UNIT-1

PHARMACOVIGILANCE

YEAR 24

UNIT -1

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INTRODUCTION TO 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. • Spontaneous reporting of adverse events and adverse drug reactions is the commonest method utilized for generating safety data.

• The etymological roots for the word Pharmacovigilance are: Pharmakon (Greek) = medicinal substance, and Vigilia (Latin) = to keep watch.

• Pharmacovigilance is branch of pharmacoepidemiology but is restricted to the study, on an epidemiological scale, of drug events or adverse reactions.

• Here ‘events’ means, recorded happenings during a period of drug monitoring in the patients notes, it may be due to the disease for which the drug is being given. 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 dissemination of information needed to improve drug prescribing and regulation.

• Pharmacovigilance promotes the systematic, rational use and assures the confidence for the safety of drugs. It improves Patient care and safety, Public health and safety. • The related fields to promote or encourage the Pharmacovigilance studies are Pharmaceutical industry, Paramedics, Pharmacists, and Practicing Clinicians etc

. • Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable. Pharmacovigilance concentrate on only drug monitoring and its process includes – Collect and record of AEs/ADRs – Causality assessment and analysis of ADRs – Collate and code in database – Compute risk-benefit and suggest regulatory action – Communicate for safe use of drugs among stakeholders

• Adverse effects are manifold and numerous. Pharmacovigilance and signal detection are the activities to try and do for a drug (both pre and post marketing) to see adverse events & to suggest a new potentially causal association.

• AE/ADR REPORTS: SOURCES

– Reporting Systems: From Health care Professionals (voluntary)-high incidence of under reporting

– Published scientific literature: From Pubmed, Scopus etc.

– Periodic Safety Update Reports (PSUR) 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:

– 1. Medication errors and irrational use of medicines

– 2. Herbal, traditional and complimentary medicines

– 3. Substandard medicines and counterfeit medicines

– 4. Blood products, biologicals, 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 was 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

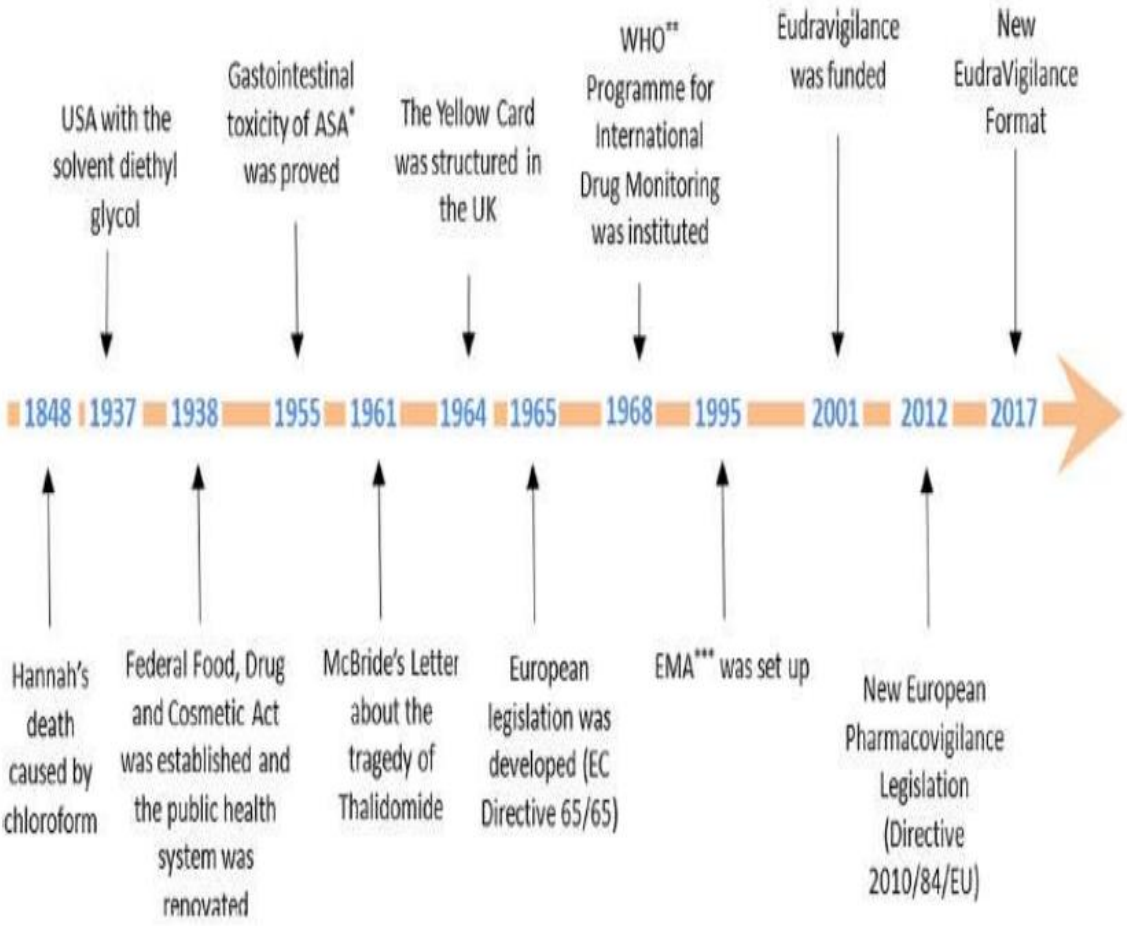


Fig. 1 Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; **WHO: World Health Orgnaisation; ***EMA: European Medicines Agency

Thalidomide: The tragedy of birth defects

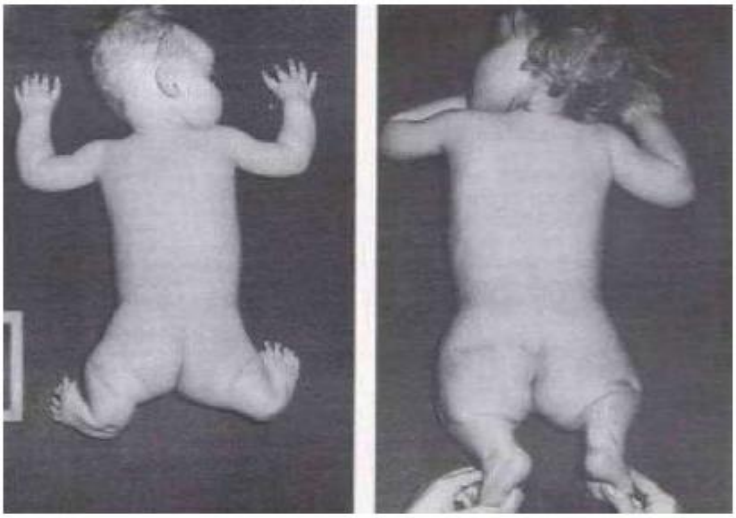
• Thalidomide was a widely used drug in the late 1950s and early 1960s for the treatment of nausea in pregnant women.

• It became apparent in the 1960s that thalidomide treatment resulted in severe birth defects in thousands of children (teratogenicity).

• Though the use of thalidomide was banned in most countries at that time, thalidomide proved to be a useful treatment for leprosy and later, multiple myeloma.

Thalidomide Disaster:

The thalidomide tragedy marked a turning point in toxicity testing, as it prompted United States and international regulatory agencies to develop systematic toxicity testing protocols; the use of thalidomide as a tool in developmental biology led to important discoveries in the biochemical pathways of limb development.



Importance of safety monitoring of medicine

• The US Federal Food and Drug Act was formed on June 30, 1906, and it established that drugs must be pure and free of any contamination. Furthermore, in 1911, this organization forbade false therapeutic indications of drugs.

• Drug safety monitoring is a risk mitigation exercise in which the ADRs caused by therapeutic drugs, biologicals or devices can be explored, prevented or minimized.

• It is the process of identifying expected and unexpected adverse reactions resulting from the use of medicines in the post-marketing phase.

• It is known, that the medicines developed for treatment of diseases, have also side effects, sometimes dangerous for life.

• Revealing, registration and analysis of the ADR (Pharmacovigilance) are necessary for the subsequent specification of the drugs' indications, contra-indications, side effects, dosages, etc.

• "Health care institutions, drug stores, institutions and the organizations which are consuming and using medicines, are obliged to inform the authorized governmental body about all cases of development of unknown adverse reactions immediately".

• Other relevant issues regarding safety monitoring of medicine

- Substandard medicines
- Medication errors
- Lack of efficacy reports
- Use of medicines for indications that are not approved and for which there is inadequate scientific basis.
- Case reports of acute and chronic poisoning
- Assessment of drug-related mortality
- Abuse and misuse of medicines
- Adverse interactions of medicines with chemicals, other medicines, and food

Report Form:

The Report Form has four sections:

A. INFORMATION ABOUT PATIENT:

This section includes the personal information of the patient:

– Name, surname (may be encoded in purpose of keeping confidentiality)

– Age or date of birth

– Sex

– Weight

B. ADVERSE DRUG REACTION OR MANUFACTURING PROBLEM :

This section is for the description of the adverse drug reaction or manufacturing problem and includes the following information: –

Marking of adverse reaction or manufacturing problem

– Date of event

– Date of report

– Motivation for sending the report (death, life-threatening, hospitalization, disability, congenital anomaly, other)

– Description of adverse reaction or manufacturing problem

– Used diagnostic methods

– Short description and peculiarities of the disease

C. SUSPECTED DRUG(S)

This section is for pointing out the suspected drug or drugs that are related to the adverse reactions. The section includes the following information: –

- Name

-Drug form

- Manufacturer

-Batch

-Dose

–Indications for use

-Duration

D. INFORMATION ABOUT THE REPORTER

This information has to be introduced completely, in case it is necessary to contact the reporter for getting detailed data of the case. The section includes the following information: -

-Name

-Address

-Phone no.

-Profession

-Occupation

WHO International Drug Monitoring Programme

1) The WHO Programme for International Drog Monitoring (PIDM) was established in 1968. This Programme provides a forum for Member States of WHO for working together in monitoring of drug safety. It also facilitates in identifying and analyzing the adverse reaction signals from the documented data handed over to the WHO global individual case safety report (ICSR) database by the respective member countries

2) There are more than 150 countries in the WHO Programme for International Drug Monitoring. All these countries have a common vision of safer and more effective use of medicines. They operate their working nationally and internationally work as a team for identification and monitoring the harm caused by medicines, to reduce patient's risks and to establish the pharmacovigilance systems and standards globally. However, since 1978 the Uppsala Monitoring Centre (UMC) controls and operates all the technical and operational aspects of the programme.

3) In 1968 the WHO programme was established to make sure that all the data on adverse reactions on patients was collected from maximum sources. This would allow the individual countries to become alert about the pattern of adverse reactions occurring all over the world and that may not be evident from the local reported adverse drug reactions only.

4) The WHO programme includes three-part network:

(i) The headquarters of WHO located in Geneva, Switzerland manages all the issues related to any type of policy.

(ii) National pharmacovigilance centers from member countries of WHO coordinated for all the case reports sent to the WHO Individual Case Study Report (ICSR) database. The Uppsala Monitoring Centre (UMC) located in Sweden manages all the reports.

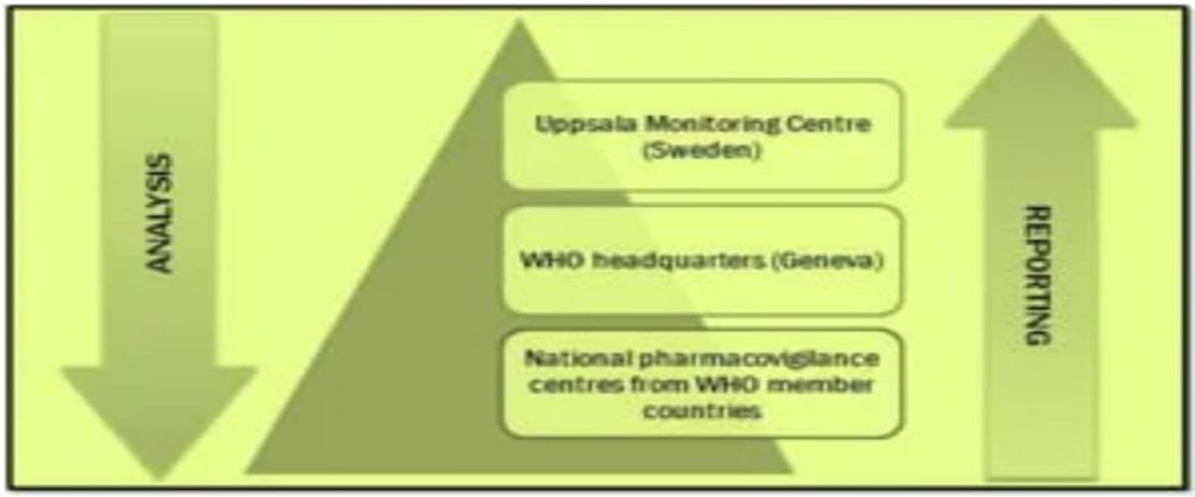
(iii) The Uppsala Monitoring Centre (UMC) supervises the WHO programme operations, including:

a)Collection, assessing and communicating the information from all the WHO member countries about the effectiveness, toxic effect, benefits, and risks of medicinal products

b) Collaboration with member countries for practice and developing pharmacovigilance,

c) Warning the National Regulatory Authorities (NRAs) of member countries about probable drug safety problems through WHO signal process.

5) As per the data, more than 100 countries joined the WHO programme till June 2012, and more than 30 members associated were waiting for compatibility between the national and international formats of reporting.



Pharmacovigilance Programme of India (PvPI)

Directorate General of Health Services, Central Drugs Standard Control Organization (CDSCO), under the guidance of Ministry of Health & Family Welfare, Government of India in collaboration with Indian Pharmacopeia commission, Ghaziabad initiated a nation-wide Pharmacovigilance Programme (PVPI) for the protection of patient's health by providing safety from the drugs. However, Indian Pharmacopeia commission (IPC), Ghaziabad coordinates these Programs as a National Coordinating Centre (NCC).

1) On 14th July 2010 the Government of India started the Pharmacovigilance Programme of India (PvPI) with All India Institute of Medical Sciences (AIIMS), New Delhi as its first National Coordination Centre (NCC) for monitoring Adverse Drug Reactions

(ADRs) in the country for purpose of safety and protection of public health.

2) 22 ADR monitoring centres including AIIMS, New Delhi in the year 2010 were set up under this Programme.

3) However, on 15th April 2011 the National Coordination Centre was later shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh from All India Institute of Medical Sciences (AJIMS, New Delhi) in order to safeguard and protect implementation of this programme in a better way.

4) Join India Indian Pharmacopoeia Commission- Pharmacovigilance Programme in India (IPC-PVPI) became the National Coordination Centre (NCC) for Materiovigilance Programme of India (MvPI).

5) In July, 2017 Indian Pharmacopoeia Commission (IPC), National Coordination Centre for Pharmacovigilance Programme in India (NCC-PVPI) became a WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes & Regulatory services.

Mission and vision of PvPI

• The mission of PvPI is to safeguard the health of the Indian population by ensuring that the benefit of use of medicine outweighs the risks associated with its use.

• Since there exist considerable social and economic consequences of adverse drug reactions and the positive benefit/cost ratio of implementing 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 vision of PvPI is to improve patient safety and welfare in Indian population by monitoring drug safety and thereby reducing the risk associated with use of medicines.

• The ultimate safety decisions on medicines may need considerations of comparative benefit/risk evaluations between products for similar indications, so the complexity is great

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

• The broadened patient safety scope of Pharmacovigilance includes the detection of medicines of substandard quality as well as prescribing, dispensing and administration errors.

• Counterfeiting, antimicrobial resistance, and the need for real time surveillance in mass vaccinations are other Pharmacovigilance challenges which need to be addressed.

Scope and Objectives

• To create a nation-wide system for patient safety reporting.

• To identify and analyze new signal from the reported cases.

• To analyze the benefit – risk ratio of marketed medications.

• To generate 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 centre 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 across globe.

• To promote rational use of medicine.

ADVERSE DRUG REACTIONS (ADRS)

Definition :

Adverse drug reactions can be defined by different terms by different scientists.

1) Schatz et al in 2015 defined ADR as "undesirable, unwanted effect of any drug that occurs when used at any usual clinical condition".

2) Edwards et al in 2000, defined adverse drug reaction as "an unpleasant or appreciably harmful reaction occuring due to an intervention related to medication use, which might predict harm from forthcoming administration and permits specific treatment or prevention, or change in the the dosage regimen, or product withdrawal."

3) Adverse drug reactions as per WHO (2005) can be defined as "any response to a drug which is noxious and unintended and which occurs or doses normally used in a man of prophylaxis diagnosis or therapy of disease or for the modification of physiologic function".

Classification of ADRS

Adverse drug reactions can be classified into five types depending on:) Depending on Onset of Event: Acute (<60 minutes), Sub-acute (1-24hours), latent (> 2 days)

2) Based on Type of Reactions:

i) Rawlins and Thompson classification (1991):

Type A (Augmented Reactions),

Type B (bizarre reactions),

Type C (chronic reactions),

Type D (Delayed type reactions),

Type E (end of treatment).

ii) Wills and Brown Classification: Type A (Augmented Reactions), Type B (bizarre reactions), Type C (chronic/Chemical reactions), Type D (Delayed type reactions), Type E (end of treatment), Type F (Familial reactions), Type G (Genotoxicity), Type H (Hypersensitivity), Type U (Unclassified).

3) Based on Severity: Minor, Moderate, Severe, Lethal.

4) Depending on Whether They Could Take Place in Any Patient, or in a Specific Susceptible Population:

i) Reactions that might take place in anyone: Drug overdose, Drug side effect, Drug interaction.

ii) Reactions that Take Place Only in Susceptible Individuals: Drug intolerance, Drug idiosyncrasy, Drug allergy, Pseudoallergic reaction.

5) Others: Secondary effects, Toxic effects, photosensitivity, drug dependence, drug withdrawal reactions, teratogenicity, mutagenicity, carcinogenicity, drug induced disease (latrogenic reactions).

Objectives of ADR Monitoring

1) To identify the nature and frequency of ADRs.

2) To assist the Drug Regulatory Authority, Public Health Programmes, Scientists and Consumer Society to minimise ADRs.

3) To deliver updated Drug Safety Information to Health Care Professionals.

4) To spread information by organising proper education programme to consumers.

5) To find the risk factors which can predispose induce or influence the development, severity and incidence of ADRs.

Benefits of ADR Monitoring

1) It provides information regarding quality and safety of pharmaceuticals products.

2) It introduces risk management plans.

3) It inhibits the possible adverse effects and assists in determining ADR occurrence.

4) It provides information to health care team, patients, pharmacists and nurses regarding adverse drug effects and spread awareness about ADRs.

DETECTION OF ADRS:

Patients susceptible to adverse drug reactions must be properly identified and monitored. However, specific group of patients include:

1) Those having muliple disease processes.

2) Those patients taking multiple medicines in large number

3) Those having history of adverse drug recations.

4) Thosepatients alreay suffering from kidney or liver diseases.

5) Paediatric or geriatric patients.

6) Patients who are undergoing treatment with medicines having high incidence of adverse effects.

7)Patients treated with medicines having low therapeutic index.

8) Patients undergoing treatment with medicines already known to be associated with serious adverse effects.

9) Patients having abnormal investigation results.

Subsequently the ADRs might act through the same pathological and physiological pathways for different diseases there it becomes sometimes difficult or impossible to distinguish that whether the toxic effect is due to pathological effect or physiological effect. However, the following step-wise approach might be helpful in assessing possible drug-related ADRs:

1) It must be ensured that the ordered medicine is correct and is actually administered to the patient at the advised dose.

2) The onset of the suspected reaction must be verified that it occurred after and not before the administration of drug and also the observation made by the patient must be carefully discused.

3) It helps in determining the interval of time between the beginning of treatment of drug and the onset of the event;

4) Suspected ADR must be evaluated after the drug is discontinued or the dose is reduced and then after the status of the patient must also be monitored. However, if found suitable, then the drug treatment must be restarted and relapse of any adverse events must be monitored regularly.

5) Alternative causes must be analysed (other than the drug) that could have caused the reaction on their own.

6) Relevant updated literature and personal experience as a health care worker on drugs and their adverse reactions must be used and also must be verified that whether there are any earlier conclusive reports on the same reaction.

7) The Drug regulation authority and National Committee are very important resources to obtain information on any type of adverse drug reactions. The drug manufacturer can also be a resource to consult.

8) Any suspected ADR to the person nominated for ADR reporting must be eeported in the hospital or directly to the health District.

Detection Method of ADRs

1) Pre-marketing studies
2) 2) Post-marketing surveillance
3) Assessing Causality
4) Communicating ADRs
5) 5) Postal Survey Method.

REPORTING OF ADRS :

Reporting of an adverse drug reaction (ADR) is one of the most important parameter of medical treatment. ADR or adverse event reporting involves the triage, receipt, data entering, distribution, assessment, archiving and reporting of adverse event data and documentation.

Benefits

1) It helps in evaluating the safety of drug therapies, especially of those drugs that are approved recently.
2) It offers updated drug safety information to health care professionals and other stakeholders.
3) It aids in evaluating the economic impact of ADR inhibition by reducing hospitalisation, using optimal and economical drug, and by minimising organisational liability.
4) It ensures patient's safety by carrying out following regulatory action on the basis of ADR reports:
i) Advancing Inserting package
ii) Marketing Authorisation Recall (withdrawal)
iii) Recalling batch on the basis of ADR cluster
iv) Classification changes such as:
a) From over the counter to prescription only medicines.
b) Special prescription.

c) Restricted prescription.

ADR Reporting Procedure

- Who can report
- What to report
- How to report
- Whom to report
- Where to report

- Who can report?
    - All healthcare professionals

(Clinicians, Dentist, Pharmacist, Nurses, Physician, Physiotherapist etc)

- All non-healthcare professionals including consumers/ patients etc can report ADRs.

- What to Report?
    - All types of suspected adverse reactions
    - Known or unknown,
    - Serious or non-serious and
    - Frequent or rare

Reactions from all types of pharmaceutical products

- Allopathy,
- Ayurvedic,
- Vaccines,
- Medical devices etc.

How & Whom to Report ?

