Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Pharmacy
4(2), 2015, 201-212

ISSN 2321 – 0958

Review Article

# EXPLORING PHARMACOVIGILANCE: A NARRATIVE REVIEW

**Bhumeshwar Sharma[1], Sourabh Kosey[1], Neelesh Kumar Mehra[1,]**
**Deepanshu Kumar Chitra[1], Raj Kumar[2]**

[1] Department of Pharmacy Practice, I.S.F. College of Pharmacy, Moga, India
[2] Guru Gobind Singh Medical College, Faridkot, India

**Abstract:** In recent years an increase in drug safety concerns, accompanied by some high profile drug withdrawals has steeped the bar of drug safety by various stakeholders, more significantly by the regulatory authorities. With the increasing reporting of Adverse Drug Reactions, volumes of data to be handled have simultaneously increased. Rapid detection of drug risks as well as the ability to defend the marketed product against an inappropriate serves as the essential expertise, skills, which are attained by those personnel having a sound understanding of Pharmacovigilance.

The future path and providence of drug safety is solely dependent on Proactive pharmacovigilance throughout a product's life cycle. In the context of clinical trials and post-marketing pharmacovigilance codification followed by standardization of the act of signal detection and risk management remains a great challenge in the progression and fluorishment of the field. Advancements of the discipline are at an infancy stage in India whereas the west has already reached the mountain in the same prospect. By the passage of time and with more clinical trials and clinical research activity being conducted in India, understanding and implementation of pharmacovigilance have become an essential need. A positive change can occur in Indian Scenario if the outlook of the workforce of regulatory agency (DCGIOffice) and the Indian Pharmaceutical companies is varied. This review describes and discusses the various policies and propositions to build, maintain and implement a stout pharmacovigilance system for various stakeholders and eventually make it functional in India.

**Key Words:** Pharmacovigilance, Adverse Drug Reaction, Adverse Events.

**For Correspondence:**
boneysharma.sharma479@gmail.com
Received on: May 2015
Accepted after revision: June 2015
Downloaded from: www.johronline.com

**Introduction:** Adverse reactions are a recognized hazard of drug therapy. Although some adverse drug reaction (ADRs) are minor but, others can cause permanent disability or death. Even though many studies have assessed the incidence of ADRs in numerous settings, these estimates vary considerably (1).

ADR are diverse, and any organ can be the principal target or several systems can be involved simultaneously, it becomes very difficult to prescribe a medicine safely. Although many drug reactions are preventable such as those associated with prescription errors but there are others which are not preventable (2).

The ADR are often not discovered until and unless the drug has been marketed. Pharmaceutical companies strive to work out the adverse effect profile of a drug before it is marketed, but because the complete range of adverse effects is not known, therefore, most severe drug induced reactions cannot be elucidated before licensing, therefore efficient post marketing surveillance is needed. However, even if improved surveillance is carried out the problem will not be resolved. As more drugs are marketed and as more individuals take multiple drugs, the occurrence of ADR will probably continue to increase. Therefore, better approaches must be devised for reporting and for assessment and management of individuals who present with drug induced diseases. Some of the patients are allergic to only one drug but many others state that they have multiple drug “allergies”. Here the Physicians become confused because they do not know that which medicine can be prescribed safely (3).

With the passage of time Pharmacovigilance has extended it’s watchful eye over the monitoring of herbal, traditional, and complementary medicines, blood products, biologicals, medical devices and vaccines with a vision for identifying latest and upgraded information on hazards about the said products to patients(4).Henceforth pharmacovigilance is not only confined to ADRs but also take into account issues related to polypharmacy, iatrogenesis, paradoxical reaction and serious adverse event of a drug (5). Clinical trials now a days provide an early signal to major pharmaceutical companies indicating risks associated with their products. Such signal detection and risk management has provided a newer element to the field of Pharmacovigilance and is continuously evolving (6).

The studies related to admission in all hospitals due to ADR in UK shows that ADR related admissions were 0.5% of total admission, while a study in two hospitals with medical and surgical departments the ADR related admissions corresponding to 5.2% of total hospital admissions. When similar studies were done in medical department in Europe to certain ADRs according to WHO criteria encounter 3.2% in France and 6.2% in Germany of all admitted patients, while in a prospective computerised "event monitoring" study in internal medicine departments in Swiss general and teaching hospitals admissions due to ADRs encounter 3.3%. When studies were done in even more specialised department there was highest percentage of admission due to ADR for example, up to 27.4% of patients had at least one possible, likely or very likely ADR on admission in medical intensive care units in France When different studies were compared it was assumed that wide variation in the frequency of ADR related admissions could be the result of different detection methods and specialities of the included departments and hospitals(3).

**The World Health Orgarnisation (WHO)** has defined an ADR as a reaction which is noxious and unintende” and which occurs at doses normally used in humans for prvention, diagnosis or thearapy of disease, or for the modification of physiological function(7).

