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# Pharmacovigilance: A Discourse Functional Perspective

**SK. Arifa Begum[1]*, G. Pooja[1], K. Niharika[1], K. Padma Latha[1]**
*1.Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada-521108, A.P, India.*

## ABSTRACT

Pharmacovigilance is an integral part of clinical research. The potential awareness regarding adverse drug reactions has resulted in the emergence of the practice of Pharmacovigilance. Both clinical trials safety and post marketing pharmacovigilance are very significant in ensuring the drug safety. Pharmacovigilance methods can be categorized as Passive surveillance, Active surveillance, Comparative observational studies, targeted clinical investigations and Descriptive studies. The Central Drugs Standard Control Organization (CDSCO) already initiated a nationwide Pharmacovigilance programme under the aegis of Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare and Government of India. The pharmacovigilance system in India has to be refined with the collaboration of pharmacovigilance experts. Implementation of a robust pharmacovigilance program in India in accordance with the objectives and recommendations of World Health Organization by Central Drugs Standard Control Organization is a prerequisite. It is the need of the hour to improve communication between the healthcare professionals and the public; and educating the health professionals well to understand the benefits/ risks of medicines they prescribe. Developing own national database and sharing information with other regulatory agencies will contribute a lot of required information from worldwide data to take the correct decision on medicines and products.

**Keywords:** Pharmacovigilance, adverse drug reactions, central drugs standard control organization, drug safety.

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# INTRODUCTION

Drugs are used to treat illnesses as they can able to alter physiological functions in the body. However, due to various factors they always pose unwanted or unintended effects known as adverse drug events[1]. An adverse event is defined as any un toward medical occurrence that may present during treatment with a drug but which does not necessarily have a relationship with its use[2].The under-reporting of adverse drug reactions is the major setback worldwide which may be attributed to the lack of time and report forms. It has been known that World Health Organization has initiated the program of reporting all adverse reactions possessed by the drugs[3]. The potential awareness about the adverse drug reactions has resulted in the emergence of the practice of Pharmacovigilance, which is defined according to World Health Organization, as the branch of pharmacological science dealing with the detection, assessment, understanding and prevention of adverse effects, in particular the long-term and short-term adverse effects of medicines[4,5]. Recently, herbal, traditional and complementary medicines, blood products, biologicals, vaccines as well as medical devices have been included as a part of Phrmacovigilance concerns[6]. Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product lifecycle especially in ensuring the safety[7]. It is widely accepted that a drug has to pass through the phases of clinical trials to establish its safety and efficacy before it is launched in to the market. However, clinical trials offer many limitations like exclusion of some population groups such as children, pregnant women and old age population which is not studied during the trials. Further some other factors causing adverse drug reactions such as genetic factors, environmental factors and drug-drug interactions may not have been studied during the clinical trials[8]. Hence, systematic pharmacovigilance is essential to build up reliable information on the safety of all category medicines for the development of appropriate guidelines for safe and effective use.

**Importance of Pharmacovigilance**

Even though a pharmaceutical drug is launched in the market, there are still a lot of safety concerns that are unknown about the new drugs. These medicines may adversely affect various patients as they might be using them with several other drugs for different diseases and must be following different traditions and diets. In addition, adverse drug reactions might also occur when drugs are administered along with traditional and herbal medicines that have to be monitored through pharmacovigilance. In few cases, occurrence of adverse drug reactions of certain medicines might be limited to citizens of one country or region. Hence pharmacovigilance is

indeed required for the prevention of drug-induced physical, mental sufferings by patients and to avoid financial risks associated with unexpected adverse effects. Pharmacovigilance proves to be an essential monitoring system for the safety of medicines in a country that can be achieved with the support of doctors, pharmacists, nurses and other health care professionals of the country.

The importance of pharmacovigilance includes:

- Drug monitoring
- Safety monitoring of medicinal products
- Adverse effects of Pharmaceutical preparations
- Reporting of Adverse Drug Reactions
- Product Post marketing surveillance
- Laws and Regulations[9].

**Role of Pharmacovigilance**

The role of pharmacovigilance is to check the safety monitoring of new drugs in clinical trials involves collection of adverse events, laboratory investigation reports and details of the clinical examination of patients. Participation of pharmacovigilance staff may be to the varying extents in all the phases of clinical trials, inclusive of planning, execution, data analysis as well as reporting of safety[10].

