WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 13, 1017-1028. Review Article ISSN 2277–7105

# CURRENT SCENARIO OF PHARMACOVIGILANCE IN INDIA AND ITS COMPARISION WITH U.S.A. AND E.U

**P. V. Siva Krishna*, M. V. Nagabhushanam and G. Ramakrishna**

Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

Article Received on
09 Sept. 2021,

Revised on 30 Sept. 2021,
Accepted on 21 Oct. 2021

DOI: 10.20959/wjpr202113-22163

***Corresponding Author**
**P. V. Siva Krishna**
Department of Pharmaceutical Regulatory Affairs, Hindu College of Pharmacy, Amaravathi Road, Guntur, Andhra Pradesh, India-522002.

## ABSTRACT

Pharmacovigilance (PV) is an integral part of the drug regulation system. PV plays an indispensable role in the identification, assessment, and publicizing of adverse drug reactions (ADRs) through various methods. ADRs account for serious harm to the patients and even lead to morbidity and mortality. The PV databases help in the promotion of safe drug use and protection of public health safety. This article compares the PV system in the USA, Europe, and India, highlighting the challenges and future perspectives to be adapted to widen the horizon of the existing PV structure in India. In India, PV programs are still at the dawning stage when paralleled to the other countries. The National Pharmacovigilance Program and the Pharmacovigilance Program of India are the most recent advancements in this field in the country. The USA and Europe have well-established PV systems in place thanks to technological progress and other resources. India is the largest producer of pharmaceuticals in the world and a major clinical research hub; hence, it requires a more stringent PV setup. With the increase in population and novel drugs in the market each day, there is a need for an effective PV system in India.

**KEYWORDS:** Pharmacovigilance systems, Legislation, European Union, United States of America, Adverse Drug Reaction; European Medicines Agency (EMA), USFDA, Marketing Authorization Holder (MAH).

## 1. INTRODUCTION

Pharmacovigilance (PV) was officially introduced in December 1961 with the publication of a letter (case report) in the Lancet by W. McBride, the Australian doctor who first suspected a causal link between serious fetal deformities (phocomelia) and thalidomide, a drug used during pregnancy: Thalidomide was used as an antiemetic and sedative agent in pregnant women.[1] In 1968, the World Health Organization (WHO) promoted the "Programme for International Drug Monitoring", a pilot project aimed to centralize world data on adverse drug reactions (ADRs). In particular, the main aim of the "WHO Programme" was to identify the earliest possible PV signals. The term PV was proposed in the mid-70s by a French group of pharmacologists and toxicologists to define the activities promoting "The assessment of the risks of side effects potentially associated with drug treatment".[2] PV is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, blood products, herbals, vaccines, medical device, traditional and complementary medicines with a view to identifying new information about hazards associated with products and preventing harm to patients. The challenge of maximizing drug safety and maintaining public confidence has become increasingly complex. Pharmaceutical and biotechnology companies must not only monitor, but also proactively estimate and manage drug risk throughout a product's lifecycle, from development to post-market.[3] PV is particularly concerned with ADRs, which are drug responses that are noxious and unintended, and which occur at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.[4] Continuous monitoring of drug effects, side effects, contraindications and outright harmful effects which could result in a high degree of morbidity, and in some cases, even mortality, are essential to maximize benefits and minimize risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the country and outside. Because clinical trials involve several thousands of patients at most, less common side effects and ADRs are often unknown at the time a drug enters the market. Post marketing PV uses tools such as data mining and investigation of case reports to identify the relationships between drugs and ADRs. The drug regulatory agencies have the responsibility of having a well-established PV system to monitor ADRs during the drug development phase and later during the life time of a marketed drug.[5] A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring such as government, industry, health care centers, hospitals, academia, medical and

pharmaceutical associations, poisons information centers, health professionals, patients, consumers and media.[6-8] Sustained collaboration and commitment are vital if future challenges in PV are to be met in order to develop and flourish.

