IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2023 Vol.:28, Issue:4

A Comprehensive Review on: Current Trends in Pharmacovigilance

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Mr. Swapnil R. Patil[*1], Mr. Pawan I. Naik[2], Miss. Asmita D. Vasaikar[3], Miss.Harshada A, Patil[4]

[1]*Assistant Professor, Department of Pharmaceutics, SPBS'S Shatabdi Institute of Pharmacy, Bamdod, Shamsherpur, Nandurbar, Tal Dist. Nandurbar, (MH) INDIA – 425412*

[2]*Assistant Professor, Department of Pharmaceutical Chemistry, SPBS'S Shatabdi Institute of Pharmacy, Bamdod, Shamsherpur, Nandurbar, Tal Dist. Nandurbar, (MH) INDIA – 425412*

[3,4]*Lecture, SPBS'S Shatabdi Institute of Pharmacy, Bamdod, Shamsherpur, Nandurbar, Tal Dist. Nandurbar, (MH) INDIA – 425412*

Submitted: 25 October 2023
Accepted: 31 October 2023
Published: 30 November 2023

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Pharmacovigilance, ADR, WHO, Clinical Trials, Clinical Studies, Challenges of PV

ABSTRACT

Pharmacovigilance (PV,or PhV), also known as drug safety, is the pharmaceutical science relating to the collection, detection, assessment, monitoring, and prevention" of adverse effects with pharmaceutical products. Medicines safety monitoring is a continuous and dynamic process throughout all the phases of the life cycle of a drug. During the drug development, safety is investigated in different phases. In preclinical studies, the primary goal of safety evaluation is the identification of a safe dose in humans and of safety parameters for clinical monitoring. The adverse effects range from milder side effects to severe hypersensitivities and often result in new illness, disabilities and death. The health care system requires new processes to understand the risk-benefit ratio of drugs. The challenges in implementation of better pharmacovigilance in country due to nonavailability of trained staff in pharmacovigilance, lack of training of health-care professionals on drug safety, and adverse drug reaction reporting the perspective of drug store understudies on pharmacovigilance and ADR revealing additionally been examined with an intend to center the need to improve content identified with ADR announcing and pharmacovigilance in undergrad drug store educational programs. There is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product. This will enable the integration of good pharmacovigilance practice in the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post-marketing surveillance. Only such an approach can greatly influence bringing reporting culture among healthcare professionals and may improve the reporting rates of ADR in our country. Pharmacists, as doctors opined that their involvement may increase the reporting rate, have a greater role to play in the area of pharmacovigilance.

INTRODUCTION

According to WHO, Adverse drug reaction (ADR) is defined as "any 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 the modifications of physiological function". An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use. [(1)] It is widely accepted that a drug has to go through phases of clinical trial to establish its safety and efficacy before it is marketed. However, clinical trial offers various limitations, as excluding some population groups such as children, pregnant women, and old age population are not studied during the trials. Moreover some other factors causing adverse drug reactions such as genetic factors, environmental factors, and drug-drug interactions may not have been studied during the clinical trial.[(2)] The history routes of the word "Pharmacovigilance" are: Pharmakon (Greek word of 'drug') and vigil (Latin word for 'to keep watch').[(3)] Pharmacovigilance is not new to Asian nations and has infect been going on from 1998.[(4)] When Asian nations decided to join the Uppsala Center for adverse event monitoring. Spontaneous reporting of adverse drug reactions and adverse events is an important tool for gathering the safety data for early detection.

It is widely accepted that a drug has to go through various phases of trial to establish its safety and efficacy before it is marketed commercially. [(4)] However, the clinical trials offer various limitations, like; strict criteria of inclusion and exclusion make it to be used in a very selective group of patients; special population groups like kids, pregnant ladies, and maturity populations are not studied during the trials; and other factor causing drug reactions such as genetic factors, environmental factors, and drug interactions may not have been studied during the clinical trials. [(5)]

Pharmacovigilance plays a multi-modal role in promoting and improving public health. The key goals of Pharmacovigilance are:

- To identify the risks associated with the use of medicines by the patients.
- To participate in comparative assessment of potential beneficial and adverse effects of the drugs and help optimize the nature of use.
- To promote safe, effective and rational use of medicines.

❖ To promote awareness among patients and the general public regarding the safe use of medicines via effective communication.

These goals are achieved only with the collaborative efforts and contributions from the key partners in the area of Pharmacovigilance. Inputs from a variety of sources such as government, academia, pharmaceutical and medical associations, health professionals and the media will help towards achieving improved management of risks associated with the use of medicines. [6]

History of Pharmacovigilance in India: -

Pharmacovigilance in India started in 1986. A formal Adverse Drug Reactions (ADR) monitoring system was initiated with 12 regional centers, each covering a population of 50 million. However, no noteworthy growth was made. Afterward, in 1997, India joined the World Health Organization (WHO) and Adverse Drug Reaction (ADR) scrutinizing program based at 2 Uppsala, Sweden but failed. Hence, after 2005 WHO supported and World Bank – funded National Pharmacovigilance Programmed (NPPV) of India was made operational. [7, 8, 9, 10]

Table 1: The sequential Pharmacovigilance developments with special reference to India.[11]

YEAR	DEVELOPMENTS
1747	Very first known clinical trials by James Lind, proving the usefulness of lemon juice in preventing scurvy
1937	Death of more than 100 children due to toxicity of sulfanilamide.
1950	A plastic anemia reported due to Chloramphenicol toxicity.
1961	Worldwide tragedy due to thalidomide toxicity
1963	16th World Health congregation recognizes significant to rapid action on Adverse Drug Reactions (ADRs).
1996	Global standards level clinical trials initiated in India.
1968	WHO research project for international drug monitoring on pilot scale.
1997	India attached with WHO Adverse Drug Reaction Monitoring Program.
1998	Initiation of Pharmacovigilance in India.
2002	67th National Pharmacovigilance Center established in India.
2002-05	India launched the National Pharmacovigilance Program.
2005	Accomplishment of structured clinical trials in India.
2009-10	Pharmacovigilance Program (Pv. PI) started.

