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Review Article

A REVIEW ON PHARMACOVIGILANCE

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ABSTRACT

Pharmacovigilance is a crucial scientific discipline focused on detecting, assessing, understanding, and preventing adverse drug reactions (ADRs) and other drug- related problems. It plays a significant role in ensuring drug safety beyond clinical trials, which have limited scope in identifying rare or long-term adverse effects. The term "Pharmacovigilance" originates from Greek and Latin roots, meaning "to keep watch over medicines." Key terminologies include absolute risk, adverse events, ADRs, and clinical trials, which are essential for evaluating drug safety. The major objectives of Pharmacovigilance include early detection of unknown adverse reactions, identification of risk factors, and improving drug regulation. Its scope extends to monitoring medication errors, counterfeit medicines, biological products, and vaccines. The discipline has evolved over the years, with its historical roots tracing back to 1848 when an adverse reaction to chloroform anesthesia was first documented. With continuous advancements, Pharmacovigilance remains vital in optimizing patient safety and promoting rational drug use.

KEYWORDS

Pharmacovigilance, Adverse Drug Reaction (ADR), Drug Safety, Clinical Trials, Risk Assessment, Medication Errors, Drug Monitoring, Therapeutic Efficacy, Pharmacology, Drug Regulation.

INTRODUCTION

Pharmacovigilance:- Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The world Pharmacovigilance is a mixture of two languages that are Greek & Latin.

Pharmakon (Greek) = Medicinal Substances.

Vigilia(Latin) = To keep watch.

Terminologies: -

Absolute risk:

Risk in a population of exposed persons; the probability of an event affecting members of a particular population (e.g. 1 in 1,000). Absolute risk can be measured over time (incidence) or at a given time (prevalence).

Adverse Event (AE):

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment

Adverse (Drug) Reaction (ADR):

A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (WHO, 1972).

"A response to a medicinal product which is noxious and unintended."

Clinical trial:-

A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion (ADME) of the products with the objective of ascertaining their efficacy and safety.

Terms commonly used in Pharmacovigilance

Benefits are commonly expressed as the proven therapeutic good of a product, but should also include the patient's subjective assessment of its effects.

Risk is the probability of harm being caused, usually expressed as a percent or ratio of the treated population; the probability of an occurrence.

Harm is the nature & extent of actual damage that could be caused. It should not be confused with risk.

Effectiveness is used to express the extent to which a drug works under real world circumstances, i.e., clinical practice (not clinical trials).

Efficacy is used to express the extent to which a drug works under ideal circumstances (i.e., in clinical trials).

Major aims of Pharmacovigilance are as follows: –

- Early detection of unknown adverse reactions and interactions.
- Identification of risk factors and possible mechanisms underlying adverse reactions.
- Estimation of quantitative aspects of benefit/risk analysis and Spreading fact of information needed to improve drug prescribing and regulation.

Importance of Pharmacovigilance:

Complete information of unintended and severe adverse events could be finding through the Pharmacovigilance. It could not be done through clinical trials which are conducted in an In vivo method.

Scope in Pharmacovigilance:

Pharmacovigilance conducting advanced drug monitoring study based Adverse drug reactions, adverse events report of new drugs include:

- Medication errors and irrational use of medicines
- Herbal, traditional and complimentary medicines
- Substandard medicines and counterfeit medicines
- Blood products, biological, medical devices and vaccines ADR
  - Pharmacovigilance main aim is to give clear information regarding drug safety and its risk or benefits of drugs to the patients.

History and development of Pharmacovigilance

- The history of Pharmacovigilance started 169 years ago, on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform anesthetic before removal of an infected toenail.
- Sir James Simpson had discovered that chloroform was a safer and powerful anesthetic, and he had introduced it in clinical practice.
- The causes of Hannah's death were investigated to understand what happened to Hannah, but it was

impossible to identify what killed her. Probably she died of a lethal arrhythmia or pulmonary aspiration.

Introduction to ADR:-

ADR stands for Adverse Drug Reaction.

It refers to any harmful or unintended response to a medication or drug that occurs at normal doses used for prevention, diagnosis, or treatment.

ADRs can vary in severity, from mild side effects like nausea or headaches to more serious reactions such as organ toxicity or life-threatening conditions.

Classification of ADRs Types A Effects:

1. Due to pharmacological effects.
2. Are dose related – may often be avoided by using doses which are appropriate to the individual patient.
3. Example: hypnotic effect after H2 antihistaminic.

Types B Effects:

1. Generally rare and unpredictable.
2. Occur in predisposed, intolerant patients – can be explained by rare genetic polymorphism, allergic reactions.
3. Example: Penicillin allergies.

Types C Effects:

1. Adverse reactions after long term therapy.
2. There is often no suggestive time relationship and the connection may be very difficult to prove. The use of a drug increases the frequency of "spontaneous" disease.
3. Example: carcinogenesis.

Types D Effects:

1. Adverse effect may be presented years after a drug was used.
2. Example: Vagina cancer of daughters when their mother was treated by diethylstilbestrol.

Types E Effects:

1. Absence of drug after withdrawal – rebound effect.
2. Example: corticosteroids in asthma treatment.

Causes:

PATIENT: age, gender, genetic predisposition, Allergic diathesis, disease, personality,

- DRUG: e.g. anticancer drugs are cytotoxic; Digoxin has steep DRC-type a reaction, AMAs –type B reactions
- PRESCRIBER: ADR may occur if drug used for inappropriately long time (Type C), at a critical Phase in gestation (Type D) or is abruptly discontinue (Type E) or given with other drugs (Drug-drug Interactions).

