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A Comprehensive Review on Drug Development and Pharmacovigilance: From Discovery to Post-Marketing Surveillance

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Abstract: *Pharmacovigilance is an essential part of the healthcare systems around the world, ensuring the safe and effective use of drugs. It encompasses the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs) and other drug related problems. Since its formal inception after the World Health Organization Programme for International Drug Monitoring in 1968, pharmacovigilance has developed into a globalized scientific field. This review aims to cover the stages of drug development, scope, objectives, and significance of pharmacovigilance, classification and causality assessment of adverse drug reactions, regulations, ICH guidelines, and its role in the drug development process. This review article also focuses on contemporary approaches, risk management plans, and future directions in drug safety surveillance.*

Index Terms **–** Pharmacovigilance, Adverse drug Reactions, Causality assessment Drug development, Clinical trials, ICH Guidelines

Pharmacovigilance - The World Health Organization describes pharmacovigilance "as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem".
Origin of the term: Pharmakon – Medicine or drug, **Vigilance** – Careful observation

Accordingly, pharmacovigilance can be defined as the continuous surveillance of drugs once they are marketed to identify harmful reactions and ensure safe use.

Importance of Pharmacovigilance:

- ✓ Protection of Patient Safety
- ✓ Improvement of Therapeutic Outcomes
- ✓ Identification of Adverse Drug Reactions
- ✓ Continuous Monitoring of Drug Safety
- ✓ Regulatory Requirements compliance
- ✓ Assessment and Management of Drug Related Risks
- ✓ Role in Drug Development
- ✓ Global Cooperation for Drug Safety
- ✓ Aid to Clinical Decision Making
- ✓ Building Public Confidence in Medicines

Aims and Objectives of Pharmacovigilance:

- To systematically identify, document, and report suspected adverse drug reactions, and to work towards reducing their occurrence through continuous and careful surveillance.
- To protect public health by promoting the safe use of medicines in the population.
- To contribute to the assessment of the benefit-risk balance, therapeutic efficacy, and risks of medicines, with the aim of reducing harm and maximizing benefits.
- To promote the rational, safe, effective, and cost-effective use of medicines in practice.
- To improve awareness, education, and training in pharmacovigilance and ensure that safety information about medicines is communicated clearly to healthcare professionals and the general public.

Scope of Pharmacovigilance:

- ✓ Role in Drug Development
- ✓ Adverse Event Monitoring
- ✓ Safety Signal Identification
- ✓ Risk Assessment
- ✓ Regulatory Decision Support
- ✓ Post-Marketing Safety Surveillance

Important Historical Events in the Evolution of Pharmacovigilance

- **1848 – Chloroform Tragedy -** In 1848, the death of a 15-year-old girl who had been administered chloroform created serious safety concerns. This was followed by several deaths that could not be explained. These events highlighted the risks associated with anesthetic drugs and thus represented one of the first milestones in the need for pharmacovigilance.
- **1937 – Sulfanilamide Disaster (USA) -** In 1937, a disaster struck in the United States when a liquid preparation of sulfanilamide, which had been formulated using diethylene glycol as a solvent, caused the deaths of 107 people, including 76 infants. The toxic properties of the solvent caused the deaths. This disaster highlighted the need for assessing the safety of all parts of a drug, including the inactive ingredients, and led to a significant shift in the regulation of drugs.
- **1961 – Thalidomide Crisis -** The use of thalidomide among pregnant women in the late 1950s and early 1960s led to an increase in the number of babies born with severe congenital malformations. In December 1961, Dr. William McBride observed a possible association between the use of thalidomide during pregnancy and congenital malformations. The public awareness of this observation led to a pivotal moment in the history of pharmacovigilance, turning drug safety monitoring into a systematic and regulated field.

Evolution of Pharmacovigilance Systems and Regulatory Frameworks

- In **1938,** the United States passed the **Food, Drug, and Cosmetic Act,** which gave the Food and Drug Administration (FDA) expanded powers, originally created in 1906. This act gave the FDA the duty to oversee the safety of foods, drugs, medical devices, and cosmetics, which remains the foundation of modern pharmaceutical regulation.
- In **1948,** the **World Health Organization (WHO)** was founded in Geneva with the aim of coordinating and responding to global public health issues, including the safety of medications.
- In the **United Kingdom**, a significant milestone was reached in **1964** with the establishment of the **Yellow Card Scheme,** the first organized system allowing physicians to submit notifications of suspected adverse drug reactions.
- To encourage international collaboration, the WHO initiated the **Programme for International Drug Monitoring** in **1968**, with the goal of compiling and analyzing worldwide data on adverse drug reactions.
- A major achievement was realized in **1978**, when the **Uppsala Monitoring Centre** was established as a result of collaboration between the Swedish government and the WHO, which became the international center for the analysis of adverse drug reaction data.
- At the European level, the **European Medicines Agency** (EMA) was established in **1995**, and subsequently, EudraVigilance was introduced in 2001, which is a European centralized database intended to handle and analyze data on adverse reactions.

