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The Importance Of Pharmacovigilance In India

Mr. Dhananjay Dahatonde

Student

Institute of Pharmacy, Badnapur, Dist. Jalna, (MS) India

Abstract: Pharmacovigilance is defined by the World health organization as "the science and activities relating to the detection, assessment, understanding, assessment and prevention of adverse effects or any other drug related problems". Pharmacovigilance currently raises awareness in India about adverse drug reactions (ADR), and this review provides data on effectiveness in addressing existing issues. This essay's description of living in India, its difficulties, and its prospects for the future perfectly encapsulated the ideal and approach utilized in pharmacovigilance. In this article's goals are to make the argument for the importance of pharmacovigilance, to document its development and eventual recognition as a significant field of medical knowledge, and to discuss its effects on patient welfare and overall public health.

Keywords **-** Pharmacovigilance, Adverse drug reaction, Uppsala monitoring center, Drug safety, World Health Organization, Pharmacovigilance Program in India (PvPI)

Introduction

Pharmacovigilance (PV) data are essential for maintaining the safety and efficacy of medications and for providing details about regulatory activities like drug safety alerts, updates to product information on the label, drug recalls, or the removal of a drug from the market. The WHO defines PV as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems" [1]. Effective communication of information will enable the informed, evidence-based use of medicines by allowing good PV to quickly recognize dangers related with drugs medications that may be able to stop many negative responses. WHO and its regional offices are crucial in aiding nations in promoting the development of long-lasting monitoring systems. It acts as a clearinghouse for PV knowledge and effectively disseminates this knowledge. National centers assembling reports of alleged Adverse Drug Reactions (ADRs) are coordinated by the WHO and its Collaborating Centre for International Drug Monitoring [the Uppsala Monitoring Centre (UMC) in Sweden][2] . They are transmitted to UMC for entry into the database after review in order to produce signals for previously unknown ADRs. the combining of PV is essential to the success of public health initiatives that use medications [3].

The procedures involved in the clinical development of drugs. Once a medication is sold, it exits the safe and effective tested scientific setting of clinical trials and is freely available for general public consumption. Currently, only a small number of carefully chosen individuals have been used to test the short-term safety and effectiveness of the majority of medications. A product may have been given to as few as 500 people, and very seldom more than 5000, before to release (Figure 1). Therefore, it is crucial that novel and medically-evolving medicines are examined for their efficacy and security in real-world situations post-release tions. In general, more knowledge is required on the use in particular population groups, most notably children, pregnant women, and the elderly, as well as the effectiveness and safety of chronic use, particularly when combined with other medications. Experience has shown that many negative effects, interactions (such as with foods or other medications), and risk factors are only discovered years after a medicine is released (See table 3) [4].

Aim of pharmacovigilance [4]

- Enhance patient care and safety with regard to medication use and all other medical and paramedical procedures.
- Increase public health and safety with regard to using medications.
- To contribute to the evaluation of a medicine's value, damage, effectiveness, and risk while promoting its safe, logical, and more effective use (including inexpensive) use.
- Advance knowledge of pharmacovigilance, clinical training in it, and its efficient dissemination to medical professionals and the public.

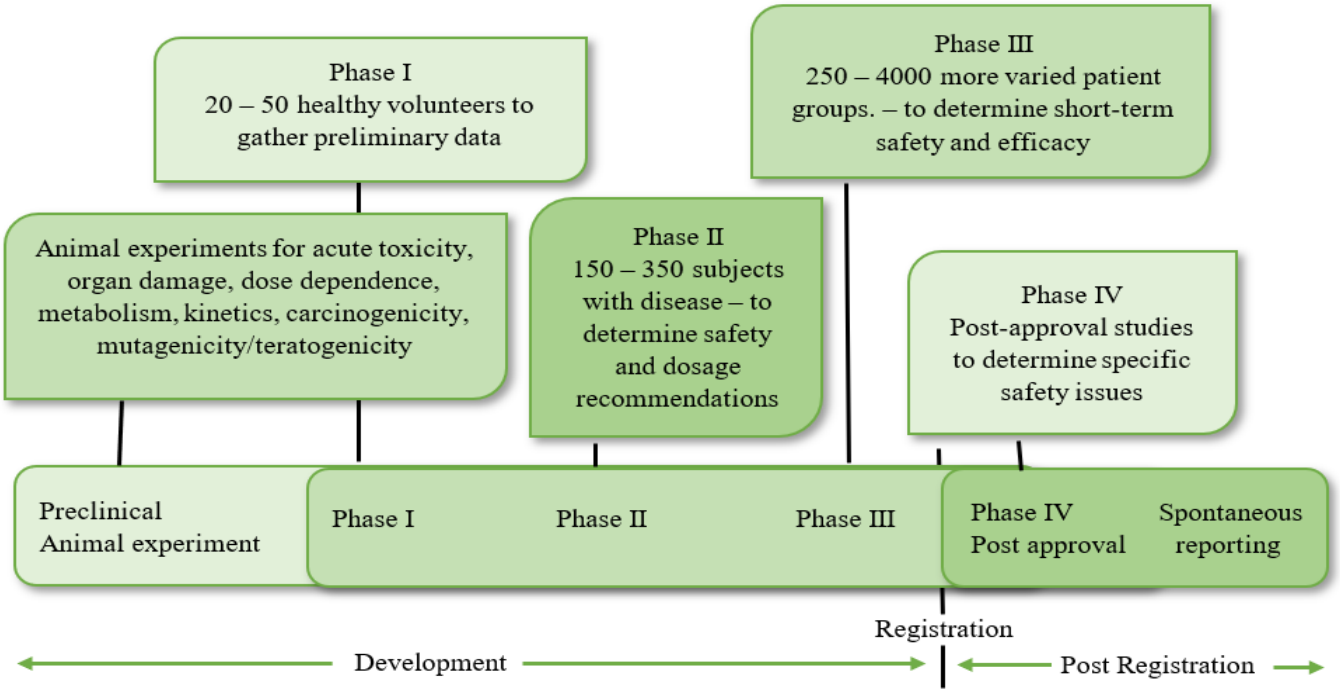

Figure 1 : Clinical development of medicines/drug

Need for pharmacovigilance

For the purpose of ensuring the safe use of medications, an effective pharmacovigilance system is now more important than ever. Numerous factors contribute to this growth. Unreliability of preclinical safety data When a medicine is offered for the first time, experiences with regard to concern about safety and potency are mostly dependent on the outcome of clinical trials. Some of these reasons include the necessity for pharmacovigilance, some of which are included in Box 3.1. It is particularly time-consuming to determine potency, adverse effects, and the overall risk-benefit ratio in a specific clinical environment because clinical trials are typically conducted in well-controlled settings. Research during the drug development process generally concentrated on assessing the efficacy of medications. Although the negative impacts are also identified, their applicability in everyday life is restricted. Preclinical drug development entails evaluating drug efficacy and safety in animal trials, and it's typically not practical to extrapolate human outcomes from such experiments. Clinical trials with human participants are often conducted under well monitored conditions with a modest sample size (occasionally the sample size is greater than 3000). The information gathered is carefully chosen and private. professional trials are typically not conducted in settings typical of professional practice and do not involve particular populations like children, the elderly, or pregnant women. This makes it challenging to predict the incidence of negative pharmacological effects in the special population and in unique situations like the coadministration of other medications or in the presence of illness conditions.[3,4]

Partners in pharmacovigilance

he essential players in the field of pharmacovigilance must work closely and effectively together to manage the risks related to the use of medications. In order to meet pharmacovigilance's future difficulties and ensure that the field's growth and success, continued commitment to this type of collaboration is essential. People in charge must work together to foresee, articulate, and meet the constantly evolving needs and expectations of the general public, health administrators, policy makers, legislators, and health professionals.