**Adverse drug event** has been defined as an untoward and unexpected experience by a patient following the use of a medicinal product but does not necessarily have a causal relationship with the treatment(7).

**Population wise ADR occurrence**

According to a report by Pharmacovigilance programme of India (PvPI) newsletter published in 2014, of all the ADR occurences, 83% have been in adult population, followed by 5,9, and 3% in Elderly, Paediatric and Adolescent age groups respectively as depicted below Fig.1 (23)

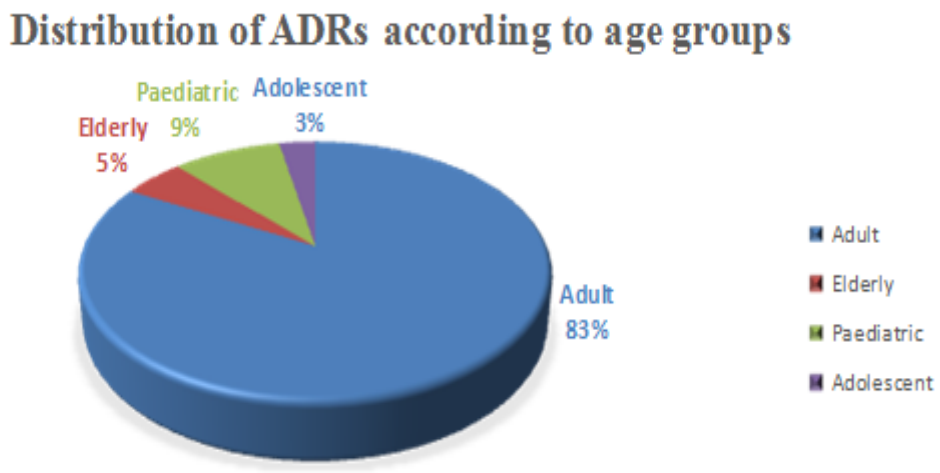



**Figure 1: Distribution of ADRs according to age groups(23).**

**Serious Adverse event or Reaction**:

It is any untoward medical occurrence that at any dose:

- Results in death
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability.
- Is life threatening?

**Pharmacovigilance**

Pharmacovigilance is defined as the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines (ADRs)(8) .

The word pharmacovigilance has derived from the Greek word pharmacon means, "drug" and the Latin word vigilare means, to keep awake or alert, to keep watch." On a generalized note, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to identifying new information about hazards associated with medicines and preventing harm to patients. Therefore the concerned areas of pharmacovigilance are not only limited to adverse effects of drugs but also emphasise on polypharmacy, iatrogenesis, paradoxical reaction and serious adverse event of a drug (9). Pharmacovigilance is a vital and indivisible part of clinical research. A product's life cycle is majority and critically effected by both clinical trials safety and post-marketing pharmacovigilance (Popularly known as Post marketing studies or Phase IV clinical trials). Both the pharmaceutical industries as well as various regulatory agencies across the globe have elevated the bar in accordance with the reasonably high number of recent high-profile drug withdrawals. Major Pharmaceutical Firms and Companies in order to identify the risks associated with their medicinal product/s in the early hours have started adapting primitive detection of signals from the post-marketing surveillance studies. Application of robust risk management plans throughout the life cycle of the product remains as a prerequisite for effectively managing the risks, if present. These risk management plans are also widely known

as Risk Minimisation Programmes/Strategies. Thalidomide which is reintroduced for Multiple Myeloma and Lepra reactions through programme System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) is a classical example. The revolution in the reporting of ADR's has been brought up by setting up of a world based centre inaugurated by World Health Organisation(WHO) called Uppsala Monitoring Center (UMC) in Sweden. UMC is maintaining the international database of ADR reports received from several national centres. In September 2005, the database had 3.5 million ADR report and 78 countries were participating in this programme. Vigibase online (web based) system is used for submission of ADR reports (10).

Although India is participating in this programme, its contribution to UMC database is very little. The major reason being the absence of a vibrant ADR monitoring system and also the lack of a reporting culture among health care workers. People generally wonder what could be the effect of not reporting any ADR. To counter this misbelief some statistical data would cater to throw light on the confrontational outcomes on not reporting the ADR's. A study in the UK showed that 6.5% of people admitted to hospitals had experienced at least one ADR, and that in 80% of those cases, ADR was the direct cause of hospitalization. ADRs are also accounted for the projected annual cost of £466 million to the UK's National Health Services. In the United States, it was reported that over two million ADRs occur annually resulting in more than 100,000 deaths, making ADRs the fourth leading cause of death ahead of pneumonia, AIDS, automobile accidents and diabetes(10).

Focussing on the Indian system of Pharmacovigilance, the establishment of National Phramcovigilance Programme has proven fruitful for this field in terms of reporting ADRs but with some associated anomalies or lower strength as compared to the pharmacovigilance programmes of other developed nations (11).

