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Review Article

Role of Pharmacovigilance in Drug Safety: An Overview of Activities at an Adverse Drug Reaction Monitoring Centre (AMC) of Delhi

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Abstract

Pharmacovigilance plays a vital role in the safety of drugs and rationalization of therapies. The main aim of this life science mission is to save and improve the quality of the lives of patients worldwide. The adverse drug reactions (ADRs) monitoring is essential for each drug starting from preclinical stages of drug development to all stages of clinical trials as well as after marketing of the drug. The WHO has developed International Drug Monitoring centre at Uppsala, Sweden which encourages and integrates Pharmacovigilance programs of various countries and provides access to Vigibase. At present more than 148 Countries are members of the International Drug Monitoring Program being run under WHO. The aim of the WHO Programme is to ensure that early signs of previously unknown medicines-related safety problems are identified; the information is shared globally so that action to protect patients may be taken by individual countries where necessary. A database of Individual Case Safety Reports (ICSR) submitted by member countries of the WHO's International drug Monitoring Program has been developed and named VigiBase, it is the single, largest repository to support that goal of drug safety in the world. In India, the pharmacovigilance program was initiated by Central Drugs Standard Control Organization (CDSCO) to monitor the safety of drugs in patients and was named as Pharmacovigilance Program of India - PvPI. Across the country PvPI has identified several teaching and corporate hospitals (Medical Council of India approved) as ADRs Monitoring Centres (AMCs). The AMCs report ICSR to National Coordinating Centre (NCC) which submit the reports to WHO-Uppsala Monitoring Centre through Vigiflow (a UMC software). This paper gives an overview of the pharmacovigilance activities of AMC at Vallabhbhai Patel Chest Institute, a tertiary health care centre of University of Delhi, Delhi, India.

Keywords: *Adverse Drug Reactions; History - Pharmacovigilance Program of India Spontaneous Reporting - Causality Assessment; Patient Safety*

Abbreviations

PV: Pharmacovigilance; ADR: Adverse Drug Reactions; AMC: Adverse Drug Reaction Monitoring Centre

Introduction

The term "Pharmacovigilance" is derived from the Greek word "pharmakon" which means drug and the word "vigilare" that means keep watch in Latin. In 1961, the World Health Organization (WHO) initiated the pharmacovigilance program in response to the thalidomide disaster, for international monitoring of drug safety [1]. WHO defines "Pharmacovigilance" as the science and activity relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The term pharmacovigilance was first proposed in the 1970s [2,3]. WHO also defines that adverse drug reaction is a response to a drug which is noxious and unintended, and which occurs at dose normally used in humans for the prophylaxis, diagnosis, or therapy of diseases or for the modification of a physiological function [4,5]. The important role of pharmacovigilance is to monitor the safety of a drug and efficacy when used in clinical practice. Worldwide during the drug development program, all the drugs, to be marketed, undergo a whole array of tests, preclinical studies in animals and clinical trials in human subjects to assess the safety of the drug and to know the associated specific side effects during its use in a particular disease. However, in spite of that there is chance that a part of ADRs may go undetected due to rare occurrence or standardized conditions during clinical trials. Adverse reactions can be detected at any stage during the drug development program or after marketing of the drug to the public. Such ADRs are usually unmasked in post marketing surveillance. It is estimated that there is a significant amount of ADRs which decreases the quality of life, increases hospitalization stay and increases the mortality [6]. Pharmacovigilance program focuses on identifying the health risks involved in the administration of certain drugs, preventing harm to people, monitoring the quality and efficacy of drugs [7]. The Pharmacovigilance programme of India is focused to improve safety and care of patients during use of medicines from any branch of medicine i.e. allopathic or traditional medicine. PvPI also provides reliable information and true assessment of the risk-benefit ratio of therapeutics, thus supporting public health programme of Govt. of India. Currently, the program has included various other products under its surveillance for e.g. materiovigilance for medical devices; hemovigilance for blood products; herb vigilance for herbal traditional and complementary medicines.

The newly adopted pharmacovigilance of herbal products is a systematic research of the safety of herbal medicines. Herbal medicines are widely used throughout the world and form a part of the well-accepted healthcare system, mainly in local communities that use those medicines since ages. WHO defines "Traditional medicine" as the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences native to different cultures, whether accountable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. WHO also emphasises that those traditional medicines should be included in the pharmacovigilance system and published guidelines in 2004 regarding this matter. The country with maximum consumption of medicine from herbal sources is Germany. Since the older ages, India also is a big user of traditional herbal medicine i.e. more than 70% of population (1.1 billion people) use them. Government of India has established AYUSH Ministry to encourage development of herbal medicine from traditional medicine (Ayurveda, Homeopathy, Unani, yoga and Siddha) as India can be a potential source of herbal medicines for the world. It is a myth that herbal drugs are always safe in spite of unpredictable pharmacodynamics, this needs to be broken in order to establish the faith of end users as most of herbal drugs are not subjected to preclinical and clinical assessment. There are several factors that contribute to the increased demand for monitoring the adverse events arising from consumption of herbal medicines. The factors can be wrong identification of plant species, adulteration of herbal preparation with other plants, heavy metals or other hazardous material, wrong dosage of herbal medicines or interactions with food or medicines from other systems of therapy. The mistake can happen during prescribing or dispensing by the healthcare providers or during administration by the consumer. Therefore, government of India launched National Medicinal Plants Board in 2000 to deal with the safety issues of the herbal medicines. Standardisation of herbal compounds and quality of clinical trials with herbal drugs remain a major challenge for researchers. There is under reporting of ADRs, lack of awareness and unavailability of sufficient reporting centres with regard to herbal medicine throughout the world. Hence, there is need to increase phytopharmacovigilance centres in India as the number of people using herbal medicines is more than those using allopathy. Therefore, by increasing the reporting centres the safety of herbal medicines can be boosted up [8].

History of pharmacovigilance

About 172 years ago concern for the safety of patients from adverse drug effects was started, although at that time it was not named the pharmacovigilance. It was a structured activity in the professional health field, with important social and commercial implications aimed at monitoring the risk/benefit ratio of drugs, improving patient's safety and the quality of life. The first patient reporting ADR was Hanna Greener in 1848, who probably died when anaesthetised with chloroform as a routine process before removal of an infected toe-nail. In 1937, about 107 deaths were reported in USA following administration of sulfanilamide elixir which contained diethyl glycol as the solvent. The cause of deaths was assigned to be the solvent but the manufactory companies were ignorant about toxicity of the compound. In 1938, Douthwaite first described the gastroscopic appearances of aspirin-induced gastric mucosal injury and suggested that acetylsalicylic acid (ASA) could cause melena. However, in 1955, ASA was shown to cause gastrointestinal dysfunction and was contraindicated in patients with ulcers like gastrointestinal conditions. In 1961, thalidomide disaster brought stringent changes in European Pharmacovigilance. It was highlighted by a publication of an Australian doctor, Dr. McBride in Lancet Journal, where he indicated correlation between congenital malformations of babies and thalidomide. In fact, he observed that the incidence of congenital malformations of babies went up by 20% in women who had consumed thalidomide for nausea during first trimester of pregnancy. Around that time, Dr. Lenz also suggested an association between thalidomide intake and phocomelia malformations during a Pediatric Convention in Germany. In 1973, a retrospective study also confirmed that intake of thalidomide during pregnancy resulted in congenital malformations of babies. The tragedy of thalidomide raised many questions about safety of the drugs, in particular, the reliability of preclinical and clinical studies to evaluate the adverse effects. The responsibility of the industrial company was also stressed upon in drug safety and need to monitor the adverse drug reactions after their marketing was realized. This resulted in a more systematic, organized, and regulated system of Pharmacovigilance and the spontaneous reporting of adverse drug reactions improved. In 1964, the "Yellow card" was structured in the UK. Yellow Card was designed to compile adverse reaction to drugs by spontaneous reporting. This Card contained many informations on drugs and the side effect which were needed to establish a cause-effect relationship between the drug and the adverse effect with temporal relation. In 1962, USA approved the amendment that safety and efficacy data of drugs is necessary before application of marketing authorization. As a result of this amendment, the safety data have to also include teratogenicity test in three different animals. In Europe in 1965, the thalidomide disaster resulted in establishment of European legislation with the EC Directive. In 1966, Boston Collaborative Drug Surveillance Program started a pilot study on epidemiologic researches and calculated the probable adverse effects of drugs by in-hospital monitoring and established the development and application of methods in drug epidemiology. In 1968, International Drug Monitoring Programme was started by the WHO and 10 countries, Australia, UK, USA, Germany, Canada, Ireland, Sweden, Denmark, New Zealand, and Netherlands took part in this ADR monitoring program and later in 1975 Italy also became a member of this program. Currently, WHO Programme for International Drug Monitoring is a group of more than 150 countries and many associate member countries are in the early stages of establishing their Pharmacovigilance systems in preparation for full membership. These countries have common goal of safer and efficient use of medicines. These countries collect ADRs at the national level and collaborate internationally to identify the harm caused by various drugs to enhance the patients' safety and to establish worldwide data base of outcomes of pharmacovigilance activities [9,10].

In 1992, the European Society of Pharmacovigilance (ESoP) was funded, turned into the International Society of Pharmacovigilance (IsoP). The aims of this society were to promote safety use of drugs and rationalize therapy through Pharmacovigilance. In 1995, the European Medicines Agency (EMA) was established and EudraVigilance was founded in 2001. In 2012, after approval of new legislation of Directive 2010/84/EU, many changes occurred in European Pharmacovigilance. The major changes included redefining adverse drug reactions, more participation of patients and citizens in Pharmacovigilance program and improving the Eudravigilance database containing all reports of suspected ADRs, transparent systems and stringent timeliness of submitting information regarding ADRs to competent authorities, additional monitoring was also advised for drugs/products contained in specific list by the EMA, formation of the Pharmacovigilance Risk Assessment Committee in the EMA etc.

The pharmacovigilance programme of India (PvPI)

In India, for the first time the pharmacovigilance program was started in 1986 with 12 adverse drug reaction (ADR) monitoring centres, under Government of India initiative [11]. Later, in 1997, India joined the International Drug Monitoring Programme of WHO with its base in Uppsala, Sweden. This program identified three centres in the teaching hospitals for ADR monitoring, these were 1) Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi; 2) KEM Hospital, Mumbai; and 3) JLN Hospital, Aligarh. It was the responsibility of these centres to collect ADR and submit to the drug regulatory authority of India. These centres were mainly involved in monitoring ADRs to drugs being marketed in India. However, this initial program was a failure due to poor financial support to the program and communication gaps. Thereafter again attempts were made and in January, 2005 National Pharmacovigilance Program (NPVP) for India was formed. The NPVP was under the control of the National Pharmacovigilance Advisory Committee regulated by the Central Drugs Standard Control Organization (CDSCO). Two zonal centres were formulated, the South-west Zonal Centre at Department of Clinical pharmacology at KEM Hospital and North-east Zonal Centre at Department of Pharmacology at AIIMS, Delhi. These centre were assigned to collect ADRs throughout their zones and submit to the National Pharmacovigilance committee as well as International monitoring centre at Uppsala. There were three Regional Centres for reporting ADRs to South-west Zonal Centre and two for the North-east centre. Each Regional centre, was supported by several peripheral centres (24 in total) for collecting ADRs. The program was mainly focussed on three objectives viz. short, intermediate and long term objectives. The focus of the short term objectives was to inculcate a habit of reporting ADRs, the intermediate focussed to include and encourage HCPs to participate in the reporting ADRs; and the long term objective was to set standards for International drug monitoring. Unfortunately, this program was also a failure and was not able to meet its goal.

In 2009, it was realized that there is a need to restart the pharmacovigilance program and to avoid earlier mistakes a workshop was organized at AIIMS in collaboration with CDSCO and the framework was prepared. The program was finally launched by Government of India in July, 2010 and renamed as the Pharmacovigilance Programme of India (PvPI). The centre at AIIMS at Delhi was made the National Coordination Centre (NCC) for collecting ADRs from all over the country. There were 22 ADR monitoring centre throughout the country to collect ADRs for submission to NCC. In April, 2011 the NCC from AIIMS, Delhi was shifted to Indian Pharmacopeia commission (IPC), Ghaziabad, Uttar Pradesh for better management of the program. The main responsibility of NCC is to collect all the ADRs to various drugs occurring in Indian population so that regulatory intervention can be planned to improve the safe use of drugs. Currently, the ADR monitoring centres have been increased to about 311 and they collect ADRs, analyse and send it to NCC for analysis and causality assessment. Finally these reports are sent to UMC, Sweden to contribute the data in the VigiBase. Thus, NCC-PvPI monitors all the ADRs being reported by the Indian population and take measures and decision through regulatory body of India (CDSCO) to improve patient safety [12].

The PvPI are involved in compilation of safety data of drug over a prolonged period termed as the aggregate Reporting. This play a key role in safety assessment of drugs and provides information about long term safety of a drug. The most important aggregate report is the Periodic Safety Update Report (PSUR). The term PSUR was changed to Periodic Benefit Risk Evaluation report (PBRER) in 2012 with more focus on complete details of benefit versus risks of a drug. The PSURs need to be submitted every 6 months for the first 2 years of marketing in India, and subsequently yearly for 2 years. In case of a serious ADRs to a drug that ICSR are rapidly forwarded to Regulatory Authorities in a designated format in compliance with the standards and timelines specified by legislation and local regulatory guidelines. The serious ADR usually is a not listed ADR to a drug which has temporal relationship with the drug, results in hospitalization or prolongation of stay in hospital, results in any disability or death of the patient. The timelines for submission of such ADR is usually between 7 - 15 days (depending on guidelines of different countries) of first report to drug company.

Methods of collection of ADRs

Spontaneous reporting: It is the most common and economical mode of collecting ADRs. It is defined as an unsolicited communication by health care professionals or consumers, pharmaceutical company to regulatory authority or any other organization (WHO, Regional

centres) that describes one or more Adverse Drug reactions in patient who was given one or more medicinal products that does not derive from a study or any organized data collection scheme [13]. Spontaneous reporting is considered as the back-bone of any pharmacovigilance program. It relies on healthcare professionals and in some places consumers to report any suspected ADRs to the national pharmacovigilance centre. Spontaneous reporting is most common, effective and relatively inexpensive method in pharmacovigilance. However, one of the drawback of the spontaneous reporting is the under-reporting which varies from country to country depending upon the awareness and culture of reporting. Further, the denominator population is not clear for calculating the % patients developing ADRs. Moreover, the physicians are always overburdened and do not consider it a priority to report ADRs. In addition, due to their busy schedule they may miss some ADRs which are not that prominent or are not very severe. Sometimes the information reported may be limited and insufficient for clinical/regulatory decisions.

Although, PvPI is mainly following spontaneous reporting system to collect data on drug safety, spontaneous reports are not sufficient on their own to provide a reliable or comprehensive picture of the harm caused by drugs. This makes it necessary to use other investigative methods, therefore, worldwide hundreds of research projects are conducted by health authorities, academics, practitioners and manufacturers to collect ADRs for safe medication. Direct patient reporting has been established in many countries and is recognised as a valuable, complementary source of information about medicines safety and patients' experience of therapy. New electronic methods of reporting, online and mobile apps (ADR PvPI) for example, show promise in enriching and enlarging the information available.

Cohort event monitoring (CEM): Cohort event monitoring (CEM) is an intensive and well planned form of monitoring the adverse effects of drugs to evaluate the safety of drugs. In Cohort Event Monitoring (CEM), specific group of patients (cohort) with some common factor/criteria (for e.g. birth during the same year or suffering some common disease etc.) are monitored during treatment with some specific drugs during therapy [14].

Prescription-event monitoring (PEM): is again an intensive, a non-interventional method for monitoring the ADRs to drugs. This monitoring is usually done for recently marketed medicines under post marketing surveillance. PEM studies are a kind of cohort studies where drugs are prescribed from a centralized service and events are recorded by filling specific, validated questionnaires by the physicians. Follow-up forms are sent for selected events. PEM differs from other methods of monitoring as all the events are recorded and not only the suspected ADRs Because PEM captures all events and not only the suspected adverse drug reactions [15,16].

Other methods of pharmacovigilance: The other methods used for collection of ADRs include the following methods:

- Hospital based intensive monitoring/active surveillance
- Epidemiological studies
- Case control networks
- Literature reporting.

The pharmacovigilance centres and other related organisations, including UMC, promote the message about safer use of medicines and the importance of reporting ADRs. The efforts to make patients aware about the active part they can play in their own welfare and treatment are gaining success. There has always been a priority to motivate patients to report adverse drug reactions to their health providers or directly to local or national pharmacovigilance centres. To monitor ADRs, till now 311 ADR monitoring centres (AMCs) have been established throughout the country which are coordinated by NCC-PvPI. These AMCs are functioning in various hospitals, medical

colleges or institutes, private hospitals or clinics etc. AMCs all over India collect suspected ADRs through Patient safety Pharmacovigilance Associates (specially appointed by CDSCO, IPC for AMCs), doctors, nurses or patients directly.

An overview of activities of an AMC in a tertiary care centre in Delhi

The paper focuses on reporting of ADRs by one of the AMC at a tertiary care centre in India. AMC at Vallabhbhai Patel Chest Institute (VPCI), University of Delhi, was approved under Pharmacovigilance Programme of India (PVPI), Government of India in December 2013. VPCI is a specialized, postgraduate medical institute under Central University of Delhi which is focussed on research, teaching and patient care in the field of chest diseases and other related conditions.

ADRs reporting by VPCI-AMC: Since its inception the AMC at VPCI is involved in following activities:

1. Disseminating the awareness about reporting ADRs among PG medical students, nurses, health care professional and other staff.

2. Collection of ICSRs from OPD, IPD, HCPs, periphery. The PsPvA pursues the ICSRs to get the complete information for scientific assessment and causality is confirmed by the Causality assessment Committee. Following this, the ICSRs are communicated to NCC through Vigiflow software which is a web-based ICSR management system that is specially designed to be used by the member national centres in the WHO Programme for International Drug Monitoring. The reports are finally submitted to UMC, Sweden by NCC. The ICSRs reported by VPCI-AMC from February 2014 to August 2021 to National coordination Centre (NCC) have been shown in figure 1.

3. Processing and reporting of voluntary ICSRs from non-AMCs to NCC-PvPI.

4. Every year on the National deworming day i.e. 10 February, the AMC coordinates with the State Nodal Officer of Deworming Programme and contacts principals of schools for collection of ADRs from students, for e.g. focussed ADRs to albendazole.

5. The centre is also involved regularly in the review and analysis of Marketing Authorization Holder (MAH)-– ICSRs from IPC and prepare the score sheets and submits to IPC through Vigiflow.

6. Disseminating the new programs launched by IPC for e.g. Introduced the newly developed Suspected ADR reporting Form for Drugs used in prophylaxis and treatment of COVID-19 to Health care professionals and complied with reporting of any such ADRs on every Monday to IPC from 10th April, 2020

7. Participates in Social Media Campaign organized by IPC under Uppsala Monitoring Centre, viz. “Med Safety Week” 2020 between 02nd to 08th November.

8. Spreading awareness about medical devices adverse events for e.g. falsified HIV rapid diagnostic test kits; adverse events related to personal protective equipment (PPE) widely used during Covid-19; promoting PvPI Helpline number TOLL FREE: 1800 180 3024 by placing posters in OPD, Library and other peripheral departments.

9. Participation of staff in Skill Development Programme on various issues of pharmacovigilance, materiovigilance, AEFI etc. help in making medicines and medical appliances safer for everyone.

10. Updating HCPs regarding various Drug Alerts for e.g. Clobazam cause Drug rash with eosinophilia and systemic symptoms DRESS Syndrome, Clarithromycin may cause burning sensation.

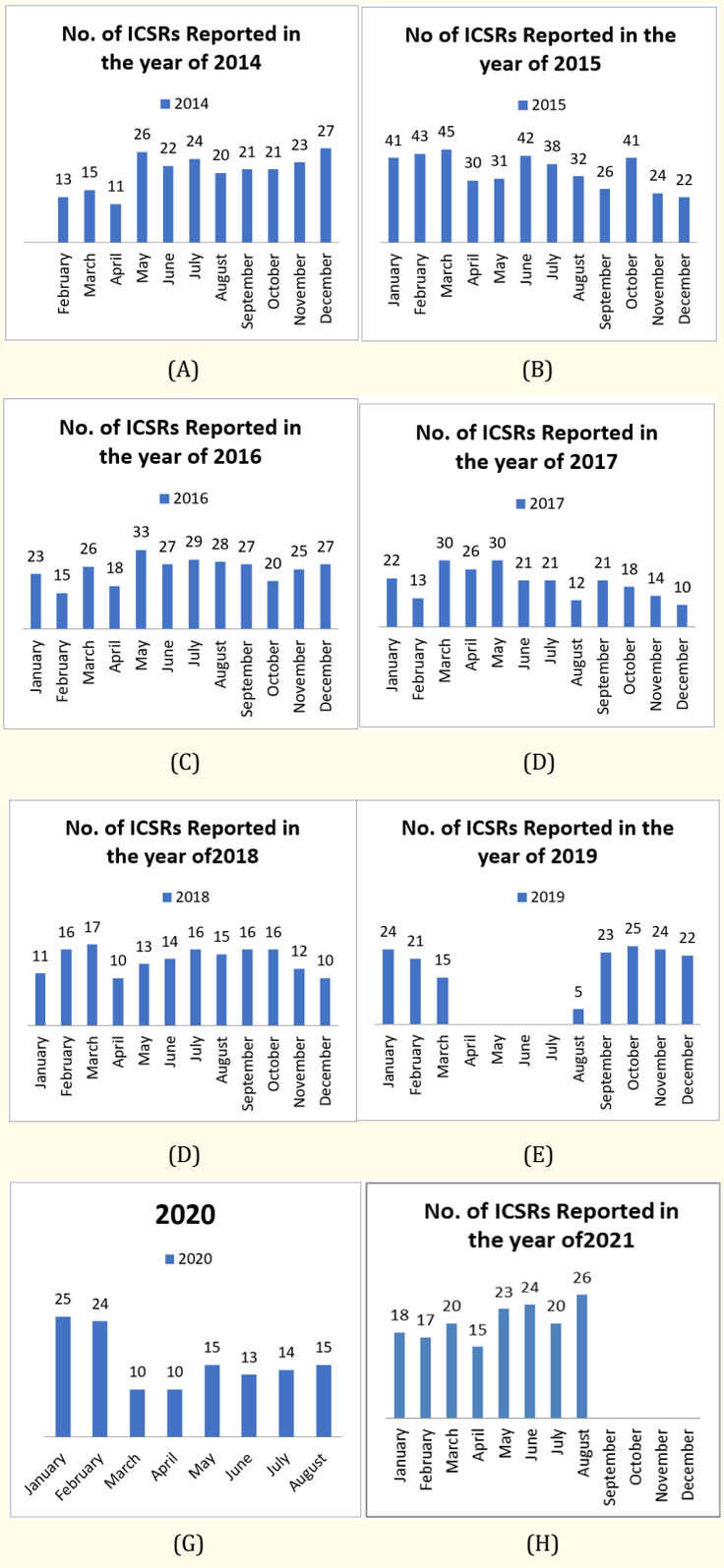


Figure 1: *(A-G) Depicts the month-wise yearly reporting of Focussed ICSR on respiratory disease related drugs by VPCI-AMC from the year of its inception i.e. 2014 to 2021.*

Causality assessment of ICSRs

Causality Assessment- Hutchison defined causality assessment as a "method for eliciting a state of information about a particular drug-event connection as input and delivering as output a degree of belief about the truth of the proposition that the drug caused the event to occur". Causality assessment of a ADR helps in determining the strength of relationship of that ADR with the drug exposure. During assessment of causality of occurrence of an adverse event in response to a drug treatment, several factors are considered. Some of the most important being prior reports of such adverse reactions to the drug, temporal relationship, response to stoppage of the drug administration (de-challenge) or restarting the drug (re-challenge), dose-response relationship, alternative aetiologies which can explain that ADR and past history of reaction to same or similar medication. More than 34 scales are available for performing Causality Assessment which are mainly classified as:

1. Expert judgement/global introspection- Individual assessments based on previous knowledge and experience. No specific tool is required, one of the widely acknowledged example is the WHO- Uppsala monitoring centre (UMC) Scale.

2. Algorithms- It consists of specific questions related to that ADR and each question is assigned a specific score. After completion of questionnaire, total score is calculated and likelihood of a cause-effect relationship is established as per pre-set criteria. Naranjo' scale is one of the most commonly used scale to determine cause-effect relationship of the drugs.

The WHO-UMC causality assessment scale depends upon the following criteria as shown in table 1:

a) Time sequence between the drug use and the adverse event.

b) Ruling out presence/absence of other drugs or diseases which can be the cause of that event

c) Response to dechallenge, i.e. drug withdrawal or reduction of dose.

d) Response to rechallenge, i.e. again administration of [17].

Categories	Time sequence	Other drugs/ disease rule out	Dechallenge	Rechallenge
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

Table 1: *WHO-UMC causality assessment method.*

The level of causal association is groped into six categories which are based on a number of the above criteria being met. The dug-event relation is considered 'Certain' if all the four criteria mentioned above are fulfilled. It is considered 'Probable' if three criteria (a, b, c) are matched. Likewise, if only two criteria are met the relationship is 'Possible' and if just one criteria is fulfilled it is termed as 'Unlikely'. Beside these four categories in WHO-UMC causality assessment, ADR can also be categorised into 'Unclassified/Conditional' if more data is required to comment about the cause-effect relationship of drug and the ADR; and 'Unassessable/ Unclassifiable' when the information in ICSR is incomplete or contradictory The Causality assessment of total 1852 ICSRs was done by WHO-UMC scale and the distribution has been shown in figure 2.

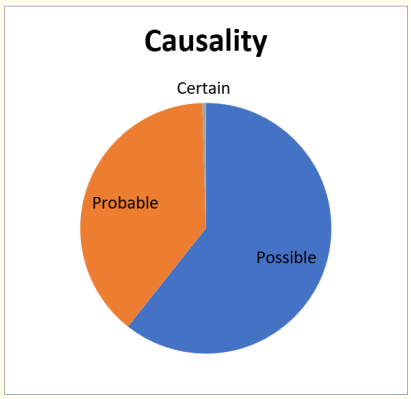


Figure 2: *Distribution of causality assessment of 1852 ICSR cases as 'certain, probable or possible' relationship with drugs as per WHO scale.*

Naranjo' causality assessment scale

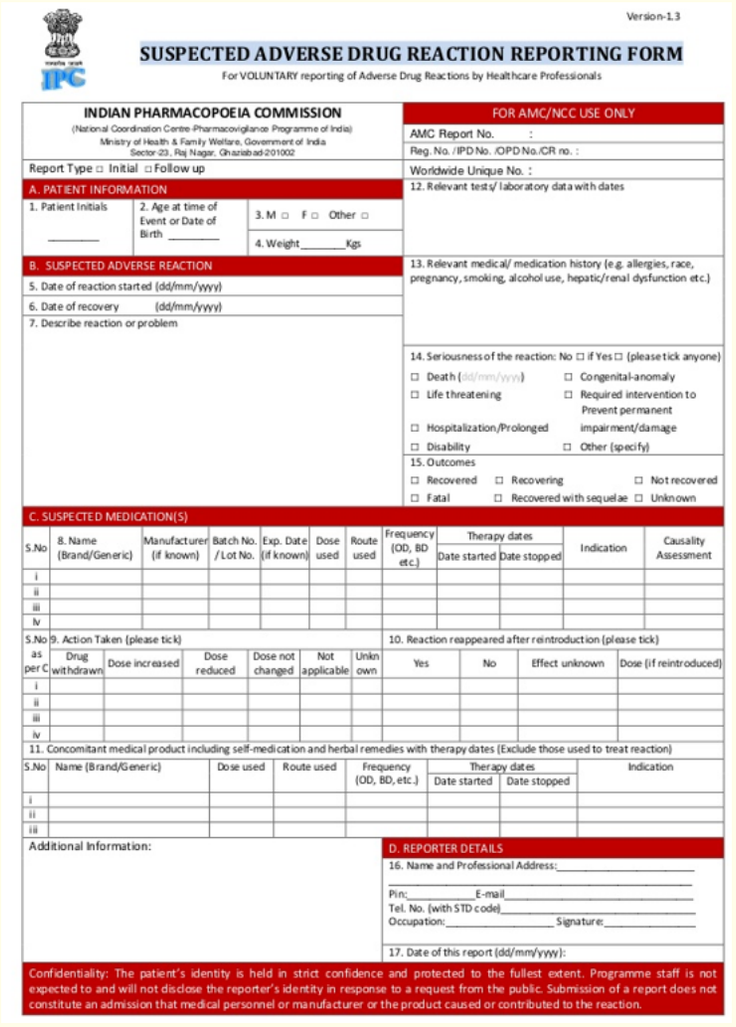
Naranjo., *et al*. [18] described a method for estimating the probability of ADR being specifically related to a particular drug by giving an algorithm. It consists of ten specific questions which are assigned certain scores ranging from +1 or -1 or 0 for calculating the probability of cause-effect relationship. It is an objective scale as shown in table 2.

Questions	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or (other fluids) in concentration known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
Total Score				

Table 2*: Naranjo' causality assessment scale.*

Workflow for pharmacovigilance activity

The AMC's collect all the ADR reports from various sources through spontaneous reporting by the patients in the OPD or IPD or through health professional on duty. Pharmacovigilance (PV) staff at AMC study the ICSRs, validate and prioritise the report and perform provisional causality assessment. The suspected ADR Form used in the Pharmacovigilance Program of India is shown in the figure 3. The ICSRs are then sent to NCC for further processing and onward submission for global reporting. The assessed ADR forms are then directed towards authorised coordinating centre for further proceedings. The staff of AMC maintains a record of the pharmacovigilance activities as per the SOPs and guidelines of IPC. The National Coordinating centre, IPC performs final Causality assessment and feed the reports into the PV database. The findings of PV analysis are discussed for implementation and finally integrated into the general population Health Program to avoid ADRs to therapeutics. At the end, the reports are transferred to UMC, Sweden through Vigiflow, a specific software for member countries of International drug monitoring Program. The UMC team then analyses and collates ADR reports from various countries and detects any new adverse effect to drugs which is termed as 'signal'. The WHO has defined 'signal' as ''Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented". Actually, it is a new finding within Safety data that needs to be further investigated. More than one ICSR is generally required to generate a `signal, however, sometimes less number of reports can also be considered as signal depending on seriousness of Adverse Event and quality of information. As per WHO three "index cases" are required to generate a signal. A case is termed as n index case if contains information on all following 11 major items:



Version-1.3

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions 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

FOR AMC/NCC USE ONLY
AMC Report No. :
Reg. No. /IPD No. /OPD No./CR no. :
Worldwide Unique No. :

Report Type □ Initial □ Follow up

A. PATIENT INFORMATION
1. Patient Initials _____
2. Age at time of Event or Date of Birth _____
3. M □ F □ Other □
4. Weight_____Kgs

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

12. Relevant tests/ laboratory data with dates
13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)
14. Seriousness of the reaction: No □ if Yes □ (please tick anyone)
□ Death (dd/mm/yyyy) □ Congenital-anomaly
□ Life threatening □ Required intervention to Prevent permanent
□ Hospitalization/Prolonged impairment/damage
□ Disability □ Other (specify)
15. Outcomes
□ 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.	Exp. Date (if known)	Dose used	Route used	Frequency (OD, BD etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication	Causality Assessment
i											
ii											
iii											
iv											

S.No as per C	9. Action Taken (please tick): Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown	10. Reaction reappeared after reintroduction (please tick): Yes	No	Effect unknown	Dose (if reintroduced)
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 used	Route used	Frequency (OD, BD, etc.)	Therapy dates: Date started	Therapy dates: Date stopped	Indication
i							
ii							
iii							

Additional Information:

D. REPORTER DETAILS
16. Name and Professional Address:_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____Signature:_____
17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

Figure 3: *The suspected adverse drug reaction monitoring form of pharmacovigilance program of India.*

- Information source
- Identification of case
- ADR description
- Name of drug
- Treatment dates
- Reaction date
- Age, Sex
- All other drugs with dose and date
- Indication of treatment.

Outcome of Signal is very important aspect and if found serious ADR, it is communicated to NCC-PvPI via CDSCO to stop the marketing or use of drug in India. There is a separate Quality Review Panel to maintain the quality of ADR processing, timely completion of the work records and adherence to the PV program protocol [19]. The workflow for Pharmacovigilance activity has been shown in figure 4.

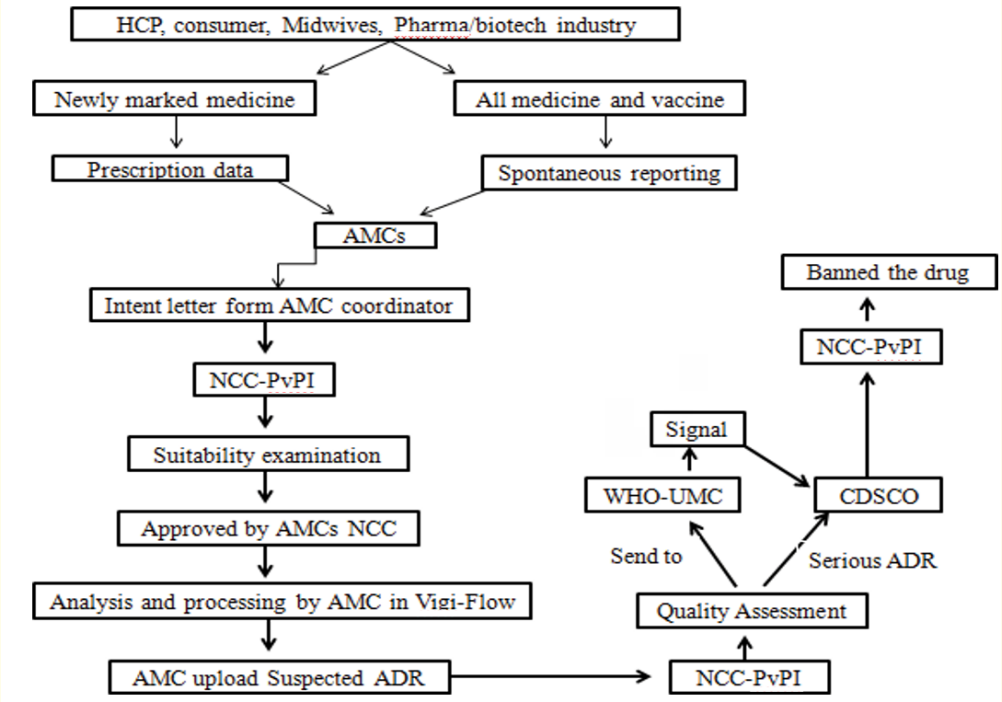


Figure 4: *Workflow for pharmacovigilance activity [19].*

The healthcare professionals including physicians, nurses and pharmacists are persuaded to report any suspected ADRs particularly related to exposure to new therapeutic. Some of the examples of ADRs reported by HCP of VPCI AMC are shown in table 3. The safety and efficacy of a drug are the two important aspect of a drug, while the efficacy can be quantified relatively easily by pharmacodynamics studies but it takes time to comment on the complete safety aspects of a drug. This is due to the fact that the ADRs may be rare but serious and many patients may be affected or subjected to a potential risk before the cause-effect relationship is identified [20,21].

Sl. No	Suspected Drugs	Indication	Adverse Drug Reactions
1.	Pyrazinamide	Tuberculosis	Arthralgia
2.	Defcort	Sarcoidosis	Cataract
3.	Omnacortil	Interstitial Lung Disease	Shingles
4.	Gentamicin	Respiratory Infection	Breathlessness, Wheezing
5.	Azimax	Upper Respiratory Tract Infection	Anaphylaxis
6.	Septran	Pcp Prophylaxis	Thrombocytopenia
7.	Piczar	Copd	Palpitation
8.	Solumerdrol	Asthma	Fungal Infection
9.	Foracort	Asthma, Copd	Oral Candidiasis
10.	Albendazole	Deworming	Acute Gastritis
11.	Nsaids	Tooth Pain	Urticaria, Angiodeema
12.	Disprin	Headache	Eye Swelling
13.	Magnesium sulfate	Respiratory Disease	Metabolic Acidosis, Severe Respiratory Disease
14.	Asthalin	Asthma	Tremor Of Hands
15.	Rantac	Gastritis	Abdominal Pain
16.	Unicontin-E	Asthma	Rash, Itching

Table 3: *Examples of few ADRs observed from AMC VPCI, under pharmacovigilance program of India (PvPI).*

Conclusion

Adverse reactions to drugs is an important public health issue for rational drug therapy. Safety monitoring of medicines is the responsibility of all stakeholders of the healthcare system since it continues to be an important cause of morbidity and mortality. This requires a well-organised pharmacovigilance system to be established to monitor the ADRs to authorised drugs and medical products. As per industry experts, ADRs are responsible for approximately 5 to 7% of all hospital admissions, and account for nearly 50 deaths out of 1000 patients admitted to hospitals. Due to serious ADRs about 150 drugs have been withdrawn from the market in last 50 years. Thus, monitoring adverse effects of the drugs are very crucial and Pharmacovigilance program was started by WHO and currently 150 countries are members of the WHO Programme for International Drug Monitoring.

Various means are used to collect ADRs viz. prescription-event monitoring, hospital based intensive monitoring/active surveillance, epidemiological studies, case control networks, cohort studies and literature reporting. These ICSRs are reviewed and analysed, and if some signals are detected further investigations are done. In case of confirmation of serious ADRs stringent guidelines are followed for regulatory action. All member countries of International Drug Monitoring contribute their ADR findings to the VigiBase to facilitate the drug safety globally. The Pharmacovigilance program of India has established approximately 311 ADR monitoring centres (AMCs) all over India, which are coordinated by NCC. These AMCs are functioning in various medical colleges, hospitals and medical /central/autonomous

institutes to collect ADRs to various drugs. In this article the contribution of individual AMCs in PvPI for drug safety has been highlighted by describing the pharmacovigilance activities of an AMC in a tertiary health care centre in Delhi.

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