CHAPTER

1

# Introduction

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## 1.1 INTRODUCTION

Pharmacovigilance is the branch of pharmacology that detects, assesses, understands and prevents short-term and long-term adverse drug reactions (ADRs)[1]. The word pharmacovigilance is made up of two words, i.e. '*Pharmakon*' and '*Vigilance*'. *Pharmakon* is a Greek word which means drug whereas *Vigilance* is a Latin word which means to keep watch[2]. In simple words, pharmacovigilance is the science of collecting, monitoring, assessing and evaluating information from healthcare professionals (HCPs) and patients on the adverse effects of medications, biological products, vaccines, blood products, medical devices as well as herbal and traditional medicines[3]. The main objective of the collected information is to identify new information about the risks related to medicines and to prevent patients from harm.

The process of pharmacovigilance allows the regulatory authorities to continue to assess the risks and benefit profile of medicines throughout their life cycle. Apart from this, the process of pharmacovigilance detects serious adverse events and new drug safety signals that were not detected in preclinical and clinical trials[4]. Previously, pharmacovigilance included only adverse drug reactions related to traditional medicines, but now it covers herbal, traditional and complementary medicines, blood products, medical devices as well as vaccines[5].

## 1.2 ADVERSE DRUG REACTION (ADR) AND ADVERSE EVENT (AE)

An adverse drug reaction (ADR) is any noxious and unintended response to medicines at a therapeutic dose normally used for the prophylaxis, diagnosis, and treatment of the disease. ADRs are causally associated with the use of medicinal products[6]. An adverse event (AE) is a medical occurrence that is temporarily associated with the use of medicinal products but not necessarily causally related to them[6].

## 1.3 CLASSIFICATION OF ADRS

ADRs are classified based on seriousness, listedness, and etiology. Based on seriousness, ADRs are classified into two main types, i.e. serious and non-serious. As per the ICH

guidelines, a serious adverse drug reaction or adverse event is any untoward medical occurrence at any dose[7] which results in:

- The death of the individual
- A life-threatening situation
- A patient requiring hospitalization or prolonged existing hospitalization
- A persistent or significant disability
- A medically important event or reaction.

In the pre-marketing phase, the medically important event or reaction should be considered based on medical and scientific judgment. For example, any important medical event which immediately not life-threatening or results in death but may be required intervention to prevent one of the other outcomes, which are mentioned above. The treatment is at home for allergic bronchospasm, blood dysphasia or convulsions that do not require hospitalization but require intervention to prevent the death of the patient is one of the examples of the medically important event[7].

### Non-Serious ADR

The ADRs apart from the above-mentioned criteria of serious ADRs are known as non-serious ADRs[7].

Based on the listing, the ADRs are also classified mainly into two types, i.e. listed/expected and unlisted/unexpected.

#### *Listed/expected adverse drug reaction*

An ADR whose nature, severity, specificity, and outcome are consistent with the applicable product information investigator's brochure (IB) for an unapproved investigational medicinal product and summary of product characteristics (SMPCs) or company core data sheet (CCDS) for marketed products is called listed/expected adverse drug reaction[8].

#### *Unlisted/Unexpected drug reaction*

An ADR whose nature, severity, specificity, and outcome are not consistent with the applicable product information investigator's brochure (IB) for an unapproved investigational medicinal product and summary of product characteristics (SMPCs) or company core data sheet (CCDS) for marketed products is called unlisted/unexpected drug reaction[8].

On the basis of etiology, ADR are classified into various types which are mentioned below:

- *Type A or dose-dependent ADR:* Approximately 80% of ADRs are usually fallen under type A ADRs. These ADRs occur at the therapeutic dose and often predictable.
- *Type B or dose-independent ADR:* These ADRs are rare, unpredictable and unrelated to the dose of the medicinal product. The major reason for these types of ADR is immunological and genetic mechanisms. The well-known example of type B-ADR is hypersensitivity and idiosyncratic reactions[9].

Apart from these two main types, ADRs are also further classified as Type C (chemical), Type D (delayed), Type E (exit and end of treatment), Type F (familiar), Type G (genotoxicity), Type H (hypersensitivity) and Type U (unclassified)[9].

## 1.4 CONSEQUENCES OF ADRS

All medicinal products have the potential to produce adverse drug reactions (ADRs). Whenever a drug is consumed, the risk is taken, but the magnitude of the risk has to be considered along with the magnitude of expected therapeutic benefits. This information will be helpful to decide whether to use or not to use the particular drug in a given patient, adverse drug reactions (ADRs) are the 4th to 6th commonest cause of death. Approximately, 6.5 to 6.8 % of all the hospital admissions are due to the ADRs. Fortunately, more than 50% of ADRs are definitely or potentially avoidable[10].

*"Sometimes dying from the disease is unavoidable*
*But dying from medicines is unacceptable"*

## 1.5 NEED OF PHARMACOVIGILANCE

In the pre-marketing phase, the safety information related to the drug is collected by conducting animal studies (preclinical) and human studies (clinical trials). However, these studies are not optimal due to the below-mentioned reasons.

