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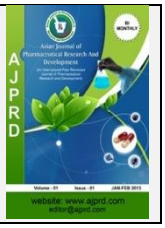

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Review Article

# Ensuring Data Safety: Pharmacovigilance Processes, ADR Reporting, Regulatory Bodies, and Software Solutions

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## A B S T R A C T

Pharmacovigilance (PV) is essential for ensuring drug safety by monitoring, detecting, assessing, and preventing adverse drug reactions (ADRs). Pharmacovigilance can be traced back to the thalidomide disaster in the 1960s, which resulted in the implementation of stringent drug safety regulations around the world. Signal detection, case processing, risk assessment, periodic reporting, and regulatory compliance are all part of the pharmacovigilance process, which aims at minimizing risks. Pharmacovigilance processes are monitored by a number of regulatory authorities around the world, including the FDA (Food and Drug Administration) in the United States, the EMA (European Medicines Agency), the MHRA (Medicines and Healthcare Products Regulatory Agency) in the United Kingdom, the CDSCO (Central Drugs Standard Control Organization) in India, and WHO's Uppsala Monitoring Centre. These organizations ensure that pharmaceutical companies follow safety guidelines and report ADRs properly. ADRs are reported using standardized forms such as MedWatch (FDA), Yellow Card (UK), and suspected adverse drug reporting forms (India). The data is processed using pharmacovigilance software such as Argus Safety, ArisG, VigiFlow, Vigi base, and Oracle AERS, facilitating case management, signal detection, and regulatory submissions. Beyond drug safety, pharmacovigilance has developed into specialized domains such as materiovigilance, which monitors the safety of medical devices, and ecovigilance, which evaluates the environmental impact of pharmaceutical products. Both fields ensure medical advancements do not harm public health or ecosystems.

**Key Words:** Pharmacovigilance, Signal Detection, Drug Safety, Materiovigilance, Ecovigilance

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## INTRODUCTION:

The WHO defines Pharmacovigilance (PV) as "the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problems." "An adverse event is defined as any untoward medical occurrence that may present during treatment with a drug but does not necessarily have a relationship with its use." "An adverse drug reaction is any noxious, unintended, and undesired effect of a drug that occurs at a dose used in humans for prophylaxis, diagnosis, therapy, or modification of physiological function" [1]. In 1961, Australian doctor W. Mc Bride introduced the domain of pharmacovigilance after the thalidomide tragedy, which involved fetal deformities due to the use of thalidomide during pregnancy for nausea and vomiting. The WHO initiated the "Programme for International Drug Monitoring" in 1961 to identify early PV signals [2].PV aims to detect and identify adverse drug reactions (ADRs), at-risk populations, and product safety to minimize risks associated with medication and safeguard public health [3]. The development of drugs occurs within a small, selected population. However, pharmacovigilance assesses the safety of drugs in real-world scenarios, which include a diverse population and prolonged drug use [4]. Low and middle-income countries (LMICs) face significant challenges in promoting pharmacovigilance practices, such as low awareness, low reporting rates, high use of traditional medicines, lack of trained personnel, and limited access to drug use data [5]. In clinical trials, pharmacovigilance plays a major role in suspecting ADRs in study participants through clinical examination, lab reports, and submitting information to regulatory authorities during drug approval [3,6]. Databases such as VigiFlow, VigiAccess, VigiBase, and VigiLyze are used by the Uppsala Monitoring Center, along

with Vigi Grade, Vigi Match, and Vigi Rank for case report analysis [7]. Electronic data capture and machine learning (ML) techniques are advanced technologies that optimize the benefit-risk profile of the drug in real-world settings [8]. The pharmacovigilance process consists of four stages: detection, assessment, understanding, and prevention of adverse drug reactions [9]. The Pharmacovigilance Programme of India (PvPI), with 250 monitoring centers around India, became a WHO collaborating center for Pharmacovigilance. This comprehensive review gives a brief explanation of the history of pharmacovigilance in India, types of adverse drug reactions, signal detection, clinical trials, risk-benefit analysis, post-marketing surveillance, materiovigilance, software used in PV, and the regulatory framework of pharmacovigilance.

