New Drug Discovery & Development (Overview)

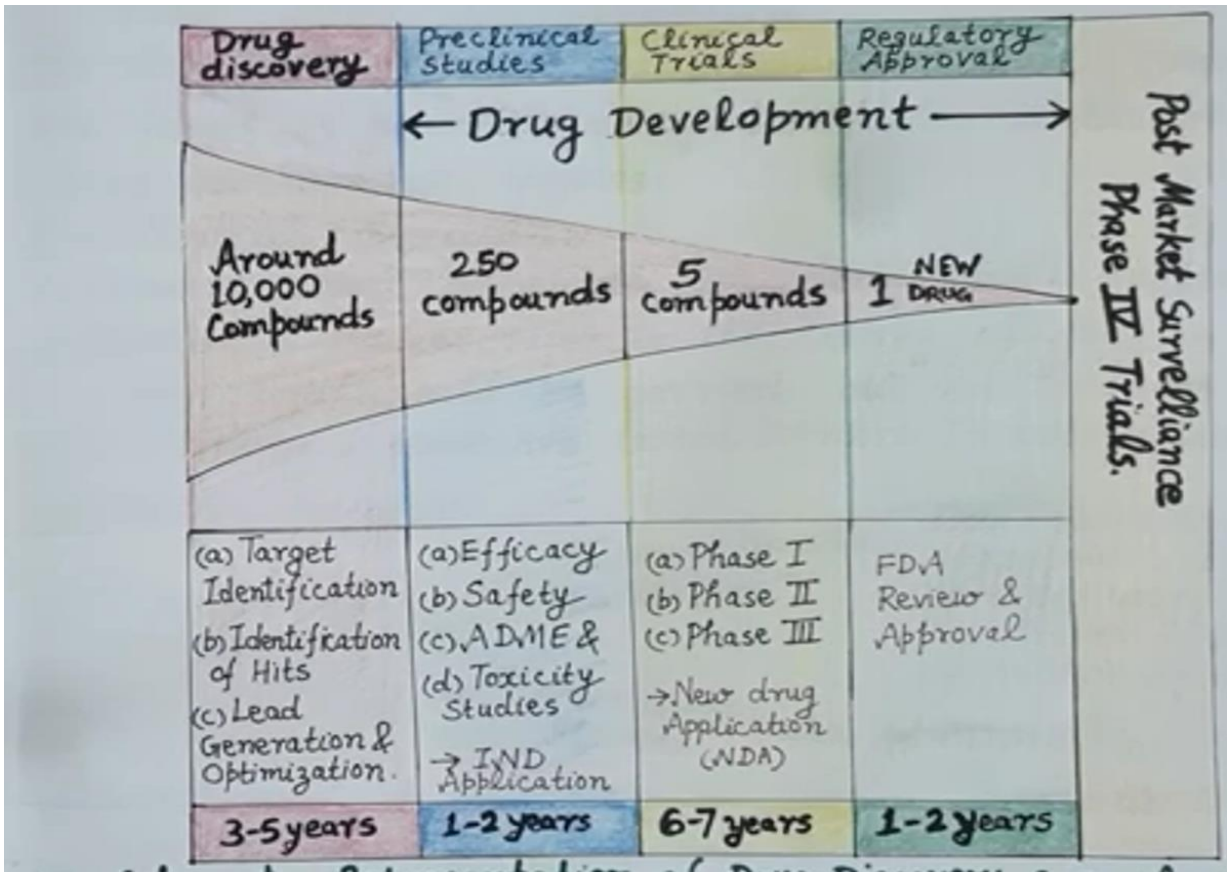
Major stages in the discovery & development of New drug are:

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



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.

New Drug Development

The drug discovery process ends when lead compounds are found as potential drug candidates & the process of drug development begins.

Preclinical Studies:

(a) Around 250 compounds are designed & tested.

(b) Preclinical studies refer to the testing of drug in animals before trial could be carried out in human beings.

(c) Wide Range of doses are tested In vitro, In vivo & Insilico.

(d) Studies Performed (in vivo)

(i) Pharmacological Studies
- → Pharmacodynamic Studies (DRC) → Determination of therapeutic Index, Max. Efficacy, Safety, Elucidation of Mechanism of Action of drug.
- → Pharmacokinetic Studies → ADME, V_d, $t_{1/2}$

(ii) Toxicological Studies → Acute, Subacute, Chronic } Determination of Safe dose & dose Range

Preclinical Studies:

(iii) Other studies performed are Reproductive and teratogenic studies, Mutagenic & Carcinogenic Studies.

(d) Product Formulation & Drug Delivery by Oral, Topical or Parenteral Route: Formulation Optimization goes on throughout preclinical & Clinical Stages.

Investigational New Drug (IND) Application & its Review by FDA

(a) IND Application include data of Preclinical Studies & Manufacturing Information of Drug.

(b) IND Application is submitted to FDA for Approval

(c) FDA Approval is essential for initiating Clinical trials.

Clinical Trials

After obtaining IND licence, clinical trials are initiated.
Drug is formulated into a suitable dosage form

1. Phase I

(a) A very small group of 20-80 healthy volunteers are exposed to drug.
(b) A trial is started with lowest estimated dose & dose is increased stepwise to achieve the effective dose.
(c) Potentially dangerous effects are detected on Vital functions
(d) Pharmacokinetic parameters are studied.

Primary Aim is to establish safety & tolerability of drug.

2. Phase II

(a) Involves 100-500 patients & carried out at 2-4 Centres.

Primary Aim is to establish therapeutic efficacy, dose range & Ceiling effect of drug.

3. Phase III

(a) Involves 1000 - 3000 patients
(b) Safety & tolerability are determined on a wider scale.

Aim is to establish value of drug in comparison with existing standard drugs.

New Drug Application (NDA) - FDA Review

If the drug is found safe & efficacious in clinical trials, a NDA is submitted to FDA, the licencing authority.

FDA Reviews data & either approve or drop the drug.
If FDA is convinced, drug is given marketing Approval.

Postmarketing Surveillance / Phase IV Studies

(a) Monitoring of Drug Safety after the New Drug reaches the Market.

(b) Safety of New Drug is monitored using FDA Adverse Event Reporting System (FAERS) database.

(c) Data obtained from this phase include:

(i) Unpredicted Idiosyncratic ADRs

(ii) Unsuspected drug Interactions.

(iii) Emergence of potential additional Indications.

(iv) Modification of dosage may be Required.

(d) Many a times drug is withdrawn from Market because of Serious ADRs.