Pharmacovigilance plays a vital role to initiate the drug regulatory authorities to go further beyond the approval of new medicines, to encompass a wider range of issues that relates to the safety of medicines, such as clinical trials; the safety of traditional medicines, vaccines and biological products; the reporting of adverse events; continuous follow up with reporters to get further details about a case report; providing an information service to the healthcare professionals as well as patients on product safety; and providing safety expertise to internal cross-functional colleagues[11].

The regulatory authorities also have to understand the significant role of pharmacovigilance in assuring the ongoing safety of medicinal preparations. Further, the cooperation and impact of many stakeholders in society with decision-making powers is a requisite, in order to achieve different roles of pharmacovigilance, that involve, politicians at national, regional and local levels; healthcare administrators; drug regulatory authorities; pharmaceutical companies; healthcare professionals like physicians, dentists, pharmacists and nurses; academic institutions; media representatives; health insurance companies; lawyers; and patient group[12].

**Need for Pharmacovigilance**

Although medicines have led to considerable advancement in the treatment and control of various diseases, they also produce adverse effects on the human body as shown in Table 1 & 2. Most of

the drugs are targeted precisely to the causes and mechanisms of disease, but they may also have minor effects on other parts of the body; or interact negatively with the systems of the particular individual or with other drugs or substances they are administering, or not work well or at all for some, may or all of those who take them for illness.

**Classification of Adverse Drug Reactions[13]:**

Adverse drug reactions are classified by Rawlin & Thompson in1991 as following:

**Table 1: Classification of Adverse Drug Reactions:**

| Type of Adverse Drug Reaction | Examples |
|---|---|
| Dose related or Augmented | Common related to pharmacological action of drug, predictable .e.g., haemorrhage seen with warfarin. Respiratory depression with opiates, bradycardia with β lockers and hypotension with antihypertensive. |
| Non dose related or Bizarre<br>Uncommon,<br>unpredictable, not related to pharmacological action of the drug | Phocomelia with thalidomide tragedy which revolutionized the monitoring to ensure safe and effective use of medicine, effects with cox-2 inhibitors, vaginal cancer in young women with stilbestrol penicillin hypersensivity, malignant hyperthermia |
| Dose and time related or Chronic<br>Uncommon, related to cumulative dose | HPA axis suppression by corticosteroids,<br>Benzodiazepine dependence |
| Time-related or Delayed Uncommon,<br>Usually dose related. Delayed onset | Teratogens, carcinogenesis, tardive dyskinesia |
| Withdrawal or End of use<br>Uncommon.<br>Occurs soon after drug is stopped. | opiate withdrawal syndrome |
| Unexpected failure of therapy or Failure<br>Common, dose-related, often caused by interactions with other drugs | Decreased oral contraceptive effectiveness |

**Table 2: Examples of adverse effects associated with specific medications:**

| Class of Drugs | Adverse Effects |
|---|---|
| Misoprostol (Cytotec), a Labor-Inducing Drug | Abortion, Miscarriage or Uterine Hemorrhage |
| Sedatives and Analgesics such as Diazepam, Morphine etc. | Addiction |
| Thalidomide and Accutane | Congenital malformations |
| Aspirin | Bleeding of the intestine |
| COX-2 inhibitors (Vioxx) | Cardiovascular disease |
| Gentamicin (an antibiotic) | Deafness and kidney failure |
| Propofol (Diprivan) use in children | Death, following sedation |
| Heart's bypass surgery | Dementia |
| Interferon | Depression or hepatic injury |
| Atypical antipsychotic medications | Diabetes |
| Antidepressants | Erectile dysfunction |
| Vaccination | Fever |

| | |
|---|---|
| Corticosteroid based eye drops | Glaucoma |
| Chemotherapy against Cancer, Leukemia etc. | Hair loss and Anaemia |
| Orlistat (Xenical) | Diarrhoea |
| Spinal Anesthesia | Headache |
| Ephedrine, Adderall etc. | Hypertension |
| Ritalin | Insomnia |
| Stavudine or Metformin | Lactic Acidosis |
| Paracetamol | Liver damage |
| Estrogen-containing oral contraceptive pills | Melasma and Thrombosis |
| Fluoroquinolone medications[14, 15, 16] | Irreversible Peripheral Neuropathy |
| Statins | Rhabdomyolysis |
| Withdrawal from Benzodiazepine | Seizures |
| Antihistamines | Drowsiness or Increase in appetite |
| Sildenafil (Viagra) when used with Nitroglycerine | Stroke or Heart attack |
| Fluoxetine and other SSRI Antidepressants | Suicide, increased tendency |
| Long-term use of Metoclopramide and Anti-psychotic medications | Tardive dyskinesia |