DRUG DEVELOPMENT

Drug : A chemical substance given to human beings or animals with the aim of diagnosing, preventing, treating, or curing diseases. Generally, the development of a drug involves three major steps:

1. Drug Discovery Stage
2. Preclinical Stage
3. Clinical Trial Stage

Drug Discovery Phase :

a) Identification of Lead Compounds

After new chemical substances are synthesized or isolated, their purity is established through physical, chemical, and analytical procedures. After establishing their purity, these compounds are then subjected to biological screening to assess their pharmacological properties.

The main aim of this screening procedure is **to identify lead compounds**, which are molecules that show promising pharmacological properties and can be used as the basis for developing a new drug.

b) Lead Optimization

After the discovery of lead compounds, the subsequent process is lead optimization. This is achieved by:

- Increasing potency against the desired biological target
- Optimizing pharmacokinetic properties (absorption, distribution, metabolism, and excretion)
- Reducing unwanted side effects
- Reaching this point may take around three to five years. After the optimization of a promising lead compound, it moves on to preclinical testing.

Transition to Preclinical and Clinical Studies

The chosen lead compound is then thoroughly evaluated in preclinical studies to determine safety and biological activity in animal models. Clinical studies in human subjects are only initiated if the preclinical results show promising safety and biological activity.

Preclinical Evaluation Phase (Animal Studies)

The preclinical phase begins with animal studies to determine the pharmacological properties of the identified lead compound.

A major part of this process, especially toxicity testing, is conducted following the officially accepted standards called Good Laboratory Practices (GLP).

- ✓ The entire preclinical evaluation process takes about 1.5 to 2 years to complete.

The essential elements of preclinical assessment are listed below.

1. Pharmacodynamic Studies

These studies examine the biological effects of the drug in relation to its proposed therapeutic application, as well as other effects. For instance, if a drug is being tested for antihypertensive activity, experiments may be carried out on animals such as rats, cats, or dogs to determine changes in systolic and diastolic blood pressure. At a more advanced level, molecular studies such as receptor

binding assays are undertaken to establish receptor affinity and specificity. Quantitative analysis, including graded and quantal dose-response analysis, is undertaken to establish the effective dose (ED_{50}).

2. Toxicological Studies

If the compound shows beneficial pharmacological activity, it must then be evaluated for potential toxic effects on the major organ systems.

(a) Acute Toxicity - The aim of acute toxicity testing is to establish the dose that will be lethal to 50% of the test animals (LD_{50}). The experiment is conducted on at least two different species of animals. The compound is given in a series of increasing doses by at least two routes, one of which is intended for human administration.

(b) Subacute Toxicity - The objective of this stage is to determine which organs are susceptible to toxic damage. The compound is given in multiple doses to two species of animals over a period of four weeks to three months.

(c) Chronic Toxicity - Chronic toxicity studies are of particular relevance for drugs that will be used for a prolonged period in humans. Typically , these studies are carried out in one rodent and one non-rodent species and can extend for one to two years.

(d) Special Toxicity Studies

i. Reproductive Toxicity - Animals, usually rats, are exposed before and after breeding to determine the effects on fertility, gestation, parturition, lactation, and offspring development.

ii. Teratogenicity - Studies are conducted on at least two species (usually rats and rabbits) to determine the potential of the drug to cause congenital abnormalities.

iii. Carcinogenicity - Long-term studies are conducted to determine the potential of the drug to induce benign or malignant tumors.

iv. Mutagenicity - These studies are designed to determine the potential of the drug to cause genetic changes in cells.

3. Pharmacokinetic Studies

Once the toxicological profile is satisfactory, pharmacokinetic studies are carried out on different animal species like rats, dogs, and sometimes monkeys. These studies evaluate: Absorption ,Distribution ,Metabolism ,Excretion

They also measure the bioavailability of the drug given orally or parenterally and the elimination half-life ($t_{½}$) of the drug.

4. Calculation of Safety Margin

Values like LD_{50} and ED_{50} are determined using pharmacodynamic and toxicological information. From these, the therapeutic index and other safety measures are determined.

Other safety measures include:

- Maximum Tolerated Dose (MTD)
- No Observed Adverse Effect Level (NOAEL)
- Human Equivalent Dose (HED)

These measures are used to determine the correct First-in-Human (FIH) dose for Phase I clinical trials.

Transition to Clinical Trials - If preclinical results show that the compound is both effective and relatively safe, the compound is ready for human testing. At this point, a suitable pharmaceutical form for the intended route of administration is developed, and its stability is determined.

If all these processes are successful, the compound is ready for clinical trials, where it will be tested to see if it has the potential to become an approved therapeutic drug.

Clinical Trial Phase (Human Studies)

Clinical trials are carefully designed research studies conducted in human subjects to assess a new drug. The aim of these studies is to obtain scientific proof that supports or disproves claims of efficacy, defines pharmacological effects, reveals adverse reactions, and finally determines the safety and efficacy of the new drug.

