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Current scenario of pharmacovigilance in India and its comparision with U.S.A. and E.U

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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

1. Introduction
Pharmacovigilance (PV) was officially introduced in December 1961 with the publication of a letter in The Lancet by Dr. William McBride, the Australian obstetrician who first suspected a causal link between serious fatal deformities (phocomelia), thalidomide used during pregnancy: Thalidomide was used as an anti-emetic and sedative agent in pregnant women. In 1968, the WHO promoted the 'Programme for International Drug Monitoring' a pilot project aimed to centralize world data on Adverse Drug Reactions (ADRs) [1, 2]. 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'. WHO defines PV as 'the pharmacological science relating to the detection, assessment, understanding and prevention of ADRs, particularly long-term and short-term ADRs of medicines, PV serves various roles such as identification, quantification and documentation of drug-related problems which are responsible for drug-related injuries. PV is mainly the post marketing surveillance (phase-4 study) of drug development; the main objective of PV is to quantify previously recognized ADRs, to identify unrecognized ADRs, to evaluate the effectiveness of medicines in real-world situations, and to decrease mortality and morbidity associated with ADRs. The UMC located at Uppsala, Sweden co-ordinates the International Drug Monitoring program (IDM) [3-5]. Till now there are 104 official member countries and 33 associate members throughout the world, including developed, developing and under-developed countries. India is the world's second most populated country with over one billion potential drug consumers. Although, India is participating in the UMC program, its contribution to this database is relatively small. This problem is essentially due to the absence of robust ADRs monitoring system and also the lack of awareness of reporting concepts among Indian health care professionals. It is very important to focus the attention of the medical community on the importance of ADRs to ensure maximum benefits for public health and safety. In India ADRs are considered among the leading cause of morbidity and mortality. Approximately 8% of hospital admissions are estimated due to ADRs and regarding 8-19% of hospitalized patients experience a serious ADR. When the FDA approves a new drug or marketing, its complete adverse events profile may not be known because of the limitation of pre-approval clinical trials.

Typically, clinical trials for new drugs are not of short durations and are conducted in populations that number up to 5000, therefore, the most common dose related ADRs are usually detected in the pre-marketing phase while ADRs which are rare and those detected on long term use [6-8].

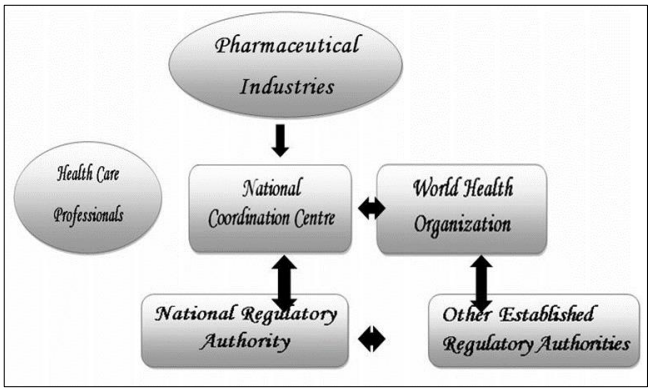


Fig 1: Diagrammatic representation of PV

1.1 Types of ADR

ADR is a response to a drug which is noxious and unintended, and which occurs at doses normally used in human being for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function [9-12].