**Aim:**

The aim of pharmacovigilance is[17, 18, 19],

- Detection of the frequency of known adverse reactions of drugs.
- Detection and quantification of previously unrecognised severe and unexpected adverse drug reactions to the established drugs and even the minor adverse effects to newer drugs.
- Identification of sub-groups of patient population at specific risk of adverse drug reactions (the risk related to dose, age, gender and underlying disease).
- Continuous monitoring of the safety of medicines throughout the duration of their use, to ensure that their risks/benefits remain acceptable.
- Comparative assessment of adverse drug reaction profile of medicinal preparations within the same therapeutic class.
- Elucidation of a product's pharmacological and/or toxicological properties as well as the mechanism by which adverse drug reactions are produced.
- Detection of significant drug–drug interactions between new medicines and co therapy with products already proven in the market, which may only be detected during widespread use.

**Objectives:**

The major objectives of Pharmacovigilance are[20, 21, 22, 23]

- To improve patient care and safety.
- To ensure public confidence by improving public health and safety.

- To contribute to the identification and assessment of benefit, harm, effectiveness as well as risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
- To promote understanding, education and clinical training in pharmacovigilance and its effective communication to healthcare professionals and the public.
- To promote international co-ordination towards the highest ethical, professional and scientific standards for protecting and promoting safe use of medicines
- To establish a new dimension of transparency, equity and accountability in communicating information regarding drug safety.
- To assess quantitative aspects of benefit/risk analysis and dissemination of information needed to improve prescribing and regulation of drugs.

**Pharmacovigilance Methods**

According to International Conference on Harmonization Efficacy Guidelines (ICHE2E), the pharmacovigilance methods can be classified as[24]:

**Passive surveillance**

(a) Spontaneous reporting system

(b) Case series

**Stimulated reporting**

**Active surveillance**

(a) Sentinel sites

(b) Drug event monitoring

(c) Registries

**Comparative observational studies**

(a) Cross sectional study

(b) Case control study

(c) Cohort study

**Targeted clinical investigations**

**Descriptive studies**

(a) Natural history of disease

(b) Drug utilization study

Pharmacovigilance methods can also be categorized as hypothesis generation methods and hypothesis testing methods as:

**Hypothesis generating methods**

(a) Spontaneous adverse drug reaction reporting

(b) Prescription event monitoring

**Hypothesis testing methods**

(a) Case control study

(b) Cohort studies

(c) Randomized controlled trials

**Framework for Pharmacovigilance In India**[25]

The Central Drugs Standard Control Organization (CDSCO) has taken initiation for a nationwide Pharmacovigilance programme under the aegis of Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare and Government of India. The programme is coordinated by the National Pharmacovigilance Centre at CDSCO.

**Pharmacovigilance guideline for India:**

The International Conference on Harmonization contain six guidelines pertaining to different aspects of drug safety[26,27]:

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-Pharmacovigilanve planning, and

E2F- Development Safety Update Report

Many countries have framed their own pharmacovigilance guidelines with the motive to have a systematic process of drug safety reporting. The USFDA has title 21 of Code of Federal Regulations (chiefly part 312-Investigational New Drug and part 314-Applications for FDA Approval to Market a New Drug) and the European Medicines Evaluation Agency (EMEA) has entire Volume 9A for pharmacovigilance in humans[28]. In contrast, India has only a small section of Schedule Y dedicated to drug safety, which when viewed in light of contemporary global practice, seems to have many lacunae. Thus, there is a strong need that Central Drugs Standard Control Organization must formulate a detailed pharmacovigilance guideline. Such guideline shall cover all relevant areas of pre and post marketing safety, address to current lacunae and bring about clarity on issues. Most significantly, the guidelines shall be in line with the present international scenario, so as to support India's growth as any participant in multinational clinical trials[29].