- Limited numbers of patients in clinical trials (up to a few thousand patients)
- Strict inclusion and exclusion criteria (eliminate patients that have other diseases and take other medications)
- Exclusion of special groups (children, elder, pregnant women in clinical trials) unless our medication is being developed for use in these groups of the population
- Difficult to detect ADRs with long latency as the duration of clinical trials is limited or short.

After the launch of the drug in the market, a large number of patients will be exposed including the ones with concomitant disease, taking concomitant medications, pediatric, geriatric, pregnant women which will put the patient at risk of ADRs. Thus, to study rare ADRs, ADRs with long latency and ADRs in a specific group of populations, careful monitoring of drugs in the post-marketing phase is essential[11].

## 1.6 OBJECTIVES OF PHARMACOVIGILANCE

The main objectives of pharmacovigilance are mentioned below[12]:

- Quantification of previously recognized ADRs
- Identification of ADRs
- Evaluation of the effectiveness of medicines in real-world situations
- Improve patient care and concerning the use of medicines
- Detection of an increase in the frequency of known ADRs
- Identification of risk factors and possible mechanisms underlying ADRs
- Risk and benefit analysis of medicines
- Promote understanding, education, related to ADRs
- Promote reporting of ADRs.

## 1.7 OVERALL PROCESS OF PHARMACOVIGILANCE

The general overview of the overall process of pharmacovigilance is mentioned below:

a. Data collection, verification (quality check) and triage

b. Data entry in the database
c. Case processing (case narrative writing, coding of ADRs and drugs)
d. Quality check (QC)
e. Causality assessment (Medical review)
f. Timely reporting of Individual Case Safety Report (ICSR) to regulatory authorities (individual reporting or expedited reporting)
g. Signal detection and assessment
h. Aggregate reporting (PSURs)
i. Submission of periodic safety update reports (PSURs) to regulatory authorities
j. Action.

The process generally starts with a collection of information regarding ADRs from patients, healthcare providers, medical literature, physicians, pharmaceutical company's sales team or pharmacists, etc. (Fig. 1.1). The various sources of information regarding ADRs are fully described in Chapter 3. A valid case needs to have four elements; an adverse event, a reporter, a patient, and a drug. The next step is Triage of cases which means prioritizing the case for reporting to regulatory authorities. An over-simplification of triage would be to report deaths and life-threatening unexpected reports in 7 days and other adverse reactions in 15 days as there are also other occasions where expedited reporting is required[13]. The reporting of ADR is varying among regulatory authorities. The next step is to enter the data in the database and quality check of data in terms of all details [patient information, drug information (formulation, dose, etc.), ADR information, reporter information)]. After that, the medical reviewer writes the narrative for the particular case based on the available information and does the coding of an event by using medical dictionaries (MedDRA, WHO-ART, WHO-DDE, CONSTART, ICD9CM, etc.)[14].

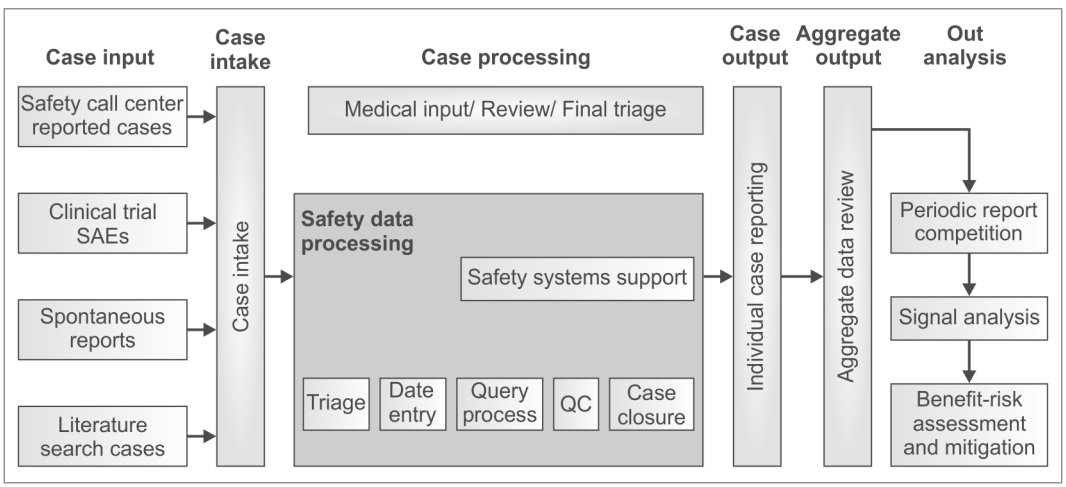


**Fig. 1.1:** Overall process of pharmacovigilance

Finally, medical reviewers do the causality assessment between the drug and event by using the most commonly used methods, i.e. WHO causality assessment scale and Naranjo Scale. After causality assessment, a case with ADR, reports to the regulatory authority (as per requirements). This is all about expedited reporting of ADRs. In aggregate reporting, periodic safety update reports (PSURs / PBRERs) will be submitted

by pharmaceutical companies or sponsor to a regulatory authority. For the writing of these reports, various types of data are required such as marketing authorization status (MAS) of the drug, sale data, update of regulatory actions, literature data, signal data, clinical trial data, efficacy data, etc.). Finally, these reports are submitted to regulatory authorities for the necessary action (Fig. 1.1).

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