Drug Dictionary:

The main goal of a medical dictionary is to bring structure and clarity to what might otherwise seem like chaos. It helps organize the countless terms that healthcare professionals and patients use to describe medical conditions, as well as the vast range of medications prescribed for treatment. By shortening complex descriptions and standardizing terminology into codes or specific terms, medical data can be efficiently recorded in databases.

This not only makes it easier to search for related conditions and treatments but also allows for clear summaries and organized data presentation, such as in reports or numerical tables.

The quality of a dictionary plays a crucial role in how data is processed. If the dictionary contains too few terms, data may need to be simplified, leading to a loss of important details.

For instance, conditions like staphylococcal bronchopneumonia and acute exacerbation of chronic bronchitis might both be generalized as "respiratory infection," erasing key distinctions. Additionally, if the dictionary's internal relationships are flawed, a case labeled as "psychological problems" could mistakenly be categorized as "psychotic" in the database an error that could cause unnecessary confusion

The World Health Organization Drug Dictionary:

This contains of the order of 45 000 proprietary drug names, with about 2600 being added annually (Uppsala Monitoring Centre, 2002). It is an international classification, giving the names used in different countries, together with all active ingredients with unique reference numbers. Drugs are classified according to ATC code.

The dictionary was started in 1968 and includes all drugs mentioned on adverse reaction reports submitted under the World Health Organization (WHO) Programmed on International Drug Monitoring. Drugs from almost 70 countries are represented, and updates are issued quarterly.

Drugs containing the same active ingredient(s) are referred to by preferred name – the international non-proprietary name (INN) in English for single ingredient drugs (or other approved name, if there is no INN). For multiple ingredient drugs, the preferred name is the first reported drug name of a given combination. Drugs are given various designations,

Medical Coding:

Medical coding is the conversion of procedures, healthcare diagnoses, medical services, and equipment into medical alphanumeric codes.

These codes act as the communicating language between doctors, insurance companies, insurance clearinghouses, hospitals, government agencies, and other health-specific organizations. ICD codes (International Classification of Diseases) to a patient's injury or sickness.

Hence medical coding is required by using standardize medical dictionaries. Data listed above like AEs, SAEs, MH, CM and any other category generally are coded. However coding AEs, SAEs and CM is mandate in any given clinical trial. There are five standardized medical coding dictionaries in the market;

COSTART:

The Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) was developed by the United States Food and Drug Administration (FDA) for the coding, filing and retrieving of post marketing adverse reaction reports. COSTART provides a method to deal with the variation in vocabulary used by those who submit adverse event reports to the FDA. Use of this dictionary allowed for standardization of adverse reaction reporting towards the FDA in a consistent way.

ICD9CM & ICD10CM:

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) is based on the World Health Organization's Ninth Revision, International Classification of Diseases (ICD-9). ICD-9-CM is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States. The ICD-9 was used to code and classify mortality data from death certificates until 1999, when use of ICD-10 for mortality coding started.

MedDRA:

Medical Dictionary for Regulatory Activities (MedDRA®) is a medical coding dictionary developed by Maintenance and Support Services Organization (MSSO). MedDRA is supported by International Conference on Harmonization (ICH) on Technical Requirements for Registration of Pharmaceuticals for Human use. Prior to development of MedDRA, there was no internationally accepted medical terminology for biopharmaceutical regulatory purposes.

WHO-ART:

The WHO Adverse Reactions Terminology (WHOART) is a dictionary meant to serve as a basis for rational coding of adverse reaction terms. The system is maintained by the Uppsala Monitoring Centre (UMC), the World Health Organization Collaborating Centre for International Drug Monitoring. The system is no longer actively maintained.

WHO-DDE:

The Uppsala Monitoring Centre (UMC) WHO Drug Dictionary Enhanced. (WHO DDE) is the most comprehensive and actively used drug coding reference work in the world. The information it contains helps ensure that clinical trial data as well as safety data is accurately coded, analyzed, interpreted and reported. MedDRA is widely used medical coding dictionaries used for coding medical terms generated in clinical trials. To maintain uniformity in reporting a term is next to impossible in any given clinical trial. However for a coder it is a challenging task to ensure that the term recorded/reported on data collection instrument (CRF/eCRF) is coded appropriately.

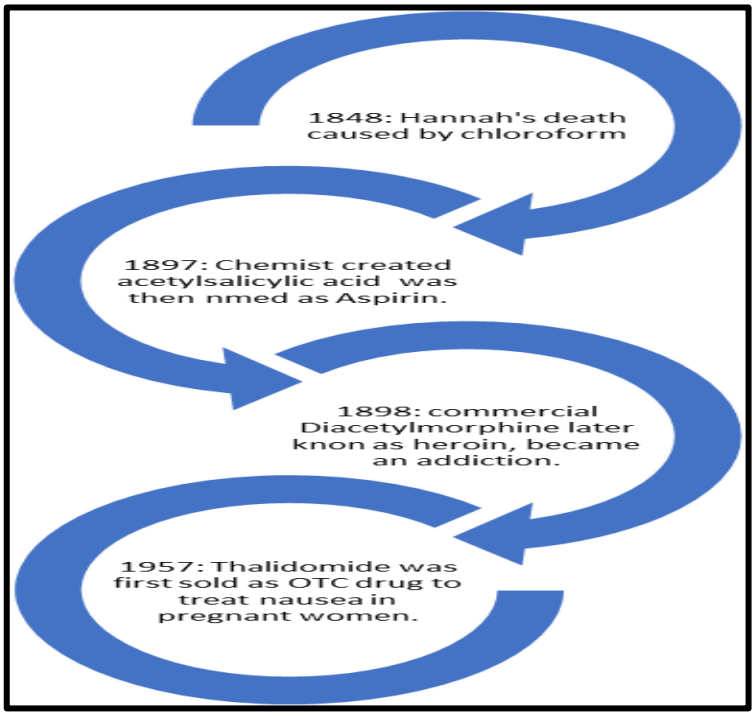
MedDRA:

