UNIT-I

New Drug Discovery & Development

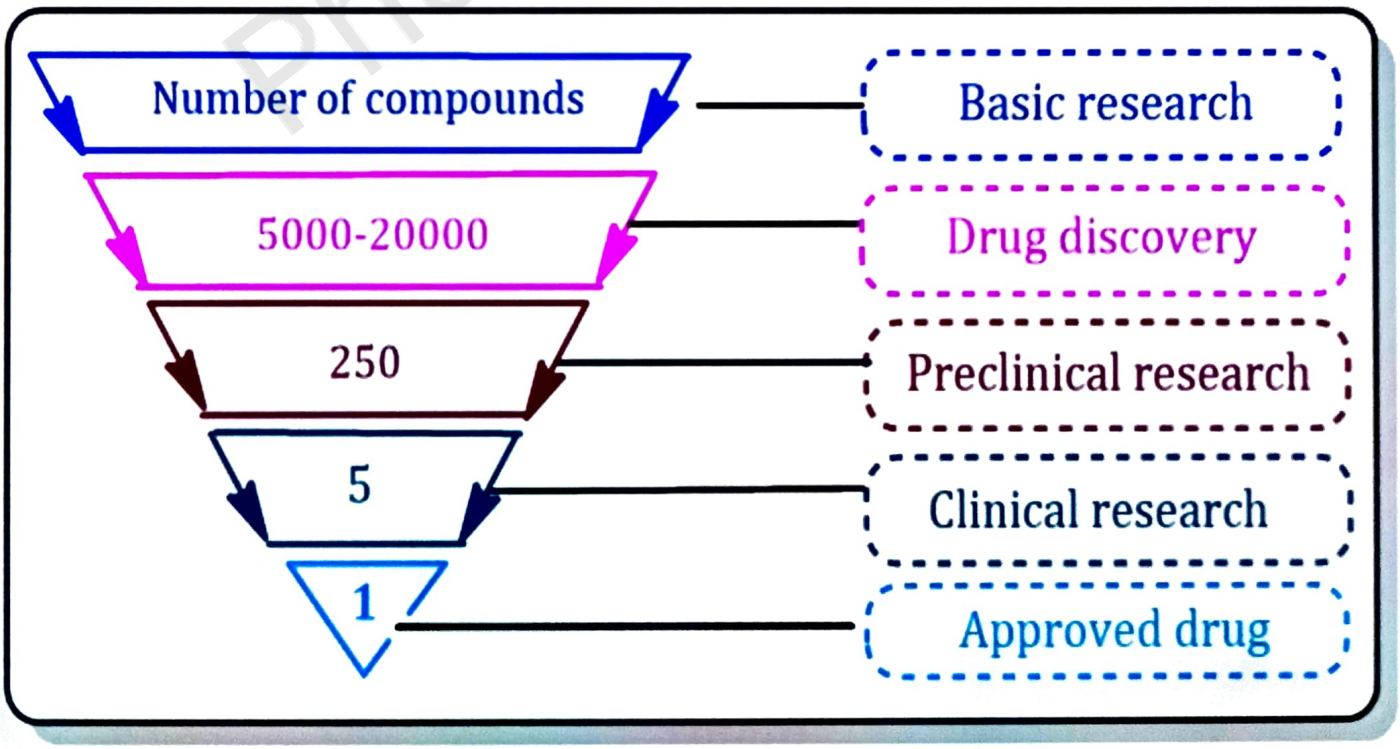
Points to be covered in this topic

- ❑ Stages of Drug Discovery
- ❑ Drug development Process
- ❑ Preclinical Studies
- ❑ Nonclinical activities
- ❑ Innovator & Generics
- ❑ Concept of Generics
- ❑ Generic drug Product development