**Establishment of pharmacovigilance**

As a result of this horrifying epidemic, many countries established agencies concerned with the drug safety such as our own committee on safety of drugs and later the WHO set up an International bureau in 1968 to collect and collate information from National Drug Monitoring Organisation. The WHO has since taken up the mantle and now plays a major role in spreading these programmes around the world(12).

At that time spontaneous reporting schemes were set up in some western countries and these initiatives can be recognised as the first generation of progress in Pharmacovigilance (13).

The WHO Programme for the International drug monitoring provides a forum for WHO members states to collaborate in the monitoring of drug safety. Within the programme individual case reports of suspected ADRs are collected and stored in a common database presently containing over 3.7 million case reports. The WHO Programme which was established in 1968, consists of a network of National Centres, WHO headquarters, Geneva and the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centres, Sweden. In March 2006, 79 countries had joined the Drug Monitoring Programme (14).Fig no.2

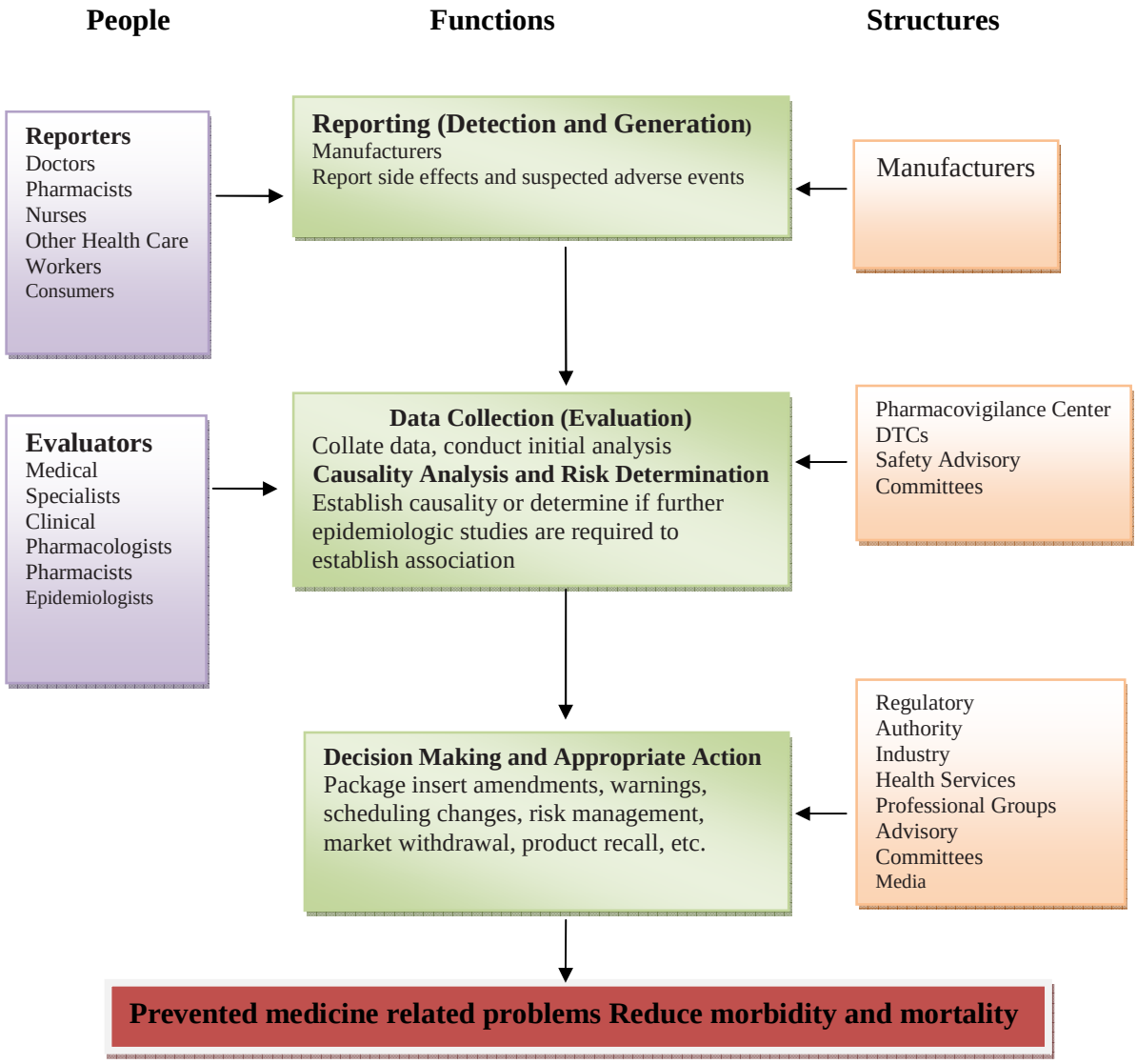



**Figure 2. The pharmacovigilance framework: relating people, functions, structures, and expected outcome and impact.**

**History of Pharmacovigilance in India**

The history of pharmacovigilance goes back more than 40 years. In 1965 the eighteenth World Health Assembly (WHA) drew attention to the problem of adverse drug reaction monitoring and following further resolution in 1966, 1967 and 1970 the International Drug Monitoring Programme came into being. It was not until 1986 that a formal ADR monitoring system consisting of 12 regional centres, each covering a population of 50 million, was proposed for India(15). In 1997, India collaborated with the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centres for ADR monitoring were identified, mainly based in teaching hospitals: A National Pharmacovigilance Centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centres Mumbai (KEM, Hospital) and Aligarh (JLN Hospital, Aligarh Muslim University). These centres were to report ADRs to the drug