All clinical studies must adhere to globally accepted ethical and scientific norms called Good Clinical Practice (GCP).

Regulatory Approval Prior to Initiation of Human Studies

After the successful completion of preclinical testing, the sponsor is required to submit an Investigational New Drug (IND) application to the concerned national regulatory authority.

Examples of Regulatory Authorities

- U.S. Food and Drug Administration (USA)
- Drugs Controller General of India (India)
- Committee on Safety of Medicines (UK)

The IND application should include:

- Chemical constitution, origin, processing, and purity
- Preclinical pharmacodynamic, pharmacokinetic, and toxicological data, including ED_{50} and LD_{50} values
- Proposed dosage forms for human use
- Detailed clinical trial protocol outlining the dose and route of administration
- Qualifications and facilities of the investigator
- Sponsor's agreement to submit periodic progress reports
- Written assurance that informed consent will be sought and that ethical standards will be upheld

Informed Consent and Ethical Considerations

Before inclusion in the study , written informed consent from each participant must be obtained in the manner specified by the regulatory authorities .

Essential Elements of Informed Consent

- Statement that the study involves research and its purpose
- Expected duration of participation
- Description of procedures, including invasive procedures if any
- Explanation of potential risks and discomforts
- Expected benefits to the participant
- Information on alternative treatments available
- Assurance of confidentiality of medical records
- Treatment schedule and possibility of random assignment
- Contact details for study-related queries or injury
- Details of compensation or payment, if any
- Information about treatment or compensation for trial-related injury
- Confirmation that participation is voluntary and withdrawal is allowed at any time

Stages of Clinical Trials

Clinical trials in humans subjects are carried out in four successive stages to determine the safety and efficasy of a new drug before and after its launch in the market.

1. Phase I – First Human Safety Studies

Phase I is the first stage of clinical trials of a new drug in human subjects. This stage is normally conducted on a small number of 25–100 healthy volunteers. However, if the new drug is highly toxic , patients with the target disease are chosen instead of healthy volunteers.

Objectives of Phase I:

- Evaluating safety and tolerability
- Evaluating the effects on vital organs like the heart, liver, and kidneys.
- Comparing pharmacokinetics in animals and humans
- Determining a safe dose range
- Evaluating pharmacokinetics in humans
- Evaluating whether poor drug response is due to poor absorption or rapid elimination.
- Evaluating predictable toxic effects

Phase I trials are usually unblinded, meaning that both the researchers and the participants are aware of the identity of the administered drug.

2. Phase II – Therapeutic Evaluation

Phase II trials are carried out on patients who have the particular disease for which the drug is being developed. This is the first phase where the therapeutic efficacy of the drug is assessed.

Early Phase II: Involves up to 200 patients, single-blind (patients are not aware of their allocation to treatment or control groups).

Late Phase II: Involves 200-400 patients, Randomized double-blind study, where neither the investigator nor the patient knows the treatment assignment.

3. Phase III – Large-Scale Confirmation Trials

Phase III trials are large-scale, multi-center studies involving large and varied patient populations (often 1,000-5,000 or more participants). These trials are intended to confirm safety and efficacy on a larger scale and to address remaining uncertainties from previous phases.

These trials are usually randomized, double-blind studies and may employ cross-over designs, in which patients are given different treatments (standard drug, placebo, or new drug) in a predetermined order.

- ✓ **The total duration of Phases I, II, and III typically takes about 5-6 years.**

New Drug Application (NDA)

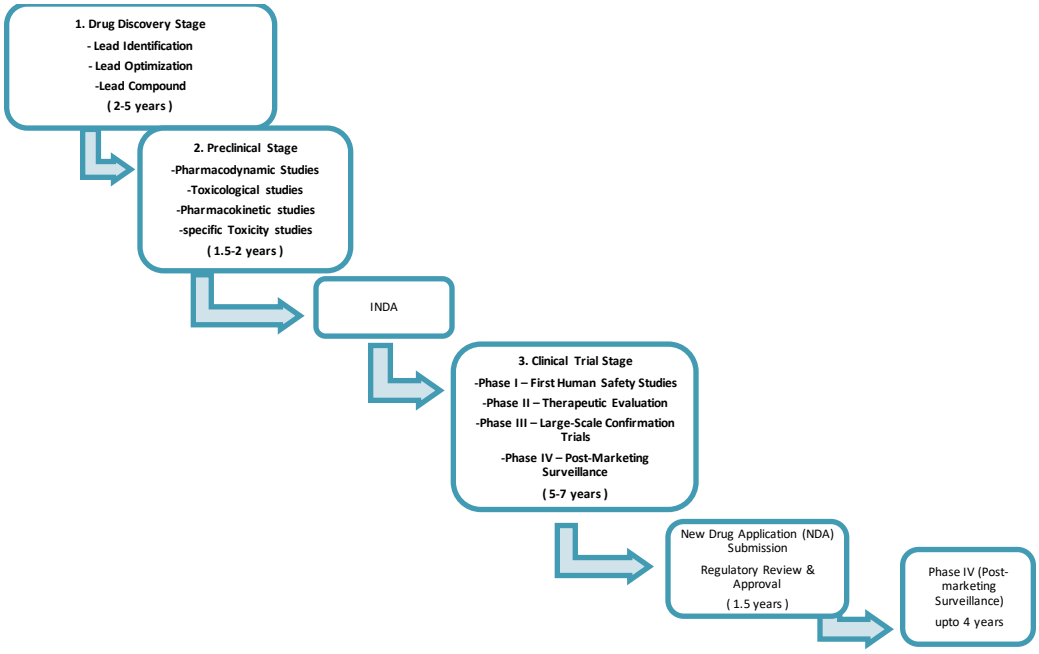
Once satisfactory results are obtained from Phase III trials, the sponsor files a New Drug Application with the national drug regulatory agency. This application contains all the clinical information, product information, proposed brand name, labeling, and prescribing information.