MedDRA is a rich and highly specific standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. Products covered by the scope of MedDRA include pharmaceuticals, vaccines and drug-device combination products. MedDRA is open to anyone who would like to use it, although on its initial implementation in 1999, most users were based in Europe, Japan and USA. Today, it's growing use worldwide by regulatory authorities, global pharmaceutical companies, clinical research organizations and health care professionals, allows better global protection of patient health. In the entire regulatory process starting from premarketing to post-marketing and also for data entry, retrieval evaluation and presentation, the terminology is used.

In Pharmacovigilance, medical coding is required by using standardize medical dictionaries. MedDRA is a rich and highly specific standardized medical terminology developed by ICH to facilitate sharing of regulatory information internationally for medical products used by humans. It is used for registration, documentation and safety monitoring of medical products both before and after a product has been authorized for sale. This is a continually evolving area, and we are just beginning the process of standardization in the Pharmacovigilance field. If true standardization of dictionaries and their mode of use are ever achieved, then it will greatly facilitate the sharing of safety data and should improve the effectiveness of the Pharmacovigilance process.

Establishment of Pharmacovigilance Program

Pharmacovigilance is defined by the World's Health Organization as " the science and activities related to the detection, evaluation, understanding and prevention of adverse effects or other medicines/vaccine related problems."



History

Because of these events which happened in earlier years the decision was made by the Government to establish Pharmacovigilance. The Indian government has changed and amended Schedule Y of the Drug and Cosmetic Rules of 1945, realizing the promise of clinical research for new therapies. Schedule Y establishes a set of clinical trial guidelines and requirements. The Indian Council of Medical Research (ICMR) released the Ethical standards for Biomedical Research on Human Subjects in 2000, while the CDSCO issued the Indian Good Clinical Practice (GCP) guidelines in 2001.

India joined the World Health Organization (WHO) programmed for International Drug Monitoring in 1998,

but was not successful. Later, the National Programmed of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Programmed of India (PvPi) in 2010.

Development	Year
James Lind conducted the first documented clinical research establishing the effectiveness of lemon juice in scurvy prevention.	1747
More than 100 children have died as a result of sulfanilamide poisoning	1937
Chloramphenicol poisoning has been associated with aplastic anemia.	1950
Toxicity to thalidomide has caused worldwide tragedy.	1961
The 16th World Health Assembly recognizes the importance of quick action on adverse drug reactions (ADRs).	1963
The WHO is conducting research for international drug surveillance on a small scale.	1968
In India, clinical trials at the global standard level have started.	1996
India has joined the adverse drug reaction monitoring program of the world health organization.	1997
Pharmacovigilance is started in India.	1998
In India, the 67th national pharmacovigilance center was formed.	2002
The national pharmacovigilance program was established in India	2004-05
Structured clinical trials have been completed in India.	2005
PvPI (Pharmacovigilance Program) has started.	2009-10

Table no.1 Development of PV in India

- Method of causality assessment in pharmacovigilance.
  Many researchers developed various methods of causality assessment of ADRs by using different criteria like chronological between the administration of drug and the occurrence of ADRs.
- Three board categories of various methods of causality assessment.

1. Expert judgement/global introspection
2. Algorithm
3. Probabilistic method (Bayesian approaches)

1. Expert judgement/global introspection :
   Expert judgement is an individual assessment based on previous knowledge and experience in the field using no standardized tool to arrive at conclusions regarding causality.

- These are some evaluated causal relationship considering different factors: Swedish method by Wilhom.
  It was used by a Swedish regulatory agency. The clinician evaluates the causal relationship by considering seven different factors:

1. The temporal sequence
2. Previous information of drug

3. Dose relationship
4. Response pattern of drug
5. Rechallenge
6. Aetiological candidate
7. Concomitant drugs

World Health Organization (WHO) - Uppsala Monitoring centre (UMC) causality assessment criteria -
WHO-UMC system has been developed in consultation with the National Centers participating in the programmed for international drug monitoring and it is meant as a practical tool for the assessment of case reports. Since, PV is particularly concerned with the detection of unknown and unexpected adverse reactions then this method gives guidance to general arguments which should be used to select one category over another.

The WHO-UMC causality assessment method includes the following criteria :

A) Time relationship between drug use and adverse event.
B) Absence of other competing causes. (Medication, disease process itself)
C) Response to drug withdrawal or dose reduction. (dechallenge)
D) Response to drug administration. (rechallenge)

Categories	**Time sequence**	**Other drugs/disease rule out**	**Dechallenge**	**Rechallenge**
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

Table no.2 WHO-UMC causality assessment method.

- Algorithms

An algorithm is a problem specific flow chart with step-by-step instructions on how to arrive at an answer. It is a clinical instrument in the form of a questionnaire that gives detailed operational criteria for ranking the probability of causation when an ADR is suspected. Algorithms give structured and standardized methods of assessment in a systematic approach to identifying ADRs based on parameters such as time to onset of the ADR or temporal sequence, previous drug/ adverse reaction history and rechallenge or dechallenge.

Individual cases are approached systematically, resulting in a high degree of consistency and reproducibility. Clinical judgement is, however, required at various stages to arrive at a conclusion.