❑ DRUG DISCOVERY

❖ Introduction

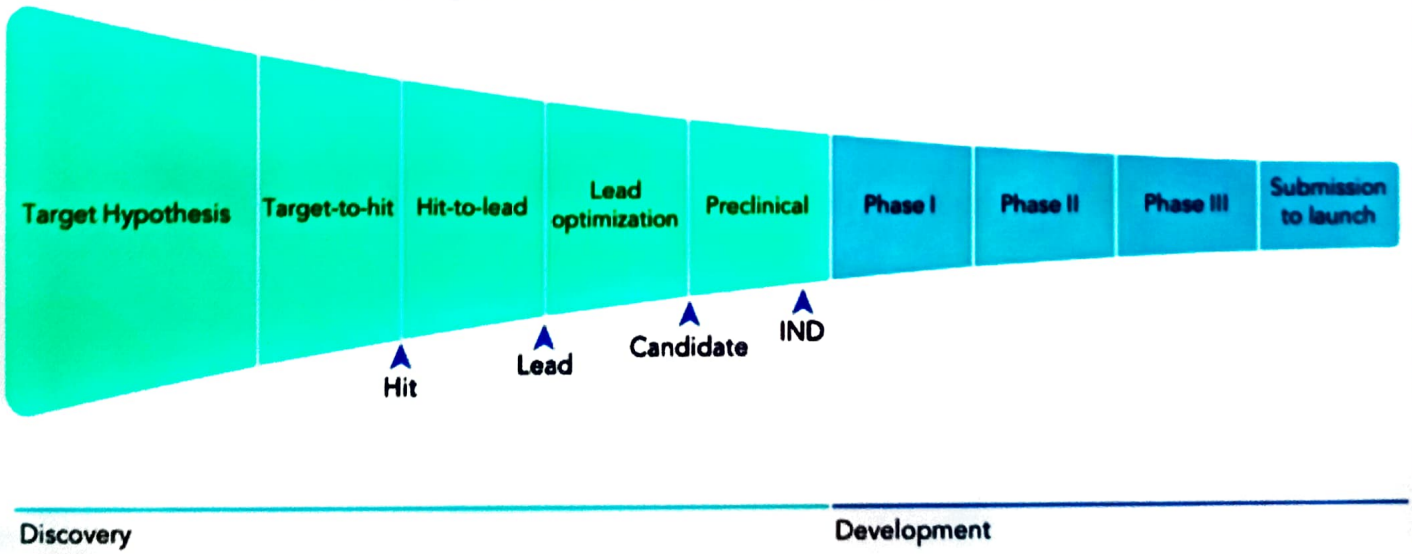
- Drug discovery is a process which aims at **identifying a compound therapeutically** useful in curing and treating disease.
- This process involves the **identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy.**
- Once a compound has shown its significance in these **investigations**, it will initiate the process of drug development earlier to **clinical trials.**
- New drug development process must continue through several stages in order to make a medicine that is **safe, effective**, and has approved all **regulatory requirements.**
- This process is sufficiently long, complex, and expensive so that many biological targets must be considered for every new medicine.
- **It takes about 12 - 15 years from discovery to the approved medicine.**
- On an average, a million molecules screened but only a single is explored in **late stage clinical trials** and is finally made obtainable for patients.



❑ STAGES OF DRUG DISCOVERY AND DEVELOPMENT

1. Target Identification

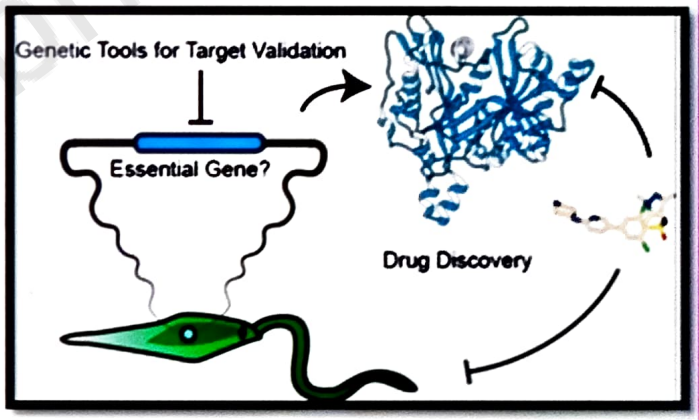
- The first step in the discovery of a drug is **identification** of the **biological origin of a disease**, and the **potential targets** for intervention.
- Target identification starts with **isolating** the function of a **possible therapeutic target (gene/nucleic acid/protein)** and its role in the disease.
- Identification of the target is followed by **characterization** of the **molecular mechanisms** addressed by the target.
- An ideal target should be **efficacious, safe, meet clinical** and **commercial requirements** and be **druggable**.



- The techniques used for target identification may be based on principles of **molecular biology, biochemistry, genetics, biophysics, or other disciplines.**

APPROACHES FOR TARGET IDENTIFICATION	
Data mining using bioinformatics	Identifying, selecting and prioritizing potential disease targets
Genetic association	Genetic polymorphism and connection with the disease
Expression profile	Changes in mRNA/protein levels
Pathway and phenotypic analysis	In vitro cell-based mechanistic studies
Functional screening	Knockdown, knockout or using target specific tools

2. Target Validation



- Target validation is the process by which the **expected molecular target** – for example **gene, protein or nucleic acid** of a small molecule is actually involved in a **disease process**, and that binding of a drug to the target is likely to have a **curative effect.**

TARGET VALIDATION INCLUDES:-
✓ Determining the structure activity relationship (SAR) of analogs of the small molecule
✓ Generating a drug-resistant mutant of the presumed target
✓ Knockdown or over expression of the presumed target
✓ Monitoring the known signaling systems downstream of the presumed target.

- Target validation is the process of demonstrating the functional role of the **identified target** in the disease phenotype.
- Whilst the validation of a **drug's efficacy** and **toxicity** in numerous disease-relevant cell models and animal models is extremely valuable – the ultimate test is whether the drug works in a clinical setting.