The regulatory agencies scrutinize the application and may demand further clarification. If the information is satisfactory, the drug receives marketing approval with the status of "New Drug."

4. Phase IV – Post-Marketing Surveillance

Phase IV starts after the drug has been approved and marketed. This phase does not have a fixed time limit and continues as long as the drug is in use. The aims of this phase are:

- To detect rare or long-term adverse reactions
- To study drug interactions
- To note reactions in special groups of patients
- To discover new uses of the drug



Stages of Drug Development

Adverse Drug Reaction : WHO defines an **Adverse drug reaction** as any 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 physiological function.

An **Adverse Drug Event** is defined as any untoward medical occurrence presenting during the administration of a drug.

The most widely accepted system for classifying adverse drug reactions is the **Rawlins and Thompson classification**, which categorizes ADRs based on their predictability, mechanism, and relationship to dose.

- **Type A (Augmented) Reactions** - These reactions are predictable and occur at therapeutic doses. They are directly related to the known pharmacological effects of the drug and are usually dose-dependent. **Ex:** Hypoglycemia due to insulin therapy.
- **Type B (Bizarre) Reactions** - These reactions are unpredictable and do not correlate with the drug's established pharmacological action. They often involve immune-mediated or idiosyncratic mechanisms. **Ex:** Hypersensitivity reaction due to penicillin.
- **Type C (Chronic) Reactions** - Chronic reactions develop as a result of long-term drug administration and are commonly associated with cumulative dose or prolonged exposure. **Ex:** Suppression of adrenal function due to prolonged corticosteroid therapy.
- **Type D (Delayed) Reactions** - These reactions occur after a considerable delay following exposure to the drug and may occur even after the drug has been stopped. **Ex:** Delayed hypersensitivity reactions, carcinogenic effects, or teratogenic effects.
- **Type E (End-of-Use) Reactions** - These reactions occur when a drug is suddenly stopped, resulting in withdrawal symptoms or rebound phenomena. **Ex:** Rebound hypertension due to abrupt withdrawal of beta-blockers.
- **Type F (Failure) Reactions** - Failure reactions occur when a drug fails to produce its intended therapeutic effect. This may be due to interactions, resistance, or loss of efficacy in some individuals. **Ex:** Failure of oral contraceptives due to enzyme induction.

The Central Drugs Standard Control Organization (CDSCO), functioning under the aegis of the Directorate General of Health Services, Ministry of Health & Family Welfare, is the National Regulatory Authority (NRA) for India. The headquarters of CDSCO is located at FDA Bhawan, Kotla Road, New Delhi.

As per the Drugs and Cosmetics Act, the CDSCO is responsible for approving drugs, regulating clinical trials, establishing drug standards, monitoring the quality of imported drugs, and advising state drug control authorities to ensure a uniform enforcement of rules across the country.

Pharmacovigilance Programme of India (PvPI)

The Central Drugs Standard Control Organization (CDSCO), New Delhi, under the Ministry of Health & Family Welfare, Government of India, initiated a pharmacovigilance programme nationwide in July 2010. The programme was organized by the All India Institute of Medical Sciences (AIIMS), New Delhi, which functioned as the National Coordinating Centre (NCC) for the monitoring of Adverse Drug Reactions (ADRs) nationwide to ensure public health safety. At the time of the programme's initiation, 22 ADR Monitoring Centres (AMCs), including AIIMS, were established.

To improve the efficiency and implementation of the programme, the National Coordinating Centre was shifted in April 2011 from AIIMS, New Delhi to the Indian Pharmacopoeia Commission , Ghaziabad (U.P.).

Aims and Objectives:

- Establish a national system for ensuring patient safety through drug safety monitoring.
- Identify and assess new safety signals from reported adverse drug reactions.
- Assess the benefit-risk profile of medicines already marketed.
- Develop evidence-based information on the safety of medications.
- Help regulatory bodies in making informed decisions on the use of medications.
- Share information on medicine safety with stakeholders to prevent or reduce risks.
- Share information on medicine safety with other national pharmacovigilance centers for information exchange and data management.
- Provide training and technical assistance to pharmacovigilance centers worldwide.
- Celebrate National Pharmacovigilance Week (17th-23rd September every year) and create awareness among stakeholders.
- Promote rational and safe use of medications.

