UNIT 2 (Pharmacology-I)

❖ Pharmacodynamics: Principles and Mechanisms of Drug Action

◇ 1. What is Pharmacodynamics?

Pharmacodynamics (PD) is the branch of pharmacology that studies the **biological and physiological effects of drugs**, and their **mechanisms of action**. In simpler terms, it means:

"**What the drug does to the body**."

It answers:

- How does the drug work?
- Where does it act in the body?
- What effects does it produce?
- How strong and long-lasting are these effects?

◇ 2. Components of Pharmacodynamics

🏵 2.1. Drug-Receptor Interactions

Most drugs act by binding to specific **macromolecules** in the body called **receptors**.

- **Receptor**: A biological molecule (usually a protein) on the surface or inside a cell that responds to a specific drug (ligand).
- When a drug binds to its receptor, it can **activate or inhibit** the receptor's normal function.

📌 Example:

- **Salbutamol** binds to β_2-receptors in bronchial muscles → relaxes airways → helps in asthma.

◇ 3. Types of Drug-Receptor Interactions

➤ Agonist

- Binds to the receptor and **activates** it.
- Mimics the action of natural substances (like hormones or neurotransmitters).

💊 Example: Adrenaline (agonist at β-receptors)

➤ Antagonist

- Binds to the receptor but **does not activate** it.

- It **blocks** the receptor so that natural agonists or other drugs cannot activate it.

💊 Example: Propranolol (β-blocker)

➤ **Partial Agonist**

- Binds and activates the receptor but produces a **weaker response** than a full agonist.

💊 Example: Buprenorphine (partial opioid agonist)

➤ **Inverse Agonist**

- Binds to the receptor and produces an effect **opposite to that of an agonist**.

💊 Example: Rimonabant (CB1 inverse agonist)

◇ 4. Mechanisms of Drug Action

Drugs act by interacting with different targets in the body:

🌀 4.1. Receptor-Mediated Action

◇ Types of Receptors:

Type	Location	Example
Ion Channel-Linked Receptors	Cell membrane	Nicotinic ACh receptor
G-Protein Coupled Receptors (GPCRs)	Cell membrane	β-adrenergic receptor
Enzyme-Linked Receptors	Cell membrane	Insulin receptor
Intracellular (Nuclear) Receptors	Cytoplasm/Nucleus	Steroid hormone receptor

🛍 Examples:

- Acetylcholine activates nicotinic receptors → muscle contraction
- Adrenaline activates β-receptors → increases heart rate

🏵 4.2. Enzyme Inhibition

Some drugs work by **inhibiting enzymes**, thus stopping chemical reactions in the body.

🛍 Examples:

- Aspirin → Inhibits COX enzyme → anti-inflammatory
- Neostigmine → Inhibits acetylcholinesterase → used in myasthenia gravis

🚺 4.3. Ion Channel Modulation

Drugs can **open or block ion channels** in cell membranes.

Examples:

- Local anaesthetics (lidocaine) block Na^+ channels → prevents nerve impulses
- Benzodiazepines enhance Cl^- entry via GABA-A receptor → sedative effect

4.4. Transporter Blockade

Some drugs block **transport proteins** that carry substances across cell membranes.

Examples:

- SSRIs (e.g., fluoxetine) block serotonin reuptake → antidepressant
- Digoxin inhibits Na^+/K^+ ATPase pump → increases cardiac output

4.5. Non-Specific Drug Actions

Some drugs act **without binding to receptors**.

Examples:

- Antacids: Neutralize HCl in the stomach directly
- Osmotic diuretics: Increase osmotic pressure in kidneys → promote urine formation

5. Dose-Response Relationship

This describes **how the body's response changes with increasing doses** of a drug.

Types of Dose-Response Curves

➤ Graded Dose-Response Curve

- Shows the **magnitude** of response in a single individual.
- X-axis = Dose; Y-axis = Response

➤ Quantal Dose-Response Curve

- Shows the **number of individuals** who show a specific response at different doses.