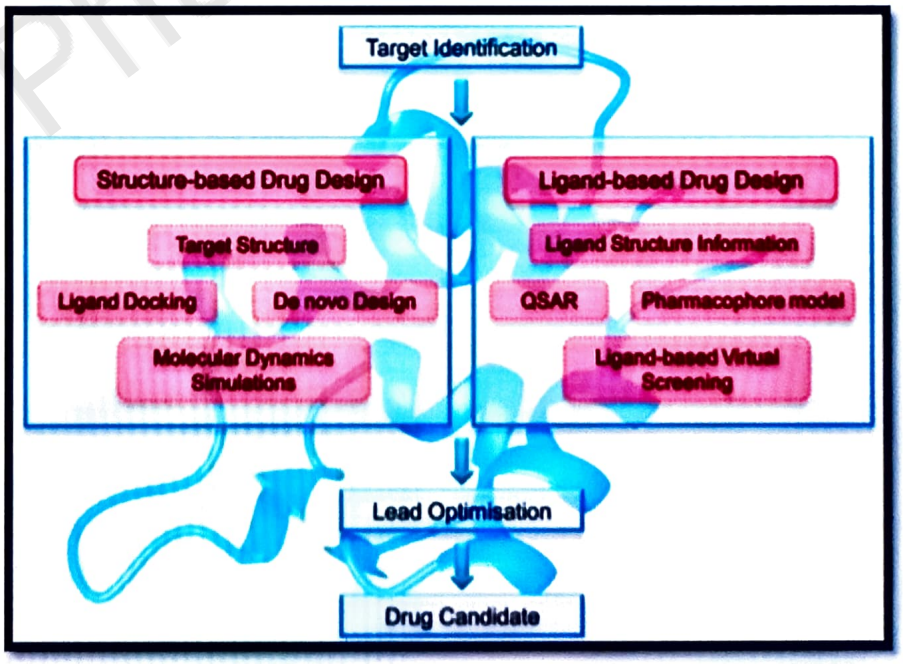
3. Identification of Lead

CHEMICAL LEAD

- A chemical lead is defined as a **synthetically stable, feasible**, and **drug** like molecule **active in primary** and **secondary** assays with acceptable specificity, affinity and selectivity for the target receptor

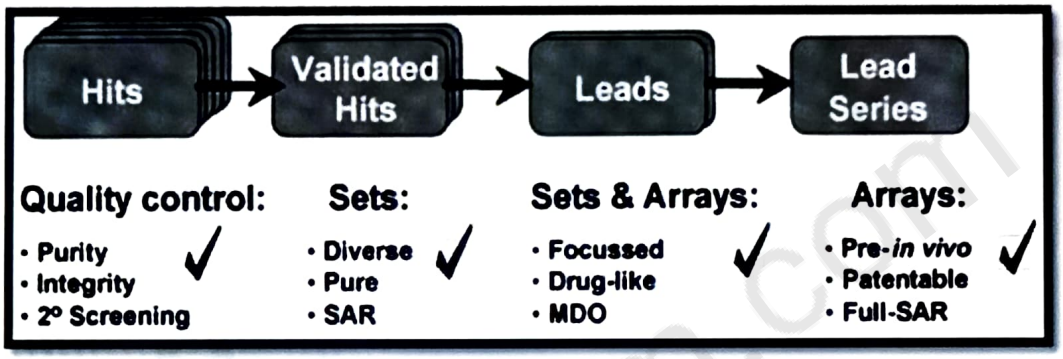
CHARACTERISTICS OF A CHEMICAL LEAD ARE:

1. SAR defined
2. Drug ability (preliminary toxicity)
3. Synthetic feasibility
4. Select mechanistic assays
5. In vitro assessment of drug resistance and efflux potential
6. Evidence of in vivo efficacy of chemical class
7. PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies



- In this phase, compounds which interact with the **target protein and modulate its activity are identified.**

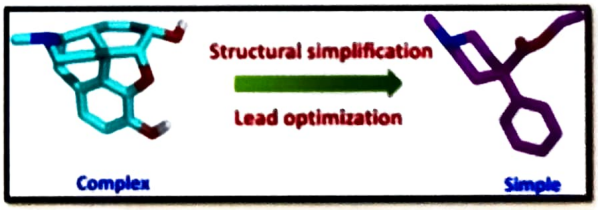
- The lead identification process starts with the development of an **assay** which will be followed by **screening of compound libraries.**
- **The quality of an assay determines the quality of data.**
- The assay used should fulfill these criteria: relevance, reliability, practicability, feasibility, automation and cost effectiveness.
- **Primary screens will identify hits.**
- confirmation screens and counter screens will identify leads out of the pool of hits. This winnowing process is commonly referred to as **"hits-to-leads."**



4. Lead Optimization

- Lead optimization is the process by which a **drug candidate** is designed after an **initial lead compound** is identified.
- Lead optimization employs a combination of **empirical, combinatorial,** and **rational approaches** that optimize leads through a continuous, multi-step process based on knowledge gained at each stage.
- One or more confirmed hits are evaluated in **secondary assays,** and a set of related compounds, called **analogs**, are synthesized and screened.

Medicinal chemists change the lead molecules based on these results in order to optimize pharmacological properties such as bioavailability or stability.



- **Pharmacokinetics (PK)/Pharmacodynamics (PD)/Absorption, Distribution, Metabolism, Excretion (ADME) studies** are an integral part of lead optimization.

- They feed back into the medicinal chemistry effort aiming to optimize the **physicochemical properties** of new leads in terms of **minimal toxicity** and **side effects**, as well as of maximum efficacy toward disease.

5. Product Characterization

- When any new drug molecule shows a promising **therapeutic activity**, then the molecule is characterized by its **size, shape, strength, weakness, use, toxicity, and biological activity.**
- Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

❑ DRUG DEVELOPMENT INCLUDES

6. Formulation and Development

- Pharmaceutical formulation is a **stage** of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a **bioavailable, stable** and **optimal dosage form** for a specific administration route.

