Drug Discovery:-

- It is the programmed process by which drugs are discovered and/or design.
- It is an intense, lengthy process. Therefore, to bring a drug from discovery to the market, a pharmaceutical company requires approximately 10-15 years and up to 600-800 million dollars.

Aim of Drug Discovery:-

1. To develop effective & more safer drugs.
2. To develop economical drugs.
3. To discover new uses of already established drugs.
4. To determine the mechanism of drug action.

New Drug Discovery & Development (Overview)

Major stages in the discovery & development of New drug are:

I. New Drug Discovery

1. Target Identification & Validation.
2. High throughput Screening (HTS) of Compounds.
3. Identification of Hit
4. Lead Generation & Optimization.

II. Drug Development

5. Preclinical Studies.
6. Investigational New Drug (IND) Application - FDA Review
7. Clinical Trials:
   Phase I, II & III Studies
8. New Drug Application (NDA) - FDA Review
9. Post Marketing Surveillance
   Phase IV Studies

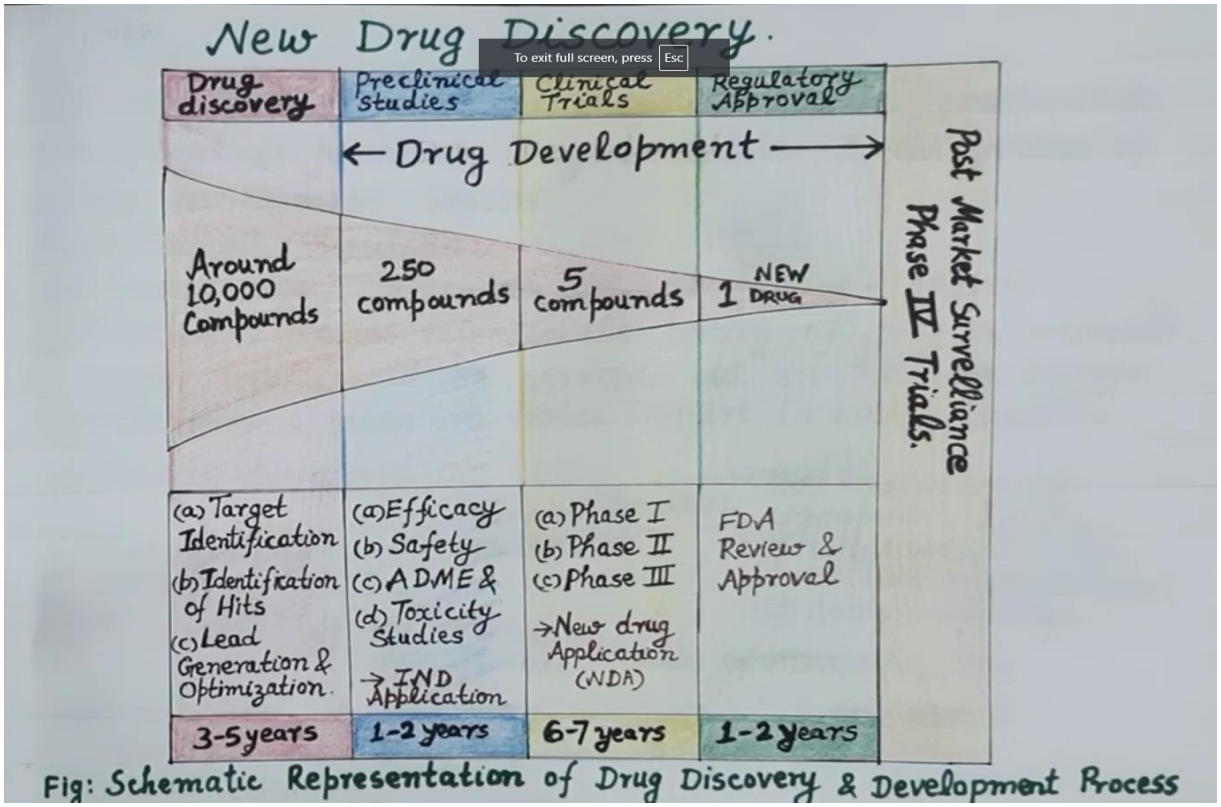


Fig: Schematic Representation of Drug Discovery & Development Process

New Drug Discovery.

1. Target Identification & Validation.

In Vitro Research is performed to identify & isolate Molecular Target involved in Specific Disease.

(a) Target could be a Gene or Protein.

→ For identifying Gene, Sequencing of DNA is studied.