Use the 'Suspected Adverse Drug Reaction Reporting Form/ Medicine side effect Reporting form which are available on the official website of IPC (www.ipc.gov.in) to report any ADR

Link for ADR form
http://ipc.nic.in/showfmkl;ile.asp?lid=416&EncHid=

➢Filled ADR form submitted to nearest ADR Monitoring Centres (AMCs) or directly to the NCC-PVPI.

A reporter can also email the Suspected ADR form at pvpi@ipcindia.net or pvpi.ipcindia@gmail.com.

Who can report? How to report ?and whom to report?

Health Care Professionals

NCC-PvPI Ghaziabad

AMCs

Consumer

Industry

Worldwide Reporting Forms

CIOMS for US

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

II. SUSPECT DRUG(S) INFORMATION

III. CONCOMITANT DRUG(S) AND HISTORY

IV. MANUFACTURER INFORMATION

MED-WATCH FOR UK

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of 3

FDA USE ONLY

A. PATIENT INFORMATION

B. ADVERSE EVENT, PRODUCT PROBLEM

C. PRODUCT AVAILABILITY

D. SUSPECT PRODUCT(S)

E. SUSPECT MEDICAL DEVICE

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

G. REPORTER (Use confidentiality section on back)

FORM FDA 3500 (10/16)

What Happens to Submitted Information

1) At Adverse Drug Reaction Monitoring Centres (AMCs) by using WHO- UMC scale the causality assessment should be carried out.

2) The analysed forms should be forwarded to the National Coordinating Centre via ADR database.

3) At last the data should be examined and sent to the Global Pharmacovigilance Database that is managed by the WHO UppsalaMonitoring Centre in Sweden.

4) The reports should be revised from time to time by the National Coordinating Centre (PvPI).

5) The information produced based on these reports aids in continuous evaluation of the benefit-risk ratio of medicines.

Methods in causality assessment

• Causality assessment is the method by which an association is evaluated between a drug and a suspected reaction.

• It assesses the relationship between a drug treatment and the occurrence of an adverse event and establishes the same.

• It is an important tool which is used in Pharmacovigilance programmers for evaluating suspected ADR reports for assessing the safety of drugs for use & for regulatory purposes also.

• This assessment may be undertaken by clinicians, academics, pharmaceutical industry, and regulators. • Causality assessment can be done by treating health professionals as a tool for decision making regarding a drug treatment & by regulators as a help in signal detection and assist in risk-benefit decisions regarding medicines.

• Algorithms, structured tools specifically designed for the identification of an ADR, should theoretically make a more objective decision on causality.

• The objective of causal assessments are based on four basic principles:

• Temporal eligibility

• Dechallenge and outcome

• Rechallenge and outcome

• Confounding factors

• It is often difficult to decide if an adverse clinical event is because of therapeutic failure or an ADR and therefore in a patient who is on a drug treatment, the differential diagnosis should include the possibility of an adverse drug reaction.

• Immediately after an adverse event it is wise that the first step is to find out whether a patient is taking a medicinal product, including over-the-counter formulations.

• The next step is to assess the possibility of the effect being caused by the medicine and in cases of poly pharmacy it is often a denting task to pinpoint the causative drug.

• There are many characteristics looked for assigning probability of causation to a suspected adverse drug reaction.

• **Timing**- The time relation between the use of the drug and the occurrence of the reaction should be assessed.

• **Pattern recognition**- The pattern of the adverse effect may match the known pharmacology or allergy pattern of one of the suspected medicines, or of chemically related or pharmacologically related compounds.

• **Investigations**- It is wise to establish baseline functions like liver function & kidney function tests, allergic tests etc. at the start of therapy in anticipation of an adverse drug reaction.

• Algorithms are structured tools specifically designed for the identification of an ADR and to make a more objective decision on causality.

• A number of algorithms or decision support have been published including the Jones algorithm, Naranjo algorithm, the Begaud algorithm, the Karch algorithm, the Yale algorithm, the WHO-UMC and a newer quantitative approach algorithm. Each of these algorithms has similarities and differences.

• WHO-UMC system has been developed in consultation with the National Centers participating in the Program for International Drug Monitoring and is meant as a practical tool for the assessment of case reports.

• It is basically a combined assessment taking into account the clinical and pharmacological aspects of the case history and the quality of the documentation of the observation.

• The most commonly used algorithms is the Naranjo algorithm which is a questionnaire designed by Naranjo et al for determining the possibility of whether an ADR is actually due to the drug rather than the result of other factors.

• The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions, which examine factors such as the temporal association of drug administration and event occurrence, alternative causes for the event, drug levels, and previous patient experience with the medication.

• Probability is assigned via a score termed definite, probable, possible or doubtful. It is also called the Naranjo Scale or Naranjo score.

Severity and seriousness assessment

Severity defines the ten to which the ADRs efffects livelihood of the patient

Modified Hartwig and Siegel Severity Scale

Severity wedding to be clasification provided in Hartwig, Severity Assemment Scale which one for severity assessment. On th bets of severity of the spected reaction, bis scale can be divided into the categories in mild, moderate, and severe

Severity describes the extent to which the ADRs influence the everyday life of the patients. According to Hartwig's Severity Assessment Scale adverse drug reactions was categorized into 7 levels of severity by I Seigel and PJ Schneider

1) Level I: In this level no change is needed in treatment with the suspected drug in case of 'mild type reaction.

2) Level 2: In this level, the ADR requires that the suspected drug to be withdrawn or changed. Antidote or other treatment is not required, and the patient does not require further hospitalisation.

3) Level 3: It is same as level 2

4) Level 4: It is classified in two parts:

1) Level 4(a): The patient requires further hospitalisation (at least for a day) because of level 3 reactions.

ii) Level 4(b): The patient can be hospitalised due to ADR.

5) Level 5: In this level the produced reactions may need an intensive care unit attention in the severe type of ADR.

6) Level 6: In this level the reactions may cause permanent harm to the patient.

7) Level 7: In this level the patient may die directly or indirectly due to ADR.

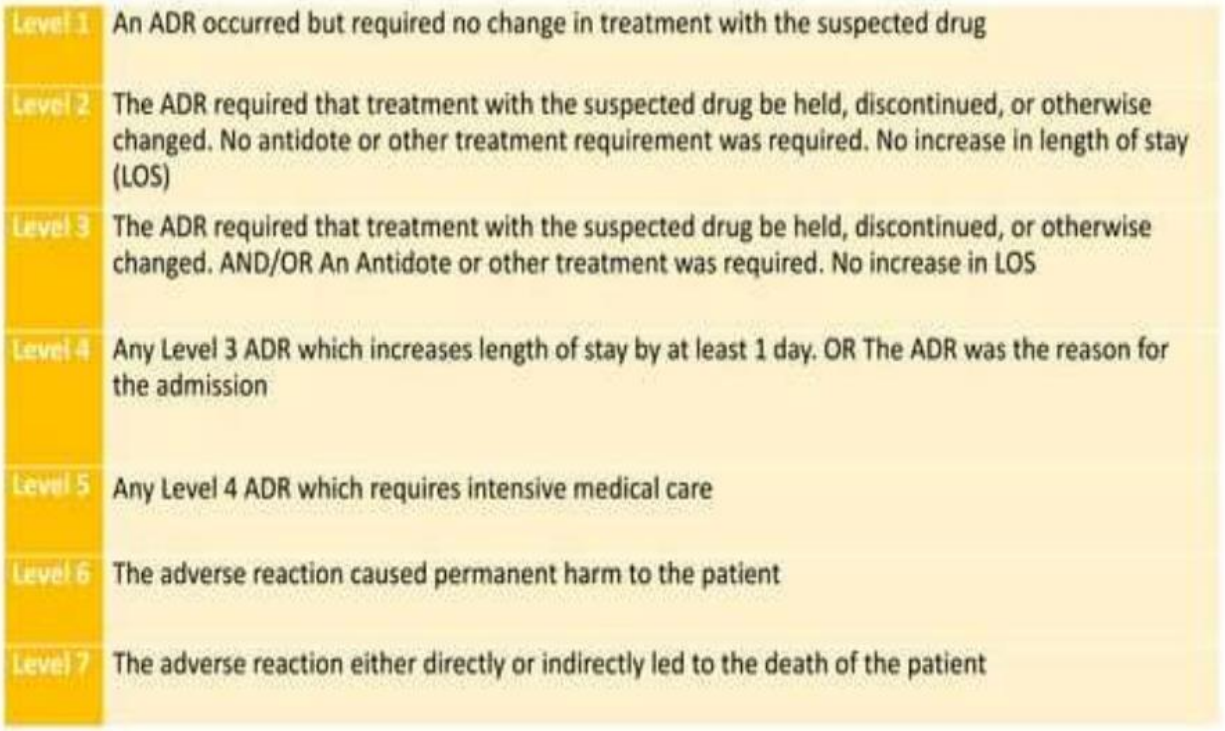
* Seriousness of an ADR is related to its life threatening nature and is defined as any untoward reaction to the medicinal product that may result in death and requires patient hospitalization.

* Seriousness of reaction is categorized according to FDA criteria on the basis of their life threatening nature.

* Death, Life-threatening, Hospitalization (initial or prolonged, Disability or Permanent Damage, Congenital Anomaly/Birth Defect

* Required Intervention to Prevent Permanent Impairment or Damage (Devices)

Hartwig's Severity Assessment Scale



Level 1	An ADR occurred but required no change in treatment with the suspected drug
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in LOS
Level 4	Any Level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission
Level 5	Any Level 4 ADR which requires intensive medical care
Level 6	The adverse reaction caused permanent harm to the patient
Level 7	The adverse reaction either directly or indirectly led to the death of the patient

Mild = Levels 1 and 2; **moderate** = Levels 3 and 4; **severe** = Levels 5, 6 and 7.

Predictability and preventability assessment

* According to WHO factsheet, it is estimated that at least 60% of ADRs are preventable. In some countries ADR-related costs, such as hospitalization, surgery and lost productivity, exceed the cost of the medications.

* Historically, studies have shown that between 20% and 80% of ADES and ADRs are preventable with the majority of latter studies showing around 60-70% preventability.

* Preventability of ADRs is assessed by using Schumock and Thornton scale.

Predictability

•Type A(Predictable)

Extension of pharmacologic effect

Often predictable and dose dependent

Responsible foe at least 30% od ADRS

➢E.g. anticholinergics and dry mouth

* Type B(unpredictable)

Idiosyncratic or immunologic reactions

Rare and unpredictable

E.g. chloramphenicol and aplasticianemia, penicillin induced anaphylactic shock

Preventability criteria according to Schumock and Thornton Scale

Definitely Preventable
1. Was there a history of allergy or previous reactions to the drug?
2. Was the drug involved inappropriate for the patient's clinical condition?
3. Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4. Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5. Was there a known treatment for the Adverse Drug Reaction?
Probably Preventable
6. Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?
7. Was a drug interaction involved in the ADR?
8. Was poor compliance involved in the ADR?
9. Were preventative measures not prescribed or administered to the patient?
Not preventable
If all above criteria not fulfilled

MANAGEMENT OF ADRS

The main and primary step in management is withdrawal of suspected drugs. However, in case the reaction is expected to be dose related, then dose of the drug must be reduced, and treatment for suspected reaction must be considered. When an adverse drug reaction is managed, clear therapeutic objective must be maintained. The drug treatment must not be unnecessarily continued conti for longer time period and the patient must be reviewed regularly and simplify management should be followed. Commonly used plan of action while dealing with suspected adverse drug reaction is as follows:

Following steps must be followed during the managemnt of any type of suspected, or unexpected adverse drug recations.

1) Monitoring patient who are at greater risk of developing ADRs.

2) Monitoring patients who are prescribed with drugs highly likely to cause ADRs.

3) Assessing and documenting the patient's previous allergic status.

4) Assessing patient's drug therapy for its appropriateness.

5) Changing dose of drug.

6) Replacement with alternate medicine.

7) Use of prophylactic regimen.

8) Assessing possible drug interactions in multiple therapies.

9) Assistant health care professionals in the detection and assessment of ADRs.

10) Stimulating health care professionals in reporting an ADR.

11) Documentation of suspected reported reactions for further references

12) Obtaining feedback about the reported reaction

13) Educating health care professionals about the importance of reporting an ADR

14) Educating patients

15) Creating awareness aoout ADRs amongst health care professior.als, patients and public

16) Presentation of reports in meetings and conferences

17) Conducting workshops/seminars/conferences on ADRs for health care professionals.

Terminologies of adverse medication related events – Regulatory terminologies

Eudravigilance medicinal product dictionary

• EudraVigilance: European Union Drug Regulating Authority Pharmacovigilance

• ATC: Anatomical Therapeutic Chemical

• CIOMS: Council for International Organisations of Medical Sciences

• EEA: European Economic Area • EMA: European Medicines Agency

• ESTRI: Elecronic Strandards for the Transfer of Regulatory Information

• EVDAS: Eudravigilance Data Analysis System

• EVCTM: Eudravigilance Eudravigilance Clinical Trial Module

• EVPM: Eudravigilance Post-Authorisation Modole

• ICH: International Conference of Harmonisation Glossary of important terms used in Pharmacovigilance

• Adverse Event/ Adverse Experience: 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: A response to a drug 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.

• An adverse drug reaction, contrary to an adverse reaction, is characterized by the suspicion of a causal relationship between the medicine and the occurrence, i.e. judged as being at least possibly related to treatment by the reporting or a reviewing health professional.

• Serious Adverse Event or Reaction: A serious adverse event or reaction is any untoward medical occurrence that at any dose results in: – Death – Is life-threatening – Requires inpatient hospitalization or prolongation of existing hospitalization – Persistent or significant

disability/incapacity – Congenital Anomaly – Medically important event or reaction

• To ensure no confusion or misunderstanding of the difference between the terms ‘serious’ and ‘severe’ , the following note of clarification is provided:

• The term “severe“ is not synonymous with serious. In the English language, „severe“ is used to describe the intensity (severity) of a specific reaction (as in mild, moderate or severe); the reaction itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on patient/reaction outcome or action criteria serves as guide for defining regulatory reporting obligations.

• Case Control Study: Study that identifies a group of persons with the unintended medicine effect of interest and a suitable comparison group of people without the unintended effect. The relationship of a medicine to the medicine reaction is examined by comparing the groups exhibiting and not exhibiting the medicine reaction with regard to how frequently the medicine is present.

• Cohort Study: A study that identifies defined populations and follows them forward in time, examining their rates of disease. A cohort study generally identifies and compares exposed patients to unexposed patients or to patients who receive a different exposure.

• Causality assessment: The evaluation of the likelihood that a medicine was the causative agent of an observed adverse reaction. Causality assessment is usually made according established algorithms.

• 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 of the products with the objective of ascertaining their efficacy and safety.

• Clinical trials are generally classified into Phases: I to IV. Phase IV trials are studies performed after marketing of the pharmaceutical product. They are carried out on the basis of the product characteristics for which the marketing authorization was granted and are normally in the form of post-marketing surveillance.

• Drug/ Medicine: Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient. The term drug/medicinal product is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information.

• Drug Alerts: The action of notifying a wider audience than the initial information holder(s) of a suspected association between a drug and an

adverse reaction. Note that the term is used in different contexts that can be confusing, for example, an alert may be from a manufacturer to a regulator or from a regulator to the public.

• Dechallenge: The withdrawal of a medicine from a patient; the point at which the continuity, reduction or disappearance of adverse effects may be observed.

• Rechallenge: The point at which a medicine is again given to a patient after its previous withdrawal.

• Individual Case Safety Report (ICSR): A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual patient at a particular point of time.

• Lack of Efficacy: Unexpected failure of a medicine to produce the intended effect as determined by previous scientific investigation.

• National Pharmacovigilance Centre: A single, governmentally recognized centre (or integrated system) within a country with the clinical and scientific expertise to collect, collate, analyze and give advise on all information related to medicine safety.

• Pharmacoepidemiology: The study of the use and effects of medicines in large numbers of people.

• Prescription Event Monitoring: A system created to monitor adverse drug events in a population. Prescribers are requested to report all events, regardless of whether they are suspected adverse events, for identified patients receiving a specified medicine.

• Record Linkage: Method of assembling information contained in two or more records, e.g., in different sets of medical charts, and in vital records such as birth and death certificates. This makes it possible to relate significant health events that are remote from one another in time and place.

• Side Effect: Any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the medicine.

• Signal: Reported information on a possible causal relationship between an adverse reaction and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the reaction and the quality of the reaction and the quality of the information.

• Spontaneous Reporting: A system whereby case reports of adverse drug reactions are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority.

• Unexpected Adverse Reaction: An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the medicine.

UNIT-2

PHARMACOVIGILANCE

-

YEAR 24

UNIT-2

A. Drug and disease classification

Anatomical ,therapeutic and chemical classification of drugs

International classification of diseases

Daily defined doses

International Non proprietary Names for drugs

B. Drug dictionaries and coding in pharmacovigilance

WHO adverse reaction terminologies

MedDRA and Standardised MedDRA queries

WHO drug dictionary

Eudravigilance medicinal product dictionary

C. Information resources in pharmacovigilance

Basic drug information resources

Specialised resources for ADRs

D. Establishing pharmacovigilance programme

Establishing in a hospital

Establishment & operation of drug ssafety department in industry

Contract Research Organizations (CROs)

Establishing a national programme

[A] Drug and disease classification –

Anatomical, Therapeutic and Chemical Classification of Drugs (ATC)

- In the ATC system the active substance is divided into different groups according to the organ or system on which they act and their therapeutic, Pharmacological and chemical properties.

The Anatomical Therapeutic Chemical (ATC) classification system is a globally accepted system used to classify drugs based on their:

1. Anatomical site of action (body system or organ)
2. Therapeutic use (indication or disease treated)
3. Chemical structure (pharmacological subgroup)

Purpose of ATC classification:

1. Facilitates drug utilization research and evaluation
2. Enables comparison of drug use across different regions and populations
3. Supports pharmacovigilance activities (e.g., adverse event reporting)
4. Aids in drug regulation and policy development

ATC classification structure:

The ATC system consists of five levels:

1. Anatomical group (1st level): 14 main groups, each representing a different body system or organ (e.g., nervous system, cardiovascular system)
2. Therapeutic subgroup (2nd level): Subdivisions within each anatomical group, based on therapeutic use (e.g., analgesics, anti hypertensives)

3. Pharmacological subgroup (3rd level): Subdivisions within each therapeutic subgroup, based on chemical structure or mechanism of action (e.g., opioids, beta blockers)

4. Chemical subgroup (4th level): Further subdivisions within each pharmacological subgroup, based on specific chemical structure or moiety (e.g., morphine, atenolol)

5. Chemical substance (5th level): The specific active ingredient (e.g., acetylsalicylic acid, simvastatin)

Examples of ATC classification:

- Acetylsalicylic acid (aspirin):
  - Anatomical group: Nervous system (N)
  - Therapeutic subgroup: Analgesics (N02)
  - Pharmacological subgroup: Salicylic acid and derivatives (N02BA)
  - Chemical subgroup: Acetylsalicylic acid (N02BA01)
  - Chemical substance: Acetylsalicylic acid
- Simvastatin:
  - Anatomical group: Cardiovascular system (C)
  - Therapeutic subgroup: Lipid modifying agents (C10)
  - Pharmacological subgroup: HMG-CoA reductase inhibitors (C10AA)
  - Chemical subgroup: Simvastatin (C10AA01)
  - Chemical substance: Simvastatin

Importance in pharmacovigilance:

The ATC classification system is essential in pharmacovigilance as it:

1. Facilitates identification of drug-related adverse events
2. Enables comparison of safety profiles across different drugs
3. Supports signal detection and evaluation
4. Aids in risk-benefit assessment and decision-making

➢ ATC/DDD Methodology

- Drug utilization research uses the Anatomical Therapeutic Chemical (ATC) as the classification system and Defined Daily Dose (DDD) as a unit of measure.
- DDD is the assumed average maintenance doseperday for a drug used for its main indication in adults.
- The methodology is endorsed by WHO and is recommended as the international standard for drug utilisation monitoring and research.

Why ATC / DDD?

- ATC/DDD methodology facilitates the presentation and comparison of drug consumption statistics at international,national and regional levels despite differences in nomenclature (both branded&generic),packing sizes, pricing and customary dosages.
- This methodology is useful for valid presentation & comparison of drug utilization within and across countries to support better outcomes & quality use of medicines.

➢ General Principles for ATC Classification

- Drugs are classified based on their main therapeutic use
- Onlyone ATC code for each ROA(routeofadministration).
- SeveralATCcode:ifclearlydifferenttherapeuticusesreflectedin different
  - Routesofadministration(e.g.topical,systemic)
  - Strengths

➢ **ATC Groups**

In the Anatomical Therapeutic Chemical(ATC)classificationsystem,the active substances are divided into different groups accordingto the organ or system on which they act and their therapeutic, pharmacological and chemical properties.

Drugs are classified in groups at five different levels.

1. **ATC1stlevel**

- The system has **fourteen main anatomical or pharmacological groups** (1stlevel). TheATC1st levels are shown in the figure.

2. **ATC2nd level**

- Pharmacological or Therapeutic sub group

3. **ATC3rd&4th levels**

- **Chemical, Pharmacological or Therapeutic sub group**

4. **ATC5thlevel**

- **Chemical substance**

The 2nd, 3rd and 4th levels are often used to identify **pharmacological subgroups** when that is considered more appropriate than **therapeutic or chemical subgroups**.