DURING PRE-FORMULATION STUDIES THE FOLLOWING PARAMETERS ARE EVALUATED:	
1.	Solubility in different media and solvents
2.	Dissolution of the active pharmaceutical ingredient (API)
3.	Accelerated Stability Services under various conditions
4.	Solid state properties (polymorphs, particle size, particle shape etc.)
5.	Formulation services and capabilities
6.	Formulation development of new chemical entities (NCE)
7.	Optimization of existing formulations
8.	Process development for selected dosage forms
9.	Novel formulations for improved delivery of existing dosage forms
10.	Controlled release and sustained release formulations

11.	Self-emulsifying drug delivery systems
12.	Colloidal drug delivery systems
13.	Sub-micron and nano-emulsions

7. Preclinical Testing

- Pre-clinical research in drug development process involves **evaluation of drug's safety** and **efficacy** in animal species that conclude to prospective human outcome.
- The pre-clinical trials also have to **acquire approval** by corresponding regulatory authorities.
- The regulatory authorities must ensure that trials are conducted in **safe** and **ethical way** and would give approval for only those drugs which are confirm to be safe and effective.
- **ICH** has established a basic guideline for technical necessities of **acceptable preclinical drug development.**
- The pre-clinical trials can be conducted in two ways:

General pharmacology **Toxicology**

- Pharmacology deals with the **pharmacokinetic** and **pharmacodynamic** parameters of drug.
- Pharmacokinetic studies are very important to make **known the safety and efficacy parameters** in terms of **absorption, distribution, metabolism and excretion.**
- Toxicological studies of the drug can be performed by **in-vitro** and **in-vivo** test which evaluate the **toxicological effects** of the drug.
- In-vitro studies can be performed to inspect the direct effects on cell proliferation and phenotype.
- In-vivo studies can be performed for **qualitative** and **quantitative** determination of **toxicological effects.**
- As many drugs are species specific, it is essential to select **appropriate animal species** for toxicity study.

- In-vivo studies to evaluate **pharmacological** and **toxicological** actions, including **mode of action**, are often used to support the basis of the proposed use of the product in clinical studies.

8. The Investigational New Drug Process (IND)

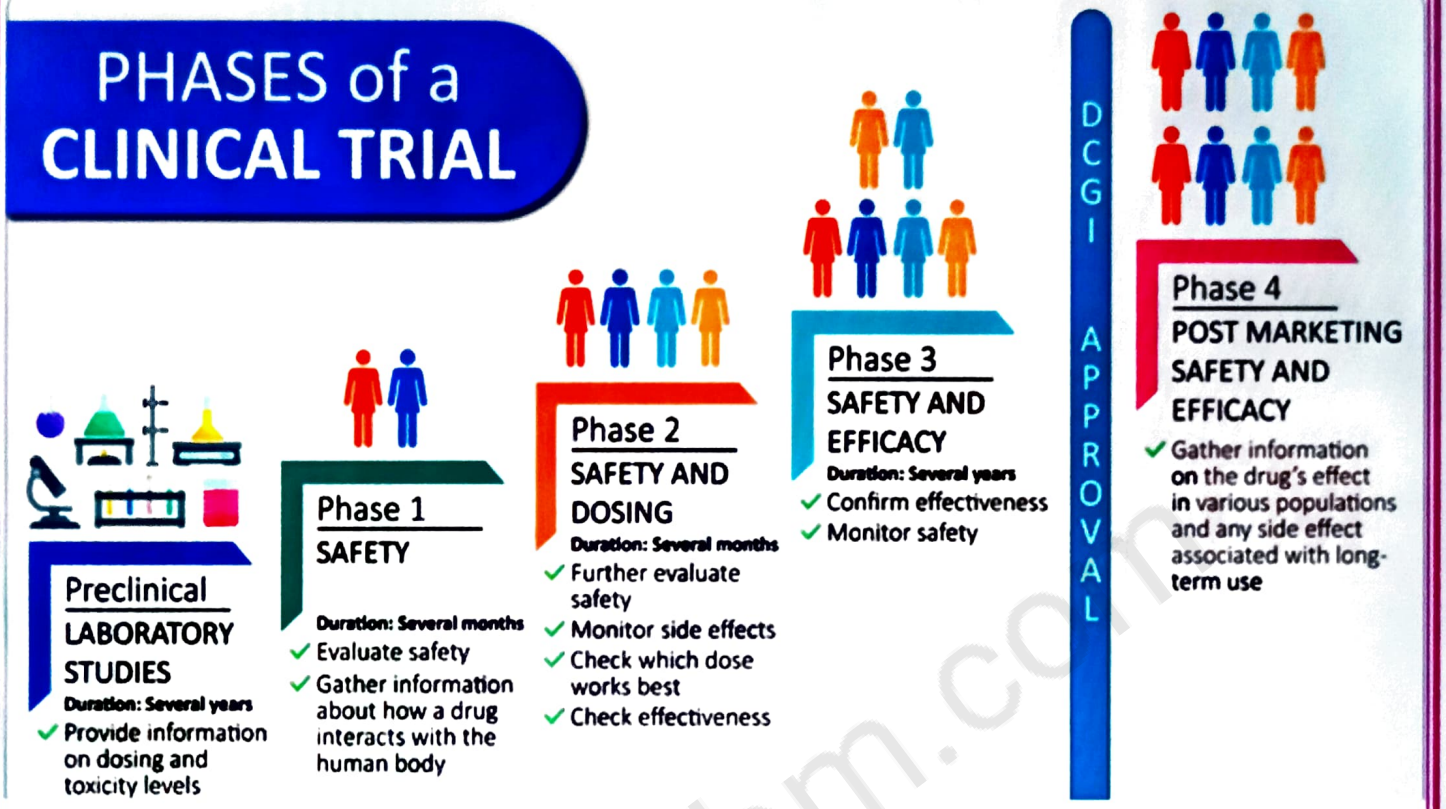
- Drug developers must file an Investigational New Drug application to FDA **before** commencement clinical research. In the IND application, developers must include:
  - ✓ **Preclinical and toxicity study data**
  - ✓ **Drug manufacturing information**
  - ✓ **Clinical research protocols for studies to be conducted**
  - ✓ **Previous clinical research data (if any)**
  - ✓ **Information about the investigator/ developer**

9. Clinical Research

- Clinical trials are conducted in **people (volunteer)** and intended to answer **specific questions** about the **safety** and **efficacy** of drugs, vaccines, other therapies, or new methods of using current treatments.
- Clinical trials follow a **specific study protocol** that is designed by the researcher or **investigator** or **manufacturer**.
- As the developers design the clinical study, they will consider what they want to complete for each of the different **Clinical Research Phases** and starts the **Investigational New Drug Process (IND)**, a process they must go through before clinical research begins.
- Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

1.	Selection criteria for participants
2.	Number of people take part of the study
3.	Duration of study
4.	Dose and route of administration of dosage form

5.	Assessment of parameters
6.	Data collection and analysis



A. Phase 0 clinical trial

- Phase 0 implicates investigative, **first-in-human (FIH) trials** that are conducted according to **FDA guidelines.**
- Phase 0 trials besides termed as **human micro dose studies**, they have single **sub-therapeutic doses** given to **10** to **15 volunteers** and give pharmacokinetic data or help with imaging specific targets without exerting pharmacological actions.
- Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the **pre-eminent pharmacokinetic parameters** in humans.

B. Phase 1: Safety and dosage

- Phase I trials are the first tests of a drug with a **lesser number** of **healthy human volunteers.**
- In most cases, **20** to **80 healthy volunteers** with the disease/condition participate in Phase 1.

- Patients are generally only used if the **mechanism of action of a drug** indicates that it will not be tolerated in **healthy people.**
- Phase 1 studies are closely **monitored** and **collect information** about **Pharmacodynamics** in the human body.
- Researchers adjust **dosage regimen based on animal study data** to find out what dose of a drug can tolerate the body and what are its acute side effects.
- This is imperative to the design of Phase 2 studies Almost 70% of drugs travel to the next phase.

C. Phase 2: Efficacy and side effects

- Phase II trials are conducted on **larger groups of patients (few hundreds)** and are aimed to evaluate the efficacy of the drug and to endure the **Phase I safety assessments.**
- These trials aren't sufficient to confirm whether the drug will be therapeutic.
- Phase 2 studies provide with **additional safety data** to the researchers.
- Researchers use these data to **refine research questions, develop research methods, and design new Phase 3 research protocols.**
- Around 33% of drugs travel to the next phase.

D. Phase 3: Efficacy and adverse drug reactions monitoring

- Phase III of a clinical trial usually involves up to **3,000 participants** who have the condition that the new medication is meant to treat. Trials in this phase can **last for several years.**
- The purpose of phase III is to evaluate how the new medication works in comparison to **existing medications for the same condition.**
- To move forward with the trial, investigators need to demonstrate that the medication is at least as safe and effective as existing treatment options. To do this, investigators use a process called **randomization.**
- This involves randomly choosing some participants to receive the new medication and others to receive an **existing medication.**

- The FDA usually requires a **phase III clinical trial** before approving a **new medication.** Due to the larger number of **participants** and **longer duration or phase III, rare** and **long-term side effects** are more likely to show up during this phase.
- If investigators demonstrate that the medication is at least as safe and effective as others already on the market, the FDA will usually approve the medication.

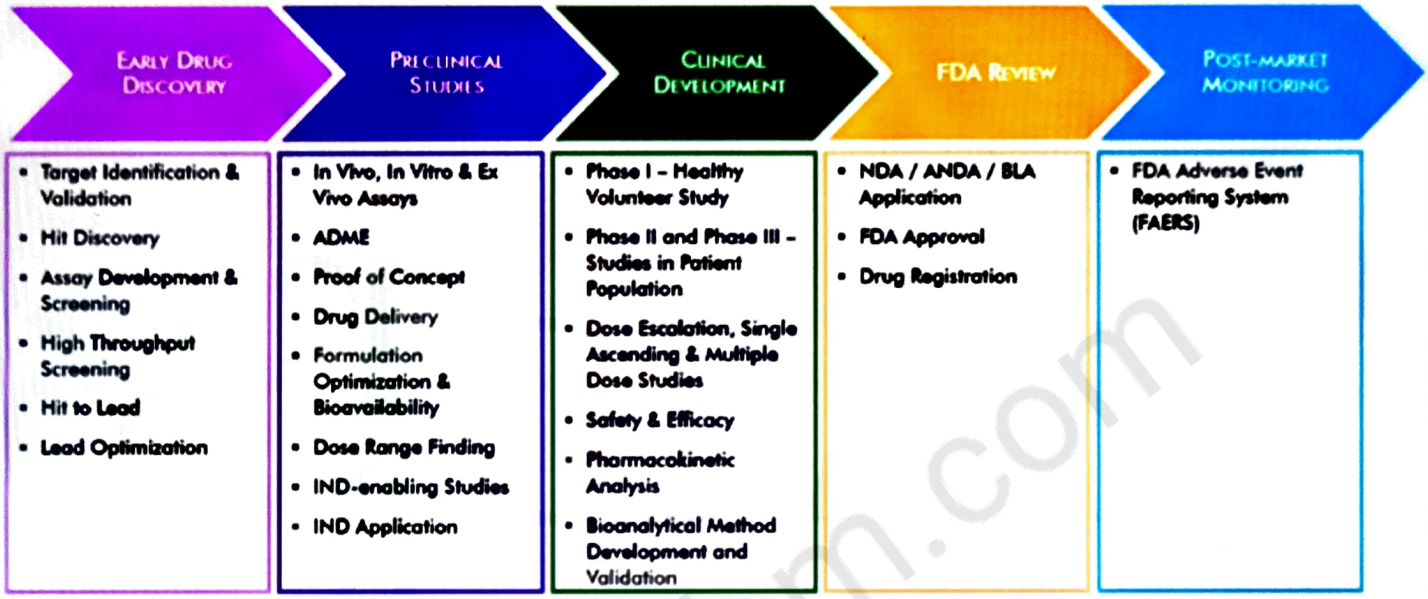
E. Phase 4: Post-Market Drug Safety Monitoring

- Phase 4 trials are conducted when the **drug or device has been approved by FDA.**
- These trials are also recognized as **post-marketing surveillance** involving **pharmacovigilance** and **continuing technical support** after approval.
- There are **numerous observational strategies** and **assessment** patterns used in Phase 4 trials to evaluate the efficacy, cost-effectiveness, and safety of an involvement in real-world settings.
- Phase IV studies may be required by **regulatory authorities** (e.g. change in labelling, risk management/minimization action plan) or may be undertaken by the sponsoring company for **competitive purposes** or other reasons.
- FDA reviews reports of **complications** with **prescription** and OTC drugs, and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions.

10. New Drug Application

- A New Drug Application (NDA) expresses the **full story of a drug molecule.**
- Its purpose is to verify that a drug is **safe** and **effective** for its proposed use in the people studied.
- A drug developer must include all about a drug starting from preclinical data to Phase 3 trial data in the NDA.

- Developers must include reports on all studies, data, and analysis. Beside with clinical trial outcomes, developers must include:
  - ✓ **Proposed labeling**
  - ✓ **Safety updates**
  - ✓ **Drug abuse information**
  - ✓ **Patent information**



11. FDA Review

- Once FDA obtains a complete NDA then FDA team of review may require about 6 to 10 months to take a **pronouncement on whether to approve the NDA.**
- If Once FDA obtains a incomplete NDA then FDA team of review refuse the NDA.
- If FDA governs that a drug has been revealed to be safe and effective for its proposed use, it is then essential to work with the developer for upgrade prescribing information.

❑ PRE-CLINICAL STUDIES (RESEARCH)

- Preclinical drug development is a stage that begins before clinical trials (testing in humans) during which important **safety** and **pharmacology data is collected.**
- Preclinical research includes **synthesis, purification** and **animal testing** which is done to measure the **biological activity** and **safety** of an **investigational drug or device.**

- Preclinical research is conducted by **pharmaceutical companies** early in the process of new drug development.
- This research takes place in either the part or whole animal to determine important **information**, including: **therapeutic effects** the **drug may have, potential side effects** and **toxicities** and **metabolism** and **clearance** of the drug in the body.
- Good results in the **preclinical** or **animal stage** do not necessarily mean that similar results will be found when the drug is given to **healthy volunteers or patients.**
- The main goals of preclinical studies are to determine a **drug's pharmacodynamics (PD), pharmacokinetics (PK)** and **toxicity** through animal testing. This data allows researchers to estimate a safe starting dose of the drug for clinical trials in humans.

TYPES OF PRECLINICAL STUDIES

1. **In vitro studies**
2. **In vivo studies**
3. **Ex vivo studies.**

1.	**In vitro studies**	• They are done for testing of a drug or chemical's effect on a specific isolated tissue or organ maintaining its body functions. • Basic instruments used for isolated tissue experiments are organ baths, recording devices.
2.	**In-vivo studies**	• It indicates the use of a whole organism/animals (for an experiment).
3.	**Ex-vivo studies**	• This experiment is performed in vivo and then analyzed in vitro. • The organs of the animals are detached from the body and replaced once an experiment is performed. • Then the animals are kept under observation and findings recorded for a set duration.

❑ NON-CLINICAL ACTIVITIES

- Non-Clinical testing is done throughout all phases of the drug development in order to survey the **safety profile, pharmacokinetic** and **toxicokinetic (PK/TK) characteristics** of therapeutic substances.
- If the **Non-Clinical** and **Pre-clinical studies** improvement is performed well, it can enhance the chances of success in the **clinical development phases.**
- Techniques for the Non-Clinical advancement of products follow general regulatory guidelines, but are also designed on a case-by-case premise as per the specific medication.

REASONS BEHIND THE NON-CLINICAL STUDIES IN ANIMALS BEFORE ADMINISTRATED TO MAN	
1.	To check the pharmacological effects are same in man as in animal.
2.	Toxic effects in species will predict adverse effects in man.
3.	Giving high doses in animals improve predictability to man.
4.	Risk assessment can be made by differentiation of toxic doses in test species with predicted therapeutic dose in man.

ACCORDING TO GOOD LABORATORY PRACTICES, NON CLINICAL STUDIES EXPLAINS ABOUT	
1.	Safety Pharmacology
2.	Pharmacokinetics
3.	Pharmacodynamics
4.	General Toxicology
5.	Local Tolerance
6.	Genotoxicity
7.	Carcinogenicity
8.	Reproductive Toxicology

❑ INNOVATOR & GENERICS

1. Innovator

- An innovator drug is the **first drugs** created containing its specific active ingredient to receive approval for use.
- It is usually the product for which **efficacy, safety** and **quality** have been fully established.
- When a new drug is first made, drug patent usually will be acquired by the **founding company.**
- Most drug patents are protected up to **20 years.** During the patent period, other companies cannot make or sell the same drug until the **patent expires.**

2. Generics

- A generic drug is made of the **same active ingredient** as its innovator drug.
- An active ingredient is the chemical contained **inside a drug that makes it work.**
- In other words, the pharmacological effect of a generic drug is exactly the same as those of its **innovator counterpart.**
- Other companies can manufactures the generic drugs when patent expires.

➢ There are similarities between generic and innovator drug, such as:

1. **Active ingredient**
2. **Strength (dose)**
3. **Therapeutic effect**
4. **Side effects**
5. **How to take**

❑ CONCEPT OF GENERICS

- On **September 24, 1984**, in the 98th U.S. Congress, the Act named 'The Drug Price Competition and Patent Term Restoration Act' was passed, also known as the **Hatch- Waxman Act.**
- The objective of this act was to encourage the **manufacturing of generic drugs** by the pharmaceutical industries and to establish the modern system of government generic drug regulation in the USA.
- The requirement for this was to submit an **Abbreviated New Drug Application (ANDA)** by the pharmaceutical companies to the regulatory authorities for getting the approval to market a generic drug.
- Generics are formulated, developed, and manufactured by other companies when **patent** and **other exclusivity rights** of the innovator have **expired.**
- As generic drug development does not involve large investment for **drug discovery** and **preclinical** and **clinical trials,** they are available at a lower cost and provide an opportunity for savings in **drug expenditure** of a country.

ACCORDING TO WHO

"Generic drug is a pharmaceutical product which is usually intended to be interchangeable with an innovator product, is manufactured without a license from the innovator company, and is marketed after the expiry date of the patent or other exclusive rights".

- In generic pharmaceutical products, there is no standard categorization as it does not cover the specifics of this industry.
- Thus, the new generic products can be defined as:
  i. **Line extensions:** Line extensions are small adaptations of an existing product, which is normally already available on the market.
  ii. **Retargeting:** Retargeting refers to existing products registered, launched, and marketed in a new market.
  iii. **New product**: A new product is a completely new product for the company and for the market in the generics segment.

- Generics products may be marketed either under the approved non-proprietary name or under a brand (proprietary) name.

A generic drug is approved by the regulatory agency if it is-

1. Pharmaceutically equivalent to an approved safe and effective reference product in that it:
   a) **Contains identical amounts of the same active drug ingredient in the same dosage form and route of administration and**
   b) **Meets compendial or other applicable standards of strength, quality, purity, and identity.**
2. Bioequivalent to the reference product in that it:
   a) **Does not present a known or potential bioequivalence problem and it meets an acceptable in vitro standard (usually dissolution testing) or**
   b) **If it does present such a known or potential problem, it is shown to meet an appropriate bioequivalence standard.**
3. Adequately labeled.
4. Manufactured in compliance with cGMP regulations.

❑ GENERIC DRUG PRODUCT DEVELOPMENT

- Drug product development is a **creative** and **multidisciplinary process** that turns a **technological innovation** and a **market** opportunity in products with **economic profitability** for the company.
- Generic drug products are **proven therapeutically** equivalent to the corresponding **innovator's product**, and hence can be substituted in **clinical practice.**
- The objective of generic drug product development is to develop a **stable** and **bioequivalent generic drug product** with desirable properties.
- The process of development includes three sequential stages essential for successful generic drug development.

a.	• First, a predevelopment stage involves collecting and evaluating data and information related to a drug such as its physicochemical properties and critical quality attributes, before implementing any development activities. • Trade-related information on a patent or any market relating to the innovator's product is searched.
b.	• Second, development stages begin with a thorough characterization of the innovator's product, followed by an initial compatibility study between the drug and proposed excipients to be used in the formulation, suitable selection of method for formulation development, and suitable selection of manufacturing process. • The development stages should result in a model generic product with in-vitro similarity with the innovator's product for a pilot bio-batch.
c.	• Third, Once a pilot biobatch of the generic product is obtained, an in vivo bioequivalent test is conducted in accordance with the GCP to assure that the generic drug product is therapeutically equivalent to the innovator's product. • In addition to the science and technical aspects of generic drug product development, achieving a quality generic drug product requires that generic manufacturers fully understand and respect the regulatory guidelines that govern its development and manufacturing. Otherwise a generic product may fail during a during a drug registration process.

