# Pharmacovigilance Programme of India

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**Abstract**

*Pharmacovigilance is defined as "the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, principally long term and short term adverse effects of medicines." It is an important and integral part of clinical research. India is the world's second most populated country with over one billion potential drug consumers. Although, India is participating in the Uppsala monitoring center program, its contribution to that database is relatively small. This problem is essentially due to the absence of a robust ADR monitoring system and also the lack of awareness of reporting concepts among Indian health care professionals. The specific aims of pharmacovigilance are to advance patient care and safety in relation to the use of medicines and all medical and paramedical interventions, contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, promising their safe, rational, and more effective use, promote indulgent, education, and clinical training in pharmacovigilance and its effective communication to the public. Pharmacovigilance methods must also be capable to designate which patients are at risk of developing an adverse drug reaction. A suitably working pharmacovigilance system is important if medicines are to be used prudently. It will be advantageous for healthcare professionals, regulatory authorities, pharmaceutical companies and consumers to monitor medicines for risk.*

## Introduction

The world health organization (WHO) initiated a program for reporting all adverse reactions possessed by drugs. Further awareness about adverse drug reactions has resulted in the emergence of the practice and science of pharmacovigilance.[1] The word pharmacovigilance is derived from the Greek word pharmacon meaning 'drug' and the Latin word vigilare meaning 'to keep awake or alert, to keep watch.' Pharmacovigilance is defined as "the pharmacological science relating to the recognition, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines." [2, 3] After discovery and pre-clinical phases, a drug typically undergoes trials in human volunteers. Clinical trials are highly regulated and closely monitored by the investigators and the manufacturing company. It is a mandatory regulatory requirement to report all the adverse events in a clinical trial setting in a given time frame. In the clinical trial setting, "good clinical practice" has moved pharmacovigilance from a reactive to a proactive approach. A robust, well-defined system for monitoring adverse events is in a place for evaluating the safety of the drugs. [4] Pharmacovigilance serves various roles such as identification, quantification and documentation of drug-related problems which are responsible for drug-related injuries. [5, 6]

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India is the world's second most populated country with over one billion potential drug consumers. Although, India is participating in the Uppsala monitoring center program, its contribution to this database is relatively small. This problem is essentially due to the absence of a robust adverse drug reaction monitoring system and also the lack of awareness of reporting concepts among Indian health care professionals. In India, it is very important to focus the attention of the medical community on the importance of adverse drug reporting to ensure maximum benefits for public health and safety. For regulatory reporting purposes, if an event is instinctively reported, even if the relationship is mysterious or unstated, it meets the definition of an adverse drug reaction.

An adverse event is any untoward medical occurrence in a patient who is administered a medicinal product and which doesn't necessarily have a causal relationship with this treatment. Adverse drug reactions are noxious and unintended responses to a medicinal product. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence are supposed. [7, 8]

A serious adverse event (SAE) is any untoward medical manifestation, that at any dose:

- Results in death

- Is life-threatening (well-defined as an event in which the subject was at risk of death at the time of the event)
- Requires in-patient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon suitable medical & scientific judgment, may require intervention to prevent one of the serious outcomes as listed above). [9, 10]

This review article provides a brief overview of the current situation and the future prospects of pharmacovigilance in India.

The Pharmacovigilance exertion in India is organized by The Indian Pharmacopoeia Commission and conducted by the Central Drugs Standard Control Organization (CDSCO). The main responsibility of the IPC is to maintain and develop the pharmacovigilance database consisting of all suspected serious adverse reactions to medicines observed. Indian Pharmacopoeia Commission (IPC) is functioning as a National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI). National Coordination Centre is operating under the observation of steering committee which recommends procedures and guidelines for regulatory interventions. The main duty of National Coordination Centre is to monitor all the adverse reactions of medicines being observed in the Indian population and to develop and maintain its own pharmacovigilance database.

**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 is initiating a nation-wide Pharmacovigilance Programme for protecting the health of the patients by promising drug safety. The Programme shall be coordinated by the Indian Pharmacopeia commission, Ghaziabad as a National Coordinating Centre (NCC). The center will operate under the supervision of a Steering Committee.

