Guideline on Good Pharmacovigilance Practices

Module VII - Signal Management

TURKISH MEDICINES AND MEDICAL DEVICES AGENCY

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Abbreviations:
EEA: European Economic Area
BCPNN: Bayesian Confidence Propagating Neural Network
DME: Designated Medical Event
ICSR: Individual Case Safety Report
IC: Information Component
TME: Targeted Medical Event
SmPC: Summary of Product Characteristics
PIL: Patient Information Leaflet
MedDRA: Standard medical terminology developed for information exchange in international area by ICH (the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)
MedDRA MSSO: MedDRA Maintenance and Support Services Organization
SDR: Signals of Disproportionate Reporting
PRR: Proportional Reporting Ratio
IME: Important Medical Events
PT: Preferred Term
PBRER: Periodic Benefit/Risk Evaluation Report
RMP: Risk Management Plan

SECTION I
Introduction

1.1. Introduction

The aim of this module is to make recommendations on the structures and processes in signal management. Accordingly, the signals originating from the monitoring of data from spontaneous reporting systems will be considered as the starting point of the signal management process. The same principles will be applied to the data from other sources.

In order to better understand the signal management process, three basic elements below should be considered:

1. The starting point of signal detection is the presence of a certain amount of uncertainty and constant need for a reasonable judgment. Probability of a signal may be at different levels depending on the sufficiency and strength of the available data. Evidence may be found in different sources, may be of different strengths, and may be collected over time.
2. Signal is a hypothesis. It does not necessarily indicate a causal relationship in all cases. For instance, European Medicines Agency (EMA) evaluated 2372 possible signals in 2015, of which only 61 have been validated.
3. All signals do not pose risks, and after necessary examinations are conducted a further regulatory action (e.g. Summary of Product Characteristics (SmPC) update) may not be necessary for all signals.

In this Module, the methodology for signal analysis will also be outlined to guide the marketing authorization holders.

1.1.1. The Term Signal

Signal is defined as 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 set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [Regulation on Safety of Medicines Article 4(1)s].

The circumstances indicating a new aspect of a known causal relationship include the changes in frequency, duration, severity and outcome of adverse events.

Generally, the signal applies to the all medicines containing the same active substance including combination products. While certain signals only apply to a medicine in particular, some signals may apply to a certain indication, strength, pharmaceutical form and route of administration. Also certain signals may be applicable to all the medicines in the same class.

Signal management process

Signal management process is defined as the 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, 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 and to make recommendations, make decisions, have communication and perform monitoring regarding these risks.

Signal management process includes all the steps below from signal detection to recommendations for action:

- Signal detection
- Signal validation
- Signal confirmation
- Signal analysis and prioritization
- Signal evaluation

- Recommendations for action

Signal Detection

Act of searching and/or detecting signals using the data from any source.

Signal validation

Signal validation is the process of evaluating the data supporting the detected signal in order 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.

At this step, the strength and clinical significance of the evidence and previously awareness of the association should be considered (see 2.3.).

Confirmation of the signal

It means that the validated signal is examined and discussed by the administrative authority. In European Economic Area (EEA), this process is performed by EMA.

Emerging safety issue

Emerging safety issue is a safety warning considered by a marketing authorization holder in relation to an authorized medicinal product under its responsibility to require urgent attention of the competent authority because of the potential major impact on the risk-benefit balance of the product and/or on patient or public health, that could warrant prompt regulatory action and communication to patients and healthcare professionals

SECTION II
Structures and Processes

2.1. Sources of Data and Information

Sources of data which make new signals be identified vary. These sources include all scientific data regarding the use of drugs and the outcome of the use (e.g. quality data, non-clinical data, clinical data including pharmacovigilance and pharmacoepidemiology data).

The sources commonly used in signal detection are as below:

- Spontaneous reporting systems,
- Active surveillance systems,
- Studies including systematic reviews and meta-analyses.
- Scientific literatures.

Obtaining signals from spontaneous reports can be possible thanks to;

- Monitoring of ICSRs, suspected adverse reaction databases, and scientific articles.
- The information obtained from marketing authorization holders as part of regulatory actions (e.g. post-authorization commitments, extension of the period of validity of authorization, periodical benefit/risk evaluation report (PBRER), Risk Management Plan (RMP) updates),
- Other activities regarding monitoring of ongoing benefit/risk balance of medicines.

Signal analysis is periodically performed in large databases such as European Union Adverse Reaction Database (EudraVigilance), US FDA Adverse Event Reporting System (FAERS) or Collaborating Center for International Drug Monitoring (VigiBase).

