inexpensive computing resources. The data sources (databases) may be owned by a pharmaceutical company, a drug regulatory authority, or a large healthcare provider. Individual Case Safety Reports

(ICSRs) in these databases are retrieved and converted into structured format, and statistical methods (usually a mathematical algorithm) are applied to calculate statistical measures of association. If the statistical measure crosses an arbitrarily set threshold, a signal is declared for a given drug associated with a given adverse event. All signals deemed worthy of investigation, require further analysis using all available data to confirm or refute the signal. If the analysis is inconclusive, additional data may be needed such as a post-marketing observational trial.

Signal detection is an essential part of drug use and safety surveillance. Ideally, the goal of signal detection is to identify ADRs that were previously considered unexpected and to be able to provide guidance in the product's labeling as to how to minimize the risk of using the drug in a given patient population.

2. Safety Signal

There is variation in the use of the term “signal” in pharmacovigilance. One commonly cited definition is from the Council for International Organizations of Medical Sciences (CIOMS), which defines a safety signal as “information that arises from one or multiple sources (including observations or experiments), which suggests a new, potentially causal association, or a new aspect of a known association between an intervention [e.g., administration of a medicine]and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.” An example of a “new aspect of a known association” would be refinement of an existing safety signal by identifying subgroups of individuals who may be at greater risk (see sidebar). Usually more than a single report is required to generate a safety signal, depending on the seriousness of the event and the quality of the information.

Various factors about an adverse event are considered to determine the existence or strength of a safety signal. These include the frequency, nature/type, time to onset and duration, and presence of documented high-quality re-challenge/de-challenge information of the adverse event. Detecting, or generating, safety signals is generally carried out by pharmaceutical companies, regulatory agencies (such as the FDA), or other government agencies such as the World Health Organization (WHO).

2.1 OBJECTIVES OF SIGNAL DETECTION

The first and foremost objective of signal detection is to protect patient’s safety. The other objective is to meet the regulatory requirements. All the relevant data sources should be included e.g. The clinical trials, individual case safety reports (ICSR), periodic safety update reports (PSUR), registries, external databases (FDA WHO). The relationship between the product and the adverse event must be discovered. The risk-benefit ratio of the product must be understood. The last objective of signal detection is that it must lead to communication of the signal to the patients, MAH, Regulators

2.2 TYPES OF SIGNAL DETECTION

Signal detection is of following two types.

1. Clinical (Traditional – astute clinicians)
    a. Individual case review
        i. Unusual events in the target population
        ii. Unusual severity of a specific event
    b. Periodic review of aggregate information
        i. Frequency tables – Plain old counts
        ii. Increased frequency calculation
    c. Case series analysis
2. Data Mining
    a. Statistical methods for disproportionality assessment
    b. Caveat – non-intended for hypothesis testing

Clinical (Traditional – astute clinicians)

There are certain data needs for signaling and risk assessment study. We need complete and accurate data. For that we must know what information must be exactly collected from the CIOMS-VI form to know the accuracy of the data. Study of the patient population to know the natural history, epidemiology, which will help in marketing the product well. Genetic factors to understand the pharmacogenetics is also important. The other environmental influences such as diet, smoking and alcohol need to be studied. Any concurrent illnesses and concomitant drugs or supplements used should be taken into consideration. The benefit risk ratio of existing treatment is also important. The relative and absolute attributable risk must be taken in consideration.

There are certain signaling and risk assessment tools which are used in the traditional method. These includes information from previous studies, preclinical human PK/PD data which talks about the mechanism of action, metabolism, and toxicology. It also includes phase II and III trial, their size, duration, population and limitation. The post approval trials i.e. IIIB/IV also large simple safety studies, database studies and registries are important.

