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**Review Article**

# A Comprehensive Review On Pharmacovigilance: Enhancing Drug Safety And Surveillance

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## ABSTRACT

Pharmacovigilance (PV) is a relatively new discipline in the pharmaceutical industry. Having undergone rapid growth over the past 2 decades, PV now touches many other disciplines in the research and development enterprise. With its growth has come a heightened awareness and interest in the medical community about the roles that PV plays. This article provides insights into the background and inner workings of PV.

Pharmacovigilance plays a pivotal role in ensuring the safety of pharmaceutical products throughout their lifecycle. This comprehensive review explores the multifaceted landscape of pharmacovigilance, focusing on its integral role in enhancing drug safety and surveillance. The review begins by elucidating the fundamental concepts of pharmacovigilance, emphasizing its significance in identifying, assessing, and preventing adverse drug reactions (ADRs). It delves into the historical evolution of pharmacovigilance, tracing its development from a reactive post-marketing activity to a proactive and integrated system. All healthcare providers have roles to play in maintaining a balance between a medicine's benefits and risks. Once a drug is available to the public, making a determination about its safety is the shared responsibility of all who are part of the prescribing process, including patients. The role of healthcare professionals is vital in recording and reporting suspected ADRs in order that regulatory agencies are alerted of emerging safety concerns and thereby facilitating timely and appropriate action. As a part of health care team every pharmacist must have knowledge about adverse drug reaction monitoring systems and pharmacovigilance

## INTRODUCTION

A century-long history of numerous catastrophic incidents has greatly influenced the structures and procedures involved in drug development today, particularly those related to pharmacovigilance (PV). In an era of diverse therapeutic modalities and increasing globalization of drug development and distribution, the need for robust surveillance

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mechanisms has never been more pronounced. This review aims to delve into the multifaceted realm of pharmacovigilance, examining its evolving role in enhancing drug safety and surveillance. Pharmacovigilance, derived from the Greek words pharmakon (drug) and vigilare (to keep watch), encompasses the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems. Post-marketing drug surveillance (keeping a tab on the adverse effects after it is launched in the market) is the heart of Pharmacovigilance. It enables effective long-term monitoring to ensure safety of drugs. As pharmaceutical interventions continue to advance, pharmacovigilance becomes paramount in safeguarding patients from potential risks associated with drug therapy. It serves as the sentinel for identifying adverse drug reactions (ADRs), ensuring that the benefits of medications outweigh their potential harms. [1]

The roots of pharmacovigilance trace back to seminal drug safety crises that underscored the need for systematic monitoring. Notable events, such as the thalidomide tragedy, spurred the establishment of formalized pharmacovigilance systems globally. Over the years, regulatory frameworks and reporting mechanisms have evolved, reflecting a collective commitment to enhancing drug safety.

The primary objectives of pharmacovigilance extend beyond mere surveillance. This review explores how pharmacovigilance endeavors to detect signals of potential harm early in a drug's life cycle, assesses the causality of adverse events, understands the underlying mechanisms, and implements preventive measures. It delves into the comprehensive scope of pharmacovigilance, examining not only adverse reactions but also other aspects of drug safety, such as medication errors, misuse, and abuse.

Pharmacovigilance is a collaborative effort involving healthcare professionals, regulatory agencies, pharmaceutical industries, and, increasingly, patients. The importance of engaging patients in reporting their experiences with medications is recognized as a cornerstone in understanding the real-world impact of drugs. [2]

## 2. PHARMACOVIGILANCE ACROSS THE GLOBE

Every country has its own pharmacovigilance system based on WHO guidelines. Let us see how some countries maintain their Pharmacovigilance systems.

### i. Europe

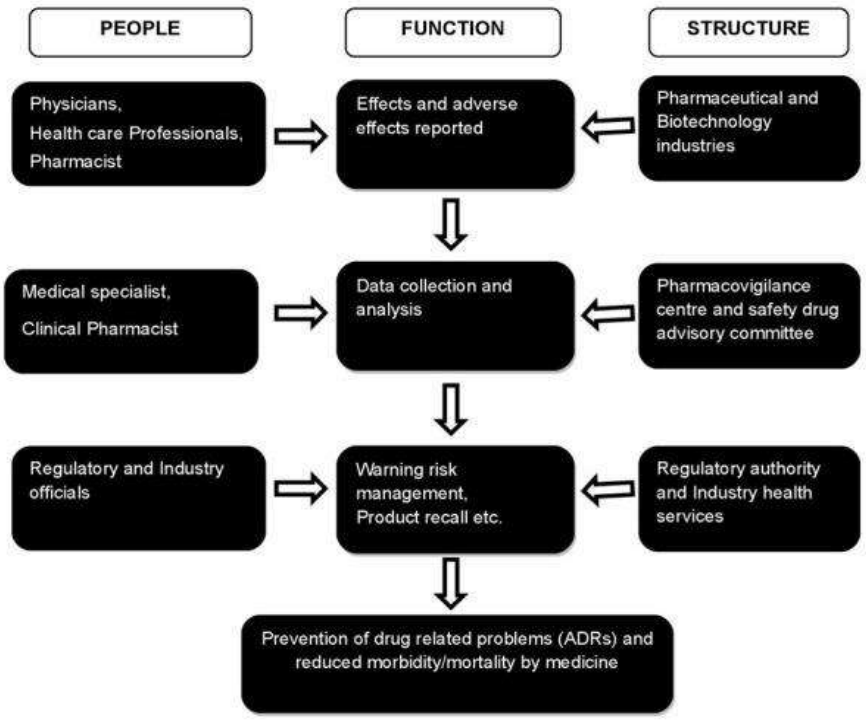
In Europe, the European Medicines Agency (EMA) coordinates and maintains the pharmacovigilance database called EudraVigilance, which contains the records of all the suspected adverse drug reactions. It also includes a separate database for veterinary adverse drug reactions.