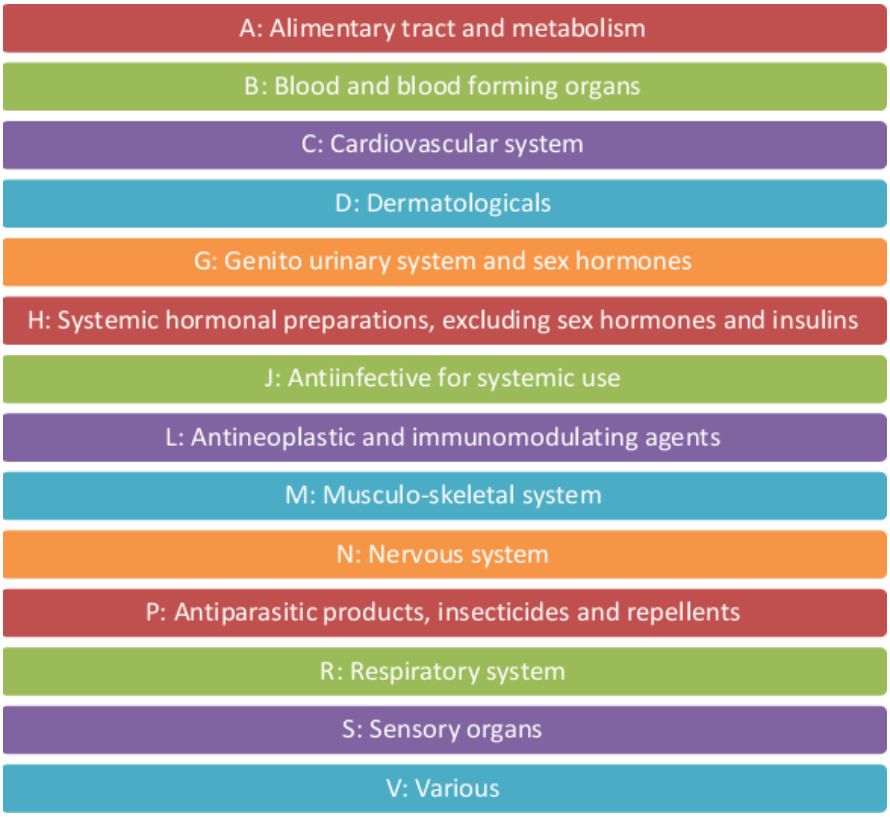


Figure : Coding of drugs based on their anatomical groups

Table:Coding of drugs based on their anatomical groups

Code	*Contents*
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Antiinfectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Antiparasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

Thecompleteclassificationofmetforminillustratesthestructureofthe code:

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	metformin (5th level, chemical substance)

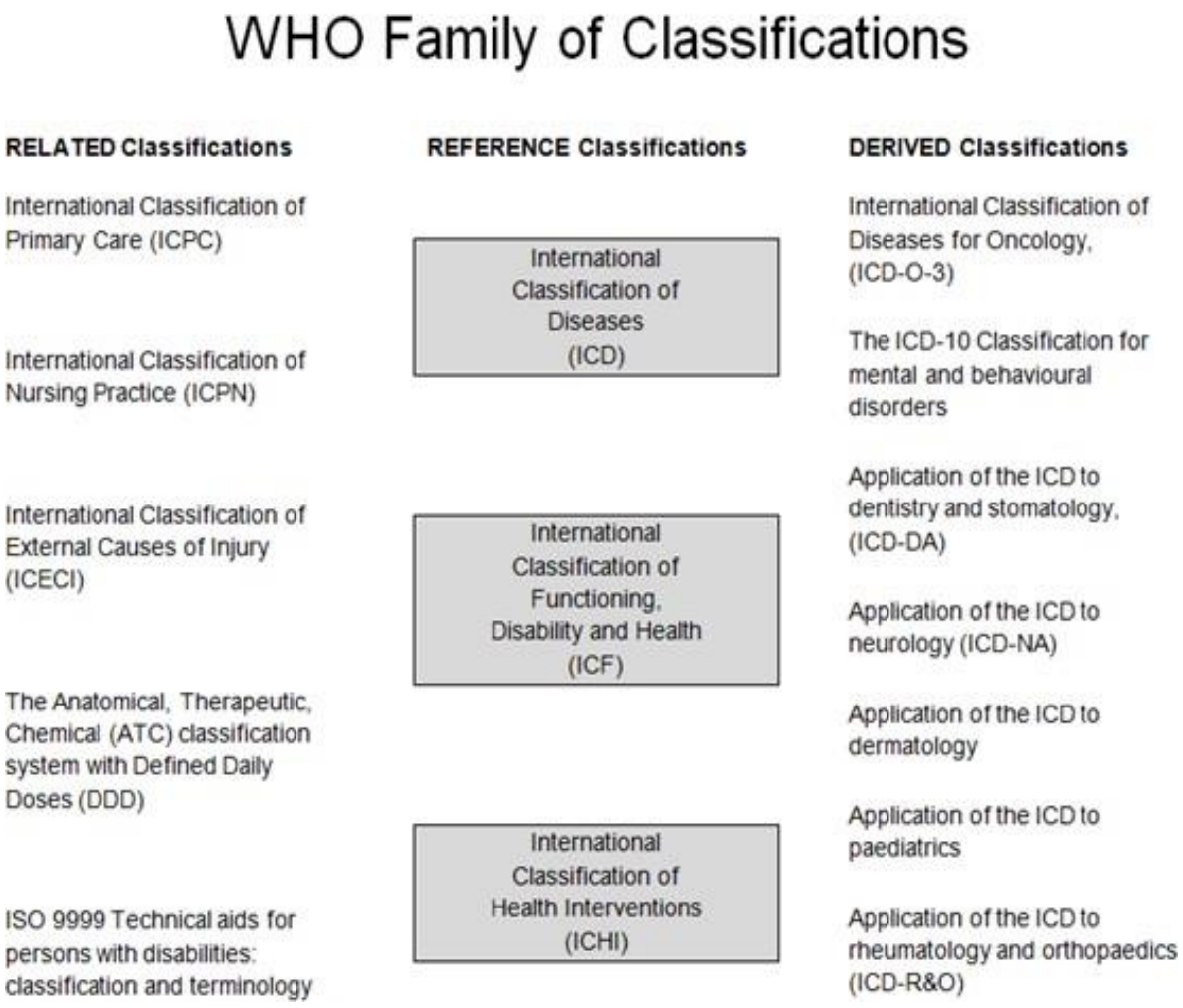
Thus, in the ATC system all plain metformin preparations are given the code A10BA02. For the chemical substance, the International Nonproprietary Name (INN) is preferred. If INN names arenot assigned, USAN (United States Adopted Name)or BAN (British Approved Name) names are usually chosen.The coding is important for obtaining accurate information in epidemiological studies. The five different levels allow comparisons to be made at various levels according to the purpose of the study.

Applications of ATC/DDD

International Classification of Diseases

The **ICD** is originally designed as a health care **classification system,** providing a **system** of diagnostic codes for classifying diseases, including nuanced **classification s**o fawide variety of signs ,symptoms ,abnormal findings, complaints, social circumstances, and external causes of injury or disease.

Classification of Diseases



Importance of ICD

The ICD is **important** because it provides a common language for reporting and monitoring **diseases**.This allows the world to compare and shared in a consistent and standard way-between hospitals, regions and countries and over periods of time.

Historyof ICD

- In1860,*Floresence Nightingale* ,made1st model of systemic collection of hospital data.
- In1893,French Physician *Jacques Bertillon* introduced bertillon classification of cause of death.
- In1898,American public health association recommended revision of ICD system every 10 years
- There vision followed minor changes until l6th version of ICD, morbidity & mortality conditions and section on mental disorders
- WHO has responsibility of preparing & publishing the ICD revision every 10 years.

Who uses ICD?

1. Users include physicians, nurses, other providers, researchers, health information managers and coders,health information technology workers, policy-makers, insurers and patient organizations.
2. ICD has been translated into 43 languages and it is being used by all member States.Most countries(117)use the system to report mortality data, a primary indicator of health status.
3. All Member States are expected to use the most current version of the ICD for reporting death and disease statistics (according to the WHO

Nomenclature Regulations adopted by the World Health Assembly in 1967).

Daily Defined Dose (DDD)

- DDD is a unit of measurement used to quantify the consumption of drugs
- It represents the average maintenance dose of a drug per day for a specific indication
- DDD is used to standardize drug utilization and facilitate comparisons across different drugs and populations

Purpose of DDD:

- To provide a standardized measure of drug exposure
- To enable comparison of drug utilization patterns across different regions and populations
- To support pharmacovigilance activities, such as signal detection and risk assessment
- To facilitate drug utilization research and evaluation

Key characteristics of DDD:

- Based on the average maintenance dose, not the maximum or minimum dose
- Specific to a particular indication or therapeutic use
- Expressed in terms of the active substance, not the formulation or brand name
- Reviewed and updated periodically to reflect changes in clinical practice

How is DDD calculated?

- DDD is calculated based on the average dose used for a specific indication
- It takes into account the dose, frequency, and duration of treatment
- DDD is usually expressed in units of mass (e.g., milligrams or grams) per day

Examples of DDD:

- Paracetamol (acetaminophen): 3000 mg/day
- Ibuprofen: 1200 mg/day
- Simvastatin: 30 mg/day

Applications of DDD in pharmacovigilance:

- Signal detection: DDD helps identify unusual patterns of drug use or adverse events
- Risk assessment: DDD informs the evaluation of drug safety profiles and risk-benefit

assessments
- Drug utilization studies: DDD facilitates the analysis of drug use patterns and trends
- Comparison of drug safety profiles: DDD enables standardized comparisons across different drugs and populations

Limitations of DDD:

- May not reflect actual doses used in clinical practice
- May not account for variations in dosing regimens or patient populations
- May not be suitable for all types of drugs or therapeutic areas

International NonProprietary Names for Drugs (INN)

INN facilitates the identification of pharmaceutical substances or active pharmaceutical ingredient. Each INN is a unique name that is globally recognized & is public property. **A nonproprietary name is also called generic name.**
It provides clear identification, safe prescription and dispensing of medicines to patients. It is also important for the communication and exchange of information among health professionals worldwide.

Historyof INN

- The system was established in 1950 by World Health Assembly and the first list of International Nonproprietary Names for pharmaceutical substances was published in 1953.
- The cumulative list of INN now stands at some 7000 names designated since that time, and thus number is growing every year by 120-150 new INN.

What are International Non-Proprietary Names (INN)?

- INN is a unique name given to a pharmaceutical substance or active

pharmaceutical ingredient (API)

- It is a non-proprietary name, meaning it is not owned by any single company or entity
- INN is assigned by the World Health Organization (WHO) to ensure consistency and clarity in drug naming across the globe

Purpose of INN:

- To provide a unique and universal name for each pharmaceutical substance
- To avoid confusion between similar-sounding proprietary names
- To facilitate communication among healthcare professionals, patients, and regulatory agencies worldwide
- To enable accurate identification and reporting of adverse drug reactions

Characteristics of INN:

- Unique and distinctive
- Not trademarked or owned by any company
- Consistent across languages and regions
- Based on the chemical structure or pharmacological action of the substance
- Usually derived from the chemical name or a shortened form of it

Examples of INN:

- Acetaminophen (paracetamol)
- Ibuprofen
- Metformin
- Sertraline

Benefits of INN:

- Ensures clarity and consistency in drug naming
- Facilitates international communication and collaboration
- Enhances patient safety by reducing errors
- Supports regulatory oversight and pharmacovigilance
- Encourages generic drug development and competition

How are INN assigned?

- WHO's International Nonproprietary Names (INN) Programme is responsible for assigning INN
- Applications for INN are submitted by pharmaceutical companies or regulatory agencies
  - INN are assigned based on a set of rules and guidelines, considering factors like chemical structure, pharmacological action, and existing names

Uses of INN

Nonproprietary names are intended for use in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regulation and scientific literature and as a basis for product names.

[B]Drug dictionaries and coding in pharmacovigilance

What is **MedDRA**?

Med=Medical

D=Dictionary

R=Regulatory

A=Activities

Definition:

- The MedDRA is a **medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g. medical devices and vaccines).**
- It is used to classify the adverse drug events (ADEs) data from clinical trials, spontaneous adverse event reports by healthcare professionals, patients and others; and from other sources of the ADEs.

MedDRA has been developed by an ICHWorking Group to provide:

- **Aninternational,multi-lingual,medicalterminology**‰
  - Medical personnel can code ADR data in their nativelanguage
  - Safer– less likelyto miscode data
- Standardized communication between regulators and industry/sponsors of clinical trials‰
  - Within regions and between regions

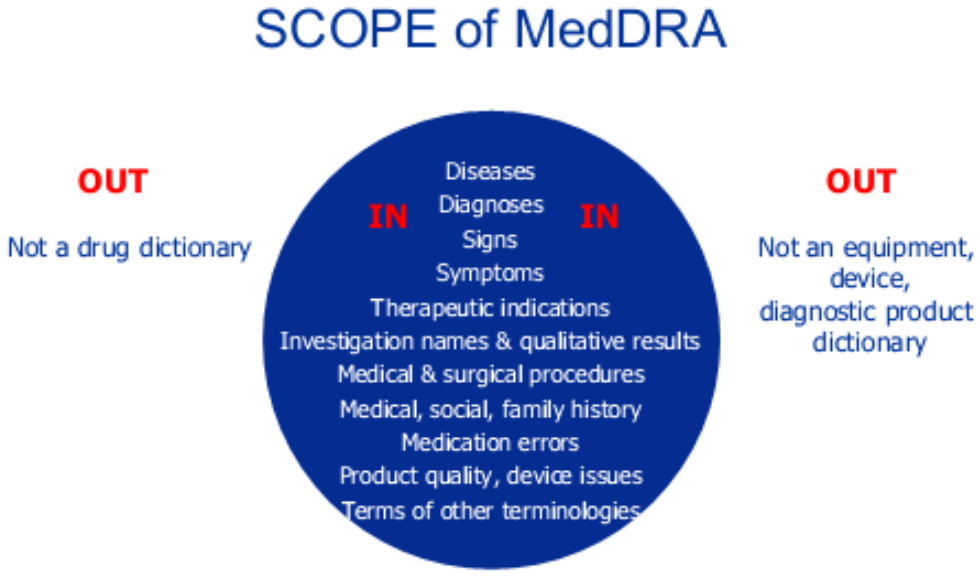
A single terminology for use through all phases of development cycle (both pre- and post-marketing)

- Clinical Trials (medical information, adverse events)
- Registration (study reports, analyses ,summary of product characteristics /labeling – undesirable effects section)

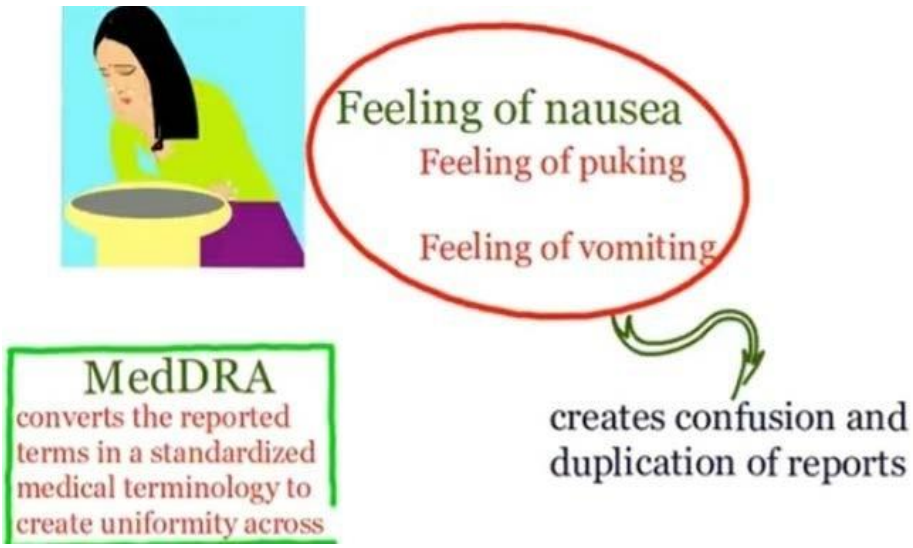
Post-authorization (adverse events) Support for electronic submissions

- EachMedDRAtermisassignedaunique**8-digitnumeric code**

- Codes can fill certain data fields in e-submission types (**E2B*: ICSR-Individual Case Safety Reports, eCTD*: e-Common Technical Document**)
- Codes easier to transmit as no language boundaries



(https://www.meddra.org/sites/default/files/page/documents_insert/pharmacon_conference_meddra_belgrade_thouvay_2012.pdf/accessedon 24.04.2020)



Who develop MedDRA?

- It is developed by the International Council for Harmonization (ICH) ofTechnical Requirements for Pharmaceuticals for Human use.
- ICH has created a governance structure to nature and protects the integrity of MedDRA.
- ICH MedDRA committee over sees all the activitiesof the MedDRA maintenance and support services organization.

The Maintenance and Support Service Organization(MSSO)

- MSSO is the managementBoard appointed by ICH steering committee.
- Maintain and upgrades MedDRA.
- Releases updated MedDRA versions twice a year (in March and September).

MedDRAMSSO

MedDRA is actively developed and maintained

- **Two releases per year**
- **Evolves to meet need so regulators ,industry ,other users**
- **Success depends on these activities**

ICH contracted MSSO for this purpose

MSSO activities are governed by ICHMedDRA Management Board

ICH MedDRA Management Board

SixParties:EU,EFPIA,FDA,MHLW,JPMA,PhRMA,

Three Observers:WHO,EFTA,Canada European

1. **Commission-EuropeanUnion(EU)**
2. **European Federation of Pharmaceutical Industries and Associations (EFPIA)**

3. **US Food and Drug Administration(FDA)**
4. **Pharmaceutical Research and Manufacturers of America(PhRMA)**
5. **Ministry of Health ,Labor and Welfare ,Japan(MHLW)**
6. **Japan Pharmaceutical Manufacturers Association(JPMA)**

(https://www.who.int/medicines/areas/quality_safety/regulation_legislation/WB_2.pdf?ua=1/accessed on 24.04.2020)

Objectives of MedDRA's Development

International multi-lingual terminology

- Usedin60 countries
- Availablein11languages

Standardised communication between industry and regulators

Application throughout all phases of development

Classification of a wide range of clinical information

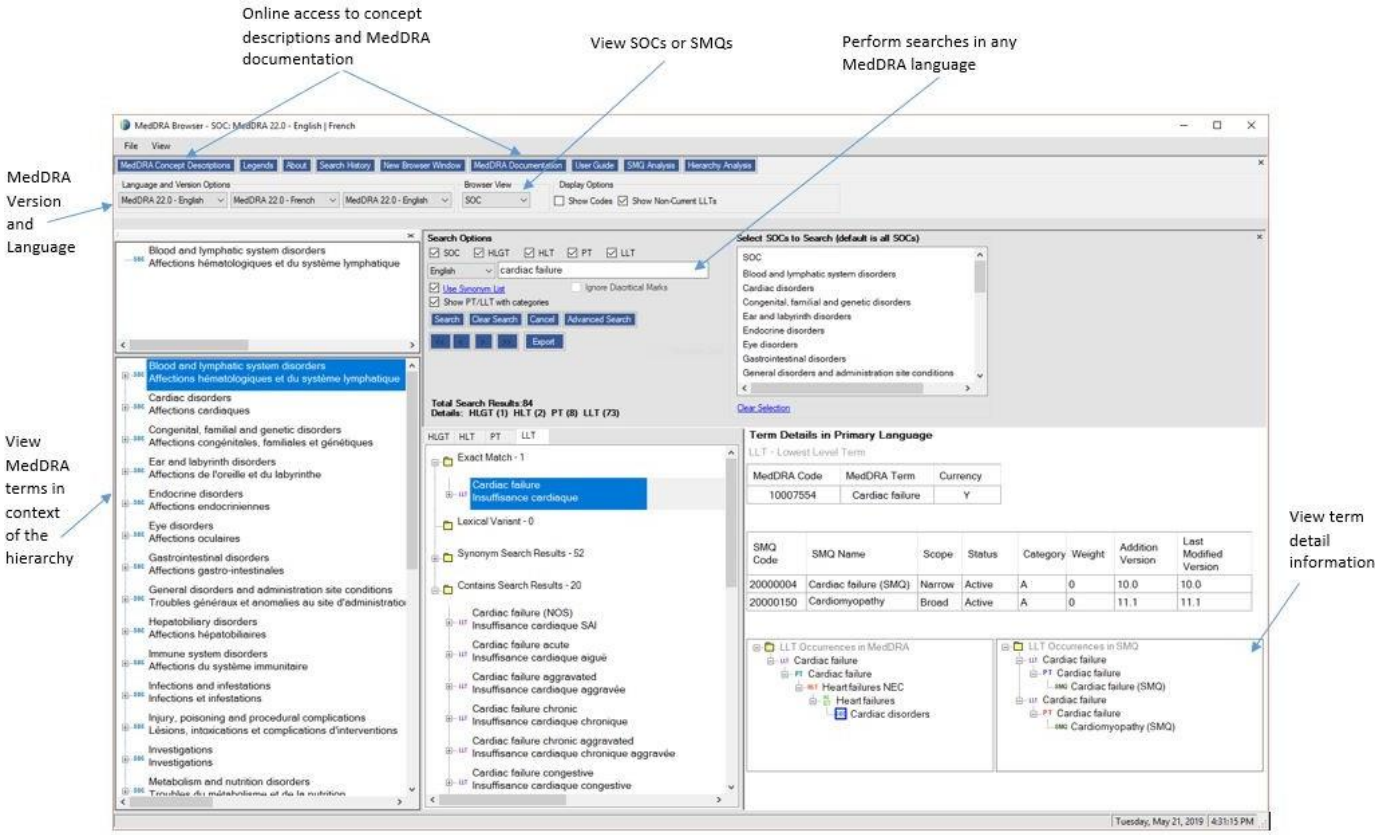
Support multiple medical product areas

Support electronic submissions

- Unique8-digitscodesfor allterms
- For data fields in e-submission types (e.g.E2B)

MED-DRACODE

- **Unique number assigned to each term in the dictionary**
- **8 digit number**
- **Starts with 10000001, initially started alphabetically**
- **As term added,codes assigned sequentially.**



WHO Drug Dictionary

The WHO Drug Dictionary is an international classification of the medicines created by the WHO Programme for International Drug Monitoring (IDM) and managed by Uppsala Monitoring Centre (UMC).

- A data base with information about medical products from all over the world.
- It contains medicinal products and information related to the mina relational database system.
- Information is provided in a consistent and structured way
- It provides useful groupings of data useful for both data input and output.
- It is continuously updated.

