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"The Role of Pharmacovigilance in Drug Development"

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ABSTRACT

Pharmacovigilance (PV) plays a key role in the healthcare system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human.Pharmaceutical andbiotechnological medicines are designed to cure, prevent or treat diseases; however, there are also risks particularly adverse drug reactions (ADRs) can cause serious harm to patients. Thus, for safety medication ADRs monitoring required for each medicine throughout its life cycle, during development of drug such as pre-marketing including early stages of drug design, clinical trials, and post-marketing surveillance. PV is concerns with the detection, assessment, understanding and prevention of ADRs.

Pharmacogenetics and pharmacogenomics are an indispensable part of the clinical research. Variation in the human genome is a cause of variable response to drugs and susceptibility to diseases are determined, which is important for early drug discovery to PV. Moreover, PV has traditionally involved in mining spontaneous reports submitted to national surveillance systems. The research focus is shifting toward the use of data generated from platforms outside the conventional framework such as electronic medical records, biomedical literature, and patient-reported data in health forums.The emerging trend in PV is to link premarketing data with human safety information observed in the post-marketing phase.

KEYWORDS: Pharmacovigilance; Adverse drug reaction; Clinical trials; Pharmacogenomics; Data mining:
Indian Pharmacopoeia Commission

I. INTRODUCTION

Health includes not only being disease-free but also being in good bodily, psychological, and social health. The treatment of the sickness is the first step towards achieving a state of balance. Such treatment necessitates the categorical requirement that the medication used to treat the disease does not hurt the patient in a way that further reduces the quality of life or causes death.

This vigilance in finding out all aspects of a drug. positive and negative, has led to the evolution of a new branch of pharmacological science, known as Pharmacovigilance. It is one of the fundamental wings of the healthcare system and pharmaceutical companies. It is aimed to ensure guaranteed patient safety and is considered an arm of patient care.

The Australian physician W. McBride, who first hypothesized a connection between thalidomide, a medication used during pregnancy, and severe fetal abnormalities (phocomelia), officially established pharmacovigilance [PV] in December 1961 with thepublication of a letter (case report) in the Lancet: In pregnant women, thalidomide was administered as a sedative and antiemetic.

The French word pharmacovigilance was defined as "a discipline involving detection, evaluation, and prevention of undesirable effects of medicines." This word derives from the Greek "pharmakon," which means a drug or remedy, and the Latin "vigilans," which means attentive or careful. By the World Health Organization (WHO), pharmacovigilance is "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.[1]

Defination of Pharmacovigilance

- Known as drug safety.
- According to WHO, Pharmacovigilance is defined as "the pharmacological science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any drug related problem".
- Removes of approved and licensed products from the market because of clinical toxicity, caused by ADR in the body.