As a part of the Pharmacovigilance Programme of India (PvPI), there are presently 250 operational Adverse Drug Monitoring Centres (AMCs) in medical colleges and corporate hospitals spread across the country.

After a medical institution is registered as an AMC under PvPI, it starts sending Individual Case Safety Reports (ICSRs) to the National Coordinating Centre (NCC) through VigiFlow. At the NCC, the ICSRs are assessed for data quality. The valid ones are then sent to the Uppsala Monitoring Centre in Sweden, which is the international drug safety monitoring centre.

In case an ICSR is detected to be invalid or have some errors, it is sent back to the concerned AMC with comments or queries so that the ICSR can be corrected and then resubmitted to the NCC. In addition, the data is also sent to the CDSCO whenever required to aid in decision-making.

Detection of Adverse Drug Reactions (ADRs) in Hospital Environments

In hospitals, healthcare practitioners should be vigilant about the potential occurrence of adverse drug reactions (ADRs). ADRs can be detected during ward rounds, evaluation of patient records, or during patient counseling and medication history-taking. Discussion with other healthcare practitioners can also offer important information for the detection of ADRs.

Vigilant monitoring is particularly required for patients who are at high risk of ADRs, including:

- Patients with renal or hepatic disorders
- Patients taking medications with a narrow therapeutic index
- Patients with a history of allergic reactions
- Patients on multiple medications (polypharmacy)
- Pregnant or breastfeeding women

Data Collection for ADR Detection

The initial step in the detection of ADRs is data collection, which should cover the following:

1) Patient Information:

- Demographics
- Presenting complaints
- Past medication history

2) Drug Therapy Details:

- ✓ Current medications, including over-the-counter medications
- ✓ Medications on admission

3) Laboratory data (e.g., hematological, liver, and renal function tests)

4) Suspected ADR Details:

- Onset and duration of the reaction
- Nature and severity of the reaction
- Drug-specific information (dose, frequency, timing, duration of therapy)

4) History of previous reactions

5) Other potential causes or predisposing factors

Evaluating Causality in Adverse Drug Reactions

Causality assessment is the method applied in evaluating the likelihood of a specific drug being the causative agent of a suspected adverse drug reaction. In the context of reporting, a temporal or potential association between the drug and the reaction is sufficient. In the case of a suspected ADR, the process of causality assessment involves Comprehensive data collection. After the data has been collected, it is reviewed to establish the degree of association between the suspected drug and the ADR.

Methods for Causality Assessment of ADRs

1) Expert Opinion/Clinical Judgment (Global Introspection Methods)

In this method, the causality is assessed based on the clinical judgment of an individual expert (such as a treating physician or clinical pharmacologist) or a group of experts.

Examples of such methods include the WHO-Uppsala Monitoring Centre (UMC) scale, Visual Analogue Scale, and the method used by the Swedish Regulatory Agency.

WHO Causality Assessment Categories:

Certain: Reaction has a plausible time relationship with drug intake, cannot be explained by other causes, shows a response on withdrawal, is pharmacologically or phenomenologically definitive, and may be confirmed by rechallenge if necessary.

Probable: Reaction has a reasonable temporal relationship, is unlikely due to other causes, improves on withdrawal, rechallenge not required.
Possible: Reaction has a reasonable time relationship but could also be explained by other factors; data on withdrawal are unclear or lacking.
Unlikely: Temporal relationship makes causation improbable; other causes plausible.
Conditional / Unclassified: Additional data needed to confirm causality.
Unassessable / Unclassifiable: Insufficient or contradictory information; cannot be verified or supplemented.