In the absence of reliable and comprehensive systems, which make such collaboration possible, there is little chance of this occurring. Constraints frequently include a lack of education, funding, political backing, and, most importantly, scientific infrastructure.[4]

- Government
- Industry
- Hospitals and academia
- Medical and pharmaceutical associations
- Poisons and medicines information centers
- Health professionals
- Patients
- Consumers
- The media
- World Health Organization

Pharmacovigilance Program in India (PvPI)

The necessity to record PVs was not mandated by Indian law. Using voluntary reporting was the foundation of post-marketing surveillance. India's PV requirements and regulations schedule Y of the Drugs and Cosmetics Act, as amended in 2005, were outlined [5]. It outlined the obligations of pharmaceutical businesses with regard to their marketed goods as well as obligations for reporting adverse events, the terminology was compatible with the WHO definition of PV despite not being clearly defined and coming from clinical trials. A pharmaceutical business with a product license in India needs to make sure that it has a sufficient PV system in place, including the creation and upkeep of suitable systems to gather, compile, and assess data regarding potential adverse reactions. The Periodic Safety Update Report (PSUR) for a medication sold in India must be provided by a pharmaceutical company, even if it is not required by law. ADR reports from marketed medications and from clinical studies were to be kept on file by all pharmaceutical companies. They received a report from the All India Institute of Medical Sciences (AIIMS) Delhi. Additionally, businesses used their internal reporting systems to send ADRs to their parent corporations.

Since 1986, efforts have been undertaken to implement a nationwide PV system in India. For ensuring the safety of medicines, the most recent Pharmacovigilance Programme for India (PvPI) was put into effect.in 2010. To coordinate the PvPI, the Indian Pharmacopoeia Commission (IPC), Ghaziabad, and the Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services, under the sponsorship of the Ministry of Health and Family Welfare (MHFW), government of India [6,7]. Even with the new PvPI, PV activities were still not adequately funded [7].

The WHO UMC and the IPC, an independent organization under the MHFW, worked together to set up the National Coordinating Centre (NCC) and provide technical assistance. The PV efforts were not involving the state drug regulatory agencies. The Medical Council of India was given charge of the PvPI. Every medical institution in India was expected to have a PV department, with government medical colleges housing the great majority of the monitoring facilities. Tertiary centers were one of the three levels of reporting, and they reported to secondary centers, which in turn reported to regional centers. The regional centers provided information to the WHO and reported to NCC-AIIMS. The reporting of ADRs was passive in India. Recently, PV centers were set up in private sector hospitals [6]. (Figure 2 indicates the communication pathway of ADRs in India)

According to the PvPI guidelines, doctors, chemists and other healthcare professionals should submit a specified form with all suspected ADR reports to CDSCO. India's research examining data collecting examined the ADR form. India received thirteen out of the 18 points that were deemed necessary for an acceptable ADR report [8]. Pharmaceuticals for human use must be registered with the International Conference on Harmonization (ICH) of Technical Requirements for Pharmaceuticals. ADRs must be recorded during clinical studies, per guidelines. However, due to a lack of information, the general public's low level of consumer awareness of the need to report ADRs remained a problem [9]. (Figure 2)

On 14th July 2010 the Government of India started the Pharmacovigilance Programme of India (PvPI) with All India Institute of Medical Sciences (AIIMS), New Delhi as its first National Coordination Centre (NCC) for monitoring Adverse Drug Reactions (ADRs) in the country for purpose of safety and protection of public health. 22 ADR monitoring centers including AIIMS, New Delhi in the year 2010 were set up under this Programme. However, on 15th April 2011 the National Coordination Centre was later shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh from All India Institute of Medical Sciences (AIIMS, New Delhi) in order to safeguard and protect implementation of this programmed in a better way.

July, 2015 onwards Indian Pharmacopoeia Commission- Pharmacovigilance Programme in India (IPC-PvPI) became the National Coordination Centre (NCC) for Materiovigilance Programme of India (MvPI). In July, 2017 Indian Pharmacopoeia Commission (IPC), National Coordination Centre for Pharmacovigilance Programme in India (NCC-PvPI) became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes & Regulatory services.

Objectives

1. A nation-wide system must be formed for reporting of patient safety
2. Identification and analysis of new ADR (signal) from the reported cases
3. Analysis of benefit - risk ratio of marketed pharmaceutical products
4. Evidence based information must be generated on safety of medicines
5. Supporting the regulatory agencies in the process of decision making on use of medicines.
6. Emerging as a national centre of excellence for pharmacovigilance activities
7. Communicating over the safety information on use of medications to different stakeholders for minimizing the risk
8. Collaborating with other national centres for data management and exchange of information.
9. Providing consultancy and training support to other National Coordination Centre for Pharmacovigilance Programme in India located across the world

National pharmacovigilance program (NPP)

Understanding the value of pharmaceutical vigilance, the Indian government's Ministry of Health and Family Welfare and CDSCO launched the NPP in November. ADR disclosure by healthcare professionals was encouraged in 2004. It then aims to produce extensive ADR data on the Indian population and share it with the WHO's Uppsala Monitoring Centre database. The National Pharmacovigilance Advisory Committee (NPAC), a 16-person committee created by the Indian government, reviews the operation of NPP on a regular basis. Additionally, the government assesses the pharmacovigilance data obtained from various centers and suggests any necessary regulatory actions [10].