Eudravigilance medicinal product dictionary

Glossary

- EudraVigilance: European Union Drug Regulating Authority Pharmacovigilance
- ATC: Anatomical Therapeutic Chemical
- CIOMS: Council for International Organisations of Medical Sciences
- EEA:European Economic Area
- EMA: European Medicines Agency
- ESTRI: Elecronic Strandards for the Transfer of Regulatory Information
- EVDAS: Eudravigilance Data Analysis System
- EVCTM: Eudravigilance Eudravigilance Clinical Trial Module
- EVPM: Eudravigilance Post-Authorisation Modole
- ICH: International Conference of Harmonisation

Introduction

The history of pharmacovigilance is closely linked to the history of drug safety crises. With each crisis, the public and the media have demanded, and the legislators and regulators have provided, improved safety monitoring. The media and the public appear to expect zero-risk medicines. In the real world, zero risk medicines do not exist. For each new drug presented to the regulators forapproval, the potential benefits for public health need to be balanced against known safety risks. Information on safety risks at the moment of approval comes from pre-clinical and more importantly, clinical data originating from clinical trials. As the time intervals and the number of patients involved in clinical trials are necessarily limited, the benefit risk balance must be continuously monitored after authorising a new medicinal product. The new medicines legislation also explicitly provides for risk management plans to be submitted by the applicants for marketing authorisation. It is therefore essential that we have in place systems which will allow us to collect, validate, store and process reports on adverse drug reactions for investigational and authorised medicinal products. The better thedata quality and the larger the number of such reports received and processed the earlier will significant signals be detected. In view of the number of adverse drug reactions reported, this has to be carried out using modern tools of informationand communications technology.

EUDRAVIGILANCE: (European Union Drug Regulating Authority Pharmacovigilance) is the European data processing network and management system for reporting and evaluation of suspected adverse reactions to medicines which have been authorized or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network.

The European Eudravigilance system deals with the:

- Electronic exchange of individual case safety reports (ICSR, based on the ICH

E2B specification):

Eudravigilance Clinical Trials Module (EVCTM) for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs).

Eudravigilance Post-Authorisation Module (EVPM) for post- authorization ICSRs.

- Early detection of possible safety signals from marketed drug for human use.
- Continous monitoring and evaluation of potential safety issues in relation toreported adverse reactions.
- Decision-making process, based on broder knowledge of the adverse reaction profile of drugs.
- The first operating version was launched byEMA in December2001

Eudravigilance medicinal product dictionary(EVMPD):

The EudraVigilance Medicinal Product Dictionary (EVMPD) has been designed to support in a standardised and structured way the collection, reporting, coding and evaluation of data on authorised medicinal products and investigational medicinal products.

The EVMPD offers:

- A distributed and common approach for data collection through user-friendly and easy accessible software solutions available free of charge for pharmaceutical companies
- Integrated standard terminology to code e.g. active ingredients, excipients, pharmaceutical forms, routes of administrations, concentration ranges and units, country codes, marketing authorisation holders and sponsors.
- A hierarchical data structure accommodating coding requirements in pharmacovigilance to reliably capture product information in safety reports

Taking into account the possible vagueness of the reported data bythe primary source .

- A hierarchical, multi-axial data structure to support scientific data analysis of medicinal product data and grouping of data based on ingredients, strengths and pharmaceutical forms.
- Automated data import and systematic workflow with integrated quality control and audit checks.
- A standardised XML schema to support the collection and exchange of structured medicinal product information.
- Defined data ownership ensuring controlled data update through therespective product owner.
- A standardised approach to support updates, variations and withdrawals to medicinal product through the defined responsible product owner.
- Traceable and auditable regulatory changes to product information (recording of medicinal product history).

EudraVigilance contain so their dictionaries:

MedDRA:

MedDRA is the Medical Dictionary for Regulatory Activities. It was developed in the frame of the ICH M1 activities as a clinically validated international medical terminology for regulatory authorities, and is maintained by the MedDRA's Maintenance and Support Services Organisation (MSSO). MedDRA is used by regulators and pharmaceutical industry for data entry, retrieval, evaluation and presentation during all phases of the drug regulatory processi.e.thepre- and post-authorisationphase. Theseprocesses includeclinical studies, reports of spontaneous adverse reactions, events, regulatory submissions and regulated product information.

- VEDDRA

- RoutesofAdministration
- DosageUnits
- Pharmaceuticalforms
- ATC

Purpose of Eudravigilance

- To support the public health of EU citizens by collecting safety informationon medicines and making this available for scientific assessment.
- This assessment is carried out by regulatory authorities in the EU that supervise and monitor the correct use of the medicines in all EU countries ona continuous basis.
- Medicinal product authorization information.
- Pharmacovigilance information.

Eudravigilance support

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between European Medicines Agency(EMA), National Competent Authorities (NCA's), Marketing Authorization holders, and sponsors of clinical trials in the EEA.
- Early detection of possible safety signals from marketed drug for human use.
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions.
- Decision-makingprocess,basedonbrooderknowledgeoftheadversereaction profile of medicinal products especially in the frame of risk Management.

Conclusion

- EudraVigilance is a powerful tool for monitoring the safety of medicinal products

- Once the complete feed of data has been established, it will be the largest database of its kind in the world.
- It will become an extremely useful resource for academic and commercial research once full access to data mining and statistical evaluation can be provided.

Information resources in pharmacovigilance

- **DEFINTION:-**The branch of science who`s activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problem.

- **ORIGIN OF PHARMACOVIGILANCE:-**

- The Thalidomide disaster in 1956 - Thalidomide launched in market andin 1956-61 report of foetal abnormalities (20000 cases) maximum in Germany.
- In 1962 USA revised law requiring proving the safety and efficacy before issuing marketing authorization.
- In1963British committee on safety of drug monitoring.
- In1964 UKstartsthe“YELLOWCARDS” system.
- In 1964-65 National ADR reporting system UK, Australia, New Zealand, Canada, West Germany, Sweden .

- **OBJECTIVE:**

1- To know what are the various sources of drug information.

2- To select the appropriate source depending on the information.

- **BASIC DRUG INFORMATION RESOURCES-** Drug information is current, critically examined, relevant data about drugs and drug use in a given patient or situation.

- Current information uses the most recent,up-to-date sources possible.
- Critically examined information.
- Relevant information must be presented in a manner that applies directlyto the circumstances under consideration (e.g. patient parameters, therapeutic objectives, alternative approaches).

- **TYPESOFRESOURCES:-**

(I) Primaryresources

(II) Secondaryresources

(III) Tertiaryresources

(I) **PRIMARYRESOURCES-**

- Researcher`s and manufacturer`s information.
- Patents containing original information regarding the discovery of drug.

- Reports containing scientific data before product can be sold, supplied or represented.
- Scientific Journals
- Provideoriginal studies or reports

➢ ADVANTAGES

- Most current evidences.
- Provide data on newdrugs.
- Original document that was created at the time of the actual events.

➢ DISADVANTAGES

- Data can be controversial.
- Every study has limitation
- Complicated
- Time consuming.

(II) **SECONDARYRESOURCES-**

- Abstract or index which summarizes the information arising in primary resource.
- Indexing and abstracting services are valuable tools for quick and selective screening of the primary literature for specific information, data, citation, and article.
- Bibliographic data base that provide abstract or full-text of studies.

➢ **ADVANTAGES-**

- Find specific information at high granularity.
- Pick out keypoint.
- Quicktoread.

- **DISADVANTAGES-**
  - Detail missing.
  - Two different authors can interpret the same piece of original material in two widely different ways.
  - May be in accurate.

(III) **TERTIARYRESOURCES-**

- Compilation of knowledge in the field. e.g. Textbooks, handbook, online drug compendia.

- **ADVANTAGES-**

- Provide comprehensive information.
- Information reflects view so multiple experts in field.
- Fast,easyto use,and may be good for patients.

- **DISADVANTAGES-**

- Information may be dated due to gap between when resources is written and published.
- Chances of distortinga topic.

- **OTHERSOURCES-**

- Libraries
- Research association
- Government bodies
- Information center in industries

ADVERSE DRUG REACTION

Any noxious change which is suspected to be due to drug , occur at doses normallyused in man,require treatment or decrease in dose or indicates caution in future use of the same drug.

CLASSIFICATION:-

1. **Type A effect:-** Augmented pharmacologic effects – dose dependent and predictable are those which are due to pharmacologic effects.
2. **Type B effect:-** Bizarre effects(idiosyncratic)- dose independent and unpredictable .
3. **Type C effect:-** Chronic effect refer to situation where the use of a medicine, often for unknown reasons, increase the frequency of a "spontaneous" disease.
4. **TypeDeffect:-**Delayedeffects.
5. **TypeEeffect:-**End-of-treatment effect.
6. **TypeFeffect:-**Failureoftherapy.

- SPECIALISED RESOURCE OF ADR

- Individual reporting
- Comprehensive Monitoring
- PopulationMonitoring
- Individual case safetyreport (ICSR)
- Spontaneous Reporting

- INDIVIDUAL REPORTING

- Inindividual reporting Doctor are the major source of report.
- The physician, during an outpatient or inpatient examination, may decide that the patient has are cognizable syndrome of signs,symptoms and/or

laboratory finding and that this syndrome may be associated with a previously administered drug.

- Since most severe reaction are seen in hospitals, physicians who are Hospital-based are often able to ascertain previous drug administration, link it to the reaction, and submit a report.

➢ COMPREHENSIVE MONITORING:-

- Comprehensive monitoring is typically performed in a hospital setting and the input of abstract of patient identification, drug administration, and patient reaction.
- Specialised method are used to ensure that this information is complete, and case report or tabulated summary data can be supplied to the national centre.

➢ POPULATION MONITORING:-

- In population monitoring the record of hospital or clinic patients, or of the entire population of a district, may be employed.
- Such monitoring could be effective when a large stable population is surveyed in an organized medical care system.

➢ INDIVIDUAL CASE SAFETY REPORT(ICSR):-

- Individual Case Safety Report is a report which contains information describing suspected adverse drug reaction related to administration of one or more medicinal product.
- A document providing the most complete information related to an individual case at a certain point of time.

➢ SPONTANEOUSREPORTING:-

- Spontaneous reporting is a system whereby case report of adverse drug event are volunteer submitted by healthy professionals, pharmaceuticals companies or consumers to the national pharmacovigilance centre.
- It is basically the reportingof a suspected adverse reaction on the initiative of the health professional who became aware of the problem, or the patient initiative. These report can be communicated by any means,but in countries with a well developed pharmacovigilance system they are most often reported on the country- specific reporting card.
- Such reporting is sometime referred to as intensified spontaneous reporting, or ideally, prospective

[D]Establishingpharmacovigilanceprogramme

Established pharmacovigilanace program in a hospital and national programme

PVis a major post-marketing tool to ensure the safety of amedicinal 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.

After the thalidomide disaster in the year 1961, WHO worked along with its Collaborating Centre to establish a programme for International Drug Monitoringand through this programme, WHOpromoted PVat the countrylevel. Attheendof2010,134countrieswerepartoftheWHO-PVProgramme.Togive

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 bottle necks to pay some dividends. In this backdrop, the article discusses the essentials of setting up a PV center and getting it operational

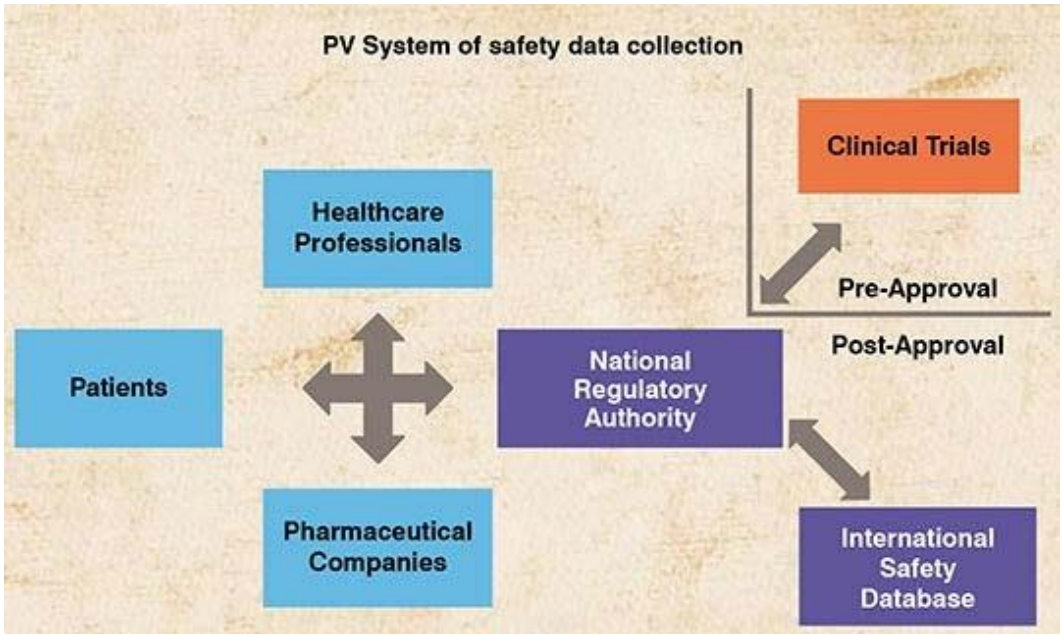
Essential for a Pharmacovigilance program:-

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
- Anational PVadvisorycommittee
- 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.

BasicStepsinSettingupaPVSystemInclude:-



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 thatWHOand partners agree should be met in any national pharmacovigilance system.

1. A national pharmacovigilance centre with designated staff (atleastone fulltime), stable basic funding, clear mandates, well-defined structures and roles,and collaborating with the WHOProgramme 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 data base 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 communications trategy 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 centreincludes: **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.

It may soon become necessary to have one expert who is responsible for pharmacovigilance for most of his/her time and for secretarial assistance to be expanded. When the reporting of adverse reactions increases, staff resource requirements maybe calculated by assuming that the average assessment time per case report is about one hour.

2. Planning the basics

A blueprint should bedrawn up toestablish andgeta PV system towork. 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. Datacollectionandassessment
2. DataInterpretation
3. Informationpublication

A network of experienced advisors in various specializations is helpful

b) Communication process

Gettingin 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 whichthey 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,wordprocessors,databasemanagement,bibliographysupport 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,signaldetection,riskmanagement,andactionincaseofserious/fataladverse 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) Data base and information serivce

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 forthe 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 anddrug 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 ofEssential 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

Pharmacovigilanceat present thrives heavilyon aregional/countrywidereporting 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.

ACRF 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 to fAD Rreports telephonically or through personal communication
- Providing journal articles,ADR bulletins,news letters 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.
- Collaboratingwithprofessionalassociations
- Utilizing PV data for development of clinical pharmacy and clinicalpharmacology

5. Tasks for pharmacovigilance

a) Information service

Oneoftheprimaryresponsibilitiesofacenteristomakehighqualitycredibleand 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 thatthe data can be globally shared.

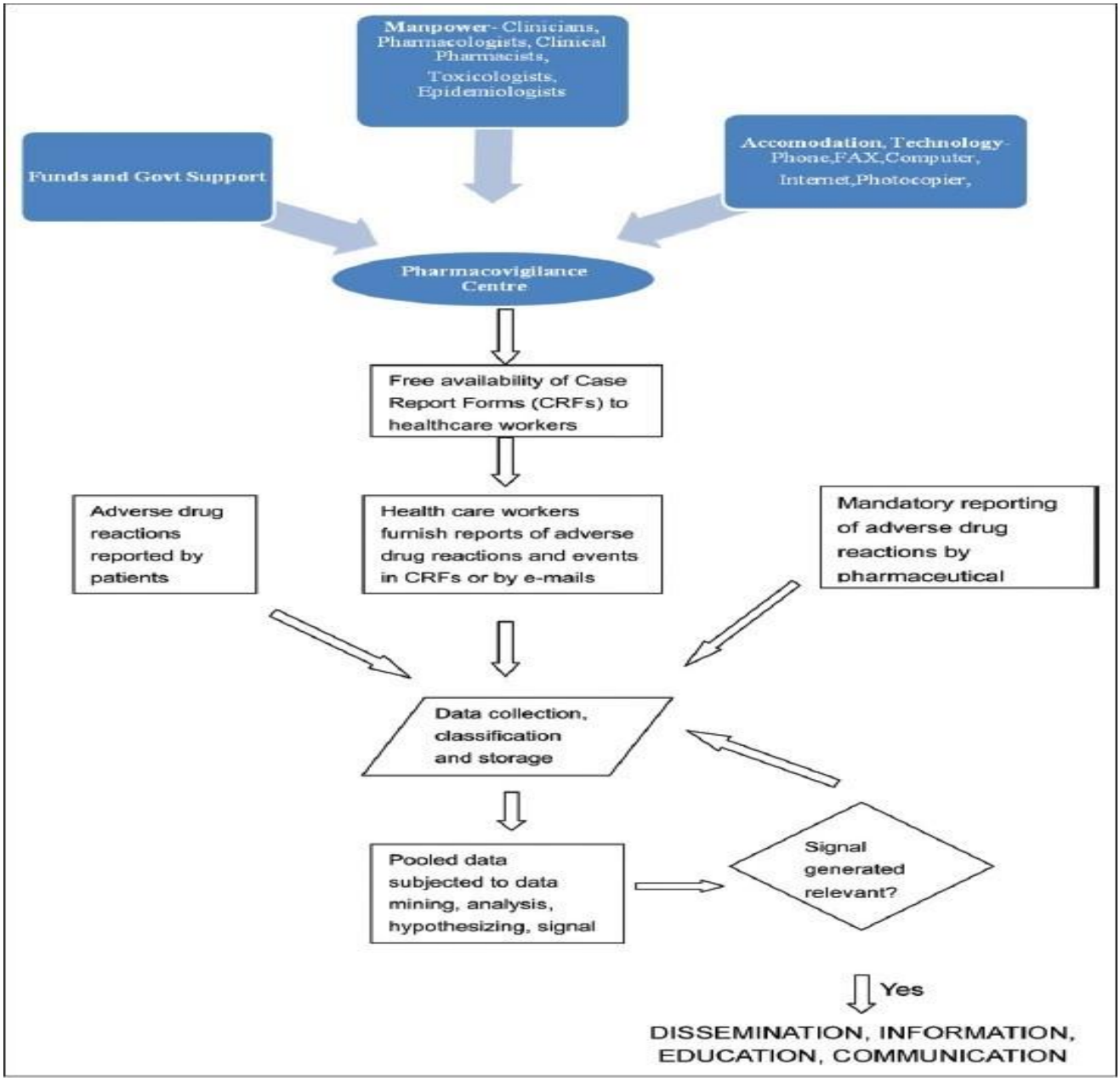
f) Hypothesizing

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) Medicineregulation

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 transformingitin to a Regulatory reportable format.Funding can be obtained from various parties, such as drug Regulatory authority, university departments, health insurance companies, and professional associations.


Manpower- Clinicians, Pharmacologists, Clinical Pharmacists, Toxicologists, Epidemiologists
Funds and Govt Support
Accomodation, Technology- Phone,FAX,Computer, Internet,Photocopier,
Pharmacovigilance Centre
Free availability of Case Report Forms (CRFs) to healthcare workers
Adverse drug reactions reported by patients
Health care workers furnish reports of adverse drug reactions and events in CRFs or by e-mails
Mandatory reporting of adverse drug reactions by pharmaceutical
Data collection, classification and storage
Pooled data subjected to data mining, analysis, hypothesizing, signal
Signal generated relevant?
Yes
DISSEMINATION, INFORMATION, EDUCATION, COMMUNICATION

Establishment & operation of drug safety department in industry

Introduction:-

- Pharmacovigilance has grown as a discipline over the past10to15year.
- An educational survey in 1994 revealed that more than 320 people currently worked in company pharmacovigilance function in the UKalone.
- 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 productsoften more than 1000case reports a year are received worldwide from healthcare professionals and other sources.

Aimof pharmacovigilancewithinthe industry:-

- Protect patients from unnecessary harmby identifying previously unrecognised drug hazards.
- Refutingfalsesafetysignals andquantifyingriskin relationto benefit.

Scientificcharacteristics:-

- 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 analys is 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 clinicaltrials:-

- Safety monitoring in clinical trials involves collecting adverse event, laboratoryinvestigation 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 informationi.edata sheet.

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

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

Signalgeneratedthroughfourdifferentmethods

- **Spontaneous reporting**
  - Recording and reporting clinical observation of as uspectedADRwith a marketed drug is known as spontaneous reporting.
  - The Nationa lsystemintheUKistheyellowcard.
  - 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 interventionalcohort type studies to answer safety question rose after marketing or general hypothesis generatingand testingtool to be used as need arises.
- **Post marketing clinical trials**
  - Larger and o missed 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 individualcases.
- **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 testingshould 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 allowautomated distribution of case reports within companies and to regulatory authorities.