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 country 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.

Before registration and marketing of medicine in the country, its safety and efficacy experience is based chiefly on the use of the medicine in clinical trials. These trials primarily detect common adverse reactions. Some important reactions, such as those, which take a long time to develop, or those, which occur rarely, may not be detected in clinical trials. In addition, the controlled conditions under which medicines are used in clinical trials do not necessarily reflect the way they will be used in practice. For a medicine to be considered safe, its predictable benefits should be greater than any associated risks of harmful reactions. So, in order to gain a complete safety profile of medicine, a continuous post-marketing monitoring system i.e. pharmacovigilance is essential. In order to screen the safety of medicine, information from many sources is used for pharmacovigilance. These include spontaneous (ADRs) reporting mechanism; medical literature published worldwide, action taken by regulatory authorities in other countries, etc. Meanwhile there exist considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of employing appropriate risk management (there is a need to engage healthcare professionals and the public at large, in a well-structured programme to build synergies for monitoring adverse drug reactions in the country). The purpose of the PvPI is to collate 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 nation-wide system for patient safety reporting
- To identify and analyze the new signal (ADR) from the reported cases

- To analyses the benefit - risk ratio of marketed medications
- To generate the evidence based information on safety of medicines
- To support regulatory agencies in the decision-making process on use of medications
- To communicate the safety information on use of medicines to various stakeholders to minimize the risk
- To emerge as a national center of excellence for pharmacovigilance activities
- To collaborate with other national centers for the exchange of information and data management
- To provide training and consultancy support to other national pharmacovigilance centers located across globe[11]

**Implementation of PvPI**

IPC assumed the need for establishing local hospital based centers across the nation for the better patient safety. It was significant to monitor both the known and previously unknown side effects of medicines in order to determine any new information available in relation to their safety profile. In an enormous country like India with a population of over 1.2 billion and with vast ethnic variability, different disease prevalence patterns, practice of different systems of medicines, different socioeconomic status, it was imperative 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 enroll, 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 centers 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 ADR reporting mandatory for healthcare professionals

Effective communication channels are the key to a successful running of PvPI. The Indian pharmacopoeia commission was summarized in Figure 1. Program communications is described in Figure 2 and ADR monitoring centers are displayed in Figure 3. The functions of the ADR monitoring center are shown in Figure 4 with regional resources for training in India summarized in figure 5. The process of collection, analysis and evaluation of ADRs are described in Figure 6.

**Causes of failure of implementation of pharmacovigilance in India**

Many new drugs are being introduced in the country, so there is a need to improve the pharmacovigilance system in order to protect the Indian population from potential harm that may be caused by some of the new drugs. However, there are numerous issues and problems that have prevented building a robust pharmacovigilance system, which are described below:

1. Pharmacovigilance systems are not well-funded and systematized for a vast country like India to serve patients and the public.
2. The data obtained to date in the zonal centers from various peripheral centers is often poor and not well-analyzed. There is inadequate research on ADRs in India, so the exact incidence of specific ADRs is unknown.
3. Involvement of healthcare professionals (both in rural areas and urban cities and hospitals) and knowledge and motivation for pharmacovigilance is negligible. There little encouragement from the department of health to provide more training and create more awareness amongst them for better reporting.
4. In India, there are several consumers' groups who encourage patients to report any adverse reactions encountered by them, although there is no information for patients to report ADRs directly to the regulatory authority.

**Pharmacovigilance Methods**

**Passive surveillance:**

- encompasses all spontaneous AEFI reporting
- from immunisation service providers / hospitals / patients

- up to next levels: state/territory then national (TGA) and then global

**Active surveillance:**

- primarily used for characterization of the AEFI profile, rates and risk factors
- logistical and resource constraints limit wide application
- only for selected AEFI at selected institutions (sentinel) sites
- can also be carried out in the community setting (e.g. cohort event monitoring)

**Ad hoc studies:**

- epidemiological studies (e.g. cohort study, case-control study, case series studies)
- focus on selected vaccine safety concerns (e.g. testing causality hypotheses)
- retrospective or prospective