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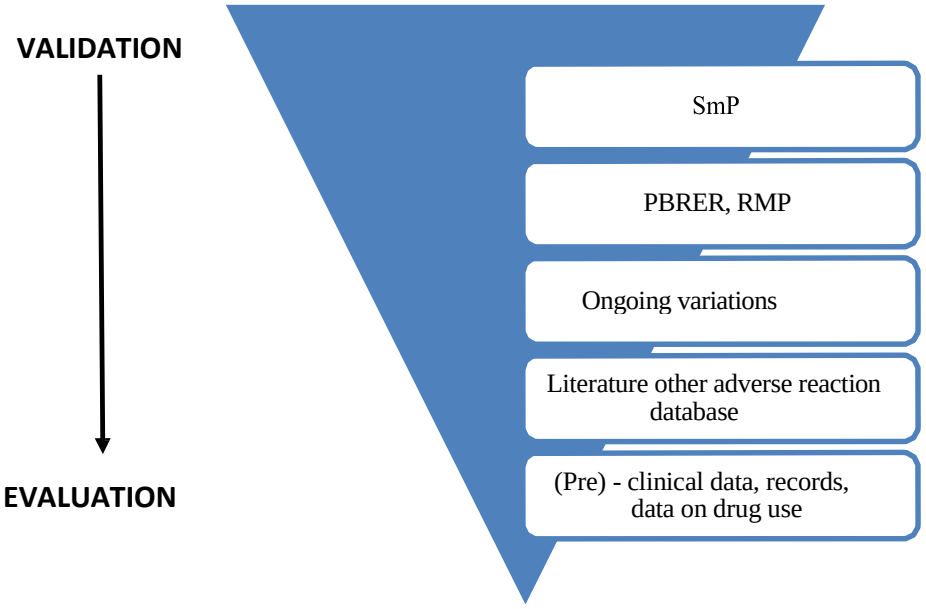

Figure 1. Information sources in signal management steps

2.2. Signal Detection

Signal detection should be based on multidisciplinary approach. An appropriate methodology that changes according to the nature of the data and type of the relevant drug should be followed. Vaccines, orphan drugs and drugs for pediatric use are drugs requiring special methodological strategies.

Signal detection may include review of ICSRs, statistical analyses or a combination of the two, depending on the data set. Collective data should be taken into consideration in cases where it is impossible to evaluate each individual case (such as the signals detected from published studies or health record data).

2.3. Evaluation of the Evidence Supporting a Signal

The following elements should be considered when evaluating the evidence supporting a detected signal:

- Strength of the evidence obtained from ICSRs
    - The total number of cases (after exclusion of duplicates), and amongst those, the number of supportive cases, e.g. cases showing a compatible temporal association, positive de- or rechallenge, lack of potential alternative causes, assessed as possibly related by the reporting healthcare professional, supportive results of relevant investigations,
    - Additional cases reported with related terms (e.g. other MedDRA terms indicating clinical complications or different stages of the same reaction).
    - Consistency of the evidence across cases (e.g. pattern with repeated observations of an association),
    - Quality of the data and their documentation,
    - Presence of cases matching internationally agreed case definitions if applicable,

- Plausibility of a biological and pharmacological relationship / possible mechanism;
- Number of cases in the context of patient exposure,
- Measures of disproportionality, if applicable.

- Clinical relevance, for example;
  - Seriousness and severity of the reaction,
  - Reactions occurring in the context of drug-drug interactions,
  - Reactions occurring in vulnerable populations (e.g. pregnant women, children or the older population or in patients with pre-existing risk factors,
  - Reactions occurring in different patterns of use (e.g. overdose, misuse, off-label use, medication errors),
  - Whether the signal may provide additional insight on an expected reaction in terms of e.g. its severity, outcome, incidence or management.
- Previous awareness, for example:
  - The extent to which information is already included in the product information (i.e. SmPC, PIL and the labelling),
  - Whether the reaction is already included in the SmPC for other products including the same substance (some signals may only apply to a specific medicinal product),
  - Whether the association has already been assessed in the initial application for marketing authorization, the RMP, the PBRER or any other regulatory procedure.
    Example: It is not always easy to check whether the adverse event is included in the SmPC, Section 4.8.
      - The event may have been described with a similar however different PT (e.g. it may have been described as anaphylactic shock or anaphylaxis, vertigo or dizziness, swelling of tongue or angioedema).
      - The event may be included in SmPC, however the signal may provide new information (e.g. anatomical characteristics, severity or duration).
      - The term included in the SmPC may not reflect the event (e.g. rash includes morbilliform rash, however it does not include Stevens Johnson syndrome; the fact that the SmPC includes liver damage does not indicate fulminant hepatitis).
- Additional sources of information may provide further evidence on the association, for example:
  - Clinical trial data,
  - Findings regarding similar cases in the scientific literature, including information on substances of the same class of medicinal products,
  - Experimental or non-clinical findings,
  - Databases with larger datasets, when the signal was detected from national or company-specific databases,
  - Healthcare databases that may provide information on characteristics of exposed patients and medicines utilization patterns,
  - Information from other regulatory authorities worldwide.

The evaluation of the evidence supporting a signal may require expert group discussions and different levels of decision-making. This may result in various decisions, such as:

- **Closing the signal:** When the available data do not support a causal relationship or when there is sufficient information on the association in the product information.

The signal may be re-opened at a later stage if new evidence arises.

Monitoring the signal: The signal is monitored by reviewing new information from ICSRs or the scientific literature at appropriate time intervals to determine whether the new data are supportive of a causal relationship.

- **Proposing actions**: Actions such as changes to the product information is proposed by means of a variation, if there is sufficient evidence of a causal relationship.

2.4. Signal Prioritization

A key and continuous consideration of the signal management process is to promptly identify signals that may have an important impact on patient or public health and/or on the risk-benefit balance of the medicinal product.