Table 1: Types of Adverse 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

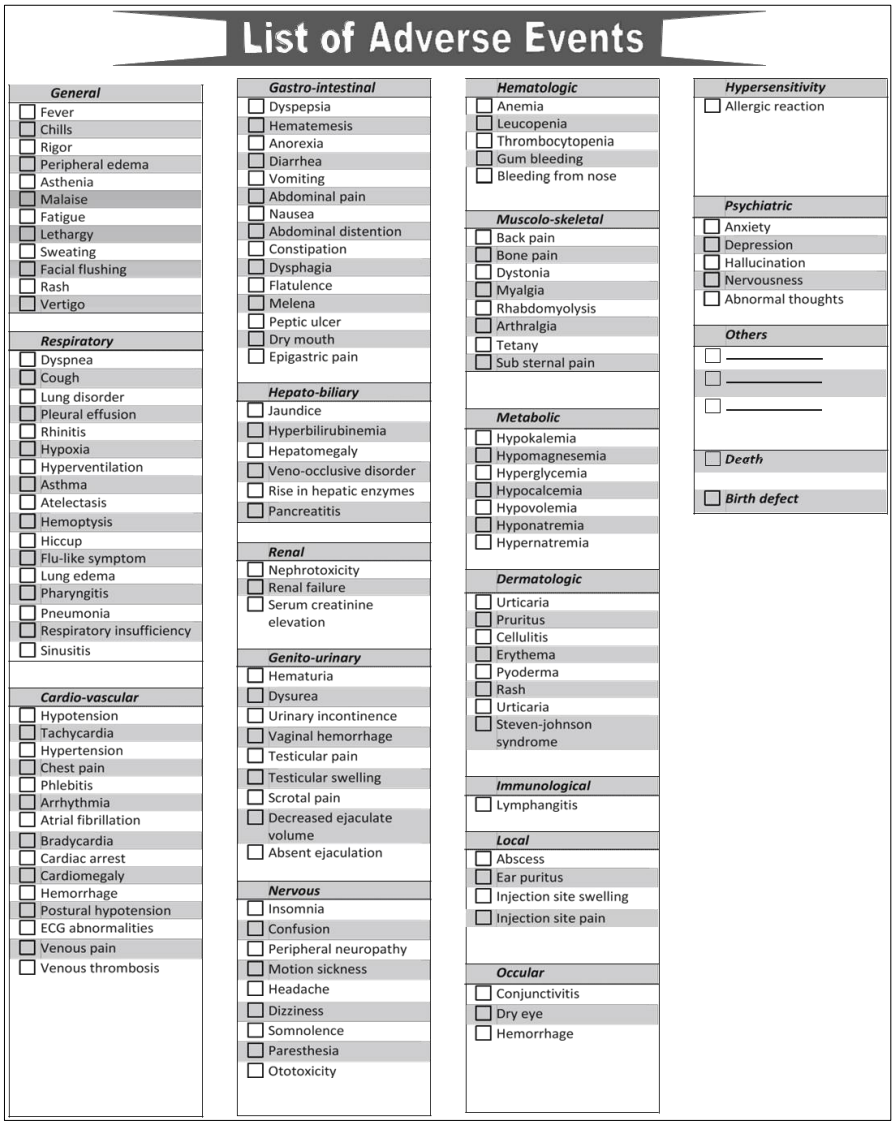
1.2 Pharmacological classification of adverse reactions [8-10]

Type A: Augmented e.g.: S/E.
Type B: Bizzare e.g.: drug allergy, idiosyncrasy.
Type C: Continuous: d/t long term use.
Type D: Delayed: duration or critical time exposure e.g.: teratogenesis.
Type E: End of use e.g.: acute adrenal in stuff d/t abrupt steroid cessation.
Type F: Failure of therapye.g.: accelerated hypertension.

ADRs Reporting: Three main elements follow the ADR reporting

- Patient
- A drug

An adverse reaction Composer/Reporter of the report.



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
- Epigastric pain

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
- Testicular swelling
- Scrotal pain
- Decreased ejaculate volume
- Absent ejaculation

Nervous
- Insomnia
- Confusion
- Peripheral neuropathy
- Motion sickness
- Headache
- 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
- Hypovolemia
- Hyponatremia
- Hypernatremia

Dermatologic
- Urticaria
- Pruritus
- Cellulitis
- Erythema
- Pyoderma
- Rash
- Urticaria
- Steven-johnson syndrome

Immunological
- Lymphangitis

Local
- Abscess
- Ear puritus
- Injection site swelling
- Injection site pain

Occular
- Conjunctivitis
- Dry eye
- Hemorrhage

Hypersensitivity
- Allergic reaction

Psychiatric
- Anxiety
- Depression
- Hallucination
- Nervousness
- Abnormal thoughts