**I. Passive surveillance**

**a) Spontaneous reports**

A spontaneous report is a voluntary communication by healthcare professionals or consumers to a company, regulatory authority or other organization that defines one or more adverse drug reactions (ADRs) in a patient who was given one or more medicinal products and that does not originate from a study or any structured data collection scheme. [12] It plays a key role in the identification of safety signals once a medicine is marketed. In various occurrences, spontaneous reports can vigilant a company to rare adverse events that were not noticed in earlier clinical trials or other pre-marketing studies. It can also deliver important information on at-risk groups, risk factors and clinical features of known serious ADRs. [13-16]

Newly, systematic methods for the recognition of safety signals from spontaneous reports have begun to be used. Several of these methods are static in development and their utility for identifying safety signals is being assessed. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection. [17-19] Data mining techniques have also been used to examine medicine-medicine interactions [20], but these techniques should always be used in conjunction with, and not in place of, analyses of single case-reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals that merit further evaluation. However, this tool does not quantify the magnitude of risk, and caution should be exercised when comparing medicines. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence reporting of spontaneous adverse events are not removed from data mining. The results of data mining should thus be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate for different medicines and the many potential biases inherent in spontaneous reporting. All signals should be evaluated while recognizing the possibility of false-positives. In addition, the absence of a signal does not mean that a problem does not exist.

**b) Case series**

A series of case-reports can deliver signs of an association between a medicine and an adverse event, but they are normally more valuable for producing theories than for confirming a relationship between medicine exposure and outcome. [21, 22]

**c) Stimulated reporting**

A number of methods have been used to reassure and simplify reporting by health professionals in definite circumstances for new products or for partial time periods. [23] Such systems comprise on-line reporting of adverse events and methodical motivation of reporting of adverse events based on a pre-designed method. While these methods have been shown to advance reporting, they are not invulnerable to the confines of passive surveillance, particularly discriminating reporting and imperfect information. This should be considered as a procedure of spontaneous event reporting, and thus data acquired from stimulated reporting cannot be used to make precise incidence rates, but reporting rates can be projected.

**II) Active surveillance**

Active surveillance, in contrast to passive surveillance, pursues to determine the particular number of adverse events through a constant pre-organized process. [24] In common, it is more achievable to acquire wide-ranging data on discrete adverse event reports through an active surveillance system than through a passive reporting system.

**a) Sentinel sites**

Active surveillance can be attained by revising medical records or questioning patients and/or physicians in a section of sentinel sites to guarantee that comprehensive and precise

data on reported adverse events are collected from these sites. The selected sites can deliver information, such as data from specific patient subgroups, which would not be accessible in a passive spontaneous reporting system. [25] The major weaknesses of sentinel sites comprise difficulties with selection bias, small numbers of patients and augmented costs. Active surveillance with sentinel sites is most effective for those medicines used primarily in institutional settings such as hospitals, nursing homes and haemodialysis centers. Institutional settings may use certain medicinal products more commonly and can deliver an arrangement for enthusiastic reporting. Intensive monitoring of sentinel sites can also be supportive in recognizing risks among patients taking orphan medicines.

**b) Medicine event monitoring**

This is a process of active Pharmacovigilance surveillance. Studies using this process are cohort-based and prospective and observational. For medication event monitoring, patients can be acknowledged from electronic or automated health insurance claims. A single prescription or a series might be composed over the period of monitoring. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to acquire outcome data. Requests for data on patient demographics, indication for treatment, duration of therapy, dosage, clinical events, reasons for termination and applicable past history can be involved in the questionnaires. [26-30] The restrictions of medicine event monitoring can comprise the poor physician and patient reply rates. [31, 32]

**c) Registries**

A registry is a list of patients presenting with the identical representative(s). This representative can be a disease (disease registry) or a specific exposure (medicine registry). Both types of registrations, which vary only by the type of patient data of interest, can gather a cordless of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help to gather data on medicine exposure and other factors related to a clinical condition. A disease registry might also be used as a veil for a case control study associating the medicine exposure of cases recognized from the registry with controls selected either from patients with another condition within the registry, or from patients outside the registry.