### ii. United States

The United States uses a multi-faceted approach to maintain pharmacovigilance systems that include FDA, the pharmaceutical manufacturers, academic/non-profit organizations, and public citizens. Case reports related to adverse drug reactions are collected and managed by the US FDA.

### iii. India

In 2004, the Central Drugs Standard Control Organization (CDSCO), along with the Ministry of Health and Family Welfare, Govt. of India, launched the National Pharmacovigilance Programme (NPP) based on the WHO recommendations. The pharmacovigilance system is maintained by dividing the whole country into zones and regions. [3]




## 4. REPORTING SYSTEMS AND DATABASES:

**Pharmacovigilance Regulatory Reporting**

Pharmacovigilance regulatory reporting entails submitting different safety reports, based on the region or nation, to regulatory agencies like the FDA, EMA, and MHRA. These reports give regulatory authorities crucial information about the safety profile of medications and medical devices, allowing them to keep an eye on their safety and take appropriate action as needed.

**Types of Regulatory Reports**:

1. Individual Case Safety Report (ICSR)
2. Periodic Safety Update Report (PSUR)
3. Development Safety Update Report (DSUR)
4. Risk Management Plan (RMP)
5. Post-Authorization Safety Study (PASS) Report
6. Signal Detection Reports

Common pharmacovigilance regulatory reports, along with a detailed description for each:

**1. Individual Case Safety Report (ICSR):**

A comprehensive report on a specific instance of a suspected adverse medication reaction or device incident is called an ICSR. These reports come from a variety of sources, including literature, post-authorization safety investigations, spontaneous reporting, and clinical trials. CSRs include information on patient demographics, medical history, details of the suspected drug/device, description of the adverse event, and any relevant laboratory data. It is essential to submit ICSRs to regulatory bodies on time in order to track the safety of drugs and devices.

**2. Periodic Safety Update Report (PSUR):**

An aggregate report known as a PSUR gives a summary of a medication or device's safety profile over a given reporting period. It contains a risk-benefit analysis, cumulative safety data, and any new safety issues found during the reporting period. Regulatory bodies utilize PSURs to keep an eye on the safety of products that have been approved; the results may include label revisions, steps to reduce risks, or more research.

**3. Development Safety Update Report (DSUR):**

An annual safety report for investigational medications used in clinical trials is called a DSUR. A risk-benefit analysis, a cumulative summary of major adverse events, and any new

safety issues pertaining to the clinical trial are all included in the DSUR, which offers an overview of safety data regarding the study. This report assists regulatory bodies in keeping an eye on the safety of experimental medications while they are being developed clinically.

**4. Risk Management Plan (RMP):**

An RMP is a comprehensive document outlining the risk management system for a drug or device. It includes risk identification, risk evaluation, risk minimization, and risk communication strategies. RMPs are submitted to regulatory authorities and updated as new safety information becomes available. A well-designed RMP is essential for ensuring that potential safety risks are effectively managed throughout the product life cycle.

**5.Post-Authorization Safety Study (PASS) Report:**

A PASS report is generated from a study conducted after a drug or device has been approved to further assess its safety or to measure the effectiveness of risk management measures. These studies may be required by regulatory authorities or initiated voluntarily by the manufacturer. PASS results may be submitted as part of a PSUR or in a separate report, depending on the study and regulatory requirements.