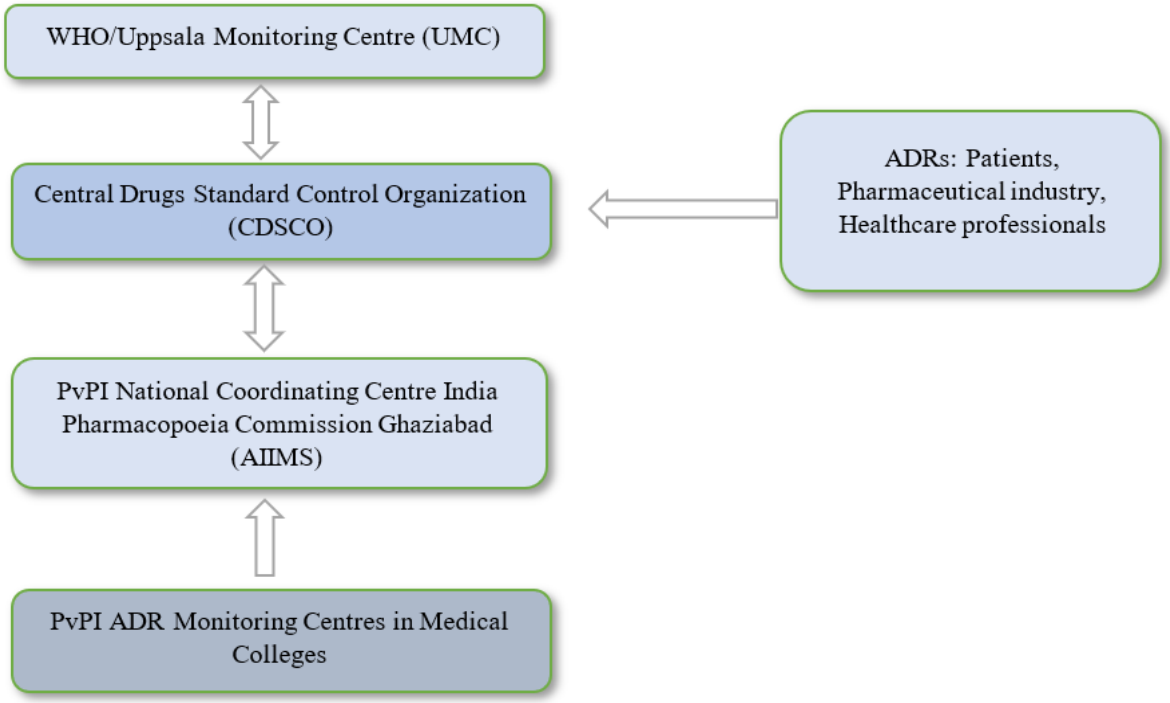

Figure 2 : Adverse Drug Reaction (ADR) communication channels in India.

Table 1 : History of PvPI [23]

Year	Events
1747	First reported clinical trials by James Lind, proving the effectiveness of lemon juice in preventing scurvy.
1937	Death of 107 children due to sulfanilamide toxicity
1950	Aplastic anemia reported due to chloramphenicol
1961	Global disaster due to thalidomide toxicity
1963	16th World Health Assembly recognize to rapid action on ADR's
1968	WHO pilot research project for international drug monitoring
1996	Clinical trials of global standards started in India
1998	Pharmacovigilance initiated in India
2002	67th National Pharmacovigilance Center established in India.
2005-05	National Pharmacovigilance Program launched in India
2005	Conduct of structured clinical trials in India
2009-10	PvPI initiated

World Health Organization-Uppsala Monitoring Centre & India

India and other WHO members can collaborate on the monitoring of drug safety through the WHO Programme for International Drug Monitoring. Individual case reports of suspected ADRs are periodically gathered and maintained in an incredibly common database, which at this time has over 3.7 million case reports. Considering that 1978, the Uppsala Monitoring Centre (UMC) in the Programme is now gone from Sweden. The responsibility for obtaining information about ADRs from around the world is on the UMC world, especially from nations that are WHO members together with India. Wherever they are processed, reviewed, and entered into the WHO International database, member countries send their reports to the UMC. This procedure may result in the detection of a signal—an alarm about a potential hazard—that is communicated to member countries when there are several reports of adverse responses to a certain medicine. This only occurs after a thorough analysis and professional assessment. These ADR reports are evaluated regionally and will prompt responses across the nation. The WHO International Drug Monitoring Programme membership allows a country to identify whether or not similar reports are being produced elsewhere. India has a sizable patient population and a big number of medical personnel, but ADR reporting is still in its infancy [11,12,13]. (Table 2)

Table 2: Responsibilities and functions of the stakeholders in the programmed [11,12,13,14]

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Centre	Role
AMC	Data entry into Vigiflow, follow-up with the complainant to ensure that the ADR report is complete in accordance with SOPs, and reporting to PvPI-NCC through Vigiflow with the source data (original) attached to each ADR case. Through newsletters distributed by the PvPI-NCC, physicians are trained, made more aware of issues, and given feedback.
PvPI AMC other than medical colleges (Corporate hospitals, autonomous institutes, pharmaceutical industry and public health Programmer)	Collection of ADR reports, follow-up with the complaint to ensure that they are complete and in accordance with SOPs, and reporting of the data to CDSCO-HQ.
PvPI NCC, IPC (Ghaziabad)	the creation of SOPs, instructions and training manuals, the gathering of data, the cross-checking of its completeness, the causality assessment, etc., in accordance with SOPs, conduct training sessions for all enrolled facilities, publish a bulletin on medication safety, report to CDSCO-HQ, Analyses of the CDSCO-HQ data on adverse events following immunisation, periodic safety update reports, and performance measurement system analysis.
Ministry of Environment & Forests (MOEF)	Guidelines for entering data from the information given by environmental specialists through field experiments for agricultural products and clinical studies for medical items are approved by the PAC (Project Advisory Committee).
Indian Council of Medical Research (ICMR)	Released the "Policy Statement on Ethical Considerations involved in Research on Human Subjects" in 1980, and these standards were updated in 2000 to become the "Ethical Guidelines for Biomedical Research on Human Subjects."
Ministry of Health and Family Welfare (MHFW)	An independent authority for creating standards for medicines, pharmaceuticals, and medical equipment and technology in India
Zonal/Sub-zonal CDSCO Offices	Giving ADR monitoring centres administrative, financial, and procurement support while reporting to CDSCO-HQ
CDSCO-HQ (New Delhi)	Take the proper regulatory choices and steps in accordance with the recommendations made by the PvPI NCC at the IPC. You should also inform all relevant parties about decisions relating to movie safety. Work with the WHO-UMC.

Role of Indian pharmaceutical companies

A pharmaceutical business with a marketing permit in India should make sure they have a sufficient pharmacovigilance system in place to guarantee the accountability and liability of the items they promote, as described in Schedule Y. Each pharmaceutical business having a marketing license is required to comply with the pharmacovigilance duties when two or more marketed products are similar in all respects other than their trade names. This comprises the creation and upkeep of suitable pharmacovigilance systems to gather, compile, and assess data on probable adverse effects. All of these reports of adverse reactions and data pertaining to a product's benefit-risk analysis must be given to DCGI (Drug Controller General of India). In order to fulfil its pharmacovigilance duties, a pharmaceutical company can either set up internal pharmacovigilance systems or enter into contractual agreements with CROs (Contract Research Organizations) that specialize in this function [15].

Adverse Drug Reaction

A response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.[16]

1. Unlisted/Unexpected Adverse Drug Reaction

An unfavorable reaction is a drug's harshness or character, which is unreliable given the correct product information accessible during clinical studies.[17]

During investigators' brochure for an unapproved medicine, the company needs assistance.