regulatory authority of India. The major role of these centres was to monitor ADRs as a result of administration of medicines, which are marketed in India. However, their functionality was almost negligible as the information about the need to report ADRs and about the functions of these monitoring centres were yet to reach the prescribers and an added effect of lack of funding from the government contributed to a greater extent. This attempt resulted in vain and hence, again from the 1st of January 2005, the WHO- sponsored and World Bank-funded National Pharmacovigilance Program for India was made operational(6).

**Beginning of a new era: Setting up of PvPI**

Monitoring of ADR started in India about two decades ago (1982). Under the chairmanship of the Drug Controller of India, five centres were established with the idea of starting a monitoring programme nationwide. It consisted of three phases:

- first one being monitoring of reactions in the institutes,
- second one in governmental bodies like Central Government Health Scheme (CGHS), and
- third phase proposed to include general practitioners.

A multi-institutional pilot study involving 58,194 cases was done in 1987 under the aegis of Indian Council of Medical Research (ICMR,New Delhi). Its nodal centre (National Pharmacovigilance Centre) is located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi. It is affiliated to WHO collaborating Centre for ADR Monitoring, Uppsala, Sweden. The others are located in Post Graduate Institute of Medical Education and Research (PGI) (Chandigarh), Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) (Pondicherry), King George's Medical University (KGMC) (Lucknow), and Seth Gordhandas Sunderdas Medical College (SGSMC) (Mumbai) – special centre(16).

To improve the current state of functioning of pharmacovigilance activities, the central drug regulatory agency the Central Drugs Standard Control Organization (CDSCO) launched the National Pharmacovigilance Program in November 2004 under the aegis of Directorate General of Health Services, Union Ministry of Health and Family Welfare. The basic purpose of this program is to collate, analyse and archive ADR data for making regulatory decisions regarding drugs marketed in India(16).

The program has a three-tier structure consisting of peripheral, regional and zonal Pharmacovigilance Centres in addition to the National Pharmacovigilance Advisory Committee and the National Pharmacovigilance Centre based at the CDSCO, New Delhi. All centres can report alarming or critical ADRs to the National Pharmacovigilance Centre directly so that regulatory decisions can be taken promptly(16).

Under the program, Peripheral Pharmacovigilance Centres will be established in teaching and non-teaching hospitals, clinics and pharmacies in each state and union territory. Each Peripheral Pharmacovigilance Centre will record adverse events and forward the ADR forms and relevant information to its respective Regional Pharmacovigilance Centre on a weekly basis(16).

The Regional Pharmacovigilance Centres would cover five regions of the country: North, East, Central, West, and South and will be responsible for recording ADR data locally and scrutinizing data received from the Peripheral Pharmacovigilance Centres situated in their respective regions. Each Regional Pharmacovigilance Centre will subject its data to causality assessment and also report to its Zonal Pharmacovigilance Centre(16).

Two Zonal Pharmacovigilance Centres have been established: at KEM Hospital, Mumbai and at All India Institute of Medical Sciences, New Delhi. In addition to generating its own ADR data and performing causality assessment, each Zonal Pharmacovigilance Centre would also prepare reports for the National Pharmacovigilance Centre and conduct special

pharmacovigilance projects on any drug of special concern to the National Pharmacovigilance Programme(17).

The National Pharmacovigilance Centre would recommend the Central Drugs Standard Control Organization regarding regulatory actions (including amendments to label and suspension or withdrawal of the product) based on the adverse drug reaction data generated in the country and Periodic Safety Update Reports submitted by pharmaceutical companies. It would disseminate relevant information through adverse drug reaction news bulletins, drug alerts and seminars. As a part of international collaboration, the National Pharmacovigilance Centre will network with national pharmacovigilance bodies from other countries and also provide data for the World Health Organization International Drug Monitoring program(16).(Fig.3)