**PHARMACOVIGILANCE PROGRAMME OF INDIA (PvPI):**

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in association with Indian Pharmacopeia commission, Ghaziabad has initiated a country-wide Pharmacovigilance Programme for protecting the health of the patients by promising drug safety. The Programme is coordinated by the Indian Pharmacopeia Commission, Ghaziabad as a National Coordinating Centre (NCC). Functions of the Indian Pharmacopoeia Commission are illustrated in **Figure 1**. The centre will work under the supervision of a Steering Committee[30]. The Pharmacovigilance Programme of India (PvPI) was started by the Government of India on 14th July 2010 with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordination Centre for monitoring Adverse Drug Reactions (ADRs) in the nation for safe-guarding Public Health. In the year 2010, 22 ADR monitoring centres including AIIMS, New Delhi was set up under this Programme. To safeguard implementation of this programme in a more effective way, the National Coordination Centre was shifted from the All India Institute of Medical Sciences (AIIMS), New Delhi to the Indian Pharmacopoeia Commission, Ghaziabad, Uttar Pradesh on 15th April 2011.

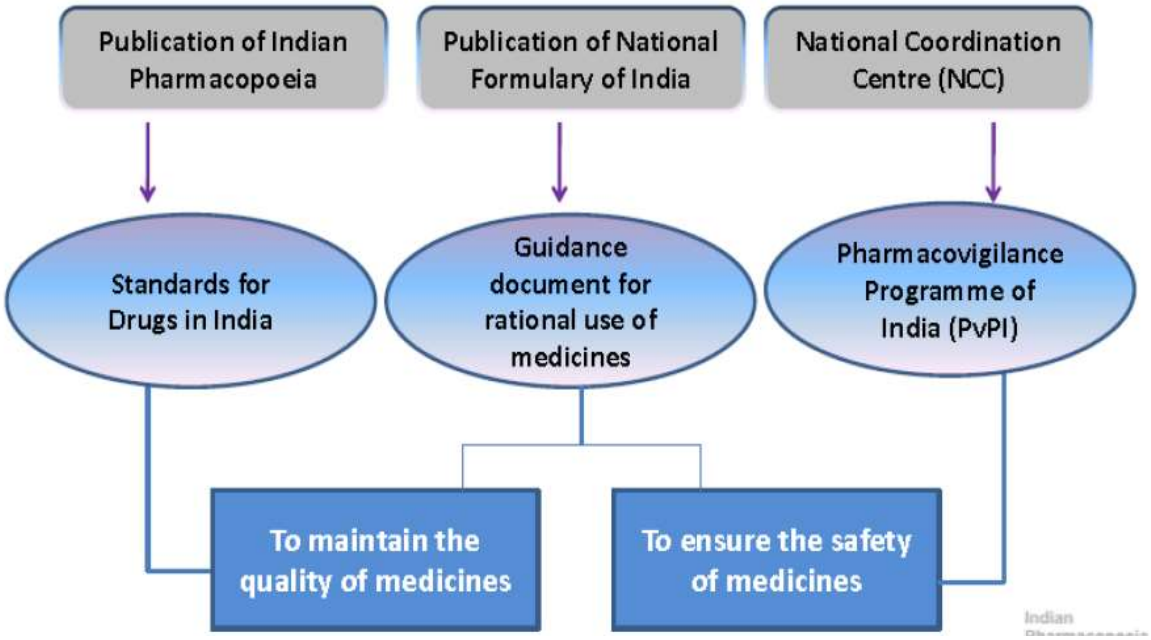


**Figure 1: Functions of Indian Pharmacopoeia Commission (IPC).**

The purpose of the PvPI is to collect data, process and analyze it and use the inferences to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public.

**Mission:** Safeguard the health of the Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use.

**Vision:** To improve patient safety and welfare in Indian population by monitoring the drug safety and thereby reducing the risk associated with use of medicines.

**Objectives**

- To create a country-wide system for patient safety reporting.
- To identify and analyze the new signal (ADR) from the reported cases.
- To analyze the benefit/risk ratio of marketed medicines.
- To develop the evidence based information on safety of medications.
- To support regulatory authorities in the decision-making process on use of medicines.
- To communicate the information on safe and rational use of medicines to various stakeholders to minimize the risk.
- To emerge as a national centre of excellence for pharmacovigilance activities.
- To collaborate with other national centres for the exchange of information and data management.
- To provide training and consultancy support to other national pharmacovigilance centres located across the globe[31].