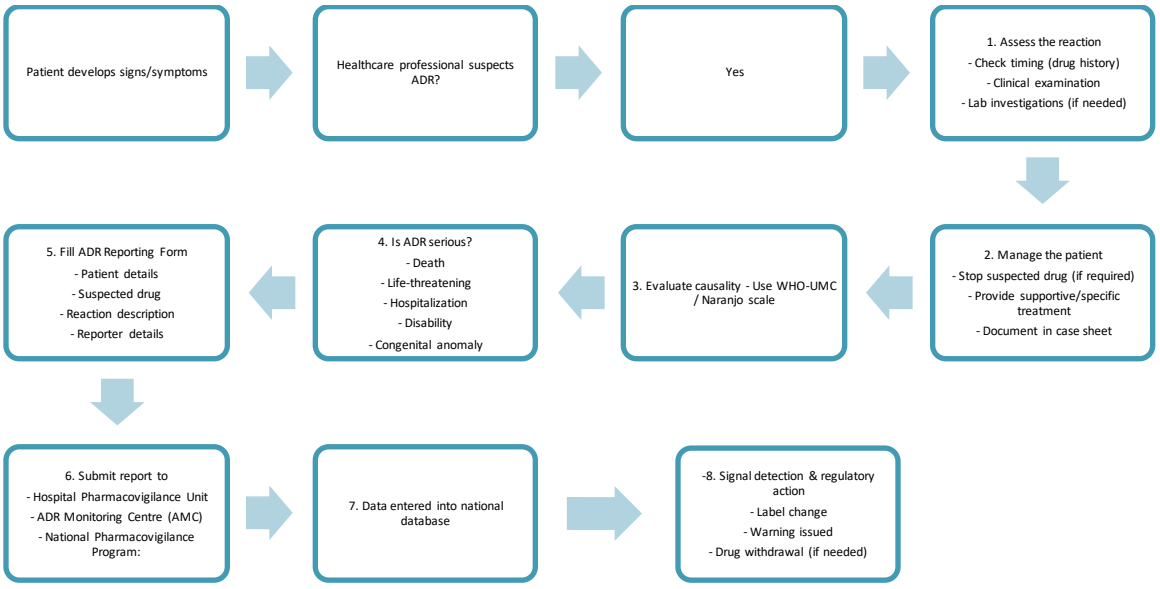
2) Algorithm-Based Methods

These methods involve the use of structured questionnaires or scoring systems to objectively assess the relationship between a drug and an ADR. The most common algorithms are the Naranjo criteria, Karch and Lasagna, Kramer's method, and the French imputation method.

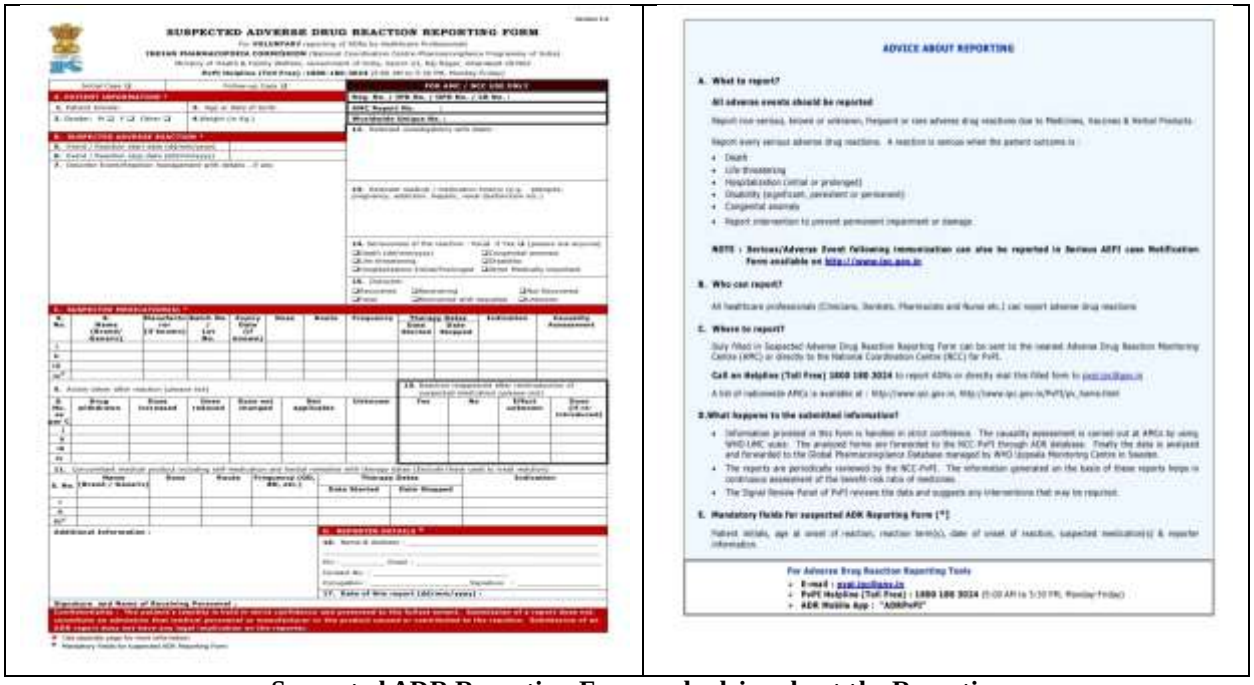
Example – Naranjo Scale: [Definite: Score ≥ 9 ,Probable: Score 5-8 ,Possible: Score 1-4 ,Unlikely: Score ≤ 0]

Sl. No.		YES	NO	DON'T KNOW
01.	Are there previous conclusive reports on this reaction?	-1	0	0
02.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0
03.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
04.	Did the adverse drug reaction reappear when the drug was re -administered?	+2	-1	0
05.	Are the alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
06.	Did the reaction re-appear when a placebo was given?	-1	+1	0
07.	Was the drug detected in blood (or other fluids) in a concentration known to be toxic?	+1	0	0
08.	Was the reaction more severe when the dose was increased, or less severe when the dose was detected?	+1	0	0
09.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10.	Was the adverse event confirmed by objective evidence?	+1	0	0

Naranjo Scale



Workflow of Adverse Drug Reaction Reporting and Signal Management



Suspected ADR Reporting Form and advice about the Reporting

Methods of Pharmacovigilance

Pharmacovigilance uses different methods to identify, assess, and prevent adverse drug reactions (ADRs). These methods can be generally categorized into passive surveillance, active surveillance, and other supportive methods.