Exposure (medicine) registries address populations exposed to the medicines of interest to govern if a medicine has a distinct influence on this group of patients. Some exposure (medicine) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can quantity incidence, but, without a comparison group, cannot deliver proof of association. This type of registry can be very valuable when examining the safety of an orphan medicine indicated for a specific condition. Customary epidemiological methods are a key constituent in the evaluation of adverse events. There are numerous of observational study designs that are valuable in validating signals from spontaneous reports, case series or medicine event monitoring. The most imperative of these designs is cross-sectional studies, case-control studies and cohort studies. [33, 34]

**d) Cross-sectional study (survey)**

Data collected on inhabitants of patients during a specified interval of time, regardless of exposure or disease status constitute a cross-sectional study. These types of studies are principally used to collect data for surveys or for ecological analyses. The major disadvantage of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be straight addressed. These studies are paramount used to scrutinize the prevalence of a disease at one time point or to inspect trends over time, when data for serial time points can be captured. These studies can also be used to observe the crude relationship between exposure and outcome in ecological analyses. Cross-sectional studies are utmost valuable when exposures do not change over time.

**e) Case-control study**

In a case-control study, cases of disease (or events) are recognized. Controls, or patients in whom the disease or event of interest has not happened, are then carefully chosen from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls exemplifies the prevalence of exposure in the source population. The exposure status of the two groups is then paralleled using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be acknowledged from an existing database or using data collected unambiguously for the purpose of the study. If safety data is sought for special populations, the cases and controls can be stratified according to the population of interest. For rare adverse events, prevailing large population-based databases are a useful and efficient means of providing the necessary data on medicine exposure and medical outcome relatively quickly. Case-control studies are predominantly useful when the goal is to examine whether there is a relationship between a medicine (or medicines) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can

include conditions, such as renal and hepatic dysfunction, which might modify the relationship between the medicine exposure and the adverse event. Under particular conditions, a case-control study can deliver the complete incidence rate of the event.

**f) Cohort study**

In a cohort study, a population at risk for the disease (or event) is monitored over time to record the occurrence of the disease (or event). Information on exposure status is accessible during the follow-up period for each patient. A patient might be exposed to a medicine at one time during follow-up, but not exposed at another time. Meanwhile the population exposure during follow-up is acknowledged, incidence rates can be calculated. In many cohort studies concerning medicine exposure, appraisal cohorts of interest are selected on the basis of medicine use and monitored over time. Cohort studies are useful when there is a requisite to know the incidence rates of adverse events in addition to the relative risks. Multiple adverse events can also be scrutinized using the similar data source in a cohort study. Conversely, it can be problematic to recruit adequate numbers of patients who are exposed to the medicine of interest or to study very rare outcomes. Similar to case-control studies, patients in cohort studies can be recognized from large automated databases or from data collected precisely for the study at hand. In addition, cohort studies can be used to scrutinize safety issues in special populations through oversampling of these patients or by stratifying the cohort if adequate numbers of patients are included. There are numerous automated databases obtainable for pharmacoepidemiological studies.[35, 36, 37] They consist of databases that contain automated medical records or automated accounting/billing systems. Databases that are fashioned from accounting/billing systems might be connected to pharmacy claims and medical claims databases. These datasets may contain millions of patients. Subsequently, they are fashioned for administrative or billing purposes; they might not have all the detailed and precise information needed for some research, such as authenticated diagnostic information or laboratory data. Even though medical records can be used to establish and authenticate test results and medical diagnoses, one should know about the privacy and privacy regulations that apply to patient medical records.

**g) Targeted clinical investigations**

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called in to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamics and pharmacokinetic studies might be conducted to define whether a particular dosing instruction can put patients at an increased risk of adverse events. Moreover, based on the pharmacological properties and the predictable use of the medicine in general practice, conducting specific studies to scrutinize potential medicine-medicine interactions and food-medicine interactions might be entitled to. These studies can comprise population pharmacokinetics studies and medicine concentration monitoring in patients and normal volunteers. One drawback of this method is that the outcome measure might be too shortened and this might have an influence on the quality and eventual usefulness of the results of the trial. Large, simplified trials are similarly resource-intensive.