A National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers Mumbai (KEM, Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs as a result of the administration of medicines, which are marketed in India. However, their functionality was almost negligible as the information about the need to report ADRs and about the functions of these monitoring centers was yet to reach the prescribers and an added effect of lack of funding from the government contributed to a greater extent.

This attempt resulted in vain and hence, again from the 1st of January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational.

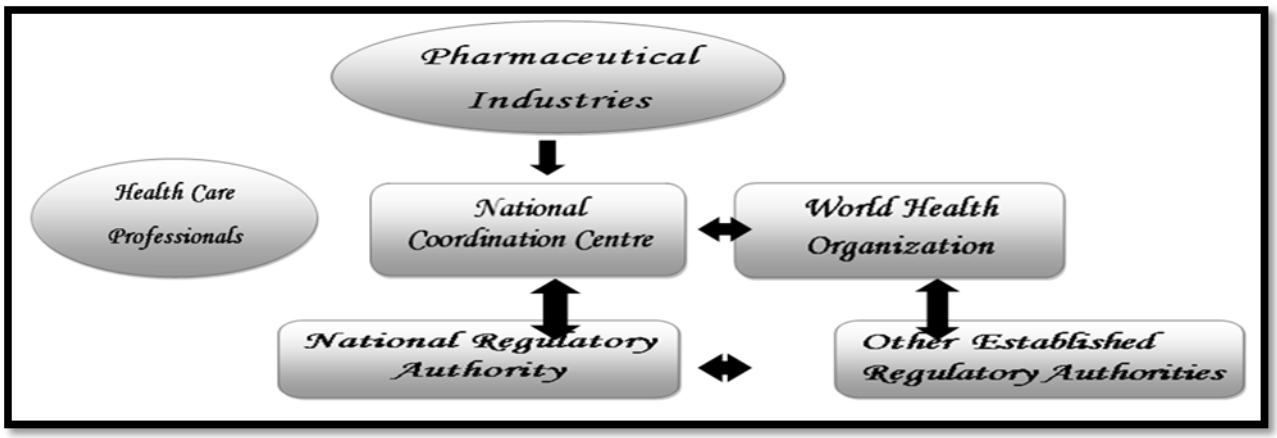

Figure 1: Diagrammatic representation of PV

Definitions of Pharmacovigilance: -

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. [12-13] it focuses on investigating and monitoring adverse drug reactions after medicinal products are licensed. 19 The term "Pharmacovigilance" first appeared in French in the late 1960s, when the terms "Pharmacovigilance intensive" and "Pharmacovigilance spontaneous" were contrasted. [14]

❖ **Detection:** In the case of clinical trial, it's the investigator or in case of post marketing trial, it's either the physician or the prescriber or the patient himself who reports the adverse event or any drug-related problem.

❖ **Assessment:** The investigator or the health care professional (HCP) would be assessing if the adverse event or drug-related problem is due to the drug or is it due to some other reason.

❖ **Understanding:** The reporter and safety specialist is involved in understanding the adverse event or drug related problem.

❖ **Prevention:** By proactively reporting the adverse event or drug related problem to the regulatory authority and taking precautionary actions would help in preventing the adverse event in the future.

AIM AND OBJECTIVES OF PHARMACOVIGILANCE

❖ Detection of severe and unexpected adverse drug reactions to the established drugs and even minor ones to newer drugs. [15]

❖ Identification of the risk factors associated with the development of adverse drug reactions and mechanisms of their causation like Type A, Type B, Type C, etc. [16]

❖ Quantitative estimation of the risk factors, incidence, and prevalence of adverse drug reactions. Estimation of the pharmacoeconomic data related to ADRs. [17]

❖ Improvement of patient care and safety about the use of medicines with medical and paramedical interventions remains to be an important parameter, clinical training in Pharmacovigilance and effective communication to the generic public. [18]

Figure 2: Aims of Pharmacovigilance

NEED FOR PHARMACOVIGILANCE

Reason 1: Humanitarian concern - Insufficient evidence of safety from clinical trials Animal experiments Phase 1-3 studies before marketing authorization.

Reason 2: Medicines are supposed to save lives Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.

Reason 3: ADR-related cost to the country exceeds the cost of the medications themselves.

Reason 4: Promoting rational use of medicines and adherence.

Reason 5: Ensuring public confidence.

Reason 6: Ethics, to know of something harmful to another person who does not know, and not telling, is unethical.

Increasing requirement of Pharmacovigilance system. The bases of need are as follows. **(19)**

1. **Untrustworthiness of pre-clinical safety information.**

- Well-controlled environment.
- Appropriate and precise sample size.
- Pressure from various systems to decrease time to Authorization.

2. **Altering pharmaceutical marketing policies.**

- Aggressive marketing
- Launch the drug in many countries at a time

3. **Varying physicians, patients, and other health professional's preferences.**

- Increasing use of newer drugs
- Increasing use of drugs to get better quality of life
- Shift of manage to self-administered treatment.

4. Easy convenience.

- Growing conversion of prescription drugs to over-the-counter drugs
- Easy access to drug information on the Internet.

CHALLENGES OF PV [20]

The Pharmacovigilance Programmed of India (Pv PI) is an Indian government organization that identifies and responds to drug safety problems. Its activities include receiving reports of adverse drug events and taking necessary action to remedy problems.

❖ **Administration**

Government has a key role in the proper functioning of the program. In India, the government is the major stakeholder in the implementation of health care. It is through the public sector, the programmed can reach every nook and corner of the country.

❖ **Self-Medication**

Self-medication is one of the problems in our country as people are not educated about drugs and they take drugs prescribed by pharmacists without proper prescription. Advertisements by the drug companies and the readily available drug over-the-counter with available pamphlets about the dose, indication, side-effects make the patients to take their own therapeutic decisions, without assistance from a doctor or pharmacist.