## The Representation of Pharmacovigilance Systems:

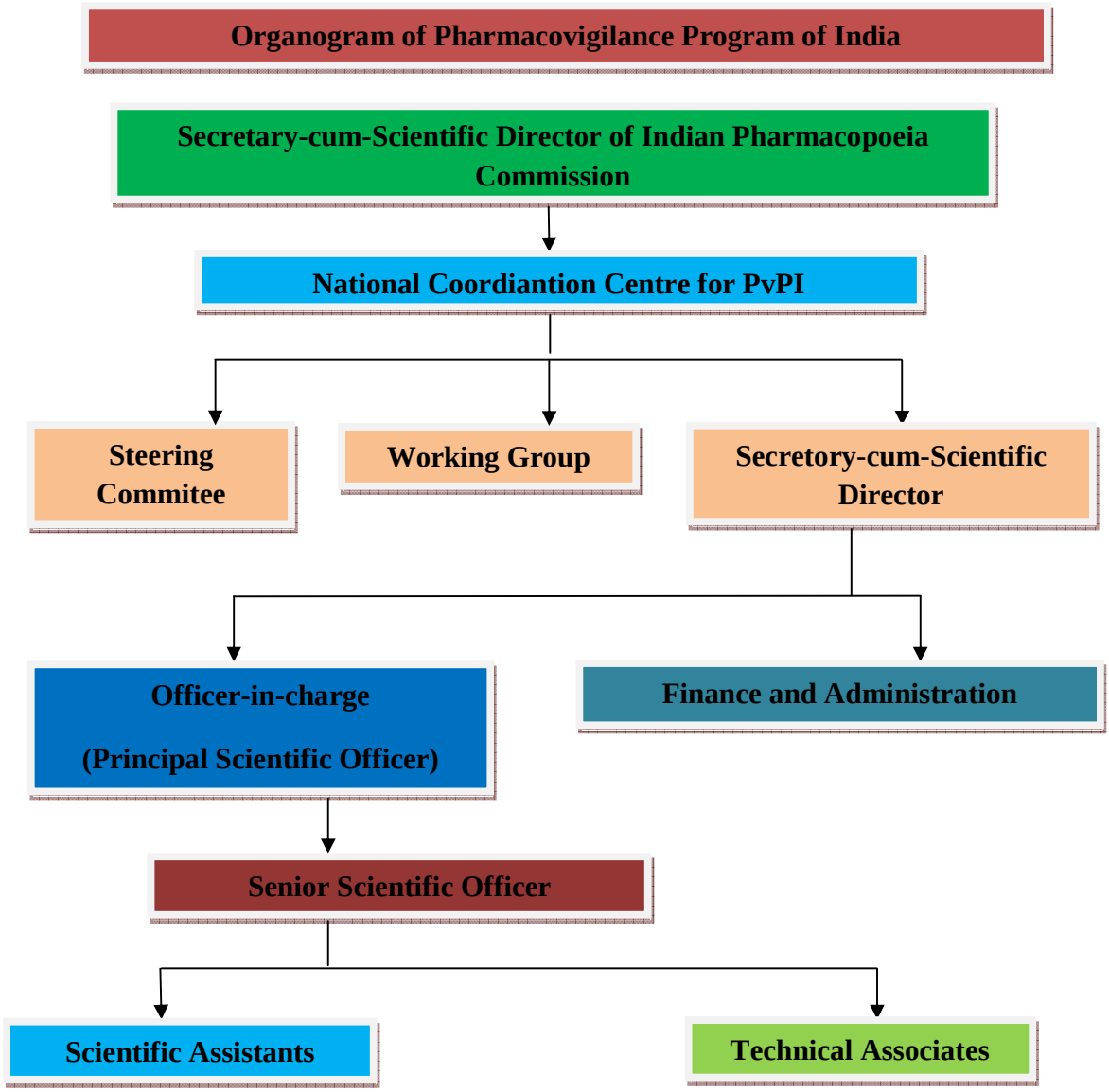



**Figure 3: Representation of Pharmacovigilance Systems (24).**

**Functional Objectives of Pharmacovigilance Program of India**

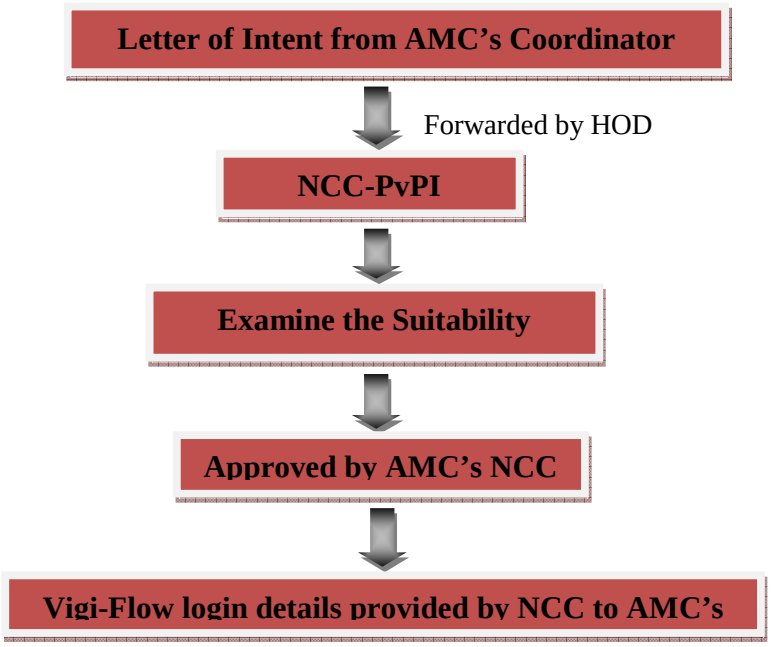
- Creating a nation-wide system for patient safety reporting.
- Identifying and analysing the new signal (ADR) from the reported cases.
- Analysing the benefit - risk ratio of marketed medications.
- Generating the evidence based information on safety of medicines.
- Supporting regulatory agencies in the decision-making process on use of medications.
- Communicating the safety information on use of medicines to various stakeholders to minimise the risk.
- Emerging as a national centre of excellence for pharmacovigilance activities.
- Collaborating with other national centres for the exchange of information and data.

Management (24).

**Roles & Responsibilities of PvPI Personnel at ADR Monitoring Centre (AMC)**

1. At PVPI - AMC, the designated Centre Co-ordinator is responsible for the proper functioning of AMC. In absence of the coordinator, the designated Sub-coordinator is responsible for the smooth functioning of the centre.
2. The Technical Associate appointed by NCC will be responsible for the collection and follow up of ADRs, which have to be reported to the AMC coordinator, all the scrutinized and signed ADR reports should be entered in Vigi-Flow by technical associate. Every report has to be sent to the central assessment at NCC.
3. Collection, checking completeness for a valid case, causality assessment and scrutinizing the ADR reports received will be done as per SOPs by Centre Coordinator/ Sub-Coordinator.
4. The centre coordinator is responsible for sending the monthly reports of their AMC to NCC.
5. Sensitization of the physicians/ healthcare professionals/ students/ patients of the hospitals for spontaneous ADRs reporting by various modes (lectures on ADR reporting, email, telephone, pamphlet and newsletter) should be undertaken by the centre coordinator.
6. Feedback to all healthcare professionals involved in reporting, should be sent by the AMC Centre Coordinators (Fig.4) (24).

## The ADR journey: From AMC to WHO-UMC



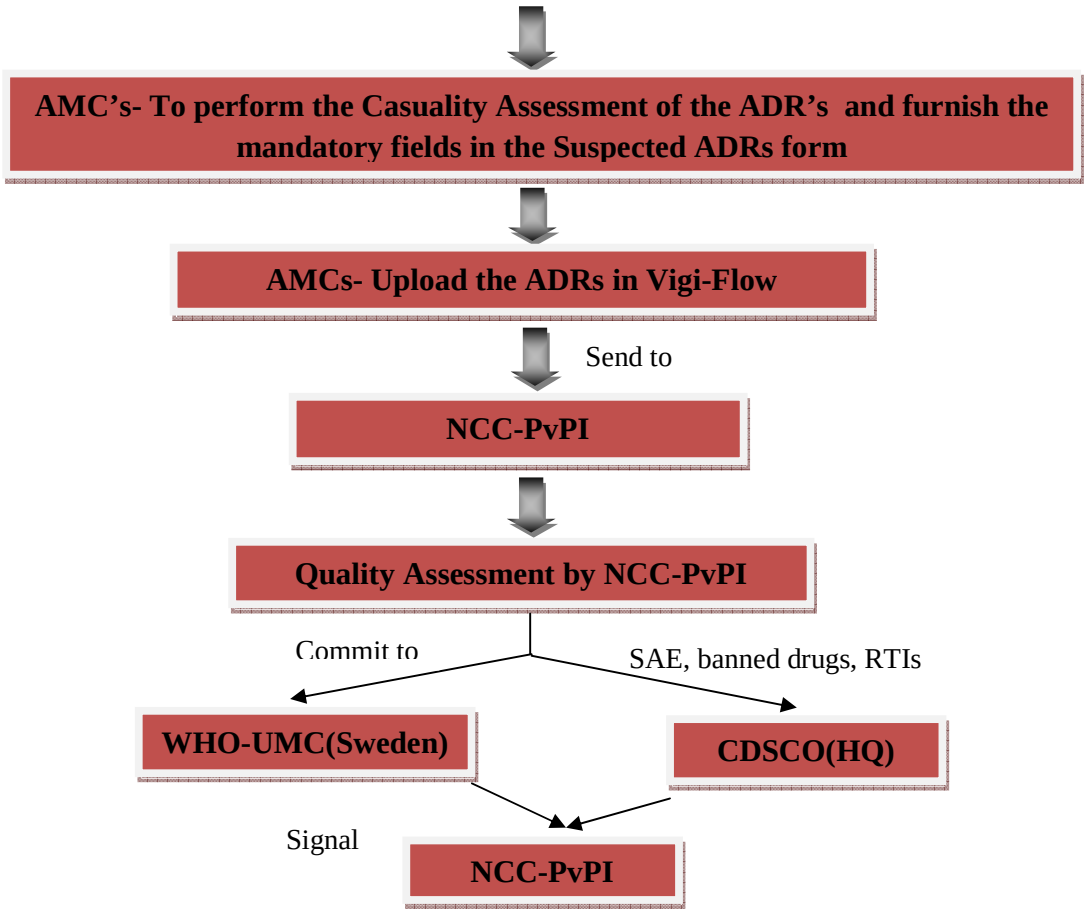



**Figure 4: ADR journey:From AMC to WHO-UMC.** (24).

**Loopholes exaggerating the dissemination of ADRs despite the functional PvPI**

A number of studies conduct throughout the world have demonstrated that ADRs significantly decrease the quality of life, increase hospitalization, prolong hospital stay and increase mortality. A landmark study by Lazarou in 1998 demonstrated ADRs to be the $4^{th}$ – $6^{th}$ leading cause of death in the US and ADRs are estimated to cause 3-7% of all hospital admission (9).

More than half of these ADRs are left unrecognized by the physicians on admission and ADRs may serve as a protagonist for death of 15 of 1000 patients admitted (10). The huge financial cost of ADRs to the healthcare system also worsened the situation critically. With more new medicines beaing approved for marketing more quickly without long-term safty studies by the regulatory authorities and switching of prescription-only medicine (PMO) to over the –counter (OTC) to be used more widely by patients for self-medication , the general public is arisk of exposing itself to ADRs. As far as our country is concerned where poverty, illiteracy, corruption and practicing by quacks is very rampant, the scenario will be further uglier (9).

In past regulatory agencies and companies based their safety assesment on experiences derived from long-term drug use in the western marketes and there was no real urgency for government to establish a strong pharmacovigilance system of its own. In past

few decades, however, the intervel between when a drug is placed on the market and its subsequent availability in India has decreased considerably so that the much need long-term safety data is no longer available. In addition, India based drug companies raised their to develop and launch new drugs via their individual R&D unit and this has steeped the importance of developing adequates internal pharmacovigilance standards to detect adverse drug event (18).

However, focused vision and effective strategy for developing the pharmacovigilance system, especially in the Drug Controller General of India (DCGI) Office, the lacking factors, requires to be more important along with the funding. Traditionally, pharmacovigilance was never practised in India in pharmaceutical companies, either of an India origin or MNCs, so there is an immense shortage of knowledgeable people who will be able to advice and guide the DCGI on this matter, as pharmacovigilance is a very complex subject, entangled with regulation and complex system. The need there for revolves around to employ a completely independent advisor who has an extensive and practical knowledge on pharmacovigilance, who can act as a pharmacovigilance. Advisor to the Government of India to effectively implement the systems and policies on pharmacovigilance. This will help the DGCI to be the driving force for the activities and implementation of pharmacovigilance(6).

India is a vast country and there is a surfeit of drug brands-more than 6,000 licensed drug manufactures and over 60,000 branded formulations. India amongst the world stands as the fourth largest producer of pharmaceutical and quite recently is also emerging as a clinical trials and health tourism hub(6).

• For a nation with vast area and population like India the pharmacovigilance systems are not well funded and organized to serve patients and the public. The Drug Controller General of India (DCGI) Office, which handles the pharmacovigilance system is embedded within the Ministry of Health and Family Welfare. Yet there is very little sharing of information on ADRs between the regulatory authority and health professionals. There is also an extreme shortage of qualified trained people to handle pharmacovigilance within the DCGI. The World Bank has made The National Pharmacovigilance Program to be functional at present by providing the necessary funding, but the budget of Health Ministry has not provided even a minute support. However, along with the funding few more critical factors that are needed to be stressed upon are focused vision and effective strategy for developing the pharmacovigilance systems, especially in the DGCI office, where in the will and strong commitment for carrying out the practice are still lacking(6).

• The information obtained to date in the zonal centres from various peripheral centres is often poor and not well-analyzed. Research on ADRs in India is carried out limitedly and that too is insufficient, hence the exact incidence of specific ADRs is unknown(19). On an educational scenario, various local teaching hospitals in India carry out some work on pharmacovigilance as a part of postgraduate theses, but the project work is rarely shared with the regulatory authorities or other peer groups within the country. Contributing further, these hospitals never to the pharmaceutical manufacturer regarding the particular causative product and the ADRs. Even the reporting forms used by various people engaged in some pharmacovigilance work hugely differ from the reporting form used by the National Pharmacovigilance Program, which in turn creates an extremely hassle work to transfer data to the national database, even if this has been shared by the various parties(20).

• Supportively, understanding by healthcare professionals (both in rural areas and urban cities and hospitals) and knowledge and motivation for pharmacovigilance itself is almost negligible. There is hardly any

encouragement from the department of health to provide more training and create more awareness amongst them for better reporting(21).

