

UNIT-II

ESTABLISHING PHARMACOVIGILANCE PROGRAMME



CENTURION
UNIVERSITY
*Shaping Lives...
Empowering Communities!*

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- **Establishing in a hospital**
- **Establishment & operation of drug safety department in industry**
- **Contract Research Organizations (CROs)**
 - **Establishing a national programme**

✦ Established pharmacovigilance program in a hospital and national programme

PV is a major post-marketing tool to ensure the safety of a medicinal product. Apart from the respective drug regulating authorities in each country, International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, Pharmacovigilance Planning-ICH E2E and World Health Organization-Uppsala Monitoring Centre (WHO-UMC) also play key roles towards developing, enhancing and monitoring global PV system. A PV system is defined as a system used by an organization to fulfill its legal tasks and responsibilities in relation to PV that monitors authorised medicinal products' safety and detect if any change to risk benefit balance.

it a further impetus and fortify the drug regulatory framework in the country, the Drug Controller General of India (DCGI) has announced the CDSCO's "VISION 2020" which proposes to create a PV center in every medical college in the country which is an ambitious task keeping in view the fact that it is still at low ebb in many government medical colleges and the condition is the same or may be worse in the private institutes. Therefore, it is likely that the proposal may have to negotiate many bottlenecks to pay some dividends. In this backdrop, the article discusses the essentials of setting up a PV center and getting it operational

After the thalidomide disaster in the year 1961, WHO worked along with its Collaborating Centre to establish a programme for International Drug Monitoring and through this programme, WHO promoted PV at the country level. At the end of 2010, 134 countries were part of the WHO-PV Programme. To give

Essential for a Pharmacovigilance program:-

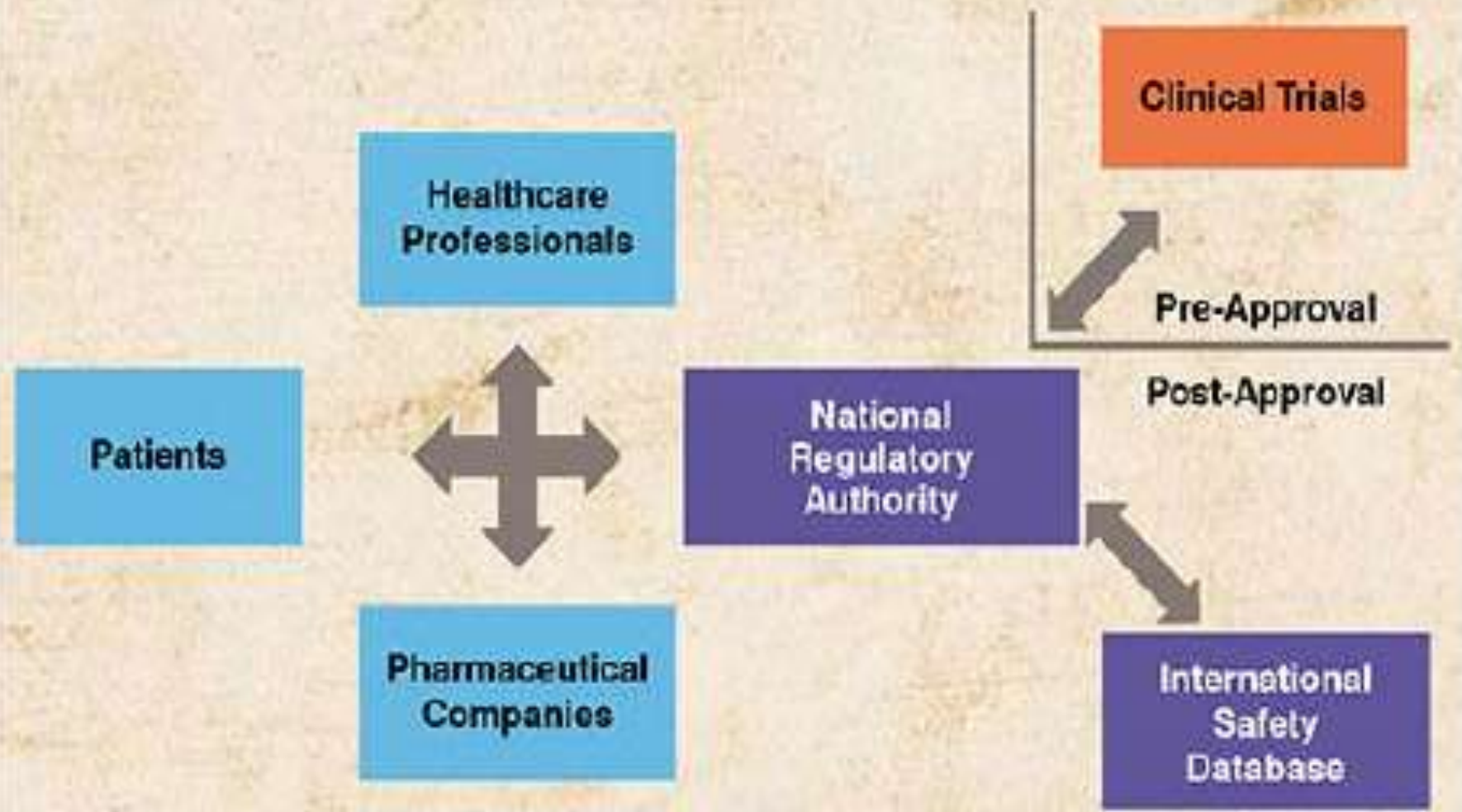
Pharmacovigilance is all about drug regulations and is based on thorough collaborative ties, coordination, communications, and public relations. The most suitable location for setting up a PV centre is dictated by the political governance and its healthcare priorities, including willingness to do, law enactment, its enforcement, funding, organisation, staffing, training, and development.