6. Potency and Efficacy

Property	Meaning	Example
Potency	Amount of drug needed for an effect	Morphine is more potent than codeine
Efficacy	Maximum effect a drug can produce	Morphine has higher efficacy than aspirin

A drug can be **highly potent** but **low in efficacy**, and vice versa.

7. Therapeutic Index (TI)

Measures **drug safety**:

TI=LD50ED50\text {TI} = \frac {\text {LD}_{50}}{\text {ED}_{50}}TI=ED50LD50

- **LD_{50}** = Lethal Dose for 50% of population
- **ED_{50}** = Effective Dose for 50% of population

A **higher TI** means a **safer drug**.

◇ 8. Factors Affecting Drug Action

Factor	Description
Age	Children and elderly are more sensitive
Body weight	Dosage often based on kg body weight
Genetic factors	Genetic makeup can affect drug metabolism
Disease conditions	Liver/kidney disease alters drug effect
Tolerance	Decreased response over time
Drug interactions	One drug may increase or reduce the effect of another

◇ 9. Receptor Regulation

▼ Downregulation

- Continuous stimulation → fewer receptors
- Leads to **decreased drug response** (tolerance)

▲ Upregulation

- Continuous blockade → more receptors
- Leads to **increased sensitivity** (withdrawal effects)

✸ 1. What Are Receptors?

Receptors are **special proteins** present on or inside our cells that **recognize and bind to drugs or natural substances** (like hormones or neurotransmitters).
When a drug binds to a receptor, it **starts a chain reaction** that causes a **biological effect** — like lowering blood pressure, reducing pain, or increasing heart rate.

❑ 2. Receptor Theories

Receptor theories help explain **how drugs interact with receptors** to produce effects. Let's understand the main ones in simple words:

2.1 Occupancy Theory (Clark's Theory)

- **Proposed by:** A.J. Clark
- **Idea:** The more receptors a drug occupies, the stronger the response.
- **Key Point:** Maximum effect is produced when all receptors are occupied.

🔍 *Example:* A full dose of a painkiller binds to all pain receptors and gives complete relief.

2.2 Rate Theory

- **Proposed by:** Paton
- **Idea:** Drug response depends on **how fast** the drug binds and unbinds from the receptor.
- **Key Point:** It's not just occupancy, but the **rate of interaction** that matters.

🔍 *Example:* A drug that binds and unbinds quickly may give a strong and quick response.

2.3 Two-State Theory

- Receptors exist in **two forms**: Active (R*) and Inactive (R).
- **Agonist drugs** push the receptor to the **active form** → gives a biological effect.
- **Antagonists** just block the receptor → no effect.

🔍 *Example:* Salbutamol activates β2-receptors in the lungs (R*) → opens airways.

2.4 Induced Fit Theory

- Receptor changes its shape slightly when a drug binds.
- This **"fit" activates** the receptor like a key turning in a lock.

🔍 *Example:* Like an enzyme changing shape to work better when a drug binds.

2.5 Macromolecular Perturbation Theory

- Drugs cause **disturbances (perturbations)** in the receptor structure:
    - *Specific perturbation* → desired effect.
    - *Nonspecific perturbation* → may cause side effects.

🔧 3. Classification of Receptors

Receptors are classified based on **location, function, and structure**.

A. Based on Location:

1. **Cell Surface Receptors**
    - Found on the **cell membrane**
    - Bind to water-soluble drugs (e.g., adrenaline)
2. **Intracellular Receptors**
    - Found **inside** the cell (nucleus or cytoplasm)
    - Bind to lipid-soluble drugs (e.g., steroid hormones)

B. Based on Function or Signal Mechanism:

Type of Receptor	Examples	Function/Mechanism
Ion Channel-linked (Ligand-gated)	GABA, Nicotinic receptors	Drug binds → opens channel → ions move
G-protein coupled (GPCR)	β-adrenergic, Muscarinic	Drug binds → activates G-protein → cascade
Enzyme-linked receptors	Insulin, Growth factor	Drug binds → activates enzyme → cell response
Nuclear receptors	Estrogen, Thyroid	Drug enters cell → binds to DNA → protein made