**Descriptive studies**

Descriptive studies are a vital component of Pharmacovigilance, even though not for the recognition or authentication of adverse events related to medicine exposures. These studies are principally used to acquire the circumstantial rate of outcome events and/or to inaugurate the prevalence of the use of medicines in specified populations.

**a) Natural history of disease**

The discipline of epidemiology initially concentrated on the natural history of disease, including the features of diseased patients and the dissemination of disease, in particular populations, as well as appraising the incidence and prevalence of possible outcomes of interest. These outcomes of interest currently comprise a narrative of disease treatment outlines and adverse events. Studies that scrutinize precise facts of adverse events, such as the contextual incidence rate of, or risk factors for, the adverse event of interest, can assist in placing spontaneous reports into viewpoint. [38]

**b) Medicine utilization study**

Medicine utilization studies (DUS) define how a medicine is marketed, prescribed and used in a population, and how these factors affect outcomes (including clinical, social and economic outcomes). [39]These studies deliver data on definite populations, such as the elderly, children, or patients with hepatic or renal dysfunction, habitually stratified by age, sex, concomitant medication and other characteristics. It can be used to define if a product is being used in these populations. It has been used to define the effect of regulatory actions and media courtesy on the use of medicines, as well as to improve evaluations of the economic burden of the cost of medicines. It can also be used to scrutinize the relationship between optional and definite clinical practice. These studies can help to govern whether a medicine has the probable for abuse by inspecting whether patients are taking mounting doses or whether there is an indication of incorrect duplication

prescribing. The main limitations of these studies can comprise an absence of clinical outcome data or information on the indication for use of a product.

**Future aspects of pharmacovigilance in India**

A suitably working pharmacovigilance system is vital if medicines are to be used safely. It will advantage all parties including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It aids pharmaceutical companies to monitor their medicines for risk and to devise and implement effective risk management plans to save their drugs in difficult circumstances.

Having considered the problems and challenges facing the development of a robust pharmacovigilance system for India, the following proposals [40] might be follows:

1. Building and maintaining a robust pharmacovigilance system.
2. Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections.
3. High-level discussions with various stakeholders.
4. Strengthen the drug control general of India office with trained scientific and medical assessors for pharmacovigilance.
5. Creating a single country-specific adverse event reporting form to be used by all.
6. Creating a clinical trial and post marketing database for SAEs / SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders.
7. List all new drugs / indications by maintaining a standard database for every pharmaceutical company.
8. Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance.
9. Collaborating with pharmacovigilance organizations in enhancing drug safety with advancements in information technology, there has been the emergence of new opportunities for national and international collaborations that can enhance postmarking surveillance programs and increase drug safety. [41, 42]
10. Building a network of pharmacovigilance and pharmacopeidemiologists in India.

**Conclusion**

Pharmacovigilance systems are needed to safeguard public health. Diminutive prominence has been put into engendering information that can assist a healthcare professional or a patient in medication decision-making processes. The collecting and dissemination of this information is a chief goal of Pharmacovigilance. Pharmacovigilance methods must be capable to designate which patients are at risk from medication use. A suitably working Pharmacovigilance system is important if medicines are to be used prudently. It will be advantageous for healthcare professionals, regulatory authorities, pharmaceutical companies and consumers to monitor medicines for risk.

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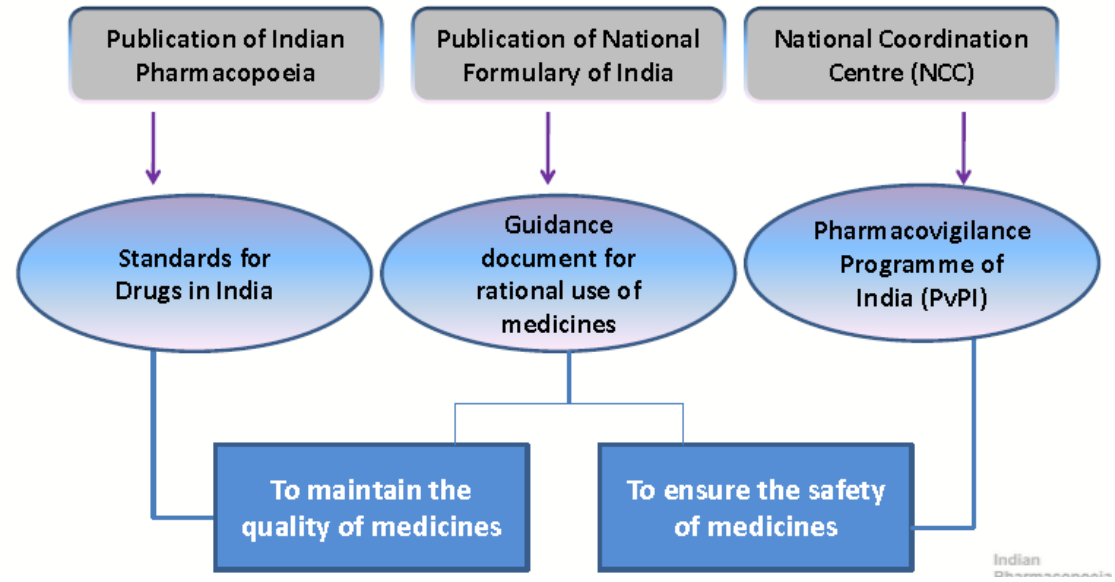
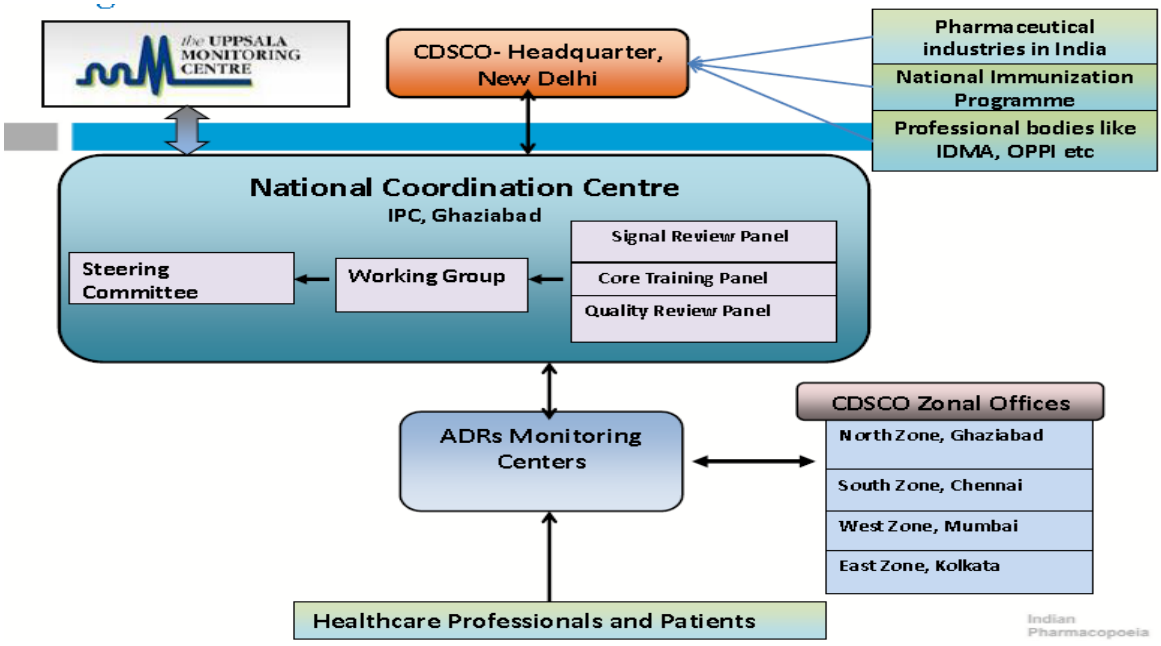
**Figure 1- Indian pharmacopoeia commission**