→ Target protein could be: G-protein coupled Receptors, Enzymes, Hormones, Ion Channels, Nuclear Receptors etc.

(b) Individual target is identified & isolated.

(c) Target should be druggable.

Target Validation:

(a) Reconfirmation on Identification of Correct target.

(b) Exclusion of wrong target.

Drug Discovery:

2. Compound Screening (Around 10,000 Compounds):
Thousands of potentially Active Compounds are Screened.
These compounds are: (i) Natural Compounds.
(ii) Synthesized in laboratory.
(iii) Obtained by Genetic Engineering.

Method: **High throughput Screening (HTS)**
HTS uses Robotics, Data processing Control Software, liquid handling devices & sensitive detectors to Rapidly conduct millions of Pharmacological, Chemical & Genetic Test.
More than 50,000 compounds can be screened in a day.

3. Identification of HITS:
(a) Unfavourable compounds are rejected by HTS.
(b) Best 100-200 HITS are selected.
(c) HIT is a comp. that exhibits specific activity at the target.

4. Lead Generation & Optimization / Refinement:
HITS are further screened by target Selectivity Assay, in Vitro efficacy Assay, in vitro ADME & physical chemistry Assays.
From 100-200 HITS dozens of leads are selected.
a) A lead is a chemical compound that is more selective to target, more potent & with good SAR & ADME profile.
b) Lead Optimization involves modification of lead molecules to improve potency & reduce side effects.
c) Leads are used as templates for designing around 250 compounds through Chemical Modification, This marks the end of drug discovery process & the process of Drug Development Begins.

Preclinical Evaluation Phase

Testing of potential drug candidates in Animals.

→ Provide information on Safety & Efficacy of potential drug candidates before they could be tested in human beings.
→ Must comply with the guidelines of Good Laboratory Practice.
→ Highly Valuable in determining Safe dose & dose Range
→ Around 250 optimized lead compounds are tested.

Experimental Methodology

In Silico, In Vitro & In Vivo Experimental Models

1. In Silico Experimental Model:

(a) Based on Computer Simulation.
(b) Often precede or Complement In Vitro & In Vivo Studies.
(c) Provide information on Investigational New Drug behaviour used in subsequent In Vitro & In Vivo Experiments.

In Vitro Model

Studying the Investigational Drugs in a Petridish

(a) The Models use cells, tissues, organ cultures, cell components.

(b) Provide information on mode of action of Investigational Drug Molecules.

In Vivo Model

Studies are done on Intact Complete Animal.

(a) Studies are performed in two species.

(i) Rodents eg. Mouse, Rat, Guinea Pig, Rabbits &

(ii) Non rodents eg. Dog, Non human Primate like Monkey, Apes.

(b) Mostly Mouse & Dog are used.

(c) Oral & Parenteral Routes are tested.

In Vivo Preclinical Studies Include:

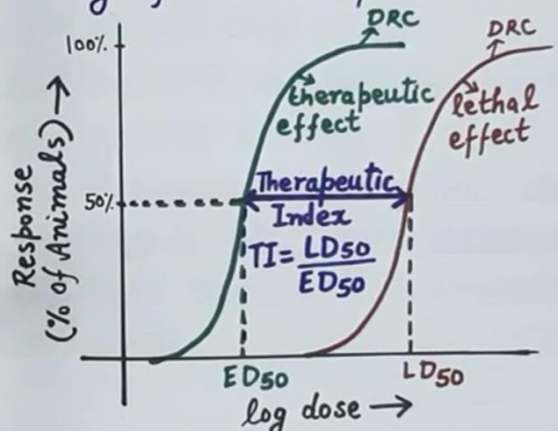
(1) Animal Pharmacological Studies

(a) Pharmacokinetic Studies:

→ ADME profile of drug, V_d, $t_{1/2}$ are determined.

(b) Pharmacodynamic Studies:

Study of Dose Response Relationship



(i) In Experimental Animals:

$$\text{Pharmacological Therapeutic Index} = \frac{LD_{50}}{ED_{50}}$$

(ii) Maximum Efficacy, Safety of Investigational drug molecules are evaluated. Mechanism of Action is also elucidated.

2. Toxicological Studies in Animals:

Aims to determine Safe dose & dose range of drug.

These are of three types: (a) Acute
(b) Subacute
(c) Chronic

(a) Acute Toxicity Studies:

(i) **Single Dose Studies**: Investigational drug is administered in a single dose, usually Mouse & Dog. Animal is observed for 1 to 3 days.

(ii) **Dose is Escalated**: In next animal dose is increased.

(iii) Signs of toxicity & death are observed.