C. Based on Drug Type or Ligand:

1. **Cholinergic Receptors**
    - Bind to **acetylcholine**
    - Types: **Nicotinic** and **Muscarinic**
2. **Adrenergic Receptors**
    - Bind to **adrenaline/noradrenaline**
    - Types: **Alpha (α1, α2)** and **Beta (β1, β2, β3)**
3. **Dopaminergic Receptors**
    - Bind to **dopamine**
    - Types: D1, D2, D3, etc.

🔄 4. Regulation of Receptors

Receptors are not always fixed — the body **adjusts their number or activity**. This is called **receptor regulation**.

A. Upregulation

- **Increase in receptor number** or sensitivity
- Happens when receptors are **under-stimulated**
- The body adds more receptors to "catch" the missing signal

🔍 *Example:* In Parkinson's disease, low dopamine → brain increases dopamine receptors

B. Downregulation

- **Decrease in receptor number** or sensitivity
- Happens when receptors are **over-stimulated**
- The body removes receptors to avoid overstimulation

🔍 *Example:* Repeated use of decongestant nasal sprays → nose becomes less responsive

C. Desensitization or Tolerance

- After constant exposure to a drug, receptors become **less responsive**
- Seen with **long-term drug use**

🔍 *Example:* Needing more morphine over time for the same pain relief.

✸ 1. Drug-Receptor Interactions

◇ What is a Receptor?

A receptor is a **protein molecule** found either on the **cell membrane** or **inside a cell**. Drugs bind to receptors to **produce effects** in the body.

◇ What is a Ligand?

A **ligand** is any molecule that binds to a receptor. It can be:

- A **drug** (e.g., morphine)
- A **hormone** (e.g., adrenaline)
- A **neurotransmitter** (e.g., acetylcholine)

◇ Types of Ligand-Receptor Interactions:

1. **Agonist**: Activates the receptor and produces a response
   → Example: Salbutamol (agonist at β2-receptors) → opens airways in asthma
2. **Antagonist**: Binds to receptor but **blocks** the effect
   → Example: Propranolol blocks β-receptors → lowers blood pressure

3. **Partial Agonist**: Produces **weaker effect** than full agonist
   → Example: Buprenorphine (used in opioid addiction)
4. **Inverse Agonist**: Produces effect opposite to agonist
   → Example: Rimonabant (CB1 inverse agonist)

✸ 2. Signal Transduction Mechanisms

Once a drug binds to a receptor, it triggers a chain of events called **signal transduction**. This process converts the **extracellular signal** (drug binding) into an **intracellular action** (response).

◇ A. G-Protein Coupled Receptors (GPCRs)

🧬 **Structure**: 7 transmembrane helices
🎯 **Function**: Activates G-protein → affects enzymes/ions inside the cell

Steps:

1. Drug (agonist) binds to receptor.
2. G-protein is activated (GTP replaces GDP).
3. Activated G-protein interacts with **enzymes** like adenylate cyclase or **ion channels**.
4. Second messengers like **cAMP**, **IP3**, **DAG** are generated.
5. These second messengers produce the final cellular response.

📌 **Example**:
Adrenaline → β2 receptor → activates adenylate cyclase → ↑ cAMP → bronchial dilation

◇ B. Ion Channel-Linked Receptors

🧬 **Structure**: A central pore/channel
🎯 **Function**: Opens or closes in response to ligand → changes ion flow

Steps:

1. Drug binds to receptor.
2. Channel opens → ions like Na^+, K^+, Ca^{2+} flow in/out.
3. This changes the electrical potential and triggers a response.