Detailed summary of a product's drug information sheet.

2. Listed / Expected Adverse Drug Reaction

Information about ADRs, such as their nature, severity, and medication specificity, has already been recorded.[18]

Table 3 : Classical examples of serious and unexpected adverse reactions

Medicine	Adverse reaction
Aminophenazone (amidopyrine)	Agranulocytosis
Chloramphenicol	Aplastic anaemia, Gray baby syndrome
Clioquinol	Myelooptic neuropathy (SMON)
Erythromycin estolate	Cholestatic hepatitis
Fluothane	Hepatocellular hepatitis
Methyldopa	Haemolytic anaemia
Oral contraceptives	Thromboembolism
Practolol	Sclerosing peritonitis
Reserpine	Depression
Statins	Rhabdomyolysis
Thalidomide	Congenital malformations, Phocomelia
Aspirin/Indomethacin	Premature closer of ducts arteriosus
Carbamazepine	Neural tube defects
Rifampicin	Orange colour urine
Methotrexate	Multiple defects, Fatal death.
Tetracycline	Discoloured or deformed teeth, retarded bone growth
Alcohol	Low IQ baby, growth retardation
Phenytoin	Various malformations
Lithium	Fatal goitre, cardiac and other abnormalities

Types of ADR [19] (Table 4)

1) **Predictable (Type-A) Reactions** : These are based on pharmacological properties like augmented but quantitatively normal response to the drug which include side effects, toxic effects and consequences of drug withdrawal.

Examples : Haemorrhage (anticoagulants), Hypoglycaemia(antidiabetics), Baldness (oncolytic), Severe bradycardia (beta-blocker), Bronchospasm (non-selective BB), Sedation (antihistamines), Hepatitis (paracetamol)

2) **Unpredictable (Type- B) Reactions** : These are based on indication of patient and not on drug's known actions such as allergy and idiosyncrasy. They are more serious and require withdrawal of drug.

Examples : Anaphylaxis, SJS/Toxic epidermal necrolysis, Agranulocytosis, Guillain-Barré syndrome, Cardiomyopathy, Pneumonitis, Hepatitis

Table 4 : Summary of type A and B ADRs [19]

	Type A	Type B
Understanding	• Dose dependent, • Genetics in metabolism /target • Predictable, pharmacology	• Immunological reactions • Genetics in e.g. HLA genes • Mechanisms unknown
Methods of study	• Clinical trial / follow-up study • Spontaneous reporting • Prescription event monitoring • Hospital studies • Experiments	• Spontaneous reporting • Prescription event monitoring Case control surveillance • Large databases / record linkage
Diagnosis	• Therapeutic drug monitoring (TDM) • suggestive time relationship • Pharmacology	• Clinical picture • suggestive time relationship • Immunology
Management	• Identify patient at risk • Dose titration/reduction	• Identify /avoid patient at risk • Monitor patient/Stop treatment

Table 5 : ADR Classification Based on Severity

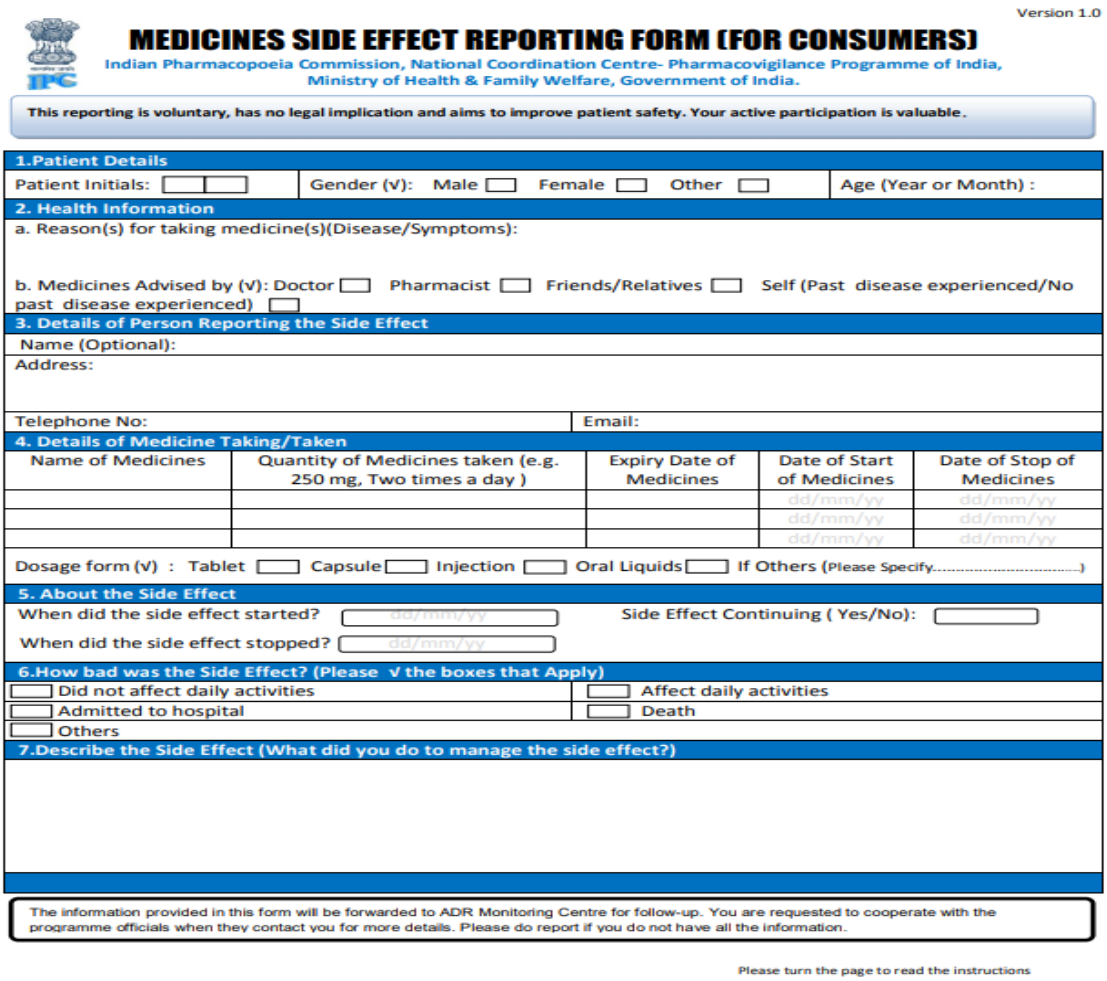
Severity	Description	Examples
Mild	No treatment or antidote for overdosage required; Longer duration hospitalization also not required	• Opioids causing constipation • Antihistamines cause some drowsiness
Moderate	Specific or change in the existing treatment may be required, but the drug is not necessarily discontinued (e.g., addition of drug to the regimen, dose modification)	• Non-steroidal anti-inflammatory drugs cause edema and hypertension • Hormonal contraceptives causing venous thrombosis
Severe	The drug reaction can cause a potential life-threatening event, drug and specific treatment of drug reaction must be discontinued	• Phenothiazines: abnormal heart rate • ACE inhibitors: Angioedema
Lethal	An adverse reaction can cause death of the patient, either directly or indirectly	• Overdosage of Anticoagulants: Haemorrhage • Overdosage of acetaminophen: liver failure

Table 6 : Types of ADR

Type A Augmented	Type A (augmented) reactions result from an exaggeration of a drug's normal pharmacological actions when given at the usual therapeutic dose and are normally dose-dependent. Examples include respiratory depression with opioids or bleeding with warfarin. Type A reactions also include those that are not directly related to the desired pharmacological action of the drug, for example dry mouth associated with tricyclic antidepressants
Type B Bizarre	Type B (bizarre) reactions are novel responses that are not expected from the known pharmacological actions of the drug. These are less common, and so may only be discovered for the first time after a drug has already been made available for general use. Examples include anaphylaxis with penicillin or skin rashes with antibiotics
Type C Chronic/ continuing	Type C (continuing) reactions, persist for a relatively long time. An example is osteonecrosis of the jaw with bisphosphonates
Type D Delayed	Type D (delayed) reactions become apparent some time after the use of a medicine. The timing of these may make them more difficult to detect. An example is leucopoenia, which can occur up to 6 weeks after a dose of lomustine
Type E End-of-use	Type E (end-of-use) reactions, are associated with the withdrawal of a medicine. An example is insomnia, anxiety and perceptual disturbances following the withdrawal of benzodiazepines. Other classification schemes have also been proposed

Reporting of Adverse drug reaction

On the IPC website, suspected ADR reporting forms are offered for consumers (Figure 3) and health care providers (Figure 4). The consumer reporting form is accessible in 10 vernacular languages (Hindi, Tamil, Telugu, Kannada, Bengali, Gujarati, Assamese, Marathi, Oriya, and Malayalam) to remove language barriers in ADR reporting. Additionally, ADRs may be reported by calling the PvPI helpline at (18001803024) on weekdays from 9:00 am to 5:30 pm. Additionally, a mobile Android application for ADR reporting has been developed and made public [20].(Figure 5)



Version 1.0

MEDICINES SIDE EFFECT REPORTING FORM (FOR CONSUMERS)

Indian Pharmacopoeia Commission, National Coordination Centre- Pharmacovigilance Programme of India, Ministry of Health & Family Welfare, Government of India.

This reporting is voluntary, has no legal implication and aims to improve patient safety. Your active participation is valuable.

1.Patient Details

Patient Initials: ☐☐ | Gender (√): Male ☐ Female ☐ Other ☐ | Age (Year or Month) :

2. Health Information

a. Reason(s) for taking medicine(s)(Disease/Symptoms):

b. Medicines Advised by (√): Doctor ☐ Pharmacist ☐ Friends/Relatives ☐ Self (Past disease experienced/No past disease experienced) ☐

3. Details of Person Reporting the Side Effect

Name (Optional):

Address:

Telephone No: | Email:

4. Details of Medicine Taking/Taken

Name of Medicines	Quantity of Medicines taken (e.g. 250 mg, Two times a day)	Expiry Date of Medicines	Date of Start of Medicines	Date of Stop of Medicines
			dd/mm/yy	dd/mm/yy
			dd/mm/yy	dd/mm/yy
			dd/mm/yy	dd/mm/yy

Dosage form (√) : Tablet ☐ Capsule ☐ Injection ☐ Oral Liquids ☐ If Others (Please Specify.....)

5. About the Side Effect

When did the side effect started? dd/mm/yy | Side Effect Continuing (Yes/No): ☐

When did the side effect stopped? dd/mm/yy

6.How bad was the Side Effect? (Please √ the boxes that Apply)

☐ Did not affect daily activities | ☐ Affect daily activities

☐ Admitted to hospital | ☐ Death

☐ Others

7.Describe the Side Effect (What did you do to manage the side effect?)

The information provided in this form will be forwarded to ADR Monitoring Centre for follow-up. You are requested to cooperate with the programme officials when they contact you for more details. Please do report if you do not have all the information.

Please turn the page to read the instructions

Figure 3 : ADRs reporting form for consumers. and the selections of emotions.

Version 1.4

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For **VOLUNTARY** reporting of ADRs by Healthcare Professionals

INDIAN PHARMACOPOEIA COMMISSION (National Coordination Centre-Pharmacovigilance Programme of India)

Ministry of Health & Family Welfare, Government of India, Sector-23, Raj Nagar, Ghaziabad-201002

PvPI Helpline (Toll Free) :1800-180-3024 (9:00 AM to 5:30 PM, Monday-Friday)

Initial Case ❑ Follow-up Case ❑

FOR AMC / NCC USE ONLY

Reg. No. / IPD No. / OPD No. / CR No. :

AMC Report No. :

Worldwide Unique No. :

A. PATIENT INFORMATION *

1. Patient Initials:

2. Age or date of birth:

3. Gender: M ☐ F ☐ Other ☐

4. Weight (in Kg.)

B. SUSPECTED ADVERSE REACTION *

5. Event / Reaction start date (dd/mm/yyyy)

6. Event / Reaction stop date (dd/mm/yyyy)

7. Describe Event/Reaction management with details , if any

12. Relevant investigations with dates :

13. Relevant medical / medication history (e.g. allergies, pregnancy, addiction, hepatic, renal dysfunction etc.)

14. Seriousness of the reaction : No ☐ if Yes ☐ (*please tick anyone*)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly

☐ Life threatening ☐ Disability

☐ Hospitalization-Initial/Prolonged ☐ Other Medically important

15. Outcome:

☐ Recovered ☐ Recovering ☐ Not Recovered

☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S) *

S. No.	8. Name (Brand/ Generic)	Manufacturer (if known)	Batch No. / Lot No.	Expiry Date (if known)	Dose	Route	Frequency	Therapy Dates		Indication	Causality Assessment
								Date Started	Date Stopped		
i											
ii											
iii											
iv#											

9. Action taken after reaction (*please tick*)

10. Reaction reappeared after reintroduction of suspected medication (*please tick*)

S. No. as per C	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	10. Yes	10. No	10. Effect unknown	10. Dose (if re-introduced)
i										
ii										
iii										
iv										

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

S. No.	Name (Brand / Generic)	Dose	Route	Frequency (OD, BD, etc.)	Therapy Dates		Indication
					Date Started	Date Stopped	
i							
ii							
iii#							

Additional Information :

D. REPORTER DETAILS *

16. Name & Address : _____

_____

Pin : _____ Email : _____

Contact No- : _____

Occupation : _____ Signature : _____

17. Date of this report (dd/mm/yyyy) :

Signature and Name of Receiving Personnel :

Confidentiality : The patient's identity is held in strict confidence and protected to the fullest extent. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction. Submission of an ADR report does not have any legal implication on the reporter.

Figure 4: Suspected ADR reporting form for Healthcare professionals.

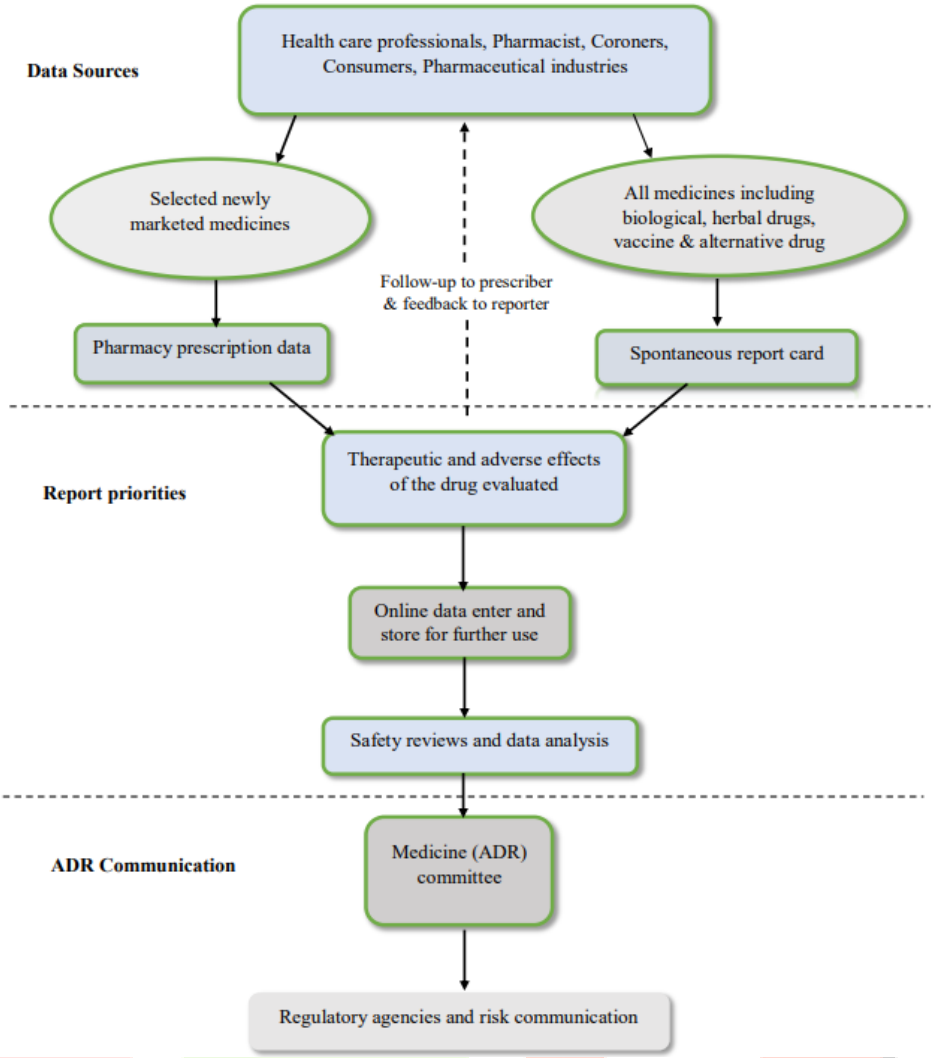


Figure 5 : Pharmacovigilance systematic methods for the Evaluation of Spontaneous Reports collected from different data sources

The WHO-UMC causality assessment system

The WHO-UMC system was created in collaboration with the National Centers taking part in the Programme for IDM and is intended to be a useful tool for evaluating case reports. In essence, it is a combination evaluation that considers the case history's clinical-pharmacological elements as well as the calibre of the observation's documentation. Other factors like prior information and statistical chance play a less significant impact in the system because PV is mainly focused on the detection of unknown and unexpected ADRs. It is acknowledged that the definitions' semantics are crucial, and as a result, individual assessments may vary. Other algorithms are either more complicated or too specialized for widespread use. This approach provides direction for the broad justifications that ought to be made when choosing one category over another. Table No 4 contains a list of the numerous causality categories. The evaluation standards for the major categories are presented point by point, as they have been created for hands-on instruction during the UMC instruction courses [22].

Table 7 : WHO-UMC Causality assessment scale

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed • Additional data under examination
Unassessable/Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

The International Council for Harmonization (ICH)

ICH is a global organization with members from the United States, Japan, and the European Union. Its objective is to suggest international standards for pharmaceutical businesses and drug regulatory authorities. The ICH Steering Committee (SC) is in charge of guiding harmonization efforts all across the world. The European Federation of Pharmaceutical Industries and Associations, the Japanese Pharmaceutical Manufacturers Association, the FDA, and the Pharmaceutical Research and Manufacturers of America are its six co-sponsors, and each of them has two seats on the SC. The SC has requested additional parties with major ICH interests to appoint observers; the three present observers are the WHO; International Federation of Pharmaceutical Manufacturers Association is participating as a non-voting member of the SC alongside Health Canada and the European Free Trade Association [21].

The Council for International Organizations of Medical Science (CIOMS)

CIOMS, a unit of the WHO, is a global think tank that offers recommendations on issues relating to drug safety through its Working Groups. Many of the CIOMS' proposed policies have been accepted over the years. The CIOMS creates reports that are used as a guide for creating future drug regulation policy and procedures. Current Challenges in PV: Pragmatic Approaches (CIOMS V), Management of Safety Information from Clinical Trials (CIOMS VI), and the Development Safety Update Report are a few examples of topics that have been covered in these reports. Creating Consistency in Periodic Safety Reporting Format and Content During Clinical. A report from the CIOMS Working Group on Practical Aspects of Signal Detection in PV and Trials (CIOMS VII and CIOMS VIII) are two related topics.

Haemovigilance Programme

Haemovigilance is the ongoing process of gathering and analyzing data on adverse reactions to blood transfusions in order to understand what causes them, what happens when they do, and how to stop it from happening again. As part of the PVPI, IPC and the National Institute of Biological Sciences (NIB) in Noida have started the Haemovigilance Programme of India (HVPI), which has two main goals. In order to improve patient care and safety while lowering overall healthcare costs, it is important to first keep track of adverse reactions/events and their frequency associated with blood transfusion and the administration of blood products [24] . Patient safety during and following a blood transfusion depends on the identification and management of transfusion reactions (TRs). Acute transfusion responses (ATRs) and delayed transfusion reactions are the two categories into which transfusion reactions are divided, and each category contains a variety of subtypes. At the outset of the reaction, categorization might be challenging because different ATRs exhibit similar signs and symptoms. Additionally, TRs are frequently not acknowledged or reported. Implementing a nationwide hemovigilance system and a set of national regulations setting policies for blood transfusion as well as the detection and management of TRs is important to ensure standard practice and safety[25].