Currently, there are many algorithmic methods of causality assessment but no single algorithm is accepted as the 'gold standard', because of the shortcomings and disagreements that exist between them.

There are few algorithmic methods:

- **Dangaumou's French method :**

This method has been used by a French regulatory agency since 1977. This method separates an intrinsic immutability (possible cause between drug and clinical event) from an extrinsic immutability (bibliographical data) using seven criteria. There are 3 chronological and 4 semi logical criteria.

- **The chronological criteria are as follow:**

1. Drug challenge
2. Rechallenge and
3. Dechallenge

With an overall score of four possible criteria.

- **The semi logical criteria are as follow:**

- Semiology (clinical sign) per se (suggestive/other)
- Favoring factor
- Alternative non-drug related explanation (none/possible)
- Specific laboratory test with three possible outcomes (positive, negative or no test for event-drug pair).
- **Kramer et. al method :**
  This algorithm is applied to a single clinical manifestation occuring after administration of a single suspect drug. In cases where multiple drugs are involved, each is assessed separately. One of the advantages of this algorithm is its transparency. However, certain levels of expertise, experience and time are required to use this method effectively.
- **Naranjo et. al method (Naranjo scale) :**
  It is used to assess causality in a variety of clinical situations using the conventional categories.
  It consists of 10 questions (Table no.3) that are answered as 'Yes', 'No' and 'Unknown' (don't know).

Questions	**Yes**	**No**	**Don't know**
Presence of previous conclusive report on adverse reaction.	+1	0	0
Did the adverse event appear subsequent to administration of the suspected drug?	+2	-1	0
Did adverse events improve on drug discontinuation or on administration of specific antagonists?	+1	0	0
Did the adverse event reappear when the drug was re-administered?	+2	-1	0
Are there any alternative causes other than the suspected drugs that could have caused the reaction on their own?	-1	+2	0
Did the adverse event reappear when the placebo was administered?	-1	+1	0
Was the incriminated drug detected in toxic concentrations in blood (fluids)?	+1	0	0
Did the adverse event worsen on increasing the dose or decreased in severity with lower doses?	+1	0	0
Past history of any similar reaction to the same or similar drugs.	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Table no.3 Naranjo Scale

- **Balanced assessment method (Lagier et. al)**
  It evaluates the case reports on a series of Visual Analogue Scale (VAS), according to the likelihood each criterion is fulfilled. Its advantage is that it considers the possibility of an alternative to causation for each of the factors and not just as a separate factor. Although each case is assessed by two independent assessors, the evaluation still depends to a large extent on the level of assessor's knowledge. An evaluator needs to be an expert in the particular area to make a reliable evaluation.
- **Ciba geigy method (Venulet et. al) :**
  This method resulted from a number of expert consensus meetings. Experts used their clinical judgement to assess events and assign causality on a VAS. This method was updated and replaced with a checklist of 23 questions, split into 3 sections:

1. History of present adverse reactions.
2. Patients past adverse reaction history.

3. Monitoring physician's experience
   This method reflects the knowledge and experience of the evaluator, and the type of ADR is evaluated.

- **Loupi et. al method :**
  It is developed to assess the teratogenic potential of drugs. The first section of algorithms (Chrono- semi logical axis) allows for the drug to be excluded if not implicated in the origin of the abnormality. The second section (bibliographical axis) weights the bibliographical data. The three questions consider alternative etiological candidates other than the drug; chronology of the suspect drug and other bibliographical data, to arrive at a conclusion on causality.
- **Roussel Uclaf causality assessment method (RUCAM) :**
  This method is designed for predetermined disease states such as liver and dermatological injuries. Although this method seems quite easy to use, it is organ specific.
- **Maria and victorino (M & V) scale :**
  M&V developed this scale for diagnosing drug induced liver injury (DILI). Probability was expressed as a score between 6-20, divided into five causality degrees (score of > 17, Definite; 14-17, Probable; 10-13, Possible; 6-9, Unlikely; < 6). Diagnosis of DILI is complex and requires experienced clinicians in order to be accurate.
- **Probabilistic or Bayesian Approaches :**
  Bayesian methods for causality assessment make use of specific finding in a case to transform a prior into a posterior probability of drug causation. The prior probability is calculated from epidemiological information with the evidence in the individual case. This method allows the simultaneous assessment of multiple causes.
- **Australian method :**
  It is one of the first probabilistic methods used. Conclusions are drawn from internal evidence, such as timing and laboratory information from case reports. Previous knowledge on the suspect drug profile is deliberately excluded in the assessment. Likelihood decisions are made only on the likelihood of a causal relationship.
- **Bayesian Adverse Reaction Diagnostic Instrument (BARDI) :**
  Bayesian Adverse Reaction Diagnostic Instrument (BARDI) was developed to overcome the numerous limitations associated with expert judgements and algorithms. The BARDI is used to calculate the odds in favor of a particular drug causing an adverse event compared with an alternative cause. These odds are referred to as the posterior odds. The posterior odd factor is calculated by considering six assessment subsets: one deals with background epidemiologic or clinical trials information (the prior odds) and the other five deal with case specific information (the likelihood ratios). The prior odds (PrO) factor is the ratio of the expected drug-attributable risk and the background risk of a certain adverse event in a population sharing basic characteristic with the patients being considered (such as medical condition).the five likelihood ratios (LRs) deal with any information of differential diagnostic value under the categories of the adverse event (Ch); drug dechallenge (De), which refers to any sign, symptoms, occurrences after the drug withdrawal; and drug rechallenge (Re) or read ministration of the suspected causal drugs. The product of these factors is the posterior odds (PsO).
  PsO = PrO × LR(Hi) × LR(Ti) × LR(Ch) × LR(De) × LR(Re). Re).
  The Bayesian approach can be implemented as a spreadsheet programmed on either paper or computer. It calculates and provides instant numerical and graphical feedback as soon as new piece of evidence of the suspected ADR are evaluated.
- **Information resources in pharmacovigilance :**
  There are six information resources in PV:

1. Primary sources
2. Secondary source
3. Tertiary sources
4. Other

1. Primary sources:
Primary sources are original material/information on which other research is based. It includes journal articles of original research, conference paper, dissertation, technical reports, and patents.

1. **Journals or Periodicals :**
   These are the main types of publication in which scientific research is reported. These may be published by learned societies or by commercial publishers. A researcher submits an article to a journal. It is referred to by an editorial board of experts in that field before being accepted/rejected for publication.
2. **Theses :**
   These present detailed accounts of research conducted for the awarding of higher academic degrees. The research is assessed by external examiners before the degree is awarded. In many cases, it will also be later reported in a condensed form as a journal article.
3. **Conference :**
   These are important avenues dor reporting new research or developments. Paper presented may or may not be subject to editorial scrutiny. Conference papers can be not published only in abstract form, published in advance of the conference as a prepoint, published in book form, or a special issue of a journal.
4. **Reports :**
   It includes individual publications reporting research. They may report internal research within an organization, or research done by an individual or organization under contract to a client. They can be freely available, available only to members of the report and will also be published in journal articles, but more often the report is the only source of information.
5. **Patents :**
   They provide research information on new products or processes. Once published, patent information is freely available but rarely republished in journal articles.

2. Secondary sources:
Secondary sources analyze, evaluate, interpret, repackage, summarize or reorganize information reported by researchers in the primary literature. These includes:

1. **Review journals :**
   These generally start with an annual review which gives more information about current drug effects.
2. **Article reviews :**
   Articles that summarize the current literature on a specific topic.
3. **Data compilations :**
   Statistical databases (SEERS), Vital & Health Statistics, etc.
4. **Article indexes/ Databases :**
   These can be abstracting or a citation (eg. Biological Abstract/ MEDLINE).

3. Tertiary sources:
Tertiary sources consist of primary and secondary source information which has been collected and distilled. The present summaries of or an introduction to the current state of research on a topic, summarize or condense information from primary and secondary sources, or provide a list of primary and secondary sources of more extensive information.
Examples are: 1. Encyclopedias, Almanacs,
2. Textbooks, reference books, Fact books,
3. Research Quick starts/library course pages/pathfinders

4. Other :

1. Daily med
2. Medline Plus
3. FDA
4. Centers for disease control and prevention (CDC)
5. Drug enforcement Administration (DEA)

There are few more methods of Pharmacovigilance:

1. Passive surveillance
2. Spontaneous reports
3. Stimulated reporting
4. Comparative observational studies
5. Targeted clinical investigation

6. Descriptive studies

1. **Passive surveillance :**
   This kind of spontaneous reporting system, known as pharmacovigilance places the onus of detecting and reporting adverse drug reaction (ADR) on healthcare personnel. Passive surveillance is simple to conduct,and in most cases,once the procedure are established (who to report, case definition, and laboratory confirmation). It is not a huge burden on the reporter.
2. **Spontaneous report :**
   A spontaneous report is a voluntary communication by healthcare professional or consumer to a company, regulatory authority or other organization (e.g. WHO, Regional centers, poison control center) that describes one or more adverse drug reactions in a patient, who was given one or more medicinal products and that does not derived from study or any organized data collection scheme. Spontaneous reports play a major role in identification of safety signals once a drug is marketed. It can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reaction.
3. **Stimulated reporting:**
   Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (eg. hospital) for new products or for limited time periods. Such methods includes on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on pre-designed method.
4. **Comparative observational studies :**
   The primary purpose of these research is validation of signals derived from case series or spontaneous reports. It is a conventional approach to assessing adverse medication occurrences.
   Major types of these designs are:

1. Cross-sectional study (survey)
2. Case-control studies
3. Cohort studies

5. **Targeted clinical Investigation:**
   When significant risks are identified from pre-approval clinical trials, further clinical studies might be called to evaluate the mechanism of action for the adverse reaction. Pharmacodynamics and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse reaction. Genetic testing can also provide clues about which groups of patients might be at an increased risk of adverse reactions.
6. **Descriptive studies:**
   Descriptive studies are an important component of Pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/ establish the prevalence of the use of drugs in specified populations.

- Communication in Pharmacovigilance:
  Central to effective and timely communication between FDA and sponsors is the ability to communicate clearly, both orally and in writing, inside and outside the formal meeting format. Communication should be conducted via the FDA project manager, typically the review division RPM, rather than FDA reviewers, team leaders, or senior management to ensure that the advice is appropriately vetted and documented.

1. Meetings between FDA and sponsors :
   Sponsors can request a meeting with FDA at any time during drug development to resolve questions and issues. These meetings may also help to minimize wasteful expenditures of time and resources and thus help to speed the drug development and evaluation process. FDA provides feedback to sponsors via the formal meeting process in three main formats: face-to-face, teleconferences, and written response only.
2. **Written correspondence from FDA :**
   FDA project managers will use established letter templates to ensure consistency and accuracy in regulatory communications. Project managers should send courtesy copies of written FDA correspondence to sponsors when such communications are time-sensitive or communicate action.Submission from sponsors :
   FDA regulations describe general principles of as well as content and format requirements for INDs complete

and well-organized sponsor submission can increase the efficiency of FDA review. FDA encourages sponsors to identify issues or areas of concern in their submission by describing them fully and soliciting feedback on specific areas of concern where further progression in drug development depends largely on receiving FDA feedback.

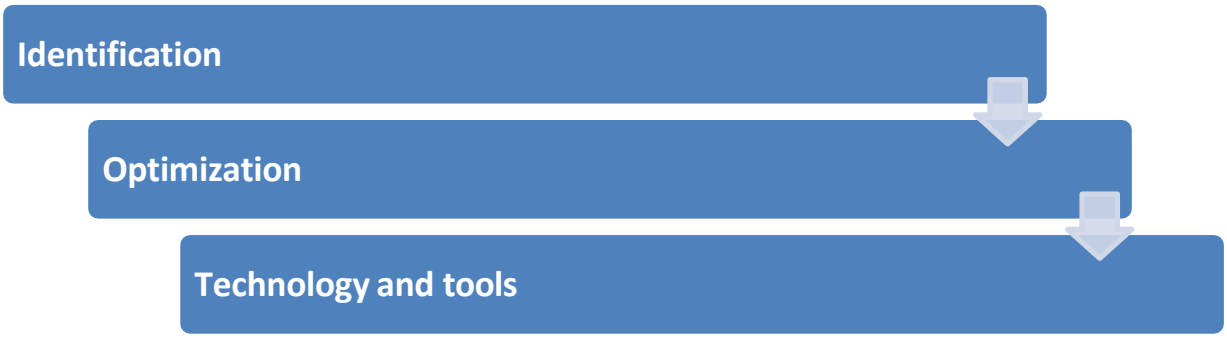
3. **Email between FDA and Sponsors :**
   Sponsors should establish secure email with FDA to allow for informal communications that may include commercial confidential information. Use of secure email allows transparent and complete communication between FDA and sponsor. However, it is not a substitute for formal submission. Formal submission should be submitted to the respective centers document room (paper submission) or via the electronic gateway, as applicable.
4. **General Telephone Calls Between FDA and Sponsors :**
   General or administrative questions are suitable for informal telephone communications between sponsors and FDA project managers. However, when complex, regulatory or technical issues are discussed via telephone between the sponsor and the FDA project manager, the caller should follow-up with a written communication to document the discussion and/or respond to information requested during the conversation.
5. **Faxes between FDA and Sponsors :**
   Although it is not a substitute for formal submissions, a fax can be used when secure email has not been established between FDA and sponsors. Before transmitting the fax, sponsors and FDA managers should contact their respective counterparts to arrange for confirmation of receipt.

DATA GENERATION IN PHARMACOVIGILANCE-

The medicinal product's safety and efficacy should be demonstrated by clinical trials which follow the guidance in 'Good Clinical practice: Consolidated guidelines' (ICH E6) adopted by the ICH 1May 1996. The statistic's role in clinical trial design and analysis is acknowledged as essential in that ICH guidelines. Clinical trials provide the affording evidence basis for regulatory approvals of safe and effective medicines. With long development cycles and ever- increasing costs in conducting clinical trials, both the pharmaceutical industry and regulators are to do something to be more proactive in safety evaluations. Early safety signal detection detected both the better patient protection and the potential to save development costs. Since clinical trials experiment are in humans, they must be conducted that established standards in that order which protect the rights, safety and wellbeing of the participants. These standards contain the International Conference of Harmonization Good Clinical Practice (ICH-GCP) guidelines. The Clinical trials globalization has presented additional challenges to the sponsors. The sponsors are held accountable to comply with contingent local legal and regulatory requirements wherever the clinical trials are accompanied. For example, clinical trial accompanied in the European Union is required to be accompanied in accordance with the Clinical Trials Directives. Central Component that is safety evaluation in all stages of drug development lifecycle. Proceeding to the marketing legitimatization of drug, meticulous safety monitoring and evaluations from preclinical to all stages of clinical trials are required. Pharmaceutical sponsors need to competently characterize the safety profile of the product in order to obtain consistently approval and marketing legitimatization. The authorized product label contains the prerequisite information about the product's benefits and risks. In some cases, new appearing safety profiles may cast the original benefit-risk judgments in doubt. These are revealed in some High profile market withdrawals, such as Troglitazone , Rofecoxiband Rosiglitazone (Avandia). In 2005, the United States Food and Drug Administration (FDA) issued guidance documents on risk management activities, Including premarket risk judgement and post marketing pharmacovigilance and Pharmacoepidemiologic judgments of project.

The data generation includes different phases-It include drug discovery and development.

DRUG DISCOVERY



DEVELOPMENT

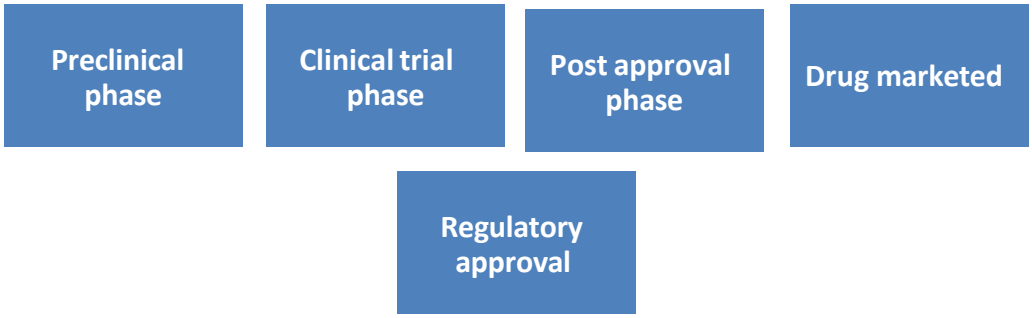


Fig.1 Data generation at different phases.

Drug discovery-

1. Identification-It is the process of identification of chemical components for discovery process. It include solubility,stability,purity,bioavailability.
2. Optimization-In optimization involve synthesis and characteristic properties of component.
3. Technology and tools-It is used for extract information on the molecular structure of components and interaction at atomic level.

Development-

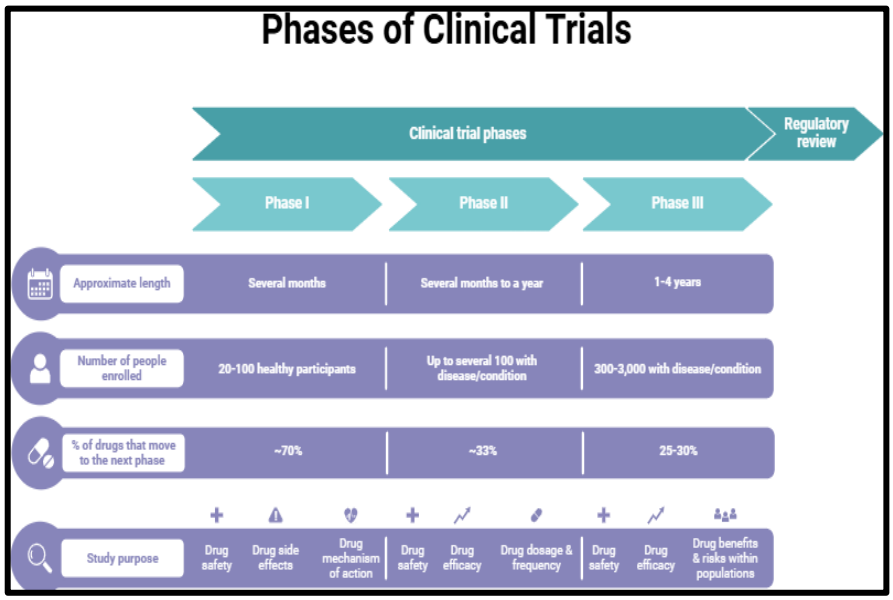
1. Pre-clinical phase-

- It involve in-vivo and in-vitro studies.
  Ex-toxicity,include repeat dose toxicity,nephrotoxicity,hepatotoxicity,carcinogenecity.
- It include general pharmacology
- Drug interaction
- Toxicity related data

2. Clinical trial phase-

- It include 4 phases -phase 1,2,3,4
- In **phase 1** clinical trial it is study of how drug absorbed ,distributed,metabolized and excreted by the human body
- It also identify side effects.
- In phase 2 clinical trial may satisfaction from their involvement if they encounter an active treatment .
- This **phase 2** clinical studies are scrambled .Larger no.of patients collect a treatment in phase 2 clinical trials there is information on side effects as well as effectiveness.
- In **phase 3** clinical trials it confirm effectiveness,monitor side effects so in this multiple patients are treated.Testing on large no. of patient populations permits continuous generation of data on drug safety and efficasy.

- In **phase 4** they provide additional information after approval .



Post approval phase-

- It is based on core principle that patient health and safety are critical factors to be considered when manufacturing and marketing pharmaceutical products.
- It monitor the risk associated with pharmaceutical products.

4. Drug marketed-

- In this there is planed to secure the safety of a drug once it announced onto the market.
- They monitor adverse effects

5. Regulatoryapproval –

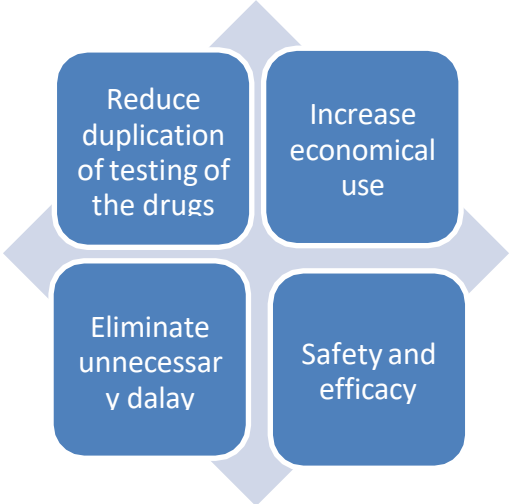
- Regulatory approval for process for ensuring that a medicine is safety and ifficasy for use in patients.
- It involve process of monitoring .

ICH GUIDELINES IN PHARMACOVIGILANCE-

ICH stands for **International conference on harmonization**. It is established in April 1990.

Purpose of ICH-

ICH has published a number of documents for safety, both clinical and pre-clinical. These guidelines include



S designation .eg.S1, S2.Clinical safety guidelines are designates as E.

ICH Guidelines are -

E1A-The population extent exposure to asses to clinical safety.

E2A-Clinical safety data management-definition and standard for accelerated reporting.
E2B-Clinical safety data management -Data elements for transference of individual case reporting.
E2C-Clinical safety data management-periodic safety update report for Merchandise drugs.
E3-Clinical study reports contents and structure.
E4-Dose -Response details to support drug registration.
E4-Ethnic factors in the applicability of foreign clinical data.
E5-Consolidated guideline of good clinical practice.
E7-Considered in support of special population geriatric.
E8-General deliberation for clinical trials.
E10-Alternative of control group in clinical trials.
M1-Hormonization of medical terminology for regulatory purpose.
M3-Non-clinical safety studies for the managing of human clinical trials for pharmaceutical.