**IMPLEMENTATION OF PvPI:**

Indian Pharmacopoeia Commission assumed the need for establishing local hospital based centres across the nation for the better patient safety. Monitoring both the known and previously unknown side effects of medicines is important to gather any new available information with respect to their safety profile. In a big country such as India with a population of over 1.2 billion and with vast ethnic variability, different disease prevalence modes, practice of various systems of medicines, different socioeconomic status, it was found significant to have a standardized and robust pharmacovigilance and drug safety monitoring programme for the nation.

**Short term goals:**

- To develop and implement pharmacovigilance system in India.
- To enrol, initially, all MCI approved medical colleges in the program covering north, south, east and west of India.
- To encourage healthcare professionals in reporting of adverse reaction to drugs, vaccines, medical devices and biological products.
- Collection of case reports and data.

**Long term goals:**

- To expand the pharmacovigilance programme to all hospitals (Govt. & Private) and centres of public health programs located across India.
- To develop and implement electronic reporting system (e-reporting).
- To develop reporting culture amongst healthcare professionals.
- To make adverse drug reaction reporting mandatory for healthcare professionals.

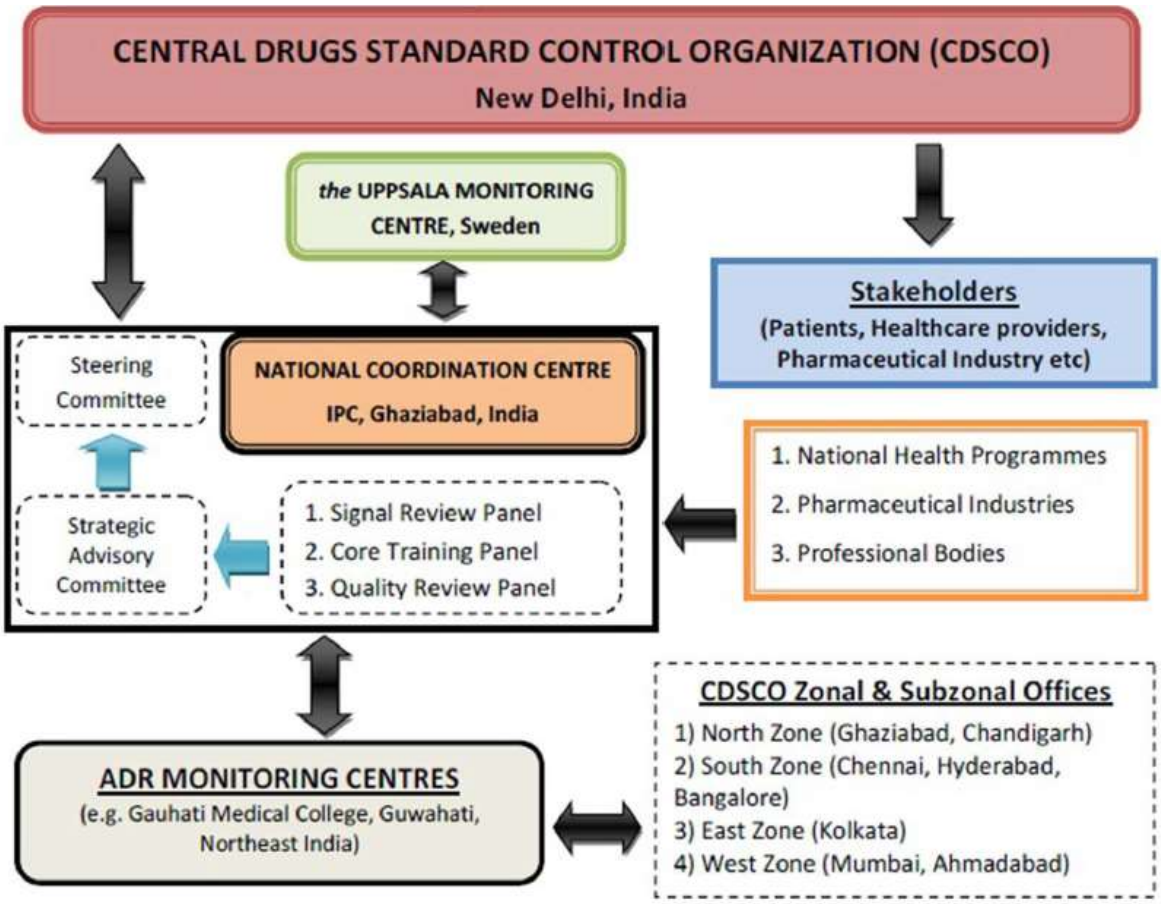


**Figure 2: Pharmacovigilance programme communication and flow of adverse drug reaction reports[32].**

**ISSUES AND PROBLEMS THAT PREVENT TO BUILD A ROBUST PHARMACOVIGILANCE SYSTEM:**

1. Lack of well funding and organization of Pharmacovigilance systems to serve patients and the public in a vast country such as India.
2. Improper analysis of the information obtained from the zonal centers and various peripheral centres.
3. Because of insufficient research on adverse drug reactions in India, the exact incidence of particular adverse drug reactions is unknown.

4. Negligible understanding, knowledge and motivation for pharmacovigilance by healthcare professionals. They are not well encouraged from the department of health to undergo training and get awareness for better reporting.
5. Many consumers' groups in India encourage patients to report any adverse reactions encountered by them, yet there is no information for patients to report adverse drug reactions directly to the regulatory agency.

**FUTURE ASPECTS OF PHARMACOVIGILENCE IN INDIA:**

In the present scenario, there is a strong need to understand the significance of pharmacovigilance and how it affects the life cycle of the product since more and more clinical trials and other clinical research activities are being conducted in India. According to this, Drug Controller General of India (DCGI) should act promptly to improve pharmacovigilance so as to integrate Good Pharmacovigilance Practice into the systems to help ensure regulatory compliance and enhance clinical trial safety and post marketing surveillance. A robust pharmacovigilance system is essential if medicines are to be used rationally and safely. This will benefit all parties inclusive of healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It also helps pharmaceutical industries to monitor their medicines for risk and to devise and implement effective risk management plans to protect their drugs in difficult situations. In order to overcome the problems and challenges facing the development of a robust pharmacovigilance system for India, the following proposals might be helpful[33]:

1. Building and maintaining a robust pharmacovigilance system.
2. Making pharmacovigilance reporting mandatory, initiating pharmacovigilance inspections.
3. High-level discussions with various participants (stakeholders).
4. Strengthening the Drug Controller General of India office with the well trained scientific and medical evaluators for pharmacovigilance.
5. Creating a single country-specific adverse event reporting form that may be used by all.
6. Creating a clinical trial and post marketing database for adverse drug reactions for signal detection and access to all relevant data from various stakeholders.
7. Listing of all new drugs / indications by maintaining a standard database for every pharmaceutical industry.
8. Focused Education and well training of medical students, pharmacists and nurses in the area of pharmacovigilance.

9. Collaborating with various pharmacovigilance organizations in order to improve drug safety. The Uppsala Monitoring Center (UMC) is an example for an international collaboration to establish a harmonized post marketing surveillance database[34].
10. Building a network of pharmacovigilance linked to pharmacopeidemiologists, pharmacoenvironmentologists and academicians.

## CONCLUSION

India is now emerging as a clinical research hub. With introduction of new drugs, a systematic and organized pharmacovigilance system is essential to protect the patients and the public from the potential harm and adverse effects due to some of the new drug molecules. Pharmacovigilance plays a vital role in meeting the challenges offered by the ever increasing range and potency of medicines. The foundation for building a robust pharmacovigilance system has already been initiated and done to some extent by the staff of Drug Controller General of India. However, the pharmacovigilance system in India has to be refined with the collaboration of pharmacovigilance experts. There must be implementation of a robust pharmacovigilance program in India in accordance with the objectives and recommendations of World Health Organization by Central Drugs Standard Control Organization. The perspective of all stakeholders including the bureaucrats and politicians and healthcare professionals must be changed. They should actively participate in the National Pharmacovigilance Program by reporting adverse events and help to ensure that people in India receive safe drugs. Drug Controller General of India should take some firm resolutions and make commitments to make pharmacovigilance mandatory and initiate the practice of pharmacovigilance inspections. Moreover, improving communication between the healthcare professionals and the public; and educating the health professionals to understand the benefits/effectiveness and risk of medicines they prescribe, is the need of the hour. Further, by developing own national database and sharing information with other regulatory authorities will provide the much required information from global data to take the correct decision on medicines and products.

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