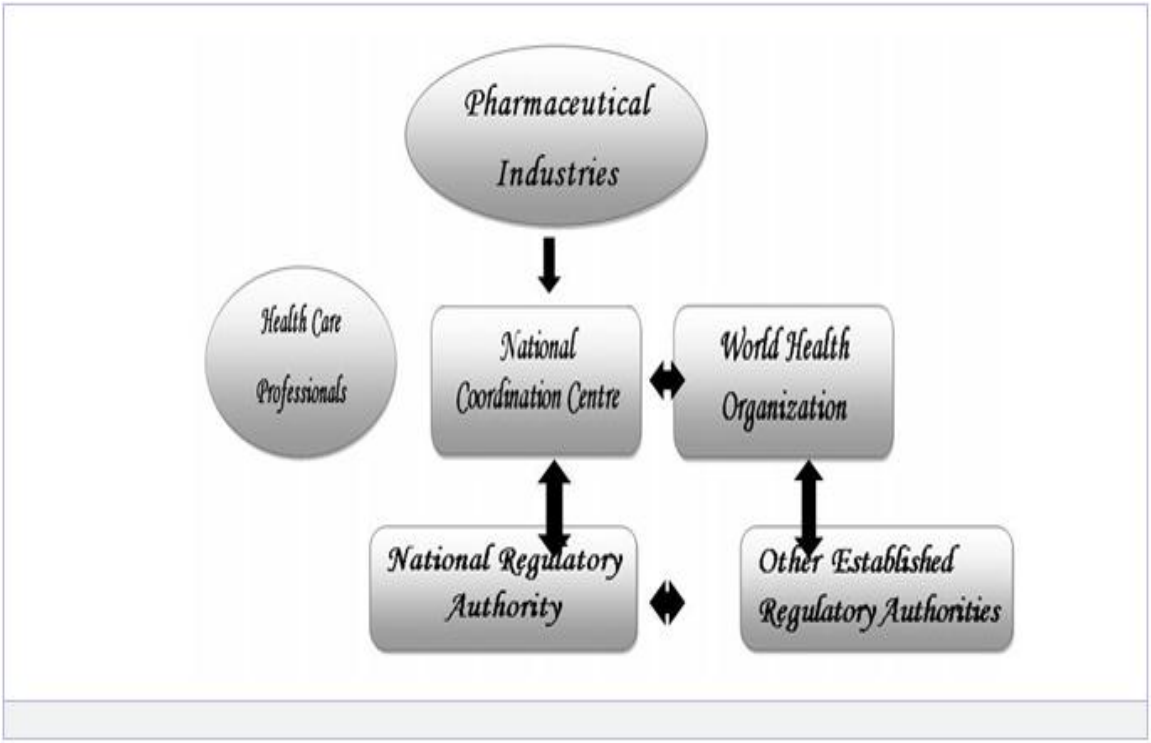
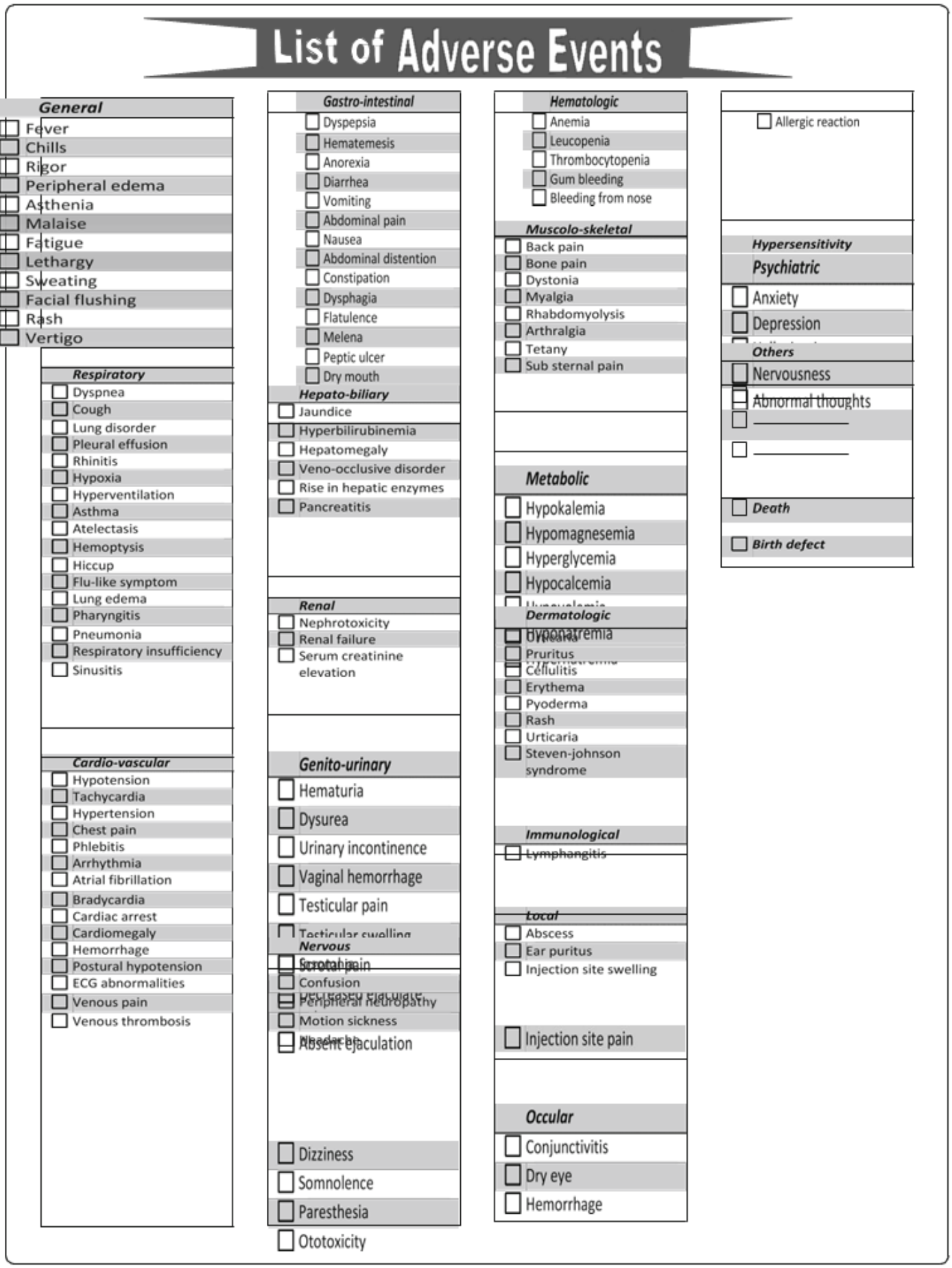