## HISTORY:

A young girl, Hannah Grenner from England, died due to arrhythmia and pulmonary aspiration after the administration of chloroform as an anesthetic to remove an infected toenail in 1848 [10]. In 1906, the US Food and Drug Administration was established to look after the approval and safety of drugs. The tragedy of Thalidomide in 1961 changed European Pharmacovigilance, leading to the development of the "Yellow card" in the UK and the EC Directive 65/65 in the USA [11]. In India, clinical trials were globally recognized in the year 1996. In 1997, India joined with the WHO Adverse Drug Reaction Monitoring Program and it was not successful.

### Pharmacovigilance centres in India

In 2002, India established the 67th National Pharmacovigilance Center. In 2005, India's National Pharmacovigilance Program was initiated, and it was replaced by the Pharmacovigilance Program of India (PvPI) in 2010 [2].

The Central Drug Standard Control Organization (CDSCO) established the PvPl program, but later the responsibilities of the program were taken by the Indian Pharmacopeia Commission in Ghaziabad on 15 April 2011. The primary aim of the PvPI is to safeguard the health of the Indian population by preventing and reporting ADRs. PvPI coordinates with 250 adverse drug monitoring centers within India, and it became a WHO Collaborating Centre for Pharmacovigilance [2, 3, 12].

## OBJECTIVES OF PHARMACOVIGILANCE

- Improve the safety of public health related to drugs and medical interventions
- Identification of medication-related problems and communication with regulatory authorities
- Assessment of benefit v/s risk ratio
- Prevention of risk and maximizing benefits
- Promoting the rational use of medicines
- Education and training related to pharmacovigilance [13]

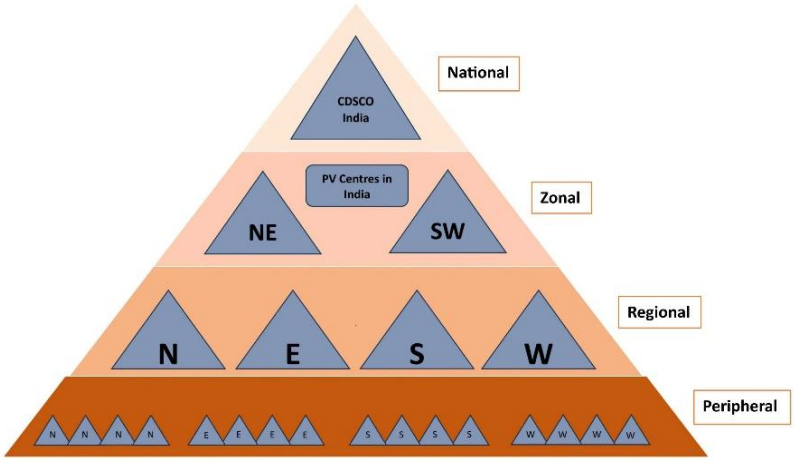


**Figure 1:** Pharmacovigilance centres in India

- **ADR Monitoring Centres (AMC's)** are responsible for the collection and reporting of ADRs to PvPI NCC, answering queries and checking for follow-ups, entry of collected data into databases such as vigiflow, and providing feedback to physicians.
- **PvPI-NCC (PvPI National Coordinating Centre):** helps in developing standard operating procedures (SOPs), casuality assessment, reporting of ADRs to CDSCO, and analysis of cases.
- **Zonal or Sub-zonal centers** are helpful for financial and managerial help to AMC (Zonal centers are located in Ahmedabad, Hyderabad, Ghaziabad, Kolkata, Mumbai, and Chennai)
- **CDSCO, New Delhi**: It takes the major decisions, provides recommendations, and collaborates with WHO-UMC
- **Zonal Centre**: Ahmadabad
- **Zonal Centre:** Hyderabad
- **North Zonal centre: Ghaziabad** a) Sub-Zone Office-Ghaziabad, b) Chandigarh, c) Sub-Zonal Office, Jammu
- **East Zonal Centre**: Kolkata-Air Port and Sea Office, Kolkata
- **West Zonal Centre**: Mumbai-Air Port and Sea Office, Mumbai, Jawaharlal Nehru Port Office, Navi Mumbai
- **South Zonal Centre**: Chennai, a) Airport and Sea Office, b) **Sub-Zonal** and Port Office, Chennai; c) Port Office, Kochi, Bangalore [15] as shown in Figure 1.

