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# PHARMACOVIGILANCE: A WAY FOR BETTER TOMORROW

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**ABSTRACT**
Pharmacovigilance procedures are necessary for evaluation of medicines. Thus Pharmacovigilance aims at detection, assessment and prevention of adverse effects or of any possible drug related problems. Reports of suspected adverse drug reactions (ADRs) are the basis of pharmacovigilance surveillance of drugs. So there is need of method for summarising the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. Need for a Pharmacovigilance Plan and sets out its principles of good practice for the design and conduct of observational studies.

**KEYWORDS:** Pharmacovigilance, Surveillance, Medicines, Adverse drug reactions.

## INTRODUCTION

Pharmacovigilance is more than spontaneous reporting alone, and the evaluation of medicines is more than pharmacovigilance. Pharmacovigilance aims at the detection, assessment and prevention of adverse effects or of any other possible drug- related problems[1-2]. The ultimate goal of pharmacovigilance is to foster the rational and safe use of medicines.The main aim of pharmacovigilance is to:

- Identify new information about hazards associated with medicines.
- Prevent harm to patients[3].

Modern medicines have changed the way in which diseases are managed and controlled. However, despite all their benefits, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and even death. In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality. Aside from the intrinsic dangers associated with the products themselves, individual patients may exhibit particular and unpredictable sensitivities to certain medicines. In addition, if more than one medicine is prescribed, there is always a risk of negative interactions. The selection and use of the best and safest medicine(s) for a given individual out of the many choices available thus requires considerable skill on behalf of the prescribing practitioner[4].

After approval is granted for a medicine, case reports of suspected adverse reactions are direct evidence both -scientifically and legally- in further regulatory and decision making. However, because of variable underreporting and a causal relationship in most case reports, these data are difficult to interpret and may not suffice as a legal evidence. Through the years doubt has been expressed on several occasions regarding the validity of spontaneous reporting[5-7].

Reports of suspected adverse drug reactions (ADRs) are the basis of pharmacovigilance surveillance of drugs. The occurrence of phocomelia related to thalidomide use by pregnant women in the 1960s brought an increased awareness of the necessity to detect, in as early a stage as possible, effects of marketed drugs which are unknown at the time a drug goes to market.

In a number of countries the pharmacist plays an important role in the reporting of suspected ADRs, but in other countries, mainly the Nordic countries, reports from pharmacists are not accepted by registration authorities[8-9].

So there is need of method for summarising the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. Need for a Pharmacovigilance Plan and sets out its principles of good practice for the design and conduct of observational studies[10-11].

### Need For Pharmacovigilance

- While medicines have led to major improvement in the treatment and control of diseases, they also produce adverse effects (Table 1)[12-15] on the human body from time to time.
- While many drugs are precisely targeted to the causes and mechanisms of disease, they may also have minor or distressing effects on other parts of the body, or interact negatively with the systems of the particular individual or with other drugs or substances they are taking, or not work well or at all for some, many or all of those who take them for illness.
- There are risks in any intrusion into the human body, whether chemical or surgical. Nothing in this field is entirely predictable as the interaction between chemicals and the human body may produce surprise.
- Efficacy is used to express the extent to which a drug works under ideal circumstances (i.e., in clinical trials)[4,16].

### Finding The Risks Of Drugs

Pharmaceutical companies are required by law in all countries to perform clinical trials, testing new drugs on people before they are made generally available. The manufacturers or their agents usually select a representative sample of patients for whom the drug is designed – at most a few thousand – along with a comparable control group. The control group may receive a placebo and/or another drug that is already marketed for the disease.

### Pharmacovigilance vs Clinical Trials

- The purpose of clinical trials is to discover: if a drug works and how well
- If it has any harmful effects, and
- Its benefit-harm-risk profile - does it do more good than harm, and how much more? If it has a potential for harm, how probable and how serious is the harm[17]?

Clinical trials do, in general, tell us a good deal about how well a drug works and what potential harm it may cause. They provide information which should be reliable for larger populations with the same characteristics as the trial group - age, gender, state of health, ethnic origin, and so on. On the other hand, the pharmacovigilance provides an efficient tool.

### Aims Of Pharmacovigilance

- to improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions;

- to improve public health and safety in relation to the use of medicines;
- to contribute to the assessment of benefit, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use;
- to promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public[4,18-19].

**Limitation Of Clinical Trials**

- A clinical trial can never tell you the whole story of the effects of a drug in all situations.
- A clinical trial has a limitation in determining the ADRs of any drug.

On the other hand, pharmacovigilance determines the whole ADME of the drug and efficient procedure in rectifing the ADRs associated with any drug.

**Why Pharmacoviglance Essential: The Example Of Thalidomide**

Thalidomide was introduced in 1957 and widely prescribed as an allegedly harmless treatment for morning sickness and nausea. It was soon linked to a congenital abnormality which caused severe birth defects in children of women who had been prescribed this medicine during pregnancy. By 1965, thalidomide had been removed from the market in most countries. Nevertheless, it continued to be used for the treatment of leprosy, and in more recent years, its indications have been extended to a much wider range of medical conditions. These uses are allowed only under strict supervision and specialist advice. Despite these precautions, between 1969 and 1995, 34 cases of thalidomide embryopathy were registered in leprosy endemic areas in South America by the Latin American Collaborative Study of Congenita Malformations[16-19].

So to protect the people from the tragedy such as the above, there is need to monitor the effects of the medicines.