2.3 IDENTIFYING SAFETY SIGNALS: SPONTANEOUS REPORTS

Data contained in spontaneous adverse event reports are collected from patients, health care providers, lawyers, health authorities, the medical literature, and other sources. This information is entered by pharmaceutical companies into their safety databases so that first, serious events meeting certain reporting criteria can be reported to regulators in an expedited manner, and, second, the cumulative adverse event data can be analyzed for potential safety signals. Where a spontaneously reported serious adverse event meets expedited reporting criteria, it must be reported to regulatory agencies within the required expedited timeframe.

In addition to reports forwarded by pharmaceutical companies, the FDA also receives reports via its MedWatch system from health care professionals and consumers. The agency forwards these to the manufacturer of the medicine.

Example of New Information on an Already Identified Safety Signal

1. An oncology drug is associated with a characteristic form of cardiomyopathy (a weakening of the heart muscle sometimes seen with certain types of chemotherapy).
    - This was initially identified based on a small number of spontaneous reports.
2. Ongoing surveillance is initiated to gather more information about the association.
3. The new/additional information obtained through surveillance suggests that the risk for this adverse effect may be especially high in:
    - Pediatric patients.
    - Patients previously treated with radiation to the chest region.
    - Patients receiving a cumulative dose above a certain threshold.

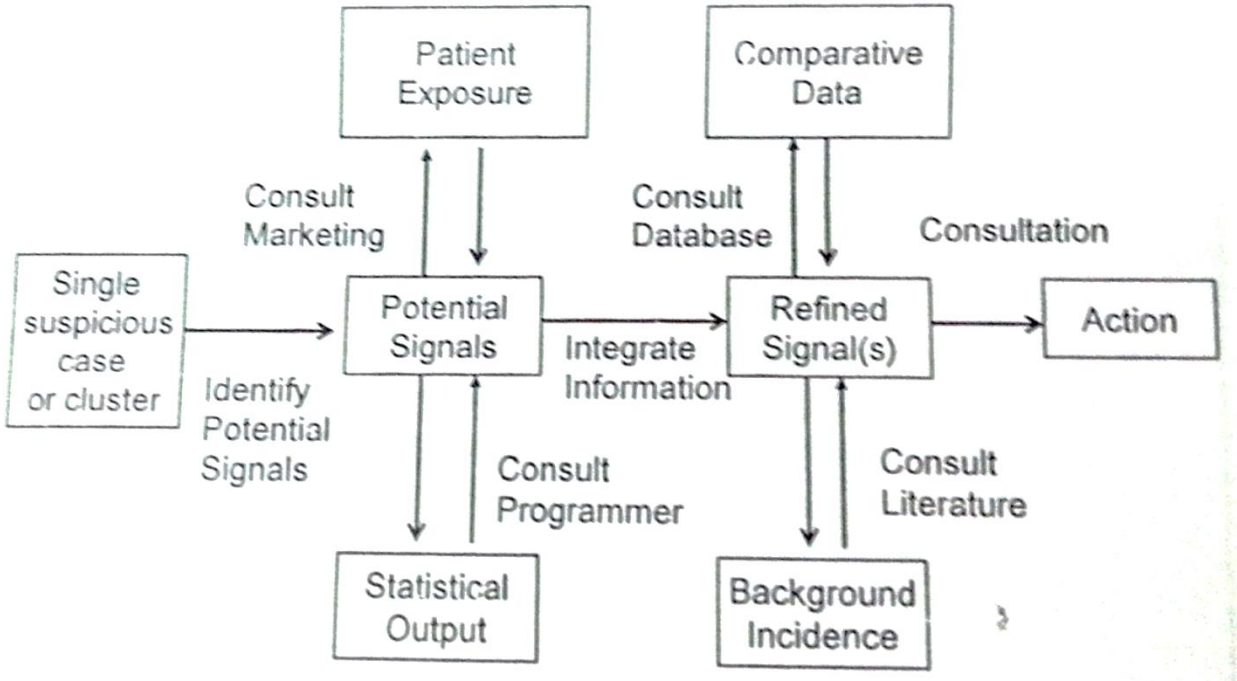
Investigating safety signals

Potential signals identified through qualitative and/or quantitative methods can be evaluated using more reliable data sources such as observational/pharmacoepidemiologic studies, additional randomized clinical studies, or mechanistic studies.

Safety signals that warrant further investigation include, but are not limited to:

- New adverse events, not currently documented in the product label, especially if serious and in rare untreated populations.
- An apparent increase in the severity of an adverse event that is already included in the product label.
- Occurrence of serious adverse events known to be extremely rare in the general population.
- Previously unrecognized interactions with other medicines, dietary supplements, foods, or medical devices.
- Identification of a previously unrecognized at-risk population, such as populations with specific genetic or racial predisposition or coexisting medical conditions.
- Confusion about a product's name, labeling, packaging, or use.
- Concerns arising from the way a product is used (e.g., adverse events seen at doses higher than normally prescribed, or in populations not recommended, in the label).
- Concerns arising from a failure to achieve a risk management goal.

2.4 SIGNAL GENERATION – THE TRADITIONAL METHOD



Data Mining

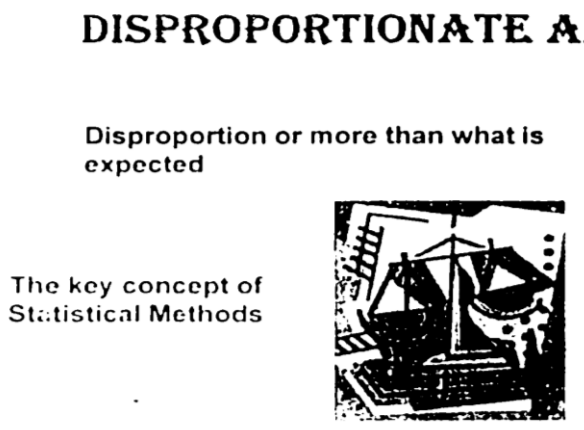
In data mining, we detect rare unpredictable ADRs. We detect interactions that are

A. Drug-Drug based (OTC, Herbal, Traditional, etc...)
B. Drug-Food based (supplements, etc...)
C. Drug-Disease based

We also identify the high-risk patients group. Plain old counts and frequencies are studied. Mathematical upon statistical i.e. 2x2 tables is used. In this, we calculate ratio of event A to all events for Drug 1 vs. ratio of event A to all events for other drugs (All Class). We multiply corrections possible (blank cells event rarity). Tools used are PPR (Proportional Reporting Rate), EBGM (Empirical Bayesian Geometric Mean), MGPS (Multi Gama Poison Shrinker), BCPNN (Bayesian Confidence Propagation Neural Network). Signals of disproportionate reporting referred to statistical associations between medicinal products and AE.

	Suspected ADEs	All other ADEs	Total
Suspected drug	a	b	a + b
All other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

Abbreviations: ADE: adverse drug event.



CAVEATS

Causality assessments are more than just figures. Statistics are no substitutes for judgment. We cannot prove causal relationships beyond doubts for single cases and difficult for aggregate data. There are reasons like most diseases multifactorial. Also, no good methods are available to record aggregate data. Sometimes apt to subjectivity is not possible and data is incomplete. There are cases when confounding factors are may be known or unknown.

From the regulatory agency perspective, data mining is particularly useful for regulators. They can monitor large number of marketed products for public health protection. They also have databases which contain events for all relevant products. It is easy to examine the benefit risk ratio within and across structural and/or therapeutic classes for the regulators.

Signal validation: The process of evaluating the data supporting the detected signal to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal. This evaluation should consider the strength of the evidence, the clinical relevance and the previous awareness of the association. The extent of evaluation performed during signal validation versus further assessment may vary according to the organization's internal procedures.

Validated signal: A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Non-validated signal: A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted

Signal assessment: The process of further evaluating a validated signal considering all available evidence, to determine whether there are new risks causally associated with the

active substance or medicinal product or whether known risks have changed. This review may include nonclinical and clinical data and should be as comprehensive as possible regarding the sources of information.

Refuted signal: A validated signal which, following further assessment has been determined to be "false" i.e. a causal association cannot be established at that point in time

2.5 SIGNAL ANALYSIS

Signal Analysis Methods

Signal analysis procedures should be implemented during the pre- and post-approval phases of product development as shown in Figure below. Standardized, methodical descriptive algorithms and appropriate statistical methods should be applied in screening of data, both pre and post market data, and should feed into an iterative benefit-risk assessment.

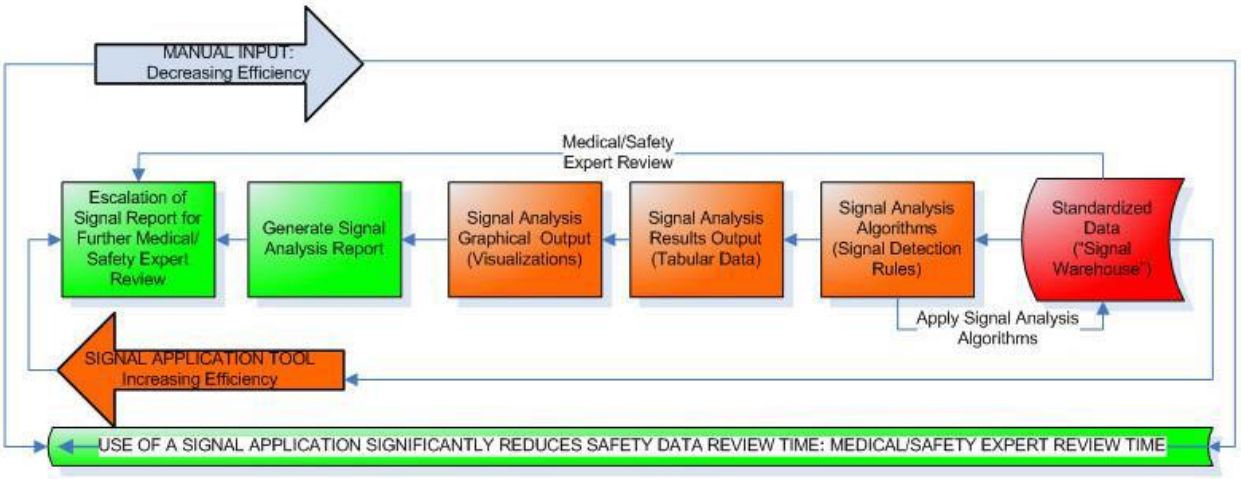
Statistical signal analysis methods applied in spontaneous databases are considered exploratory and not confirmatory. Exploratory signal analyses of adverse event databases for hypothesis generation can be integrated into traditional medical review and the risk assessment process. It is important to emphasize that statistical signal analysis scores, or SDRs, are primarily used for generating plausible hypotheses regarding a potential safety issue or concern. As such, statistical signal scores generated should not be directly used to define or compare the safety profile of any product without careful medical review and evaluation in the appropriate clinical context.

A pre-market approval signal analysis process adds to the traditional review process for:

- Standardized routine signal detection and evaluation approach that is reproducible.
- Identification of potential or true signals, or EOIs based on probable or possible association of an AE/ADR and the index product.
- Assessment of the medical significance of a signal and a signal strength (where quantified) and unexpectedness, along with review of reporter and company causality assessment.

- Evaluation of alternative explanations for causal association of a potential or true signal, or EOI.
- Prioritization of potential or true signals, or EOIs, for review by medical/safety experts for further assessment, where warranted, to determine those of any or significant safety concerns.