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II. HISTORY AND DEVELOPMENT OF PHARMACOVIGILANCE

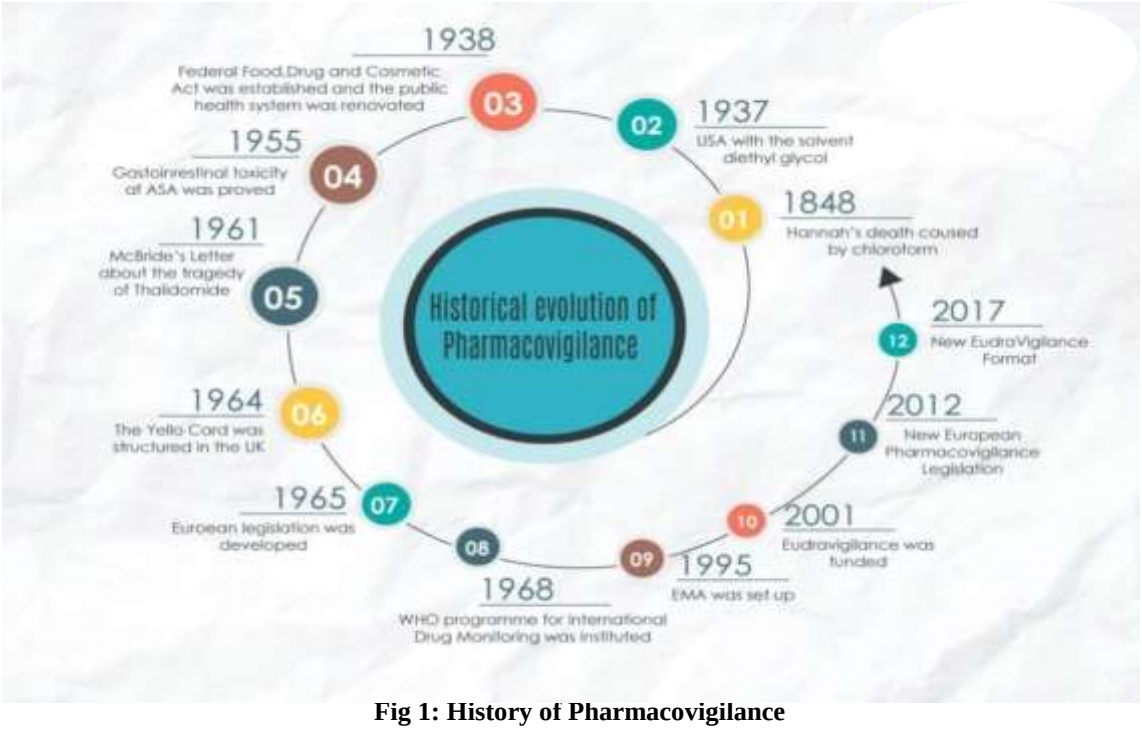

Fig 1: History of Pharmacovigilance

- **1848 :** USA - Suspected dates following the use of Chloroform as an Anaesthetiser.
- **1937 :** USA- deaths due to the administration of diluent diethyl glycol.
- **1938:** USA - establishment in food ,drug and cosmetic are to appoint FDA for drug safety control
- **1955:** Gastrointestinal toxicity at ASA was proved.
- **1961:**Fetal malformations following the intake of Thalidomide during pregnancy .
- **1964:** Great Britain - Introduction of the yellow card, spontaneous reporting form.
- **1965:**European legislation was developed.
- **1968:** USA- Program on International Drug Monitoring introduced to centralize global data.
- **1995:**EMA (European Medicines Agency) was set up.
- **2001 :**Europe - Eudravigilance, the European reporting database,implemented.
  Italy - RNF, the National Pharmacovigilance network , has been created for the collection of report.
- **2012:** Europe - The PRAC , a committee for the evaluation and monitoring of the safety of medicine, is established.
- **2017:** New Eudravigilance was format.[2]

III. ROLE OF PHARMACOVIGILANCE IN DRUG DEVELOPMENT

➢ **Drug Development Stages**

1.	**Preclinical trials**
2.	**Clinical trials**
3.	**FDA Review**

1) Preclinical Trials:-

- Preclinical trial- as the name indicates, the preclinical trial is a study of the drug in an experimental animal, before using it in human.
- This ensures the safety and efficacy of the drug in the animal so that sufficient safety data may be collected for further study may be conducted in humans.
- A study to test a drug, a procedure, or another medical treatment in animals.
- The aim of a preclinical study is to collect data in support of the safety of the new treatment.
- Preclinical studies are required before clinical trials in humans can be started.
- Each type of product may undergo different type of preclinical research.
- This data allows researchers to estimate the safe starting dose of drug for clinical trials in human.

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- Drug may undergo pharmacodynamic, pharmacokinetics and toxicological testing.
- While performing preclinical studies, good laboratory practice (GLPs) are followed.
- Examples- Rat, monkey, guinea pig, frog, etc.[3]

2. Clinical Trials :-

Set of procedures in medical research and drug development to study the safety and efficacy of new drug. Essential get marketing approval from regulatory authorities.

- May require upto 7 years.

Phases of clinical trials:

Phase-I

- Clinical pharmacologic evaluation.
- First stage of testing in human 20-80 healthy volunteers.
- The main purpose of this phase to check the safety and side effect (toxicity) of the drug. In this phase study of pharmacokinetic, Pharmacodynamics, Pharmacological effect.
- tolerability, side effects and toxicity at different doses

Phase-II

- This phase is also called therapeutic exploration & dose ranging
- Phase II trials are performed on subjects in large groups (20-300) and are designed to assess the efficiency of the drugs, once its initial safety has been confirmed in Phase I trials.
- Also, during this phase, safety assessments of Phase I are continued on volunteers and patients in a larger group.
- Phase II studies historically have recorded lowest success rate.

