

UNIT-I

INTRODUCTION TO PHARMACOVIGILANCE



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*Shaping Lives...
Empowering Communities!*

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- **INTRODUCTION TO PHARMACOVIGILANCE**
 - History and development of Pharmacovigilance
 - Importance of safety monitoring of medicine
 - WHO international drug monitoring programme
 - Pharmacovigilance programme of India (PvPI)

- **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

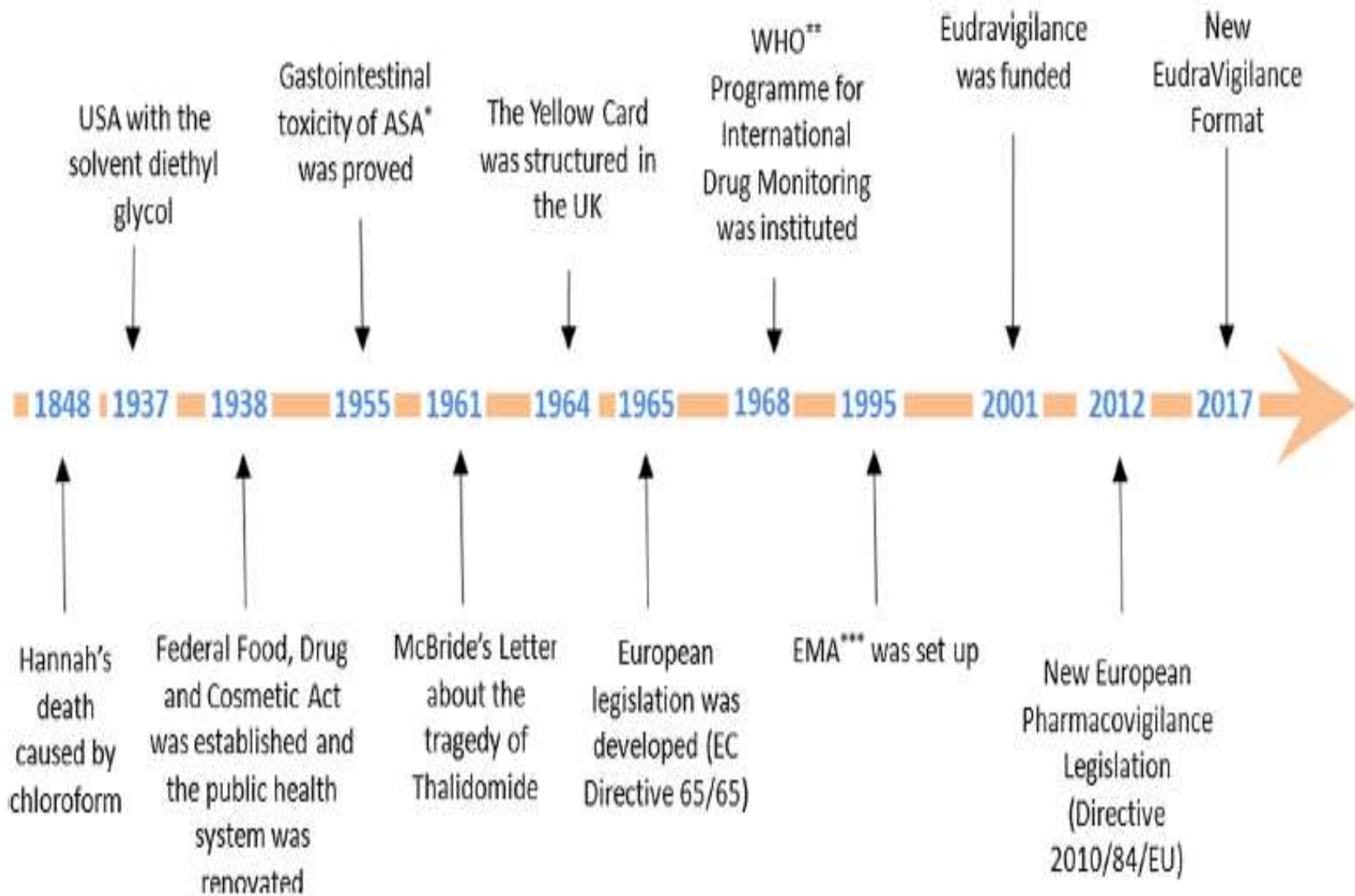


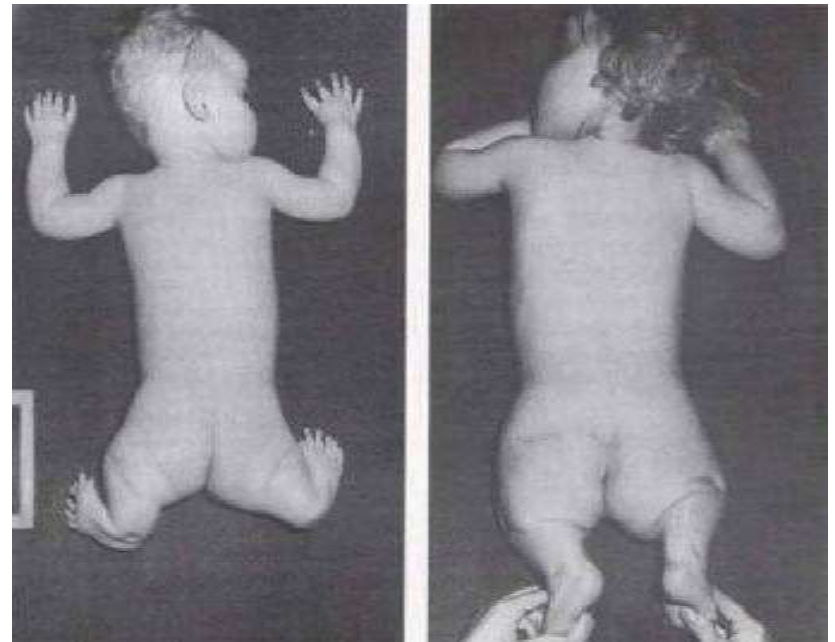
Fig. 1 Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; **WHO: World Health Organisation; ***EMA: European Medicines Agency

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

Functions of WHO programme for international drug monitoring

It includes:

- **Identification and analysis of new adverse drug reaction signal from the case report information** submitted to the national centers and from them to the data base.
- **Information exchange between WHO and national centers** mainly through **VIGIMED** and email information exchange system.
- **Publication of periodical news letters, guidelines and books** in the PV and risk management area.

- **Supply of tools for management of clinical information** including ADR case reports
 - WHO drug dictionary
 - WHO ADR terminology
- **Provision of training and consultancy support** to the national centers and countries establishing PV systems.
- **Computer software for case report managements design to suit the needs of national centers (VIGIFLOW).**

WHO & UMC

- **UMC (Uppsala Monitoring Centre)** is a field name of the WHO collaborating centre for International Drug Monitoring.
- It is responsible for the **management of the WHO programme for International Drug Monitoring.**

Functions of UMC

- **To coordinate the WHO programme for International Drug Monitoring and its more than eighty member countries.**
- **To collect, assess and communicate information from member countries about the benefits, harms and risks of drugs and other substances used in medicine to improve patient therapy and public health world wide.**
- **To collaborate with member countries in the development and practice of the science of PV.**

Pharmacovigilance Program of India (PvPI)

- The **Central Drugs Standard Control Organization (CDSCO)**, New Delhi, under the aegis of **Ministry of Health & Family Welfare, Government of India** has initiated a **nation-wide Pharmacovigilance programme** in **July, 2010**, with the **All India Institute of Medical Sciences (AIIMS), New Delhi** as the **National Coordinating Centre (NCC)** for **monitoring Adverse Drug Reactions (ADR)** in the country **to safe-guard Public Health**.