(iv) **Maximum tolerated dose is determined.**

(v) **ED_{50} & LD_{50} are determined.**

(vi) Organ toxicity is examined by histopathology of all animals.

(b) Subacute Toxicity Studies:

(i) Doses are Selected on the basis of ED_{50} & LD_{50}.
(ii) Investigational drug is given by Clinical Route
(iii) Repeated doses are given for 2 to 12 weeks.
(iv) Animals are examined for Overt effects, food intake, body weight, haematology etc & Organ toxicity.

(c) Chronic Toxicity Studies:

(i) Similar to Acute Toxicity Studies.
(ii) Investigational drug is given for 6-12 months.

Main Goal of toxicity Studies is to determine safe dose & dosage Range.

Reproduction & Teratogenicity Studies:

→ Effects are studied on Spermatogenesis, Ovulation, fertility & developing foetus.

Mutagenicity Studies:

→ Ability of drug to induce genetic damage is studied in Bacteria, Mammalian Cell Cultures & Rodants.

Carcinogenicity Studies:

→ Drug is given from years to whole life of Animal & animal is Studied for development of tumors.

Phases of Clinical Trial

Pharmacology	Exploratory	Confirmatory	Post Marketing

Success rates:

Approximately 70% → Approximately 33% → Approximately 25-30% → Approximately 70-90%

PHASE 0

- Considerably a new idea from the US Food and Drug Administration.
- It is also known as human micro dosing study.
- Have single sub-therapeutic dose.
- Small number of subjects are needed around (10 to 15).
- Provides preliminary data on the drugs Pharmacokinetics and Pharmacodyn[illegible]s.

PHASE I

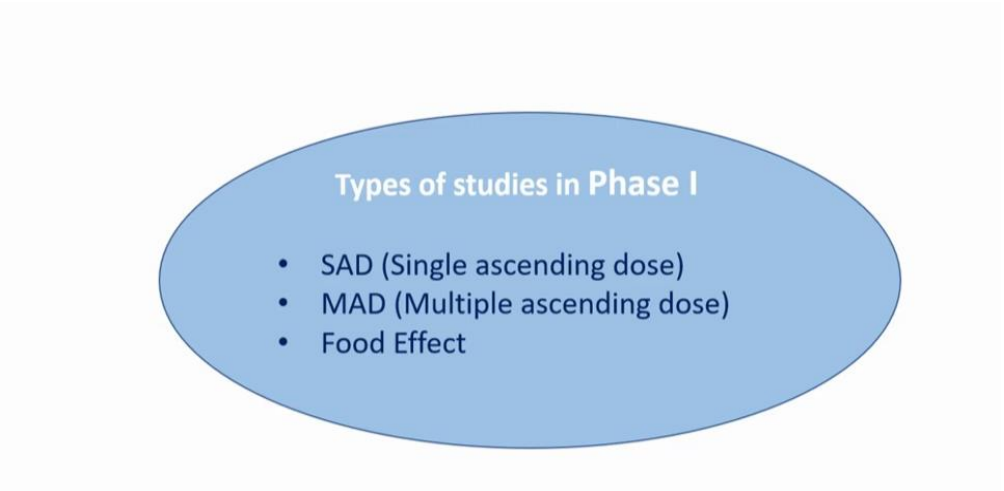
- **Study Participants**: 20 to 100 healthy volunteers or with the disease/condition.
- **Length of the study:** Up to several months.
- **Purpose:** Determine safety and dosage.

Safety (pharmacovigilance)
Safe dosage range
Identify side effects
Tolerability
Pharmacokinetics
Pharmacodynamics
Route of administration

PHASE I

Pharmacokinetics
What the body does to a drug?
A- Absorption
D- Distribution
M- Metabolism
E- Excretion

Pharmacodynamics
What a drug does to the body?
- Receptor binding
- Post receptor effects
- Chemical interactions.



Single Ascending Dose (SAD)

- Small group of subjects given single dose of drug and observed for a period.
- If PK data is in line with predicted safe values, the dose is increased in a new group of subjects
- Dose escalation is continued till Maximum Tolerated Dose (MTD) is reached.

Single Ascending Dose (SAD)					
Subject Cohort	Week 1	Week 2	Week 3	Week 4	Week 5
Cohort 1	05 mg				
Cohort 2		10 mg			
Cohort 3			20 mg		
Cohort 4				50 mg	
Cohort 5					100 mg

Multiple Ascending dose

- A group of subjects receives multiple low doses of drug and observed for a period.
- Samples of blood and other body fluids are collected at various time points and analyzed.
- Gives better understanding of pharmacokinetics and pharmacodynamics of the drug .