The following should be considered when evaluating this impact:

- The severity, seriousness, outcome and reversibility of the adverse reaction and the potential for prevention,
- The patient exposure and the estimated frequency of the adverse reaction,
- The patient exposure in vulnerable populations and/or in populations with different patterns of use, where appropriate,
- The consequences of treatment discontinuation and the availability of other therapeutic options,
- The expected extent of the regulatory intervention (e.g. addition of adverse reactions, warnings, contraindications, additional risk minimization measures, suspension, revocation),
- Whether the signal is likely to apply to other substances of the same class of medicinal products.

Special consideration should be given to the signals that cause concerns in large mass of people such as adverse events emerged after intensive vaccination program.

How the signal is further managed including timelines will depend on the prioritization. Because prioritization is a continuous process, appropriate measures should be considered at any stage if the information available supports the conclusion that there is a risk that requires prevention or minimization in a timely manner. Such measures may be required before a formal assessment of the signal is concluded. Professional judgment and flexibility should be applied throughout the process.

2.5. Quality requirements

Signal management is a critical process. Signal management system should be clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardized, that these tasks are conducted by staff with appropriate qualifications and expertise and that there are provisions for appropriate control and, when needed, improvement of the system. This includes the rationale for the method and periodicity of signal detection activities. Therefore, a quality assurance and quality control system consistent with quality system standards should be available in place, and a system of quality management should be applied to all signal management processes (see Module IV). Therefore, a system of quality management should be applied to all signal management processes. The performance of the system should be controlled and, when used, performance indicators should be presented in the pharmacovigilance system master file.

The organizational roles and responsibilities for the activities including maintenance of documentation, quality control and review, and for ensuring corrective and preventive action should be assigned and recorded.

As a critical process, signal management activities should be audited at regular intervals, including tasks performed by any service providers and contractors. Data and document

confidentiality, security and validity (including data integrity when transferred between organizations) should be guaranteed.

Through a tracking system, all parties should keep an audit trail of signal management activities including detection, validation, confirmation and evaluation of the signals and relevant query and results. The audit trail will enable retrospective monitoring of how signals are detected and how validated and confirmed signals have been evaluated.

The Agency may request documentation for review from marketing authorization holder to demonstrate compliance with these requirements before or after authorization, including justification/evidence for the steps taken and decisions made.

Staff members should be specifically trained in signal management activities in accordance with their roles and responsibilities. Information on location for training system and training records should be documented and the curriculum vitae and job description of the staff should be archived

SECTION III
Signal Analysis Methods

3.1. Methodology for Signal Detection

3.1.1. Traditional methods

Two types of signal detection are performed in spontaneous reporting systems: Qualitative and quantitative. From historical perspective, the methods can be classified as traditional and developed, statistical or automatic signal detection methods. Traditional methods include both qualitative (e.g. review of individual case and case series) and simple quantitative approaches (e.g. frequency/reporting speed, grouping, cross tabulation etc.). More complex quantitative methods are needed to be developed because of the renaissance in statistical approaches, increase in the number of spontaneous reports, and enlargement of the size of the databases.

In quantitative signal detection, the analysis should be conducted at the MedDRA (Standard Medical Dictionary for Regulatory Activities) preferred term (PT) level.

3.1.1.1.Review of the cases and case series

One of the techniques most frequently used in traditional pharmacovigilance is the method of "index case" or "striking case". Trained pharmacovigilance officials mostly detect signals during routine examination of the data acquired, the first examination conducted when ICSRs (spontaneous adverse reaction reports, systematic data collection systems or cases published in literature) are obtained. While detection of a single well-documented ICSR with unusually striking feature may be interpreted as a signal, in practice, mostly, strong suspicions about possible drug-event associations are based on case series with similar features (aggregation). In addition, positive de-/rechallenge is one of the most important criteria that is used to define a signal. Undoubtedly, these examinations are subjective. Therefore, the expert who performs the examination should have sufficient information on the pharmacology of the drug, the indication used, and the patient population exposed to the drug.

One of the basic steps of the examination of case reports is "designated medical events (DME)". DMEs are rare, serious adverse events with high risk attributable to drug. In such events, one to three reports may be interpreted as a possible signal. Typical examples may include aplastic anemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, Torsade de pointes, hepatic failure. However, there are events that are considered as DME even if it does not meet the criteria above although the definition is not clear. For example; pancreatitis (most of the risk is due to the alcohol use and gall bladder disease).

Therefore, any event considered to be of special interest is also describe as DME.

No universally accepted list of DME is available. There may always be changes in this list. Every organization has its own list. The list of EMA dated 17 August 2016 is included in annex 2.

Other events of special interest associated with a certain drug and/or patient population are called targeted medical event (TME). These events are similar to DMEs, however their classification depends on the drug. At this circumstance, pharmacovigilance logic and scientific information on the drug, treatment indication and/or patient population facilitate our prediction about issues that will possibly emerge.

A group of selected events considered serious are called Important Medical Events (IME). This list has developed by the organization which created MedDRA (MedDRA MSSO) and is coordinated by EMA.

Special caution may need to be exercised for other clinical features. For instance, a careful assessment should be conducted for hyperacute (needle tip) events. These events occur within a very short time when the drug is administered parenterally, while the condition is stable in other routes, and the occurrence of these events are biologically reasonable. The clinical characteristics of the event indicate that the drug at least participate in the occurrence of this event. For example, kidney and gallbladder stones comprised of pure drug.

