

UNIT-I

INTRODUCTION TO PHARMACOVIGILANCE



CENTURION
UNIVERSITY
*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

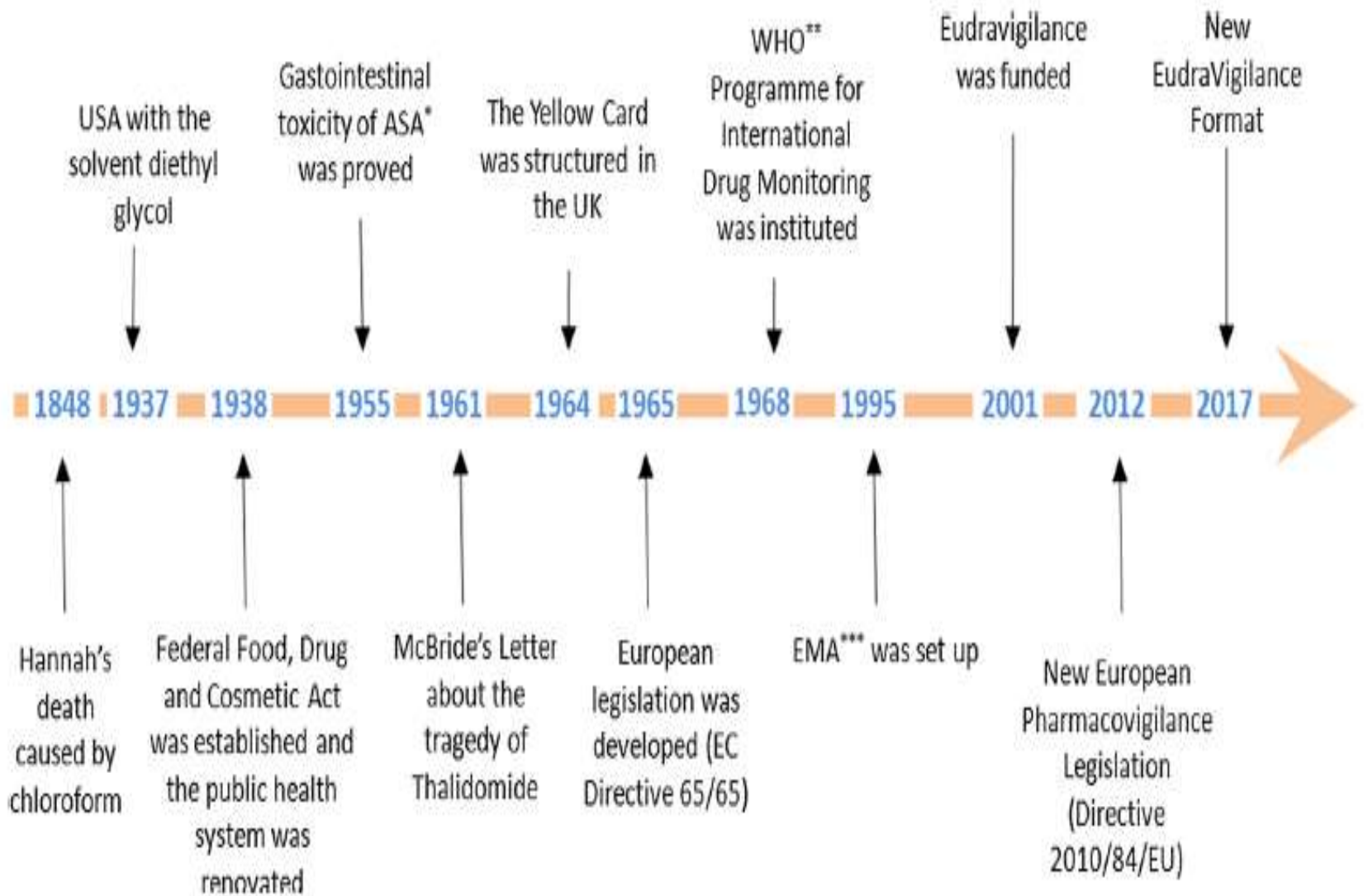


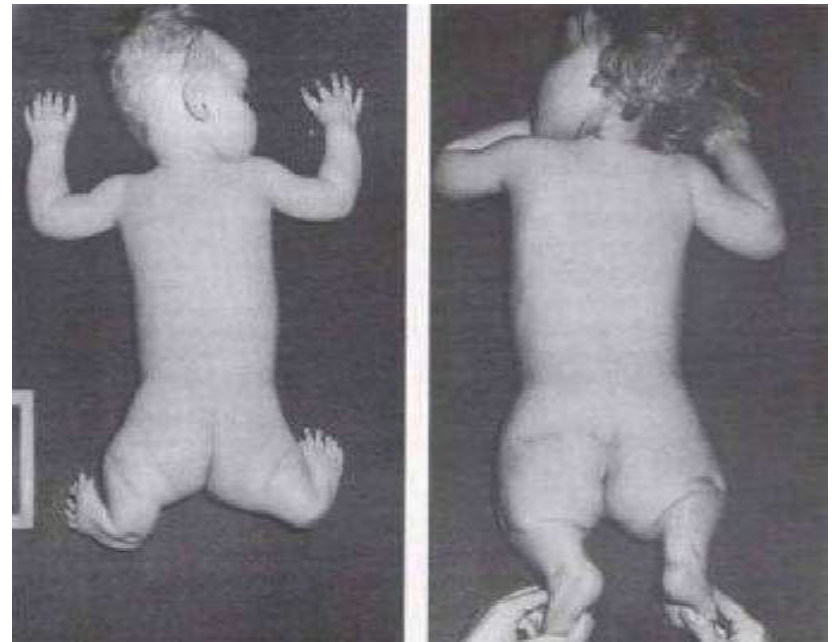
Fig. 1 Timeline of the historical evolution of Pharmacovigilance. *ASA: acetylsalicylic acid; **WHO: World Health Organisation; ***EMA: European Medicines Agency

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.**

INTRODUCTION TO ADVERSE DRUG REACTION

- Definitions and classification of ADRs
- Detection and reporting
- Methods in causality assessment
- Severity and seriousness assessment
- Predictability and preventability assessment
- Management of adverse drug reaction

- **An adverse drug event** is *“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”* (WHO definition, 2005)
- **An adverse drug reaction** is *“a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.”* (WHO definition, 2005)

Traditionally, ADRs have been classified into two types:

- **Type A reactions** – sometimes referred to as **augmented reactions** – which are ‘dose-dependent’ and predictable on the basis of the pharmacology of the drug.
- **Type B reactions** – **bizarre reactions** – which are idiosyncratic and not predictable on the basis of the pharmacology.

Table 1: Characteristics of Type A and Type B Adverse Reactions

Characteristics	Type A	Type B
Dose dependency	Usually shows good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors might be important	Dependent on host factors