Others
- _____
- _____
- _____

Death

Birth defect

1.3 Process of pharmacovigilance in ADR monitoring ADR can be monitored in two ways [11-13]

1. Passive Surveillance System
2. Active Surveillance System

2. Pharmacovugillance program of India [14]

The Central Drugs Standard Control Organization (CDSCO), New Delhi, under the aegis of Ministry of Health & Family Welfare, Government of India has initiated a nation-wide Pharmacovigilance programme in July 2010. The Pharmacovigilance Program of India (PvPI) was launched with a broad objective to safe guard the health of 1.27 billion people of India. Adverse Drug Reactions (ADRs) are reported from all over the country to National Coordination Centre (NCC)-PvPI, which also works in collaboration with the global ADR monitoring centre (WHOUMC), Sweden, to contribute in the global ADRs data base. NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authorities of India (CDSCO, Indian Pharmacopeia Commission (IPC)) in taking decision for safe use of medicines. (http://www.who.net). PvPI collects and evaluates spontaneous reports of Adverse Drug Reactions (ADRs) due to use of medicines, vaccines, medical devices and herbal products from all healthcare professionals and consumers/patients. To monitor ADRs and reporting the same to NCCPvPI, ADR Monitoring Centres (AMCs) have been set up all over India. At present 250 AMCs (medical colleges, district and corporate hospitals etc) are enrolled under PvPI across the country. (http://ipc.nic.in)