1. Passive Surveillance

a) Spontaneous Reporting System - ADRs are reported voluntarily by healthcare professionals, patients, and pharmaceutical companies. Reports are collected in national and international databases.

Examples: Yellow Card Scheme (UK) ,MedWatch (USA) , Pharmacovigilance Programme of India

Stimulated Reporting - Stimulated reporting is a technique employed to facilitate increased reporting of adverse drug reactions (ADRs) via particular communication or awareness strategies. It is regarded as a type of improved passive surveillance.

This technique is usually employed in the following situations:

- A new safety concern has been discovered
- There is a problem of underreporting of a specific type of adverse event
- There is a need for rapid accumulation of supplementary safety information

Techniques employed in stimulated reporting include:

- Safety alerts
- Direct Healthcare Professional Communications (DHPC)
- Educational programs
- Public health alerts
- Regulatory notifications

2. Active Surveillance

a) Sentinel Sites - Selected hospitals or healthcare centers monitor and report ADRs actively.

Provides high-quality and reliable data.

b) Drug Event Monitoring - Patients are followed up after administration of a specific drug.

Example: Prescription Event Monitoring (PEM).

c) Registries - Organized systems that collect information on patients exposed to specific drugs or with specific diseases. Commonl y used for monitoring ADRs in pregnancy, cancer, and rare diseases.

3. Observational Studies

a) Cohort Studies - Compare the incidence of ADRs in exposed and unexposed populations.

Helpful in estimating incidence and relative risk.

b) Case–Control Studies - Compare drug exposure in patients with ADRs (cases) and those without ADRs (controls). Helpful in investigating rare ADRs.

c) Cross-Sectional Studies - Data collected at a single point in time.Of limited value in investigating causality.

4. Clinical Trials

Pre-marketing (Phase I-III): Common ADRs and safety assessed prior to approval.

Post-marketing (Phase IV): Rare and serious ADRs in larger populations.

International Council for Harmonisation (ICH)

- The International Council for Harmonisation (ICH) is a worldwide body that gathers representatives from the European Union (EU), United States (US), Japan, and other countries. The main aim of ICH is to establish common guidelines for the development of pharmaceuticals. This makes the drug approval process easier across different countries.
- ICH aims to achieve this by establishing common pharmacovigilance guidelines that will ensure the safety of patients and enable effective communication of adverse events and drug risks.

ICH Pharmacovigilance Guidelines

- **E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting**
    - Establishes a foundation of common terminology for adverse events and adverse drug reactions. Describes criteria for assessing serious and unexpected events and expedited reporting deadlines during clinical studies
- **E2B(R2) and E2B(R3) – Electronic Transmission of ICSRs**
    - Ensures a common format for ICSRs, including mandatory data elements, message structures, and transmission methods. E2B(R3) facilitates contemporary digital safety reporting systems for worldwide submissions.
- **E2C (E2C(R2)/PBRER) – Periodic Benefit-Risk Evaluation Reports**
    - Harmonizes the writing of long-term benefit-risk evaluation reports. Authorities rely on these reports to track potential risks and the overall safety profile of the drug after approval.
- **E2D – Post-Approval Safety Data Management: Expedited Reporting**
    - Defines the mandatory transmission requirements for MAHs for expedited post-marketing submissions and harmonizes transmission schedules for serious and unexpected adverse reactions.
- **E2E – Pharmacovigilance Planning**

  Ensures proactive safety monitoring, including:
  - Safety specification: Known risks, potential risks, and gaps in knowledge
  - Pharmacovigilance plan: Regular and supplemental PV activities, including observational studies Serves as a foundation for a Risk Management Plan (RMP).
- **E2F – Development Safety Update Reports (DSURs)**
    - Describes the preparation of annual safety reports during the development stages. Compiles all adverse events, interprets the cumulative safety information, and helps in the early identification of potential risks prior to obtaining marketing approval.
- **ICH E6(R2) Good Clinical Practice -** Ensure ethical and safe conduct of clinical trials.
- **ICH E8 (R1) – General Considerations for Clinical Studies**
- **ICH E9 – Statistical Principles for Clinical Trials**
- **ICH M1 – MedDRA Terminology**

MedDRA is an acronym that stands for **Medical Dictionary for Regulatory Activities**. It is a globally accepted medical terminology used for coding, classifying, and reporting adverse events (AEs) and other safety information in clinical trials and pharmacovigilance.

MedDRA is managed by the MedDRA Maintenance and Support Services Organization (MSSO) and is supported by ICH.