Frequency	Common	Uncommon
Severity	Variable but usually mild	Variable, proportionately more
Clinical burden	High morbidity and low mortality	High morbidity and mortality
Overall portion of adverse drug reaction	80%	20%

Some of the ADRs could not be explained by the mechanism of either type A or B reactions which led to ABCDEF classification:⁴

1. Dose-related (Augmented)
2. Non-dose-related (Bizarre)
3. Dose-related and time-related (Chronic)
4. Time-related (Delayed)
5. Withdrawal (End of use)
6. Failure of therapy (Failure)

Drug reactions may be classified as:

- **Type A: Dose-related reactions** (adverse effects at either normal dose or overdose), eg. serotonin syndrome or anticholinergic effects of tricyclics
- **Type B: Non-dose-related reactions** (i.e. any exposure is enough to trigger such a reaction), eg. allergic or anaphylaxis reactions
- **Type C: Dose and time-related reactions**, eg due to dose accumulation, or with prolonged use (eg. adrenal suppression with corticosteroids)

- **Type D: Time related reactions**, i.e. due to prolonged use in a drug which doesn't tend to accumulate (eg. Tardive dyskinesia from antipsychotics/ neuroleptics)
- **Type E: Withdrawal reactions**, i.e. the undesired effects of ceasing the drug (for example, opiate withdrawal)
- **Type F: Unexpected failure of therapy**, where a drug undesirably increases or decreases in efficacy- for example, the decreased clearance of a drug by dialysis, or the decreased effect of antibiotics due to resistance.