**Fig-1-Diagramatic Presentation of PV.**

**Table-1:-Types of ADR (Adverse Drug Reactions).**

TYPES OF ADRs

| Type | Type of effect | characteristics | example |
|---|---|---|---|
| A | Augmented | Dose dependent predicted from the known pharmacology of the drug | Hypoglycaemia-insulin |
| B | Bizarre | Unpredictable Dose independent Rare,fatal | Anaphylaxis to penicillin |
| C | Chronic | Prolong treatment | Analgesic neuropathy |
| D | Delayed | After years of treatment | Antipsycotic –turdive dyskinesia |


List of Adverse Events
General
Fever
Chills
Rigor
Peripheral edema
Asthenia
Malaise
Fatigue
Lethargy
Sweating
Facial flushing
Rash
Vertigo
Respiratory
Dyspnea
Cough
Lung disorder
Pleural effusion
Rhinitis
Hypoxia
Hyperventilation
Asthma
Atelectasis
Hemoptysis
Hiccup
Flu-like symptom
Lung edema
Pharyngitis
Pneumonia
Respiratory insufficiency
Sinusitis
Cardio-vascular
Hypotension
Tachycardia
Hypertension
Chest pain
Phlebitis
Arrhythmia
Atrial fibrillation
Bradycardia
Cardiac arrest
Cardiomegaly
Hemorrhage
Postural hypotension
ECG abnormalities
Venous pain
Venous thrombosis
Gastro-intestinal
Dyspepsia
Hematemesis
Anorexia
Diarrhea
Vomiting
Abdominal pain
Nausea
Abdominal distention
Constipation
Dysphagia
Flatulence
Melena
Peptic ulcer
Dry mouth
Hepato-biliary
Jaundice
Hyperbilirubinemia
Hepatomegaly
Veno-occlusive disorder
Rise in hepatic enzymes
Pancreatitis
Renal
Nephrotoxicity
Renal failure
Serum creatinine elevation
Genito-urinary
Hematuria
Dysurea
Urinary incontinence
Vaginal hemorrhage
Testicular pain
Nervous
Confusion
Motion sickness
Dizziness
Somnolence
Paresthesia
Ototoxicity
Hematologic
Anemia
Leucopenia
Thrombocytopenia
Gum bleeding
Bleeding from nose
Muscolo-skeletal
Back pain
Bone pain
Dystonia
Myalgia
Rhabdomyolysis
Arthralgia
Tetany
Sub sternal pain
Metabolic
Hypokalemia
Hypomagnesemia
Hyperglycemia
Hypocalcemia
Dermatologic
Pruritus
Cellulitis
Erythema
Pyoderma
Rash
Urticaria
Steven-johnson syndrome
Immunological
Local
Abscess
Ear puritus
Injection site swelling
Injection site pain
Occular
Conjunctivitis
Dry eye
Hemorrhage
Allergic reaction
Hypersensitivity
Psychiatric
Anxiety
Depression
Others
Nervousness
Death
Birth defect