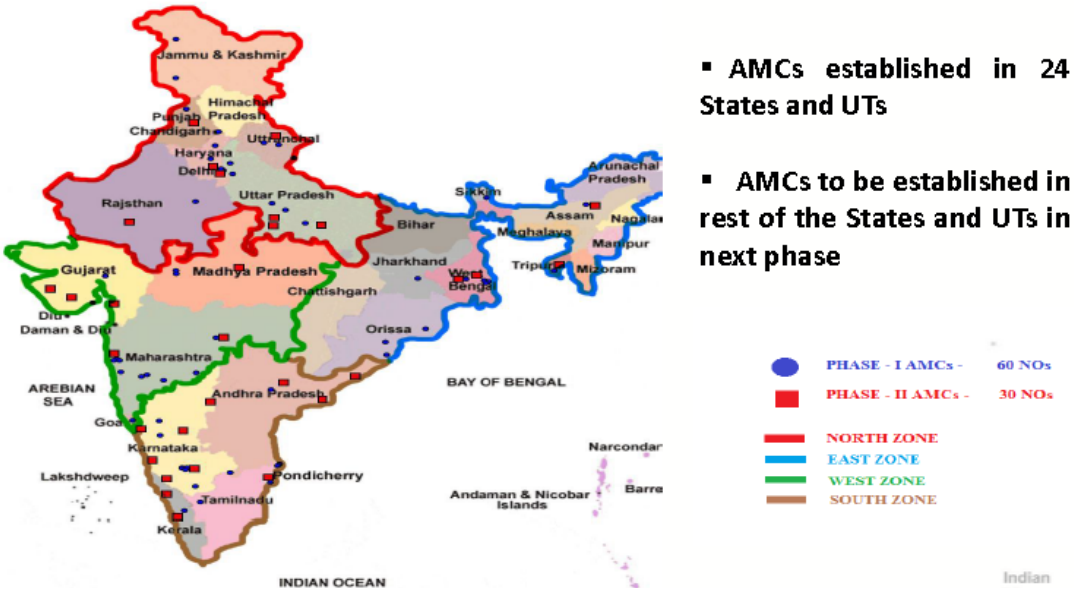

The main functions are to maintain the quality of medicines and ensure the safety of medicines.

**Figure 2- Pharmacovigilance programme communications**




This figure explains the process of communication from health care professionals to the adverse drug reaction monitoring centers, zonal offices and to the national coordinating center.