Detection and reporting of ADR

- The pharmaco-epidemiological methods are used now days to detect **new signals of possible** adverse drug reactions (**ADRs**) and these methods can either be **'hypothesis generating'** where the **aim is to detect new & previously undetected ADRs** with a new drug or **'hypothesis testing'** where these methods **aim to prove whether any suspicions that may have been raised are justified.**

Hypothesis generating methods include

- **Spontaneous ADR Reporting-** which is a system whereby any suspected ADRs are voluntarily notified by health professionals, pharmaceutical companies and other stakeholders to a central authority (CDSCO in India).
- **Prescription Event Monitoring-** represents a method which is **hybrid of spontaneous reporting** with aspects of **formal epidemiological** studies.
- **Systematic methods-** public health surveillance data such as death registries are used to identify patterns of reactions that might be associated with drug use.

Hypothesis testing methods include

- **Case-Control Studies-** In case control studies the research compares the exposure rate in the cases with the exposure rate in the control.
- **Cohort Studies-** These studies involve a group **of** patients (cohort) followed up for a time duration long enough to detect the outcome of interest.
- **Randomized Controlled Trials-** These studies involve patients divided into two groups randomly into exposed and the other not exposed, so that the outcomes can be compared.



WHY ADR Reporting ?

- ADRs are among **the leading causes of death** in many countries (World Health Organization, 2008)

- **Account for 5% of all hospital admissions in India.**

Source: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3795320/>

- Constitutes a **significant economic burden** on the patient and government



Benefits of ADR Reporting

- Assess the safety of drug therapies, especially recently approved drugs.
- Provides updated drug safety information to health care professionals and other stakeholders
- **Measuring the economic impact of ADR prevention** as manifested through reduced hospitalization, optimal and economical drug use, and minimized organizational liability



Benefits of ADR Reporting

Cont.....

- Regulatory action on the basis of ADR reports to ensure patient's safety
 - Upgrading package insert
 - Marketing Authorization Recall (withdrawal)
 - Batch recall based on clustering of ADR
 - Changes in classification, e.g.
 - From over the counter to prescription only medicines.
 - Special prescription
 - 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.



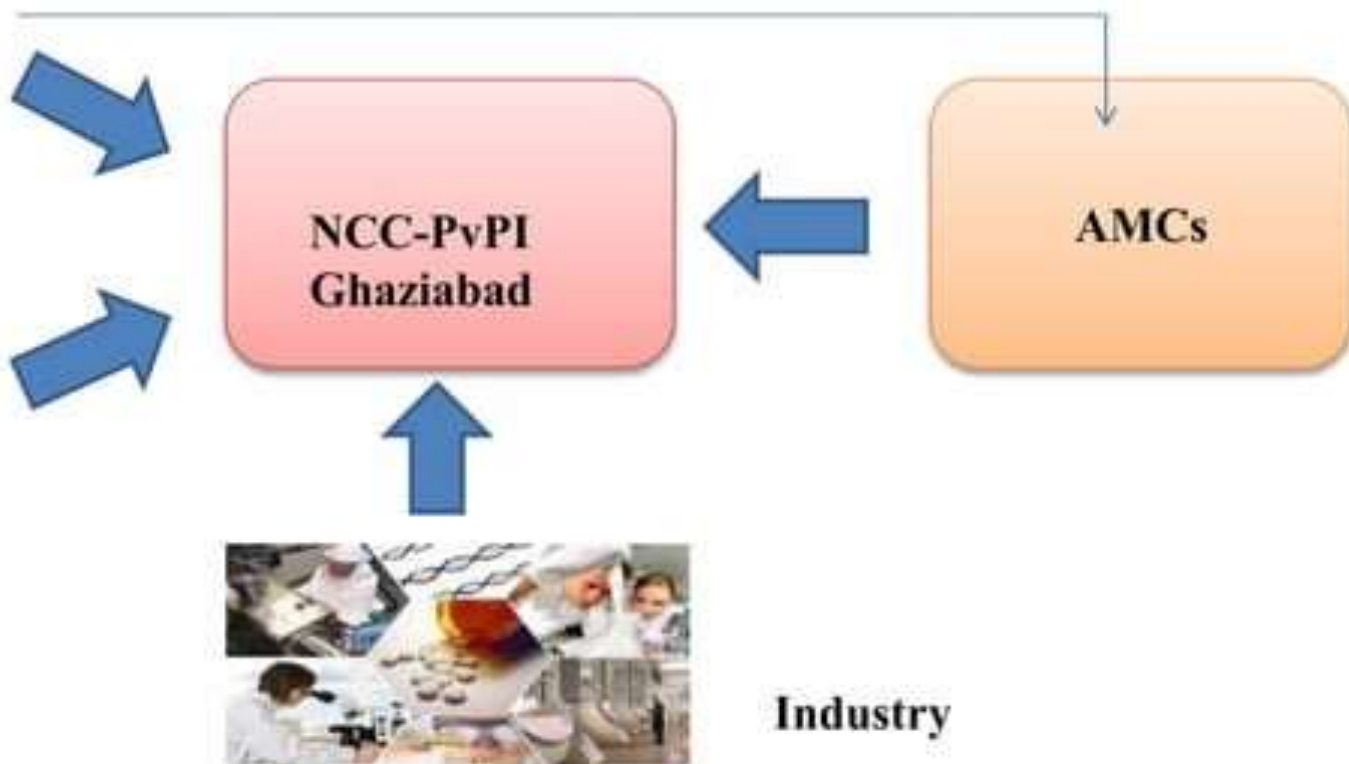
Who can report? How to report ?and whom to report?