**Pharmacovigilance In Practice: The Example Of Cerivastatin**

Cerivastatin was first approved as a lipid-regulating agent in 1997. By 2000 a total of 549 cases of rhabdomyolysis associated with cerivastatin use had been reported to the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. Consequently a signal was issued regarding an association between cerivastatin, myopathy and rhabdomyolysis. In November 1999 in the United States, and in March 2000 in Canada, prescribing information was changed to include a contraindication for the combined use of cerivastatin and gemfibrozil, another lipid-regulating medicine. A similar action was taken in Australia in February 2001, and a warning issued to alert prescribers to the possibility of rhabdomyolysis occurring with all statins. In June 2001 Europe-wide regulatory action was taken to contraindicate the combined use of cerivastatin and gemfibrozil. On 8 August 2001, the manufacturer voluntarily withdrew cerivastatin from the market on the grounds of an increased risk of rhabdomyolysis, particularly when used in combination with gemfibrozil[20].

**Pharmacovigilance Methods (fig. 1)**

The best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors should employ the most appropriate design. The Annex provides a summary of the key methods used in pharmacovigilance. This is provided to aid sponsors considering possible methods to address specific issues identified by the Safety Specification. This list is not all-inclusive, and sponsors should use the most up-to-date methods that are relevant and applicable.

**Design and conduct of observational studies:** Carefully designed and conducted pharmacoepidemiological studies, specifically observational (non-interventional, non-experimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator "observes and evaluates results of ongoing medical care without 'controlling' the therapy beyond normal medical practice"[21]. Before the observational study that is part of a Pharmacovigilance Plan commences, a protocol should be finalised. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the Pharmacovigilance Plan. Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings. It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology[22]. In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed. The highest possible standards of professional conduct and confidentiality should always be maintained and any relevant national legislation on data protection followed.

**1. Passive surveillance**

**Spontaneous reports:** A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organisation (e.g., WHO, Regional Centres, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme[23].

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions.

Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug[24-27].

**Systematic methods for the evaluation of spontaneous reports:** More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection[28-30]. Data mining techniques have also been used to examine drug-drug interactions[31]. Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should

be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity).

Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognising the possibility of false positives.

**2. Stimulated reporting**

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods.[32] Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information. During the early post-marketing phase, companies might actively provide health professionals with safety information, and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early post-marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). This should be regarded as a form of spontaneous event reporting, and thus data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

**3. Active surveillance**

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous pre-organised process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact[33]. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

**Sentinel sites:** Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites[34]. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, haemodialysis centres, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

**Drug event monitoring:** Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.

Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

**Registries:** A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardised questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition[33,35].

**4. Comparative observational studies**

Traditional epidemiologic methods are a key component in the evaluation of adverseevents. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are crosssectional studies, case-control studies, and cohort studies (both retrospective and prospective)[36-39].

**CONCLUSION**

Communicating the potential harm of drug-use to physicians and patients is a matter of high priority and every manufacturer should carry out the responsibility or actively participate in the process. Early detection of safety signals from clinical trials and proactive postmarketing surveillance is necessary to identify the risks associated with the products. Number of recent high profile drug withdrawals point towards this fact. Information collected during the pre-marketing phase of drug development may not detect rare ADRs. The use of a drug during a clinical trial is under controlled conditions, also, limited and selected numbers of patients are enrolled in the clinical trials. Drug use in special situations and population or drug interactions may not be studied. Therefore, the post-marketing surveillance of drugs is important.

Spontaneous ADR reporting, during post-marketing surveillance, has shown to detect adverse event signals resulting from drug use in the population. With this awareness, pharmacovigilance is instrumental in continuously monitoring unwanted effects and other safety aspects of drugs that are already in the market apart from being vigilant in pre marketing monitoring. It believes that proactive monitoring of the risks helps to place robust risk management plans throughout the life cycle of the product.

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**Table 1: Classical Examples Of Serious And Unexpected Adverse Reactions**

| Medicine | Adverse drug reaction |
|---|---|
| Aminophenazone | Agranulocytosis |
| Chloramphenicol | Aplastic anaemia |
| Clioquinol | Myelooptic anaemia |
| Erythromycin estolate | Cholestatic hepatitis |
| Fluothane | Hepatocellular hepatitis |
| Methyl dopa | Haemolytic anaemia |
| Oral contraceptives | Thromboembolism |
| Practolol | Sclerosing peritonitis |
| Resperine | Depression |
| Statins | Rhabdomylosis |
| Thalidomide | Congential malformations |

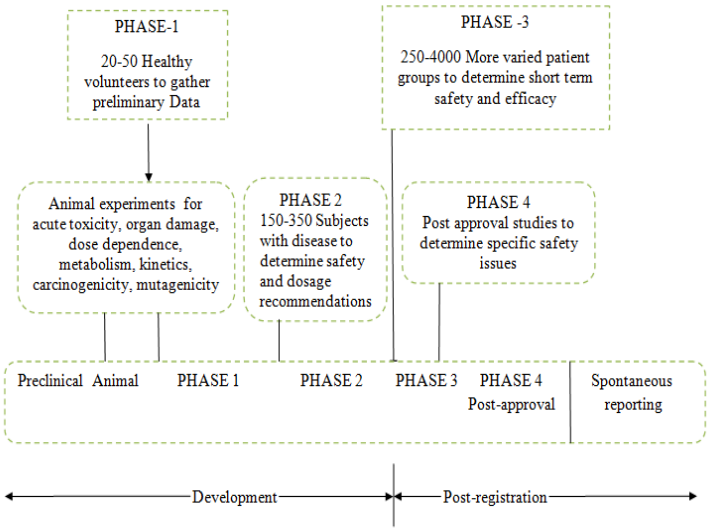


**Fig.1 clinical development of medicines**