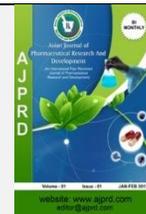


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Review Article

## A Review on Signal in Pharmacovigilance

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### ABSTRACT

A safety signal is data or information that may suggest a new causal association, or contribute new information about a known association, between a medicine and an adverse event that justifies further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. Signal is a potential medicine safety issues, which are derived from individual case safety reports in vigi Base. Signal detection is a cornerstone of drug development process ensuring drug safety. The early detection of Signals helps to improve patient safety and reduce economic burden due to escalating cost of medications and unwanted adverse effects associated with it. The present study is an initiative to make significant contribution towards health-care system by generating evidence based data to benefit health care professionals, consumers, pharmaceutical companies and regulatory authorities. Signal detection and signal strengthening is the most important aspect in Pharmacovigilance which plays an important role in ensuring that patients receive safe drugs. For detection of adverse drug reactions, clinical trials usually provide limited information as they are conducted under strictly controlled conditions. Some of the adverse drug reaction can be detected only after long term use in larger population and in specific patient groups due to specific concomitant medications or disease.

**Keywords:** Signal, Pharmacovigilance, Adverse drug reaction, Signal detection, Signal strengthening.

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### INTRODUCTION

In the WHO Programme for International drug monitoring (WHO-PIDM), India is the member country. WHO PIDM i.e., WHO-Uppsala Monitoring centre, Sweden since 1998. Ministry of Health and Family Welfare, Government of India has started a nationwide Pharmacovigilance Program of India (PvPI) in the year 2010. The aim of Pharmacovigilance is to identify and observe adverse drug reactions for patient safety and public health. <sup>1</sup>

Pharmacovigilance is also known as Phase IV in drug development process and also known as post marketing surveillance. According to World Health Organization (WHO), Pharmacovigilance is the science of detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problems. <sup>2</sup>

The aim of pharmacovigilance is the evaluation of the benefit-risk profile of the drug for better efficacy and safety of the patients. For patient safety, Pharmacovigilance plays a key role in the safe use of drugs by providing information about the adverse drug reactions. <sup>3</sup> In the Pharmacovigilance the estimation of information from health care providers and patients on the adverse effects of the medications, biological products, blood products, herbals, vaccines, medical device, traditional and complementary medicines. Pharmacovigilance is to identifying and monitoring new information about risks associated with products and preventing harm to patients. <sup>4</sup> Pharmacovigilance is particularly related to ADRs, in which drug responses are measured that are noxious and unintended, and which occur at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the changes in physiological

function.<sup>5</sup> For the identification and monitoring of drug effects, side effects and contraindication which result could observe that in a high degree of morbidity and mortality are beneficial for maximize benefits and minimize risks.<sup>6</sup>

At the pre-clinical and clinical testing stages cannot be guarantee of the degree of care and caution absolute safety in Phase IV (Post-marketing) and prescribed in the large population across the country and outside. Several thousands of patients are involved in clinical trials in which less common side effects and adverse drug reaction are often identified during post-marketing.<sup>7</sup>

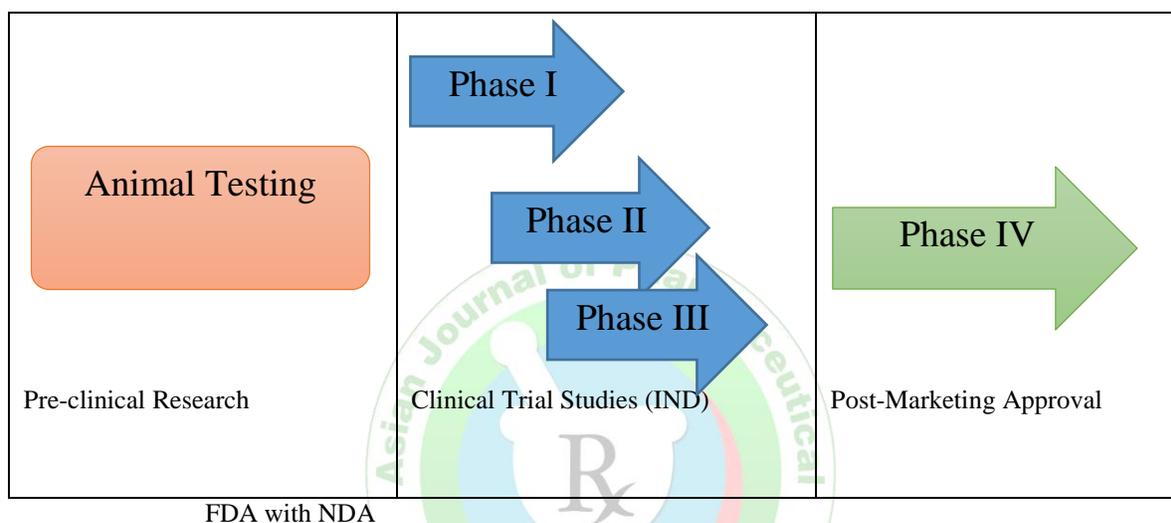
To identify the casual relationship between drugs and adverse drug reaction, data mining and investigation of case