## 2. PHARMACOVIGILLANCE PROGRAM OF INDIA[10-12]

The discipline of PV has developed considerably since the 1972 WHO technical report, and it remains a dynamic clinical and scientific discipline. It has been essential to meet the challenges of the increasing range and potency of pharmaceutical and biological medicines including vaccines, which carry with them an inevitable and sometimes unpredictable potential for harm. The risk of harm, however, is less when medicines are used by an informed health profession and by patients who themselves understand and share responsibility for their drugs. When adverse effects and toxicity appear, particularly when previously unknown in association with the medicine, it is essential that they are analyzed and communicated effectively to an audience that has the knowledge to interpret the information. This is the role of PV, of which much has already been achieved. But more is required for the integration of the discipline into clinical practice and public policy. To fulfill the PV obligations for its marketed products as per regulations, a pharmaceutical company in India has to essentially carry out activities such as collection, and expedited reporting of serious unexpected ADRs.[9] A typical setup for PV studies, including people involved on various levels, organizational units and their functions are shown in below figure.

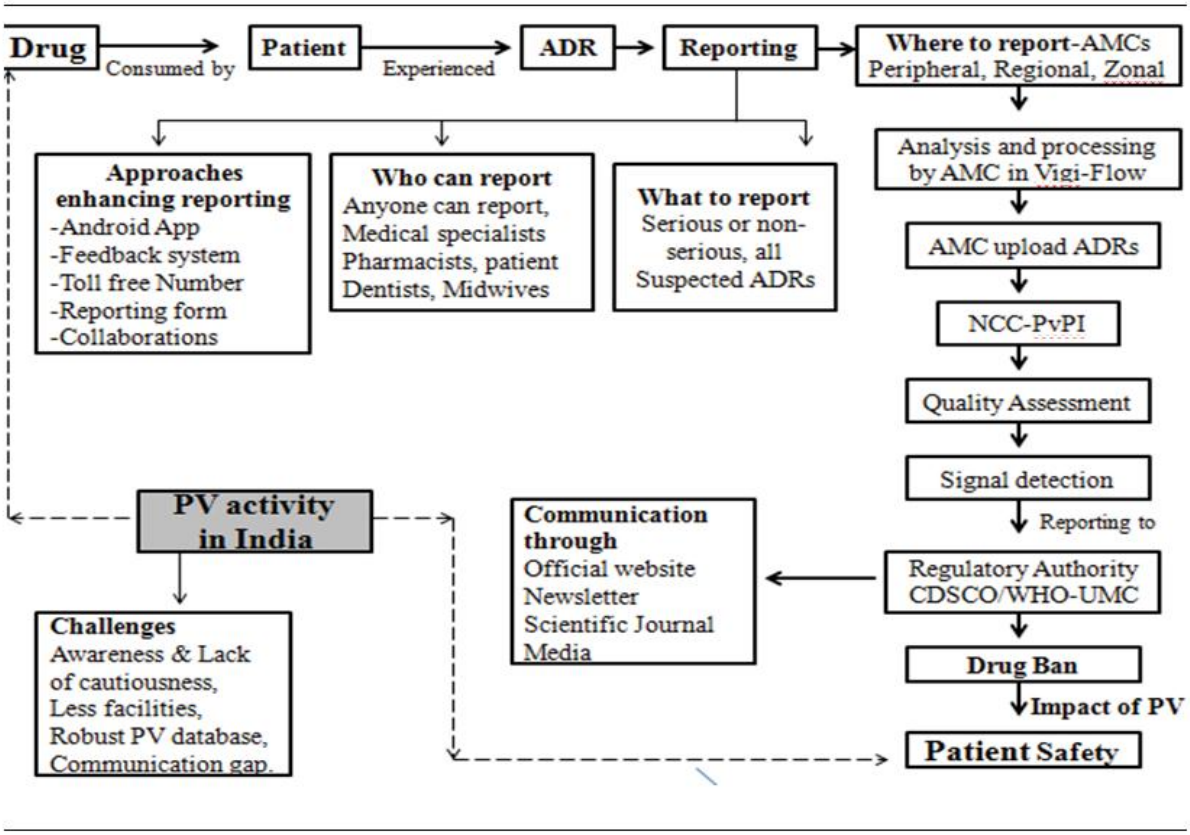



**Fig-2-Pharmacovigilance activity In India.**

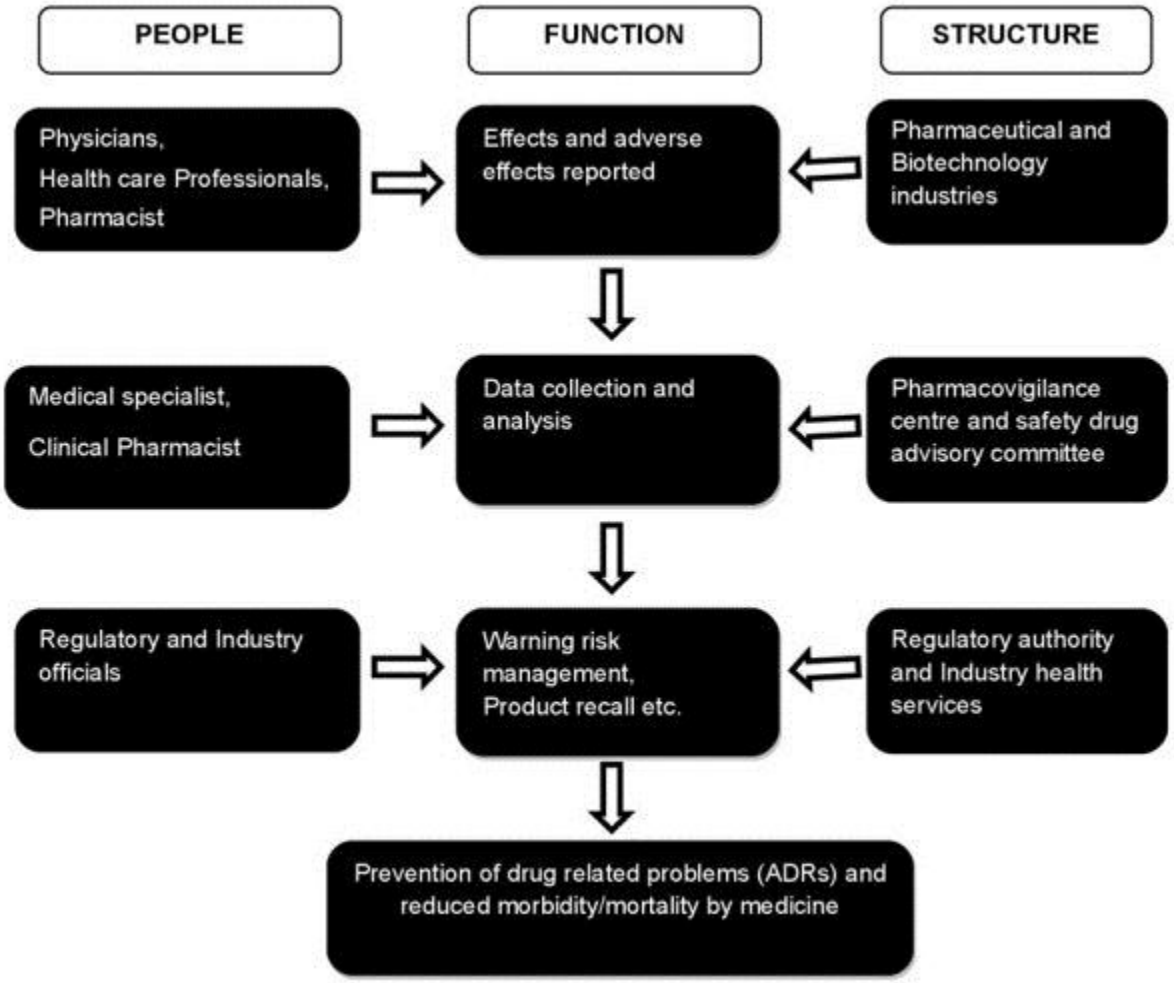



**Fig-3-A typical pharmacovigilance setup.**

**The MAHs Pharmacovigilance Guidance Document comprises following modules.**

**MODULE 1 –** Pharmacovigilance System Master File.

**MODULE 2** – Collection, Processing & Reporting of Individual Case Safety Reports.

**MODULE 3** – Preparation & Submission of Periodic Safety Update Report.

**MODULE 4** – Quality Management System

**MODULE 5 –** Audits & Inspections of Pharmacovigilance

**MODULE 6 –** Submission of Risk Management Plan.

## 3. PHARMACOVIGILANCE IN UNITED STATES OF AMERICA[13-16]

The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) of the USFDA monitor and review safety information throughout life cycle of the medicinal product, from application for MA through approval of the application and after entry of drug in the market. The Food and Drug Administration

