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REVIEW ARTICLE

A BRIEF REVIEW ON SAFETY SIGNAL MANAGEMENT PROCESS

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Abstract

The field of pharmacovigilance (or drug safety surveillance) has evolved significantly over the last few years. Important utility of pharmacovigilance is detection and dissemination of signal. It has power to prevent the epidemics of serious adverse drug reaction before damage to community. The historical medical calamities (e.g. thalidomide tragedy) could have been prevented if process like signal detection and pharmacovigilance would have been practiced since that time. Post-marketing detection and surveillance of potential safety hazards are crucial tasks in pharmacovigilance. To disclose such safety risks, a wide set of techniques has been developed for spontaneous reporting data and, more recently, for longitudinal data. This paper gives a broad overview of the signal detection process and introduces some types of data sources mostly used.

Introduction:

All drugs are capable of producing side effect or adverse effect. Benefit risk profile of drug is made before releasing drug into the market and on the basis of this profile it is decided whether to use or not to use drug in patient. All adverse effects are not disclosed during clinical trials as there are some limitations like limited number of patients, subjects having single disease, specific population (children, elderly and pregnant women being excluded), small sample size (detection of rare adverse effect is difficult), shorter duration of a trial (limits the detection of long term adverse effects), inability to detect ADRs under real life situations (drug interaction, drug food interactions etc.).These drawbacks are overcome by post marketing surveillance. Pharmacovigilance is mainly the phase 4 of the clinical trials.[1] The thalidomide tragedy marked a turning point in toxicity testing, as it prompted United States and international regulatory agencies to develop systematic toxicity testing protocols and give rise to a development of a system for early detection of unknown adverse events of medicines.[2] The World Health Organization (WHO) defines Pharmacovigilance as a science related to the detection, assessment, understanding and prevention of adverse reactions towards a medicinal product or any other medicine related problems in human beings. [3] The main aim of pharmacovigilance is continuous review of all reported drug-drug related events which are serious or unexpected.[4] In accordance with data of European Commission (EC), adverse drug reaction (ADRs) are responsible for 5% of all hospital admissions, 5% of all patients in hospital experience an ADR and lastly ADRs cause minimum of 1.91 extra days of hospitalization. In United States (US), more than 100,000 deaths annually are because of ADRs. Hence, this scenario itself makes clear the importance of pharmacovigilance (PV).[5] Pharmacovigilance – an umbrella term used to describe the processes for monitoring and evaluating ADRs – is a key component of effective drug regulation systems, clinical practice and public health programmes.[6]

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What is safety signal?

One of the most important activities of pharmacovigilance is signal detection. Taken together, adverse drug reactions (ADRs) impose an enormous burden on society, causing hundreds of thousands of deaths annually at a cost of several billion $US.[7,8] A signal in pharmacovigilance is not only a statistical association. It consists of a hypothesis together with data and arguments, which may be in favour or against these arguments. These relate to numbers of cases, statistics, clinical medicine, pharmacology (kinetics, actions, previous knowledge) and epidemiology, and may also refer to findings with an experimental character. Council for International Organizations of Medical Sciences (CIOMS), 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." The information must be suggestive of something new so that after further investigation it can suggest that the association may or may not be confirmed. 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. It can be explained by an example. An oncology drug associated with a characteristic cardiomyopathy identified by small number of spontaneous reports. To gather more information ongoing surveillance initiated which gives the information that risk is especially high in pediatric patients or patient`s previously treated with radiation to the chest region.[9] A signal in pharmacovigilance is more than just a statistical association. It consists of a hypothesis together with data and arguments, arguments in favor and against the hypothesis. These relate to numbers of cases, statistics, clinical medicine, pharmacology (kinetics, actions, previous knowledge) and epidemiology, and may also refer to findings with an experimental character.[10] In simple terms we can say signal is an important navigator of the consequences of the medicinal products. Signal not always be a safety concern sometimes it could be a probable beneficial effect of drug.

Need for signal detection:

- Provide early warning for new serious adverse events of new drugs. The detection of a previously unknown safety issue can have great impact on the overall benefit–risk balance of a drug as evidenced for example by the market withdrawal of Rofecoxib upon the detection of its increased myocardial infarction risk.
- To update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products and then reduces risks of costly failures by early detection of ADRs.
- It is a regulatory requirement for all Marketing Authorization Holders.
- Regulatory actions

Signal management process:

The signal management process can be 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 risks have changed.[10]

The steps involved in this process are signal detection, signal validation, signal prioritization, signal assessment and recommendation for action.