A Schematic Representation of Increasing Efficiency Using a Signal Analysis Application and Decreasing Efficiency with Only Manual Input Process



The role of a Signal Analyst or Safety Data Reviewer should include at a minimum the review and assessment of:

- Serious adverse events
- Discontinuation/dropout events (in clinical trials)
- Frequency or incidence of the events that are, or may be, causally related to the use of the drug or biologics product
- Dosage Analysis: Evaluation of the extent of exposure at relevant doses
- Other Dosage Analysis: Dose, plasma level, duration of exposure, etc.
- Adverse event profile of vulnerable populations such as: pediatric, elderly, pregnant women, etc.
- Adverse event profile of high-risk populations: for example, patients with impaired liver or kidney functions, consistent, spurious or intermittent spikes or abnormalities of hepatic or renal function tests, comorbid illnesses, metabolic status and genetic characteristics, such as, genetic predispositions, etc.

- Cardiac events and related events
- Drug-drug interactions or potential interactions, other drug-related factors
- Demographic analyses, e.g., age, gender, ethnicity, race, etc.
- Concomitant medications burden
- Comorbidity burden
- Rare/sentinel events
- Events whose causality are associated with the mechanism of action or pharmacology of the index drug (Type A events)
- Events not associated with the mechanism of action or pharmacology of the index drug (Idiosyncratic Type B events, Type C events, etc.)
- All other relevant safety data

2.6 SIGNAL EVALUATION

The process of Signal evaluation involves analyzing all the data available considering the strength of evidence from the cases, clinical relevance and previous awareness. It also includes:

- **Eliminate known issues**

  Whenever we are evaluating signals, we must eliminate the known issues. We take help from the data available during the clinical trials and data from Phase 2 and 3. The PI and RSI are also helpful in eliminating the known issues.

- **Identify signals of concerns**

  First eliminate the known issues by referring to the labeled events and the disease related issues. Depending upon the population background rates. We must define the clinical diagnosis / syndromes / symptoms according to the MedDRA SMQs which are available. Also, we should consider alternative clinical representation and data representation. We must focus on significant reports which are medically severe / important, HPC confirmed reports, adequate data for evaluation kind of reports.

- **Creating case series**

  Use all available data sources. Assess Bradford-hill criteria (Strength of association, temporality, consistency, theoretical plausibility, coherence, specificity of cause, dose response, experimental evidence, analogy also check for reversibility and preventability.

  If sufficient numbers are available the identify confounders, comorbidity, concomitant medications, dose response and specific risk groups. Evaluate by exposure, age, sex, dose, latency, outcome, cause of death, de-challenge and re-challenge.

- **Formulation of hypothesis**

  Test in appropriate databases about individuals with outcome of interest also try doing comparison group study and population background rate. Epidemiological analysis to study relevant sub groups. Does association exist? Check alternative explanation like chance, bias, of label use, other confounders. If further evaluation is required, go through clinical studies, pharmacoepidemiology, registries, etc... In Epidemiologic study, case control and cohort studies must be done.

- **Assess causal likelihood**

  Based on totality of information is there an apparent casual association between the drug and the event? The magnitude and the attributable risk is studied comparing population with background rate. Biological plausibility with underlying mechanisms and class effect is studied. Multiple symptoms are reported in every case hence syndromes cannot be detected. Key questions asked to know the causality are

  - Did it?

    (Did the drug cause the ADR in patient…A, B, C?)

    Sponsor-Labeling and risk management
  - Can it?

    (Is there evidence that the drug may cause the ADR?)

    Prescriber-advised, diagnosis, monitoring

- Will it?

  (What is the risk of that ADR in a given patient?)

  Prescriber information

  Patient-personal decision based on perceived risk vs. benefit.