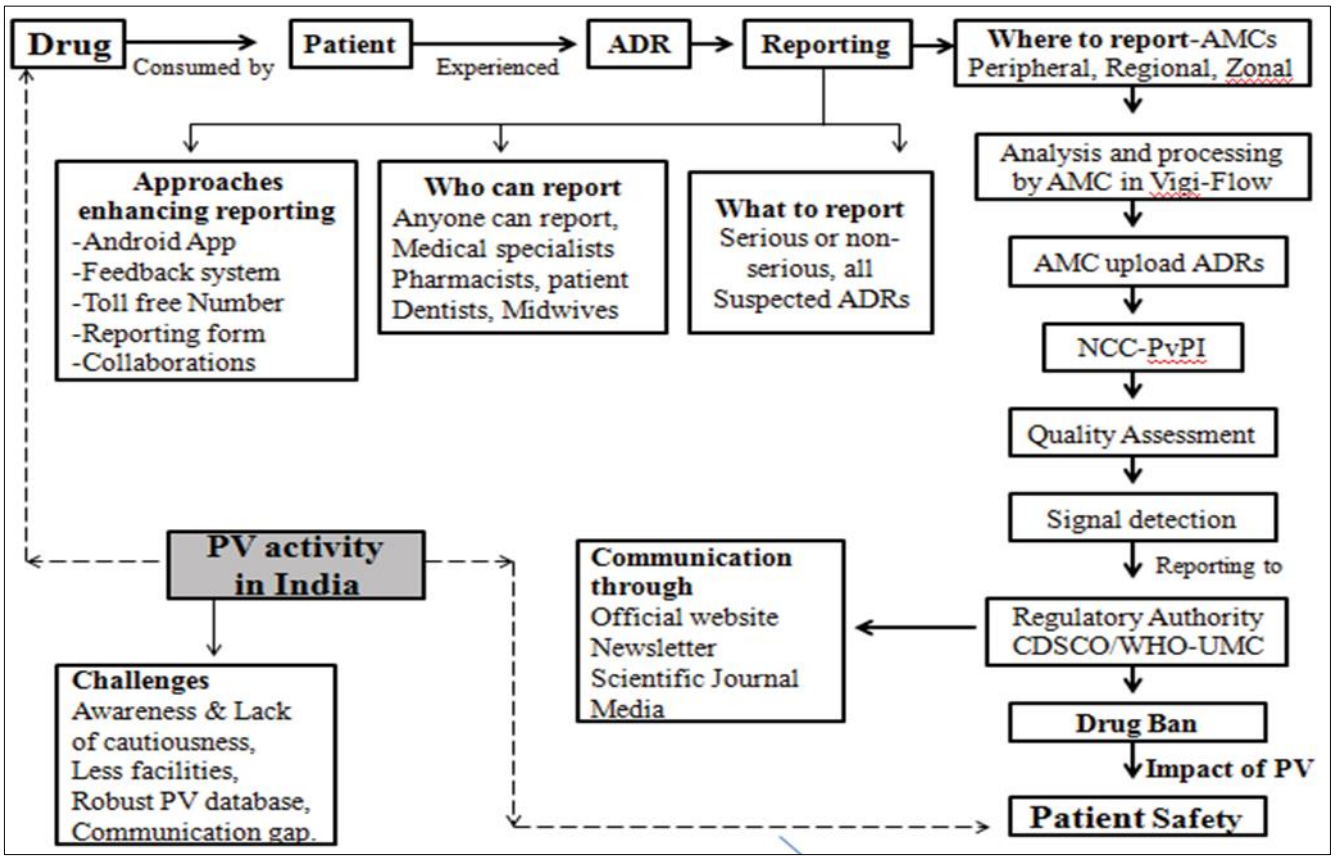


Fig 2: Pharmacovigilance activity in India

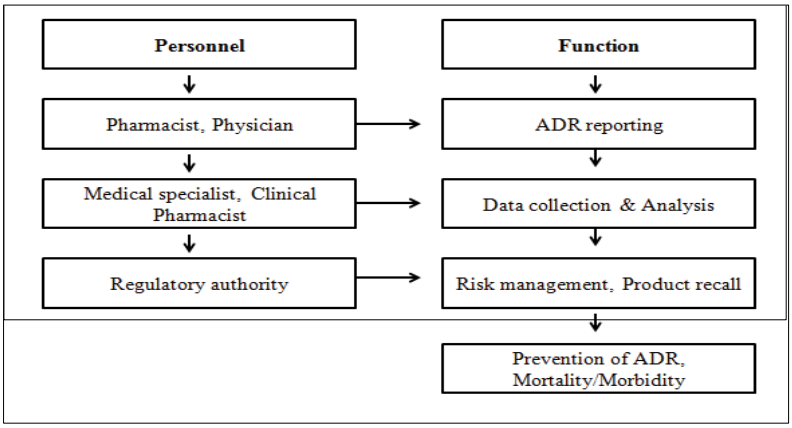


Fig 3: Stakeholders involved and their Function in PV activity

This Pharmacovigilance guidance document is introduced for the first time by the Government of India for Pharmaceutical industries which aim to establish and ensure an effective Pharmacovigilance system at their site as per recent

amendment in the Drugs & Cosmetics Rules, 1945, Schedule Y vide Gazette Notification G.S.R. 32 (E) published on March 08, 2016. This guidance document is prepared under the aegis of CDSCO by the NCC – Pharmacovigilance Programme of India (PvPI), The Indian Pharmacopoeia Commission (IPC), for guiding MAHs involved in the manufacture, sale, import, and distribution of pharmaceutical products in India. (http://www.ipc.gov.in)

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 at Marketing Authorization Holder organization.
Module 5 – Audits & Inspections of Pharmacovigilance System at Marketing Authorization Holder organization.
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.

- Post-marketing Pharmacovigilance and Pharmaco epidemiologic Assessments The PV in US encompasses all scientific and data gathering activities relating to the detection, assessment, and evaluation of safety signals :
- 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;

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]

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. After authorization the medicine may be used in a large number of patients, for a long period of time and with other medicines. Certain side effects may emerge in such circumstances. It is therefore essential that the safety of all medicines is monitored throughout their use in healthcare practice. EU law therefore requires each marketing authorization holder, national competent authority and EMA to operate a pharmacovigilance system. The overall EU pharmacovigilance system operates through cooperation between the EU Member States, EMA and the European Commission. In some Member States, regional centre's are in place under the coordination of the national competent authority. The new pharmacovigilance legislation, which came into effect in July 2012, was the biggest change to the regulation of human medicines in the European Union (EU) since 1995. It had significant implications for applicants and holders of EU marketing authorizations, as well as for patients, healthcare professionals and regulators.

Table 2: Comparison study between the regulatory requirements of pharmacovigilance in INDIA AND USA

S. No.	Parameters	India	Usa
1	Regulatory Authority	CDSCO	FDCA and FDA implementing regulations
2	Pharmacovigilance Responsible Authority	National Co-ordination Centre	CDER and CBER
3	Guidelines	PvPI follows PSUR and ADR reporting as per Schedule Y	Guidance for industry Good Pharmacovigilance Practices and Pharmaco- epidemiologic Assessment
4	Process for pharmacovigilance filling	National Authorization Process	FEARS (FDA Adverse Event Reporting System)
5	Pharmacovigilance Inspection	Not mention	Mentioned in Post- marketing Adverse Drug Experience (PADE) Reporting Inspection
6	Risk management System	Risk Management System is given in PvPI	Risk Management System is given in Risk Management Guidance under Guidance for Industry, Good Pharmacovigilance Practice and Pharmacoepidemiologic assessment.
7	Adverse Drug Reaction	PvPI and Schedule Y give information related to ADR	In Sec. 314.80 Post- marketing reporting of adverse drug experiences
8	Database	Vigiflow software	FEARS for small database and Sentinel System for Large database
9	Forms	Only one ADR form is available for reporting all products	1. Voluntary reporting for Healthcare professionals and consumers through ADR form 3500B 2. Mandatory Reporting for Regulated industry and facility User through ADR form 3500A
10	Data Lock Point for PSUR	60 days	70/90 days
11	Safety Communication	Not mentioned	Mentioned in Guidance for Industry, E2E Pharmacovigilance planning.
12	Risk Minimization Measure	Not mentioned	Risk Minimization is done through Risk Minimization Action Plans- Risk MAP guidelines
13	Periodic Safety Update Report- PSUR	They require format as per ICH E2C	They require format as per ICH E2C
14	Serious ADR reporting time period	15 days	15days
15	Pharmacovigilance System Master File-PSMF	Not Required	Not Required
16	Pharmacovigilance Audit	Not mentioned	Not mentioned

Table 3: Comparison study between the regulatory requirements of pharmacovigilance in INDIA AND EU

S. No.	Parameters	India	Europe
1	Regulatory Authority	CDSCO	EMEA
2	Pharmacovigilance Responsible Authority	National Co- ordination Centre	EC
3	Legislation & Regulation	DGHS, Ministry of Health & Family Welfare	Regulation 1235/2010 and Directive 2010/84/EU
4	Database	Vigiflow database	EudraVigilance Database
5	PV Plan	The PVPI NCC is collaborated with the WHOUMC Collaborating Centre based in Sweden	In Europe, ICH E2E guideline on PV Planning suggests that a “PV plan”
6	Risk Management System	Not mentioned	Pharmacovigilance Risk Assessment Committee (PRAC),
7	Spontaneous Case reports	To be reported by MAH within 10 Calendar days	To be reported by MAH within 15 Calendar days
8	Fatal or Life Threatening Unexpected ADRs	No specific guidelines	As soon as possible but no later than 7 calendar days after first knowledge followed by a complete report as possible within 8 additional calendar days.

5. Discussions and future prospective

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

The pharmacovigilance legislation aims to reduce the number of Adverse Reactions (ADRs). It aims to achieve this through, the collection of better data on medicines and their safety, rapid and robust assessment of issues related to the safety of medicines, effective regulatory action to deliver safe and effective use of medicines, empowerment of patients through reporting and participation, increased levels of transparency and better communication. The legislation impacts on marketing-authorization applicants and holders. It aims to make their roles and responsibilities clear, minimize duplication of effort, free up resources by rationalizing and simplifying reporting on safety issues, establish a clear legal framework for post-authorization monitoring. Research activities being conducted in India, there is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product. This will enable integration of good pharmacovigilance practice in the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and post-marketing surveillance that contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational, and more effective use. Also, this will promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public. Hence, the present article concludes with a strong urge to postulate regulations that create a comprehensive medicine safety system through careful strategic planning that envelope all aspects of pharmacovigilance.

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