Signal detection:

Signal detection is a process of identifying a signal from different data sources.

Potential Sources of Data for Signal Management[11]

- Regulatory Authority reports (e.g. Anonymised Single Patient Reports)
- Clinical Trials Serious adverse events
- Post-marketing reports (to MAH)
- clinical trials, post-authorization studies, registries, post-authorization named-patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers
- Medical and scientific literature
- Non-interventional studies e.g. marketing projects
- Post-authorization safety studies
- Medical and scientific literature

- Product quality complaints associated with adverse events
- Medical enquiries
- Periodic Safety Update Reports (PSURs)
- Regulatory databases (e.g FDA AERS, MHRA drug analysis prints [DAPs] / product analysis prints [PAPs])
- Other databases (e.g WHO Vigibase)

Databases that can be used for signal detection in post-authorization drug safety surveillance:[12]

- Yellow Card scheme in the UK
- Eudravigilance (EMA)
- Adverse Event Reporting System (AERS /FAERS) used by the Food and Drug Administration (FDA) in the USA,
- World Health Organization (WHO) International Database maintained at Uppsala Monitoring Center (UMC) in Uppsala, Sweden.
- Italian spontaneous reporting database
- Dutch spontaneous reporting to the Lareb PV centre in the Netherlands
- Drug Safety Research Unit (UK)
- Intensive Medicines Monitoring Program (New Zealand)
- Other programmes:
- Vaccine Safety Datalink (VSD)
- Sentinel Initiative
- Observational Medical Outcomes Partnership (OMOP)
- IMI-PROTECT Project

Methods for signal Detection:

Traditional method: This method also known as qualitative method and involve review of ICSRs. This method is generally applies when data set is small.

Data mining techniques: This method is also known as quantitative method. It is generally based on statistical analysis. These methods are usually applied to a broad range of combinations of drug exposures and subsequent adverse events, often without limiting the search to pre-defined drug classes or specific medical conditions. They can be regarded as a broad search over the whole spectrum of drug-event combinations (DECs) in the underlying dataset.[13]

Survelliance method: Surveillance techniques have been developed to consolidate knowledge on these already suspected DECs and are often applied after the first data-mining step.[14]

Statistical methods:[14]

Bayesian approach.

- Multi-item Gamma Poisson Shrinker (MGPS)
- Bayesian Confidence Propagation Neural network

Frequentist Approach:

- Reporting Odds Ratio (ROR)
- Proportional Reporting Ratio (PRR)

Frequentist or classical methods are particularly appealing and therefore widely used due to the fact that they are relatively easy to understand, interpret and compute as they are based on the same principles of calculation using the 2x2 table. (Table 1)

Table 1:- Formal 2x2 contingency table

	Drug of interest	All other drug in the database	Total
Adverse drug reaction of interest	A	B	A+B
All other adverse drug reaction	C	D	C+D
Total	A+C	B+D	A+B+C+D

A= number of reports containing both the suspect drug and the suspect adverse drug reaction
B= number of reports containing the suspect adverse drug reaction with other medications (except the drug of interest)
C= number of reports containing the suspect drug with other adverse drug reactions (except the event of interest)
D= number of reports containing other medications and other adverse drug reactions

Signal Validation: [15]
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.

Following factors are considered during validation of signal:

- Clinical relevance including: strength of evidence for a causal effect (e.g. number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders), seriousness and severity of the reaction and its outcome, novelty of the reaction (e.g. new and serious adverse reactions); drug-drug interactions; reactions occurring in special populations.
- Previous awareness: the extent to which information is already included in the summary of product characteristics (SmPC) or patient leaflet; whether the association has already been assessed in a PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

Signal Prioritization:[15]
Two methods for signal Prioritization:
WHO-Triage:
The aim of this adjudication process is the identification of those signals that are likely to indicate a yet-unidentified safety hazard, and the elimination of false-positives from the results (are already known and well documented; (b) occur very seldom or (c) are highly implausible from a medical perspective and thus can be regarded as artificial false-positive signals.).