❖ **Health Professional**

Lack of continuing medical education about Pharmacovigilance and dearth of drug information led to underreporting of adverse drugs events. Most of the time, doctors believe that they have to report only if the adverse events have a causal relationship with the products. In our country, due to the low ratio of doctor to patient, most of the events are not reported due to lack of time, low motivation, ignorance and lethargy.

❖ **Traditional Medicines**

Traditional drugs are considered safe with few side effects. The processing of natural drugs is not done properly, toxic and essential ingredients are not known most of the time, they are

given for long duration and there is a lack of knowledge between interaction of herbal drugs with modern medicines.

❖ **Generic Drugs**

Generic drugs are becoming popular these days and they are considered safe. They are becoming the largest supplier of essential drugs in the country. So, it is the utmost responsibility of the pharmaceutical industry to monitor the safety profile of the drugs even though they are considered safe.

❖ **Counterfeit drugs**

Counterfeit drugs are an important and underreported problem, particularly in developing countries. It causes morbidity, mortality, and loss of public confidence in medicines and health structures. The prevalence of counterfeit drugs appears to be rising and poses a greater challenge for the program in India. It has been opposed by close cooperation between drug companies, governments, or international organizations concerned with health sector in developing country like India.

❖ **Clinical Trial Monitoring**

India is becoming a hub for clinical trial in the 21st century. In most of the clinical trials, adverse drug reactions that happen due to the test drugs go unreported and not inform to the regulatory authority due to personal interest or for fear of litigation. Thus, clinical trials pose a great challenge for Pharmacovigilance programmed.

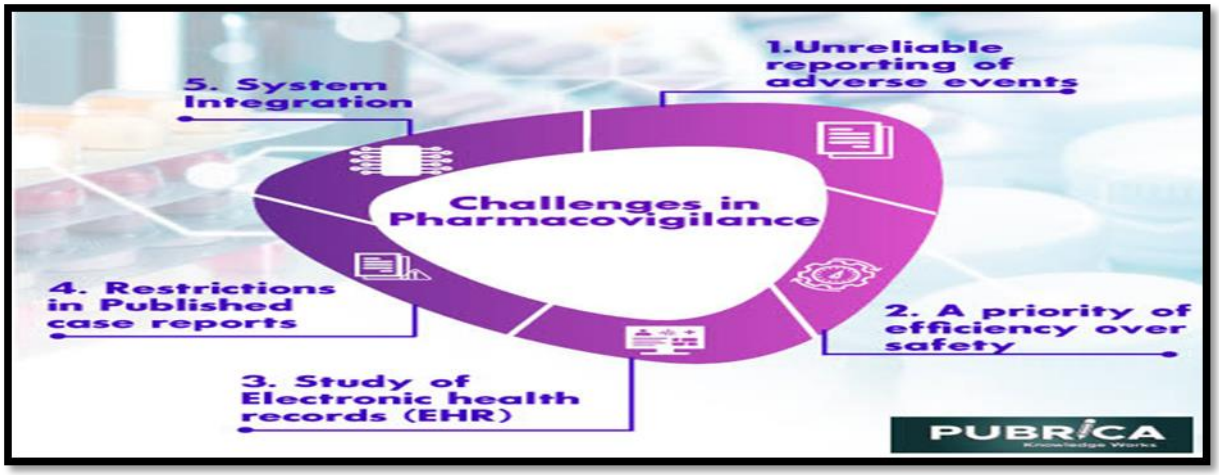

Figure 3: Challenges of PV

India Challenges of PV

India is a vast country and there is an excess of drug brands more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. India is the fourth biggest producer of pharmaceuticals in the world and is also rising as a clinical trials hub. Many new drugs are being introduced in the country, so there is an immense need to improve the Pharmacovigilance system to protect the Indian population from potential harm that may be caused by some of the new drugs. In India, a pharmaceutical company holding the marketing license should ensure that they have an adequate Pharmacovigilance system in place to ensure the responsibility and liability of their marketed products.

When two or more marketed products are identical in all aspects except their trade names, each pharmaceutical company holding a marketing license is obliged to meet the Pharmacovigilance obligations. This includes the establishment and maintenance of an appropriate Pharmacovigilance system to collect and evaluate information about suspected adverse reactions. [21]

TRENDS SHAPING THE FUTURE OF PHARMACOVIGILANCE

To continuously improve the efficacy of drugs and health outcomes for patients, the healthcare industry gradually evolves to meet changing regulations, make the most of new technologies and communication channels, and cater to individuals and their unique needs. With the evolution of the healthcare industry comes the need to change the way, frequency or guidelines by which product safety is monitored and reported. While Pharmacovigilance has long been a cornerstone of the healthcare industry, more thorough safety documentation and reviews for drug approvals along with increased warnings and awareness about adverse drug reactions within the last few years have made drug safety one of the top concerns for consumers and regulators. These safety concerns have prompted global mandates for submitting significantly more detailed product information, as well as a push for more clinical and safety data transparency.

Understanding the trends that are shaping the future of Pharmacovigilance will help your business get a head start on ensuring consistent performance with adherence to strict regulatory requirements.

Figure 4: Trends Shaping the Future of Pharmacovigilance.

1) Proactive Pharmacovigilance [22]

Our reactive Pharmacovigilance system is transforming into a proactive, benefit-risk management system to fully adapt to modern technology and the growing need of consumers to receive immediate and reliable information through any channel. The consequences of taking a reactive approach can be disastrous – halting a clinical study, delaying drug approval, recalling a marketed drug; as well as brand damage, class action suits, and exorbitant fines. Moving forward, pharmaceutical and biotechnology companies must not only monitor for adverse events but also proactively access and manage drug risk throughout a product's lifecycle. Developing a Pharmacovigilance risk management plan with a risk minimization action plan (Risk MAP) for high-risk products is becoming ever more essential.