Contract Research Organization (CRO)

- A CRO is a company that provides research services to pharmaceutical, biotechnology, and medical device companies
- CROs conduct clinical trials, preclinical studies, and other research activities on behalf of their clients
- CROs offer expertise, resources, and infrastructure to support the development of new drugs, devices, and therapies

Services offered by CROs:

- Clinical trial management
- Site selection and management
- Patient recruitment and retention
- Data management and analysis
- Regulatory affairs
- Quality assurance and control
- Medical writing and reporting
- Preclinical studies (e.g., toxicology, pharmacology)
- Bioanalytical services (e.g., laboratory testing)

Benefits of working with a CRO:

- Expertise and specialized knowledge
- Access to resources and infrastructure (e.g., equipment, facilities)
- Cost savings and efficiency gains
- Flexibility and scalability
- Accelerated timelines and faster time-to-market
- Reduced risk and liability

Types of CROs:

- Full-service CROs: offer a wide range of services
- Specialty CROs: focus on specific areas (e.g., oncology, pediatrics)
- Virtual CROs: provide services remotely, often with a smaller footprint
- Hybrid CROs: combine elements of full-service and specialty CROs

CRO industry trends:

- Increasing demand for outsourcing research services
- Growing focus on niche and specialty services
- Advancements in technology and digitalization

- Expanding presence in emerging markets
- Rising importance of data quality and integrity

Regulatory considerations:

- Compliance with Good Clinical Practice (GCP) and other regulations
- Adherence to industry standards and guidelines
- Audits and inspections by regulatory agencies
- Quality assurance and control measures

Challenges faced by CROs:

- Managing complexity and variability in clinical trials
- Ensuring data quality and integrity
- Maintaining regulatory compliance
- Managing relationships with clients and stakeholders
- Staying up-to-date with industry trends and advancements

Establishing a National Programme in Pharmacovigilance

Definition:

- A national pharmacovigilance program is a coordinated effort to monitor and evaluate the safety of medicines in a country

Key Components:

1. Clear objectives: Define specific goals, such as improving patient safety, reducing adverse drug reactions, and promoting rational drug use
2. Stakeholder engagement: Involve key stakeholders, including regulatory agencies, healthcare professionals, patients, and industry
3. Pharmacovigilance system: Establish a robust pharmacovigilance system, including spontaneous reporting, active surveillance, and signal detection

4. Data management: Develop a data management system to collect, store, and analyze pharmacovigilance data
5. Risk assessment and management: Conduct risk assessments and develop risk management plans to mitigate safety concerns
6. Communication and dissemination: Establish effective communication channels to disseminate safety information to stakeholders
7. Monitoring and evaluation: Regularly monitor and evaluate the program's effectiveness and make adjustments

Steps to Establish a National Programme in Pharmacovigilance:

1. Conduct a situational analysis: Assess the current pharmacovigilance landscape in the country
2. Develop a concept note: Outline the program's objectives, scope, and strategies
3. Build a stakeholder coalition: Engage key stakeholders and build a coalition to support the program
4. Establish a pharmacovigilance system: Develop a robust pharmacovigilance system, including reporting, surveillance, and signal detection
5. Develop a data management system: Create a data management system to collect, store, and analyze pharmacovigilance data
6. Develop risk assessment and management guidelines: Establish guidelines for risk assessment and management
7. Launch the program: Launch the program and begin implementation

Challenges and Considerations:

- Regulatory framework: Ensuring a supportive regulatory framework
- Resource constraints: Managing limited resources and funding
- Stakeholder engagement: Ensuring effective stakeholder engagement and collaboration

- Data quality and management: Ensuring high-quality data collection, storage, and analysis
- Risk communication: Effectively communicating safety information to stakeholders
- Sustainability: Ensuring long-term sustainability of the program

Best Practices:

- *Follow international guidelines and standards (e.g., WHO, ICH, CIOMS)
- *Engage with international pharmacovigilance networks and organizations
- *Foster collaboration and coordination among stakeholders
- *Continuously monitor and evaluate the program's effectiveness
- *Provide training and capacity-building for stakeholders

UNIT - 3

PHARMACOVIGILANCE

-

YEAR 24

UNIT 3

Vaccine safety surveillance

- Vaccine Pharmacovigilance
- Vaccination failure
- Adverse events following immunization

Pharmacovigilance methods

- Passive surveillance – Spontaneous reports and case series
- Stimulated reporting
- Active surveillance – Sentinel sites, drug event monitoring and registries
- Comparative observational studies – Cross sectional study, case control study and cohort study
- Targeted clinical investigations

Communication in pharmacovigilance

- Effective communication in Pharmacovigilance
- Communication in Drug Safety Crisis management
- Communicating with Regulatory Agencies, Business Partners, Healthcare facilities & Media

Vaccine safety surveillance

Vaccine Pharmacovigilance:

Definition- According to the CIOMS/WHO working group on vaccine pharmacovigilance, Vaccine pharmacovigilance is defined as "the science and activities relating to the"

- **Detection,**
- **Assessment,**
- **Understanding and**
- **Communication**

of adverse events following immunization and other vaccine or immunization-related issues, and to the prevention of untoward effect of the vaccine or immunization. Vaccine pharmacovigilance refers to the monitoring and evaluation of vaccine safety and effectiveness after they are licensed and distributed for public use. It's an essential public health function that helps ensure vaccines are safe and effective for the population.

Importance of vaccine safety:

- Decreases in disease risk and increased attention on vaccine risks
- Public confidence in vaccine safety is critical
- Low tolerance for vaccine risks
  - Higher standard of safety is expected
  - Vaccinees generally healthy
  - Lower risk tolerance = need to search for rare reaction

Steps of vaccine pharmacovigilance:

Detect signal suggesting AEFI is related to vaccine.

Develop hypothesis about causal association between an AEFI and vaccination

Test hypothesis through appropriate epidemiological method

Vaccine provide by Govt. of India:

Govt. of India is providing vaccination to prevent 7-vaccine preventable disease (VPDs) namely,

- ✓ Diphtheria,
- ✓ Pertussis,
- ✓ Tetanus,
- ✓ Polio,
- ✓ Measles,
- ✓ Hepatitis B,
- ✓ BCG
- ✓ JE vaccination,
- ✓ Hib (given as pentavalent containing Hib+DPT+Hep B)

Other vaccines.....

- ➢ Pneumococcal vaccine
- ➢ Rotavirus vaccine
- ➢ Hepatitis A
- ➢ MMR
- ➢ Influenza
- ➢ Meningococcal
- ➢ Cholera
- ➢ JE
- ➢ HPV
- ➢ Varicella
- ➢ Typhoid

Source for vaccine safety

- Local health workers
- Health education campaigns
- Visiting experts
- Online resources and communication network
- Religious and/or community leader
- Parents, guardians and vaccine

- Radio and telivision
- printed material
- Video or DVD

Key aspects of vaccine pharmacovigilance:

1. Adverse Event Following Immunization (AEFI): Monitoring and reporting of any untoward medical occurrence that follows immunization, whether or not it's causally related to the vaccine.

2. Signal detection: Identifying potential safety concerns or "signals" through data analysis and reporting.

3. Risk assessment: Evaluating the likelihood and severity of adverse events.

4. Risk communication: Informing healthcare professionals, policymakers, and the public about vaccine safety concerns.

5. Risk management: Implementing measures to minimize risks, such as updating vaccine labels or issuing safety alerts.

6. Post-marketing surveillance: Ongoing monitoring of vaccine safety and effectiveness in real-world settings.

Benefits of vaccine pharmacovigilance:

1. Early detection of safety concerns: Prompt identification and response to potential issues.

2. Improved vaccine safety: Enhanced understanding of vaccine risks and benefits.

3. Increased public trust: Transparent communication about vaccine safety.

4. Evidence-based decision-making: Informed policy and regulatory decisions.

5. Optimized vaccine development: Identification of areas for improvement in vaccine design and manufacturing.

VACCINATION FAILURE:

Vaccination failure refers to the phenomenon where a vaccine fails to provide adequate immunity or protection against a specific disease or infection. There are several reasons why vaccination failure can occur, including:

TYPES OF VACCINE FAILURE:

1. Primary vaccine failure: When the vaccine fails to induce immunity in the first place.

2. Secondary vaccine failure: When immunity wanes over time, leaving the individual susceptible to infection.

CAUSES OF VACCINE FAILURE:

Vaccine-related factors:

1. Poor vaccine quality:
   Contamination, degradation, or incorrect formulation.
2. Inadequate vaccine dose:
   Insufficient amount of antigen or incorrect dosing schedule.
3. Improper storage or handling:
   Exposure to heat, cold, or light, affecting vaccine potency.
4. Vaccine mismatch:
   Inadequate match between vaccine strain and circulating pathogen.

Host-related factors:

1. Age: Too young (immature immune system) or too old (weakened immune system).

2. Immunocompromised status: Weakened immune system due to disease (e.g., HIV/AIDS) or treatment (e.g., chemotherapy).

3. Genetic factors: Individual genetic variations affecting immune response.

4. Underlying medical conditions: Chronic diseases (e.g., diabetes, kidney disease) or immunodeficiency disorders.

External factors:

1. Exposure to high pathogen loads: High levels of pathogen exposure, overwhelming vaccine-induced immunity.

2. Inadequate public health measures: Low vaccination coverage, poor sanitation, or inadequate disease surveillance.

3. Pathogen mutations or changes: Emergence of new strains or variants, reducing vaccine effectiveness.

4. Interference from other vaccines or medications: Interactions affecting vaccine efficacy.

Other factors:

1. Vaccine administration errors: Incorrect administration technique or route.
2. Vaccine hesitancy or refusal: Failure to receive recommended vaccinations.

Consequences of vaccination failure:

1. Individual risk: Increased susceptibility to infection and disease
2. Public health risk: Outbreaks and transmission of infectious diseases
3. Economic burden: Healthcare costs, lost productivity, and economic impact

Strategies to address vaccination failure:

1. Improve vaccine development and quality control
2. Optimize vaccination schedules and boosters
3. Enhance public health measures (e.g., surveillance, contact tracing)
4. Address vaccine hesitancy and misinformation
5. Develop new technologies and approaches (e.g., mRNA vaccine

Which Adverse event following immunization (AEFI)should be reported?

- Serious AEFI
- Signal and events associated with newly introduced vaccine
- AEFI that may have been caused by an immunization error
- Significant events of unexplained cause occurring within 30 days after a vaccination
- Event causing significant parental or community concern
- Swelling, redness, soreness at the injection site IF it lasts for more than 3 days or swelling extended beyond nearest joint

Adverse event following immunization

Definition-

An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be

any unfavourable or unintended sign, abnormal laboratory finding, symptoms or disease.

Classification of AEFIs

- **Vaccine product-related reaction** – An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product. Extensive limb

  e.g. swelling following DTP vaccination.

- **Vaccine quality defect-related reaction** – An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product inducing its administration device as provide by the manufacturer.

Ex. Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio.

- **Immunization error-related reaction** – An AEFI that is caused by inappropriate vaccine handling, prescribing or administration.

Ex. Transmission of infection by contaminated multidose vial.

- **Immunization anxiety-related reaction** – An AEFI from anxiety about the immunization.

  e.g. Vasovagal syncope in an adolescent following vaccination.

- **Coincidental event**- An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.

  e.g. A fever after vaccination (temporal association) and malarial parasite isolated from blood.

AEFI Frequency Terminology

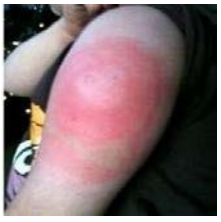
Very common*	≥ 1/10	≥ 10%
Common (frequent)	≥ 1/100 and < 1/10	≥ 1% and < 10%
Uncommon (infrequent)	≥ 1/1,000 and < 1/100	≥ 0.1% and < 1 %
Rare	≥ 1/10,000 and < 1/1,000	≥ 0.01% and < 0.1%
Very rare*	< 1/10,000	< 0.01%

Two type of vaccine reaction-

- Minor reaction
- Severe reaction

Minor reaction

- Usually occur within a few hours of injection.
- Resolve after short period of time and pose little danger.
- Local (includes pain, swelling or redness at the site of injection).
- Systemic (includes fever, malaise, muscle pain, headache or loss of appetite).



Severe reaction

- Usually do not result in long-term problems.
- Can be disabling.

- Are rarely lives threatening?
- Include seizures and allergic reactions caused by the body's reaction to a particular component in a vaccine.

Serious AEFI cases (formats and timelines)

Type of Report		Responsible	Time line
CASE REPORTING FORM(CRF)		MO	24 hours of notification
		DIO	48 hours of notification
CASE INVESTIGATION FORM (CIF)	Preliminary	DIO	10 days of notification
	Final	AEFI investigation team	70 days of notification

Vaccine Evaluation

Pre-licensing

Randomised, Blinded, Controlled Clinical Trials

Vaccine efficacy:

Protective Effect under Idealised Conditions

RTC: controlled experiments, simple interpretation

Post-licensing

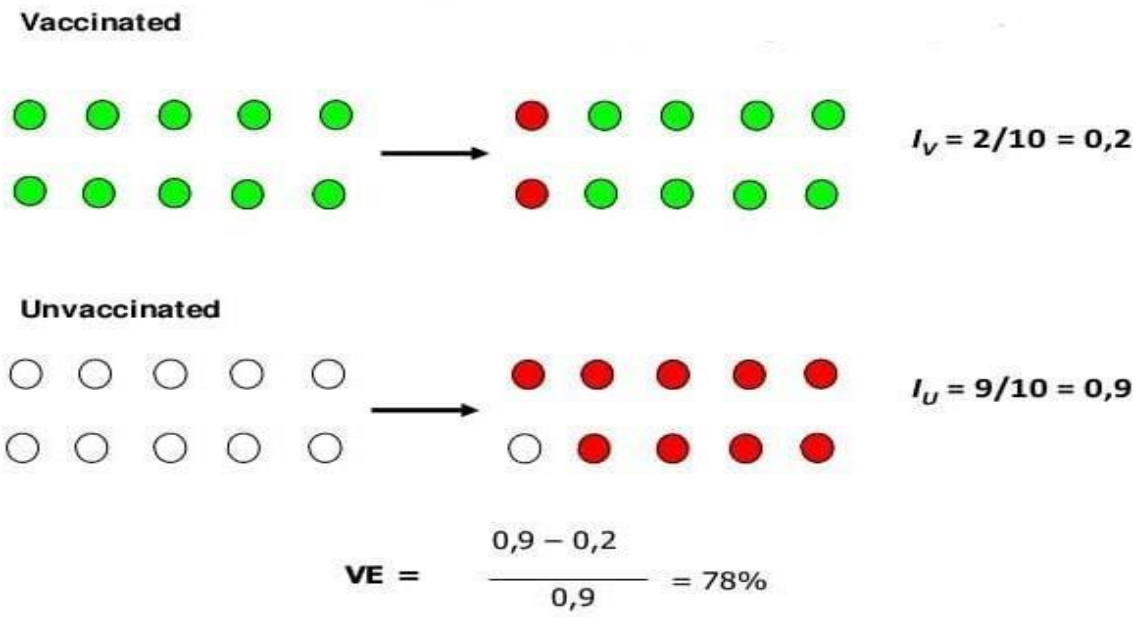
Observational Studies

Vaccine effectiveness

Protective Effect under Ordinary Conditions of a public health programme

Prone to bias, more complex interpretation

Basic Calculation of Vaccine Evaluation



VE(%) = (ARU-ARV/ARU).100

Precaution-

- A condition in a recipient which may increase the chance or severity of an adverse event, or
- May compromise the ability of the vaccine to produce immunity.

Pharmacovigilance Methods

Objective

- ✓ To establish a functional reporting system to monitor the safety of all medicines
- ✓ To learn more about the safety profile of new medicines in the early post-marketing phase
- ✓ To learn more about the ADR profile of a specific medicine(s) in your population
- ✓ To estimate the incidence of a known ADR to a specific medicine in your population
- ✓ To gather more information on the safety profile of a new chemical entity in early post-marketing phase

- ✓ To make use of existing electronic health records and registries to support pharmacovigilance activities

Methods

- Passive surveillance
  - Spontaneous reports
  - Case series
- Stimulated reporting
- Active surveillance
  - Sentinel sites
  - Drug event monitoring
  - Registries
- Targeted clinical investigations
- Comparative observational studies
  - Cross sectional study
  - Case control study
  - Cohort study
- Descriptive studies
  - Natural history of disease, Drug utilization study

Passive surveillance :

Passive surveillance in pharmacovigilance refers to a spontaneous and voluntary reporting system for monitoring the safety of vaccines, medications, or medical devices. It involves:

Spontaneous Reports

- ➢ A communication by consumers or healthcare professionals to a company or Regulatory Authority, that describes one or more ADR in a patient, who has given the drug.
- ➢ It plays a major role in the, identification of safety signals once the drug is marketed.
- ➢ Gives alerts on rare AEs that were not detected in earlier clinical trials or pre marketing studies.
- ➢ Provides important information on at risk groups, risk factors and clinical features of known serious ADRs.

Case series

- Series of case reports can provide evidence of an association of a drug and AEs.
- Generally more useful for generating hypothesis than for verifying an association between drug exposure and outcome.
- Certain distinct adverse events occur more frequently with drug therapy, such as anaphylaxis, aplastic anemia and Stevens-Johnson syndrome events such as these are spontaneously reported for detailed and rapid follow-up.

Stimulated Reporting

- A method used to encourage and facilitate reporting by health professionals for new products, or for limited period.
- Online reporting of AE, systematic stimulation of reporting of AEs.
- Drawbacks- data are often incomplete.

  Not useful to generate accurate incidence rates.

Active surveillance

- To ascertain completely the no. of AEs via a continuous pre-organized process.

  E.g. follow up of patient treated with a particular drug.
- More feasible to get comprehensive data on individual AE reports.

Active surveillance in pharmacovigilance refers to a proactive and systematic approach to monitoring the safety of vaccines, medications, or medical devices. It involves:

1. Targeted data collection: Gathering specific information on adverse events, product quality, and usage patterns.
2. Prospective monitoring: Ongoing, real-time observation of patients, healthcare providers, or electronic health records.
3. Intensive follow-up: Regular contact with patients or healthcare providers to gather detailed information.
4. Systematic analysis: Regular review and analysis of collected data to identify potential safety concerns.

Sentinel Sites:- Active surveillance carried out at Institutions, Nursing Homes and Hospitals etc. provides information such as data from specific patient subgroups, drug abuse etc.

Drug Event Monitoring: - Patients are identified by electronic prescription data or automated health insurance claims. A follow up questionnaire can be sent to each physician or patient at specified intervals. Information on patient demographics, indication for treatment, duration of therapy, dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.

Registries: - A registry is a list of patients presenting with same characteristics. E.g. Disease registry, drug registry, pregnancy registry etc. Differs from each other depending on type of patient.

Comparative Observational Studies:-

- Traditional epidemiologic methods are a key component in the evaluation of AEs.
- Observational study designs are useful in validating signals from spontaneous reports or case series.

Cross Sectional Studies:-

- Data collected from a population of patients at a single point in time regardless of exposure or disease status.
- Primarily used to gather data for surveys or for ecological analysis. Best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured.

Case Control Study:- In this case of disease are identified. Controls or patients without the disease or event of interest, are selected from the source population. Exposure status of the two groups is compared using the odds ratio.

Cohort Study:- A population at risk for the disease is followed over a time for the occurrence of the disease or events. Information on exposure status is known throughout the follow up and hence incident rates can be calculated.

Comparison cohorts of interest are selected on the basis of drug use and followed over time. Multiple AEs can also be investigated using the same data source in a cohort study.

Targeted Clinical Investigations:-

- When significant risks are identified from pre-approval clinical trials, further clinical studies might be called, to evaluate the mechanism of action for ADRs.
- PK and PD studies might be conducted.
- Specific studies to investigate potential drug-drug interactions and food-drug interactions might be called.

Descriptive Studies:-

- Primarily used to obtain the background rate of outcome events and/or to establish the prevalence of the use of drugs in specified populations.

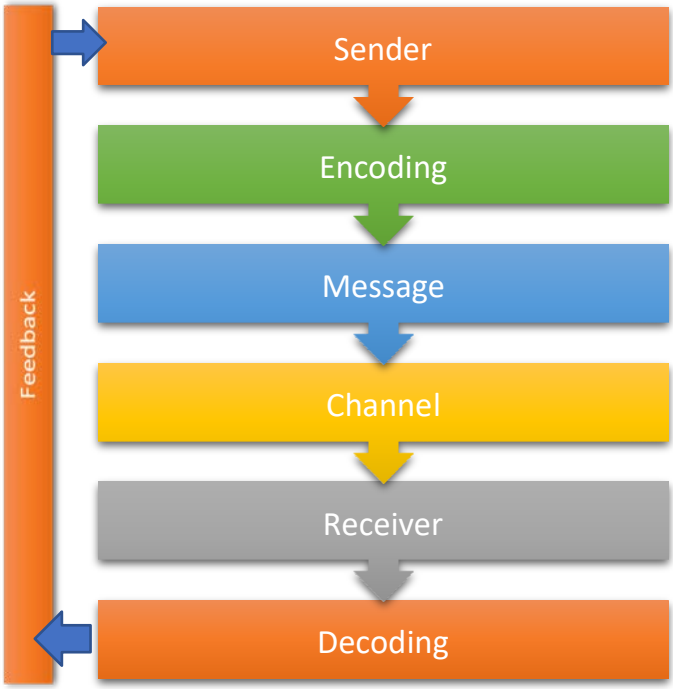
- Natural History of Disease- Focused on the natural history of disease, including the characteristics of diseased patient and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest.

- Drug Utilization Study- These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics.

Communication in pharmacovigilance:

The act of sharing or exchanging information, ideas or feelings.

Communication Process:



Principles of Good Pharmacovigilance Communication

- ✓ Relate the messages to the audience's perspective
- ✓ Avoid comparisons which trivialize the concern
- ✓ Ensure completeness of the message
- ✓ Be balanced, honest and sympathetic
- ✓ Focus on the specific issue that needs to be handled
- ✓ Pay attention to what the audience already knows
- ✓ Be respectful of people's right to be concerned
- ✓ Be honest about the limits to scientific knowledge
- ✓ Acknowledge uncertainty
- ✓ Evaluate the impact of your message

Effective Communication in Pharmacovigilance

One can achieve effective way of communication just by following the principles of good pharmacovigilance communication.

Why do we need to improve our communication?

- ✓ Improve patient care and understanding
- ✓ Eradicate disease / improve disease control
- ✓ Promote transparency and accountability

Why do Communications matter in Drug Safety?

- ✓ For Welfare of millions of people worldwide
- ✓ To overcome Extreme dangers of failure
- ✓ Communications are commonly poorly executed, second-rate and ineffective, so to improve the quality.