reports are common tools for post marketing Pharmacovigilance.<sup>8</sup>

A well-established Pharmacovigilance system is economical to identify and to monitor Adverse drug reactions during the development phase and then to regulate the life time of a marketed drugs.<sup>9</sup>

Before drug become available to the patients, they are subjected to rigorous clinical studies.

However, some ADRs are often detected only after post-marketing (**Figure :**)



**Figure-1:** Phases of clinical trials

During a medication received by a patient, around 5%-6% all hospital admissions are caused by due to an ADR and during hospital stay 10%-25% of patient having at least one ADR. Some Adverse drug reactions mimic natural disease phases and thus go unidentified and unreported because of actual incidence of adverse drug reaction. Adverse drug reactions are quickly identified, observed, detected and managed to decrease their detrimental effects on the patient. The limited valuable information are obtained during the pre-marketing clinical trials. During the pre-marketing studies, the mostly ADRs are not observed because of small sample size that lack the power to detect rare ADRs. The rare ADRs are often identified many years in larger patient population after drug approval in post marketing surveillance studies.<sup>10</sup>

Systematic pharmacovigilance is needed to generate a reliable information on the safety of all category of medicines for the development of appropriate guidelines for safe and effective use. It basically involves identification and evaluation of safety signals<sup>11</sup>

According to WHO "Signal is a reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."<sup>12</sup>

Usually, more than a single report is required for signal detection (SD), depending on the seriousness of the event

and the quality of the information. Once a signal is detected, one can then analyze and confirm it. UMC communicates signals of suspected medicines safety problems to national pharmacovigilance centers through SIGNAL, and subsequently to the wider world via WHO Pharmaceuticals Newsletter.<sup>13</sup>

**Signal-** 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 seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.<sup>14</sup>

#### Subcategories of Signals-

**Regulatory signal-** These signals are one or more serious adverse events or unexpected adverse events, frequency or characteristic of expected ADRs, severity changes and change in outcomes of known adverse drug reactions.

**Intermediate signal-** If any signal has been worked up and after this no conclusion is found in regard to whether it is validated or closed.

**Verified signal-** When a new signal is generated, it to be real or a true risk

**Refuted signal-** A signal has been generated after work-up and this signal have no risk or potential risk, that signal was false and closed.

**New signal-** A signal that is currently identified and detected.

**Ongoing signal-** A signal which has been evaluated for some time and which is being undergoing evaluation, tracked and worked-up.

**Closed signal-** A signal which has been evaluated, documented after all methodology of signal detection.<sup>15</sup>

## STEPS IN PHARMACOVIGILANCE

The basic steps in pharmacovigilance include:

- Safety data management
- Signal detection
- Signal evaluation and making decisions with regard to safety issues
- Actions, including regulatory to protect public health
- Providing information to all concerned parties or stakeholders.<sup>16</sup>

### Signal detection-

In patient safety and safer use of medicine, Signal detection play a key role in pharmacovigilance process. For identification and evaluation of adverse drug reactions, during the clinical trials they provide less information about the medication because of strictly controlled condition. Post marketing studies (Phase-IV studies) are used to observe the adverse drug reactions of a new drug in large population and in specific patients due to a disease and specific concomitant medications. To detect the unknown and unexpected signals as soon as possible from the market is the major challenge in pharmacovigilance. Spontaneous reporting is play a key role in signal detection, detecting type B adverse effects and unexpected adverse effects.

For signal detection qualitative and quantitative aspects are important. Different methodologies are used to detect different adverse events and signal detection. In 1960s, due to late signal identification and detection, thalidomide tragedy occurred.