2) Social Media and Digital Health

The traditional model of healthcare, with patients taking a passive role in their health and well-being, is changing. A new standard of patient involvement has evolved. Social media, digital health devices, and mobile applications have made multi-channel health-related interactions a part of everyday life. Social media has become an integral part of healthcare and product safety. More than 40% of consumers say that information found via social media affects the way they deal with their health. [23] of respondents 18 to 24 years of age, 90% say they would trust medical information shared by others on their social media networks. [24] of adults, 47% say they are likely to share their health information on social media sites with doctors, 43% with hospitals, 38% with health insurance companies, 32% with drug companies, and 30% with other patients. [25]

These statistics illustrate that there is immense value in companies taking a proactive approach to social media monitoring, as well as utilizing social media to provide accurate

drug-related information to consumers. Additionally, proactive monitoring could provide early warning of new adverse events or clinical insights that help both guide drug development and avoid preventable litigation.

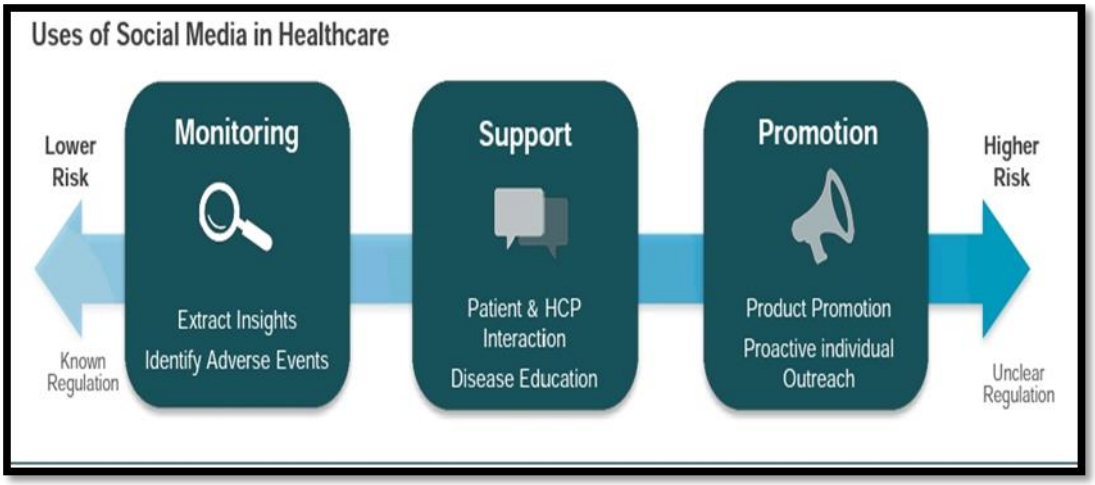

Figure 5: Social Media and Digital Health.

3) Personalized Medicine:

Personalized medicine will identify a patient's biological and disease characteristics, taking into account the patient's genetic, anatomical, and physiological characteristics, to tailor specific therapies for an individually optimized benefit-risk balance. It promises to increase benefits, reduce risks, and improve the efficacy of many products for individuals. While progress in regenerative medicine and stem cell research offers hope for some of the most personalized products imaginable, this progress also brings to light a new safety paradigm. Different risk profiles might be anticipated due to different genetic mutations which may bring about more adverse drug responses and drug interactions. Personalized medicines will also require more complex labeling since they might only be safe and effective in particular sub-populations or might need to be administered in different doses to different sub-populations.

In cases where a therapeutic product is approved with a diagnostic device, the label of the two products must be consistent. Currently, there are more than 100 approved drugs with labels that contain information on genomic biomarkers (including gene variants, functional deficiencies, expression changes, and chromosomal abnormalities).

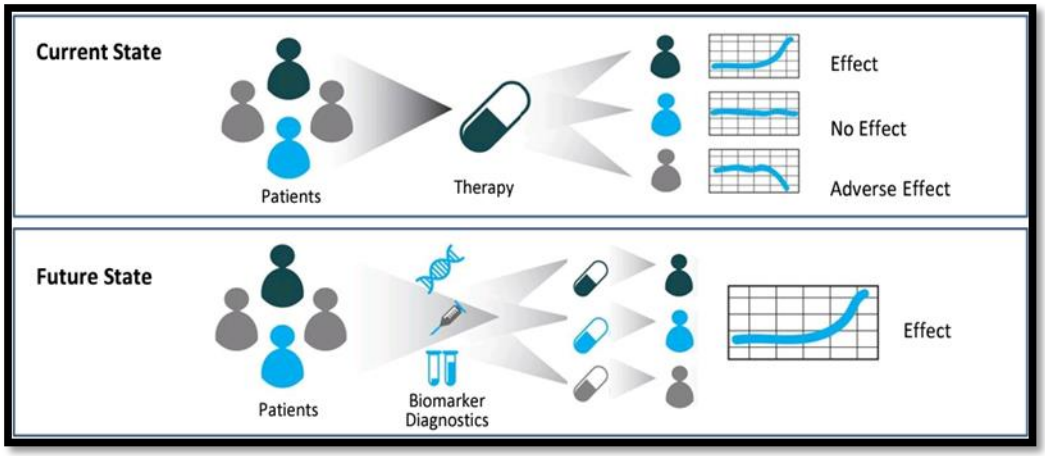

Figure 6: Personalized Medicine and Biosimilars.

4) Intensifying Global Regulatory Expectations. [25]

The global pharmacovigilance market continually faces intensifying regulatory expectations, tougher inspection systems, and an instant need for patient reporting. Organizations are more focused on introducing safer products to patients promptly. As a result of globalization, pharmaceutical companies must meet region-specific safety requirements, interpret legal requirements for their individual company structure, and harmonize international laws for different regions. Risk management plans (RMP), Pharmacovigilance system master files (PSMF), periodic reports (PSUR, PBRER, PADER), product information, adverse event and adverse drug reaction reporting, drug renewals, signal management, medical literature monitoring - these are simply the basics when considering a Pharmacovigilance strategy.

Additionally, intensifying global regulatory expectations means pharmaceutical companies must adapt and make risk management a centerpiece of global Pharmacovigilance operations. The term risk management should not be thought of as mitigating only risks of adverse events, but also in terms of risks to product quality, data integrity and patient privacy.