📌 **Example**:
Nicotine → nicotinic receptor → opens Na^+ channel → nerve signal transmission

◇ C. Transmembrane Enzyme-Linked Receptors

🧬 **Structure**: Extracellular domain (binds ligand) + intracellular **enzyme (usually tyrosine kinase)**

🎯 **Function**: Ligand binding → enzyme activation → phosphorylation of proteins → response

Steps:

1. Drug binds to receptor.
2. Receptor dimerizes (forms pairs).
3. Activates tyrosine kinase.
4. Phosphorylates proteins → triggers response.

📌 **Example**:
Insulin → insulin receptor → activates tyrosine kinase → promotes glucose uptake

◇ D. JAK-STAT Pathway (Cytokine Receptors)

🧬 **Structure**: Receptor with **no enzyme activity**, but binds **JAK (Janus Kinase)**
🎯 **Function**: Activates **STAT proteins** → go to nucleus → gene expression

Steps:

1. Drug (cytokine) binds to receptor.
2. JAK is activated → phosphorylates receptor.
3. STAT binds → gets phosphorylated.
4. STAT dimerizes → enters nucleus → changes gene expression.

📌 **Example**:
Erythropoietin → EPO receptor → activates JAK-STAT → increases RBC production

◇ E. Receptors Regulating Transcription Factors (Nuclear Receptors)

🧬 **Location**: Inside the **cell** (nucleus or cytoplasm)
🎯 **Function**: Drug binds → receptor-ligand complex binds to DNA → changes gene expression

Steps:

1. Lipid-soluble drug enters cell.
2. Binds to receptor inside the nucleus.
3. Receptor binds to DNA.
4. Promotes or inhibits transcription of specific genes.

📌 **Example**:
Corticosteroids → glucocorticoid receptor → suppress inflammation genes

3. Dose-Response Relationship

This explains how the **drug effect** changes with different **doses**.

◇ **Types:**

1. **Graded Dose-Response Curve** (single person)
    - Shows **magnitude** of effect ↑ with dose
    - Example: more paracetamol → more fever reduction (up to a point)
2. **Quantal Dose-Response Curve** (population)
    - Shows **% of people** who respond to a dose
    - Example: % of patients who get pain relief with 500 mg vs 1000 mg

◇ **Terms:**

- **ED50**: Dose producing effect in 50% of population
- **LD50**: Dose causing death in 50% of animals (preclinical)
- **Emax**: Maximum possible effect of a drug
- **Potency**: How much drug is needed to produce effect
  → Lower dose = more potent
- **Efficacy**: Maximum effect a drug can produce
  → More important than potency clinically

4. Therapeutic Index (TI)

TI = LD50 / ED50

- Measures **safety** of a drug
- **Higher TI = safer drug**
- **Narrow TI drugs** need careful monitoring
  → Example: Digoxin, Warfarin

Example:
Drug A: TI = 10 → safe
Drug B: TI = 2 → risky

5. Combined Effects of Drugs

When two or more drugs are taken together:

◇ **Types:**

1. **Additive**: A + B = A+B
   → Example: Paracetamol + Ibuprofen for better pain relief
2. **Synergistic**: A + B > A+B
   → Example: Sulfamethoxazole + Trimethoprim → stronger bacterial killing
3. **Antagonism**: A + B < A or B
   → Example: Naloxone blocks morphine → used in overdose

6. Factors Modifying Drug Action

A. Body-related factors:

1. **Age**:
   - Newborns → immature liver/kidney
   - Elderly → reduced organ function
     → Lower dose needed
2. **Weight**:
   - Dosage adjusted per kg body weight
3. **Genetics**:
   - Fast/slow metabolizers
4. **Disease states**:
   - Liver/kidney disease → drug accumulation
5. **Tolerance**:
   - Repeated use ↓ response
     → Example: Morphine
6. **Tachyphylaxis**:
   - Very rapid tolerance
     → Example: Ephedrine nasal spray

B. Drug-related factors:

1. **Route of administration**
   → IV acts faster than oral
2. **Dose & Frequency**
   → More frequent doses may cause toxicity
3. **Formulation**
   → Sustained-release tablets act longer

❖ Adverse Drug Reactions (ADRs)

1. What are Adverse Drug Reactions?

An **Adverse Drug Reaction (ADR)** is an **undesirable, harmful, or unexpected effect** caused by a drug that occurs at normal doses used for treatment, diagnosis, or prevention of diseases.

