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Editorial

# Role of Pharmacovigilance in ensuring safety of patients

## 1. Introduction

Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems particularly long term and short term adverse effects of medicines.[1] Stringent safety issues were initiated and legislated in 1938, in response to Sulfanilamide disaster. Sulfa compounds were considered the 'miracle drugs' as they killed a wide range of harmful bacteria. The drug was prepared in the form of an elixir by dissolving the drug in ethylene glycol. As a result of which, 107 people including 100 children were killed because of the poisonous solvent (diethylene glycol). In response to this, new law was made in FDA (established in 1906) which required the safety testing of new drugs before marketing and the New Drug Application (NDA) should incorporate safety data along with adequate labeling. Significant changes in the Pharmacovigilance system were brought after the Thalidomide disaster in 1961, which resulted into active participation from regulatory authorities, industry and health-care workers. Thalidomide was used for pregnant women, which resulted into congenital anomalies (i.e. phocomelia) and resulted into the withdrawal of drug from the US market in 1961. A collaborative effort was made by 10 countries in 1968 to cooperate with WHO for International drug safety monitoring (i.e. Uppsala Monitoring Centre, in Uppsala, Sweden). This cooperation emphasized the efficacy and safety of drugs and standards were set, which the new drugs were required to meet, before getting authorization for marketing.[2] Pharmacovigilance continues throughout the product life cycle of the drug. When a drug is administered or launched into the market, there exist a lot of safety problems. These problems can be easily detected by Pharmacovigilance studies. Pharmacovigilance is of core importance to identify, check and quantify the risk factors which usually occur when the drug is administered. Pharmacovigilance also promotes the rational use of drugs in mass treatment program.[3] The purpose of Pharmacovigilance is to detect the new adverse events and understand the safety profiles of the drugs and report to the national regulatory authorities. The scope of Pharmacovigilance has been extended from detection of unknown or poorly understood 'adverse drug events' to detection of 'new signals'. Now, herbals, traditional medicines, complementary medicines, blood products, biological, medical devices, vaccines, etc. have been included as well. Besides, issues like substandard medicines, medication errors, lack of efficacy reports, use of medicines for unapproved indications, case reports of acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of medicines, adverse interactions of medicines with chemicals, other medicines and food etc. have found an important place in Pharmacovigilance.[4]

## 2. Aims of Pharmacovigilance

Pharmacovigilance plays a major role in ensuring public health and safety. It improves patient care and safety in relation to the use of medicines. It contributes to the assessment of benefit, risk, effectiveness of medicines and ensures the correct, more effective, safe and rational use of medicines. Understanding, education and clinical training are provided under Pharmacovigilance system. It also provides and promotes effective communication with the public.[5]

## 3. Need for Pharmacovigilance

Clinical trials are usually conducted under well-controlled conditions, but when the drug is marketed it is extremely difficult to predict efficacy, adverse effects and total risk-benefit ratio under actual conditions. The number of patients exposed during the clinical trials is very less but when the drug is marketed it is used by a large number of patients which leads to the detection of more rare adverse events which would not usually be detected in clinical trials. One of the important factors to be considered is short duration of clinical trials; usually continue for a period of weeks to months. Once drug is approved and marketed, many drugs are taken intermittently or regularly for a period of years. Adverse experiences that require a long latency period from

time of drug exposure to event and those that occur only after chronic exposure to a drug are difficult to recognize in clinical trials. In clinical trials patients are selected based on a stringent inclusion/exclusion criteria, usually do not involve special groups of people (elderly, children, pregnant women). Besides, patients are selected for a specific disease and thus concomitant medications are limited. Also, patients included in clinical trials are closely monitored and frequently investigated for the duration of the clinical trial. When the drug is marketed the drug is used by such special groups of people, patients may be taking that drug and numerous other drugs concomitantly which leads to drug interactions. Increasing penetration of market by substandard drugs in recent years further makes it necessary to implement an effective and robust Pharmacovigilance program.

## 4. Definitions

### 4.1. *Adverse event*

Any untoward medical occurrence, that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.[5]

### 4.2. *Adverse drug reaction (ADR)*

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. An adverse reaction, contrary to an adverse event is characterized by the suspicion of a causal relationship between the occurrence i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.[5]

### 4.3. *Individual case safety reports (ICSRs)*

A report that contains information describing the suspected ADR related to the administration of one or more medicinal products to an individual patient.[5]

### 4.4. *Serious adverse event (SAE)*

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is life-threatening
- Congenital anomaly/birth defect
- May jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.[5]

### 4.5. *Signal*

A reported information on a particular causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information.[5]

### 4.6. *Suspected unexpected serious adverse reaction (SUSAR)*

A SAE becomes a SUSAR, if serious event is suspected (possibly, probably or definitely) to be related to the investigational medicinal product and is unexpected, i.e. not previously documented in any of the product information or protocol.[5]

## 5. Methods used in Pharmacovigilance

Methods to be used depend on product to be given to patient, indications for which to be used and populations being treated. Most relevant and commonly used methods are given below.

### 5.1. *Spontaneous reporting*

This is a type of unsolicited response from which new, rare and serious ADRs signals are detected.[6] Reports of suspected ADR are forwarded to Pharmacovigilance centre by health care professionals, consumers and patients. All reports are analyzed by centre and if new ADR signals appear, all stakeholders are informed of risk associated with it. These reports are also notified to drug regulatory authority of the country. Spontaneous reporting is also known as voluntary reporting. All countries have different reporting systems like National Pharmacovigilance System in India, USFDA Yellow Card Scheme but they follow same ideology. Suspected ADR reporting forms are available to health care professionals including pharmacists, nurses for giving details of suspected ADR, details of patient, suspected drug and details of the doctor (or prescriber). A complete marketed life of drug is monitored by spontaneous reporting. The main criticism of this approach is under-reporting and selective reporting.[2] Under-reporting may lead to false conclusion of absence of real risk and selective reporting may lead to false impression of presence of risk that does not exist. Even incident rates cannot be determined by spontaneous reporting.

### 5.2. *Case series*

Case series include reports on two or more people with particular outcome or experience to the drug exposed. They give the proof of association between the drug and adverse event, but they are more useful for generating hypothesis than for verifying it. In USA, case series reports of valvular heart diseases because of taking anorexant drug combination of Phentermine and Fenfluramine for weight reduction lead to withdrawal of Fenfluramine from market.[5,6]