Health Care Professionals



Consumer





Toll free-Helpline Number

**A reporter can also report ADR Via Helpline number launched in
October 2013**

1800 -180- 3024

(Monday to Friday 9:00AM to 5:30 PM)



Android Application

ADR Reporting App. can be downloaded from **Google play store** (free to download)

ADR-PvPI is the indigenously developed Mobile App for all healthcare professionals and consumers to report adverse drug reactions



Worldwide Reporting Forms

CIOMS for US

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT										
I. REACTION INFORMATION										
1. PATIENT DETAILS (incl. sex)	1A. COUNTRY	2. DATE OF BIRTH (Day, Month, Year)			3. AGE (Years)	4. SEX	5. REACTION ONSET (Day, Month, Year)			6. 12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7. + 13 DESCRIBE REACTION(S) (including relevant laboratory data)										
8. PATIENT DIED <input type="checkbox"/> INVOLVED OR INVOLVED IN PROXIMATE HOSPITALIZATION <input type="checkbox"/> INVOLVED IN SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING										
II. SUSPECT DRUG(S) INFORMATION										
14. SUSPECT DRUG(S) (include generic name)					17. DID REACTION REAPPEAR AFTER RESTART OF DRUG?					
15. DAILY DOSE(S)					18. ROUTE OF ADMINISTRATION					
16. INDICATION(S) FOR USE					19. DID REACTION REAPPEAR AFTER RESTART OF DRUG?					
20. THERAPY DATES (range)					21. THERAPY POSITION					
III. CONCOMITANT DRUG(S) AND HISTORY										
22. CONCOMITANT DRUG(S) AND DATE(S) OF ADMINISTRATION (include those used in last 30 days)										
23. OTHER RELEVANT HISTORY (e.g. diagnosis, surgery, pregnancy with last month of period, etc.)										
IV. MANUFACTURER INFORMATION										
24. NAME AND ADDRESS OF MANUFACTURER										
24a. MFR CONTROL NO.					24b. REPORT SOURCE					
24c. DATE RECEIVED BY MANUFACTURER					24d. REPORT TYPE					
DATE OF THIS REPORT					24e. REPORT TYPE					

MED-WATCH FOR UK

U.S. Department of Health and Human Services
MEDWATCH
 The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product recalls
 Page 1 of 3