Key points:

- ADRs happen even when the drug is taken correctly.
- They are different from overdose effects or poisoning.
- ADRs can affect any organ or system in the body.
- They range from mild discomfort to life-threatening conditions.

2. Importance of Studying ADRs

- ADRs can increase hospital stays and healthcare costs.
- They can cause serious illness or death.
- Understanding ADRs helps pharmacists and doctors minimize risks.
- Proper knowledge improves patient safety and drug therapy success.

3. Mechanism of ADRs

How do ADRs occur? There are multiple mechanisms:

- **Pharmacological:** Excessive action of the drug on its target receptor (e.g., excessive sedation with benzodiazepines).
- **Hypersensitivity (Allergic) reactions:** Immune system mistakenly attacks drug or its metabolites (e.g., penicillin allergy).
- **Toxic metabolites:** Some drugs are converted into harmful substances in the body (e.g., paracetamol overdose causes toxic metabolites leading to liver damage).
- **Idiosyncratic reactions:** Genetic or unknown reasons cause unusual responses.
- **Drug interactions:** One drug alters the effect of another, increasing toxicity or reducing efficacy.

4. Detailed Classification of ADRs

Beyond ABCDE, ADRs can be classified as:

Type A (Augmented):

- Dose-dependent.
- Predictable from drug's known actions.

- Usually mild, reversible.
- Most common type (about 80% of ADRs).

Example:
Hypoglycaemia from excess insulin.

Type B (Bizarre):

- Not dose-dependent.
- Unpredictable and rare.
- Often immunologic or genetic.
- More serious.

Example:
Anaphylaxis from penicillin.

Type C (Chronic):

- Caused by prolonged treatment.
- Dose and time-related.

Example:
Osteoporosis from long-term corticosteroids.

Type D (Delayed):

- Effects appear after drug exposure, even long after stopping.

Example:
Carcinogenesis from chemotherapy agents.

Type E (End-of-use or withdrawal):

- Withdrawal symptoms after stopping drug suddenly.

Example:
Opioid withdrawal causing agitation and pain.

Type F (Failure):

- Unexpected failure of therapy.

Example:
Antibiotic resistance leading to treatment failure.

5. Examples of ADRs in Common Drug Classes

Drug Class	ADR	Explanation
NSAIDs (e.g., aspirin)	Gastric ulcers and bleeding	Inhibit protective prostaglandins in stomach
Antibiotics (penicillin)	Allergic reactions	Immune-mediated hypersensitivity
Chemotherapy agents	Bone marrow suppression	Toxic to rapidly dividing cells
Opioids	Respiratory depression, constipation	Acts on CNS to reduce breathing, slows gut motility
Antidepressants (SSRIs)	Sexual dysfunction, nausea	Alter neurotransmitter levels
Diuretics	Electrolyte imbalance	Increased excretion of sodium, potassium

6. Factors Influencing ADRs

- **Age:** Infants and elderly have altered metabolism.
- **Genetics:** Some people lack enzymes to metabolize drugs properly.
- **Disease conditions:** Liver or kidney impairment slows drug clearance.
- **Drug interactions:** Combining drugs can increase ADR risk.
- **Pregnancy:** Drugs can cause harm to fetus.
- **Dose and duration:** Higher dose and longer use increase risk.

7. Clinical Manifestations of ADRs

ADRs may affect different systems:

- **Skin:** Rash, itching, Stevens-Johnson syndrome.
- **Gastrointestinal:** Nausea, vomiting, diarrhea.
- **Hematologic:** Anemia, thrombocytopenia.
- **Neurological:** Dizziness, seizures.
- **Respiratory:** Bronchospasm, pulmonary fibrosis.
- **Cardiovascular:** Arrhythmia, hypotension.
- **Hepatic:** Liver injury or jaundice.
- **Renal:** Kidney damage or failure.