**Figure 3- ADR monitoring centers**



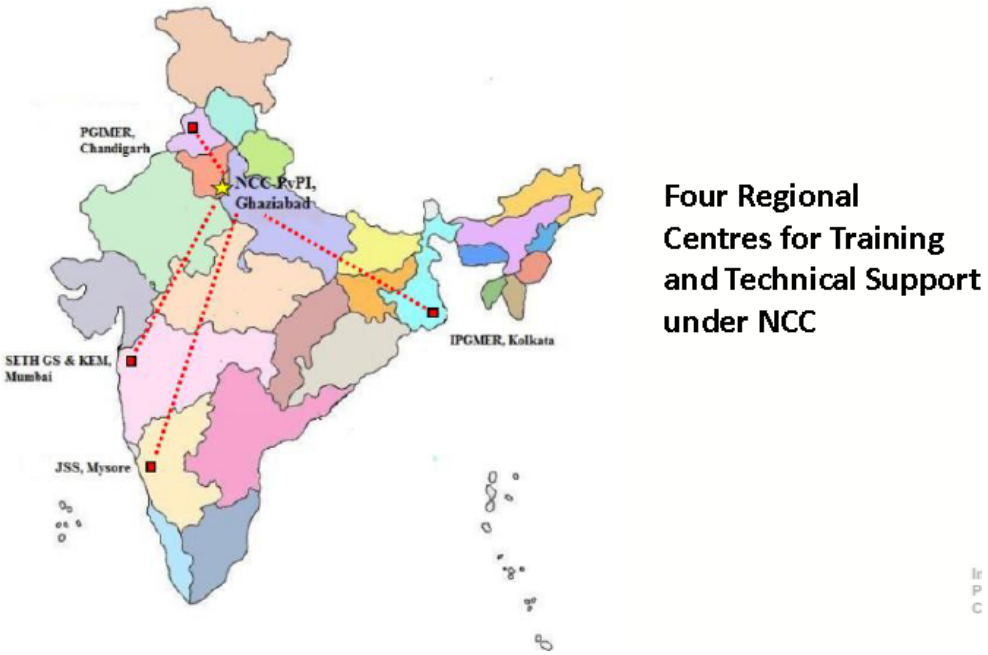

Adverse drug reaction monitoring centers are established in 24 states and union territories.
Sixty adverse drug reaction monitoring centers established in phase-I
Thirty adverse drug reaction monitoring centers established in phase-II
Adverse drug reaction monitoring centers are divided into north, east, west and south zones.

**Figure 4- ADR monitoring center functions**

| | |
|---|---|
| ADRs Monitoring Centers | • Monitoring and Reporting of ADRs |
| NCC-PvPI<br>IPC Ghaziabad, UP | • Preparation of SOPs, guidance documents & training manuals<br>• Data collation, Cross-check completeness, Causality Assessment etc as per SOPs<br>• Conduct Training workshops and CMEs<br>• Publication of Medicines Safety Newsletter<br>• Reporting to CDSCO Headquarters |
| ZONAL/Subzonal CDSCO Offices | • Provide administrative support to ADR monitoring centers |
| CDSCO, HQ, New Delhi | • Take appropriate regulatory decision & actions on the basis of recommendations of PvPI NCC<br>• Propagation of medicine safety related decisions to stakeholders |

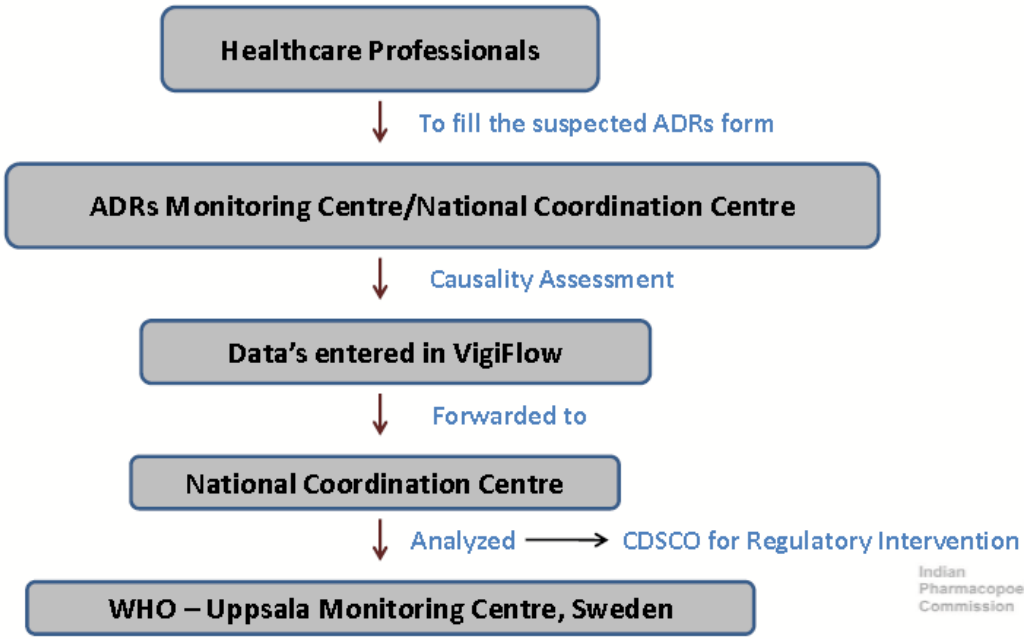
This figure explains the various responsibilities of their respective adverse drug reaction monitoring centers.

**Figure 5- Regional resource centers for training**




There are four regional centers for the purpose of training and technical support under national coordinating center.

**Figure 6- Collection, analysis and evaluation of ADRs**




This figure explains the flow of adverse drug reaction reporting to the adverse drug reaction monitoring centers.