Form Number: FDA-16 (03/2005) Expires: 03/31/2010

1. Name of individual or institution that reported adverse event (if not the patient name, include address and zip code by example: 201 Ave. Q) 2. Address (street, city, state, zip code) 3. Telephone (include area code) 4. E-mail (include domain name)		5. Date of adverse event 6. Time of day (if known) (to nearest 15 minutes) 7. Exposure to adverse to date (initials) 8. How long (days) (to nearest 15 minutes) 9. How long (days) (to nearest 15 minutes) 10. How long (days) (to nearest 15 minutes)			
A. PATIENT INFORMATION 1. Patient name (last, first, middle) 2. Sex 3. Age (years) 4. Race 5. Ethnicity 6. Height (inches) 7. Weight (pounds) 8. Date of birth (MM/DD/YYYY) 9. Social Security Number (SSN) (if known) 10. Date of admission (MM/DD/YYYY) 11. Date of discharge (MM/DD/YYYY) 12. Date of death (MM/DD/YYYY) (if applicable)		13. How long (days) (to nearest 15 minutes) 14. How long (days) (to nearest 15 minutes) 15. How long (days) (to nearest 15 minutes)			
B. ADVERSE EVENT, PRODUCT PROBLEM 1. Check all that apply: <input type="checkbox"/> Adverse Event <input type="checkbox"/> Product Problem (e.g., contamination) <input type="checkbox"/> Product Use Error <input type="checkbox"/> Problem with Different Manufacturer of Same Medicine 2. Describe (include date, duration, onset, etc.) 3. How long (days) (to nearest 15 minutes) 4. How long (days) (to nearest 15 minutes) 5. How long (days) (to nearest 15 minutes) 6. How long (days) (to nearest 15 minutes) 7. How long (days) (to nearest 15 minutes) 8. How long (days) (to nearest 15 minutes)		16. How long (days) (to nearest 15 minutes) 17. How long (days) (to nearest 15 minutes) 18. How long (days) (to nearest 15 minutes)			
C. PRODUCT AVAILABILITY 1. Product available for sale? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Product Discontinued (date) 2. How long (days) (to nearest 15 minutes) 3. How long (days) (to nearest 15 minutes)		D. SUSPECT PRODUCTS 1. Name (Manufacturer/Trade Name, Strength, Formulation) 2. Name and strength 3. Manufacturer/Company 4. Name and strength 5. Manufacturer/Company 6. Name and strength 7. Manufacturer/Company		E. SUSPECT MEDICAL DEVICE 1. Serial Number 2. Company Name 3. Manufacturer Name, City and State 4. Model # 5. Lot # 6. Expiration Date (month/year) 7. How long (days) (to nearest 15 minutes) 8. How long (days) (to nearest 15 minutes) 9. How long (days) (to nearest 15 minutes)	
F. OTHER (CONCOMITANT) MEDICAL PRODUCTS 1. Name (Manufacturer/Trade Name, Strength, Formulation) 2. Name and strength 3. Manufacturer/Company 4. Name and strength 5. Manufacturer/Company		G. REPORTER (use manufacturer's address, see 16A) 1. Name (last, first, middle) 2. Title 3. Address (street, city, state, zip code) 4. Telephone (include area code) 5. E-mail (include domain name) 6. How long (days) (to nearest 15 minutes) 7. How long (days) (to nearest 15 minutes) 8. How long (days) (to nearest 15 minutes)			

Suspected Adverse Drug Reaction Reporting Form For Health Care Professionals

This form is divided into four sections:

- A. Patient Information
- B. Suspected Adverse Reaction
- C. Suspected Medication(s)
- D. Reporter Details



A. Patient Information

A. Patient Information

<p>1. Patient Initials</p> <hr/>	<p>2. Age at time of event or date of birth</p> <hr/>	<p>3. M <input type="checkbox"/> F <input type="checkbox"/> Other <input type="checkbox"/></p> <hr/> <p>4. Weight _____ Kgs</p>
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B. Suspected Adverse Reaction

B. Suspected Adverse Reaction

5.	Date of reaction started (dd/mm/yyyy)
6.	Date of recovery (dd/mm/yyyy)
7.	Describe reaction or problem



C. Suspected Medications

C. Suspected medication(s)

S.No	8. Name (Brand /Generic)	Manufacturer (If known)	Batch No./ Lot no.	Exp. Date (if known)	Dose used	Route used	Frequency (OD,BD, etc.)	Therapy dates		Indication	Causality assessment
								Date started	Date stopped		
i											
ii.											