Amendments Act (FDAAA), has a pivotal role in safety of drugs during post-marketing phase. It provides FDA with the authority to require labeling changes with respect to new safety information. The FDAAA also gives FDA the authority to require certain post-marketing studies and clinical trials for new drugs approved under Food, Drug and Cosmetic Act (FDCA) or for biological medicinal products. The routine PV activities in US i.e. compliance with applicable post-market requirements under the FDCA and USFDA implementing regulations includes post-marketing surveillance and risk assessment. The PV plan describes efforts. Beyond the routine post-marketing spontaneous reporting and is designed to enhance and expedite the sponsor's acquisition of safety information. The sponsors have to develop a PV plan for products for which; serious safety risks. Have been identified post-approval and/or already identified safety risks need more evaluation or risk populations have not been adequately studied. Under USFDA, guidance to cover the different phases of the risk assessment and risk management for industry is divided into three parts.

- Safety signal identification
- Pharmacoepidemiologic assessment and safety signal interpretation
- Pharmacovigilance plan development Risk Evaluation and Mitigation Strategies (REMS)
- The USFDA has obligation for manufacturers to implement special risk management programs, called REMS. The Secretary, in consultation with the office responsible for reviewing the drug and the office responsible for post approval safety of the drug, determines the requirement of REMS. If the benefits of drug outweigh the risks, then the applicant having an approved application for new drug or abbreviated new drug or biological medicinal product has to submit REMS. The proposed REMS must be submitted within 120 days of the USFDA notification for the protection of public health. The risk assessment and risk minimization together is called as Risk Management and it is an iterative process throughout a product's lifecycle which consists of:
- Assessing a product's benefit-risk balance;
- Developing and implementing tools to minimize its risks while preserving its benefits;
- Evaluating tool effectiveness and reassessing the benefit-risk balance;
- Making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.

In US, under Title 21 of Code of Federal Regulation (CFR) §§ 314.80, 314.98, 600.80, Periodic adverse drug experience reports (PADERs) shall contain among other data, information about all serious expected and non-serious adverse events, which are not reported through the post- marketing "15-day Alert reports" or their follow-up reports. These periodic reports also include a narrative summary of information in the report and an analysis of "15-day Alert reports" submitted during the reporting intervals.

## 4. PHARMACOVIGILANCE IN EUROPE[13-16]

- This report reviews, analyses and applies alternative indicators and monitoring methodologies to measure the evolution of capital market integration in the European Union.
- More specifically, the report pursues three objectives. First, it provides a review of the different methodologies and indicators proposed in the economic literature on capital market integration. Second, it discusses the methodologies underlying the construction of such indicators and then computes the most suitable indicators, using recent data, to obtain measures of the degree of capital market integration in the European Union. Third, the report suggests methodological improvements to existing indicators and proposes a set of indicators to monitor future financial market integration in the European Union.
- Section 2 of the report starts out by defining financial market integration. We then present a broad classification of indicators around which we organize the subsequent discussion of the indicators proposed in previous studies. A first class of indicators refers to specific markets such as bond markets, credit markets or equity markets. A second class of indicators is instead based on household and firm decisions that should reflect the risk-sharing opportunities provided by financial markets. A third class of indicators captures differences in the legal and institutional frameworks of the countries under consideration.
- In Section 3 we discuss the relative merits of various types of indicators in terms of data availability and reliability. We also compare the merits of indicators based on prices and returns with those of indicators based on stock or flow data. Finally, we propose general convergence criteria that can be applied to estimate changes in the degree of financial market integration.
- In Section 4 we outline the specific indicators of financial market integration that we analyze and apply in the remaining part of the report. These indicators are then evaluated

and applied in the subsequent five sections of the report.