**Process of Pharmacovigilance:** As shown in Figure 2

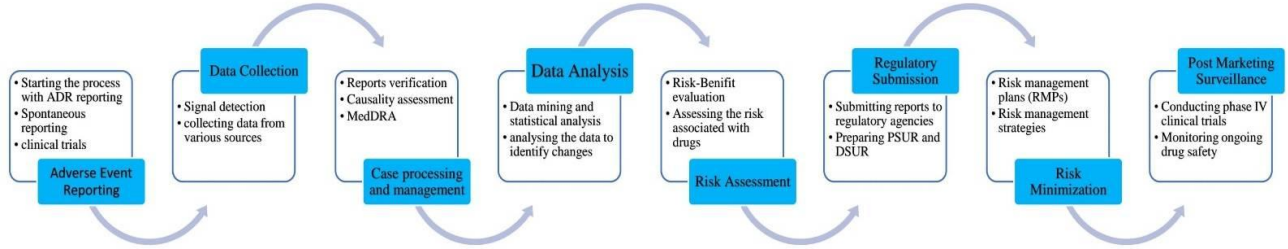


**Figure 2:** Steps in the pharmacovigilance program

## A. Signal detection

In Pharmacovigilance, signal detection includes the detection of increased frequency, severity, or specificity of a labeled event, new unlabelled adverse event, or newly identified drug-drug interactions. Signal detection not only identifies the undesirable effects of a drug, but it also identifies new populations at risk or a new beneficial effect of a drug.It is useful for reporting the causal relationship between an adverse event and a drug **[**15, 16]. Sources of signal detection include:

### a) Types of ADRs

i. **Type A** is directly related to the dosage of the drug. Sometimes, drug effects may be potentiated by hepatic diseases, genetic variations, electrolyte imbalances, etc. Hepatic diseases may lead to the production of clotting factors. Hypokalaemia and hypercalcemia caused by cardiac glycoside can also potentiate pharmacodynamic variations. ADRs can be detected as of low specificity, quantitative and controlled determination is needed. This will help validate the relationship and persistence of these adverse reactions [17,18]

ii. **Type B** ADRs are unpredictable and sensitive with little or no relationship with dosage. Type B reactions are classified into non-immunological and immunological ADRs. Non-immunological reactions are predictable ADRs because of overdose, collective effects, slow toxicity, drug interaction, metabolic modification, etc. Immunological Type B reactions are unpredictable; they may be due to cell-mediated, cytotoxic drugs induced or due to immunological reactions. The pharmacokinetic cause for type B ADRs may be due to the bizarre absorption and distribution. Pharmacodynamic reactions of type B ADRs depend on the individual's susceptibility to the specific drug [17,18]

iii. **Type C** reactions occur due to prolonged use of a drug, which is a major concern in public health. Some of the most common examples of chronic toxicities are analgesics-induced nephropathy and extrapyramidal effects due to antipsychotics. The adverse effects of the drugs gradually increase due to the use of the drug over time. Hyperadrenocorticism due to prednisolone use over time, abstinence syndrome after discontinuation of habit-forming drugs, etc are a few examples of Type c reactions [18].

iv. **Type D** reactions are called delayed ADRs. One of the examples of delayed types of adverse drug reactions is the development of secondary cancers due to the use of cyclophosphamide [18].

v. **Type E** reactions occur when the treatment is suddenly terminated. Withdrawal seizures due to stopping anticonvulsant drugs is one example which is considered Type E Adverse Drug Reaction[18].

### b) Types of Individual Case Safety Report (ICSR) in Pharmacovigilance

In pharmacovigilance, an ICSR is an important aspect for providing detailed information on the type of adverse drug reaction, which is helpful for regulatory authorities and pharmaceutical companies for monitoring safety and minimizing the risk. Individual case report forms exist in different forms, such as spontaneous reporting, reporting by using existing literature, regulatory authority reports, clinical trial reports, post-marketing surveillance, and solicited reports. ***Spontaneous reports*** are collected from volunteers and reported by healthcare professionals, pharmaceutical companies, or patients themselves. Some reports may not have enough clinical data but are used for trend analysis and signal detection. Published literature such as case series, case reports, and systematic reviews also serve as sources for reporting and this type of reporting system is called a ***literature report***. They are reported by pharmaceutical companies to the regulatory authorities after strictly monitoring the databases and medical journals. ***Regulatory authority reporting*** is done by regulatory bodies after receiving the data from spontaneous reports and clinical trials. This type of reporting contains aggregated data on drug safety and is useful for decision-making by regulatory bodies ultimately helping in the update of labels and giving safety warnings. The reporting of ADRs in phases of clinical trials is called as ***clinical trial reporting system***, which abides by Good Clinical Practice (GCP) guidelines. Mostly, these types of adverse drug reactions should be reported within 7 to 15 days. It requires complete information about the patient's medical condition, history, causality assessment, etc. Most types of ADRs reported by the clinical trial reporting system are serious adverse events and unexpected serious adverse events and this type of reporting system is useful for the approval of the drug by regulatory agencies. ***Post Marketing Surveillance (PMS) Reports*** are also one of the types of ADR reporting systems that collect data from different sources, such as patient registries, PMS studies, and risk management programs to promote risk minimization strategies. It helps to detect any rare or delayed type of ADRs from huge data to update the safety profile of a drug. A ***Solicited Reporting*** system utilizes data from surveys by

predefined proforma or systematic forms to assess real-world drug safety [19].

### Vaccine Adverse Event Reporting System (VAERS)

The Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) monitor vaccine safety issues through the Vaccine Adverse Event Reporting System (VAERS). All the adverse event reports are collected and reviewed by VAERS to promote safety and it determines whether further investigations are needed or not.CDC encourages reporting adverse events by anyone who experiences adverse events after receiving the vaccine. Clinically significant adverse events should be reported to the FDA to promote the safety of vaccines [20]. In India, adverse events are monitored by the Adverse Event Immunization Surveillance System.

### Preclinical and Clinical Trials as a source of data

**Preclinical:** The drug is tested in animals before being administered to human study participants in clinical trials. It establishes pharmacokinetic information, efficacy, and toxicology in animal models. Most of the preclinical studies are conducted in vitro or on animals.

Data is collected from the different phases of the clinical trial to assess the safety of pharmacovigilance. The phases of the clinical trial are:

i. **Phase 0**: This phase is generally composed of 10 people, where a sub therapeutic dose is administered to assess the pharmacokinetic and pharmacodynamic parameters
ii. **Phase I:** A Small group of healthy volunteers, such as 20-100 people, are recruited as study participants. If they are sub therapeutic, an ascending dose is given to establish the safety and efficacy of the drug
iii. **Phase II**: Around 100- 200 patients are recruited to assess the safety and efficacy of a drug at therapeutic doses of a drug molecule
iv. **Phase III:** These are randomized controlled trials where 1000 to 2000 patients are recruited into the study to determine the therapeutic effect
v. **Phase IV:** Phase IV is considered to be Post Marketing Surveillance, where close watch on drugs is done after the approval for use in a population of a country or all over the world.
vi. Information from different sources is submitted to the regulatory authorities for assessing drug safety [21,22].

### c) Regulatory Authorities involved in pharmacovigilance

The common goal of safeguarding public health is shared by three major regulatory bodies: the Central Drug Standard Control Organisation (CDSCO) of India, the European Medicines Agency (EMA), and the United States Food and Drug Administration (US FDA) [23].

i. **United States Food and Drug Administration (US FDA):** US FDA was established in 1906 to oversee the safety of food, drugs, biologics, medical devices, and cosmetics. USFDA is responsible for IND application, Clinical trials, New Drug Application/Biologics License Application, etc. FDA enforces strict regulations and priority review programs and maintains the FDA Adverse Event Reporting System (FAERS) through post-marketing surveillance. Adverse event reports, product quality complaints, and medication errors submitted to the FDA are stored in a database called the FDA Adverse Event Reporting System (FAERS), which supports a post-marketing safety surveillance program for every drug and biologics after the marketing approval. FAERS adheres to international safety reporting guidance and is coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology [23,24].
ii. **European Medicines Agency (EMA):** was established in 1995. It functions in collaboration with all European member states. It follows centralized, decentralized, and mutual recognition procedures. It also promotes conditional marketing authorization for life-saving drugs. It depends on certain authorities, such as the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC), to harmonize regulations across EU nations [24].
iii. **Central Drugs Standard Control Organization (CDSCO):** The CDSCO is India's national regulatory authority, operating under the Ministry of Health and Family Welfare. It regulates pharmaceuticals, biologics, and medical devices in India. The Ministry of Health and Family operates India's major regulatory authority, the CDSCO. It is responsible for receiving applications of Investigational New Drug (IND), approval to conduct clinical trials, New Drug Approval, and Subject Expert Committee (SEC) Review. The organization adheres to the Drugs and Cosmetics Act, 1940 and Rules, 1945, collaborates with state regulatory authorities, and expedites approvals for critical drugs during emergencies [24].

## B. Case processing and management:

In Pharmacovigilance, case processing is essential for safety surveillance. A causal assessment is a process of evaluation to estimate the likelihood of a specific drug, vaccine, or any other medical intervention causing an adverse event [25].

### a) Casuality assessment: Scales used for ADR reporting

1. World Health Organization (WHO) - Uppsala Monitoring Centre (UMC) causality assessment criteria
2. Dangaumou's French method
3. Kramer et al. method
4. Naranjo et al. method (Naranjo scale)
5. Balanced assessment method
6. Summary time plot
7. Ciba Geigy method
8. Loupi et al. method
9. Roussel Uclaf Causality Assessment Method (RUCAM)
10. Maria and Victorino (M and V) scale
11. Drug Interaction Probability Scale (DIPS)
12. Probabilistic or Bayesian Approaches
13. Australian method
14. Bayesian Adverse Reactions Diagnostic Instrument (BARDI) [26].

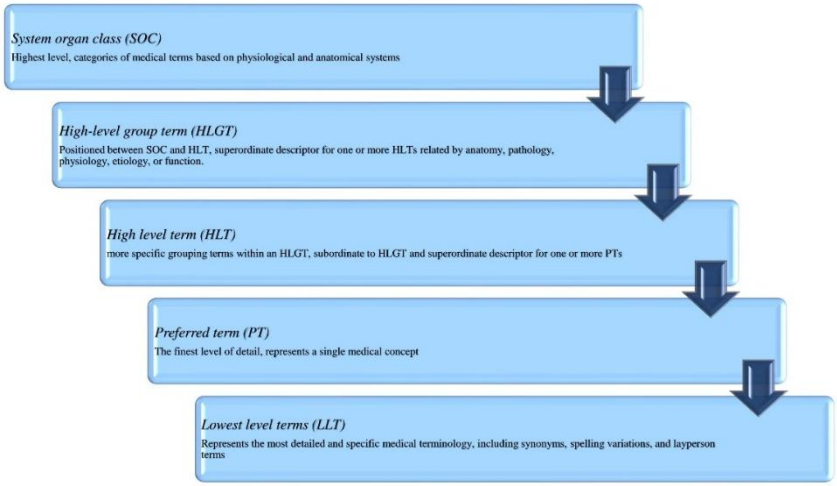


**Figure 3:** Med DRA five-level structure

### b) Medical Dictionary for Regulatory Activities (MedDRA) Overview

MedDRA, a standardized medical terminology developed by the International Council for Harmonisation (ICH), ensures consistent, comparable, and easily interpretable reporting of adverse event data across global jurisdictions, including pharmaceutical companies and academia. MedDRA is a hierarchical structure with five levels, each offering different levels of specificity. The highest level, System Organ Class (SOC), groups adverse events by body systems or disease categories. The lowest level is the Lowest Level Term (LLT), which provides the most specific detail. The levels in between, High-Level Group Terms (HLGT), High-Level Terms (HLT), and Preferred Terms (PT) allow for aggregation and more specific categorization. MedDRA is updated twice yearly to include recent developments in healthcare and to promote drug safety. MedDRA enables the use of standard medical terminology for reporting adverse drug reactions globally, and its structured vocabulary helps to report ADRs consistently from various platforms such as clinical trials and post-marketing surveillance. It helps to promote effective communication between healthcare providers, pharmaceutical companies, and regulatory authorities with standard terminology; which is helpful for signal detection with standardized coding. Regulatory agencies such as CDSCO, EMA, and FDA use MedDRA for pharmacovigilance. Pharmaceutical companies follow MedDRA for reporting ADRs during clinical trials, which is useful for smoothening drug approval processes. Other than ADRs, MedDRA is useful for other purposes in clinical trials, clinical trial safety summaries, ICSR, and periodic safety update reports (PSURs). A proper understanding of MedDRA terminology is required for accurate coding, which is essential for signal detection [27] shown in figure 3

### C. Evaluation: Data Mining and Statistical Analysis in Pharmacovigilance

The process of data mining involves statistical techniques to extract information that is previously unknown and consists of defining project goals, dataset acquisition, data cleaning, preprocessing, data mining, data interpretation, and utilization. Statistical techniques are used for data mining that are similar to conventional methods of examining data, but there is no prior hypothesis, and power calculations are performed. The main aim of statistical techniques is to generate a signal [28]. In pharmacovigilance, data mining is responsible for obtaining meaningful patterns for signal detection from a large database. Based on the type of data, there are various techniques employed for the extraction of required data through data mining. Some of them are disproportionality analysis, proportional reporting ratio, reporting odd ratio, Bayesian Confidence Propagation Neural Network (BCPNN), Multi-item Gamma Poisson Shrinker (MGPS), Temporal Data Mining, Sequence Pattern Mining, Time-to-Event Analysis, Text Mining, Clustering and Classification [29].

### D. Risk Assessment and Risk Benefit Evaluation

The potential benefits and risks of a product can be evaluated by the benefit-risk assessment process. Initially, the benefits and risks of the product should be identified for conducting a risk-benefit analysis. The second step is the collection of the data, where information from clinical trials, preclinical studies, and post-marketing surveillance is gathered to assess the safety and efficacy of a drug product [30]. Several techniques are employed for risk-benefit analysis, which include Benefit Less Risk Analysis (BLRA), Risk Benefit Assessment for Drug Safety, Quality Adjusted Time Without Symptoms and Toxicity (Q-TWiST), Incremental Net Health Benefit (INHB), Risk Benefit Plane (RBP) & Risk Benefit Acceptability Threshold (RBAT), Risk Benefit Contour (RBC), and Minimum Clinical Efficacy (MCE) [31].

### E. Regulatory agency submission[Shown in Table 1]

**Periodic Safety Update Report (PSUR)** is useful for post-authorization surveillance for assessing the safety of the drug after approval. It's used to evaluate the benefit v/s risk of a drug at a specific time point. It presents the data in a comprehensive and precise manner for critical analysis of the benefit v/s risk of a drug. New Drugs and Clinical Trial Rules 2019 in India made sure that the applicants submit Periodic Safety Update Reports (PSURs) to specify new information, post-authorization status, and safety variations. All the information about dosage forms, formulations, indications of a new drug, and its effects in a specific population when used should be submitted to regulatory authorities through PSUR. PSUR should be submitted every six months for the first two years and once yearly for the subsequent two years. In certain

circumstances, regulatory authorities may extend the period to continue the submission. For certain adverse reactions, they should be submitted within 30 calendar days after the reporting, while serious adverse events should be reported within 15 days after the reporting [32].

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**Table 1:** Regulatory agencies of different countries and their means of reporting [34 – 40]

| Sl No | Name of the Form | Country | Regulatory authority |
|---|---|---|---|
| 1 | Suspected Adverse Drug Reaction Reporting Form | India | PvPI, CDSCO |
| 2 | MedWatch Form FDA 3500 | USA | US FDA |
| 3 | Yellow Card Scheme | United Kingdom (UK) | MHRA (Medicines and Healthcare Products Regulatory Agency |
| 4 | Canada Vigilance ADR Form | Canada | Health Canada |
| 5 | Adverse Drug Reaction Reporting Form (Blue Card) | Australia | Therapeutic Goods Administration |
| 6 | EUDRA (European Union Drug Regulatory Authoritis) Vigilance ICSR Form | European Union (EU) | European Medicines Agency (EMA) |
| 7 | ADR Reporting Form (Japanese PMDA) | Japan | Pharmaceuticals and Medical Devices Agency (PMDA) |

### Development Safety Update Report (DSUR)

The Indian regulatory system lacks the DSUR requirement, which is a drawback of not staying up to date on the real-time safety profile of a developing drug. Schedule Y should be revised to provide cumulative safety reports to the regulators during the clinical development phase [33].

### F. Risk Management

Pharmacovigilance includes Risk Management Plans (RMP) and risk evaluation and mitigation strategies (REMS), which are crucial for ensuring the safety of medicinal products. These plans are essential for interventions and communication with patients and healthcare providers. Marketing Authorization Holders (MAHs) to deal with "Important identified risks", "Important potential risks", and "Important missing information" during approval review and post-marketing. Some of the major consequences of finding safety issues through a risk management plan are to amend protocols, conduct more safety studies, update RMP, suspend enrolment, discontinue studies, present signals in PSUR, provide safety information, and revoke or suspend marketing. Early Post Marketing Phase Vigilance and package insert information is required for new drugs. RMP should be implemented for a drug if it requires additional pharmacovigilance and use case surveillance. Additional actions should be taken based on the type of ADRs, disease severity, patient exposure, benefits, risk population, treatment duration, and safety profiles [41].

### G. Post Marketing Surveillance

Clinical trials are done with a limited number of participants, whereas post-marketing surveillance is a real-world scenario where a huge number of people use the drug. In post-marketing surveillance, pharmacovigilance plays a crucial role in the real-time collection of data and signal detection for assessing safety issues. Adverse event monitoring, signal detection, risk assessment, and regulatory compliance are the steps involved in pharmacovigilance during post-marketing surveillance. Adverse events are monitored by reviewing reports from patients, healthcare professionals, clinical studies, and spontaneous reporting. Signal detection is the process of identifying potential adverse drug events through large databases from various sources such as electronic health records, spontaneous reporting, and clinical trials. Risk assessment identifies the severity of adverse events and safety signals. Pharmacovigilance adheres to the regulatory guidelines of the FDA, EMA, and CDSCO, depending upon the country [42].

### 3. Eco-pharmacovigilance:

Is defined by the WHO as the science and activities concerned with the detection, assessment, understanding, and prevention of adverse events or other related problems caused by pharmaceuticals in the environment that affect people and other animal species. Pharmaceuticals, which are excreted through humans, animals, hospital wastes, drug disposal, and industrial waste, can enter the environment to cause significant negative effects. To promote eco-pharmacovigilance, eco-directed sustainable prescribing should be implemented. To advance scientific knowledge of environmental risk assessment and pharmaceuticals in the environment, more research is required [43].