CURRENT TRENDS IN PHARMACOVIGILANCE

The rapid and continuous progress of medical and pharmaceutical sciences has resulted in the availability of modern medicines that can efficiently prevent, control and/or manage disease states. Despite a plethora of benefits, adverse reactions to medicines are not uncommon and are associated with most newly developed drugs. Pharmacovigilance is ingrained, and rightly so, in several areas of healthcare management of the general population. The key areas where

Pharmacovigilance is incorporated are, National Drug Policy: For most nations, the first step to ensure safe and rational use of medicine is the establishment of drug regulatory bodies with dedicated Pharmacovigilance programs to monitor and assess the adverse drug reactions and communicate findings to relevant stakeholders.

Drug regulation: The scope of drug regulatory authorities is beyond just the approval of manufacture and marketing of new medicines. Working in close collaboration with Pharmacovigilance programs, these regulatory authorities ensure continual safety of the drugs in the public domain by conducting post-marketing surveillance and analysis of the benefits and harmful effects of the drugs in a broader population. [6]

Moving to drive operational Efficiency

Specific re-appropriating in Pharmacovigilance is turning into a broadly utilized way to deal with adapting to the developing expenses of keeping a profoundly qualified and prepared Pharmacovigilance team in-house.

For Manufacturers and Sponsors, a very much actualized Pharmacovigilance reevaluating program brings observable advantages including:

- Reduced fixed expenses;
- Increased adaptability;
- Better results in the short and long haul;

These days an ever-increasing number of organizations reevaluate their Pharmacovigilance errands to accomplish better administrative consistency, more significant, better profitability, and improved vital choices.

Information Analytics to Drive Actionable Insights

According to a clinical literature review, the successful administration of health information put away across numerous stages is imperative for away from security occasions. The developing number of Life Sciences organizations go to cutting edge logical methods in Pharmacovigilance to look at huge and changed informational collections that contain health data. They Endeavour to uncover new examples, obscure connections, patterns, and patient inclinations that help them guarantee patients' security all the more viably. These days,

Pharmacovigilance examination gives a genuine chance to outfit information adequately, guarantee administrative consistency and drive unique experiences.

Big Data to Protect and Assimilate Huge Amount of Information

As of late novel wellsprings of actual proof and trial information in the mechanical structure, have also opened up to Pharmacovigilance experts.

In Pharmacovigilance, enormous information incorporates such sources as:

- Signal discovery;
- Substantiation and approval of medication or immunization health signals;
- Online channels and web-based media.

Because of its intricacy, big information addresses both a chance and a challenge. [26]

METHODS USED IN PHARMACOVIGILANCE

The activities undertaken in the name of Pharmacovigilance can be roughly divided into three groups: regulatory, industry, and academia. Regulatory Pharmacovigilance is driven by the aim to provide drugs with a positive benefit–harm profile to the public. Some of the problems related to regulatory post-marketing surveillance will be discussed in this context, followed by a description of the methods used to detect new ADRs and a discussion of the pros and cons of each method.

❖ **Spontaneous report monitoring system (SRS)** [27]

The the most important and primary method for Pharmacovigilance to collect post-marketing information on the safety of drugs is SRS. It is the oldest, simplified, and cost-effective method of ADR reporting. The system is structured in a way the country ‘s health system is organized. An example is yellow card system in the USA where all the patient data is available online through ADROIT (ADR online tracking system). The method involves the voluntary participation of health professionals, pharmacists, nurses, and patients themselves for reporting the observations related to ADR. All health professionals can use the report form to give all relevant data related to the drug and suspected ADR. Experts then review and evaluate the reports submitted on a case-to-case basis to check whether there is a pattern

representing the possible signal. Often a single report may not be conclusive and a set of reports from independent observers is required to generate a signal. [23]

The advantage of SRS is that it is a spontaneous, most commonly used method, it covers the whole population, includes all medicines with continual monitoring throughout life-cycle of medicine, it can detects signals of new, rare or serious ADRs, it‘s an easiest method to establish, least labor intensive and relatively inexpensive. As the reporting system is voluntary it has some important limitations and the most noticeable is gross under-reporting. Sometimes the ADRs are not even suspected either due to difficulty in relating the ADR to a drug clinically or because no such reaction has previously been described or because of the long time lag between exposure and the event.

❖ **Clinical trial data insufficient to evaluate drug risk** [28]

The main method currently used to gather information on a drug in the pre-marketing phase is to conduct a clinical trial. Pre-marketing clinical trials can be divided into three phases. Phase III studies are often double-blind randomized controlled trials; these are considered to be the most rigorous approach to determining whether a cause effect relationship exists between a treatment and an outcome. However, when it comes to monitoring the safety of a drug, this study design is not optimal. Due to the limited number of patients participating, it is generally not possible to identify ADRs that occur only rarely. The relatively short duration of clinical trials makes it difficult to detect ADRs with a long latency.

Another limitation of clinical trials is the population in which a drug is tested. The characteristics of the participants do not always correspond to the characteristics of the population in which it will later be used; consequently, it may be difficult to extrapolate the results obtained from clinical trials to the population at large.

❖ **Prescription event monitoring (PEM)** [29]

It is a state-based electronic database that works on how prescription monitoring is organized in the country (UK). Virtually all patients are registered with a general practitioner (GP) who provides primary health care and issues prescriptions (FP10s) for the medicines considered medically necessary. The patient takes the prescription to a pharmacist who dispenses the medication and then sends the FP10 to a central Prescription Pricing Authority (PPA) which arranges the reimbursement of the pharmacist who sent it to Drug Safety Research Unit

(DSRU). DSRU is, under long-standing and confidential arrangements, provided with electronic copies of all those prescriptions issued throughout England for the drugs being monitored by PEM. These arrangements continue for a collection period adequate to allow exposure data (FP10s) to be collected for twenty to thirty thousand patients. For each of these patients, the DSRU prepares a record comprising all prescriptions for the monitored drug. After this, a personalized follow-up questionnaire green form) is mailed to each patient's general practitioner, usually on the first anniversary of the initial prescription, asking for information about the patient, especially any events that he or she may have experienced since beginning treatment with the drug.