C. Suspected Medications

Cont...

Action taken- Mark the appropriate option for the action taken with respect to Suspected drug.

S.No. as per C	9. Action Taken (Please Tick)					
	Drug withdrawn	Dose increased	Dose reduced	Dose not changed	Not applicable	Unknown
i						
ii						



C. Suspected Medications

Cont..

- **Rechallenge/ Reintroduction** - The point at which a drug is again given to a patient after its previous withdrawal.
- Mark the appropriate option whether the suspected drug reintroduced & reaction occurred or not or effect unknown.

10. Reaction reappeared after reintroduction (Please Tick)

S.No.	Yes	No	Effect Unknown	Dose (If reintroduced)
i				
ii				



Concomitant medications

Cont..

Concomitant medical product (s) information given in the following tabs.

11. Concomitant medical product including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

S.No.	Name (Brand /Generic)	Dose used	Route used	Frequency (OD, BD, etc.)	Therapy dates		Indication
					Date started	Date stopped	
i							
ii							



D. Reporter Details

D. Reporter Details

16. Name and professional address _____

Pin _____ E - mail _____

Tel. No. (With STD code) _____

Occupation _____ Signature _____

17. Date of this Report (dd/mm/yyyy) _____



Other important sections of ADR Reporting form

12. Relevant test and laboratory data with dates

13. Relevant medical / medication history (Allergies, race, pregnancy, smoking , alcohol use, renal and hepatic dysfunction etc.)

14. Seriousness of the reaction: No If Yes (please tick anyone)

Death (dd/mm/yyyy)

Congenital anomaly

Life threatening

Required intervention to prevent permanent impairment/ damage

Hospitalization/ prolonged Disability

Other (specify)