Communication Challenges:

- ✓ The importance of ADRs and reporting them
- ✓ Information about benefit – harm and effectiveness – risk
- ✓ Encouraging rational drug use/adherence
- ✓ Communicating uncertainty
- ✓ Dealing with traditional beliefs and practices
- ✓ Involving patients; reaching informed consent
- ✓ Preventing or resolving crises

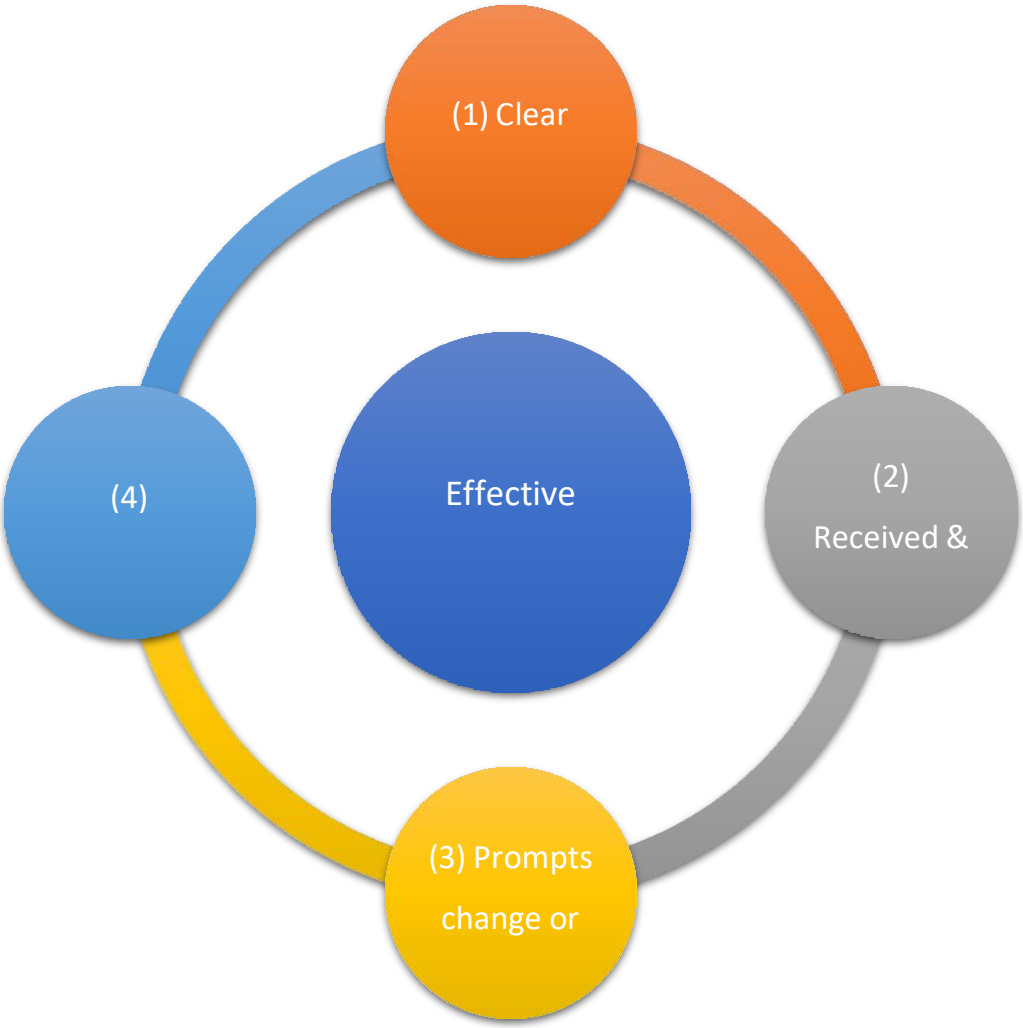
Problematic issue in Drug Safety:

all reliant on communications for safety

- ✓ Adverse effects: 'no drug 100% safe'
- ✓ Risk as a concept in medicine

- ✓ Safety and medicines (prescribing, dispensing)
- ✓ Benefit-harm
- ✓ Effectiveness-risk
- ✓ Public health and commercial goals
- ✓ Public health and individual welfare
- ✓ Access to medicines
- ✓ Uncertainty

What is an Effective Communication?



Principles of Effective Communications

- ✓ Be clear about your message and purpose
- ✓ Know your audience(s): empathy; tailor the message
- ✓ Choose appropriate methods/media
- ✓ Present message with impact
- ✓ Make benefits clear
- ✓ Pre-test and revise message
- ✓ Repeat message
- ✓ Seek feedback, monitor effects, start again

Qualities of Modern Communications:

- ✓ Intimacy
- ✓ Immediacy and high impact
- ✓ Peer-to-peer
- ✓ Addressing competition and low attention levels
- ✓ Benefits

Planning Communications:

- ✓ Today's modern standards and methods
- ✓ Simple, clear message
- ✓ Stimulating motivation and offering benefits (including rewards and feedback)
- ✓ The use of specialist skills and creative imagination

Summary:

- Our communications must:

– Be strong and visible

– Be precisely targeted and tested

– Change attitudes, values, behaviour

– Be followed up and revised

– Embrace modern standards and skills

1. Communication in Drug Safety Crisis Management

- Crisis will happen (fire, death, ADRs…)
- Assess risks
- Anticipate and plan for all likely and unlikely events
- Create, rehearse and revise crisis plans
- In crisis, communicate
  - Quickly
  - Openly and honestly
  - Express regret, apologise
  - Explain what is being done to solve the crisis and prevent repetition

Effective communication is crucial in managing drug safety crises. It involves timely, accurate, and clear dissemination of information to all relevant stakeholders, including healthcare professionals, regulatory authorities, patients, and the public. The goal is to ensure safety, maintain trust, and mitigate the impact of the crisis. Here's an overview of the key components of communication in drug safety crisis management:

1**. Preparation and Planning:**

- *Crisis Communication Plan*: Develop a comprehensive plan outlining roles, responsibilities, and procedures for communication during a crisis.
- *Stakeholder Identification*: Identify all potential stakeholders and establish communication channels in advance.

2. Timely and Transparent Communication:

- *Early Notification*: Promptly inform stakeholders about the crisis, even if all details are not yet available.
- *Regular Updates*: Provide ongoing updates as more information becomes available, maintaining transparency.

3. Accurate and Clear Messaging:

- *Consistency*: Ensure that all communications are consistent across different channels and stakeholders.
- *Clarity*: Use clear and simple language to explain the situation, potential risks, and actions being taken.
- *Honesty*: Acknowledge uncertainties and what is being done to address them.

4. Effective Channels and Tools:

- *Media and Public Relations*: Utilize press releases, media briefings, and social media to disseminate information widely.
- *Direct Communication*: Engage directly with healthcare providers, pharmacists, and patients through emails, hotlines, and webinars.
- *Digital Platforms*: Leverage websites, apps, and social media for real-time updates and engagement.

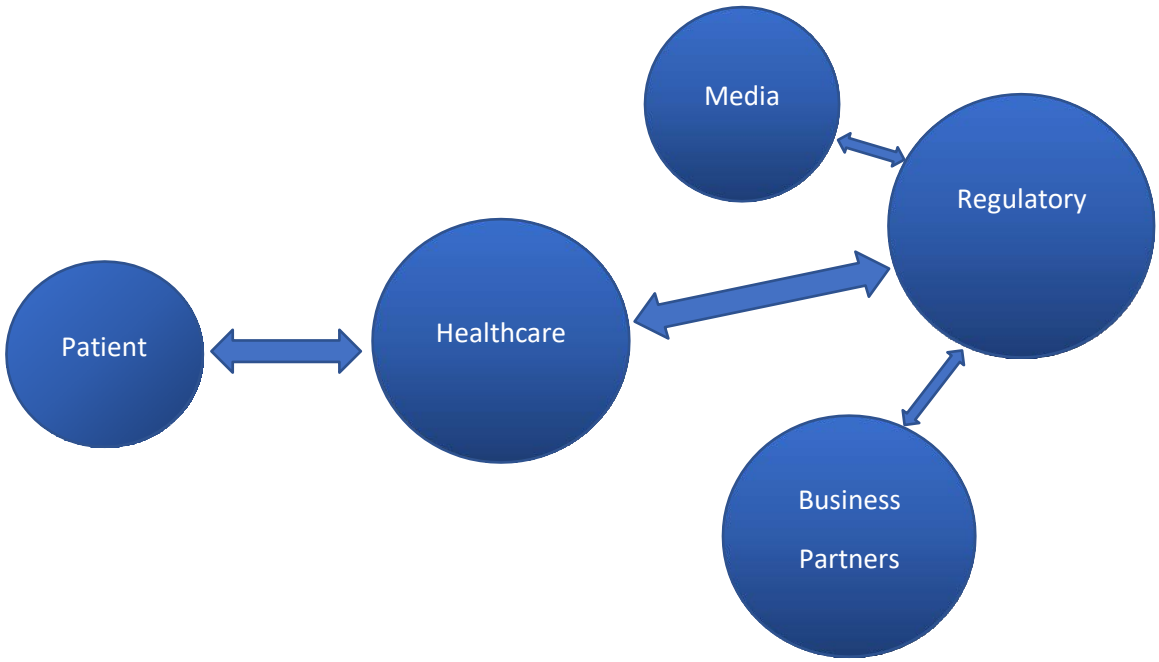
5. **Feedback Mechanisms:**

- *Stakeholder Engagement*: Encourage questions and feedback from stakeholders to address concerns and adjust communication strategies accordingly.
- *Monitoring and Response*: Monitor public and media reactions to identify misinformation and respond swiftly to correct it.

6. Post-Crisis Evaluation:

- *Review and Assess*: After the crisis, evaluate the effectiveness of the communication strategy and identify areas for improvement.
- *Documentation and Reporting*: Document the crisis management process and outcomes to inform future strategies and regulatory reporting.

2. Communicating with Regulatory Agencies, Business partners, Healthcare facilities & Media



Communication with Media:

Who are the media?

- ✓ Print -magazines, newspapers, community newspapers
- ✓ Electronic -radio, TV, internet
- ✓ Local and national levels

□ **Some basic questions a reporter will ask you….**

- ✓ WHO-is affected, responsible
- ✓ WHAT-has happened and what is being done about it
- ✓ WHERE-has it happened
- ✓ WHEN-did it happen
- ✓ WHY-did it happen
- ✓ WILL-it happen again

□ **Communications practices to avoid**

- ✓ "Spinning"! (distortion or decoration of facts for beneficial effects)
- ✓ All communications are subjective, but do not be manipulative or dishonest
- ✓ Avoid "No comment"–rather say why there's nothing to say and what is being done
- ✓ Avoid confusing statistics
- ✓ Do not avoid taking responsibility
- ✓ Don't attack the messenger/accuser
- ✓ Don't deny, justify or excuse your mistakes

□ **Partners & Audiences in Drug Safety:**

Partners

- Manufacturers
- Regulators
- Politicians
- Employees
- Health professionals
- Academics
- Bosses/managers

Audiences

- The public
- Patients
- Consumer groups
- Lawyers
- The media
- International community

UNIT - 4

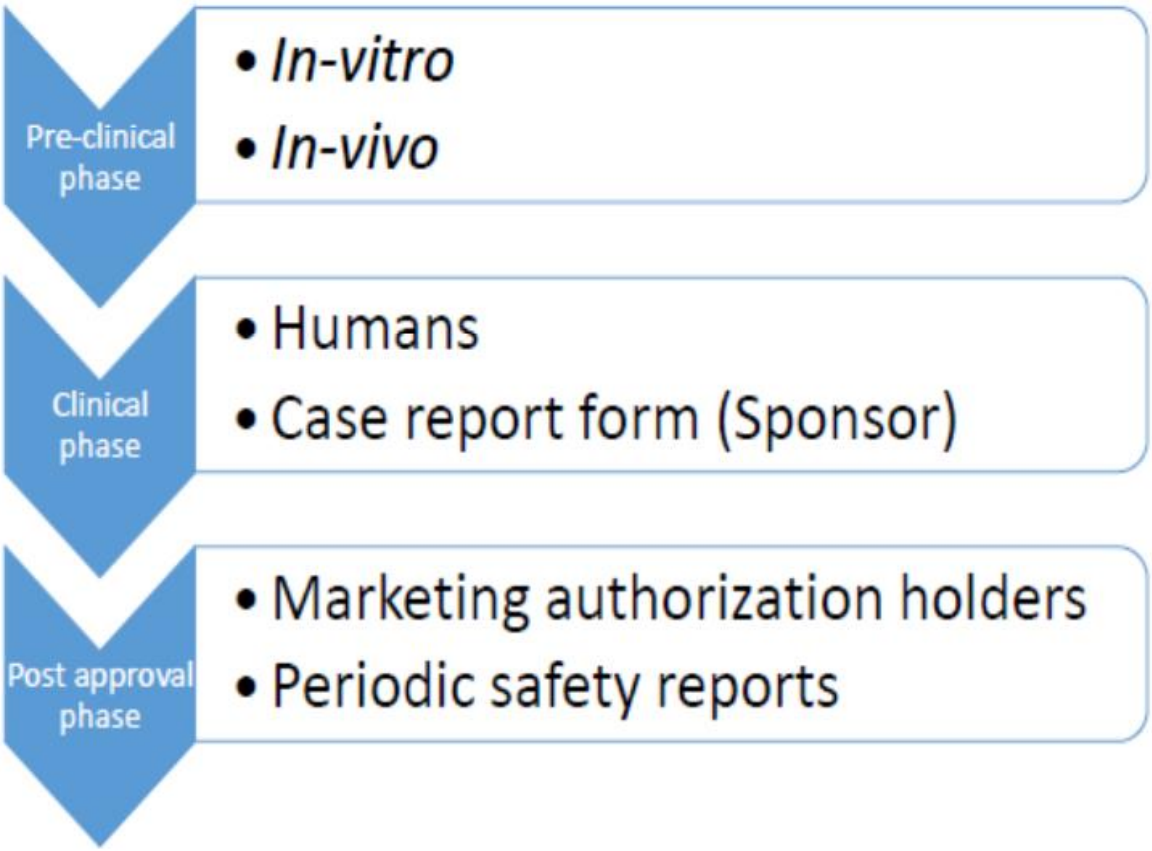
Pharmacovigilance

YEAR-24

UNIT - 4

- Safety data generation
- Pre clinical phase
- Clinical phase
- Post approval phase
- ICH Guidelines for Pharmacovigilance
- Organization and objectives of ICH
- Expedited reporting
- Individual case safety reports
- Periodic safety update reports
- Post approval expedited reporting
- Pharmacovigilance planning
- Good clinical practice in pharmacovigilance studies

SAFETY DATA GENERATION



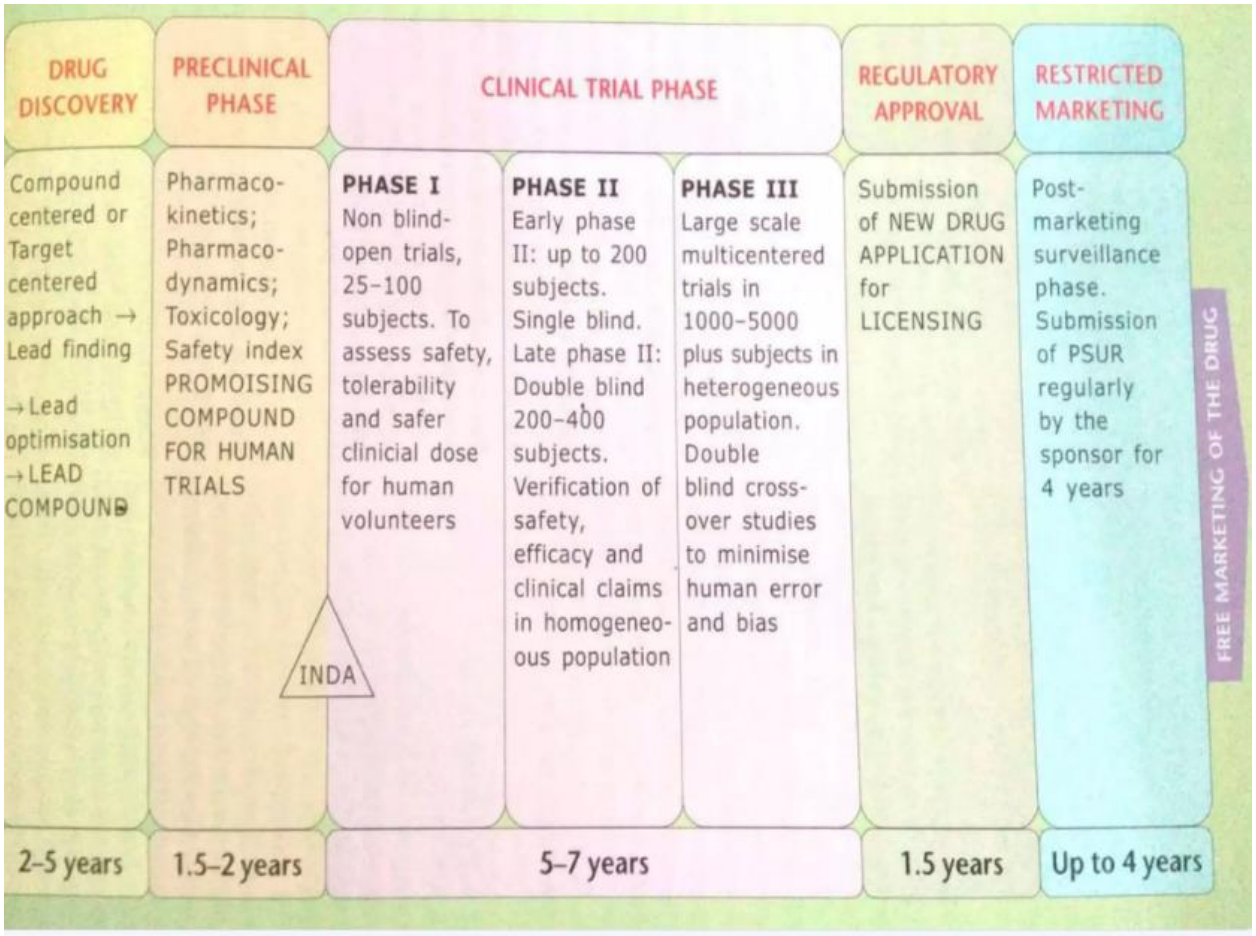
Broadly speaking the drug development process can be divided into three main phase, namely

1.Drug discovery phase:- During which the candidate molecules are chosen on the basis of their pharmacological properties

2.Preclinical phase :- During which a wide range of

animals studies are performed examples..pharmacokinetic, pharmacodynamics, toxicity studies.

3.Clinical trial phase :- During which the lead compound is evaluated for efficacy, safety and adverse effects in the human volunteers and patient



PRECLINICAL EVALUATION PHASE (ANIMAL STUDIES

➢Initially, Animals studies are performed to define the pharmacological profile of the lead compound the aim during the preclinical phase of development is to satisfy all the requirement that are needed before a compound is considered fit to be tested for first time in human.

➢Especially the toxicological studies, is done according to the

➢This ensures reliability and reproducibility of laboratory data and minimizes human errors.

➢Out of the 10,000 compound screened during drug discovery phase, only 10 qualify the phase of preclinical evaluation which are then subjected to clinical trials in humans.

standard laid down in a formal operating code known as "GOOD LABORATORY PRACTICES"

- Studies during the preclinical phase usually require 1.5 to 2 years.

Clinical trial phase(human trials)

➢Clinical trials mean a systematic study of a new drug in human subject to generate discovery or verifying the clinical Claim or pharmacological and adverse effect with an aim to determine the safety and efficacy of the drug when the new compound passes the clinical pharmacological screening, the manufacturer may file a "preclinical new drug" or "investigational new drug" application (IND application) to an authorized drug control body of the respective country.

The IND application must contain the following

1. The chemical structure, its sources, its manufacturing data with details of its purity

2. The preclinical data about pharmacodynamics, Pharmacokinetics, and toxicological studies with ED50 and LD50 data.

3.Specification of dosage forms in which its has to be administered to human beings.

4. Detailed description of investigation protocol to be undertaken (including the dose and route of administration)

5. The name and qualifications of each investigator and the facilities available to them,

6.An agreement from the sponsor to submit annual progress reports regularly.

7. A certification that "informed consent" will be obtained from human volunteer and that "ethics of research in human begins" will be strictly followed.

Note:- only when the approval is given by the regulatory body, the drugs can be administered to the men for clinical trials

PHASES OF CLINICAL TRIALS

➢Phase one

➢Phase Two

➢Phase Three

➢Phase Four

Phase one:- It is the phase of clinical pharmacological evolution of new drug and is performed on a small number (25-100) of healthy volunteers. If the drugs is expected to have significant toxicity(as in the case of anticancer drugs or drugs to be used in AIDS therapy). the volunteers with the particular disease are used rather than healthy volunteers.

Objective :-

1.To check for safety(i.e. whether the drug affect any cardiovascular, hepatic or renal function adversely) and to

check its tolerability (i.e. doses the drugs produce any unpleasant symptom like headache, nausea, vomiting.

2. To determine whether human and animals show significant pharmacokinetic differences.

3. To determine the pharmacokinetic of the drug in human so as to decide whether the deficiency in drugs effects, if any, is a results of its lack of absorption or its faster elimination.

4. To detect any predictable toxicity.

Phase Two

➢In this phase, the drug is studied for the first time in patients with target diseas to determine its efficacy (i.e., proof of claims)

➢the main purpose of phase 2 trails is to gather evidence that the drug has the effects as suggested by preclinical trials hence the end point is decided

➢These trials is divided into early and late phase

In early phase 2:-

➢A small number of patients (up the 200) are studied in details to observe the potential therapeutically benefits and side effects.

Its is usually a single blind design where only the subject does not not known whether he is taking an inert placebo(if used) or the new drugs(under trial).

In late phase 2:-

➢It is conducted on a large number of patient (200-400) in controlled double blind manner, where the investigator is also ignorant (besides the subject) whether he is prescribing a placebo, or a positive control medicine or new drugs under trail.

Phase Three

These are large-scale multicenter (heterogeneous population) randomized double-blind trials in patients 5000 plus) to further establish the safety and efficacy.

These are designed to minimize error in the information gathered in phase 1 and phase 2 trials Therefore these trials are made using double-blind cross-over designs like those set out in below.

APPLICATION:-once the phase 3 trails are completed satisfactorily the sponsors are file a "new drug application" The new drug application contains thousand of page and includes complete detailed monograph of the product, the result trails
If the documentation is acceptable and is in compliance with the regulations, the drugs control authorities can allow the drugs to enter the markets with "new drugs status

Phase Four

Once the approval is obtained to market the drugs, phase 4 of the trails begins.it is the post-licensing phase- field trails.

phase four has no fixed duration as it is the surveillance phase during the post-marketing clinical use of the drugs.

The performance of the drugs is monitored for several years immediately after marketing, to discover relatively rare side effect (e.g. congenital effects).

During the "new drug status period, the manufacturer is expected to report any new information about the drugs conceming its safety. Such periodic safety update report (PSUR) is to be submitted every six months for first 2 years and manually for next 2 years.

Limitations of Clinical Study Data

	Clinical trials	Clinical Practice
Number of patients	Hundreds (rarely thousands)	Thousands to millions
Duration	Weeks	Years
Population	Pregnant, children, elderly excluded	All
Concomitant medication and illness	Avoided	Usually present
Dose	Fixed	Variable (compliance)
Conditions	Rigorous; more information	Flexible; less information

Post-Approval Phase (PMS)

Post-approval phase (PMS) involves the collection and identification of Prormation regarding all the medicinal products after their approval by the U.S. Food and Drug Administration (FDA). This phase includes the study to assure efficacy, quality,

and safety of therapeutic drugs after their approval for marketing in the pharmaceutics.