- In year 2010, **22 ADR monitoring centers (AMCs)** including AIIMS, New Delhi had been set up under this Programme.
- To ensure implementation of this programme in a more effective way, the **National Coordinating Centre** was then shifted from the All India Institute of Medical Sciences (AIIMS), New Delhi to the Indian [Pharmacopoeia](#) Commission (IPC), Ghaziabad, (U.P.) in April, 2011.

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

Short Term Goals

- To develop and implement pharmaco-vigilance system in India
- To enroll, initially, all MCI [approved medical colleges](#) in the program covering north, south, east and west of India
- To encourage healthcare professionals in reporting of adverse reaction to drugs, vaccines, medical devices and biological products
- Collection of case reports and data

Long Term Goals

- To **expand the Pharmacovigilance programme** to all hospitals (govt. & private) and centers of public health programs located across India
- To develop and implement **electronic reporting system (e-reporting)**
- To develop **reporting culture** amongst healthcare professionals
- To make **ADR reporting mandatory** for healthcare professionals

Functions of a National Pharmacovigilance System

- To create a nation-wide system for patient safety reporting
- To identify and analyze the new signal (ADR) from the reported cases
- To analyze the benefit – risk ratio of marketed medications
- To generate the evidence based information on safety of medicines
- To support regulatory agencies in the decision-making process on use of medications
- To communicate 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 located across globe

Minimum requirements for a functional Pharmacovigilance system

- Pharmacovigilance activities may be undertaken by several organizations, individuals and agencies. The Pharmacovigilance Programme of India fulfills the minimum requirements that should be present in any functional national Pharmacovigilance system, as per WHO, which include the following:

1. A national Pharmacovigilance centre with **designated staff** (at least one full time), **stable basic funding**, **clear mandates**, **well defined structures** and roles and **collaborating with the WHO Programme** for International Drug Monitoring.
2. The existence of a **national spontaneous reporting system** with a national individual case safety report (ICSR) form i.e. an **adverse drug reaction (ADR) reporting form**.

- A **national database** or system for **collating and managing ADR reports** (Vigibase database and Vigiflow software for PvPI)
- 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.
- A clear **strategy for routine and crisis communications.**