Phase IIA and Phase IIB are the into which Phase II studies are sometimes divided two divisions:

I. Phase IIA: The dosing requirements (how many drug should be given) are assessed.

II. Phase IIB: The efficacy [how well the drug works at the prescribed dose(s)] of a drug is assessed.

Phase III:

- This phase is also called therapeutic confirmation comparison.Phase III studies are randomised controlled multicentre trials on a large patient group.
- ranging from 300-3000. These studies are aimed at being the definitive assessment of effectiveness of the drug.

Phase IV:

- This phase is also called Postmarketing surveillance/data gathering studies.
- In this phase collect data of drug that drug is safe or not.[4]

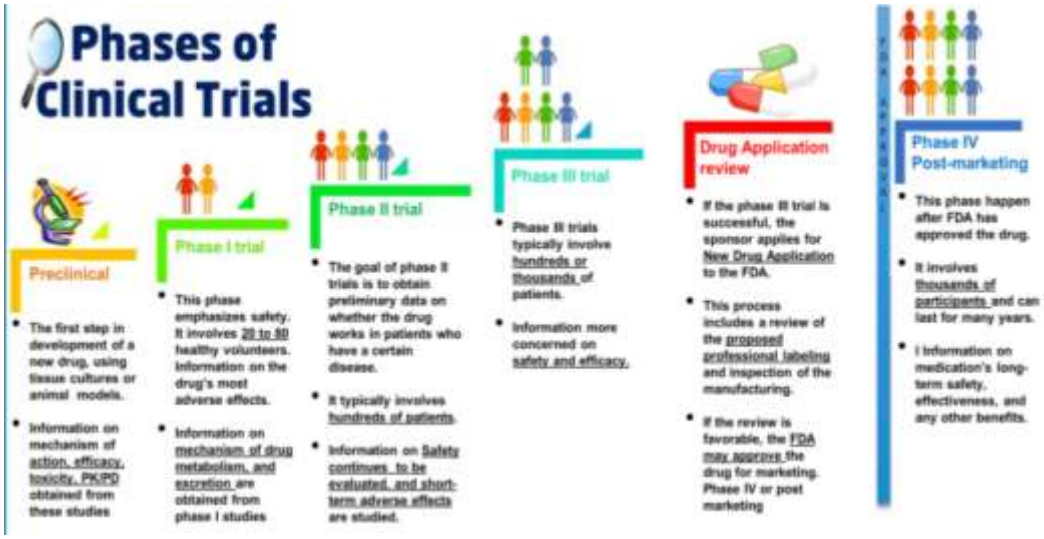

Fig 2: Phases of Clinical Trials

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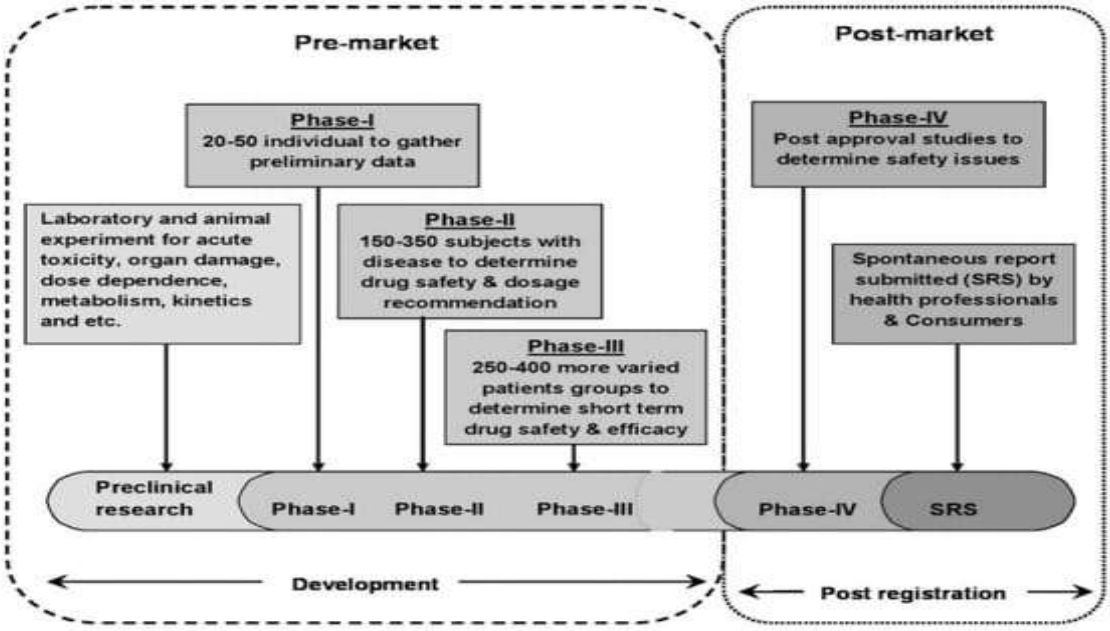