### 4. Materiovigilance:

As per WHO, Medical device means any instrument, apparatus, implement, machine, appliance, implant, reagent for in-vitro use, software, material, or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of

- Diagnosis, prevention, monitoring, treatment, or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of, or compensation for an injury
- Investigation, replacement, modification, or support of the anatomy or a physiological process

- Supporting or sustaining life
- Control of conception
- Disinfection of medical devices
- Providing information using in-vitro examination of specimens derived from the human body
- Aids for persons with disabilities
- Devices incorporating animal and/or human tissues
- Devices for in-vitro fertilization or assisted reproduction technologies
- Disinfection substances; and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, in or on the human body, but may be assisted in its intended function by such means

Adverse events related to medical devices are systematically collected through the Materiovigilance Programme of India (MvPI). It promotes scientific analysis and safe use of medical devices through the submission of Medical Device-associated Adverse Events (MDAE) information to regulatory authorities. Evidence-based recommendations can be generated by the materiovigilance, which can be helpful to communicate safety issues with stakeholders [44].

## 5. PV Softwares:

Some of the most common pharmacovigilance softwares are Vigibase, Vigiflow, Oracle Argus, ArisGlobal, etc. **Vigibase** is a global database for ICSRs, which are submitted by the member states of WHO's international drug monitoring program. **Vigiflow** is a national web-based program developed by WHO in which ICSRs are sent to the Uppsala Monitoring Center. **Oracle's Argus Safety** Database is a top-tier pharmacovigilance tool that offers global case processing, analysis, signal detection, electronic case intake, expedited reporting, and the ability to store large amounts of data. **Arisglobal's Life Sphere Safety (ARISg)** is one of the most popular software used by pharmaceutical companies, it provides additional features which include regulatory affairs and clinical solutions. Databases are chosen by the preferences of stakeholders based on the cost, features, and needs. **Rep Clinica** is a secure web-based service that manages critical pharmacovigilance activities effectively. It collects adverse event data, generates regulatory reports, and shares ICSRs with regulators and business partners. The service enables users to create, modify, and track cases, safety reports, and messages, and it keeps an audit trail of all data changes. **PV NET** is a leading pharmacovigilance solution that includes adverse event reporting, data management for adverse drug reactions, and ICSR regulatory reporting. It provides workflow support, data validation, global dictionary support, audit records, a management dashboard, automated narrative writing, duplicate case detection, and add-on modules [45].

## 6. Artificial Intelligence (AI) in Pharmacovigilance

AI enhances the detection of adverse events, serious reactions, risk factors, and signals. AI helps in analyzing large data from different sources. FDA's Sentinel System is an AI tool that helps analyze the amount of data through automated algorithms to detect signals. **VigiLanz** is one of the software that uses machine learning and natural language processes for signal detection and to identify safety issues. IBM Watson for Drug Discovery does predictive analysis, which is useful for hastening drug discovery and development. The integration of genomic data with pharmacovigilance allows for personalized treatment. Some of the major challenges for AI in pharmacovigilance are the lack of sufficient quantity and quality of the data, the complexity of data standardization, the requirement of regulatory compliance in terms of pharmacovigilance, and the lack of expertise [46].

## CONCLUSION:

Pharmacovigilance plays an important role in drug safety and ADR prevention. The PV process involves signal detection, risk assessment, and regulatory actions to enhance patient safety. Despite its significance, issues such as underreporting of ADRs, lack of awareness among healthcare professionals, and insufficient resources hinder its effectiveness. Furthermore, national regulatory frameworks vary which makes it difficult to maintain global drug safety standards. Future advancements in PV include the integration of artificial intelligence can enhance drug safety surveillance. Electronic health records and mobile applications are two examples of digital health technologies that can improve the effectiveness of ADR reporting. Improving collaborations between regulatory agencies, pharmaceutical industries, and healthcare professionals will be critical in addressing current issues. Choosing a proactive approach to PV can lead to safer medications, improving global public health and patient outcomes.

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