Systematic PMS of drugs began in the early 1970s and has increased since then substantially. Other factors contributing to the need for PMS include changes in the approval process of U.S. Food and Drug Administration (FDA). PMS is conducted by different types of agencies and organisations including government agencies, pharmaceutical manufacturers, universities, private companies, and many others.

Objectives

1) Quantifying the potential or identified risks

2) Providing evidence about the absence of a risk

3) Evaluating the risk of the therapeutic product used in patient volunteers for which the information about safety profile of drug is missing or limited, like in patients with kidney or liver diseases, pregnant women, people of a specific age group.

4) Measuring effectiveness of a risk minimisation activity.

5) Assessing the patterns on utilisation of drugs that ass the information about the safety of pharmaceutical product, i.e., dosage, indications, medication errors, co-medications, etc.

Significance

1) To obtain complete information about the risk-benefit ratio of the newly developed drug molecule as until it has been marketed

and used by large and diverse group of patients the safety and benefit-risk ratio cannot be determined.

2) To determine the efficacy and all the possible risk factors of the drugs being marketed as the clinical trial phases being conducted before the drug approval takes the limited volunteers for limited period of time based on the surrogate endpoint.

ICH guidelines for pharmacovigilance

Introduction

* ICH is the "International Conference on Harmonization" of technical requirements for the registration of pharmaceuticals for human use.

* To assure safety, quality and efficacy of medicines, the members of ICH who include members from drug regulatory authorities and research based industries of European Union, US and Japan will discuss on the technical procedures and documents required.

History

* In 1956 Thalidomide was approved for marketing in Europe and Africa for treating morning sickness in pregnant women.

* Lack of proper policies, Legislations and guidelines to ensure the safety, efficacy of the drug, 10,000 to 20,000 babies suffered from birth defects like phocomelia

* This disaster has initiated many policies, Legislations and amendments in acts to ensure the safety, efficacy, quality of the drugs, thus leading to the formation of International conference on harmonization in 1990.

Need for harmonization

* The difference in the technical requirements and the procedures followed by different countries made the global marketing of drugs as time consuming and expensive

* To reduce the cost and time required for the global marketing of drugs

* Harmonization of technical requirements has been promoted

* Special guidelines have been framed to ensure the quality, safety and the efficacy of the drugs

Objective of ICH

* To promote international harmonization of technical requirements to develop safe, effective, and high quality medicines. D

* To reduce the registration cost.

* To promote public health

* To prevent the duplication of clinical trials in Humans

* To minimize the animal use without compromising on the safety and quality of drugs

Goal of ICH

* Promote international harmonization by bringing together representatives from the three ICH regions (EU, Japan and USA) to discuss and establish common guidelines

* Make information available on ICH, ICH activities and ICH guidelines to any country.

Members of ICH

* ICH is comprised of representatives from six parties that represent the regulatory bodies and research based industry in the European Union, Japan and the USA

* In Japan, the members are the Ministry of Health, Labour and Welfare (MHLW), and the Japan Pharmaceutical Manufacturers Association (JPMA)

* In Europe, the members are the European Union (EU), and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

* In the USA, the members are the Food and Drug Administration (FDA), and the Pharmaceutical Research and Manufacturers of America (PhRMA).

* Additional members include Observers from the World Health Organization (WHO), European Free Trade Association (EFTA), Canada

ICH steering committee

Governs ICH

Determines the policies and procedures for ICH

Selects topics for harmonization

Monitors the progress of harmonization initiatives

ICH coordinator

The Coordinators are fundamental to the smooth running of the ICH and are nominated by each of the six parties of ICH. Coordinator acts as the main contact point with the ICH Secretariat.

* Operates from the IFPMA offices in Geneva, Switzerland

ICH coordinators (Responsibilities)

Provides support to the ICH Steering Committee.

Documents the meetings of the steering committee.

Promotes coordination between Working Groups.

Provides information on the ICH guidelines and ICH process. Provides administrative support for MedDRA management board.Provides administrative support for Global cooperation Group.

ICH global cooperation group

* Formed on March 11, 1999, as a subcommittee of ICH steering committee to Globalise the ICH and its guideline

One representative from each of the six parties of ICH steering committee

* ICH secretariat at IFPMA

ICH working groups

* Expert Working Group

* Implementation Working Group

* Informal Working Group

* Discussion group

ICH guidelines for pharmacovigilance

* This document gives standard definitions and terminology for key aspects of clinical safety reporting

* Gives guidance on mechanisms for handling expedited (rapid) reporting of adverse drug reactions in the investigational phase of drug development.

* The ICH has published a number of documents setting standards for safety, both clinical and pre-clinical.

* Pre-clinical guidelines have an "S" designation e.g. S1, S2 etc.

* The clinical safety guidelines are designated as "E", standing for "Efficacy"

* E1 The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions

* E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

* E2B (R2) Maintenance of the Clinical Safety Data Management including Data Elements for Transmission of Individual Case Safety Reports

* E2B (R3) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

* E2C (R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

* E2C (R2) Periodic Benefit-Risk Evaluation Report

* E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

E2E Pharmacovigilance Planning

* E2F Development Safety Update Report

Expedited Reporting

Expedited reporting in pharmacovigilance refers to the Process of Promptly reporting certain Serious and Unexpected Adverse drug reactions associated with medicial poducts to regulatory authorities. These reports are crucial for Ensuring the ongoing Safety Monitoring of Pharmaceutical products Post Market approval.

1. Criteria for reporting:-

Serious and unexpected adverse reactions such as death, life-threatening Events, hospitalization, disability, Surgery require Expedited reporting

2. Time lines-

They are strict timelines within these events must be reported

Example. In some cases, Serious unexpected Events Must be reported within 7 or 15 days of awareness by the Marketing authorization holder or sponsor

3. Reporting channels

It usually involves submitting detailed reports , including information about the patient, the adverse event, the Medicinal Product, and any actions taken. The reports are Subtitted to regulatory authorities Such as FDA in United Stated, EMA (in Europe) via using Various channels including electronic submission System & paper form

4. Follow-up:

Following the intial report, additional information may be requested by regulatory authorities to better understand the Event.

5. Regulatory oversight Regulatory agencies closely Monitor the Expedited reporting to ensure the Safety and Efficacy of medical products on the Market

Individual Case Safety Reports (ICSR)

1) An Individual Case Study Report is a safety service document which includes data (information) required for reporting any

adverse drug events or problems related to therapeutic or medicinal products and complaints filed by consumers regarding any product.

2) It can also be considered as a document providing the most complete information related to an individual case at any specific point of time.

3) ICSRs are also sometimes referred as safety reports which are used for reporting suspected adverse reactions to the Eudravigilance database with respect to any medicinal drug that occur in a single patient at a certain time period.

4) During the triage phase of a potential adverse event report, it is important to check that whether the "four elements" of a valid ICSR are present in the report or not

i) An adverse event

ii) A suspect drug

iii) An identifiable patient

iv) An identifiable reporter

5) The primary focus of Individual Case Study Reports is to obatin reports from healthcare providers and patients in member countries of the WHO Programme.

6) An individual case is the information provided by a primary source to describe suspected adverse reactions/suspected unexpected serious adverse reactions related to the administration of one or more medicinal product/investigational medicinal products to an individual patient at a particular point of time.

Periodic Safety Update Reports (PSUR)

1) A Periodic Safety Update Report is a pharmacovigilance document required for providing an update of the safety profile of the medicinal drug occurring across the world to the regulatory authorities at some specific time points after their approval for mark

2) PSURs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorisation.

3) The main objective PSUR reporting is to present a critical and comprehensive analysis of the risk-benefit ratio of the therapeutic product, with reference to the new or emerging safety information in the context of cumulative information on risk and benefits of the medicinal drug.

4) The sources of efficacy, effectiveness and safety information that can be used in PSURs preparation include following examples:

i) Clinical and non-clinical studies data;

ii) spontaneous reports, e.g., on the marketing authorisation holder's safety database

iii) Data from product usage and drug utilisation information

iv) Observational studies, including registries

v) Scientific literature.

5) The most important aggregate report all around the world is Periodic Safety Update Report (PSUR) and it is submitted to drug regulatory agencies in Europe, the US and Japan (ICH countries), as well as other countries across the world.

6) In 2012, the PSUR was updated and now in many countries it is referred to as the Periodic Benefit Risk Evaluation report (PBRER) which focuses on the benefit-risk profile of the drug including a review of relevant safety data compiled for a drug product since its development.

Post-Approval Expedited Reporting

1) A new drug molecule (medicinal product) goes through many stages before it is finally approved to be used as an authorised therapeutic drug in human beings like, preclinical, clinical, and post approval safety surveillance throughout its lifecycle.

2) Post marketing monitoring is required to identify rare adverse effects, adverse effects in special group of population, long term effects and effects of interaction with other drugs.

3) However, clinical safety of drug and post approval safety data is required to be processed in the safety database of the pharmaceutical company and must be reported to different regulatory agencies as per regulatory requirements in various countries.

4) During post-approval phase, the prescribing information or summary of product characteristic is used as a source document.

5) During clinical trial phase, clinical trial or epidemiological investigation is the source of ICSRs and during post approval phase, the sources are divided into unsolicited or solicited sources.

PHARMACOVIGILANCE PLANNING

The Pharmacovigilance Plan should be based on the Safety Specification. The Specification and Plan can be written as two parts of the same document. The Plan would normally be developed by the sponsor and can be discussed with regulators during product development, prior to approval (i.e., when the marketing application is submitted) of a new product, or when a safety concern arises post-marketing.

Objectives

1) The pharmacovigilance plan gives the guidance to help in planning the activities associated with pharmacovigilance based specifically on the safety specification, particularly in preparation for the early post-marketing period of a new drug

molecule, e.g., biotechnology-derived products, chemical entities, and vaccines.

2) The primary emphasis of this guideline is on a safety specification and pharmacovigilance plan that would be submitted at the time when application for license is submitted.

3) This guideline can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the Safety Specification and Pharmacovigilance Plan into the Common Technical Document (CTD).

4) The guideline details to provide summary of the important identified drug risks, important potential risks, and important missing data (information), including the population at potential risk and situations where the product is likely to be used that have not been studied pre-approval.

5) It proposes a structure for a pharmacovigilance plan and sets out principles of good practice for designing and conducting observational studies.

Structure

A suggested structure for the Pharmacovigilance Plan is discussed below that can vary according to the product in question and the issues identified in the safety specification.

Summary of On-going Safety Issues

Summary must be provided at the beginning of the Pharmacovigilance Plan including

Important identified risks

Important potential risks

Important missing information

Routine Pharmacovigilance Practices

It must be conducted for all therapeutic irrespective of fact that if the additional actions are suitable as of a pharmacovigilance plan or not. This routine pharmacovigilance cludes:

1)Systems and processes which ensure that information about all suspected adverse reactions reported to the employees of the company are collected and collated in a manageable manner.

2) The preparation of reports for regulatory authorities:

i) Periodic Safety Update Reports (PSURs)

ii) Expedited adverse drug reaction (ADR) reports

3) Regular monitoring of the safety profile of approved products like issue evaluation, signal detection, liaison with regulatory authorities, and updating of labeling.

4) Other requirements, as discussed by local regulations.

Action Plan for Safety Issues

The pharmacovigilance plan for every crucial and chief safety issue must be presented and justified according to the following structure:

1) Safety issue

2) Objective of actions proposed

3) Purpose/Rationale for proposed actions

4) Actions proposed

5) Monitoring by the sponsor for safety issue and proposed actions

6) Milestones for evaluation and reporting.

Summary of Actions to be Completed, Including Milestones

1) The actions for all individual safety issues must be presented for bringing the product together in an overall Pharmacovigilance Plan.

2) The pharmacovigilance plan for the pharmaceutical products must be organised with respect to the actions to be undertaken and their milestones.

3) However, the reason behind this can be that one proposed action (e.g., a prospective safety cohort study) could address more than one of the identified issues.

4) It is suggested that for completion of all the studies and other evaluations, and for submission of safety results, the milestones must be included in the pharmacovigilance plan. In developing these milestones following points must be considered:

i) Exposure to the product will have reached a level sufficient to allow potential identification/characterisation of the adverse effects/adverse drug reactions of concern or resolution of a particlar concern,

ii) The results of ongoing or proposed safety studies are expected to be available.

5) These milestones could be associated with regulatory milestones and must be used to revise the pharmacovigilance plan, for example, PSURs, annual reassessment and license renewals, etc

GOOD CLINICAL PRACTICE (GCP) IN PHARMACOVIGILANCE STUDIES

Good Clinical Practice (GCP) is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected'.

It is the compilation of accepted scientific and ethical standards governing clinical research that ensure the integrity of data obtained and the protection of human research subjects.

Objectives

1) Mainly focused on the protection of human rights in clinical trial.

2) Provide assurance of the safety of the newly developed compounds.

3) Provide standards on how clinical trials should be conducted.

4) Define the roles and responsibilities of clinical sponsors, clinical research investigators, Clinical Research Associates, and monitors.

5) Compliance with GCPs provide public assurance that the rights and safety of participants in human subject research are protected and that the data that arises from the study is credible

Significance

1) GCP compliance provides public assurance that the rights, safety and well- being of human subjects involved in research are protected

2) Improved trial methods

3) Clinical trial concept better understood

4) Public/Political Concern over Safety Aspects

Principles of ICH-GCP

There are 13 core principles of ICH-GCP as follows:

1) Clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2) Before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3) The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.

4) The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5) Clinical trials should be scientifically sound, and described in clear, detailed protocol.

6) A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/ independent ethics committee (IEC) approval/favourable opinion.

7) The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8) Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9) Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10) All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

11) The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality

rules in accordance with the applicable regulatory requirement(s).

12) Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice (GMP). They should be used in accordance with the approved protocol.

13) Systems with procedures that assure the quality of every aspect of the trial should be implemented.

All clinical trials must be conducted in agreement with ethical principles, complete scientific evidence and clear detailed protocols. The benefits of conducting trials should overcome the risks. The rights, safety and well-being of volunteers participating in the trial are of primary importance and these should be preserved by obtaining informed consent and maintaining confidentiality. The care must be given by appropriately qualified personnel with adequate experience. Records should be easily accessible and retrievable for accurate reporting, verification and interpretation. Investigational products should be manufactured according to Good Manufacturing Practice.

UNIT-5

PHARMACOVIGILANCE

-

YEAR 24

What is Pharmacogenomics?

Pharmacogenomics is the study of how genetic variations affect an individual's response to drugs. It involves understanding how genetic differences can influence drug metabolism, efficacy, and toxicity.

Pharmacogenomics in Pharmacovigilance:

Pharmacogenomics plays a crucial role in pharmacovigilance by helping to:

1. Identify genetic risk factors: Genetic variations can predispose individuals to adverse reactions or affect drug efficacy. Pharmacogenomics helps identify these risk factors, enabling targeted monitoring and prevention strategies.

2. Improve adverse event reporting: By considering genetic information, pharmacovigilance professionals can better understand the mechanisms underlying adverse events and identify potential genetic contributors.

3. Enhance signal detection: Pharmacogenomics can help detect signals of potential safety issues by identifying genetic subgroups at increased risk of adverse reactions.

4. Optimize drug therapy: Pharmacogenomics informs personalized medicine approaches, enabling healthcare professionals to tailor drug treatment to an individual's genetic profile, reducing the risk of adverse reactions and improving efficacy.

5. Support regulatory decision-making: Pharmacogenomics data can inform regulatory decisions, such as drug labeling, dosing recommendations, and safety monitoring requirements.

Key Applications:

1. Genetic biomarkers: Identification of genetic biomarkers associated with adverse reactions or efficacy, enabling targeted monitoring and prevention strategies.

2. Pharmacogenomic testing: Use of genetic tests to identify individuals at risk of adverse reactions or reduced efficacy, guiding personalized treatment decisions.

3. Data analysis: Integration of pharmacogenomic data into pharmacovigilance databases to enhance signal detection and risk assessment.

Challenges and Future Directions:

1. Data interpretation: Integrating and interpreting large amounts of genetic data in pharmacovigilance.

2. Clinical implementation: Translating pharmacogenomic findings into clinical practice and regulatory decision-making.

3. Global collaboration: Standardizing pharmacogenomic approaches and data sharing across countries and regions.

Conclusion:

Pharmacogenomics is a vital component of pharmacovigilance, enhancing our understanding of drug safety and efficacy. By integrating genetic information into pharmacovigilance activities, we can improve patient outcomes, reduce adverse reactions, and optimize drug therapy. As the field continues to evolve, it's essential for students to understand the role of pharmacogenomics in pharmacovigilance and its potential to transform healthcare.

Genetic-related Adverse Drug Reactions (ADRs) focusing on pharmacokinetic (PK) parameters, along with examples:

Pharmacokinetic Parameters:

1. Absorption: Genetic variations can affect drug absorption, leading to altered bioavailability.

2. Distribution: Genetic differences can influence drug distribution, affecting tissue concentrations.

3. Metabolism: Genetic polymorphisms can impact drug metabolism, leading to altered clearance.

4. Elimination: Genetic variations can affect drug elimination, influencing half-life.

Genetic-Related ADRs:

1. CYP2D6 Polymorphism:

- Affects metabolism of drugs like tramadol, codeine, and tamoxifen.

- Example: CYP2D6 poor metabolizers may experience increased tramadol toxicity due to reduced metabolism.

2. CYP2C19 Polymorphism:

- Affects metabolism of drugs like clopidogrel, omeprazole, and diazepam.

- Example: CYP2C19 poor metabolizers may experience reduced clopidogrel efficacy due to increased metabolism.

3. UGT1A1 Polymorphism:

- Affects metabolism of drugs like irinotecan and atazanavir.

- Example: UGT1A1 poor metabolizers may experience increased irinotecan toxicity due to reduced metabolism.

4. SLCO1B1 Polymorphism:

- Affects transport of drugs like simvastatin and atorvastatin.

- Example: SLCO1B1 variant carriers may experience increased simvastatin toxicity due to reduced transport.

5. DPYD Polymorphism:

- Affects metabolism of fluoropyrimidine drugs like 5-fluorouracil.

- Example: DPYD variant carriers may experience increased 5-fluorouracil toxicity due to reduced metabolism.

Key Points:

1. Genetic variations can significantly impact PK parameters, leading to altered drug concentrations and increased risk of ADRs.

2. Understanding genetic-related ADRs can help optimize drug therapy, reduce toxicity, and improve efficacy.

3. Pharmacogenetic testing can identify individuals at risk of genetic-related ADRs, enabling personalized medicine approaches.

Examples of Genetic-Related ADRs:

1. Tramadol-induced serotonin syndrome in CYP2D6 poor metabolizers.

2. Clopidogrel resistance in CYP2C19 poor metabolizers.

3. Irinotecan-induced neutropenia in UGT1A1 poor metabolizers.

4. Simvastatin-induced myopathy in SLCO1B1 variant carriers.

5. 5-Fluorouracil-induced toxicity in DPYD variant carriers.

These examples illustrate the importance of considering genetic variations in drug therapy to minimize the risk of ADRs and optimize patient outcomes..

PAEDIATRIC

☐ DRUG SAFETY EVALUATION IN PEDIATRICS:

Drug safety studies must be done in paediatric to understand the changes in pharmacokinetic and pharmacodynamic parameters involved with drug action in the body.

Drugs that are safe and effective in one age group of paediatric patients may be ineffective or toxic in another age group. Hence, to decide appropriate drug therapy, drug safety evaluation in paediatric is essential.

Childhood is divided into :

Neonates Age: Upto 28 days om

Infants Age: 1 to 24 months

Children Age: 2 to 11 years

Adolescents Age : 12 to 18 years

Objectives:

- To ensure the safety of pediatric patients
- Children are different from adults.
- Provide safe care in the hospital.
- Prevention of accidents and injuries in children.
- Teach safety to parents and children.
- - Important safety measures that has to be followed in the hospital for pediatric patient safety.

Drug dosages:

- Drug dosages in pediatric patients are strictly calculated according to the weight of the patient and sometimes according to body surface area
- No medication are given unless checked by the registrars.
- During intravenous fluid therapy strict monitoring has to be done about intake and output every hourly to avoid fluid overload.
- Also care has to be taken to avoid extravasation by regularly checking iv line.
- Include clinical pharmacist to reduce adverse drug event.

Nursing staff:

Strictly pediatric trained nursing staff is to be appointed for monitoring patients as they should be able to prevent the alarming signs(red flag signs) in patients immediately.

Patient monitoring:

Pediatric admission need frequent monitoring as compared to adult patient as they can deteriorate fast. Vital signs to be checked at least every 2hours or as per the instructions and any unusual finding has to be informed by registrar on duty.

Guidelines for conducting drug safety studies /evaluation in paediatrics

- The drug must be first studied in older children before extending the trial to younger children and then infants.
- The trial must be conducted only after obtaining proxy consent.
- The study is initiated after obtaining initial safety and tolerability data from adults.
- The paediatric population is included in safety studies only if there are currently no or limited therapeutic option for a disease.
- If safety concern exists, then the studies in paediatric population must be done after studies in adults. e population
- The studies should be regarding relative formulation and paediatric pharmacokinetics. quivalence m.c of paediatric

Types of Drug Safety Studies in Paediatric:

(a) Pre-marketing assessment of medicine safety:

- Pre-clinical studies on reproductive toxicology, mutagenicity and carcinogenicity are mandatory.
- Juvenile toxicology studies in animal must be done. It provides useful information to 20pic guide monitoring of potential adverse effects in children especially on growth and development

- Clinical studies are done to investigate me regarding pharmacokinetic, pharmacodynamics and efficacy of the drug.

(b) Post-marketing assessment of medicine safety /Paediatric

- These studies help to identify serious ADRs and drug interactions. Also helps to detect signals.
- Child safety monitoring system is designed to monitor drug safety in paediatric.

PREGNANCY AND LACTATION

DRUG SAFETY EVALUATION IN PREGNANCY AND LACTATION

During pregnancy and lactation, extensive physiological changes occur in the body, which may alter drug pharmacokinetics and pharmacodynamics. These physiological changes directly affect the safety and efficacy of a drug administered. Hence, drug safety evaluation must be done in pregnant women to avoid the occurrence of ADRs and to prevent toxic effects of drug in fetus and infant.

Guidelines For Conducting Drug Safety Evaluation in Pregnant and Lactating Mothers:

Pregnant and nursing mothers should be included in the study only if the drug is intended for use by pregnant or nursing mother or foetus or nursing infant.