8. Diagnosis of ADRs

- Patient history and drug exposure timeline.
- Symptoms correlation with drug use.
- Laboratory tests (liver enzymes, blood counts).
- Rechallenge test (carefully done) to confirm ADR.
- Use of causality assessment scales like WHO-UMC or Naranjo algorithm.

9. Pharmacovigilance

- Monitoring and reporting ADRs is essential.
- Helps identify new ADRs and improve drug safety.
- Health professionals should report all suspected ADRs.
- Patient education encourages early reporting of symptoms.

10. Prevention of ADRs

- Proper prescribing: correct drug, dose, and duration.
- Patient education about possible side effects.
- Regular monitoring of patients on high-risk drugs.
- Avoid unnecessary polypharmacy.
- Adjust dose in renal/liver impaired patients.
- Screen for allergies and genetic risk factors.

11. Management of ADRs

- Stop or replace the offending drug.
- Treat symptoms (e.g., antihistamines for allergy).
- Provide supportive care (fluids, oxygen).
- Use antidotes if available (e.g., vitamin K for warfarin overdose).
- Hospitalization in severe cases.
- Report to pharmacovigilance centers.

❖ Drug Interactions

When two or more drugs are taken together, they can influence each other's action. These influences are called **drug interactions**, and they can either increase or decrease the effect or side effects of the drugs.

There are two main types of drug interactions:

1. Pharmacokinetic Drug Interactions

Pharmacokinetics deals with what the body does to the drug — how the drug moves through the body after administration.

Pharmacokinetic interactions happen when one drug changes the **absorption, distribution, metabolism, or excretion** of another drug, thus altering its concentration in the blood or tissues.

A) Absorption Interactions

This happens mainly in the gut, where drugs are absorbed into the bloodstream.

- **Example 1: Change in stomach pH**
    - Some drugs need an acidic environment to dissolve well (like ketoconazole).
    - If another drug (like antacids or proton pump inhibitors) raises the stomach pH (makes it less acidic), the first drug will not dissolve properly, so less drug is absorbed → reduced effect.
- **Example 2: Formation of complexes**
    - Some drugs can bind with minerals or other drugs forming insoluble complexes.
    - Example: Tetracycline antibiotics bind with calcium (in dairy products), making both less absorbable.

B) Distribution Interactions

After absorption, drugs circulate in the blood, often bound to plasma proteins (like albumin). Only unbound (free) drug is active.

- **Example:** If Drug A displaces Drug B from protein binding sites, more free Drug B is available, increasing its effect and risk of toxicity.

C) Metabolism Interactions

Most drug metabolism occurs in the liver, primarily by enzymes called **cytochrome P450 enzymes (CYP450)**.

- **Induction:** Drug A increases the activity of liver enzymes, causing faster breakdown of Drug B → less Drug B available → reduced effect.

- Example: Rifampicin (an antibiotic) induces CYP enzymes → lowers levels of oral contraceptives → risk of pregnancy.

- **Inhibition:** Drug A inhibits liver enzymes, slowing down metabolism of Drug B → higher Drug B levels → increased effect or toxicity.
  - Example: Grapefruit juice inhibits CYP3A4 → increases levels of some statins → risk of muscle damage.

D) Excretion Interactions

Drugs are removed from the body mainly by the kidneys through filtration, secretion, and reabsorption.

- **Example:** Probenecid blocks renal secretion of penicillin → penicillin stays longer in the body → increased levels and effect.

2. Pharmacodynamic Drug Interactions

Pharmacodynamics deals with what the drug does to the body — its effects and mechanism of action.

Pharmacodynamic interactions happen when two drugs affect the same receptor or physiological system, either increasing or decreasing each other's effects.