In this regard, the hemovigilance initiative, which was introduced on December 10th, 2012, has already enrolled 90 Medical Colleges of India as a core component of PVPI. The National Institutes of Health (NIB) serves as the HVPI's coordination hub for gathering and compiling data on hemovigilance from medical facilities around the nation. The NIB's IT Division created the software "Haemo-Vigil." [26]

Visibility, communication, and feedback of PVPI

PVPI is featured in a webpage made by CDSCO. Healthcare practitioners who are not programmed participants may report ADRs online under a feature of the program's phase II. In cooperation with NCC, the CDSCO main office released a quarterly 4 to 16 page "Medicine Safety Newsletter" A total of 3000 copies will be printed and distributed to medical facilities across the country. To guarantee that healthcare professionals not covered by the programmed can report ADRs directly to any of the centers, a Medicine Safety Card has been included in the Medicine Safety Newsletter and in national medical periodicals. These raise awareness of the programmed and guarantee that reporters receive enough feedback so they can stay motivated. Additionally, all the centers regularly conduct focused workshops, symposia, and group meetings on ADR reporting and causation assessment to raise understanding and visibility of the programmes.[27]

Guideline of PVPI

Globally, many countries have formulated their own PV guidelines with the aim of having a systematic process of safety reporting. The ICH has six guidelines pertaining to various aspects of drug safety

Table 8 : ICH guidelines

E2A	**Clinical Safety Data Management: Definitions and standards for expedited reporting**
E2B	Clinical Safety Data Management: Data elements for transmission of individual case safety reports
E2C	Clinical Safety Data Management: Periodic safety update reports for marketed drugs
E2D	Post-approval Safety Data Management: Definitions and standards for expedited reporting
E2E	Pharmacovigilance planning
E2F	Development Safety Update Report

The criteria of Schedule Y of the Drugs and Cosmetics Act of 1945 serve as the legal framework for PV in India. Schedule Y also covers guidelines for pre-clinical and clinical drug development investigations, as well as the needs for clinical trial import, manufacture, and getting marketing authorization for new drugs. Indian drug. On January 20, 2005, Schedule Y was updated and modified as part of the Drugs controller general of India's (DCGI) ongoing effort to ensure that pharmaceutical companies are adequately adhering to their PV duties. The revised Schedule Y makes an effort to clarify the obligations of pharmaceutical companies with regard to their products and the communication of adverse events (AEs) from clinical trials.[28]

Only a small portion of Schedule Y in India is devoted to drug safety, and when compared to current international practice, it appears to have several gaps. Thus, it is thought that CDSCO must create comprehensive PV criteria. These regulations must cover all pertinent pre- and post-marketing safety areas, fill in any gaps now present, and provide clarity on the previously mentioned difficulties. Most essential, the regulations must adhere to current international standards in order to promote India's development as any other participant in cross-border clinical trials.[29]

The challenges of PV in India

The PVPI's major problem is the egregious underreporting of negative consequences. This is due to a variety of factors, such as poor national knowledge of PV and a lack of medical experience in drug administration and competent resources in PV. The other difficulties are infrastructure that is still conservative, the long lag between regulations and laws, the traditional view of new drug research, and the almost non-existent regulatory and PV inspections. Considering that India has a highly developed IT sector, the system needs to be improved with the aid of PV professionals working with IT. Since PV deals with a lot of ADRs, it would be a good idea for PV specialists to work with software specialists to develop and build a reliable system. Software programmes can be used for data collecting and analysis, trend analysis of drug usage across a range of disease areas, compliance, medication errors, and drug interactions leading to adverse drug reactions (ADRs). Additionally, with more clinical research and PV outsourcing projects being carried out in India now, it has been beneficial for the DCGI to invest in a reliable PV system to allow assessors and decision makers to analyses safety data and take regulatory decisions without having to rely on other nations.[30]

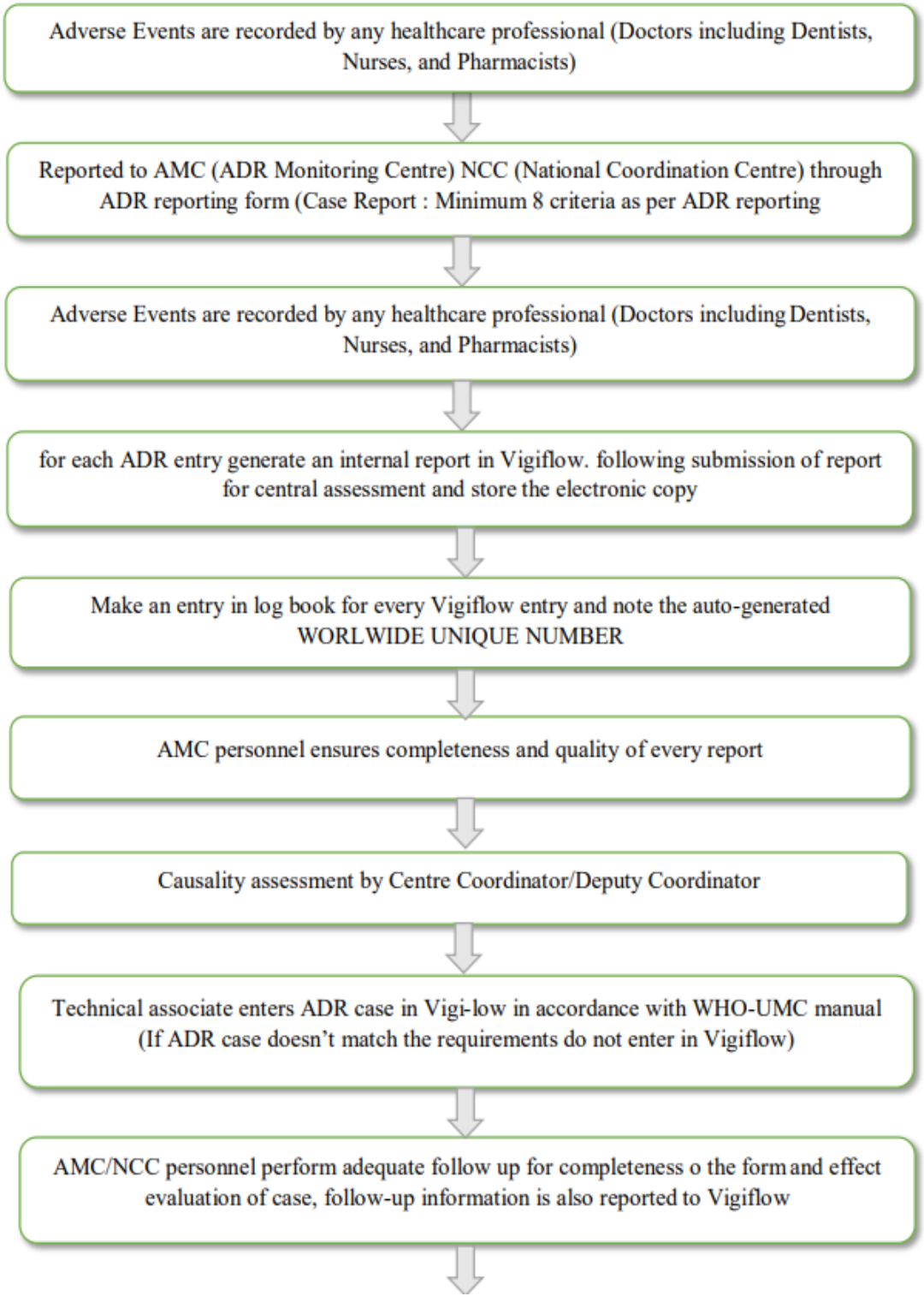
On admission, doctors may not always recognize ADRs, and as a result, many patients may die as a result of ADRs. ADRs can come at a significant financial expense to the healthcare system [31]. Patients self-medicate and increasingly convert from prescription-only (POM) to over-the-counter (OTC) medications when new drugs are introduced to the market without long-term safety evaluations by regulatory authorities, which is the main cause of ADR exposure. In the past, medication manufacturers and regulatory organizations in India focused their evaluations of a drug's safety on long-term user experiences [32].