To Ensure a Good PV System, Certain Operational Requirements must be met, which include:-

- A properly structured drug safety management team to intensify the communication among the PV network. This will assure an organised structure and smooth functioning. Meetings among the PV physicians, managers, and technical agencies need to be held from time to time
- A countrywide database which provides provision for collating and managing ADR reports
- A national PV advisory committee
- A clear approach, to be communicated in detail, in regular situations as well as situations of crisis
- Funding to run different grounds of a system.

Basic Steps in Setting up a PV System Include:-

PV System of safety data collection



Developing guidelines and communications with the health authorities-a general guideline is a standard strategy to confirm that the PV system at all levels meets the national and international standards and regulations. Getting into regular communications with the health authorities, local, regional and national bodies, and professionals involved in clinical medicine, pharmacology, toxicology, epidemiology, briefing them about the importance of the project and its applicability in modern therapeutics.

Minimum requirements for a functional national pharmacovigilance system

The following are the minimum requirements that WHO and partners agree should be met in any national pharmacovigilance system.

1. A national pharmacovigilance centre with designated staff (at least one fulltime), stable basic funding, clear mandates, well-defined structures and roles, and collaborating with the WHO Programme for International Drug Monitoring;
2. A national spontaneous reporting system with a national individual case safety report (ICSR) form, i.e. an ADR reporting form;
3. A national database or system for collating and managing ADR reports;
4. A national ADR or pharmacovigilance advisory committee able to provide technical assistance on causality assessment, risk assessment, risk management, case investigation and, where necessary, crisis management, including crisis communication;
5. A clear communication strategy for routine communication and communication during crises.

1. The Manpower and the machinery

a) Adequate qualified and experienced man power to run the system - PV staff should have complete knowledge regarding data collection and verification, coding of drugs and adverse events, causality assessment, signal detection, risk management, interpreting the data obtained etc.

***Staff**

The expertise desirable in the routines of a pharmacovigilance centre includes: **Clinical medicine, pharmacology, toxicology, epidemiology**. However, a new pharmacovigilance centre often starts with only a part-time expert

- usually a physician or a pharmacist
- and some secretarial support.