These green forms are then voluntarily filled up and submitted by the physicians. The advantages offered by this system are that these reports requested from physicians are on a voluntary basis and nothing happens to interfere with the doctor's decision regarding which drug to prescribe for each individual patient. Thus, it is an easy and convenient method and a non-interventional, observational cohort form of Pharmacovigilance. Most importantly, PEM enables the generation and testing of hypotheses regarding drug alerts or signals that may be of public health interest.

❖ **Intensive monitoring** [30-31]

In the late 1970s and early 1980s a new form of active surveillance was developed in New Zealand (the Intensive Medicines Monitoring Programmed) and the UK (Prescription Event Monitoring). These intensive monitoring systems use prescription data to identify users of a certain drug. The prescriber of the drug is asked about any adverse event occurring during the use of the drug being monitored. These data are collected and analyzed for new signals. The basis of intensive monitoring is a non-interventional observational cohort, which distinguishes it from spontaneous reporting because the former only monitors selected drugs during a certain period. Through its non-interventional character, intensive monitoring provides real-world clinical data involving neither inclusion nor exclusion criteria throughout the collection period. It is unaffected by the kind of selection and exclusion criteria that characterize clinical trials, thereby eliminating selection bias.

Strength of the methodology is that it is based upon event monitoring and is therefore capable of identifying signals for events that were not necessarily suspected as being ADRs of the

drug being studied. Intensive monitoring programs also enable the incidence of adverse events to be estimated, thus enabling quantification of the risk of certain ADRs.

❖ **General Practioners database (GPRD) [32-34]**

The General Practice Research Database (GPRD) is the world's largest computerized database of longitudinal clinical records from primary care. The results of GPRD-based pharmaco epidemiological studies have been used to inform regulatory Pharmacovigilance decision-making for drug safety signal evaluation. The Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on the type of product, prescription date, strength, dosage regimen, quantity and route of administration. GPRD has been the most widely used tool for pharmaco epidemiological research in UK.

Since 1994, this database has belonged to the UK Department of Health. Data from this source thus provide an almost complete picture of a patient, his illnesses and treatment. In any given year, GPs, who are members of the GPRD, collect data from about 3 million patients that are about 5% of the UK population.

❖ **Database studies [35]**

In order to test a hypothesis, a study has to be performed. The study can be conducted using a variety of methods, including case–control studies and cohort studies. The limitations of these methods include power considerations and study design. In order to be able to conduct retrospective cohort and case–control studies, data which have been collected in a reliable and routine fashion needs to be available.

The General Practice Research Database (GPRD) and the PHARMO Record Linkage System, which will be described in further detail in the following sections, were chosen here because they represent two different types of European databases.

❖ **General Practice Research Database**

Virtually all patient care in the UK is coordinated by the general practitioner (GP), and data from this source provide an almost complete picture of a patient, his illnesses and treatment. In any given year, GPs, who are members of the GPRD, collect data from about 3 million

patients (about 5% of the UK population). These patients are broadly representative of the general UK population in terms of age, sex, and geographic distribution. The data collected include demographics (age and sex), medical diagnoses that are part of routine care or resulting from hospitalizations, consultations or emergency care, along with the date and location of the event. There is also an option of adding free text, referral to hospitals and specialists, all prescriptions, including date of prescription, formulation strength, quantity and dosing instructions, indication for treatment for all new prescriptions and events leading to withdrawal of a drug or a treatment.

Data on vaccinations and miscellaneous information, such as smoking, height, weight, immunizations, pregnancy, birth, death, date entering the practice, date leaving the practice, and laboratory results, are also collected.

CLINICAL TRIAL

A clinical trial could be an analysis study that tests a replacement medical treatment or a replacement manner of mistreatment Associate in Nursing existing treatment to ascertain if it'll be higher thanks to stop and screen for Before pharmaceutical firms begin clinical test on a drug, they conduct in-depth pre-clinical studies. [37]

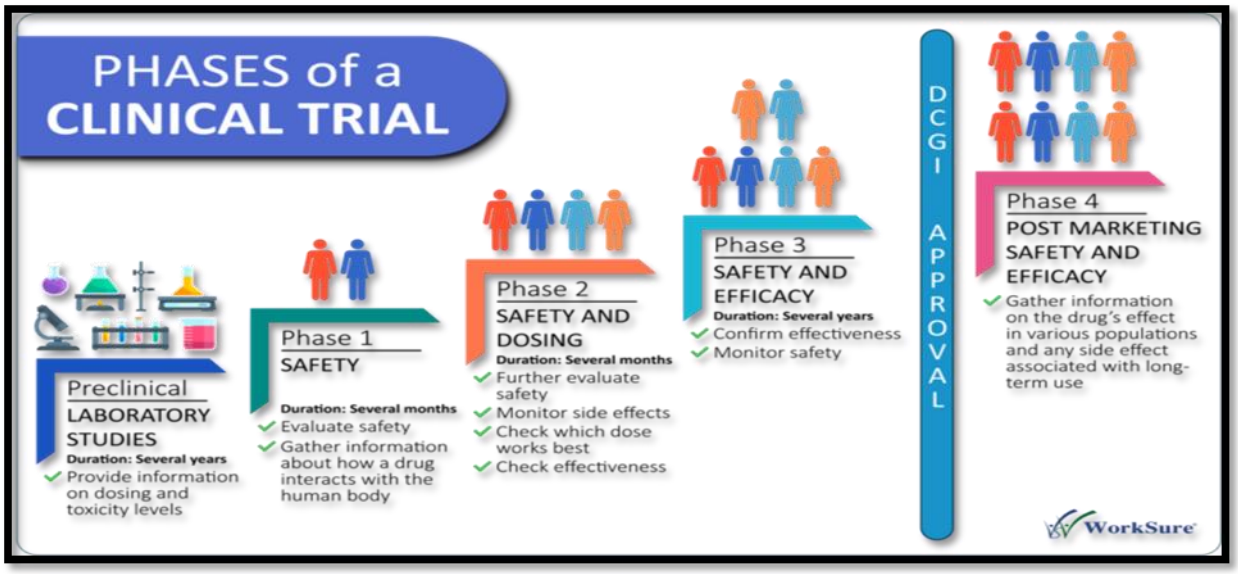

Figure 7: Phase of Clinical Trial.