**6.Signal Detection Reports:**

Potential safety signals are identified by signal detection reports using data from a variety of sources, including as literature, clinical studies, and spontaneous reports. These reports might lead to more research or action, including updated labels, risk-reduction strategies, or more studies. A key component of pharmacovigilance is signal detection, which aids in locating possible safety concerns that could not have been discovered during pre-approval clinical trials. [4,5]

**Databases used in pharmacovigilance:**

Pharmacovigilance involves the collection, monitoring, assessment, and prevention of adverse effects or any other drug-related problems. Databases play a crucial role in pharmacovigilance by storing, managing, and analyzing large volumes of data related to drug safety. Here are some databases commonly used in pharmacovigilance:

1. FDA Adverse Event Reporting System (FAERS): Managed by the U.S. Food and Drug Administration (FDA), FAERS collects and analyzes data on adverse events and medication errors submitted by healthcare professionals, consumers, and manufacturers.
2. WHO Global Individual Case Safety Reports (ICSRs) Database (VigiBase): Operated by the World Health Organization (WHO), VigiBase is one of the largest pharmacovigilance databases globally. It collects individual case safety reports from national pharmacovigilance centers and other sources worldwide.
3. European Medicines Agency (EMA) EudraVigilance Database: EudraVigilance is the European database for collecting and managing information on suspected adverse reactions to medicines that are authorized or being studied in the European Economic Area (EEA).
4. MedDRA (Medical Dictionary for Regulatory Activities): MedDRA is a standardized medical terminology used to facilitate sharing of regulatory information internationally for medical products used by humans. It is often used for coding adverse event terms in pharmacovigilance databases.
5. PubMed/MEDLINE: While not a dedicated pharmacovigilance database, PubMed and MEDLINE are widely used for literature reviews and research related to drug safety and adverse reactions.

National Pharmacovigilance Databases: Many countries have their own national pharmacovigilance databases where healthcare professionals and the public can report adverse drug reactions. These databases are often managed by the national health authorities.

**6.** Clinical Trial Databases: Information from clinical trials is crucial for pharmacovigilance. Clinical trial databases, such as ClinicalTrials.gov, may contain safety data on investigational drugs.

**7.** Pharmaceutical Company Databases: Pharmaceutical companies maintain internal databases containing safety data from clinical trials, post-marketing surveillance, and other sources. These databases are critical for monitoring the safety of their products.

**8.** Institute for Safe Medication Practices (ISMP) Databases: ISMP collects and analyzes medication error reports and provides recommendations to enhance patient safety. While not focused solely on adverse reactions, it contributes to overall drug safety efforts.

**9.** National Poison Data Systems: Poison control centers maintain databases that can be valuable for identifying and monitoring adverse drug reactions, especially in cases of overdose or poisoning.

**10.** These databases collectively contribute to the comprehensive monitoring and evaluation of drug safety throughout a product's lifecycle. The integration and analysis of data from various sources help identify potential safety issues, assess risks, and implement measures to ensure patient safety. [ 6,7,8]

## 4. ADVERSE DRUD REACTION ( ADR) MONITORING:

Adverse drug reaction (ADR) monitoring involves following steps:

I. Identifying adverse drug reaction (ADR)

II. Assessing causality between drug and suspected reaction

III. Documentation of ADR in patient's medical records

IV. Reporting serious ADRs to pharmacovigilance centres /ADR regulating authorities

### I. Identifying adverse drug reaction (ADR)

WHO defines ADR as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.

ADRs are mainly identified in the pre-marketing studies and in the post-marketing surveillance studies. Disadvantages of the pre-marketing studies are that they lack sufficient knowledge to extrapolate information collected from animal studies directly into risks in humans and very few number of subjects (not more than 4000) are exposed to the new drug prior to the general release of product into market. Another major disadvantage is that clinical trials can not be done in rare group of subjects like children, elderly and pregnant women. For cost reasons clinical trials often have short duration which means they can not generate information about long term adverse effects. As a consequence of the above reasons, only type A adverse reactions are known at the time of general marketing of a new drug. So, all other types of ADRs can only be identified in post marketing surveillance. Post marketing surveillance can be done by different methods:

1.Anecdotal reporting:

2. Intensive monitoring studies:

3. Spontaneous reporting system (SRS):

4. Cohort studies (Prospective studies) :

5. Case control studies (retrospective studies) :

6. Case cohort studies:

7. Record linkage:

8. Meta analysis:

9. Use of population statistics:

### II. Assessing causality between drug and suspected reaction:

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. There are three approaches to asses‟ causality.

These include

a) Opinion of an individual expert

b) Opinion of a panel of experts

c) Formal algorithms

Some of the important algorithms used are Naranjo, WHO, European ABO system, Kramer, Bayesian, Karch and lasanga and French imputation method. There is no gold standard for causality assessment. The categorisation of causal relationship between a drug and suspected adverse reactions varies with the scale adopted. WHO scale categorises the causality relationship into certain, probable, possible, unassessible/unclassifiable, unlikely, conditional /unclassifiable. The Naranjo's scale categorises the reaction as definite, probable, possible or unlikely. In general the following four different basic points can be considered in attributing a clinical adverse event to the drug.