- In Section 5 we evaluate and compute indicators of credit and bond market integration, some of which based on price and return data and others based on quantity data.
- In Section 6 we do the same for indicators of stock market integration, again presenting both price- and quantity-based indicators.
- In Section 7 we turn to indicators that measure financial market integration based on the household decisions,
- While Section 8 considers indicators based on corporate decisions.
- Section 9 discusses the effects of different legal systems and presents a limited set of quantitative indicators.
- Section 10 summarizes the findings and makes recommendations about the indicators to be used to monitor future developments in the integration of European financial markets.
- In Section 11 we indicate what kind of additional data could be collected through surveys conducted by the European Commission to shed light on aspects of financial market integration that could not be covered by relying on existing data sources.
- The European Medicines Agency (EMA) coordinates the European Union (EU) pharmacovigilance system and operates services and processes to support pharmacovigilance in the EU.
- The EU legal framework of pharmacovigilance for medicinal products for human use is provided for in Regulation (EC) No 726/20041 and Directive 2001/83/EC2. The legislation was amended in 20103 and 20124. Article 29 of Regulation (EC) No 726/2004 and Article 108b of Directive 2001/83/EC require regular reporting on the performance of pharmacovigilance tasks by the European Medicines Agency (EMA) and the Member States respectively.
- Before a medicine is authorized for use, evidence of its safety and efficacy is limited to the results from clinical trials, where patients are selected carefully and followed up very closely under controlled conditions. This means that at the time of a medicine's authorization, it has been tested in a relatively small number of selected patients for a limited length of time.

## 5. DISCUSIONS AND FUTURE PROSPECTIVES

Pharmacovigilance (PV) is an integral part of the drug regulation system. PV plays an indispensable role in the identification, assessment, and publicizing of adverse drug reactions (ADRs) through various methods. ADRs account for serious harm to the patients and even lead to morbidity and mortality. The PV databases help in the promotion of safe drug use and protection of public health safety. This article compares the PV system in the USA, Europe, and India, highlighting the challenges and future perspectives to be adapted to widen the horizon of the existing PV structure in India. In India, PV programs are still at the dawning stage when paralleled to the other countries. The National Pharmacovigilance Program and the Pharmacovigilance Program of India are the most recent advancements in this field in the country. The USA and Europe have well-established PV systems in place thanks to technological progress and other resources. India is the largest producer of pharmaceuticals in the world and a major clinical research hub; hence, it requires a more stringent PV setup. With the increase in population and novel drugs in the market each day, there is a need for an effective PV system in India.Therefore, EU and US legislations primarily tend toward the intensification of pharmacovigilance, moving from passive to proactive, although the usefulness of the tools provided by the legislation is controversial. The second trend is a partial harmonization of the different pharmacovigilance systems in order to simplify the sponsors' activities and increase the efficacy of pharmacovigilance. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has elaborated a pharmacovigilance guideline for medicines approved in the U.S., the E.U. and Japan. Moreover, these systems use a common methodology, based on a regulatory body, postmarketing surveillance, risk management, post-approval research and enforcement.

## 6. CONCLUSION

While much progress has been made in PV practices, many deficiencies and issues still exist in the efforts to ensure safe medicine usage. Harmonization of PV practices beyond regulation requires defining and implementing "best suitable practices" for the health-care professionals, industry and the regulatory authorities. It requires formal training for PV professionals and better communication tools. Safety information is communicated between different regulatory agencies, regulatory agencies and manufacturers, healthcare professionals and manufacturers, agencies and healthcare professionals, healthcare professionals and consumers. All parties in communication utilize different tools– from product labeling to

adverse event reports. In today's technological environment these communications are occurring more frequently over the internet, through social media and the cloud. For PV practices to become truly global, there is a further need to integrate these PV best practices with these new modes of communication. Identifying the discrepancies in existing practices is also only a first step. More work is required to establish the best practices, tools and infrastructure that will be required to address the needs of PV in the future. International organizations must continue to advance their understanding of PV and establish guidelines for shifting away from a focus on finding harm and more toward extending knowledge about safety to all appropriate stakeholders. Wallace and Evans write, "Pharmacovigilance should operate in a culture of scientific development. This requires the right balance of inputs from various disciplines, a stronger academic base, and greater availability of basic training and resource which is dedicated to scientific strategy. Of course, implementing such strategies will require legislative change; thus, the process that begins with the legislation to identify where disharmony exists, must also end with the legislation to create a framework at a national level that allows for an international harmonization of practice.

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