❖ **Pre-clinical studies [38]**

Pre-clinical studies involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations. Wide-ranging dosages of the study drug are given to the animal subjects or to an in-vitro substrate to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further testing.

❖ **Clinical Studies**

➢ **Phase-0**

Phase zero may be a recent designation for an exploratory, first-in-human trial conducted in accordance with U.S. Food and Drug administration (FDA) 2006 steerage on exploratory. Distinctive options of part zero trials embrace the administration of single sub-therapeutics doses of the study drug to a small range of subjects (10- 15) to collect preliminary information on the agent's pharmacological medicine (how to body processes the drug) and Pharmacodynamics (how the drug add the body).

➢ **Phase-I**

Phase I path area unit 1st stage of testing in human subject. Ordinarily a little (20-80) cluster of healthy volunteers is going to be elite. This part includes trials designed to assess the security (Pharmacovigilance) tolerability, pharmacological medicine, and Pharmacodynamics of a drug. There are unit totally different styles of clinical trial trials.

SAD: Single Ascending Dose studies area unit those within which tiny cluster of subjects' area unit given one dose of the drug whereas they're ascertained and tested for a amount of your time.

MAD: Multiple Ascending Dose studies area unit conducted to raise perceive the pharmacological medicine of multiple doses of drug.

➢ **Phase II**

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients.

When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Phase II studies are sometimes divided into Phase IIA and Phase IIB.

Phase IIA is specifically designed to assess dosing requirements (how much drug should be given), whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose. Some trials combine Phase I and Phase II and test both efficacy and toxicity.

- **Phase III** [39]

Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming, and difficult trials to design and run, especially in therapies for chronic medical. Conditions. It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency.

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, to obtain approval from the appropriate regulatory agencies (FDA (USA), TGA (Australia), EMEA (European Union), etc.).

- **Phase-IV**

Phase IV trial is additionally called Post promoting police work Trial. Phase IV trials involve the security police work (Pharmacovigilance) and current technical support of a drug once it receives permission to sold.

Table 2: Phase & Group

Phase	Group
0	10-15
1	22-80
1A	Single Ascending Dose (SAD)
1B	Multiple Ascending Dose (MAD)
2	20-300
3	300-3000
4	Post Marketing Surveillance Trial

FUTURE PROSPECTS OF PV

As the prospects a robust, Pharmacovigilance system capable to detect new ADRs an, taking regulatory actions needed to protect public health. Little emphasis has been put on generating information that can assist a healthcare professional or a patient in the decision-making process. However, these days the confronting issues are too many affecting the health care system. Some of the major challenges include web-based sales and information, globalization, broader safety concerns, public health versus pharmaceutical industry economic growth, monitoring of established products, developing and emerging drugs, attitudes and perceptions to benefit and harm, outcomes and impact and other related. It becomes imperative as ever to spread awareness about PV and communicate this information from diagnosis to signal to manage overall adverse drug reactions which becomes one of the important goals of PV. [27]

At present, the DCGI should act quickly to improve Pharmacovigilance so as to integrate Good Pharmacovigilance Practice (GPP) into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post-marketing surveillance. An appropriately working Pharmacovigilance system is essential if medicines are to be used carefully. It will be benefit for healthcare professionals, regulatory authorities, pharmaceutical companies and consumers.

It helps pharmaceutical companies to monitor their medicines for risk. [40] Post-marketing Pharmacovigilance is currently a challenging and laborious process, not only industry-wide, but also for regulatory agencies.

Future perspectives for, the problems & and challenges facing the development of a robust PV system of India, the following proposals might be as follows: [41]

- Build & and maintain a vigorous PV system.
- Making PV reporting mandatory and introducing PV inspections.
- High-level discussions with various stakeholders.
- Creating a single country-specific ADR reporting form to be used by all.
- Strengthen the Drug Controller General of India (DCGI) office with trained scientific and medical assessors for PV.
- Creating a clinical trial and post-marketing database for SAEs / SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders.
- Education and training of medical students, pharmacists and nurses in the area of PV.
- List all new drugs/indications by maintaining a standard database for every pharmaceutical company.

CONCLUSION

The PV in India continues to grow, evolve, and improve. India is the largest producer of pharmaceuticals and now emerging as an important clinical trial hub in the world. The knowledge of drugs Adverse Drug Reactions (ADRs) can be augmented by various means such as database studies, intensive monitoring, and spontaneous reporting. Despite of recent implementation of a well-structured Pharmacovigilance program in India by the objectives and recommendations of WHO by CDSCO, desired success is still a distant dream. The health-care professionals, patients, and pharmaceutical companies should report ADRs by own selves and actively participate in the Pharmacovigilance system of the country. The health-care professionals, patients, and pharmaceutical companies should report ADRs by themselves and actively participate in the Pharmacovigilance system of the country.

A clinical trial for any new drug follows under the guidelines of ICH and GCP, clinical trial is conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, an investigational new drug passes through clinical phases I, II, III and IV. These phases provide in detail explanation of pharmacokinetic, and pharmacodynamic profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.