After having reduced the number of potential signals by mere technical restrictions, the remainders need to be assessed on a qualitative level. A common step is to exclude—automatically if possible—all known and well-documented risks and to focus on the unknown or unexpected identified signals. The exact layout of this part of the triage highly depends on a number of factors, including the underlying data structure, the signal detection method used and personnel resources, as in-depth medical and pharmacological knowledge is necessary.

Once the triage is completed, the safety risk of every remaining signal needs to be rated to decide whether (a) impact analyses and subsequent confirmatory analyses need to be induced; (b) the signal should be monitored to sharpen the risk profile or (c) the signal can be discarded because of low potential risk.

MHRA-Impact analysis:[16]
A new method of prioritizing signals of potential adverse drug reactions (ADRs) detected from spontaneous reports that is called impact analysis. This is an interim step between signal detection and detailed signal evaluation. Using mathematical screening tools, large numbers of signals may now be detected from spontaneous ADR databases. Regulatory authorities need to rapidly priorities them and focus on those that are most likely to require significant action. Using two scores ranging from 1 to 100, each with three input variables, signals may be categorized in terms of the strength of evidence (E) and the potential public health impact (P). In a two-by-two figure with empirically derived cut-off points of ten (the logarithmic mean) for each score, signals are placed in one of four categories (A-D) that are ranked according to their priority (A being the highest and D the lowest). A sensitivity analysis is then performed that tests the robustness of the categorization in relation to each of the six input variables.

Signal Assessment: [14]

The assessment of signals is done in terms of various factors. First, the data in the report(s) need to be of good quality when a signal of a new adverse drug reaction is considered. There should be sufficient data to fully assess the relationship of the drug to the event.

The subjective assessment of the quality of the reports is mainly based on the patient and drug information. Patient information includes completeness of information with- patient initials, age, sex, date of birth (DOB), weight, diagnosis for which the medications were being taken, relevant history, adverse event description, adequate description of the event, when did the event occur? When did the event subside? How the event was managed? What was the outcome? Whether the event abated on stopping the drug or reducing the dose of the drug? Whether the event reappeared on reintroduction? Any supportive laboratory data? Drug information includes suspected medication with their brand name and/or generic name, labeled strength, manufacture, dose used, frequency of use, route used and therapy dates, concomitant medications including self medication and herbal remedies etc.

Cause and Effect Analysis:

The most commonly used methods are WHO-UMC causality categories and Naranjo's Probability Scale.

This method gives guidance to the general arguments which should be used to select one category over another as shown in Table 2.

Table 2:- WHO-UMC causality categories [17]

Categories	Time sequence	Other drug/Disease ruled out	Dechallenge	Rechallenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

Naranjo's Probability Scale:[17]

Naranjo's probability scale is the most commonly used causality assessment method, which has gained popularity among clinicians because of its simplicity. It is a structured, transparent, consistent and easy to apply assessment method. The Naranjo's criteria classifies the probability that an adverse event is related to the drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, dose – response relationships and previous patient experience with the medication. The ADR is assigned to a probability category from the total score as follows: definite if the overall score is 9 or greater, probable for a score of 5-8, possible for 1-4 and doubtful if the score is 0.

Drugs are evaluated individually for causality, and points are deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.[18]

Recommendation for action:[15]

The recommendation for action may include a request for:

- Immediate measures including the possibility of suspending the marketing authorization of the medicinal product;
- Additional information to be provided by the marketing authorization holder, e.g. in order to confirm if a conclusion is valid for all indications and patient groups;
- Periodic review of the signal, for example through PSURs
- Additional investigations or risk minimization activities;
- An update of the product information through a regulatory procedure;
- Conduct of a post-authorization safety study

Conclusion:

Pharmacovigilance is not only restricted to collecting the ADR data but also to extract the signal to prevent the investible medical disaster and harm to patients. The proper signal detection and their assessment is the most important aspect in pharmacovigilance. Various methods are used for the detection of signals. Signals in

pharmacovigilance have a variety of sources. Pharmacovigilance may not rely upon one single method, but needs a strategy of complementary activities. Further development of statistical methods and technological solutions to analyze large amounts of data to detect signals for potential safety issues, while minimizing noise, would enhance the efficiency and effectiveness of pharmacovigilance activities.

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