Evidence Based Causality

Drug	Patient	Event
• Exposure (e.g., dose, duration, frequency) • Time and date of administration prior to the event • Pharmacology • Toxicity • PK/PD • Interactions • Similar drugs • Delivery (e.g., injection location, diluents) • Concomitant medication	• Age, gender, race • Natural history of treated disease • Other underlying diseases • Past medical history • Risk factors • Patient population data	• Signs and/or symptoms • Pathological findings • Laboratory tests • Time of onset • Duration • Severity • Seriousness • Reversibility • Outcome • Sequelae • Treatment of AE • Country (location) where AE occurs

When / how signals should be communicated

All identified signals require some action to be taken. No signal can be ignored. We must establish procedures for managing signals. What to do, who is responsible, who to inform, are the common questions to which answers must be found. Resource intensive studies through preparation, knowledge of potential data needs and real time data access must be done. Legal liability needs to be checked. A signal for non-company product is also important. There are certain regulatory vs. industry norms like; for the regulatory authority it is not obligation to act before signal is characterized whereas in pharmaceutical company it is mandatory to report signals to regulatory agencies as they might act by changing label etc. In RA, additional cases from multiple manufacturers can be requested whereas pharma companies cannot obtain complete comparator information from agencies. Also, there is no legal binding in RA whereas pharma companies are legally liable when signal is first detected but not necessarily confirmed.

Novelty of the signal

- Some clinical or non-clinical similar findings were observed during the development of the medicinal product. This requires searching in the (Co-) Rapporteur's

assessment reports of the initial opinion for the granting of the marketing authorization whether the issue was already identified in other areas of the development of the medicinal product.

- The suspected adverse reaction has also been described in relevant scientific articles in relation to the suspected medicinal product (or active substance(s)), or medicinal products of the same therapeutic class.
- The suspected adverse reaction is already listed in third countries product information.

Emerging safety issue: A safety issue considered by a marketing authorization holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals.

Examples include:

- Major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- Major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contra-indication, a restriction of use of the medicinal product or its withdrawal from the market;
- Major safety-related regulatory actions outside the EU, e.g. a restriction of the use of the medicinal product or its suspension.

Writing a signal evaluation report

For each signal evaluation, a short report should be written and sent to the H-SD mailbox.
The report should include three sections:

- Conclusion (including the proposed action)
- Case review
- Additional evidence from other regulatory procedures and bibliography

3. CONCLUSION

The validator should identify, extract and summaries in the conclusion the core information that justifies the reason of the proposed action. The conclusion will be included in the Signal Detection Tracking table and needs to be concise. The conclusion should indicate:

The proposed action:

- Signal closed (there is no signal or no further immediate action is needed).

- Signal closed but requires follow-up (FU) (if some follow-up other than monitoring is required (e.g. check next PSUR submission…), the nature of the follow-up is clearly mentioned in the tracking table and the issue is flagged as “Closed+FU”

- Signal monitored (this issue might represent a signal, but the available information is currently limited (e.g. there are a small number of cases); new cases reported to EudraVigilance will need to be evaluated).

- Signal ongoing (further analyses or verifications are required before a conclusion can be reached. The signal is discussed at the next relevant surveillance meeting

- Signal validated - Rapporteur needs to be informed (a proposal for a regulatory action to be performed by the Rapporteur with the appropriate timeframe should be suggested, e.g. cumulative review to be requested in next PSUR).

The total number of cases and the number of valid cases (eliminating duplicates, cases lacking information, cases related to non-CAPs and other non-relevant cases, which should not be broken down by reason for lack of validity).

Relevant information supporting the proposed action (e.g. alternative diagnosis, selected case information, class effect, biological plausibility, literature, PSUR, SPC, RMP).

The following information should normally not be provided in the conclusion: details on non-valid cases, ID numbers, demographic information (age and gender except if relevant), outcomes and corrective treatments (unless relevant to understand the issue), history and details of symptoms. If needed, the conclusion can be further explained in the case review.

To facilitate the work of the P-PV-SDA secretaries and the population of the Signal Detection Tracking Table, it is recommended to separate the conclusion from the case review. When only a cumulative overview of the ICSRs is provided, the conclusion and the overview can be merged.