Types of Pharmacodynamic Interactions

A) Additive Effect

Two drugs with similar effects combine to produce a total effect equal to the sum of their individual effects.

- **Example:** Two sedatives (like benzodiazepines and alcohol) both depress the central nervous system (CNS). Taken together, the sedation effect is stronger.

B) Synergistic Effect (Potentiation)

The combined effect of two drugs is greater than the sum of their separate effects.

- **Example:** The combination of sulphonamides and trimethoprim antibiotics causes a much stronger antibacterial effect than either drug alone.

C) Antagonistic Effect

One drug reduces or blocks the effect of another.

- **Example:** Naloxone blocks the effect of opioids by competing for the same receptors → reverses opioid overdose.

Summary of Key Points

Type	What Happens?	Examples
Pharmacokinetic	One drug changes absorption, distribution, metabolism, or excretion of another drug	Rifampicin reduces effect of oral contraceptives (enzyme induction)
Pharmacodynamic	Drugs interact at the same target or system to increase or decrease effects	Benzodiazepines + alcohol cause stronger sedation (additive)

Why are drug interactions important?

- They can make a drug less effective.
- They can increase side effects or toxicity.
- They may require dose adjustment or avoiding certain drug combinations.
- Important to always inform your doctor about all medications you are taking (including herbal or OTC drugs).

❖ Drug Discovery Phase

- **What is it?**
  This is the very first step where scientists try to find a new drug that can treat a disease.
- **How does it happen?**
  - **Target identification:** Researchers find a biological target (like a protein or enzyme) related to the disease.
  - **Drug design:** They design or find chemical compounds that might affect the target and help cure or control the disease.
  - **Screening:** Many compounds are tested in the lab to see if they work on the target.
  - **Lead compound:** The most promising compound (lead) is chosen for further development.
- **Goal:** Find a safe and effective drug candidate to test in animals and humans.

2. Preclinical Evaluation Phase

- **What is it?**
  Testing the lead compound in the lab and animals before giving it to humans.

- **Purpose:**
  To check if the drug is **safe** and **effective** enough to move to human trials.
- **Tests done:**
  - **Pharmacodynamics:** How the drug works in the body.
  - **Pharmacokinetics:** How the drug is absorbed, distributed, metabolized, and eliminated.
  - **Toxicity studies:** Check for harmful effects on organs, reproduction, or if it causes mutations or cancer.
- **Outcome:**
  If the drug passes these tests, it gets approval to be tested in humans (clinical trials).

3. Clinical Trial Phase

- **What is it?**
  Testing the drug in **humans** to confirm safety and effectiveness.
- **How is it done?**
  Through **clinical trials**, which are carefully designed studies involving volunteers or patients.
- **Phases of Clinical Trials:**

Phase 1:

- Number of subjects: 20-100 healthy volunteers
- Purpose: Check **safety**, dosage, how the drug is absorbed and processed.
- Duration: Few months.

Phase 2:

- Number of subjects: 100-300 patients who have the disease
- Purpose: Test **effectiveness** and continue safety monitoring.
- Duration: Several months to 2 years.

Phase 3:

- Number of subjects: 1,000-3,000 patients
- Purpose: Confirm **effectiveness**, monitor side effects, compare with standard treatments.
- Duration: 1-4 years.
- If successful, the company can apply for drug approval.

Phase 4 (Post-Marketing Surveillance):

- Done after the drug is approved and marketed.
- Purpose: Monitor long-term safety and effectiveness in the general population.

4. Pharmacovigilance

- **What is it?**
  The science of **monitoring, detecting, and preventing adverse effects** (side effects) of drugs after they are on the market.
- **Why important?**
  Some rare or long-term side effects may only appear when many people use the drug over a long time.
- **Activities include:**
  - Collecting reports of adverse drug reactions (ADRs).
  - Investigating and assessing risks.
  - Taking action to ensure patient safety (like updating drug labels, restricting use, or withdrawing a drug).