In recent years, many Indian businesses have increased their investments in R&D, strengthening their ability to create and market novel medicines through in-house research. After a product is launched, more data will be produced, which could change the product's benefit-risk profile. To ensure the safe use of all products, a thorough review of the new information created by PV activities is necessary. Therefore, DCGI needs to make some difficult choices, commit to making PV necessary, and establish a culture of PV inspections.

Future perspectives pharmacovigilance in India

The following suggestions could be made in response to India's issues and obstacles in developing a reliable PV system:

- Create and keep up a strong PV system.
- The introduction of PV inspections and the requirement of PV reporting.
- High-level meetings with several stakeholders. High-level meetings with several stakeholders.
- The development of a universal, country-specific ADRs reporting form.
- By adding qualified scientific and medical assessors for PV, the Drug Controller General of India (DCGI) office will be strengthened
- Establishing a clinical trial and post-marketing database for SAEs, SUSARs, and ADRs to allow for signal detection and access to all pertinent information from different stakeholders
- Education and training in PV for nurses, pharmacists and medical students.
- List all new medications and indications by keeping a common database for each pharmaceutical firm.
- With the development of information technology, there have been new potential for national and international collaborations that can improve post-marketing surveillance programmes and promote drug safety. These collaborations can be made with PV organisations to improve drug safety.
- Establishing a PV and pharmacoepidemiology network in India.



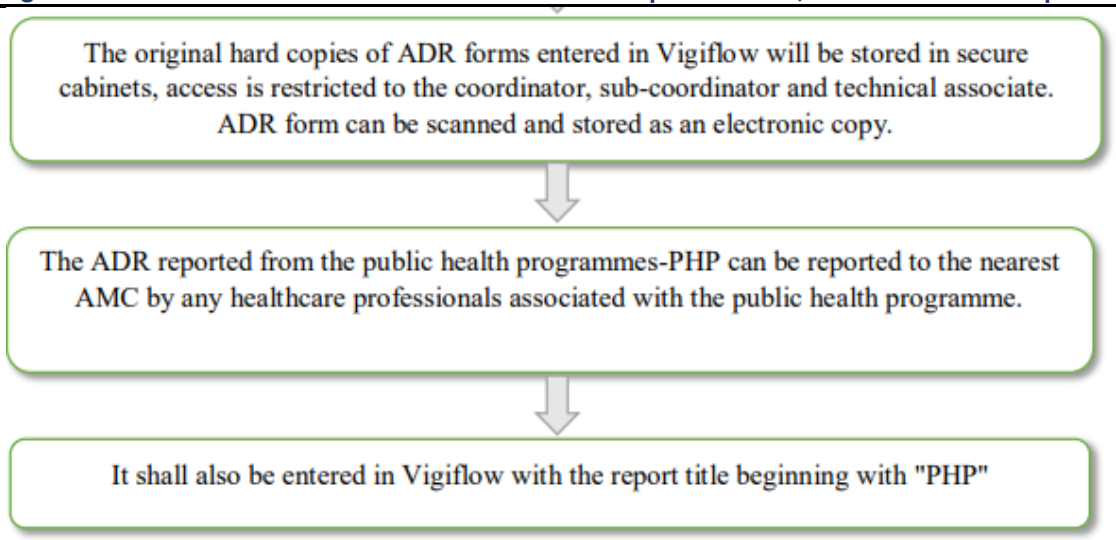


Figure 6 : ADRs Reporting System of INDIA

Abbreviation

Abbreviation	Meaning
ADR	Adverse Drug Reaction
PV	Pharmacovigilance
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
PvPI	Pharmacovigilance Program in India
AIIMS	All India Institute of Medical Sciences
IPC	Indian Pharmacopeia Commission
CDSCO	Central Drug Standard Control Organization
MHFW	Ministry of Health and Family Welfare
NCC	National Coordinating Centre
ICH	International Conference of Harmonisation
NPAC	National Pharmacovigilance Advisory Committee
PAC	Project Advisory Committee
ICMR	Indian Council of Medical Research
DCGI	Drug Controller General of India
CRO	Contract Research Organization
CIOMS	Council for International Organization of Medical Science
NIB	National Institute of Biological Science
HVPI	Haemovigilance Programme of India
OTC	Over The Counter
NPP	National Pharmacovigilance Program
AMC	ADR Monitoring Centre

Conclusion

The only way to guarantee that a medicine is safe over its entire life cycle is through pharmacovigilance. It is extremely important since clinical studies often struggle to find unusual and extremely rare ADRs. The knowledge and information available on the safety of any drug is crucial for drug regulators to make the right decisions to protect the public's health. The majority of ADR reporters are members of the healthcare industry. Health care practitioners should view ADR reporting as a very essential responsibility rather than an additional clinical burden in order to promote safer drug usage globally. The need for a critical study was highlighted in this paper in order to ascertain whether the three countries were adhering to the WHO's minimum PV standards over the time period given. A robust PV system is a crucial component of the overall medicines regulatory system, demonstrating the rigour and expertise of the regulatory authorities in carrying out their duties of market and producer monitoring. PV need greater focused attention in health science curricula to meet these objectives. The local pharmaceutical business and healthcare workers both require further training. Structures within organizations need to be enhanced. For initiatives to be coordinated and sustained, more financing is needed. PV should receive separate funding, and the human resource capacity issues in healthcare systems must be resolved. Given the rise of ADR reports, the development of WHO guidelines offers a tool that proposes opportunities to increase PV efficacy. In order to facilitate and promote adherence to fundamental requirements elsewhere, systems for monitoring and evaluating progress should be put in place in the three study nations with reference to our findings.

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