Multiple Ascending Dose (MAD)					
Subject Cohort	Week 1	Week 2	Week 3	Week 4	Week 5
Cohort 1	20 mg	40 mg	60 mg	80 mg	100 mg
Cohort 2	40 mg	60 mg	80 mg	100 mg	120 mg
Cohort 3	60 mg	80 mg	100 mg	120 mg	140 mg
Cohort 4	80 mg	100 mg	120 mg	140 mg	160 mg
Cohort 5	100 mg	120 mg	140 mg	160 mg	180 mg

Food Effect

Food effect studies are conducted to know the potential impact of food intake on the absorption of the drug. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug, one after fasting and one after a meal.

PHASE II

- Phase II trials are performed on larger groups of patients and are designed to determine the efficacy of drug and to continue the Phase I safety assessments.

Study Participants: Up to several hundred people with the disease/condition.
Length of Study: Several months to 2 years
Purpose: Efficacy and side effects

Phase IIA - specifically designed to assess dosing requirements (how much drug should be given).

Phase IIB -specifically designed to study efficacy (how well the drug works at the prescribed dose(s)

PHASE III

Phase III trials are randomized, controlled, multicenter trials and provide most of the long-term safety data.

Study Participants: 300 to 3,000 volunteers who have the disease or condition
Length of Study: 1 to 4 years
Purpose: Efficacy and monitoring of Adverse Reactions

Phase IIIA studies are used for the approval of the drug from the appropriate regulatory agencies. The results of these studies are included in the submission package to regulatory authorities.

Between submission and approval, Phase IIIB studies are often performed to obtain additional safety data or to support publication, marketing claims or to prepare launch for the drug.

PHASE IV

Post Marketing Surveillance (**PMS**) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released in the market

Study Participants: Several thousand patients who have the disease/condition
Purpose: Safety and efficacy
Length of Study: Less than 4 years

Post marketing surveillance can further refine, confirm or deny, the safety of a drug or device after it is used in the general population by large numbers of people who have a wide variety of medical conditions.

Post marketing surveillance uses several approaches to monitor drug and device safety some of them are -
electronic health records, patient registries, and record linkage between health databases

Clinical Trial

Basic steps:-

1. Need or Demand
2. concept or Idea
3. Research and study
4. Preclinical Trial – Pharmacokinetic, Pharmacodynamic, Toxicity study.
   Animal:- Small + Large – Invivo or Invitro.
5. Satisfactory Result

Clinical Trial

6. Good clinical practice:- Guidelines by – I.C.H., U.S.FDA; Schedule 'Y' G.C.P.; W.H.O., ICMR.
7. Ethical clearance – Local Institutional ethical committee / Review Board.
8. * Informed consent – All Detail Information should be given.

Phases:-

1. Phase 0 (Micro dosing) – For cost cutting, Subject – 10-15, Days – 07 Days. – P'kinetic + Dynamic
2. Phase I (Human P'cology + safety) Subject – 20-80, Safety, tolarebility, potentially Danger effect
3. Phase-II (Therapeutic exploration) – Subject – 100-500, Efficacy, Dose range, Diseased
4. Phase III (Therapeutic confirmation) – Subject – 500-3000. Safety + Tolarebility.
5. Phase IV (Post Marketing study) – All people, Safety, accetability, ADR. Side effect, off label use etc.

Pharmacovigilance

Pharmacovigilance :- Pharmakon = Drug, Vigilare = keep watching

Definition (WHO) — "Science and activity relating to the — ① Detection ② Assesment ③ Understanding ④ Prevention of Adverse effect

Aim/objective:- ↓ Drug related harm to patient

Activities:— ① Post marketing study – Report by doctors or other health professionals

Formate
- Drug Name – Brand
- Manufactured by
- Batch/Lot No.
- Exp Date
- Dose used
- Route
- Frequency
- Reason for prescription
- Therapy date.

② Prescription event monitoring.

✓③ Computerized medical record linkage.

④ Dissemination of ADR data through – 'Drug alert', Medical letters. Advisory sent to physician by regulatory agencies.

⑤ Change in the labelling of medicines – warning, precautions.

Causality Assessment –

① Relationship with time of drug administration.

② Previous knowledge about drug.

③ Dechallenge – Event subsided on stoping drug

④ Rechallenge –

Result:-

① Definite = proved.
② probable = Likely to cause event
③ possible = Drug + other cause
④ Doubtful = Unlikely to the cause, but can't ruled out