- The study should not carry no more than minimal risk to the foetus or nursing infant and the objective of the study should be to obtain new knowledge about the foetus, pregnancy and lactation.

- The benefit should be more than the risk and women should not be encouraged to discontinue breast feeding for the infant for the sake of participation in the study.
- Research related to termination of pregnancy must be done in pregnant women who desire to undergo medical termination of pregnancy.
- Research related to pre-natal diagnostic techniques can be done in pregnant women, but it should be limited to detect the foetal abnormalities or genetic disorders as per toying the Pregnant Diagnostic Techniques and not for sex determination.
- No inducements or monetary should be offered to terminate pregnancy.
- The study should be initiated after obtaining inform consent from the women participating in the study.

Reasons for Conducting Safety Evaluation in Pregnancy and Lactation:

- The data available regarding drug safety in pregnancy and lactation is limited.
- Decisions regarding prescription of drugs in pregnancy and lactation cannot be made based on the data obtained from the non-clinical studies.
- Many drugs pass into breast milk and may cause risk to breastfed infant.
- Some drugs pass placental barrier and can affect the growth of the foetus.
- Ensure safe and effective treatment during pregnancy and lactation. cy and nancy
- To detect birth defects caused by the drug.
- Study the effect of drug on milk production. duction.

- Helps to calculate infant exposure to drugs, which can be used to guide for safe use of drugs. Also helps to minimize risk to ps to reducing drug exposure. breastfed infant by

- Types of Drug Safety Studies in Pregnancy:

(a) Pre-approval pregnancy safety studies:

(i) Pre-clinical studies:

- Data regarding drug's safety is obtained from reproductive toxicity studies, pharmacological studies and toxicological studies.
- Repeated dose toxicity studies provide information regarding potential effects of drug on pregnancy.
- Reproductive toxicity helps to identify the changes in pregnancy outcomes and lactation.
- Developmental toxicity studies give data on adverse effect induced in the progeny.

They are:

(a) Teratogenic effect

(b) Fetotoxic effect

(c) Pharmacological effect

(ii) Clinical studies:

- Data regarding drug's adverse effects during all the three phases of clinical trial is obtained.
- Physiological changes caused by the drug during pregnancy is studied.

- Drug's efficacy in preventing passing of the genetic disorder or other disorder from mother to foetus is studied.
- Drug's adverse effects on the development of the foetus is observed.

(b) Post-approval pregnancy safety studies:

It is conducted after the drug is marketed. This phase can also be called as post-marketing surveillance.

Three approaches for post-approval pregnancy safety studies are:

(i) Pharmacovigilance

(ii) Pregnancy Registries.

(iii) Complementary Studies.

➤ **Types of Drug Safety Studies During Lactation:**

(a) Non-clinical lactation studies:

It gives information on transfer of the medicinal product in animal milk.

Peri and post-natal studies including survey of offspring during nursing period in animals helps to understand the drug's effects on offspring.

(b) Clinical lactation studies:

Lactating mothers are included in the study.

Lactating women (milk only) study is used to detect the presence of drug in breast ad milk, quantify the total amount of drug transferred into breast milk and to evaluate the effects of drug on milk production.

(c) Pharmacovigilance:

It collects data from case reports and pregnancy registries regarding adverse effects in breastfed infants and generates safety signal.

GERIATRICS

Drug safety evaluation in geriatrics

The geriatric population is increasing worldwide and they respond differently from younger patients to drug therapy in a number of ways. This difference in response may lead to toxicity and adverse effects if same adult dose of drug is administered. Hence, drug safety evaluation in geriatrics is essential.

➤ Guidelines for Conducting Drug Safety Studies in omudies

Geriatrics are included in the study :

The disease intended to be treated is a disease of a aging.

The new drug is likely to have different response in elderly compared to non-geriatric patients.

Study must be conducted after obtaining consent from the participant.

Geriatrics should be included in Phase 3 trials (and Phase 2 at sponsor's option).

- Types of Drug Safety Studies in Geriatrics:

It is highly difficult to conduct pre-clinical study of drug intended for use in geriatric patients, only preliminary studies are conducted in animals. To confirm

the safety and efficacy of the drug, clinical studies are conducted in geriatric population. The studies conducted are:

(a) Pharmacokinetic studies:

(i) Formal pharmacokinetic study

(ii) Pharmacokinetic screening approach

(b) Pharmacokinetics in renally or hepatically impaired patients.

CIOMS

INTRODUCTION:

- The Council for International Organizations of Medical Services (CIOMS) is an international nongovernmental organization in official relations with the World Health Organization (WHO).
- It was established under the auspices of WHO and the United Nations Educational, Scientific and Cultural and Organization (UNESCO) in 1949.
- It is to maintain collaborative relations with the United Nations and its specialized agencies, particularly with UNESCO and WHO.

CIOMS has run a program focusing on drug safety since the early 1980s which incorporates distinct working groups. These groups have published many guidelines for practice, including:

- Definition and Application of Terms for Vaccine Pharmacovigilance Safety
- Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V),
- Development and Rational Use of Standardized MedDRA Queries (SMQs),

- Management of Safety Information from Clinical Trials (CIOMS VI),
- Development Safety Update Reports (CIOMS VII),
- Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS VIII),
- Benefit-risk balance for marketed drugs (CIOMS IV),
- International Reporting of Periodic Drug Safety Update Summaries (CIOMS II),
- Guideline for Preparing Core Clinical Safety Information on Drugs (CIOMS III).

CIOMS WORKING GROUP

There are 13 working groups in CIOMS. Each group has its significant roles in pharmacovigilance. The working groups are explained below.

1. CIOMS I:

   International reporting of ADRs (1990)

   - The main aim of this working group was, "to develop an internationally acceptable reporting method which can be used by the manufacturers to report post-marketing adverse drug reactions rapidly, efficiently and effectively to regulators".

2. CIOMS II:

   International reporting of periodic safety update summaries (1992)

   This working group proposed a standard for Periodic Safety Update Reports ic Safety Update F (PSURs) of reactions received by manufacturers on marketed drugs. This standard, with

modifications from the ICH and other organizations, has been widely adopted.

3. CIOMS III:

   Guidelines for core clinical-safety information on drugs (1995)

   This report addressed the problem of variations in safety labelling around the world and proposed that manufacturers should develop a 'core data sheet' that contains all the relevant safety information which needs to be included in all countries where the drug is marketed.

4. CIOMS IV:

   Benefit-risk balance for marketed drugs - evaluating safety signals (1998)

   This report proposes a standard format and content for a benefit-risk evaluation report and also lays down the principles for good decision-making practices. The proposed structure of the report is as follows:

   - Introduction
   - Benefit evaluation
   - Risk evaluation
   - Benefit risk evaluation

5. CIOMS V:

   Current challenges in pharmacovigilance pragmatic approaches (2001)

   This report is about good case management and reporting practices, both in terms of individual cases and summaries.

6. CIOMS VI:

   Management of safety information from clinical trials (2005)

   The aim of this report was to enhance awareness of the ethical and technical issues associated with safety in clinical trials. It proposes a systematic approach to managing safety during clinical development and is wide-ranging, covering, e.g., ethical issues, statistical approaches to identifying risks and communication of safety information from clinical trials.

7. CIOMS VII: The Development Safety Update Report (DSUR) harmonising the format and content for periodic safety reporting during clinical trials (2006)

   This report proposes the content and format for a DSUR- a means of regular and timely review, appraisal and communication of safety information during the clinical development of drugs. The working group envisions that, in the future, the DSUR and PSUR could be integrated into a single harmonised safety report that would cover a product throughout its lifecycle.

8. CIOMS VIII:

   Application of signal detection in pharmacovigilance

   This working group was focused on signal detection and management in order to develop and apply quantitative methods for signal detection using pharmacovigilance databases.

9. CIOMS IX:

   Practical considerations for development and application of a toolkit for medicinal product risk management (2014)

   Its main goal was to develop a pragmatic consensus publication that would contain a harmonized list of tools for managing the risks of medicinal products intended for human use.

10. CIOMS X: Meta analysis (2016)

This working group gives the considerations for applying good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process.
The aim was to develop a consensus on scientific and methodological criteria that represents good practices when applied to meta-analyses of clinical data within the regulatory process.

11. CIOMS XI: Patient involvement (2018)

It addresses on patient involvement in the development and safe use of medicines. This will provide a comprehensive overview of present knowledge and existing initiatives, and will address a wide range of the remaining challenges and practice gaps. The optimal consideration of patient perspectives will support the safe and effective use of medicines.

12. CIOMS XII: Benefit-Risk balance for medicinal products (2019) The objective was to update CIOMS IV on Benefit-Risk Balance for Marketed Drugs: Evaluation of Safety Signals originally published in 1998, and

potentially but not necessarily, to extend the scope to include preapproval as well as post-marketing considerations for medicinal products.

13. CIOMS XIII: Real-world data and Real-world evidence in regulatory decision making

Published in 2021, this report provides guidance on the use of real-world data (RWD) and real-world evidence (RWE) in regulatory decision-making for medical products. Here's a detailed overview:

Key Points:

1. Definitions: RWD refers to data collected outside of traditional clinical trials, such as electronic health records, claims data, and patient registries. RWE is the evidence generated from the analysis of RWD.
2. Purpose: The report aims to facilitate the appropriate use of RWD and RWE in regulatory decision-making, while ensuring the quality, reliability, and interpretability of the evidence.
3. Principles: The report outlines six principles for the use of RWD and RWE:
   - Relevance
   - Quality
   - Reliability
   - Transparency
   - Avoidance of bias
   - Generalizability

4. Applications: RWD and RWE can be used for various regulatory purposes, including:

- Post-marketing surveillance
- Safety signal detection
- Effectiveness evaluations
- Label expansion
- Regulatory approvals

5. Challenges: The report discusses challenges and limitations, such as data quality issues, bias, and the need for advanced analytics and expertise.

6. Implementation: The report provides guidance for regulators, industry, and researchers on implementing RWD and RWE in regulatory decision-making, including data curation, analysis, and interpretation.

Impact:
CIOMS XIII aims to promote the responsible use of RWD and RWE, enhancing the efficiency and effectiveness of regulatory decision-making, and ultimately improving patient outcomes.

CIOMS FORM:
This form is used by the manufacturer to report suspected adverse drug reaction.
Guidelines for filling the form are:

SECTION I OF CIOMS FORM: "REACTION INFORMATION"

✓ Sub-Section 1: PATIENT INITIALS (first, last).

✓ Sub-Section 1a: COUNTRY

Sub-Section 2: DATE OF BIRTH (Day, Month, Year)

Sub-Section 2a: AGE (Years)

✓ Sub-Section 3: SEX

✓ Sub-Section 4-6: REACTION ONSET (Day, Month, Year)

✓ Sub-Section 7+13 DESCRIBE data) (including relevant tests/lab

MONACTION(S)

SECTION II OF O CIOMS FORM "SUSPECT DRUG(S) INFORMATION"

✓ Sub-Section 14: SUSPECT DRUG(S) (Include generic name)

✓ Sub-Section 15: DAILY DOSE(S)

✓ Sub-Section 17: INDICATION(S) FOR USE

✓ Sub-Section 18: THERAPY DATES (from/to)

✓ Sub-Section 19: THERAPY DURATION

✓ Sub-Section 20: DID REACTION ABATE AFTER STOPPING DRUG?

✓ Sub-Section 21: DID REACTION REAPPEAR AFTER

REINTRODUCTION?

SECTION III OF CIOMS FORM "CONCOMITANT DRUG(S) AND HISTORY"

✓ Sub-Section 22: CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction).

✓ Sub-Section 23: OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period etc.)..

UNDER SECTION IV OF CIOMS FORM "MANUFACTURER INFORMATION"

✓ Sub-Section 24a: NAME AND ADDRESS OF MANUFACTURER

Sub-Section 24b: MANUFACTURER CONTROL NO.

Sub-Section 24c: DATE RECEIVED BY MANUFACTURER

Sub-Section 24d: REPORT SOURCE

Sub-Section 25a: REPORT TYPE

DATE OF THIS REPORT

Mention the date on which the adverse reaction report was filled by the reporter. Attach additional page if required, giving reference to in the form. the Item No.

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTIONS(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. Suspect Drug(S) (include generic name)		20 DID REACTION ABBATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-DUCTION ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24b. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITAL ☐ FOLLOWUP	

FORMAT OF CIOMS FORM

CENTRAL DRUG STANDARD CONTROL ORGANISATION (CDSCO)

INTRODUCTION:

- The CDSCO of India is main regulatory body for regulation of pharmaceutical, medical devices and Clinical Trials.
- CDSCO (HQ), FDA BHAVAN, NEW DELHI
- Head office is located in NEW DELHI and functioning under the control of Directorate General of Health Services, ministry of health and family welfare Government of India.
- Drugs Controller General of India [DCGI], is a responsible for approval of New Drugs, Medical devices and Clinical Trails to be conducted in India.
- Appointed by the central government under the DCGI.
- The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committed (DCC).
- CDSCO has six zonal offices, four sub-zonal offices, thirteen port offices and seven laboratories under its control.

FUNCTIONS

- Approval of new drugs and clinical trials.
- Import Registration and Licensing
- Licensing of Blood Banks, Vaccines, Medical devices, Diagnostic agents.
- Amendment to D&C Act and Rules.

- Participation in WHO GMP certification schemes.
- Banning of drugs and cosmetics.
- Grant to test license, personal license, NOC's for export.
- Testing of drugs by Central Labs.
- Publication of Indian Pharmacopoeia
- Monitoring adverse drug reactions.
- Guidance on Technical matters.

ORGANIZATION OF CDSCO:

CENTRAL LICENSING AUTHORITY

- Approval of new drugs and clinical trials
- Import Registration and Licensing & approving of Blood Banks, LVPs, Vaccines, r-DNA products & some Medical Devices.
- Amendment to D &C Act and Rules
- Banning of drugs and cosmetics
- Grant of Test License, Personal License,
- NOCs for Export Testing of New Drugs

STATE LICENSING AUTHORITY

- Licensing of Manufacturing Site for Drugs including API and Finished Formulation.
- Licensing of Establishment for sale or distribution of Drugs
- Approval of Drug Testing Laboratories
- Monitoring of Quality of Drugs and Cosmetics marketed in the country
- Investigation and prosecution in respect of contravention of legal provision
- Recall of sub-standard drugs

INDIAN PHARMACOPOEIA COMMISSION (IPC)

INTRODUCTION

The Commission has become operational from 1st Jan., 2009 as an Autonomous Institution, under of Ministry of Health & Family Welfare, Government of India.

Sector-23, Raj Nagar, Ghaziabad 201002, Uttar Pradesh

The Indian Pharmacopoeia commission has a three-tier policy formulation and execution setup comprising of the General Body, Governing body and Scientific Body.

The Secretary-cum-Scientific Director is the Chief Scientific and Chief Executive Officer.

COMPOSITION

IPC- General Body , Governing Body ,Scientific Body

IPC Secretariat, IPL

❖ Mission

To promote public and animal health in India by bringing out authoritative and officially accepted standards for quality of drugs.

Vision

To promote the highest standards of drugs for use in human and animals within practical limits of the technologies available for manufacture and analysis,

FUNCTIONS

- ✓ Publishing Indian Pharmacopoeia (IP) and its Addenda at regular intervals.
- ✓ Preparation, certification and distribution of IP Reference Substances (IPRS) to the stakeholders.
- ✓ Publishing National Formulary of India (NFI) for rational (NFI) medicines by health professionals. use of Running Pharmacovigilance Programme of India (PvPI) through Program National Coordination Centre (NCC) at IPC.

- ✓ Analysis of the new drug candidate materials by Indian Pharmacopoeia laboratory (IPL) for their marketing authorization.
- ✓ Skill development, International collaborations etc.

DRUG AND COSMETIC ACT

INTRODUCTION:

This act was originally passed on 10th April 1940 for regulating the import, manufacture and distribution of drugs in India. This act was prepared in accordance to the recommendations of the Chopra Committee formed in 1930. The Drug Rules was passed in 1945.

- Drugs and Cosmetics Act was passed 10th April 1940 By the Indian Legislature
- Rule passed 1945
- This Act was amended 1955 By the Indian Parliament
- Subsequently amended: 1960, 1962, 1964, 1972, 1982, 1986, 1995, 2008, 2011 and 2018

OBJECTIVES

- ➢ This is an act to regulate the import, manufacture, distribution and sales of drugs, by qualified persons only.
- ➢ To prevent substandard in drugs.
- ➢ The act also provide for the control over the manufacture, sale & distribution of Ayurvedic, Siddha, Unani & Homeopathic drugs.

SCHEDULES TO THE ACT AND RULES

Schedules to the act

1.First schedule:

Names of books under Ayurvedic, siddha and unani tibbs systems.

2.Second schedule:

Standard to be complied with by imported drugs and by drugs manufactured for sale ,stocked or exhibited for sale or disturbed.

SHEDULES AND THEIR SIGNIFICANCE

- **Schedule A**: Contains various forms and formats of letters for applications of licensing etc.
- **Schedule B**: Contains fees structure for government-run labs.
- **Schedule C**: Contains various biological products] and their regulation. Examples: serums, adrenaline, vitamins etc.
- **Schedule D**: List of drugs exempted from the provision of import of drugs
- **Schedule E**: Contains various poisons and their regulation. Examples: *Sarpa Visha* (Snake venom), *Parada* (Mercury) etc.
- **Schedule F**: This contains regulations and standards for running a blood bank.
  - **Schedule F-I**: This contains regulations and standards for vaccines.
  - **Schedule F-II**: This contains regulations and standards for surgical dressing.
  - **Schedule F-III**: This contains regulations and standards for umbilical tapes

- **Schedule F-F**: This contains regulations and standards for ophthalmic ointments and solutions.
- **Schedule K**: Drugs not meant for medicinal use, quinine and other antimalarial drugs, drugs supplied by government hospitals, registered medical practitioners, contraceptive drugs, and their corresponding regulation.
- **Schedule M**: Contains various regulations for manufacturing, premises, waste disposal and equipment.
- **Schedule N**: Contains various regulations and requirements for a pharmacy.
- **Schedule O**: Contains various regulations and requirements for disinfectant fluids.
- **Schedule P**: Contains regulations regarding life period and storage of various drugs.
- **Schedule P-I**: Contains regulations regarding retail package size of various drugs.
- **Schedule Q**: Contains a list of permitted dyes and pigments in soap and cosmetics.
- **Schedule R**: Contains various regulations and requirements for condoms and other mechanical contraceptives.
- **Schedule S**: Lists various cosmetics and toiletries, and directs the manufacturers of cosmetics to conform to the latest Bureau of Indian Standards requirements.
- **Schedule T**: Contains various regulations and requirements for manufacture of Ayurvedic, Siddha and Unani drugs.
- **Schedule U**: Contains various regulations and requirements for record keeping.
- **Schedule V**: Contains standards for drug patents
- **Schedule W**: Lists generic drugs.

- **Schedule Y**: Contains requirement and guidelines for clinical trials.

Administrative Bodies :

1) Advisory

2) Drug Technical Advisory Board (DTAB)

3) Drug Consultative Committee (DCC)

4) Analytical

5) The Central Drug Laboratory (CDL)

6) Drug Control Laboratories in the state (DCL)

7) Government Analyst

8) Executive

9) Licensing Authorities (central & state)

10) Drug Inspectors

11) Custom Collector

SCHEDULE Y

Requirements and Guidelines for Permission to Import and / or Manufacture of New Drugs for Sale or to Undertake Clinical Trial:

To frame guidelines for conduct of clinical research, control and regulation for new drugs CDSCO and DTAB formulated GCP under schedule Y in 2005.

SCHEDULE-Y Rules:

Rule and Permission

122A -To import new drugs.

122B -To manufacture new drugs

122D -To import or manufacture fixed dose combinations.

122DA -To conduct clinical trials for new drug/ investigational new drug

122DAA - Definition of clinical trial.

122E -Definition of new drugs

Requirements and Guidelines on Clinical Trials for Import and Manufacture of New drug:

1. Application for permission

2. Clinical trial+

3. Studies in special population

4. Post marketing surveillance

5. Special studies: BA/BE studies

1. Application for permission

It shall made in Form 44 accompanied with the following data in accordance with appendices, namely

- Clinical and pharmaceutical information
- Animal pharmacology data
- Animal Toxicology data
- Human Clinical pharmacology data
- Regulatory status in other countries Prescribing information
- FORM 12- To import Study drug for examination, test or analysis

2. Clinical Trial

(a) Approval for Clinical trials

CT on a New drug shall Il be initiated only after permission by li authority and approval from EC by licensing bm.com

(b) Responsibilities of Sponsor

- Implementing and maintaining QA

- Submit status report to the e licensing authority periodically SAE should be reported to the licensing authority with in 14 calendar days.

(c) Responsibilities of Investigator

- Ensure adequate medical care is provided to the subject
- SAE and unexpected AE should be reported to the sponsor within 24 hrs and to the EC within 7 working days

(d) Informed consent

- Freely given informed written consent
- Provide information about the study verbally
- Non-Technically and understandable language

(e) Responsibilities of ethics committee

- Approval trial protocol to safe guard RSW of all trial subject and to protect RSW of all vulnerable subjects Conduct ongoing review of trials 6. Human Pharmacology (Phase 1) Safety and tolerability

(f) Therapeutic exploratory trials (phase II)

- To evaluate the effectiveness of a drug for a particular indication To determine the short term side effects and risk associated with the drug
- To determine the dosage regimen for phase III trials

(g) Therapeutic confirmatory trials (phase III)

(h) Demonstration of therapeutic benefit

- Drug is safe and effective for use and provide and adequate basis for marketing approval

- Post marketing surveillance
- Performed after drug approval and related to the approved indication Includes drug-drug interaction, dosage response and safety studies, mortality/morbidity studies

3. studies in special population

(a) Geriatrics

(b) Pediatrics

(c) pregnant or Nursing Women

4. Post marketing Surveillance

- Closely monitored new drugs clinical safety
- PSUR- to report all relevant new information
- PSUR shall be submitted every 6months for the first 2 years

5. Special Studies- BA/BE studies

- Conducted according to the guidance for BA and BE studies Evaluation of the effect of food on absorption following oral administration

Differences in Indian and global pharmacovigilance requirements: