



A REVIEW ON PHARMACOVIGILANCE

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ABSTRACT :

Pharmacovigilance is like a sunshade to describe the processes for monitoring and evaluating ADR and it is a key component of effective drug regulation systems, clinical practice and public health programmes. The number of Adverse Drug Reactions (ADR) reported resulted in an increase in the volume of data handled, and to understated the pharmacovigilance, a high level of expertise is required to rapidly detect drug risks as well as to defend the product against an inappropriate removal. The current global network of pharmacovigilance centers, coordinated by the Uppsala Monitoring Centre, would be strengthened by an independent system of review. This would consider litigious and important drug safety issues that have the potential to affect public health adversely beyond national boundaries. Recently, pharmacovigilance has been confined, mainly to detect adverse drug events that were previously either unknown or poorly understood. Pharmacovigilance is an important and integral part of clinical research and these days it is growing in many countries. Today many pharmacovigilance centers are working for drug safety monitoring in this global pitch, however, at the turn of the millennium pharmacovigilance faces major challenges in aspect of better safety and monitoring of drugs. In this review we will discuss about drug safety, worldwide pharmacovigilance centers and their role, benefits and challenges of pharmacovigilance and its future consideration in healthcare sectors.

Key Word : Investigational New Drug [IND], Drugs Safety, Clinical Trial, Drug Study. Etc

INTRODUCTION :

Pharmakon is a Greek word which means 'medical substances and vigil' and 'vigil' is a Latin word which means to keep watch. Therefore, pharmacovigilance is keeping a watch on the medical substances. Pharmacovigilance is also known as drug safety, the goal of pharmacovigilance is to promote safe and rational use of medicine, hence improving patient care and public health in general. Pharmacovigilance is a multidisciplinary field that involves the interaction of several working professionals like doctors, patients, nurses, paramedical staff, pharmacists, and even patients. Reporting of drug reactions in a country helps build the national database and also promotes the culture of scientific analysis of drug usage.

Defination:

WHO define pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Defination of term related Pharmacovigilance

Term	Defination
Adverse drug ⁰ reaction	Harm caused by the use of a drug at normal doses
Adverse drug ⁰ event	Harm caused by the use of a drug
Medication error	Preventable event that may cause inappropriate use of a drug or patient harm
Potential adverse drug event	Situation that could result in harm by the use of a drug but did not harm the patient

History-**► Thalidomide tragedy(1951-62)**

It was greatest of all the drug disaster the drug thalidomide was introduced as a safe and effective hypnotic and antiemetic. It rapidly became popular for the treatment of nausea vomiting in early pregnancy:-Unfortunately the drug proved to be potent human teratogen that caused major birth defects in an estimated 10,000 children. The children were born with deformity in limbs called phocomelia.

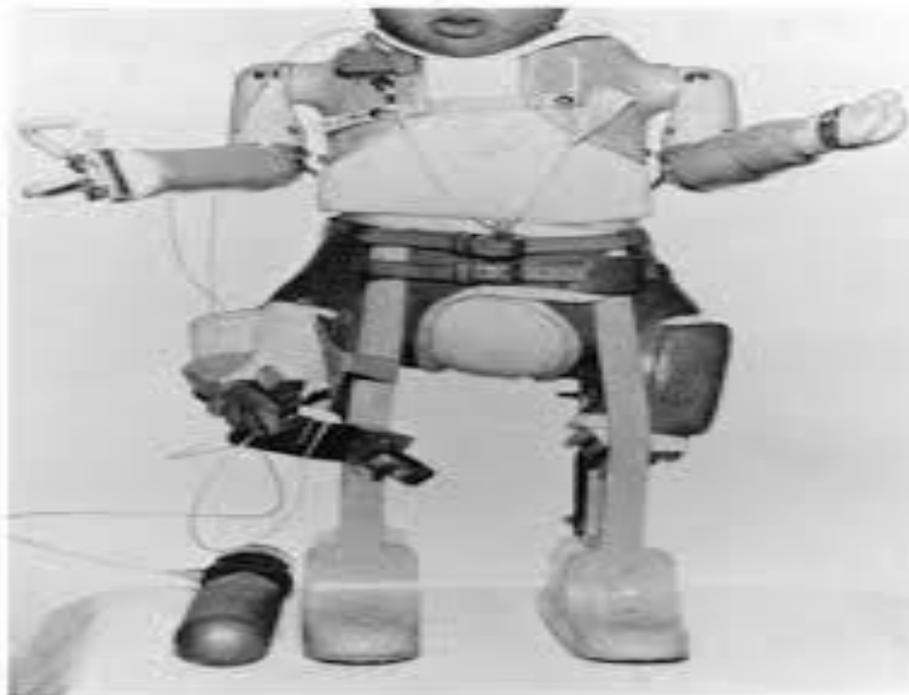


Figure 1: Child with thalidomide-induced deformities of upper and lower limb

► Sulphanilamide tragedy(1937):-It was the first antimicrobial drug, which was used to treat streptococcal infections. It was one of major mass poisoning of the 20th century. Early, the drug was available in the form of tablet and powder. Later, it was dissolved in diethylene glycol and available in liquid forms as well. During September and October 1937 more than 100 people died in the United States because of this drug. Later on investigation it was found that diethylene glycol was a toxic ingredient which was added to the formulation.

Importance of Pharmacovigilance:

The role of pharmacovigilance is to determine which adverse events cross the line of a drug's efficacy. In other words, analysing which side effects are worth the risk to patients compared with how effective they are at treating a disease. Pharmacovigilance covers the following:

- o Drug monitoring
- o Pharmaceutical preparations-adverse effects
- o Adverse drug reaction reporting
- o Product surveillance
- o Post marketing Legislation

Besides the above, many other issues are also relevant to pharmacovigilance such as follows:

- o Medication error
- o Substandard medicines
- o Lack of efficacy reports
- o Use of medicines that are not approved for
- o Case reports of acute and chronic poisoning
- o Study of drug-related deaths
- o Abuse and misuse of medicines

Aim of Pharmacovigilance:

- o Improve patient care and safety.
- o Improve public health and safety in relation to medicine, cosmetic, herbal product etc.
- o Early detection of unknown adverse reaction and interaction
- o Identification of risk factor and possible mechanisms underlying adverse reaction
- o To promote education and clinical training.
- o To promote understanding and clinical training in pharmacovigilance.

Activity of Pharmacovigilance:

- Effectiveness is the extent to which a drug works under real world circumstances, i.e., clinical practice.
- Efficacy is the extent to which a drug works under ideal circumstances, i.e., in clinical trials.
- Event refers to an adverse event (AE).
- Harm is the nature and extent of the actual damage that could be or has been caused.
- Individual Case Safety Report (ICSR) is an adverse event report for an individual patient.

➤ Life-threatening refers in an adverse event that places a patient at the immediate risk of death.

Need of Pharmacovigilance:

➤ Humanitarian concern:-Animal toxicology is often not a good predictor for human effects-Evidence of safety from clinical trials is insufficient due to some limitation;-Limitations: Limited size, narrow population(age and sex specific), Narrow indications(Only specific disease),short duration.

➤ Safe use of medicines it has been suggested that ADR's may cause 5700 death per

➤ UK ADR's are expensive

➤ Promoting rational use of medicine

Adverse Drug Reaction

• Adverse Event Reporting

➤ For pharmaceutical companies. AE reporting is a regulatory requirement in most countries.

➤ AE reporting also provides data to these companies and drug regulatory authorities that play a key role in assessing the risk-benefit profile of a given drug.

➤ The following are several facts of Aereporting: Individual Case safety Report (CSR)

➤ One of the fundamental principles of adverse event reporting is the determination of which constitutes an Individual Case safety Report (ICSR).

➤ During the triage phase of a potential adverse event report, it is important to determine if the “four elements” of a valid ICSR are present:

1. I an identifiable patient.

2. Identifiable reporter.

3. A suspect drug.

4. An adverse event.

Preclinical studies:

Pre-clinical studies involve in vitro (i.e, test tube or laboratory) studies and trials on animal populations. Wide-ranging dosages of the study drug given to the animal subjects or to the an invitro substrate order to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further test.

• Phase 0

➤Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the U.S.

➤Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug(IND) Studies Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in humas subjects as was anticipated from

preclinical studies. Distinctive features of Phase O trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body)

• Phase 1

➤ Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected.

➤ This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff.

➤ Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers.

➤ Levies are paid an vexation figure for their time spent in the levy centre. Pay ranges from a small quantum of plutocrat for a short period of hearthstone, to a larger quantum of over to approx depending on length of participation. There are different kinds of Phase 1 trials.

• SAD

Single Ascending Cure studies are those in which small groups of subjects are given a single cure of the medicine while they're observed and tested for a period of time. However, and the pharmacokinetic data is roughly in line with prognosticated safe values, the cure is escalated, If they do n't parade any adverse side goods. This is continued until pre-calculated pharmacokinetic safety situations are reached, or intolerable side goods start showing up at which point the medicine is said to have reached the Maximum permitted cure (MTD)

• MAD

Frenetic Multiple Ascending Cure studies are conducted to more understand the pharmacokinetics & pharmacodynamics of multiple boluses of the medicine.

• Phase 2

➤ Once the original safety of the study medicine has been verified in Phase I trials, Phase II trials are performed on larger groups (20- 300) and are designed to assess how well the medicine workshop, as well as to continue Phase 1 safety assessments in a larger group of levies and cases.

➤ When the development process for a new medicine fails, this generally occurs during Phase II trials when the medicine is discovered not to work as planned, or to have poisonous goods Phase II studies are occasionally divided into Phase IIA and Phase I1B

➤ Phase ITA is specifically designed to assess dosing conditions (how important medicine should be given whereas Phase I1B is specifically designed to study efficacy (how well the medicine works at the specified cure (s)). Some trials combine Phase I Phase II, and test both efficacy and toxin,

• Phase 3

- Because of their size and comparatively long the durations Phase III trials are the most precious, time-consuming and delicate trials to design and run, especially in curatives for habitual medical conditions.
- Once a medicine has proved satisfactory after Phase III trials, the trial results are generally combined into a large document containing a comprehensive description of the styles and results of mortal and beast studies, manufacturing procedures, expression details, and shelf life.
- This collection of information makeup the nonsupervisory submission that is handed for review to the applicable nonsupervisory authorities in different countries.
- While utmost medicinal a companies refrain from this practice, it is n't abnormal to see numerous medicines witnessing Phases III clinical trials in the request.

• Phase 4

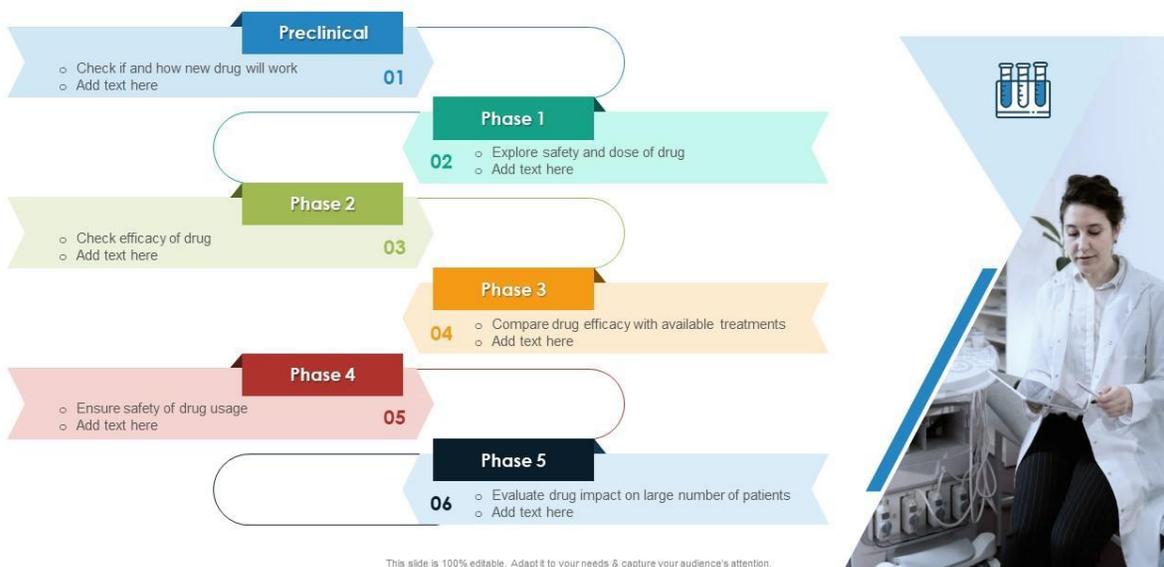
- Phase IV mal is also known as Post Marketing Surveillance Trial.
- Phase IV trials involve the safety surveillance(pharmacovigilance) and ongoing specialized support of a medicine after it receives authorization to be vended.
- Phase IV studies may be needed by nonsupervisory authorities or may be accepted by the financing company for competitive(chancing a new request for the medicine) or other reasons(For illustration, the medicine may not have been tested for commerce with other medicines, or on certain population groups as pregnant women, who are doubtful to subject themselves to trials).

TYPES OF CINICAL TRIAL

1. **treatment trials** : Test experimental treatment, new combination of bugs, or new approaches to surgery or radiation remedy.
2. **revention trials** : Look for better ways to help complaint in people who have noway had the complaint or to a complaint from returning. These approaches may include drugs, vitamins, vaccines, minerals, or life changes.
3. **individual trials** : Conducted to find better tests or procedures for diagnosing a particular complaint or condition.
4. **Webbing trials** : Test the stylish way to descry certain conditions or health conditions.
5. **Quality of Life** : Trials(or probative Care trials) explore ways to ameliorate comfort and the quality of life for individual with a habitual illness.

Process of Clinical Trials Phases :**Process Flow of Clinical Trial Phases**

This slide indicates the key steps involved in the clinical drug investigation process. The major steps involved are preclinical, phase 1, phase 2, phase 3, phase 4, and phase 5.

**Coding of adverse events :**

- Adverse event coding is the process by which information from an AE journal, called the "verbatim", is enciphered using standardized language from a medical rendering wordbook, similar as MedDRA (the most generally used medical rendering wordbook).
- The purpose of medical coding is to convert adverse event information into language that can be readily linked and analysed.
- still, both quotations describe different instantiations of a headache. As a result, in this illustration both quotations would be enciphered as PT Headache (PT Preferred Term in MedDRA).

Drug Dictionaris :

- The huge plethora of available drugs provides a challenge for those wishing to store accurate information on databases.
- When considering all the different phrasings, lozenge forms, routes of administration, remedial and pharmacological classes, manufacturers, approved and personal names for each of these, the task becomes daunting indeed.
- A number of standard groups have been produced, of which the two most extensively.

• Applicable are considered below**➤ Anatomical- remedial- chemical classification**

- ❖ The anatomical- remedial- chemical (ATC) bracket is a system for the bracket of medicines according to their point of remedial effect, remedial suggestion and pharmacological nature,
- ❖ It's extensively accepted as a useful system of grading and recording individual medicines.

❖ The main ATC groups are shown in Table 12.1 (Anonymous, 2000). The main ATC groups

A Alimentary tract and metabolism

B Blood and blood- forming organs

C Cardiovascular system

D Dermatological

G Genitourinary system and coitus hormones

H Systemic hormonal medications banning sexhormone Generalanti-infective for systemic use

L Antineoplastic and immunomodulating agents

M Musculoskeletal system

P Antiparasitic products, germicides and repellents

N Nervous system

❖ Within each main group, there's arrangement of classes of medicine assub-groups, according to broad remedial area or size of action.

The World Health Organization Drug Dictionary :

1. This contains of the order of 45 000 personal medicine names, with about 2600 being added annually(Uppsala Monitoring Centre, 2002).

2. It's an transnational bracket, giving themes used in different countries, to gather with all active constituents with unique reference figures.

3. medicines are classified according to ATC law.

4. The wordbook was started in 196 and includes all medicines mentioned on adverse response reports submitted under the world.

5. Health Organization(WHO) Programme on International Drug Monitoring. medicines from nearly 70 countries are represented, and updates are issued daily 8

6. For multiple component medicines, the Preferred name is the first reported medicine name of a given combination.

7. medicines are given colorful designations, as shown WHO medicine wordbook designation of medicine type

➤ Single component medicinenon-proprietary

➤ Name Single component drag personal

➤ name Single component medicine chemical

➤ name Single component medicine law number Multiple component drugproprietary name

➤ Multiple component medicinenon-proprietary name Non-specific name, from ATC textbooks(similar as NSAID or benzodiazepine).

8. The manufacturer name is shortened to a three- to five- letter law.

9. medicines are given successive record figures and also two sequence figures SEQI and SEO2.

MedDRA

MedDRA is a clinical- confirmation international medical language used by non-supervisory authorities and the regulated biopharmaceutical industry. The language is used through the entire non-supervisory process, from pre-marketing to post-marketing, and for data entry, reclamation, evaluation, and donation.

Med = Medical

D = Dichromatic

R = Regulatory

A = Assertion

MedDRA Data participating

- Subscription subscriptions access to MedDRA for one time.
- Subscriber can not grant any sublicense, publish or else distribute. MedDRA third party.
- Use tone- Service operation to check association's subscription status participating MedDRA with non-subscribing association is a violation of the MedDRA license.

❖ MedDRA Structure

- System organ Class(SOC)(27)
- High Level Group Term(HLGT)(337)
- High Level Term(HLT)(1,737)
- Preferred Term(PT)(23,708)

ICH guidelines

ICH is an abbreviation for the “ International Conference on Harmonisation of Technical Conditions for Registration of Medicines for Human Use”

• Objective of ICH

- To promote international adjustment of specialized conditions to develop safe, effective and high quality drugs.
- To reduce the enrollment cost.
- To help the duplication of clinical trials in Humans.
- To minimize the abuse without compromising on the safety.

• Goal of ICH

Promote transnational adjustment by bringing together representatives from the three ICH regions(EU, Japan and USA) to bandy and establish common guidelines Oaken information available on ICH, ICH conditioning and ICH guidelines to any country.

• ICH Members

➤ Regulatory Members

- o European Commission(EC)
- o US Food and Drug Administration(PDA)
- o Health Canada o Swiss medic
- o Agencia National de Vigilancia Sanitaria(ANVISA, Brazil)
- o Ministry of Food and Drug safety(MFDS, Republic of Korea)

• Industry Members

- o Japan Pharmaceutical Manufacturers Association(JPMA)
- o Pharmaceutical Research and Manufacturers of America(PhRMA)
- o International Generic and Biosimilar Medicines Association(IGBA)

E series:

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

EZA Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

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

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

E2C (R2) Periodic Benefit-Risk Evaluation Repon

E2E Pharmacovigilance Planning

E2F Development Safety Update Report

• Applications of Pharmacovigilance

- In national drug policy
- In disease control Public health programs (Problem are apparent situations for the treatment of tropical diseases.)
- In the regulation of medicine.

➤ In clinical practice

Conclusion:

For all medicines there is a trade-off between the benefits and the potential for harm. To minimize the harm, it is necessary that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. To achieve, this is to serve public health, and to foster a sense of trust in patients in the medicines they use that would extend to confidence in the health service in general. Drugs (including vaccines), which carry with them an ineluctable and occasionally changeable eventuality for harm. The threat of detriment, still, is less when drugs are used by an informed health profession and by cases who themselves understand and partake responsibility for their medicines. When adverse goods and toxin appear particularly when preliminarily unknowns in association with the medicine. Problems performing from illogical medicine use over boluses, polypharmacy and relations, adding use of traditional and herbal drugs with other drugs, illegal trade of drugs and medicines of abuse over the Internet, adding tone drug practices, unacceptable drugs, specific crimes, lack of effectiveness. This is the part of pharmacovigilance.

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