REFERENCES

1) Gupta KB, Kumar V, Vishvkarma S, Shandily R. Isoniazid-induced alopecia. Lung India. 2011; 28:60–61
2) Mann RD, Andrews EB (2002) Pharmacovigilance, John Wiley and Sons Ltd, Chichester
3) Shuka SS, Gidwani B, Pandey R, Rao SP, Singh V, Vyas A, Importance pharmacovigilance in Indian Pharmaceutical Industry, Asian Journal of Research in Pharmaceutical Science 2012; (2): 04-08.
4) WHO, Pharmacovigilance, ensuring the safe use of medicines, Geneva WHO.2004;
5) Mann RD, Andrews EB, eds. John Wiley & Sons Ltd, Pharmacovigilance, Chichester. 2002.
6) : Vivek S. Dave, St. John Fisher College, Wegmans School of Pharmacy, Rochester, NY 14618, USA, Tel: 585-385-5297.
7) Shuka SS, Gidwani Bina, Pandey R, Rao SP, Singh V, and Vyas Amber, "Importance of Pharmacovigilance in Indian Pharmaceutical Industry", Asian Journal of Research in Pharmaceutical Science, 2, 2012, 04-08.
8) Jadhav Sudhakar and Chakraborthy Guno, "Pharmacovigilance in India: Need of Hour", Journal of Advances in Pharmacy and Healthcare Research (JAPHR), 1, 2011, 01-03.
9) S Amarnath, S Jaikumar, S Basalingappa, M Thulasimani, and S Ramaswamy, "Pharmacovigilance for Health Care Professional Students", Research Journal of Pharmaceutical, Biological and Chemical Sciences (RJPBCS), 4, January-March 2013, 1204-1217.
10) Muraraiah Sushma, Rajarathna Kavitha, Sreedhar Divyasree, Basavalingu Deepashri and Jayanthi C.R. "A questionnaire study to assess the knowledge, attitude, and practice of Pharmacovigilance in a pediatric tertiary care centre", Journal of Chemical and Pharmaceutical Research, 2011, 416-422.
11) Kesharwani V, Farooqui MA, Kushwaha N, Singh RK, Jaiswal PK, An overview on pharmacovigilance: a key for drug safety and monitoring, Journal of Drug Delivery and Therapeutics. 2018; 8(5):130-135
12) The importance of pharmacovigilance-safety monitoring of medicinal products. Geneva: World Health Organization; 2002. Available at: https://apps.who.int/medicinedocs/pdf/s4893e/s4893 e.pdf. Accessed on 01 July 2020.
13) WHO cc in Uppsala (UMC). Available at: https://www.who.int/medicines/areas/quality_safety/ safety efficacy/PV_fast_facts/en/. Accessed on 01 July 2020.
14) Talbot J, Aronson JK. Stephens' Detection and Evaluation of Adverse Drug Reactions, 6th Edition. Pharmacology & Pharmaceutical Medicine, Wiley Blackwell, 2011:750.
15) Bates DW, Spell N, Cullen DJ (1997) He costs of adverse drug reactions in hospitalized patients. JAMA 277: 301-307.
16) Leape LL (1994) Errors in medicine. JAMA 272: 1851-1857.
17) Bates DW, Collen DJ, laird N (1997) Incidence of adverse drug events and potential adverse drug events in hospitalized patients. JAMA 277: 307-311.
18) WHO (2004) Pharmacovigilance: ensuring the safe use of medicines, Geneva.
19) Int. J. Pharm. Sci. Rev. Res., 26(2), May – Jun 2014; Article No. 41, Pages: 237-241.
20) Misra A.K et.al Mintage Journal of Pharmaceutical & Medical Sciences.35-36
21) Sumit et al Journal of Drug Delivery & Therapeutics; 2013, 3(4), 237.
22) http://www.adweek.com/socialtimes/files/2012/12/social-media-healthcare.png?red=at
23) http://searchenginewatch.com/sew/news/2169462/-consumers-social-media-health-care-info-survey 3http://gabi-

24) journal.net/safety-and-toxicity-of-biosimilars-eu-versus-us-regulation.html
25) Inácio, P., Cavaco, A., & Airaksinen, M. (2018). Current trends in Pharmacovigilance: value and gaps of patient reporting. *International journal of clinical pharmacy*, *40*(4), 754-757.
26) Gohil KJ. World Journal of Pharmacy and Pharmaceutical Sciences., Volume 8, Issue 12, 1295-1320.
27) Gross CP, Mallory R, Heiat A et al. (2002) Reporting the recruitment process in clinical trials: who are these patients and how did they get there? Ann Intern Med 137:10–16.
28) Layton D, Shakir AW. Prescription even monitoring. In: Strom BL and Kimmel SE (editors). Pharmacoepidemiology, 5th edition, chapter 20, Copyright © 2012 John Wiley & Sons, Ltd.
29) Mackay FJ (1998) Post-marketing studies: the work of the Drug Safety Research Unit. Drug Saf 19:343–353
30) Mann RD (1998) Prescription-event monitoring–recent progress and future horizons. Br J Clin Pharmacol 46:195–201.
31) Wood L1, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf. 2004; 27(12): 871-81.
32) Rodríguez, LAG and Gutthann SP. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol. 1998; 45(5): 419–425.
33) Härmark L, van Grootheest AC, Pharmacovigilance: Methods, recent developments and future perspectives Eur J Clin Pharmacol 2008; 64:743–752.
34) Strom BL, (Ed) (2005). Pharmacoepidemiology, 4th edn. Wiley, Chichester.
35) Gelfand JM, Margolis DJ, Dattani H (2005) The UK general practice research database. In: Strom BL (ed) Pharmacoepidemiology, 4th edn. Wiley, Chichester
36) . Kulkarni SK, Hand Book of Experimental Pharmacology, 3rd ed. Vallabh Prakashan New Delhi, 2004; P21.
37) Kesharwani V, Farooqui MA, Kushwaha N, Singh RK, Jaiswal PK, An overview on pharmacovigilance: a key for drug safety and monitoring, Journal of Drug Delivery and Therapeutics. 2018; 8(5):130-135
38) S. B. Throat, S. K. Banarjee, D. D. Gaikwad, S. L. Jadhav, R. M. Thorat, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March – April 2010; Article 019
39) European Commission. Detailed Guidance on the Collection, Verification, and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use. 2006. Available from: http://ec.europa.eu/health/files/ eudralex/vol-10/21_ susar_rev2_2006_04_11_en.pdf. [Accessed on 2010 Dec 10].
40) Nimesh S, Ashwlayan VD (2018) Pharmacovigilance: An Overview. Int J Pharmacovigil 3(1):1-6.