- **Indian agencies-**

The world health organization initiated an agencies include all adverse reactions possessed by drugs. It also include awareness about adverse drug reactions has resulted in the emergence of the practice and science of Pharmacovigilance. 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 isvery 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.

Agencies-

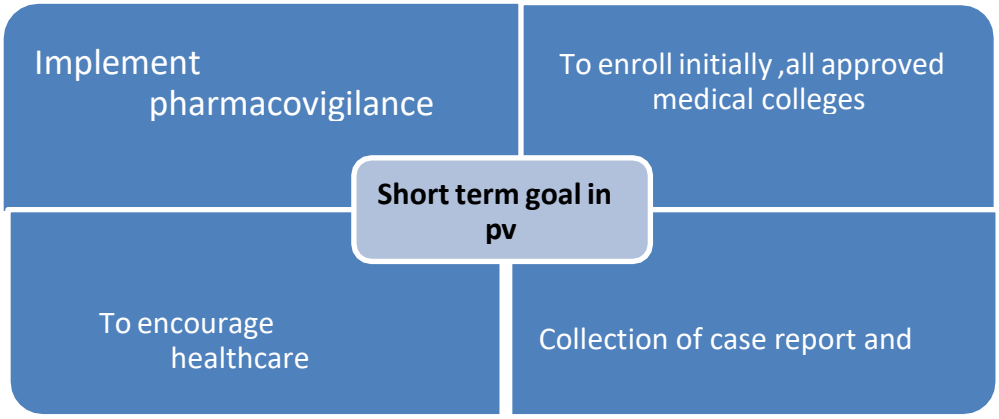
1. **Pharmacovigilance programmed in India Pvpi-**

The Pharmacovigilance Programmed 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 in the country of safe guiding public health. It is managed by the Indian pharmacopoeia commission Ghaziabad. This agency is for collect, analyze, monitoring ADRs through adverse drug reaction monitoring centers across the country.

This agency has aim to improve patient safety in Indian population by monitoring the drug safety and reducing risk regarding 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 about safety of drug to minimize the risk.
- 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 the globe.



2. **Adverse drug reaction monitoring [AMCs]-**
   Currently, 179 medical council of India approved teaching hospitals and corporate hospitals have been identified as ADRs monitoring centers across the country. This agency are connected with international networking .Number of these agencies in India is across the 600.Its main role is to collect the ADR report from healthcare professionals and forward them to PvPI for assessment.
3. **Central drugs standard control organization [CDSCO]-**
   ADR monitoring and reporting to national regulatory authority are put in place in many countries. In India PvPI closely working with CDSCO, drug regulatory authority of India. CDSCO understands that pharmacovigilance plays a specialized and pivotal role in ensuring ongoing safety of medicinal products in india and it seeks inputs from NCC before taking any kind of regulatory decisions.
   Main role of CDSCO is

1. Approves new drugs and clinical trials.
2. Ensure compliance with good pharmacovigilance practices.
3. Issues guidelines for reporting ADRs.

4. **Revised national tuberculosis control programmed [RNTCP]-**
   The monitoring of safety of medicines used in national health programmed has been identified as a matter of concern. The safety issues are apparent in the use of medicines for the treatment of tuberculosis, malaria, HIV etc. RNTCP is one of the largest program in India A diagnosed TB patients on treatment under RNTCP takes more than one anti-tubercular drug simultaneously with regimens lasting from 6 months to 2 years or more. It is the spontaneous ADR reporting system. These report are send to pharmacovigilance programmed of India and national coordination of India at IPC.
5. **Drug controller general of India [DCGI]-**
   This agency is under CDSCO. It regulate clinical trials and post marketing surveillance and issues safety alerts and drug recalls based on PV data. DCGI should act rapidly to improve PV so as to integrate good pharmacovigilance practice into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety. The DCGI establishes standards for the manufacturing, sales, import, and distribution of drug in India. It also regulates medical and pharmaceutical devices. He ensure that uniformity in the implementation of the drugs and cosmetic act.
6. **National co-ordination center [NCC]-**
   New Delhi selected as national coordinating center to safe guard public health by validating the safety of products. About adverse drug reaction monitoring centers were established in the year 2010.The NCC was transferred from AIIMS, new Delhi to IPC and Ghaziabad on 15th April 2011 for smooth and efficient functioning of program.
7. **Ayurveda, siddha, Unani program [ASU]-**
   Ayurveda, siddha, unani systems are being practiced in India It is associated with clinical safety. Ayurveda has categorized toxic plants separately and for their special processing is essential. There is wide spread misconception that all drugs of ‘natural’ origin are ‘safe’. There is also common belief that long term use of

a medicine based on tradition, it assure both safety and efficacy of medicines.ASU and H medicines are used in conjunction with other medicines, there is possibility of drug interactions. There are many ex. of ASU and H medicines being adulterated or contaminated with allopathic medicines, chemicals such as corticosteroids, on-steroidal anti-inflammatory agents etc. It was considered as remedies for natural resource are safe and devoid adverse drug reaction ,'Charka Samhita 'which is the heart of Ayurveda that ADR can occur with herbal drugs also if they are dispensed improperly, hence to put PV for Ayurveda, siddha, unani [ASU] was highly essential to provide ADR data of AYUSH drugs as per WHO guidelines.

Applications-

- Building a network of pharmacovigilance.
- To detect, assess, understand, and prevent adverse drug reaction.
- Monitoring medications.
- Safety and efficacy of drug.
- Detection and prevention of ADRs
- They help healthcare professionals
- Support regulatory agencies like FDA, EMA, WHO.
- Develop risk minimization strategies.
- Signal detection and benefit-risk assessment.

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