In signal detection, there are other criteria which are part of clinical triage of cases, apart from DME and TME. For instance, if it is known that a hypothetical drug induces moderate respiratory depression, however the reports received include apnea/respiratory arrest, this event that is an identified event, however occurs more severe should be biologically justified.

For safety of newly authorized drugs, preparation and analysis of periodical assessments are very important traditional signal detection methods. PBRER can be given as an example for reports made by periodical collection of such data. Such reports enable comprehensive overview of data within a certain time period.

In assessment of individual reports and case series, scientific examination done by experts and experience are quite important.

3.1.1.2. Simple analysis of larger data sets

If the observed value is higher than the expected value for the conditions below of an adverse event or a group of adverse events, this indicates a signal has been detected.

- Number of a certain adverse event (absolute number)
- Number of a certain adverse event/total number of reports about the drug (ratio), or
- Number of a certain adverse event/estimated exposure to the drug (ratio).

Methods for collection of post-authorization pharmacovigilance data are listed in ICH E2E Guideline on Pharmacovigilance Planning. These include the methods such as passive surveillance (spontaneous reports, case series), active surveillance (Prescription, Event monitoring, Registries etc.), comparative observational studies (case control study, cross-sectional studies, cohort studies), targeted clinical investigations (genetic tests, studies on special populations, large simple study), descriptive studies (natural history of the disease, drug use study).

In cases where data collection is performed as passive surveillance, namely where reports are routinely received (e.g. MedWatch in USA, Yellow Card System in UK, EudraVigilance in European Economic Area) or during targeted collection and prolonged follow-up of some report types (Varicella Vaccine Pregnancy Record), remarkable reports with positive rechallenge and DMEs or TMEs, collective reports where spontaneous reports are examined periodically, automatic search in adverse event database or data mining methods can be used in signal detection.

In cases where data collection is performed as active surveillance (such as Prescription

Event Monitoring), signal search is conducted with more advances methods.

Disproportionate reporting signals require careful, detailed review of cases and literature, including preclinical and pharmacological data, assessment of pharmacoepidemiological and/or clinical studies.

3.1.2. More complex quantitative methods

Quantitative methods have been developed to detect signals in databases of large spontaneous reporting system. These methods enable systematical, automated and practical search of the data that cannot be easily searched with conventional methods and minimize the human error.

Advanced quantitative methods may include computer aided statistical methodology and data mining algorithms. These methods use disproportionality analysis based on 2x2 contingency tables.

3.1.2.1. Disproportionality analyses

Disproportionality analysis is defined as searching ICSR databases to detect reporting rates which are higher than expected and aims to identify statistically significant reporting associations between drug-event pairs in spontaneous reporting system.

Signal of disproportionate reporting (SDR) represents numerical outputs of these analyses without clinical context and is used instead of the term signal in statistical calculations.

The main feature of data mining algorithms supporting disproportionality analysis is to summarize very complex safety datasets into 2x2 contingency tables for each drug-event pair. Statistical 2x2 contingency table is commonly used in drug safety and underpins the calculations for association measurements.

For drug-adverse reaction pairs, the elements below are used as common disproportionality measures:

- Proportional reporting ratio,
- Reporting odds,
- Information Component,
- Empirical geometric mean.

Disproportionality measures are available for drug-drug-adverse reaction trios. One of these measures is Omega (Ω) and it is used by WHO Collaborating Center for International Drug Monitoring.

3.1.2.1.1. Proportional reporting ratio (PRR)

The reporting disproportionality measure used to obtain a SDR in pharmacovigilance databases is PRR. It shows the prevalence of adverse event for a certain drug according to the events in the whole database.

In this method, if a SDR (including a certain adverse event) is determined for a drug (P), it is hypothesized that this adverse event is reported with the drug (P) relatively more commonly compared to other drugs. The relative increase in the adverse events reported for the drug P is shown in 2x2 contingency table, based on the total number of the individual cases included in the pharmacovigilance database, as in the table below:

Table 1: 2x2 contingency table used to calculate PRR

	Event (E)	All the other events	Total
Drug (P)	A	B	A+B
All the other drugs	C	D	C+D
Total	**A+C**	**B+D**	**N=A+B+C+D**

The elements in this table are the individual cases in the database. The basic criteria of PRR calculation are:

A value, the number of the individual cases in which the adverse event E has been associated with the drug P,

B value, the number of the individual cases in which all the the other adverse events except E have been associated with the drug P,

C value, the number of the individual cases in which the event E has been associated with all the other drugs except P

D value, the number of the individual cases in which the events except E have been associated with all the other drugs except P

PRR is calculated as:

$$\mathrm{ORO} = \frac{A/(A+B)}{C/(C+D)}$$

Example 1:

-Among all the reports associated with the drug P, the rate of individual nausea cases is 5% (5 out of 100 reports with the drug P are cases of nausea. A=5, B=95, A+B =100).

-Among all the reports associated with all the other drugs (except the drug P) in the database, the rate of individual nausea cases is also 5% (e.g. 5000 cases of nausea out of 100000 reports with all the other drugs; So, similarly C=5000, D=95000, C+D=100000). In this example, PRR is 1 (e.g. 0.05/0.05)

Example 2:

- Among all the reports associated with the drug P, the rate of individual nausea cases is 15% (15 out of 100 reports with the drug P are cases of nausea. A=5, B=95, A+B =100). A=15, B=85, A+B =100).

-Among all the reports associated with all the other drugs (except the drug P) in the database, the rate of individual nausea cases is also 5% (e.g. 5000 cases of nausea out of 100000 reports with all the other drugs; So, similarly C=5000, D=95000, C+D=100000). In this example, PRR is 3 (e.g. 0.15/0.05)

3.1.2.1.1.1. 95% confidence interval of PRR

The data analysis system to be created should calculate the confidence interval of PRR. The standard error of natural logarithm of PRR is calculated with the formula below:

$$SH = \sqrt{(\frac{1}{A} + \frac{1}{C} - \frac{1}{A+B} - \frac{1}{C+D})}$$

95% confidence interval for in(PRR) is calculated as in(PRR)±1.96SE. The result below is obtained with exponential function:

95% confidence interval of PRR = (PRR / exp(1.96SE), PRR x EXP(1.96SE))

3.1.2.1.1.2. Interpretation of SDRs

The disproportionality analysis is not an inferential exercise. Using inferential statistical methods in such exploratory analyses may cause big problems. If the statistical analysis in database is conducted in an undisciplined way, this may cause subjective decisions on the selection, distribution and interpretation of the data mining processes and outputs.

The results of the quantitative methods should be carefully interpreted, and the limitations of the spontaneous reporting system should be considered. The following considerations should be paid regard when interpreting PRR results in the analyses conducted for signal detection:

a) PRR measures the reporting association between the drug P and the adverse event E, based on the relative increase in the rate of individual cases associated with the adverse event. It does not suggest any causal relationship between the drug P administered and the occurrence of the adverse event E. Such statistical disproportionality may reflect one or more bias (such as the bias related to the underlying disease of the patient), the artifacts naturally included in pharmacovigilance system and also statistical noise. Therefore, the SDRs detected with quantitative methods should absolutely undergo medical assessment.
b) When making the first decision on whether further analysis of the drug-event pair is necessary, threshold values for the PRR applied and other statistical estimations (e.g. estimated lower limit of confidence interval) are referred. No gold standard threshold value is available for SDRs.
c) The threshold values commonly used for detecting SDRs is choice between two conflicting option: If the threshold is too low, false positive signals may be generated or if the threshold is to high the true signals may be overlooked.
d) PRR also enables comparing the association between reports for the drug P and all the other drugs in the database. PRR value and SDRs which are identified as a result with this method depend on the data in the database where PRR is calculated. Therefore, interpretation of the PRR should be made considering the factors below:

I. Types of the drugs in the database
II. Medical terminology used in the reports which constitutes the database
III. Coding
IV. Date when the database was created
V. Source of the ICSRs (e.g. all unsolicited reports)

These factors may affect the PRR value and create a masking effect. Dissimilarly, they may cause the statistical association between the drug and adverse event to be exaggerated.

e) In addition to the quantitative perspective, other factors should be taken into consideration in selection and prioritization of the identified SDRs in the database:
   I. Possible effect of SDRs for public health
   II. Authorization conditions and especially whether the adverse event is expected or unexpected (particularly whether there is evidence for a change in the reporting frequency or seriousness of the known adverse event)
   III. Whether the possible risk related to the SDR is previously or currently confirmed
   These should be evaluated regardless of whether they cross the predefined threshold value of PRR.

f) Absence of SDR does not warrant the exclusion of the possibility of the association between the drug P and the adverse event E.
g) PRR can be cleared using similar techniques to the other SDRs (e.g. pooling a great number of drugs and/or adverse events, stratification by age or sex of the patient). Based on PRR, the possibility that the association between drug and adverse event are masked by other drugs during the analysis of SDRs.

3.1.2.1.1.3. Threshold values defining SDRs in EudraVigilance database

Currently, no gold standard is available to determine a universal threshold value for a signal of disproportionate reporting. The threshold values used in EudraVigilance are empirical. PRR is an extremely sensitive method which may cause a lot of false positive signals, especially when there are few reports.
Therefore, chi-square statistic is used to reduce the threshold value for the number of cases (number of reports ≥3) and the number of false positive results, in association with the PRR.
The criteria below are used in the query performed to determine the SDR (drug-event combination) in EudraVigilance Data Analysis System.

a) When PRR is shown in 95% confidence interval:
- **The lower limit of 95% confidence interval equals to 1 or higher**
- **The number of the individual cases equals to 3 or more**

These criteria are used in weekly/monthly signal monitoring.
Chi-square statistic is also used in association with PRR. In such cases, the criteria below are used in query.

b) When PRR is shown with the statistic of χ^2:
- **ORO ≥ 2**
- $\chi^2 \geq 4$
- **If the number of the individual cases is 3 or more.**

3.1.2.1.1.4. Subgroup analyses and stratification

Stratification is a statistical process that aims to reduce the confounding factors by making corrections according to the association between drug and confounding variable and event and the same confounding variable. PRR can be calculated in a subgroup of reports as in the whole database. The field may be limited by using many variables such as age and sex. Calculation of uncorrected PRR may be adjusted by age, sex or date of reporting using stratification. In addition, it is possible to perform subgroup analyses based on drug and drug class.

3.1.2.1.1.5. Validation

A large number of methodological issues make it difficult to systematically and comprehensively evaluate the performance of quantitative methods used in signal detection. The absence of a gold standard which can be used in signal detection makes this evaluation difficult.

It is possible to draw the conclusions below from the validation studies:

a) High sensitivity calculated in these studies is based on simple definition of the signal (e.g. drug-event pair). This definition of the signal may not reflect the true causality between drug-event pair in the context of clinical evaluation in pharmacovigilance.
b) The low specificity of the statistical methods emphasized in the mentioned validation studies indicates that many false positive signals may originate.

3.1.2.1.2 Information component

Information Component (IC), developed for signal detection from the adverse drug reactions in VigiBase by WHO Collaborating Center for International Drug Monitoring and put into place through Bayesian Confidence Propagating Neural Network (BCPNN) method, is a measure of disproportionality between the observed and expected reports of a drug-adverse reaction pair.

Positive IC value indicates a combination of certain drug-adverse reaction is reported at a higher rate than the expected rate based on the rest of the reports in the database. IC value of 0 indicates no quantitative dependency, and negative IC value indicates the combination is reported less commonly than statistically expected in the database.

IC value is calculated based on the information below:

- Total number of the case reports associated with the drug X (Cx)
- Total number of the case reports associated with the adverse reaction Y (Cy)
- Total number of the reports associated with a certain drug-reaction pair (Cxy)
- Total number of the reports in the database (C)

New reports may increase or decrease IC value. If IC value is calculated from high figures, a new report does not cause a big fluctuation in IC value.

Standard deviation of every IC value is a measure of the robustness of the value. Confidence interval narrows depending on how high Cx, Cy and Cxy values become. Lower limit of 95% of confidence interval for IC value is IC025.

IC value does not provide information on qualitative causality of the combination of drug-adverse reaction. IC shows quantitative dependency between adverse reactions and drug, based on the reports in VigiBase. If IC value gradually increases and IC25 value is positive, the probability of positive quantitative association between the drug and adverse reaction increases, however clinical assessment is essential.

As of 20 September 2016, WHO Collaborating Center for International Drug Monitoring (UMC) database (VigiBase) includes 14 million ICSR. The data in the VigiBase are periodically analyzed as part of the routine signal search of UMC, and the adverse reactions which are not previously identified are detected. After combinations of drug-adverse

reactions are automatically detected, clinical assessment are conducted. The number of the combinations of drug-adverse reaction are reduced with the method of categorization by urgency (triage) using the measurement of disproportionality between the observed and expected reports of the combination of drug-adverse reaction (IC) and other statistics, and the probability for detection of the most important significant signal is increased. The predictive capacity of the data mining method in UMC has been studied; positive predictive value is 44% and negative predictive value is 85%. In order to identify the signal in signal detection process, the procedure below is followed for the combination of drug-adverse reaction:

1. Relative reporting rates are calculated for all the combinations of drug-adverse reaction reported to VigiBase. IC value shows that the combination of drug-adverse reaction is unexpectedly reported more commonly compared to the database history.
2. For the combination of drug-adverse reaction more commonly reported, triage algorithm selects the combinations including ICSRs originating from at least two countries, and these combinations should meet at least one of the criteria below:
    a. New drug and serious reaction (the drug should have been included in the database within the last five years and adverse reaction should be one of the clinical terms of WHO-ART (WHO Adverse Reaction Terminology)
    b. IC value should have remarkably increased since the last quarter.
3. The combinations of drug-adverse reaction filtered through triage algorithm are checked by UMC staff for their inclusion in summary of product characteristics of the drug or literature. If the reaction cannot be found or is not defined well enough, individual case reports are received from VigiBase.

4. ICSRs are assessed by UMC staff or UMC signal review panel members.

As a result, signal search is performed with the combination of data mining and clinical assessment of experts.

Clinical assessment of a possible signal by experts:

- **Quantitative strength of the association**
    - Number of the ICSRs
    - Statistical disproportionality
- **Consistency of the data (pattern)**
- **Exposure-response association**
    - Area, timing, dose, reversibility
- **Biological probability (biological plausibility) of the hypothesis**
    - Pharmacological, pathological
- **Experimental findings**
    - For example, dechallenge, rechallenge, blood levels, metabolites, drug dependent antibodies
- **Nature and quality of the data**
    - Neutrality, documentation, causality assessment

During the assessment, the details of the reports are requested from National Centers.

3.1.3. Integration of Statistical Methods with Classical Methods

The quantitative methods used in signal detection in pharmacovigilance should be used with other traditional methods. Traditional method may enable the detection of the safety signals which cannot be detected with data mining methods.

If a drug is newly marketed and only a certain number of ICSRs have been received, it is

more reasonable to evaluate the ICSRs individually rather than based on a statistical method. One of the reasons for this is that the safety of the statistical search is limited for a low number of ICSRs. Moreover, in the earlier stages after a drug is marketed, the information on its safety profile is primarily based on clinical experience. Therefore, search for individual cases add more value to the monitoring process.

Regular and systematic assessment of all the new ICSRs is still the mainstay of pharmacovigilance. Statistical methods enable the prioritization of ICSRs and consideration of additional factors. For instance, PRR method does not routinely examine the drug-event pairs accompanying for drug-drug interaction. These cases should be evaluated by the experts examining this condition. Information on the nature of the data is of vital importance. Since the indications of the same drug vary between countries.

3.1.3.1. Systematical evaluation of SDRs

The critical point in the integration of the classical methods with statistical methods used in pharmacovigilance signal detection is systematic evaluation of SDRs. It is scientifically accepted that signals of disproportionality reporting identified with statistical methods should be considered with medical judgment. The SDRs which need to be further evaluated should systematically undergo medical examination.

Medical examination process of SDRs includes the steps below:

- Identifying the possible duplicates:
- Checking the quality of the data: Reviewing the information such as completeness of the information given, correctness of the codes
- If possible, providing more information: If the information received is insufficient in the evaluation of the case, requesting for more information.
- Checking the authorization conditions: Checking the SmPC and PIL of the drug for more information (e.g. expectedness/unexpectedness of the adverse event, possible drug-drug interactions
- Checking the additional information: As supportive in the evaluation of SDRs; application file, RMP, Suspected Unexpected Serious Adverse Reactions (SUSAR), PBRER, post-authorization commitments and post-authorization studies can be used.

3.1.3.2. Special considerations in the use of quantitative methods in medicines used in children and vaccines

Special requirements are available for the analyses conducted on vaccines and the drugs for pediatric use. Such products and detection of new signals regarding this population should be separately assessed by scientific experts.

SECTION IV
Duties and responsibilities

4.1. 4.1. Roles and Responsibilities of Marketing Authorization Holder on Signal Management

Monitoring of the safety of the drugs during their marketing period is of vital importance. Therefore, marketing authorization holders should ensure all the sources of information are searched to detect any possible signal, appropriate actions are taken to respond to a new evidence affecting the benefit/risk balance of the drug, and the Agency, healthcare professionals and patients are notified of the changes in the benefit/risk balance.

There are many methods available to be used in signal detection. The method to be used

should be selected considering the portfolio of the products and the number of suspected adverse reaction reports. However, all marketing authorization holders should have systems and methods for systematic signal detection.

All marketing authorization holders should have official written procedural documents such as standard operation procedure in which the signal detection method used is described and explained. These documents should provide detailed information about the roles and responsibilities of all the personnel participating in signal detection, information sources included in the analysis and the method used in signal detection. Pharmacovigilance system master file should include written procedures about generating, detection and assessment of signals (see Module V).

Furthermore, it should also include written procedures regarding the action to be taken by the marketing authorization holder based on the results of signal detection activity. These procedures should involve further analyses to be conducted after the signal is identified.

Marketing authorization holder should document the signal detection activities including the decisions made and the results obtained during these activities.

Procedures such as signal analysis should be organized to minimally include the consideration below:

1. Increase in frequency and severity of adverse reaction reports and death rates: Management of adverse drug reaction reports is mentioned in Module I. Marketing authorization holder should immediately notify TUFAM of the considerations above, and for any possibility that it results from the quality of the drug, marketing authorization holder should review at which processes of the drug manufacturing there are changes, closely monitor the processes where the change has been implemented, and notify the Agency of the results after conducting necessary analyses.
2. Periodical signal search in cumulative data: PBRERs are important parts of signal detection system, since they enable reviewing of all the data in the reporting period. However, in circumstances where reports need to be prepared once in three years, this period may be too long for signal detection. All marketing authorization holders are responsible for continuous monitoring the safety of drugs, regardless of the product portfolio. Therefore, if a marketing authorization holder only analyzes the safety data during the process of creating PBRER, it should be considered that this issue will be questioned during pharmacovigilance inspections.
3. Following the signals published every month under the title "Recommendations of Pharmacovigilance Risk Assessment Committee on Safety Signals" on the official website of EMA (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp) and taking necessary actions according to the recommendations:
    a. If the recommendation requires an addition to SmPC/PIL, the marketing authorization holder of the original drug should apply to the Agency for a variation.
    b. If additional information is requested from marketing authorization holder, the issue should be notified to the Agency and the additional information should be submitted to the Agency.
    c. Other recommendations suggesting monitoring PBRERs, performing routine pharmacovigilance or that no action are also paid regard. The documentation on this situation should be archived and immediately submitted to the Agency, when requested.
4. Following the signals published every three months under the title "Possible signal of

new safety information/serious risks detected in FDA adverse event reporting system (FAERS)" on the official website of FDA (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/UCM082196) and taking necessary actions according to the recommendations

5. Following the results of the assessments of PBRERs in EEA and taking necessary actions: Following the list published under the title "Results of the Assessments of Periodical Safety Update Reports" on the official website of EMA (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/psusa_search.jsp&mid=WC0b01ac0580902b8d) and taking necessary actions:

    a. <u>If the regulatory result is "continue", no steps is necessary.</u>
    b. If the regulatory result is "variation", the marketing authorization of the original drug should submit a variation application for the consideration to be added to SmPC/PIL.

The Agency should be informed on the signal detection, and explanation should be made for the actions planned and made in EEA and the actions planned to be made in our Country. After the Agency assesses the signal, it may decide on the actions below:

- No action is required except routine pharmacovigilance.
- Additional information should be submitted by marketing authorization holder in a specified period of time.
- RMP should be submitted or updated.
- Variations should be made in the marketing authorization.
- Additional risk minimization measures should be implemented.
- The marketing authorization holder should sponsor a post-authorization study in accordance with an agreed protocol and submit the results of the study to the Agency.
- Urgent safety limitations should be implemented.
- The marketing authorization should be suspended.
- Inspection should be conducted to confirm that the marketing authorization holder complies to the pharmacovigilance requirements.

The Agency may decide on any appropriate action which is not provided above.