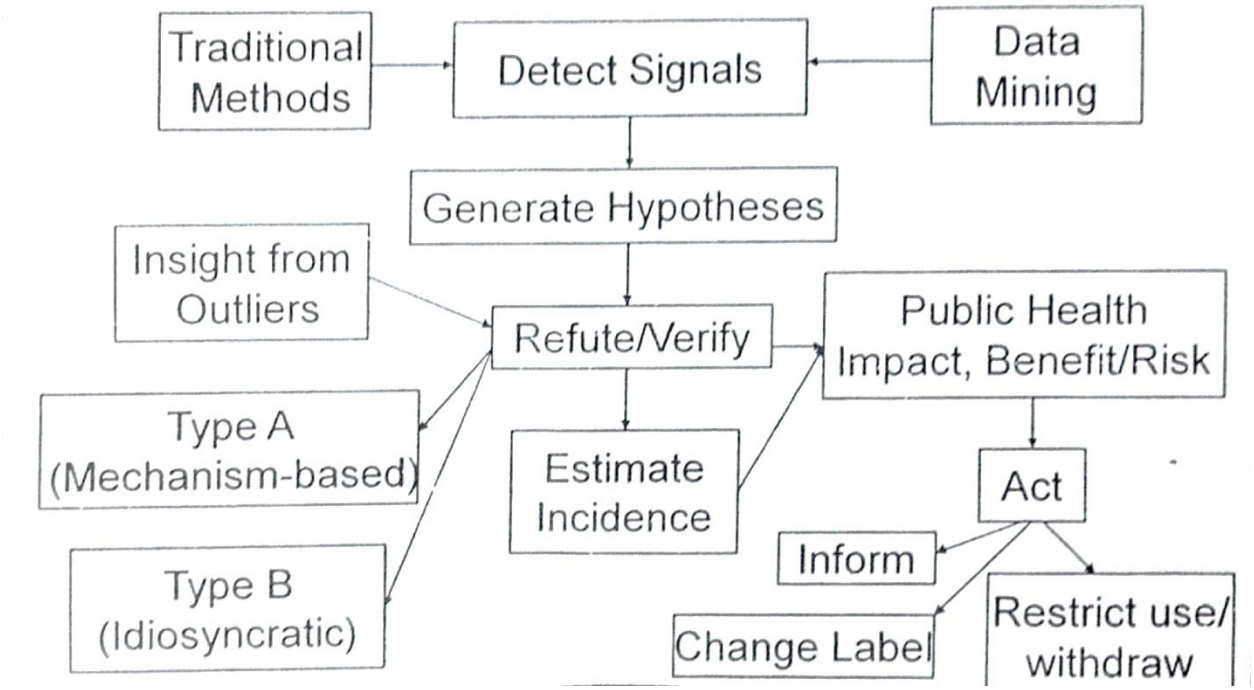
Case review

The extent of information to be provided in the case review is left to each SVT Member and will generally depend on several factors, including the number of ICSRs to be reviewed, previous evaluation of the same signal, severity of the signal, need for providing a documentation of the cases to the Rapporteur, anticipated request for further information, etc. Some signals may require a description of each ICSR, while an overview will be sufficient for others. An overview will also be presented if only the Line Listing has been reviewed. Another option is to describe only a subset of the cases, e.g. illustrative cases or cases with severity.

The ICSRs reference numbers should always be indicated to avoid duplication of work if further evaluation of the same signal is needed.

Cumulative overview of ICSRs:

The report should indicate the number of ICSRs reviewed, the date of the review and a summary of the causality assessment of the suspected medicinal product for all the ICSRs reviewed. This is to allow keeping track of this issue for a possible future re-evaluation.



Thus, signal detection is an essential public health activity. Signals are not necessarily risks; every signal must be evaluated for its potential to be a RISK. Effective signal evaluation requires a focus on key issues of concern. To meet increasingly stringent regulatory agency requirements and minimize liability, companies must develop more effective and simpler methods of signal evaluation