There are many sources to generate a signal, such as-

1. Spontaneous reporting
2. Prescription event monitoring
3. Registries
4. Periodic Safety Update Report (PSUR)
5. Signal generation by trigger tools
6. Case control studies
7. Cohort studies.

### Spontaneous reporting system-

Spontaneous reporting system (SRS) is an unsolicited communication by health care professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Regional centers, Poison center) that describe one or more ADRs in a Patient who was given one or more

medicinal products and that does not derive from a study or any organized data collection scheme. This report is voluntary in nature, i.e., it may be initiated by the health care professionals or consumers as and when they become suspicious of any adverse drug reaction by any medication. It is needed for current pharmacovigilance. Case series and case control are a part of connatural reporting system. It is important in identification and detection of type B (bizarre) effects and type A effects. The spontaneous reporting system is an important to detect new signals, rare and serious adverse drug reactions. The spontaneous reporting system is performed by a medically qualified person to a pharmacovigilance center.

### Prescription Event Monitoring-

Prescription event monitoring is a method of active pharmacovigilance surveillance. It is the way of recording all of the patients exposed to selected drugs. The Prescription event monitoring was developed in New Zealand which name is the Intensive Medicine Monitoring program and in UK which name is Prescription event monitoring. To record any selected events, the patients or their doctors can then be approached by means of a questionnaire. This method is used to detect unexpected benefits of therapy. The proportion of adverse effects that go unreported to doctors is unknown, is the limitations of the Prescription event monitoring.

### Registries-

Registries are an important aspect to generate a safety signals. There are two types of registries, disease and drug registries. Registries are a list of patient who present with the same characteristics. These registries may be disease or a specific exposure (drug registries). These registries can collect a large amount of information by using standardized questionnaire.

**Periodic Safety Update report-** The Periodic safety update report (PSUR) is helpful for the identification of new safety signal. It provides update information of the worldwide safety experience of a medicinal product.

### Signal Generation by Trigger tools-

To identify and measure ADRs in hospitalized patients, the healthcare providers generate an accurate and reliable method. The clinical pharmacist plays a key role in detection of early ADRs and other drug related problems as well as monitoring the effectiveness of pharmaceuticals by using electronic systems for example Information component (IC), Proportional Relative Risk (PRR) etc.

### Case- Control study-

The retrospective, descriptive, observational study of a person/ drug/ disease/outcome is performed in case control studies.

### Cohort study-

The prospective, observational studies are performed in Cohort studies. The early updates of the adverse effects and any new adverse event are done by this study.<sup>17</sup>

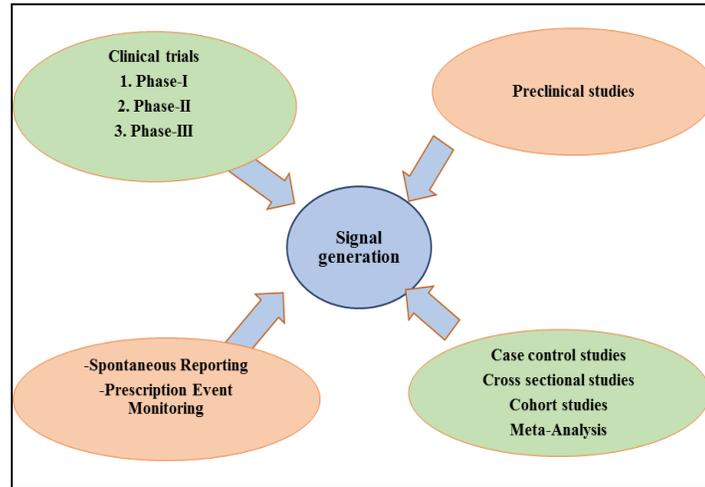


Figure-2: Sources for generate signals)

**Methods used by PvPI for Signal detection-**

Various methods are used for signal detection. The four parameters for identifying a new signal from Indian Individual Case Safety Reports (ICSRs) include:

1. Information Component (IC)
2. Proportional Relative Risk/ Proportional Reporting Ratio (PRR)
3. Chi-square ( $X^2$ ) statistics (with 1 degree of freedom)
4. Total number of reports on the specific Drug-ADR combination available in the Indian database ( $N_{comb}$ )<sup>18</sup>

**SIGNAL STRENGTHENING**

The signal strengthening is a following process of preliminary assessment data which are already discussed in NCC- PvPI newsletters in the form of signal generation and hypothesis formulation. The available preliminary data can be qualitative which are derived from clinical observations or

quantitative which are derived from epidemiological studies, case reports, experiments etc. A single report is sufficient to strengthen the Signal after the preliminary assessment of available data. When qualitative calculations are done for data analysis to find out the relative risk and higher the relative risk for making a stronger Signal.

The lengthy process of the observation of an adverse drug reaction, a signal is a snapshot on a given moment. Once a signal has been confirmed and assessed, it needs to be followed for a long time in the market.<sup>19</sup>

**SIGNAL MANAGEMENT**

Signal management is often described as a sequential process (as shown in figure 1) with the following activities detection, validation, confirmation, analysis and prioritisation, assessment and recommendation for action.

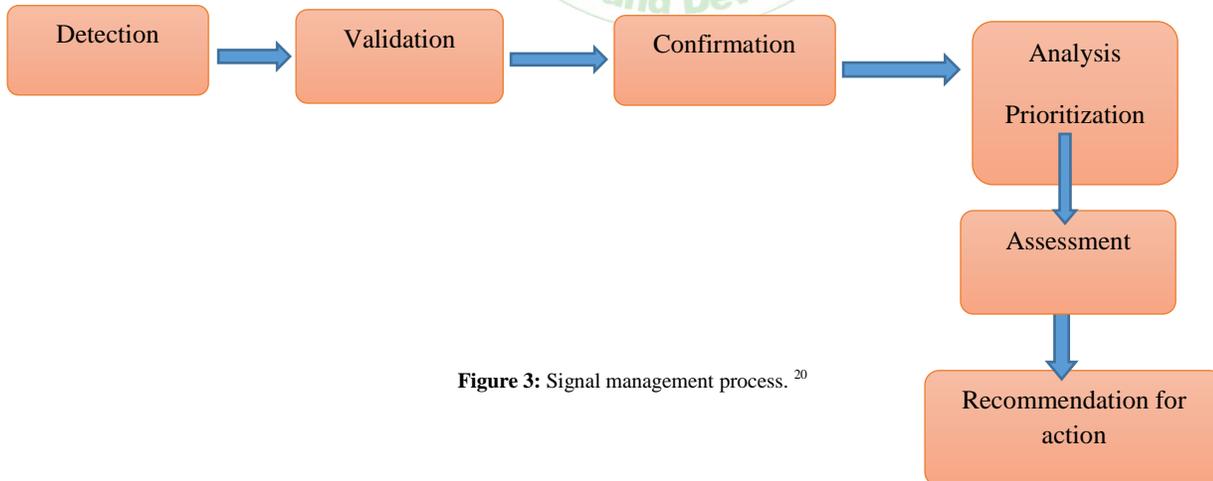


Figure 3: Signal management process.<sup>20</sup>

**CONCLUSION**

The present study suggests that there is a persistent need to vigilantly capture and timely monitor all adverse drug reactions accruing from medication use to enhance the process of Signal generation. Signal detection is a cornerstone of drug development process ensuring drug

safety. Newly identified signals can be potentially helpful in mitigating patient suffering in future by building evidence based research outcomes. The early detection of Signals helps to improve patient safety and reduce economic burden due to escalating cost of medications and unwanted adverse effects associated with it. Active surveillance by all healthcare professionals is the need of the hour in-order to

obtain drug safety information at an early stage and to make proper and rationale use of medicines. Pharmacovigilance is an essential tool to develop newer methods which can strengthen the current system of Signal generation. Adequate training and awareness programmes should be routinely conducted for healthcare professionals serving the need to create the difference and bring in the necessary change that is required.

### NEED FOR THE STUDY

The present study will help in generating information about incidence of new Drug-ADRs combinations in clinical practice with the potential to generate drug safety signals and inculcate a culture among healthcare professionals to develop pharmacovigilance practices. Early identification of associations between compounds and adverse events will generate new safety signals.

There is an impelling need to undertake clinical research studies for identification of potential adverse outcomes, identification of signals and generation of evidence based data to support clinical findings.

The pharmacovigilance of tomorrow will serve the clinical need of coming generations ensuring safe use of drugs and, improvement in health sector, reducing economic burden and building patient's confidence in the health care system.

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