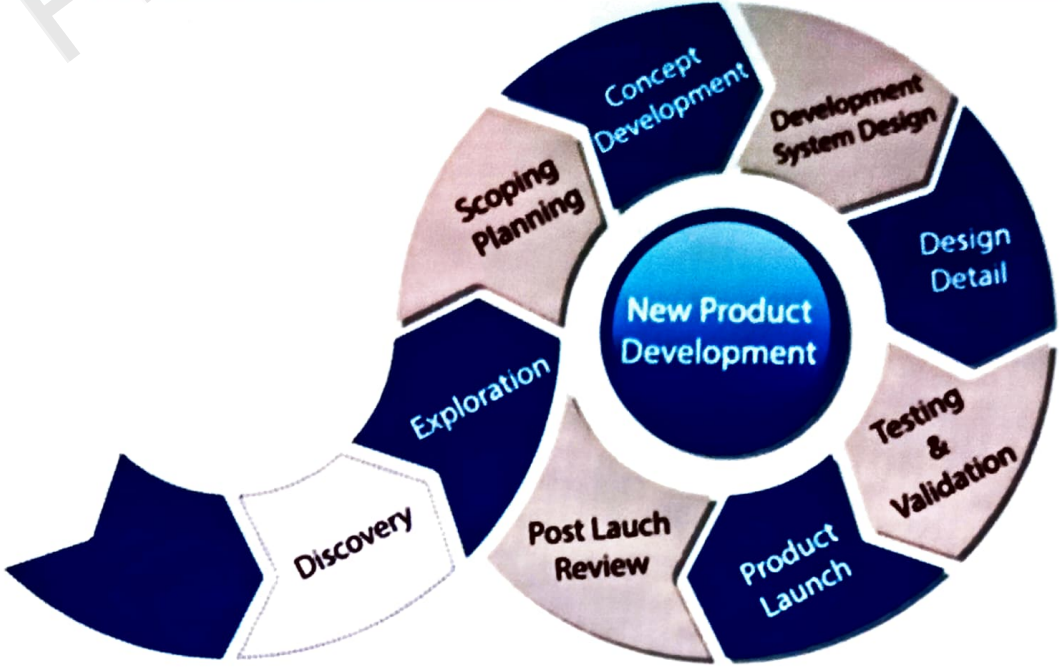
- Generic drug product development is the process that completely covers a series of stages required to bring a generic drug product to the market.
- Based on the extensive literature reviewed, development of the generic product development process includes the following phases:

1.	**Drug candidate selection**	• In this phase, the organization set up a dedicated **expert team** to select multiple solutions for a **problem identified** by a market survey. • This phase covers the **broad selection** of potential drug candidates. • A team decides which drug candidates should be selected to proceed into the **preliminary assessment phase.**
2.	**Candidate drug screening**	• In this phase **drug candidates** selected in the earlier phase is carefully **screened** to roughly assess the **potential drug candidates.** • The simple strategy followed is to accept the **best** and **eliminate the poor.** • Development proceeds with only one or **two candidates** for the **next phase.**
3.	**Concept development**	• It is an exercise in which the **screened candidate** drug is translated into the **product concept.** • The product concept is a detailed version of the **product idea.** • The needs of the target market are **identified**, alternative product concepts are generated and **evaluated**, and a **single development** is selected for further development. • A concept is the **description** of the form, function, and features of a product and is usually accompanied by a set of specifications, an analysis of competitive products, and an economic justification of the project.

4.	System-level design	• This phase includes the definition of the product composition and the division of the product into subsystems and components. • The final formulation scheme for the production system is usually defined during this phase. • The output of this phase is a product layout with functional specifications of each of the products components, and a preliminary process flow diagram for the final manufacturing.
5.	Detail design	• This phase includes the complete specification of the materials and limits of all the components in the product and the identification of all the probable suppliers. • A process plan is established within the production system. The output of this phase is the control documentation for the product.
6.	Concept testing	• This phase is the laboratory development of a generic product. • This phase starts with experimental and accelerated stability study work, the development based on a laboratory scale, including the (pilot) bio-equivalent-study and development of the primary packaging.
7.	Business analysis	• It is a significant phase for every organization. • Landmarks and milestones of the product development process and time required for the completion should are fixed. • Also, in this phase, the impacts of delays and time of product arrival in the market are analyzed carefully.

Concept testing

8.	**Development of a prototype**	• This phase includes the development of a prototype, testing of a prototype, modifications in the prototype, and pilot production. • This phase is also called production ramp-up. • It also describes the period from completed initial product development to maximum capacity utilization, characterized by product and process experimentation and improvements.
9.	**Development of technology**	• This phase includes the transfer to the industry measure and the preparation of registration documentation. • It includes clinical studies, toxicological studies, bio-equivalent studies, and completed stability studies. • This phase finishes with the production of three registration batches. • The more departments involved in this phase, the shorter is the new product development process.
10.	**Registration**	• Registration is a phase of filing of registration dossiers at regulatory authorities, Fig. 1.3. It finishes when the product is registered and the registration documentation and marketing authorization is obtained.
11.	**Launch**	• The launch phase includes all final pre-launch activities such as ordering of materials, production of launch stock, ordering of raw materials, packaging materials etc. including the launch of the product on the selected market. • The overlapping of activities from different phases described above reduces the time to launch the generics products into the market.


New Product Development
Concept Development
Development System Design
Design Detail
Testing & Validation
Product Launch
Post Lauch Review
Exploration
Discovery
Scoping Planning