Role of MedDRA in Pharmacovigilance

Standardization: Offers a common terminology for adverse events in studies, countries, and regulatory submissions.
Data Exchange: Allows for the electronic submission of ICSRs in a globally accepted format.
Signal Detection: Helps in the analysis of safety data for the detection of new risks.
Regulatory Compliance: Mandatory for submissions to regulatory bodies such as FDA, EMA, PMDA, and other ICH countries.
Structure of MedDRA - MedDRA has a five-level hierarchical structure:

Level	Description	Example
SOC – System Organ Class	Broadest category, organ/system involved	Cardiac disorders
HLT – High Level Term	Group of related conditions	Cardiac arrhythmias
HLGT – High Level Group Term	More specific grouping of related PTs	Heart rate and rhythm disorders
PT – Preferred Term	Standard medical concept used for analysis and reporting	Atrial fibrillation
LLT – Lowest Level Term	Synonyms, clinical terms, or colloquial terms	AFib", "Atrial fibrillation

Example Flow:
LLT → PT → HLT → HLGT → SOC
"AFib" → "Atrial fibrillation" → "Cardiac arrhythmias" → "Heart rate and rhythm disorders" → "Cardiac disorders"

Individual case safety report processing work flow	**Post–Marketing safety surveillance and regulatory action – Periodic safety update report**
Adverse Event Observed ↓ Healthcare Professional / Patient Identifies Event ↓ Minimum Criteria for Valid ICSR Available? (1 identifiable patient 1 identifiable reporter 1 suspected drug 1 suspected reaction) ↓ Yes ↓ Case Documentation - Clinical details - Drug history - Lab data - Outcome ↓ Causality Assessment (WHO-UMC / Naranjo) ↓ Seriousness Assessment - Death - Life-threatening - Hospitalization - Disability - Congenital anomaly - Other medically important condition ↓ Expected or Unexpected? ↓ ICSR Coding - MedDRA coding for reaction - WHO Drug Dictionary coding ↓ Data Entry into Safety Database (Argus / VigiFlow / etc.) ↓ Quality Check & Validation ↓ Electronic Transmission (E2B format) ↓ Submission to: - National Authority - Marketing Authorization Holder (MAH) - Global database (e.g., VigiBase) ↓ Signal Detection & Regulatory Review	Marketing Authorization Granted ↓ Drug Marketed ↓ Collection of Safety Data - ICSRs (Spontaneous reports) - Clinical trial data - Literature reports - Regulatory authority reports - Global safety database ↓ Signal Detection & Evaluation ↓ Cumulative Safety Data Analysis - ADR frequency - New risks identified - Benefit–Risk evaluation ↓ Preparation of PSUR Document Sections include: - Worldwide marketing status - Actions taken for safety reasons - Changes to safety information - Exposure data - Summary of ICSRs - Signal evaluation - Risk evaluation - Benefit–Risk conclusion ↓ Internal Quality Review ↓ Submission to Regulatory Authority ↓ Regulatory Assessment ↓ Regulatory Action (if needed) - Label change - Risk minimization measures - Restriction - Suspension/withdrawal

Future Directions in Pharmacovigilance

Pharmacovigilance is undergoing a transformation from passive adverse event reporting to proactive, data-driven, and patient-centric drug safety surveillance. The future outlook in pharmacovigilance encompasses the following :

1. Artificial Intelligence & Automation

- AI-driven signal detection from extensive safety databases.
- Natural Language Processing for analysis of clinical texts and literature.
- Automation of Individual Case Safety Report submissions.
- Predictive analytics for high-risk populations.

Global databases operated under the World Health Organization and analyzed by the Uppsala Monitoring Centre are increasingly using advanced analytics.

2. Real-World Evidence

- Utilizing electronic health records (EHRs), insurance claims, and registries.
- Active surveillance systems instead of spontaneous reporting.
- Continuous benefit-risk assessment over the entire product life cycle.

Regulatory authorities such as the U.S. Food and Drug Administration and the European Medicines Agency place great emphasis on post-marketing safety surveillance.

3. Patient-Centered Pharmacovigilance

- Direct patient reporting of adverse drug reactions (ADRs).
- Use of mobile apps for reporting side effects.
- Surveillance of social media for early safety signals.
- Open communication of safety information to the public.

4. Global Harmonization

- Harmonized reporting formats (e.g., ICH guidelines).
- International exchange of safety information.
- Enhancement of pharmacovigilance systems in low- and middle-income countries.

5. Pharmacogenomics & Personalized Medicine

- Elucidation of genetic components contributing to ADRs.
- Personalized drug therapy to minimize adverse reactions.
- Precision medicine strategies in safety assessment.

6. Risk Management & Proactive Safety Planning

- Mandatory Risk Management Plans (RMPs).
- Periodic safety update reports (PSURs).
- Lifecycle approach to drug safety surveillance.

7. Digital Health & Wearable Technology

- Real-time patient data monitoring using wearables.
- Remote safety monitoring in clinical trials.
- Biometric integration with digital health.

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