1.Temporal time relationship between suspected reaction and drug

2. Dechallenge (cessation of drug)

3.Rechallenge (re introducing drugs)

4. Likelihood of other possible causes

**III. Documentation of ADRs in patient's medical records**

This aids as reference for alerting clinicians and other health care professionals to the possibility of a particular drug causing suspected reaction.

IV. Reporting serious ADRs to pharmacovigilance centre's / ADR regulating authorities

According to FDA, a serious reaction is classified as one which is fatal, life threatening, prolonging hospitalisation, causing a significant persistent disability, resulting in a congenital anomaly and requiring intervention to prevent permanent damage or resulting in death .

Different ADR regulatory authorities are - Committee on safety of medicine (CSM), Adverse drug reaction advisory committee (ADRAC), MEDWATCH, Vaccine Adverse Event Reporting System18. WHO-UMC international database maintains all the data of ADRs.

In India, national pharmacovigilance programme was officially inaugurated on 23rd November 2004. It has one national pharmacovigilance center located at CDSCO in Delhi, two zonal, five regional and twenty four peripheral centers. National pharmcovigillance center communicates all the reported ADR data to WHO – UMC international database.[ 9,10,11,12]

**5. SIGNAL DETECTION AND DATA MINING:**

Overview of signal detection and data mining in pharmacovigilance:

**1. Signal Detection:**

- Definition: A signal in pharmacovigilance refers to information that suggests a new and potentially causal association or a change in the known safety profile of a drug.
- Sources of Data: Signals can emerge from various sources, including spontaneous reporting systems, electronic health records (EHRs), clinical trials, scientific literature, social media, and other healthcare databases.

**Methods of Signal Detection:**

- Disproportionality Analysis: This involves analyzing the frequency of specific adverse events reported for a drug compared to the expected background rate.
- Temporal Analysis: Examining the timing of adverse events after drug administration to identify patterns.
- Signal Triage: Prioritizing signals based on factors such as seriousness, unexpectedness, and clinical importance.
- Data Mining Techniques:Applying advanced statistical and computational methods to identify potential signals.

**2. Data Mining in Pharmacovigilance:**

Data Sources: Data mining in pharmacovigilance involves extracting knowledge from large datasets. Common sources include spontaneous reporting databases, electronic health records, clinical trial data, and scientific literature.

**Techniques:**

- Association Rule Mining: Identifying relationships and associations between drugs and adverse events.
- Cluster Analysis: Grouping similar drugs or adverse events to discover patterns.
- Text Mining/Natural Language Processing (NLP):Analyzing unstructured text data from sources like scientific literature or social media to extract relevant information.
- Machine Learning: Employing algorithms to predict adverse events or identify potential signals based on historical data.

Challenges:

- Data Quality: Ensuring the accuracy and completeness of the data.
- Data Heterogeneity: Dealing with diverse data sources and formats.
- Signal Specificity: Differentiating true signals from background noise.
- Validation: Ensuring that the identified signals are clinically relevant and meaningful.

**3. Integration of Signal Detection and Data Mining:**

• Combining different methods enhances the robustness of signal detection.

• Continuous monitoring and iterative processes are essential for refining signals over time.

• Collaboration among regulatory agencies, pharmaceutical companies, and other stakeholders is crucial for effective signal detection and management. [13,14,15]

**6. PHARMACIST'S ROLE IN PHARMACOVIGILANCE :**

Pharmacists occupy a central and indispensable role in the realm of pharmacovigilance, actively contributing to the identification, assessment, and mitigation of adverse drug reactions (ADRs). Their unique position at the frontline of patient care equips them with the expertise to recognize and manage medication-related risks. Pharmacists play a critical role in counseling patients about potential side effects, ensuring proper medication usage, and conducting medication reviews to identify any signs of ADRs. Beyond patient interactions, pharmacists are integral in the reporting and documentation of ADRs, acting as vigilant gatekeepers who contribute valuable data to pharmacovigilance databases. Their role extends to promoting a culture of safety within healthcare settings, emphasizing the importance of accurate drug dispensing, monitoring drug interactions, and actively engaging in continuous education. As the healthcare landscape evolves, pharmacists are increasingly leveraging digital tools and electronic health records to enhance their pharmacovigilance contributions, ultimately fostering a safer and more informed approach to medication management. [16,17,18]

## CONCLUSION

This overview shows how the discipline of PV has undergone dramatic changes since the thalidomide tragedy and aftermath of the late 1950s and early 1960s. It is becoming a major global hub for clinical trials. Every year, a large number of new medications are launched, thus healthcare providers need to be aware of the significance of pharmacovigilance and ADR monitoring. Keeping in mind Hippocrates' injunction to "at least do no harm," every health care provider should view it as a part of their professional duty

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