Fig 3 : Pharmacovigilance at different stages of drug development

➢ **P0ST MARKETTING SURVEILLANCE:-**

Post marketing surveillance is also known as "phase IV trials" or "post-marketing studies." Post-marketing surveillance (PMS), is the practice of keeping an eye on a drug's safety after it is approved for marketing by a regulatory body and after completing clinical studies. Finding previously unrecognized negative consequences as well as beneficial benefits is the main goal of PMS research. Off-label drug use, orphan drug challenges, and difficulties with conducting international clinical trials in children can all be considered crucial elements as well.[5]

Even when a drug is thoroughly examined before the Food and Drug Administration (FDA) approves it, many adverse drug reactions (ADRs) may still go undetected since clinical studies are frequently small, brief, and biased by excluding patients with concomitant conditions. Premarketing trials do not accurately represent real clinical use scenarios for various populations (like inpatients), hence it is crucial to maintain post-market surveillance.

PV is important to the post-market evaluation of recently produced medications. Before a new drug is introduced to the market, an intricate research and development process is facilitated by competition among pharmaceutical companies and strict regulatory evaluation procedures. Post-marketing PV can be obtained from a varietyof distinctive data sources.

Only a limited amount of information on uncommon ADRs will be available from the safety and efficacy assessments of any new medical product conducted during clinical trials. In addition, the post-marketing phase is typically the only time that "rare" and "very rare" ADRs are discovered (1 in 1000 and 1 in 10,000, respectively). This is mostly due to the limited variety of disorders, referred to as the "five toos: too few, too simple, too narrow, too median-aged, and too brief," which refers to the limited patient selection criteria, sample size, andsmall clinical study period.

Pharmacovigilance and pharmacoepidemiology are two areas of pharmacology that are addressed by post-marketing drug monitoring activities. The primary goal of pharmacovigilance sometimes referred to as drug safety surveillance, is the "timely detection" of "novel" ADRs that are distinct in their "clinical nature, severity, and/or frequency. The "population-based study of drug use and the risks associated with that use" is known as pharmacoepidemiology. The importance of pharmacovigilance should be promoted by emphasizing that a drug'sreal life begins when it is put on the market. Due to advancements in technology, PMS can now be

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actively managed with the aid of computers and electronic medical devices. Analyse how the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and Health Canada in Canada are likely to show similarities and disparities in the way the PV systems are regulated. Review the specific components and processes involved in the reporting of adverse event.[6]

➢ **Spontaneous Reports**

It is Unsolicited communication made by company, regulatory body or other organizationby consumers and health care professionals. It describes one or more ADRS in a patient who was given more medicinal product. It plays major role in identification of safety signals once a drug is marketed.Spontaneous and Reporting OF ADRS and adverse event is an important tool for gathering safety information of early detection.
spontaneous reporting has advantages that it is available immediately after a new product isreleased, last forever and include all patients taking the medication.[7]

➢ **Yellow card Scheme:-**

Yellow card Scheme (YCS) were applied to spontaneousReporting systems which is run by the MHRA and the committee of Human medicine. YCS it is one of the earliest PV programs designed to reduce ADRS.[8]
It is established in 1964 as a result of thalidomide tragedy.
The following goals are covered by Pharmacovigilance.[9]

- Monitoring the usage of medications in daily practice to spot previously undetected ADRs as well as changes in the patterns of adverse effects.
- Conducting risk-benefit analyses for medications and recommending appropriate steps, if and when required.
- Providing regular updates to healthcare professionals and patients about the safe and efficacious use of medicines

In 1991, the Ys has been enhanced by a new computer system, the ADROIT (Adverse Drug Reaction online Informationtracking]ADROITis different from other data base. Not only it store the details of the reports, but also the image of the yellow card the image in optical system.Any yellow card displayed on the screen viewedsimultaneously by any individuals.

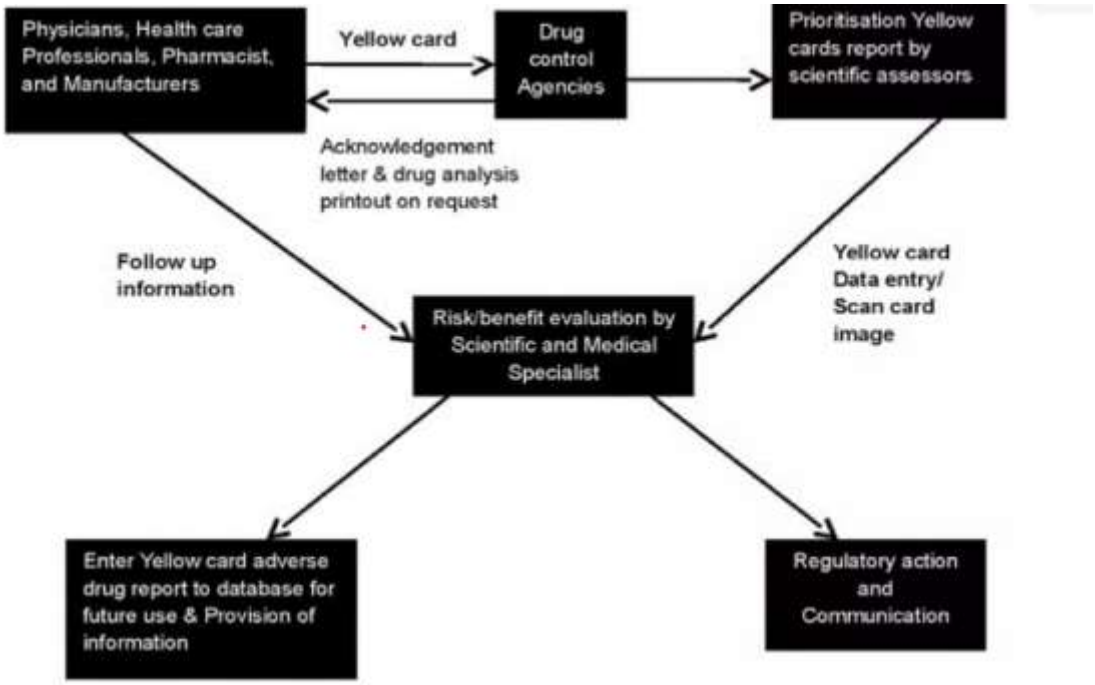

Fig 4 : Adverse drug reaction online information tracking and yellow card system source of data.

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SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

INDIAN PHARMACOPOEIA COMMISSION

(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare
Government of India
Sector-23, Raj Nagar, Ghaziabad-201002
www.ipc.nic.in

(AMC/ NCC Use only)
AMC Report No.
Worldwide Unique

A. PATIENT INFORMATION

1.Patient Initials _____
2. Age at time of Event or date of birth _____
3. Sex ☐ M ☐ F
4. Weight ___ Kgs

12. Relevant tests / laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)
6. Date of recovery (dd/mm/yyyy)
7. Describe reaction or problem

13. Other relevant history including pre-existing medical conditions (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction etc)

14. Seriousness of the reaction

☐ Death (dd/mm/yyyy)
☐ Life threatening
☐ Hospitalization/ prolonged
☐ Disability
☐ Congenital-anomaly
☐ Required intervention to prevent permanent impairment / damage
☐ Other (specify)

15. Outcomes

☐ Fatal ☐ Recovering ☐ Unknown
☐ Continuing ☐ Recovered ☐ Other (specify)

C. SUSPECTED MEDICATION(S)

S.No	8. Name (brand and /or generic name)	Manufacturer (if known)	Batch No./ Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if known, give duration) Date started	Date stopped	Reason for use of prescribed for
i.										
ii.										
iii.										
iv.										

S.No As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced dose
i.										
ii.										
iii.										
iv.										

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. REPORTER (see confidentiality section on first page)

16. Name and Professional Address : _____
Pin code: _____ E-mail _____
Tel. No. (with STD code): _____
Occupation _____ Signature _____

17. Causality Assessment
18. Date of this report (dd/mm/yyyy)

Fig 5 : Adverse Drug Reaction reporting form

2) FDA REVIEW

The FDA Pharmacovigilance Team carefully screen all the report for new risk . If a new risk is identified, the need for an action is evaluated and appropriate measures are taken into consideration .The Food andDrug Administration is responsible for protecting the public health by ensuring the safety, efficacy and security of human

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and veterinary drugs, biological products and medical device; and by ensuring the safety of our nation's food supply, cosmetics and products that emit the radiation.

Once FDA receives an NDA, the review team decides if it is complete. If it is not complete, the review team can refuse to file the NDA. If it is complete, the review team has 6 to 10 months to make a decision on whether to approve the drug. The process includes the following:

- Each member of the review team conducts a full review of his or her section of the application.For example, the medical officer and the statistician review clinical data, while a pharmacologist reviews the data from animal studies. Within each technical discipline represented on the team, there is also a supervisory review.
- FDA inspectors travel to clinical study sites to conduct a routine inspection. The Agency looks for evidence of fabrication, manipulation, or withholding of data.
- The project manager assembles all individual reviews and other documents, such as the inspection report, into an "action package." This document becomes the record for FDA review. The review team issues a recommendation, and a senior FDA official makes a decision.[10]

IV. PHARMACOVIGILANCE IN INDIA

In India, consideration for the surveillance of ADRs developed relatively late, as traditionally there was no concept of surveillance of medicines in the country. Even though PV is still in its infancy, it is not new to India. It was not until 1986 when a few physicians, mainly from academic institutions, called for greater attention to be devoted to the potential adverse effects of prescription medicines and rational prescribing of medicines. This led to the formation of the first ADR monitoring program consisting of 12 regional centers, each covering a population of 50 million, but was unsuccessful.[11] Nothing much happened until a decade later when India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden in 1997. Three centers for ADR monitoring were identified, mainly based in the teaching hospitals: A National Pharmacovigilance Center located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh). These centers were to report ADRs to the drug regulatory authority of India. The major role of these centers was to monitor ADRs to medicines marketed in India. However, they were non-functional as information about the need to report ADRs and about the functions of these monitoring centers never reached the prescribers and there was lack of funding from the government. This attempt was unsuccessful, and hence, again from 1 January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program (NPVP) for India was formulated.[12]

NPVPstructure is shown in figure.

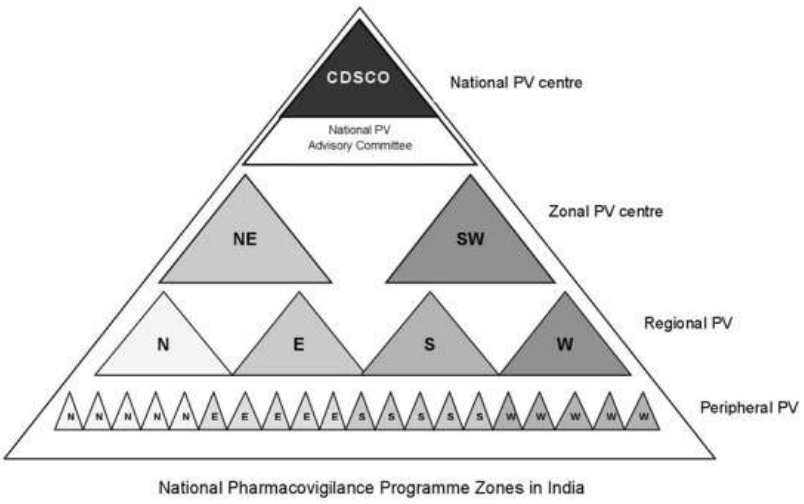

Fig 6 : National Pharmacovigilance programme zone in india

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The NPVP, established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based at the Central Drugs Standard Control Organization (CDSCO). Two zonal centers, the South-West (SW) zonal center (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East (NE) zonal center (located in the Department of Pharmacology, AIIMS, New Delhi) were to collect the information from all over the country and send it to the committee as well as to the Uppsala Monitoring Centre (UMC) in Sweden.[13] Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center, in turn, would have several peripheral centers (24 in total) reporting to it. The program had three broad objectives. The short-term objective was to foster a reporting culture, the intermediate objective was to involve large number of healthcare professionals in the system in information dissemination, and the long-term objective was for the program to be a benchmark for global drug monitoring. However, this program also failed.[14]

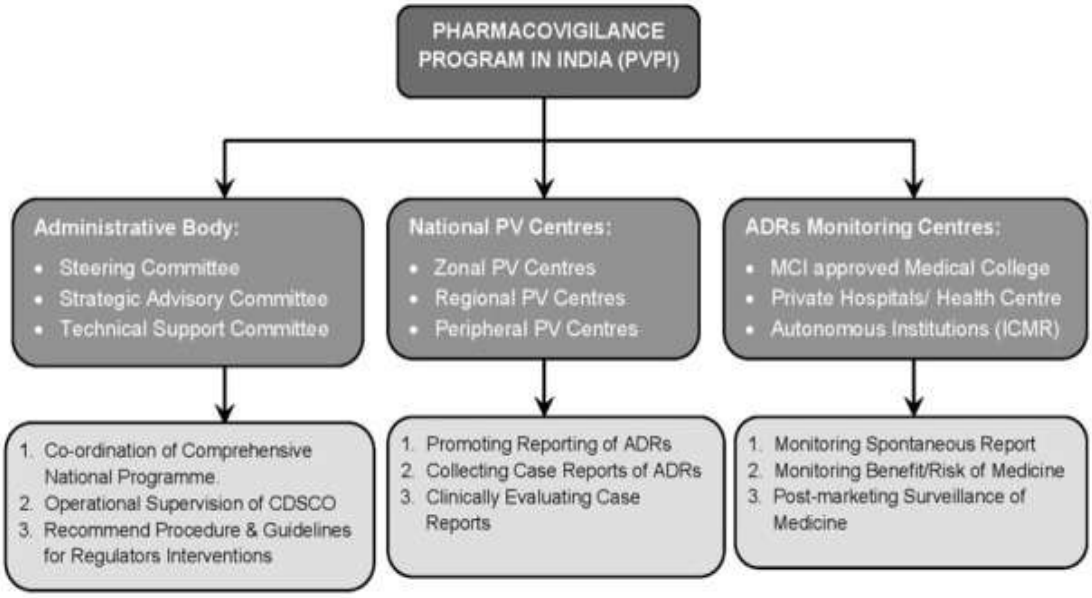

Fig 7 : Current Pharmacovigilance program in india

V. PHARMACOVIGILANCE PROGRAM IN US

To facilitate postmarket surveillance in the USA, (Table 1) the FDA created the FDA Adverse Event Reporting System (FAERS; formerly known as Adverse Event Reporting System), which enables producers, medical management experts, and subjects to present adverse event reports.The database contains data on adverse events, medication errors, product quality concerns, and patient demographics .Patients and healthcare professionals can voluntarily report severe adverse events and other problems they believe are related to the use of an FDA-regulated product through the FDA's MedWatch web-based reporting system. Patients and healthcare professionals can voluntarily report severe adverse events and other problems they believe are related to the use of an FDA-regulated product through the FDA's MedWatch web-based reporting system. The FDA or the manufacturers can be informed in detail of the adverse events. Information on both required and optional reporting is available from MedWatch. The Center for Drug Evaluation and Research or the Center for Biologics Evaluation reviews the ADR reports submitted online via 2 form 3500As or 3500Bs. Under the US FDA Amendments Act of 2007 for the mandatory submission of adverse events by the makers, the FDA launched the Sentinel Initiative.[15]

VI. PHARMACOVIGILANCE PROGRAM IN UK

The EudraVigilance system compiles, manages, and analyses suspected adverse drug reactions (ADRs) associated with medications

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licenced in the European Economic Area. The European Medical Agency was established in 1995 to assess pharmaceuticals.[16] Patients and healthcare professionals report suspected ADRs to EudraVigilance or MAHs. The Pharmacovigilance Risk Assessment Committee assesses all potential risks and oversees drug supervision. The aforementioned committee takes into account the conclusions, evaluation, reduction, and announcement regarding the risks of adverse responses while keeping the therapeutic benefit of the drug in mind.[17] In the UK, Pharmacovigilance continues to fall under the purview of the MHRA.
You, as a Marketing Authorization Holder (MAH), will be expected to report pharmacovigilance data to the MHRA in accordance with UK regulations for medicines that are authorised nationally in the UK, including:

- Reports on individual cases of safety in the UK and abroad
- (ICSRs)
- Reports on recurring safety updates (PSURs)
- Plans for managing risks (RMPs)
- Final research reports and Post-Authorisation Safety Studies

(PASS) protocols

In order to best promote patient safety in the UK, they will be evaluated while taking into consideration all pertinent facts, and decisions will be made using UK clinical practice. Abbreviations: CBER, Centre for Biologics Evaluation; CDER, Centre for Drugs Evaluation and Research; CDSCO, Central Drugs Standard Control Organization; FAERS, FDA Adverse Event Reporting System; MAHs, Market Authorization Holders.