Other important sections of ADR Reporting form

15. Outcome (please tick anyone)

Recovered

Recovering

Not Recovered

Fatal

Recovered with Sequelae

Unknown

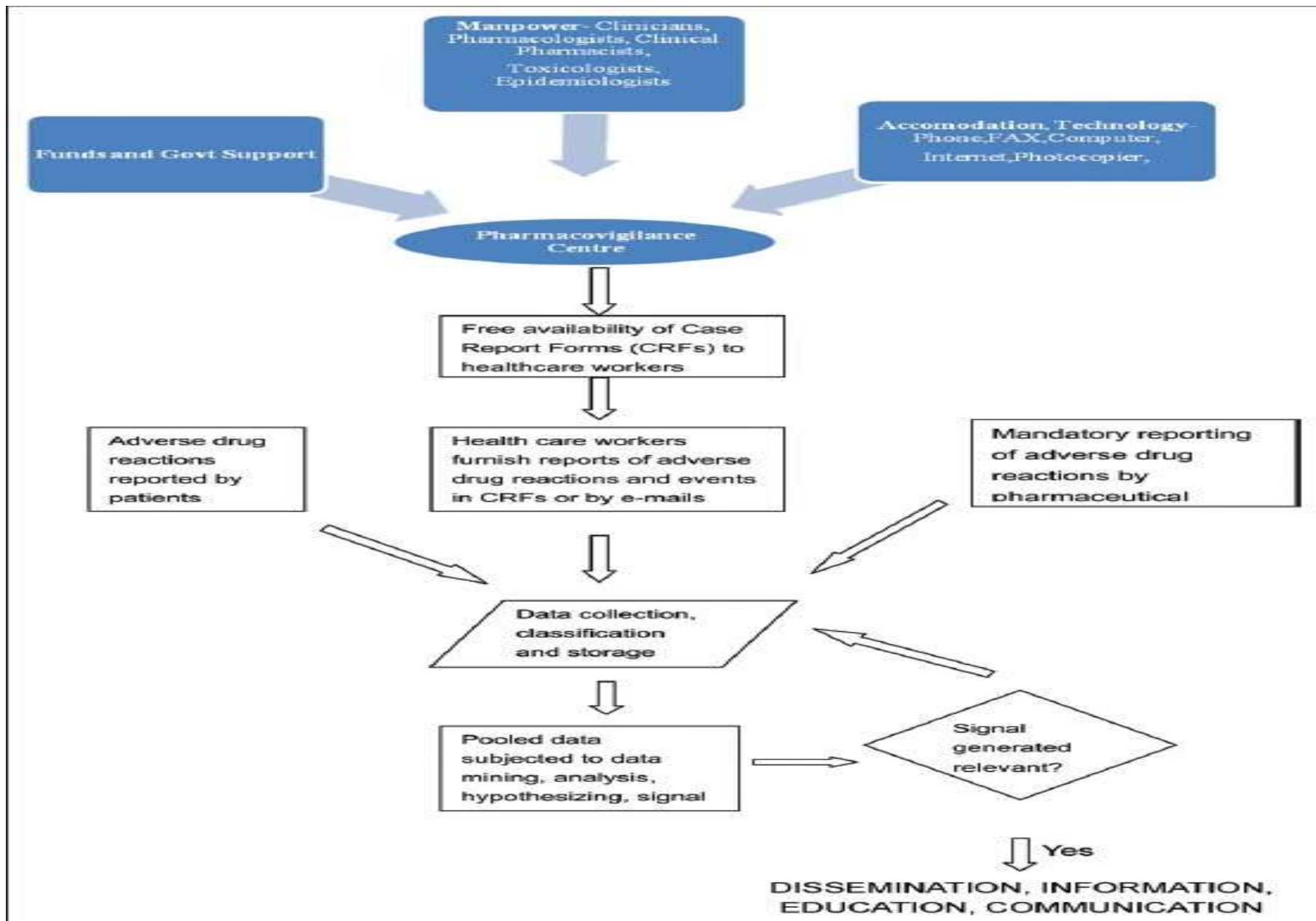


Other important sections of ADR Reporting form

Additional Information:

More information on the ADR report that are not fit in the respective column given in ADR form can be entered in the field of additional information (i.e. More information about suspected drug, indication etc.)

Pharmacovigilance system: Constitution and functioning



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 programmes **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 daunting 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 algorithm 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** describes the extent to which the ADRs influence the everyday life of a patients.
- **Karch** and **Lasagna** classify severity into minor, moderate, severe and lethal.
 1. Mild(Minor)
 2. Moderate
 3. Severe
 4. lethal

Severity	Description	Example
Mild	No antidote or treatment is required; hospitalization is not prolonged	Some Antihistamines(some) Drowsiness Opioids; constipation
Moderate	A change in the treatment (e.g. modified dosage, addition of a drug), but no necessarily discontinuation if drug is required; hospitalization may be prolonged, or specific treatment may be required	Hormonal contraceptives: Venous thrombosis NSAIDs: Hypertension and edema
Severe	ADR may be life threatening and requires immediate discontinuation of drug and specific treatment for ADR	ACE inhibitors: Angioedema Phenothiazines: Abnormal heart rhythm
Lethal	Contributes to patient's death	Acetaminophen over dosage: Liver failure Anticoagulants: hemorrhage

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.

- **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)**

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 for at least 30% of ADRS
- E.g. anticholinergics and dry mouth

○ **Type B(unpredictable)**

- Idiosyncratic or immunologic reactions
- Rare and unpredictable
- E.g. chloramphenicol and aplastic anemia, 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 adverse drug reaction

- Successful management of adverse drug reactions **requires early identification and prompt treatment of anaphylaxis**, whether due to immunoglobulin (Ig) E- or non-IgE-mediated mechanisms of mast cell mediator release.

- Good management also requires anticipation of adverse reactions whenever a therapeutic program is instituted.
- An adverse reaction can **often be minimized through use of established protocols for premedication.**
- **Desensitization, when essential, may be achieved for most drugs with graduated dosage schedules and maintained through continued administration of the drug.**
- **Identification to avoid inadvertent exposure to agents that have caused immunology reactions in the past is essential.**

- BASIC TERMINOLOGIES USED IN PHARMACOVIGILANCE
 - 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:** Electronic Standards 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.