2. Planning the basics

A blueprint should be drawn up to establish and get a PV system to work. Care needs to be taken to establish the following:

a) Advisory Committees

A multi-disciplinary advisory committee is desirable, to support the pharmacovigilance centre with regard to the quality of the procedures in:

1. Data collection and assessment
2. Data Interpretation
3. Information publication

A network of experienced advisors in various specializations is helpful

b) Communication process

Getting in conversation with health authorities and local, regional, national bodies and groups engaged in clinical medicine, pharmacology, toxicology, epidemiology, briefing them about the importance of the project and its applicability in modern therapeutics. A bulletin or newsletter distributed to all healthcare professionals or a regular column in reputed (medical and pharmaceutical) journals are good means for the dissemination of information. Prompt data-sheet amendments are important, but data-sheets may be printed infrequently and their educational impact may not be large. In urgent cases of sufficient importance 'Dear Doctor' letters may alert the profession

c) Data acquisition

Designing a template for ADR reporting and making available ADR reporting forms at all times, to hospital departments and general practitioners, on which they can furnish relevant information to the data bank of the center.

d) Dissemination

Producing printed handouts as well as conducting meetings or workshops in hospitals and academia to acquaint health care professionals about the definitions, goals, scope, and methodology of the PV system to create awareness about its relevance in present times.

e) Establishment

Hiring the right qualified and interested staff, getting suitable place for accommodating them as well as the center, making arrangements for telephones, computers, printers, word processors, database management, bibliography support services and an internet.

f) Internal education

Ensuring proper education and frequent updating of the staff belonging to the PV centers by training them in data collection, filtration, mining, verification, interpretation and coding of ADRs, medicines coding, causality assessment, signal detection, risk management, and action in case of serious/fatal adverse drug events (ADE). Data mining is a relatively nascent interdisciplinary area which involves finding correlations and patterns among many fields in large databases with the aim of categorizing the data and summarizing identified relationships.

g) Database and information service

Creating a safely stored, classified database which is retrievable and guarded by required degrees of confidentiality. The provision of a high quality information service to healthcare professionals is a basic task of a pharmacovigilance centre and a major instrument in the stimulation of reporting. For this purpose and for the assessment of case reports the centre should have access to a comprehensive and up-to-date literature source and information database.

Location of the centre in a large hospital usually has the advantage of a library within reach. National pharmacovigilance centres can have online access to the database of the UMC and be on the mailing lists of adverse drug reaction and drug bulletins produced by the World Health Organization and many national or regional centers.

h) Promotion

To inculcate and promote the habit of reporting ADRs to the higher center, medical journals, health bulletins and other professional healthcare publications.

I) Networking

To encourage healthcare professionals to contact institutions working on a global scale in PV e.g. Uppsala Monitoring Centre (UMC) WHO department of Essential Medicines and Medicines Policy, Geneva, and net groups like International Network for the Rational Use of Drugs (INRUD), E-drug, and Network for Rational Use of Medicines (NetRUM)

3. Data

Pharmacovigilance at present thrives heavily on a regional/country wide reporting of suspected ADRs through spontaneous reporting system from motivated reporters. It usually picks up signals of rare, serious, unprecedented ADRs.

Reports of suspected ADRs are taken in case report forms (CRF) which in PV is defined as a notification relating to a patient with an ADE (or laboratory test abnormality) suspected to be induced by a medicine. The CRF should be distributed to health care professionals across the area covered by a particular PV center regularly, and a suitable system has to be developed to ensure that the filled forms are either collected or could be posted free, or sent by e mail/FAX to the center, so that there is an uninterrupted and free flow of data.

A CRF should contain minimum following information

- Patient: Age, gender, medical history in brief, ethnic origin (in some countries)
- ADE monitoring: Detailed description (nature, localization, severity, characteristics), reports of investigations and tests, date of appearance, course, outcome

- Suspected medicines: Name (brand, formulation, ingredient, concentration, manufacturer), dose, route of administration, date of initiation of therapy/date of withdrawal of therapy, indications for use, and rechallenge in case of non serious ADEs
- Other medicines: All other medicines used by the patient (including self medication) including their name, dose, route, date of initiation and withdrawal
- Risk factors: e.g. impaired renal function, past exposure to suspected medicines, history of allergy, and social drug use
- Reporter: Name and address of the reporter (confidential and to be used for data completion, verification, and follow up)

Health care professionals e.g. practicing physicians, pharmacists, nurses, dentists, and midwives are reliable sources of information. Pharmacists and nurses can illuminate on concomitant medication and history of medicine usage. It is imperative for pharmaceutical companies to report any ADRs of their products to regulatory authorities. In the event of patients directly reporting ADRs, it is always better to communicate with their physicians for better understanding and verification of data.

The reporting can be done from peripheral to the regional PV centers, which sweep a particular region, which in turn pool into the zonal database, the analysis of which reflects a gross national overview. The entire national data should be reported to UMC.

4. Bringing a reporting culture

Reporting of ADR is a continuous process and important to cultivate and sustain the attention and interest of healthcare workers so that it gets incorporated as a routine procedure in healthcare. The following measures may be adopted to give a fillip to reporting:

- Easy and free availability of prepaid reporting forms and other modes of reporting
- Duly acknowledging the receipt of ADR reports telephonically or through personal communication
- Providing journal articles, ADR bulletins, newsletters to reporters
- Actively involving the PV center staff in scientific meetings, undergraduate and postgraduate education
- Collaborating with other PV committees, It is always ideal to look out for other organizations that may be able to collaborate with your PV Centre to reduce the financial and logistic burden. For example, poison control and drug information centres share similar PV interests. It may be useful to develop a PV system in conjunction with these centres.
- Collaborating with professional associations
- Utilizing PV data for development of clinical pharmacy and clinical pharmacology

5. Tasks for pharmacovigilance

a) Information service

One of the primary responsibilities of a center is to make high quality credible and latest medicine information available to health care professionals. For this, the center should have access to up-to-date and comprehensive literature database. The national centers should preferably have an online access to UMC database and be on the mailing list of ADR bulletins of WHO.

b) Reaching out

Newsletters, medicine bulletins, columns from reputed medical or pharmaceutical journals may be chosen as routes of effective propagation of latest developments in medicine research and therapy to the healthcare professionals.

c) Appraisal

The ADR case reports obtained are evaluated by the center staff, employing the collective know-how of clinical medicine, pharmacology, toxicology, and epidemiology.

d) Secondary prevention of ADRs

Secondary prevention of ADRs can be attempted by distribution of “patient alert cards” which are pocket size cards and could be carried around by patients. They provide relevant information about the medicines including ADRs and go a long way in preventing ADRs.

e) Data processing

Data is best managed electronically by computer, wherein, data is entered in a hierarchical format according to product name, medicine name or therapeutic category. This facilitates recording detailed case information and easy retrieval.

Internationally accepted terminologies regarding classification of medicines (Anatomical Therapeutic Chemical [ATC], International Nonproprietary Names [INN]) and ADRs e.g. WHO Adverse Reaction Terminology (WHO ART), Medical Dictionary for Regulatory Activity (MedDRA) should be used, so that the data can be globally shared.

f) Hypothesizing

This is one of the chief goals of PV center. Based on the case reports, the center should be able to generate hypothesis or detect a signal with regard to probable ADRs.

e) Medicine regulation

It is PV center's duty to keep a close eye on the new medicines launched in the market and follow them up to look for newer ADEs, issue warnings, unmask newer indications or changes or to advocate withdrawal of medicines in extreme cases. A center should actively take up activities towards furthering the role of PV with periodic safety update reports (PSURs), registries, risk management-minimization plans, and improved communication with changes in label of medicines.

The PV system needs to deal with large population and the rate of reporting governs the estimation of the money needed to run the complete system. Huge investment is required in terms of collection of data from the actual source to transforming it into a Regulatory reportable format. Funding can be obtained from various parties, such as drug Regulatory authority, university departments, health insurance companies, and professional associations.

Establishment & operation of drug safety department in industry

Introduction:-

- Pharmacovigilance has grown as a discipline over the past 10 to 15 year.
- An educational survey in 1994 revealed that more than 320 people currently worked in company pharmacovigilance function in the UK alone.
- Pharmaceutical companies are international, hence the number of staff working in this field within the industry, particularly in other European countries and USA.
- A major pharmaceutical company such as Astra has over 100 permanent, experienced staff in pharmacovigilance within its research and development organisation in Sweden and the UK and US similar number in local operating companies worldwide
- The number of individual reports of possible adverse drug reaction can be considerable, for key marketed products often more than 1000 case reports a year are received worldwide from healthcare professionals and other sources.

Aim of pharmacovigilance within the industry:-

- Protect patients from unnecessary harm by identifying previously unrecognised drug hazards.
- Refuting false safety signals and quantifying risk in relation to benefit.

Scientific characteristics:-

- Pharmacovigilance is related to a number of scientific disciplines
 - i. Clinical medicine
 - ii. Clinical and preclinical pharmacology
 - iii. Immunology
 - iv. Toxicology
 - v. Epidemiology ,

Identification and analysis of the safety characteristics of medicine .

- In two distinct stage:-

1. Before marketing:-

The main methodology is experimental with clinical trial comparing the new treatment to existing alternative treatment.

2. After marketing:-

Introduction of a new medicine into you generally use, the main safety methodology is observational i.e. uses data from observation of patients treated in clinical practice rather than from experimental situations.

Pre-marketing clinical trials:-

- Safety monitoring in clinical trials involves collecting adverse event, laboratory investigation and details of the clinical examination of patients.
- Pharmacovigilance may be involved to varying degrees all phases of clinical trials including planning, execution, data analysis, reporting of safety information.
- Safety issues from animal pharmacology and toxicology studies, finding in phase-1 studies, ADR with similar drugs, signals from other studies and special patient group (eg. elderly).
- The practice of collecting all adverse events rather than suspected ADR arose from the failure of clinical trials to detect serious reaction with protocol and after several years experience this is now the approach adopted by company in most studies.

- The involvement of pharmacovigilance staff in clinical trials also includes an important responsibility for the expedited reporting of individual cases and safety update required by the UK medicine control agency and other regulatory authorities.
- Safety analysis and clinical expert report in the marketing authorisation application submitted by the company and will be the basis of ADR, warning and precaution include in the prescribing information i.e data sheet.

Methods of post marketing surveillance (PMS) used by the pharmaceutical industry:-

- 1. First step in signal generation:-** Processes that can identify possible new ADR.

Signal generated through four different methods

- **Spontaneous reporting**
 - Recording and reporting clinical observation of a suspected ADR with a marketed drug is known as spontaneous reporting.
 - The National system in the UK is the yellow card.
 - Where doctors, dentists and recently hospital pharmacist are encouraged to report all suspected reactions to new medicines and serious suspected reactions to established medicines.
- **Published case reports**
 - Publishing case reports of suspected ADR in medical journals is an establish a way of alerting other to possible drug hazards.
 - A more recent development is report of possible ADR appearing on the internet and money companies are still determining how they should best handle them.

- **Cohort studies**
 - Companies may set up or sponsor prospective, non interventional cohort type studies to answer safety question rose after marketing or general hypothesis generating and testing tool to be used as need arises.
- **Post marketing clinical trials**
 - Large randomised clinical trials with wide entry criteria can be valuable in assessing the safety of marketed products as well as confirming efficacy.

Companies can use to set up or sponsor search studies to address particular safety issues.

2. Second step in signal generation:- Signals are subjected to hypothesis testing i.e. processes that determine whether the single-dose indeed indicate a new ADR or whether it is false.

- **The hypothesis testing process:-**A typical situation in company pharmacovigilance is that a small number of reports have been received, showing that the patients have developed a serious medical condition e.g.-liver function disturbance, convulsion.
- **Using spontaneous reporting data for hypothesis testing:-**It is common place in clinical practice to make decisions and take actions based on assessment of causality between an event and a certain drug in individual cases.
- **Epidemiological studies:-** during the last decade pharmacoepidemiology, the study of the use and effect of drugs in large populations e.g- NSAID treatment and gastrointestinal ulceration and bleeding.

- **National and international regulatory requirements:-**

The reporting of safety information from clinical trials and with marketed product by pharmaceutical companies to regulatory authority has been mandatory for many years but with each National authority having different requirements.

Pharmacovigilance is not just about reporting cases to the regulatory authority the result of post marketing surveillance and hypothesis testing should provide useful information.

- **Issue and crisis management:-** The signal generation and hypothesis testing processes are long-term and continuous throughout the lifetime of a product resulting in a gradual buildup of knowledge of safety properties.

- **The future:-** Pharmacovigilance in the industry will continue to grow and develop as a discipline. The strong development towards international harmonization will result in much more international requirement and the very rapid development in electronics communication will allow automated distribution of case reports within companies and to regulatory authorities.