The challenges

The underreporting of ADRs is India's main PV problem. Thereare a number of reasons for this, including a lack of qualified medicalpersonnel, insufficient national PV awareness, and inadequate available resources. Only 250 of India's more than 450 medical schools andhospitals that have been authorised by the Medical Council of India arecurrently AMCs. Lack of a reliable system for reporting and analyzing different ADRs, prescription errors, patient compliance, and druginteractions is another issue the PV system in India is dealing with.It would be sage to workwith them and create a system rather thanadopting a WHO-based ADR reporting system because India has asophisticated IT sector.[18] The most recent PvPI database availablefor ADR, drug Consumption and treatment results are insufficient accurately represent the Indian population, thus all healthcareprofessionals—including those in rural areas—should be made awareof PV.[19] Physicians reported ADRs at a higher rate than pharmacistsand other healthcare professionals. Due to a lack of assistance from thegovernment and a small PV budget, PV reporting is difficult and time consuming.

Table 1 :Contrast between Indian Pharmacovigilance, the USA and Europe[20]

Parameters	India	USA	EU
Regulatory authority	CDSCO	FDA	EMA
Authority responsible for PV	National Coordination Centre-IPC	CDER or CBER	European Commission, EudraVigilance Data Analysis System (EVDAS)
Online ADR reporting	Vigiflow	MedWatch	EudraVigilance
ADR forms	One ADR form	1. 3500A: Mandatory reporting for regulated industries and facility users 2. 3500B: Voluntary reporting for consumers and healthcare professionals	Individual Case Safety Report (ICSR) form Three ICSR forms are available: Level 1, Level 2a, and Level 3. These three forms adhere to the same guidelines and have the same structure, but they differ in the ICH-E2B(R3) data items they use to satisfy the Eudra vigilance access policy.
Guidelines	PSUR, Schedule Y, Pharmacovigilance Guidance Document for MAHs of Pharmaceutical Products	Good PV Practices and Pharmacoepidemiologic Assessment	Good Pharmacovigilance practices (GVP)
PV database	Vigibase	FAERS Sentinel System	European Database of Suspected Adverse Drug reactions Reports, EudraVigilance Data Analysis System (EVDAS), EudraVigilance WEB trader (EVWEB)
Periodic safety reports	Periodic Safety Update Report (PSUR)	Periodic adverse drug experience reports (PADERs)	Periodic Benefit Risk Evaluation Report (PBRER)
Spontaneous case reports (serious AEs)	Within 15 d	Within 15 d	Within 10 d
Risk management system	Pharmacovigilance guidance document for all MAHs of Pharmaceutical Products effective from 2018	Risk Evaluation and Mitigation Strategy (REMS)	European Risk Management Strategy

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VII. CONCLUSION:

This is an overview of the two departments where pharmacovigilance is used. For the efficient use of medications and the provision of high-quality medical care, safety monitoring is a crucial component. ARDS considerably reduce safety, lengthen hospital stays, and lower quality of life, all of which lead to a rise in mortality and morbidity. PV focuses on anticipating SRD or assessing probable ADRS at this early stage of theal Jo drug development pipeline. The fundamental tenet of PMS and PV is that patient safety and health are important considerations in the development and marketing of pharmaceutical goods. PMS completes the post-approval of the medication. In addition to possible hazards, previously unidentified adverse responses can be found when using medications.

The in India has become an important public health issue as regulators, drug manufactures, consumers, and the health care professionals are faced with a number of challenges. The PV in India continues to grow,envolve, improve. India is the world's largest manufacturer of pharmaceuticals and a centre for clinical research; demand a PV setup that is more strict.

Compared to US and EU regulations, the Indian PV system currently lacks robustness and has to be improved. PvPI was a significant shift in Indian PV sector, and it intends to broaden the breadth and reach of its operations in the year to come.

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