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Adverse Drug Reaction (ADR) Reporting

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INTRODUCTION

Human body is a very complex organisation of cells. The cells make the tissues and the tissues make up the organs. Healthy organs form a healthy body. But due to the complex structure of body, sometimes an error occurs in our system. To treat this, certain medications are prescribed which may cause noxious and unintended response in the body which occurs at normal dose. This unwanted change is known as Adverse Drug Reaction (ADR). This Adverse Drug Reaction is globally monitored by the department of pharmacovigilance. According to WHO (World health Organization) pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of the adverse effects. It can be detected through pre-marketing studies, post-marketing surveillance and communicating ADR's.

Adverse event is any untoward medical occurrence that may be present during treatment with a pharmaceutical product but does not have a causal relationship with medicinal products. An Adverse Drug Reaction is distinguished from the adverse event as adverse drug reaction has a causal relationship with medicinal product and the reaction that is judged as being atleast possibly related to the reaction by reviewing the health professional while adverse event does not have such causal relationship.

The objective of Adverse Drug Reporting is to improve patient's care and promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public. It is done to reduce the fatal effect which may be caused in the human boy due to the adverse reactions. It encourages safe, rational and cost effective use of medicines.

WHO programs for International Drug Monitoring was started in 1968 as a means of pooling existing data on ADR's. Initially, a pilot project with established national reporting systems for ADR's, the network has expanded significantly as more countries developed National Pharmacovigilance Centre for recording of ADR. The following countries participate in WHO co-ordinated program with its collaborating centre in Uppasala, Sweden (Uppasala Monitoring Centre) which is responsible for maintaining the Global ADR Database, Vigibase.

Adverse Drug Reaction

History:

Before 1960's, the health consciousness and health care regulations were liberal and instead of drug safety, efficacy of drug was the first priority. In 1961, Phocomelia due to Thalidomide tragedy forced to establish a system which ensures drug safety. In 1968, WHO developed international monitoring centre because of which the drug safety issues were globalised and systematised. In mid-1970's, French group of pharmacologists and toxicologists aimed to find out the harms related with drug therapy[1]. Since 19th century, few medicines have been developed as safe and effective out of many investigational drugs. It was well known that almost every drug possess beneficial and some adverse effects. Hence, to minimize ADR pharmacovigilance came in a picture for effective monitoring of ADR which can safeguard the public health. In 1996, India started global standard clinical trial and in 1997, joined ADR monitoring program. In 1998, pharmacovigilance activity initiated in India and in 2002, 67th national pharmacovigilance centre was established in India. In 2005, India started conducting structured clinical trials[2]. And in 2010, pharmacivigilance plan was initiated and implemented.

Types of Adverse Drug Reactions:

- **Type A effects (Augmented Pharmacological Effects)**
  These are dose dependents and predictable and is avoided by using appropriate doses. These effects are identified before marketing.
- **Type B effects (Bizarre effects)**
  These are dose independent and unpredictable which may be serious and difficult in studying. These are either immunological (rashes, anaphylaxis, vasculitis) or non-immunological (enzyme dependent or metabolic pathway disorder).

[1]https://www.who-umc.org
[2]Supra note 1

- **Type C effects (Chronic effects)**
  These refer to situations where the use of a medicine often for unknown reasons increases the frequency of a spontaneous disease. It may be serious and cause malignant tumours and effect the public health.
- **Type D effects (Delayed effects)**
  These include carcinogenicity and teratogenicity.
- **Type E effects (End of treatment effects)**
- **Type F effects (Failure of therapy)**

Scope of ADR and Pharmacovigilance:
Pharmacovigilance is an emerging concept which deals with chemical, botanical and biological medicines along with medical devices[3]. It also explains about the information collected from health care professionals and detect abnormalities in a patient. It deals with adverse effects of drug, poly-pharmacy, paradoxical reactions and severe adverse events. It also explains about vaccination failure, irrational use, lack of efficacy, drug interactions, drug misuse and over-dose and poisoning.

Importance of Pharmacovigilance:
A new medicine launched without long term safety studies may show life threatening effect. Few decades ago, in India, the evaluation of drug was based on chronic use of the drug wich was inaccurate and unsafe. Thus, many Indian organizatuions and research departments investigated on newer drugs and developed new information trends which maybe positive or negative. The complete assessment of newly generated information with the help of pharmacovigilance system safeguards the public health. The adverse effect of drugs was studied to minimize risks and maximize benefits.

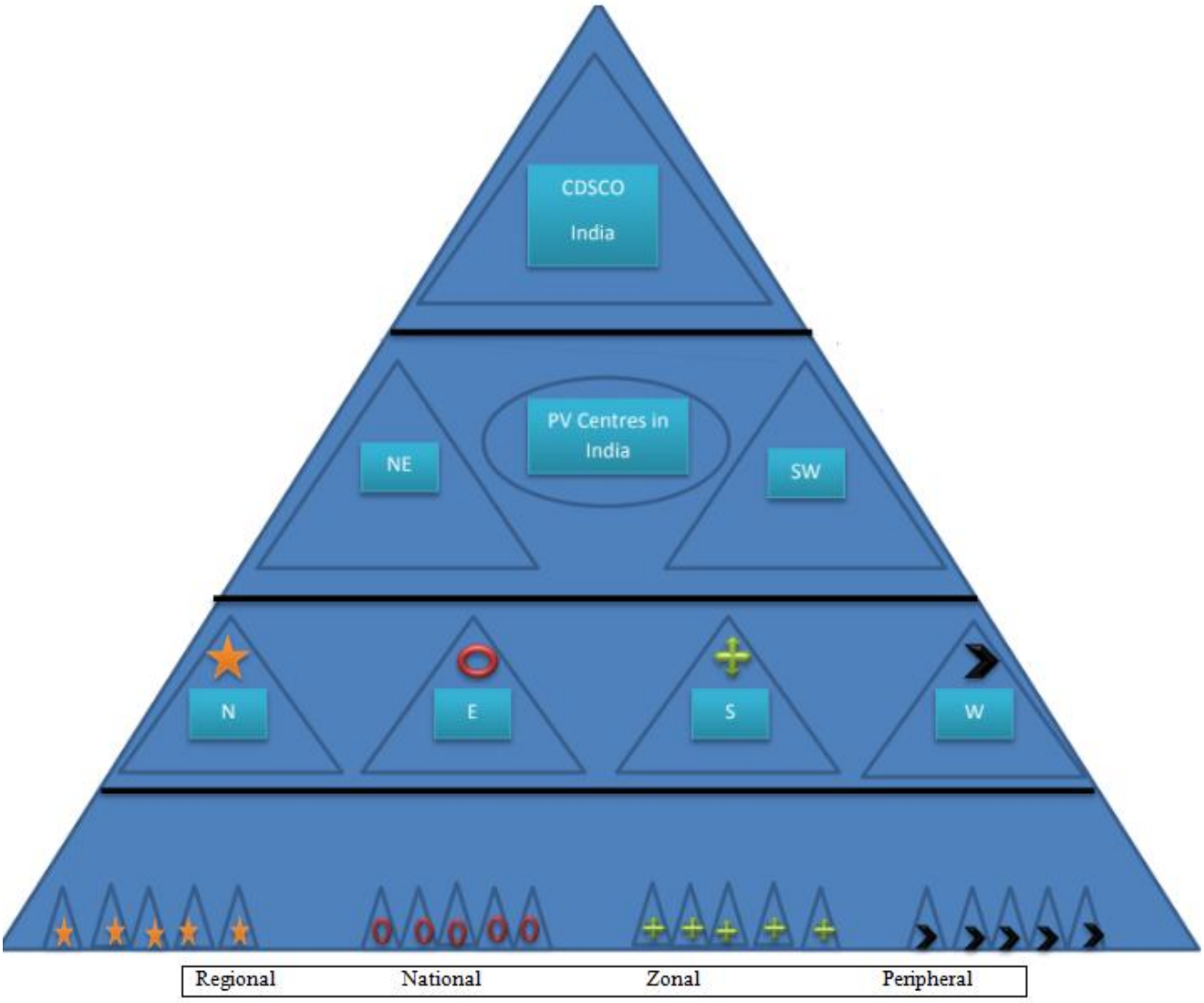
India secured 4th rank in the global pharmaceutical production and presently greater than 6000 authorized manufacturers and 60,000 brands of medicines are available in Indian market. An unwanted reaction develops in patient when he/she consumes more than 2 different prescriptions or non-prescription drugs at a time. Hence to avoid the situation, there is need to improve the pharmaovigilance system. As India is a populated country and is developing as a focal point for clinical research as pharmacovigilance system safe guards the public health by recognising risk factor and seriousness of ADR.

Pharmacoviligance program of India:
A formal ADR monitoring system having 12 centres was proposed in 1986 with special attention on pharmacovigilance activity. In 1997, India participated in WHO's ADR monitoring program organized at Uppasala, Sweden. However this participation was not sufficient for promotion of pharmacovigilance activity. Hence on 14th July, 2010, government of India started the pharmacovigilance program for India (PvPI). As a part of PvPI, All India Institute of Medical Sciences (AIIMS), New Delhi selected as National Co-ordinating Centre (NCC) to safeguard public health[4]. About 22 ADR monitoring centres were established in 2010 and NCC was transferred from AIIMS New Delhi to IPC (Indian Pharmacopia Commission) Ghaziabad, on 15th April 2011, for smooth and efficient functioning of program. The selected eligible medical colleges, hospital centres were approved as ADR monitoring Centres (AMC's) which collected individual case safety reports (ICSR) analyses and report to the regulatory authority. Till January 2017, 250 AMC's have been established under PvPI. About 20 Anti- Retro Viral Therapy (ART) and 17 Revised National Tuberculosis Program (RNTCP) centres were established for spontaneous ADR reporting. The technical associates from medical sciences, BHU is an authorize person for collecting ICSR's along with its follow up and online database entry in vigiflow software. All the primary healthcare centres and community health centres submit their ADR reports to the regional centre. The natural sources of drugs were considered safe and devoid of ADR but Charaksamhita, the heart of Ayurveda illustrates that ADR can occur with herbal drugs if compounded and dispensed inappropriately. Hence, to put pharmacovigilance for Ayurveda, Siddha, Unani (ASU) was highly essential to provide ADR data of AYUSH Drugs as per WHO guidelines.

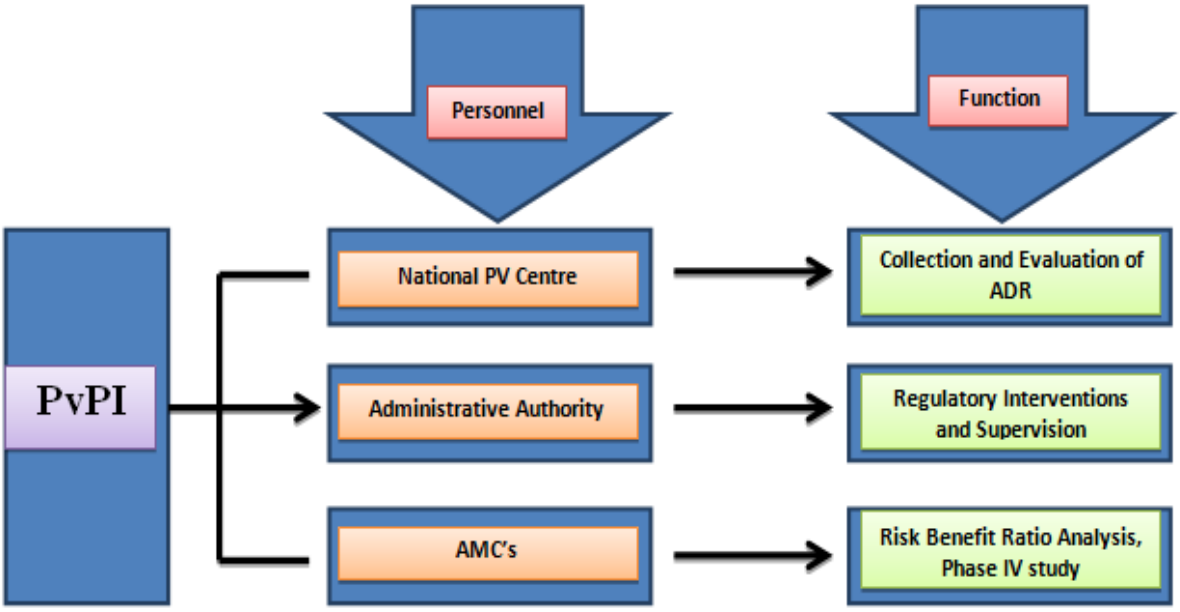
Spontaneous Reporting of Adverse Drug Reaction
It is the voluntary and the most common way through which the regulatory bodies collect Adverse Drug Reaction information for medicines once they are on the market. Ex- yellow card scheme is run by the MHRA and commission on Human Medicines in Jordan and United Kingdom (UK). The original CHM known as the Committee on Safety of Drugs was established in 1964 following the Thalidomide Tragedy.

Individual case safety Report
It is a document providing the complete information relating to an individual case at a certain point of time. An individual case is the information provided by a primary reporter to describe suspected Adverse Drug Reaction related to the administration of one or more medicinal products to an individual patient at a particular point of time.

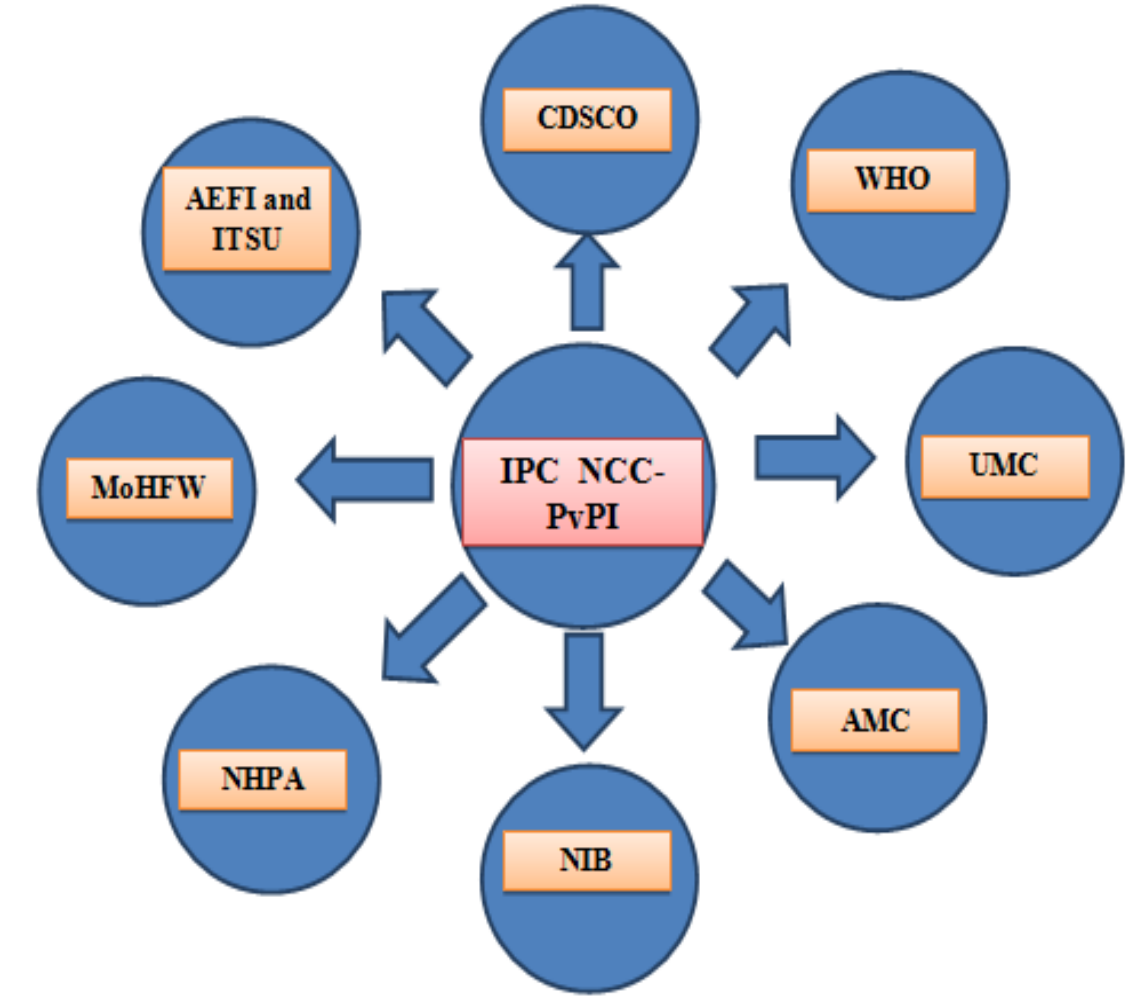
[3] https://www.longdom.org/open-access/ppharmacovigilance-process-in-india-an-overview
[4] Supra note 3

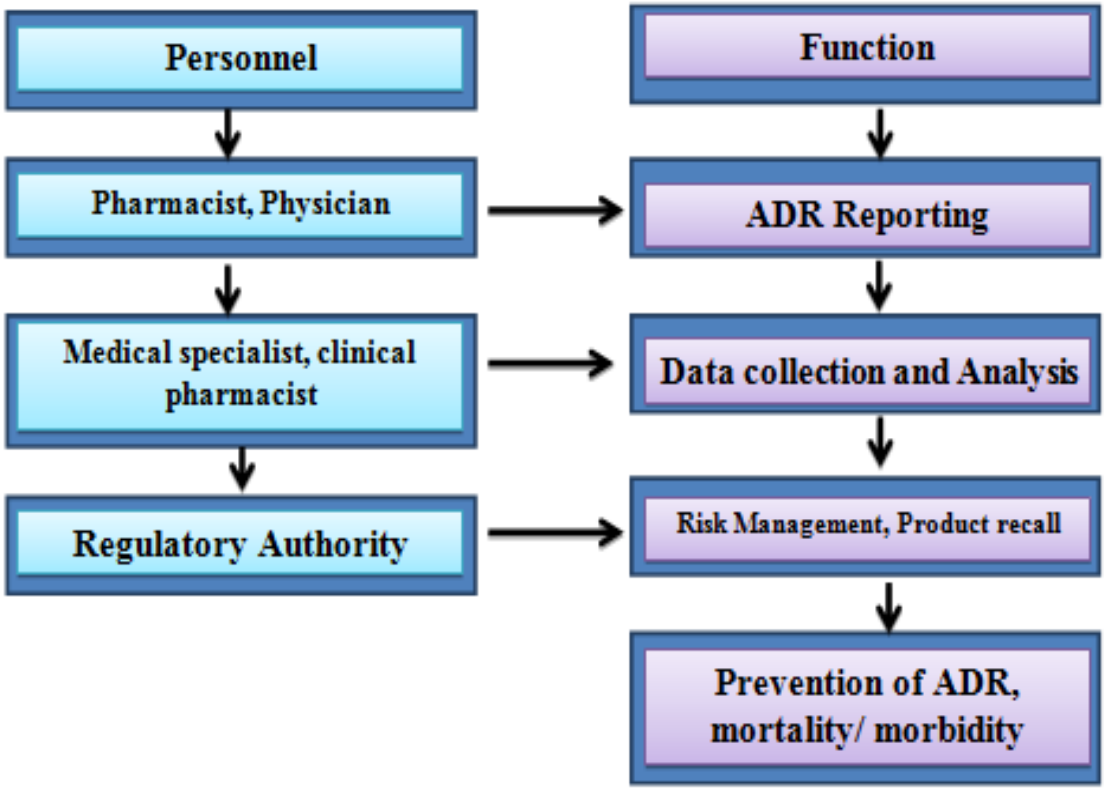


Adverse Drug Reaction Reporting Centre in India

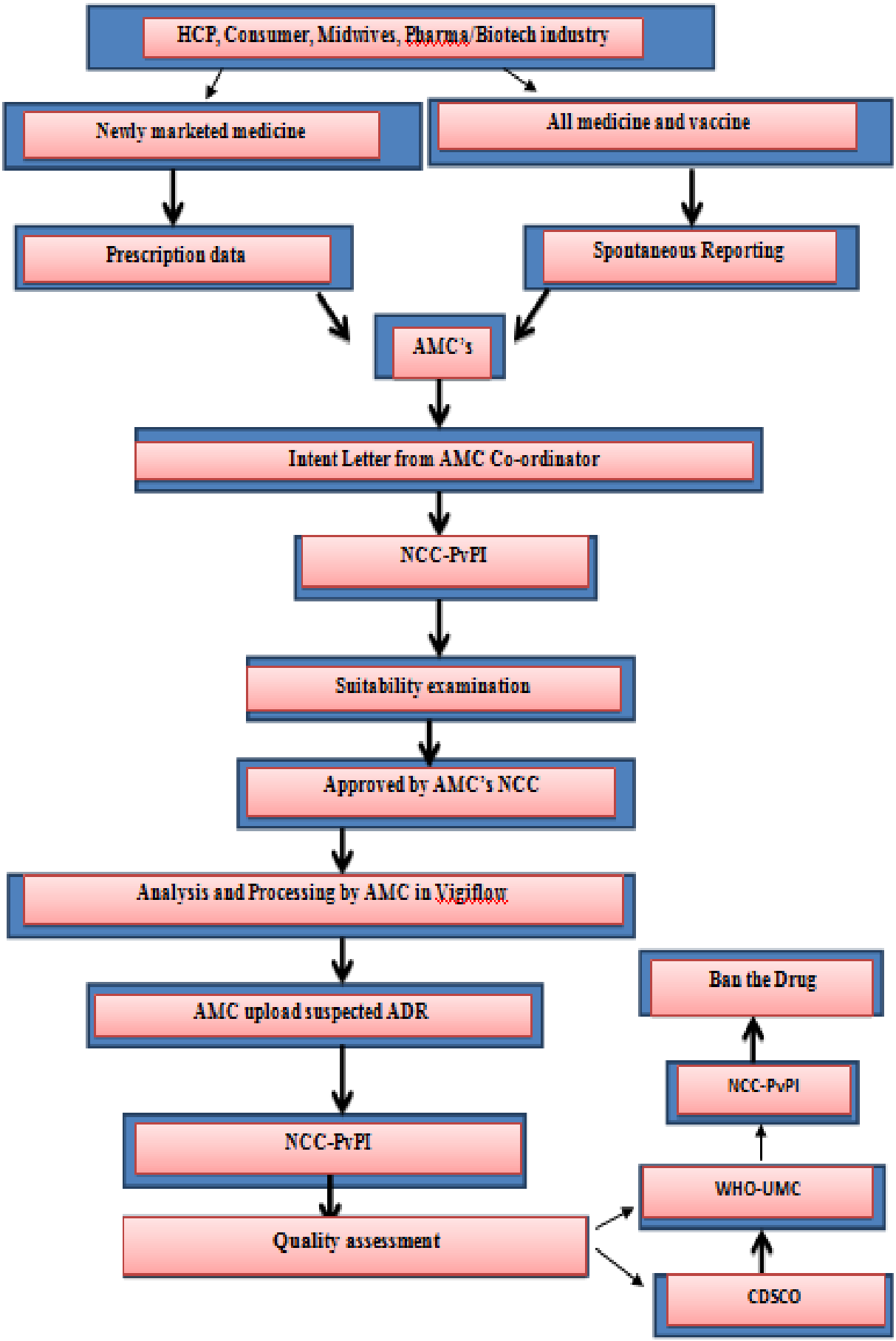


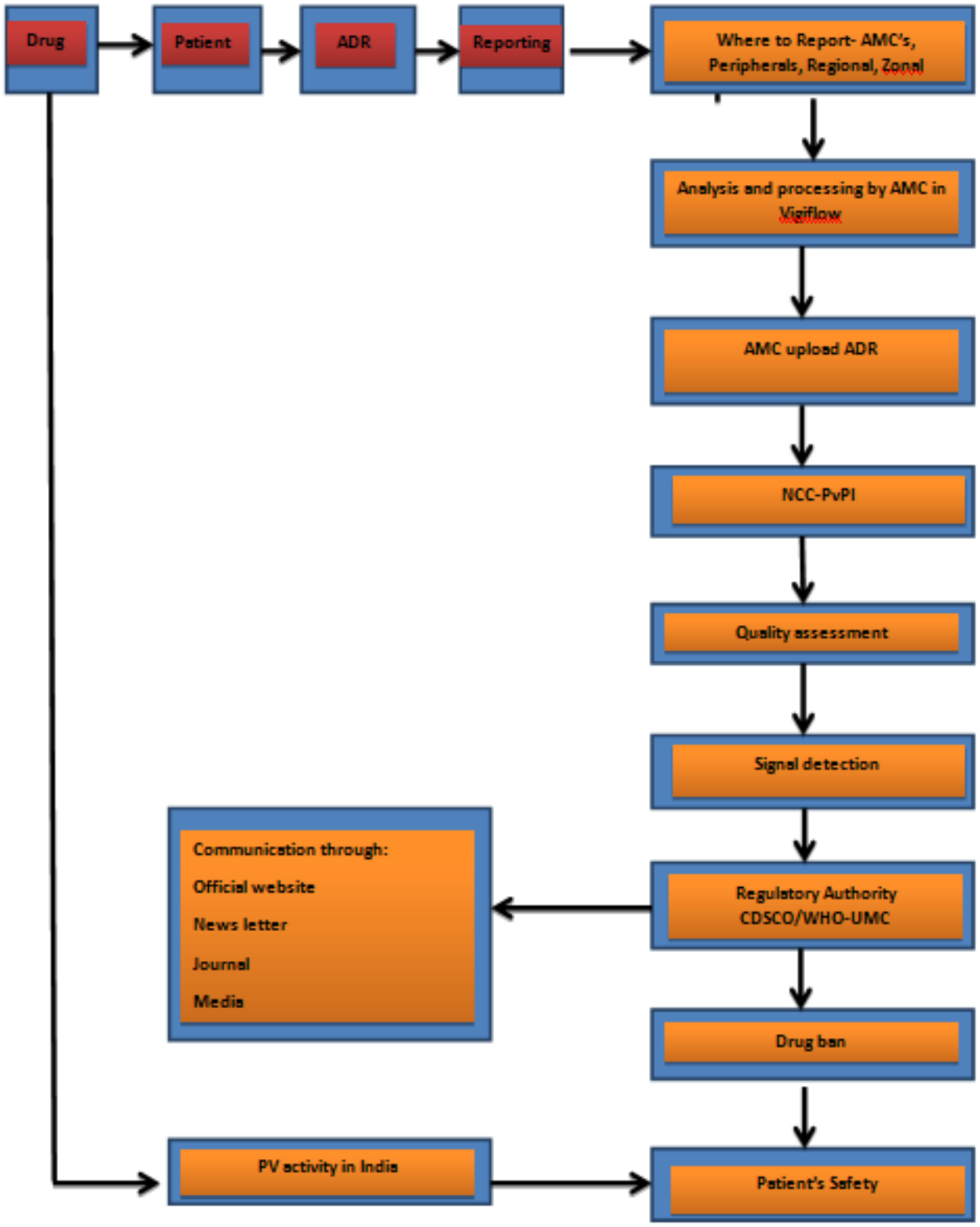
PvPI composition with functions of Personnel





Stakeholders involved and their function in PV Activity


HCP, Consumer, Midwives, Pharma/Biotech industry
Newly marketed medicine
All medicine and vaccine
Prescription data
Spontaneous Reporting
AMC's
Intent Letter from AMC Co-ordinator
NCC-PvPI
Suitability examination
Approved by AMC's NCC
Analysis and Processing by AMC in Vigiflow
AMC upload suspected ADR
NCC-PvPI
Quality assessment
Ban the Drug
NCC-PvPI
WHO-UMC
CDSCO



Adverse Drug Reaction Reporting Tools:
ADR Reporting tool or monitoring is a process of continuously monitoring undesirable effect suspected to be associated with use of medical products. ADR reporting covers all pharmaceutical products, biological, herbal, cosmetics and medical devices. ADR monitoring is done through various adverse events identification which are as follows:

Case Reports: This is done to monitor unpredictable ADR's.

Anecdotal Reporting: It is done to monitor the medicinal product whose ADR is not reported in medical bulletin.

Impulsive Reporting: It is the most spontaneous method of AFR reporting.

Intensive Monitoring: In this, selected population is screened and watched to record all the events when the drug is administered.

Contingent Studies: These are conducted on a population on a specific conditional basis and compare a particular drug with another population.

Case Control Studies: These is retrospective study designs where a patient has disease due to the use of drug which are investigated to check if they have taken the drug and then they are matched with control group.

Case Cohort Studies: Retrospective and prospective in nature.

Meta-analyses: It is performed by applying statistical analyses to predict the long term outcomes of a particular drug or treatment.

Methods and Methodologies:

- **Criteria for ADR and its reporting to Regulatory Authority**

  What to Report?
  Following events can be reported to the nearest reporting centre or Authority-

  - Life threatening event or Death
  - Hospitalization of the patient
  - Congenital anomaly
  - Medically significant event
  - Lack of efficacy with the use of medical device or drug product
  - All suspected drug interactions.
  - All known or unknown serious or non-serious frequent or rare reaction caused due to use of vaccine or drug must be reported.

When to Report?

- All spontaneous case should be reported within 10 days.
- All suspected ADR should be reported as soon as possible.
- Death event must be reported as soon as possible and all other serious ADR events should be reported within 7 days.
- All non–serious cases must be reported within 30 days.

Who can Report?
All health care workers working in health care team are the preferred source of information in PV for example, medical specialist, pharmacist, dentist, midwives, patient's relatives, witness or any common person after medical conformation can report.

Where to Report?
Various peripheral, regional and zonal centers have been proposed and established in India.
Peripheral PV Centre: it is the primary ADR information gathering center which includes private hospitals, nursing homes, pharmacies and dispensaries. ADR's are recognized and synchronized by RPC's or ZPC's. Every state, union territory and medical colleges in India have peripheral center.

Regional PV Centre: it is the secondary PV center located in medical colleges identified and co-ordinated by zonal centers. There are 5 such regional centers in India.

Zonal PV center: It is the tertiary PV center located in metro cities, medical college and is identified by CDSCO. It acts as first ADR data collection center. Zonal Center for north and east zone is AIIMS.

What will happen to the Adverse Drug Reaction Report?
The information obtained from the reported reactions promotes safe use of medicines. The reports case enters into National ADR Database and is analyzed by expert reviewers. The reported ADR's results in additional investigation of medication, changes in manufacturing of the medicine and to improve the safe use of medication by the educational initiatives.

What are the benefits of ADR Reporting?
The ADR reporting reduces the risk associated with prescribed drug and administration and ultimately improves patient's care and safety.

How to know if a patient's condition is an ADR?

- **Take a proper history and do proper examination:** A full drug and medical history should be done. The patient should be thoroughly investigated to decide what is the actual cause of new medical related problem. A drug related cause should be considered especially when other causes do not explain the patient's condition.
- **Establish time relationships:** The time from the start of therapy to the time of onset of the suspected reaction must be logical.
- **Do a thorough physical examination with appropriate laboratory investigation:** Few drugs produce distinctive physical science (exceptions: steroid induced dermal atrophy). Lab test are important to improve patient care as they describe the reaction clearly with appropriate diagnosis.
- **Effect of de-challenge and re-challenge should be determined:** de-challenge means withdrawal of drug and re-challenge is re-introducing the drug after a de-challenge.
- **Check the pharmacology of the medicine:** if the reaction is known to occur with the particular drug.

Causality classification:

WHO has provided a list of causality assessment criteria for deciding on the contribution of medicine towards the adverse events which are as follows.

- **Certain:** clinical event, lab test abnormality, positive re-challenges, pharmacological event and response to de-challenge.
- **Probable or Likely:** clinical event, lab test abnormality unlikely to be to concurrent diseases, re-challenge not required.
- **Possible:** clinical event, lab test abnormality, information on dtug withdrawal may be lacking.
- **Unlikely:** clinical event, lab test abnormality and other drugs provide explanations.
- **Inaccessible:** insufficient evidence which cannot be verified.
- **Conditional:** more data is essential for proper assessment.

What type of reactions should be reported?

- All newly marketed drugs or drugs added to essential drugs list.
- All serious reactions and interactions.
- ADR's which are not stated in packages.
- Interesting ADR's.
- Poison to herbal medicines.

What product quality problems should be reported?

Suspected contamination, questionable stability, poor packaging or labelling, therapeutic failures.

How to prevent ADR's?

- Use few drugs whenever possible
- Use drug that you know well.
- Do not change therapy.
- Use textbooks and other materials for information on drug reactions and interaction.
- Careful monitoring of anti-coagulants, hypoglycemic and drugs effecting on CNS.
- Be aware of drug interactions with certain food stuffs and alcohols.
- Review the over the counter drugs and herbal preparations.
- Be careful when prescribing to children, pregnant women, elderly, hepatic and renal disease patients.
- If there is adverse drug reaction, stop the drug or reduce the dose and notify the ADR to NCC-PvPI at the Drug Regulatory Authority.

How to report?

- Duly filled ADR reporting form is sent to the AMC or directly to the NCC.
- Dial toll-free helpline number 18001803024 to report ADR's.
- Mailing the filled ADR reporting form directly to pvpi@ipcindia.net or pvpi.ipcindia@gmail.com
- Logging on to the http://www.ipc.gov.in, http://www.ipc.gov.in/PvPI/pv_home.html for list of authorized AMC's of India[5].

[5]https://www.who-umc.org