• ADR reporting to NPP or Pharmaceutical Manufacturers is seldom by the healthcare professionals thereby reflecting their lack of confidence or trust on executing the same. Ironically the personnel mentioned above display significant interest to report as well as publish the ADRs in the form of case reports to reputed journals in view of broadening their publication bank(22).

**Conclusion**

Adverse Drug Reactions (ADRs) relating to any kind of medicine in today's world seem to be a great point of discussion in the field of medicine as they prove to be life-threatening and fatal in various patient population. Monitoring and most importantly reporting these reactions form the basis of practice of Pharmacovigilance. This practice has spread it's branches in most of the developing and certainly in all developed nations, and is working rigorously in encountering the ADR's spreadibility across the globe as a result of effective policies made by the WHO-UMC programme for the reporting system. Even in India, the Pharmacovigilance Program of India has been the backbone for dealing with the mammoth muddle of ADRs since 2005 with it's various centres across the whole nation making the count upto 33 with the major one being All India Institute of Medical Sciences(AIIMS), Delhi. The complete framework of the working protocol of NCC, PvPI describes the solemnity of the workforce of PvPI towards the discussed issue. Inspite of having an organised and structured body for dealing with ADRs, still there are some loopholes at various levels, which act as horns in the working path of the organisation thereby reflecting upon the body's efficiency negatively to some extent. Henceforth, these loopholes if dealt appropriately could result in a positive outcome for the progression of this field in this nation so that this complicated problem could be dealt effectively and therefore the main aspect which centres around safety of medicines would be ensured completely to a greater extent.

REFERENCES:

1. Zolezzi M, Parsotam N. Adverse drug reaction reporting in New Zealand: implications for pharmacists. Therapeutics and clinical risk management. 2005;1(3):181.

2. Shah S, Shah H, Khaskheli M-N, Akhtar J. Adverse drug reactions: clinical assessment of drug induced disease. J Ayub Med Coll Abbottabad. 2005;17(1):89-91.

3. Brvar M, Fokter N, Bunc M, Mozina M. The frequency of adverse drug reaction related admissions according to method of detection, admission urgency and medical department specialty. BMC Pharmacology and Toxicology. 2009;9(1):8.

4. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Safety. 1994;10(2):93-102.

5. Organization WH. WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems. 2004.

6. Biswas P, Biswas AK. Setting standards for proactive pharmacovigilance in India: The way forward. Indian Journal of Pharmacology. 2007;39(3):124.

7. Pirmohamed M, Breckenridge AM, Kitteringham NR, Park BK. Fortnightly review: adverse drug reactions. BMJ: British Medical Journal. 1998;316(7140):1295.

8. Härmark L, Van Grootheest A. Pharmacovigilance: methods, recent developments and future perspectives. European journal of clinical pharmacology. 2008;64(8):743-52.

9. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Jama. 1998;279(15):1200-5.

10. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug

events in ambulatory care. New England Journal of Medicine. 2003;348(16):1556-64.
11. Olsson S. Pharmacovigilance training with focus on India. Indian Journal of Pharmacology. 2008;40(Suppl1):S28.
12. Kumar A. Past, present and future of pharmacovigilance in India. Systematic Reviews in Pharmacy. 2011;2(1):55.
13. Foy M, Barrow P, Raine JM. Spontaneous Reporting: United Kingdom. Mann's Pharmacovigilance. 2014:185-201.
14. Vaqué A, Sust M, Gascón N, Puyada A, Videla S. A Review of Safety Data from Spontaneous Reports on Marketed Products Containing Tramadol and Celecoxib: A Vigibase Descriptive Analysis. Adv Pharmacoepidemiol Drug Saf. 2014;3(164):2167-1052.1000164.
15. Kulkarni R. Reporting systems for rare side effects of non-narcotic analgesics in India. Problems and opportunities. Medical toxicology. 1985;1:110-3.
16. Dhikav V, Singh S, Anand K. Adverse drug reaction monitoring in India. J Indian Acad Clin Med. 2004;5:27-3.
17. Bavdekar SB, Karande S. National pharmacovigilance program. Indian pediatrics. 2006;43(1):27.
18. Aripin knbn. Academic division of child health school of graduate entry medicine and health: University of Nottingham; 2010.
19. DE A, BALA N. Current problems and future aspects of pharmacovigilance in India.2011.
20. Gentle M. The CRM project management handbook: building realistic expectations and managing risk: Kogan Page Publishers; 2005.
21. Albrecht TL, Penner LA, Ruckdeschel JC. Understanding patient decisions about clinical trials and the associated communication process: A preliminary report. Journal of Cancer Education. 2003;18(4):210-4.
22. Hurwitz B, Sheikh A. Health care errors and patient safety: John Wiley & Sons; 2011.
23. Newsletter, Pharmacovigilance Programme of India (PvPI), April 2014, Vol.4, 1.
24 http://ipc.nic.in/writereaddata/linkimages /pvpi-2611733527.pdf