ANNEXES

Annex 1 Signal Validation and Evaluation Checklist Signal Validation

Key sources: SmPC, PBRER, RMP, TITCK website and other regulatory processes

1. Is it included in the SmPC of the drug for the active substance?
   i.Review the SmPC of the drug
   - Firstly, check the SmPC of the innovative drug for active substances which has generic versions.
   - Check Sections 4.3,4.4,4.5,4.6, 4.8, 4.9 of the SmPC for the adverse event.
   - Check whether the adverse event is included in the SmPC with a similar term or a higher-level term.
   - Check whether the adverse event is included in the SmPC of another drug containing the same active substance.
   - Check whether the adverse event is included in the SmPC of another drug from the same class.
   - In case of interaction, check whether the SmPCs of other drugs provide information on the interaction.
2. Does the adverse event suggest a new aspect of the known association?
   - Increase in prevalence
   - Change in the duration of an adverse reaction or change in time to the occurrence of an adverse reaction.
   - Change in severity
   - Change in the pattern of occurrence (e.g. affecting a special population)
   - Change in the previously reported outcome (e.g. new fatal cases)
3. Has the association been previously described in regulatory processes?
   - Check PBRER of the drug.
   - Check RMP of the drug.
   - Check the websites of EMA and FDA.
   - Check whether variation application has been submitted regarding the same safety warning.

Signal evaluation

Key sources: ICSRs, national databases, literature, EudraVigilance database, WHO database

1. Reviewing the cases supporting the signal
   - Number of the cases supporting the association (excluding duplicated cases and cases without temporal relationship)
   - Number of the cases properly documented with adequate information (e.g. suspected drug, reported event, age and sex, indication, outcome, concomitant drugs)
   - Consistency of the evidence between cases (e.g. patterns)
   - Route of administration and formulation of the drug
   - Aggregation of reports e.g. many reports may be sent by the same reporter.
   - Cases meeting the diagnosis criteria of the event
2. Strong aspects
   - Biological and pharmacological plausibility (possible mechanism)
   - Dose relationship

- Number of the cases with positive dechallenge
- Number of the cases with positive rechallenge
- Low background incidence of the event
- Time to onset of the event

3. Clinical relevance
    - Seriousness/severity of the event
    - Reversibility of the event
    - Events affecting special populations (e.g. pregnant women, children, elderly) or patients with underlying risk factors
    - Events occurring in different patterns of use (e.g. off-label use, misuse, overdose, medication errors),
    - Association, applicable to other active substances from the same class
    - Possibility of prevention
4. Other considerations
    - Possible class effect
    - Possible drug-drug interaction
    - Possible medication error
    - Possible quality error
    - Possible off-label use
    - Possible addiction, abuse, misuse
5. Weaknesses
    - Poor data quality of case reports
    - Large number of cases with confounding factors/alternative explanations
    - Sign of stimulated reporting (e.g. increased interest in media)
    - Abnormal reporting pattern
    - Presence of other risk factors related to the event: underlying disease, co-morbidities, co-medications

Additional Source of Information

Key sources: Literature, other adverse reaction database, clinical study data, registries, drug use data, trials

1. Additional data
    - National databases (e.g. signals detected in literature)
    - Databases including larger datasets such as EudraVigilance or Vigibase
    - Information on the active substances from the same class
    - Literature findings regarding similar case reports, pharmacoepidemiological studies or studies on possible mechanism of action
    - Clinical Studies
    - Preclinical data
2. Information on exposure
    - Drug use data from PBRER or national drug use records (national exposure, patterns of drug use)
    - Health databases
3. Additional information
    - RMP of the drug (Information on ongoing or planned studies which can provide evidence for the association)
    - Registries

Annex 2 List of Designated Medical Events

Acute hepatic failure
Acute kidney injury
Agranulocytosis
Anaphylactic reaction
Anaphylactic shock
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Aplasia pure red cell
Aplastic anaemia
Autoimmune haemolytic anaemia
Autoimmune hepatitis
Autoimmune pancreatitis
Azotaemia
Blindness
Bone marrow failure
Deafness
Deafness neurosensory
Deafness permanent
Deafness transitory
Dermatitis exfoliative
Dermatitis exfoliative generalised
Drug reaction with eosinophilia and systemic symptoms
Drug-induced liver injury
Erythema multiforme
Febrile neutropenia
Granulocytopenia
Haemolysis
Haemolytic anaemia
Hepatic failure
Hepatic infarction
Hepatic necrosis
Hepatitis fulminant
Immune thrombocytopenic purpura
Intestinal perforation
Ischaemic pancreatitis
Neutropenic colitis
Neutropenic infection
Neutropenic sepsis
Oedematous pancreatitis
Optic ischaemic neuropathy

Pancreatitis
Pancreatitis acute
Pancytopenia
Product contamination microbial
Progressive multifocal leukoencephalopathy
Pulmonary arterial hypertension
Pulmonary fibrosis
Pulmonary hypertension
Renal failure
Reye's syndrome
Rhabdomyolysis
Stevens-Johnson syndrome
Sudden cardiac death
Sudden hearing loss
Sudden visual loss
Thrombotic thrombocytopenic purpura
Torsade de pointes
Toxic epidermal necrolysis
Toxic optic neuropathy
Transmission of an infectious agent via product
Ventricular fibrillation

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