An Overview of Drug Discovery and Development

Mr. Abhishek A. Shejwal[1], Mr. Manish P. Patil[2], Mr. Omkar T. Kadam[3], Miss. Tanushree S. Jaiswal[4], Mr. Mahendra Khandare[5]
[1,2,3,4]*Student, Sayali Charitable Trust's College of Pharmacy*
[5]*Assistant Professor, Sayali Charitable Trust's College of Pharmacy*

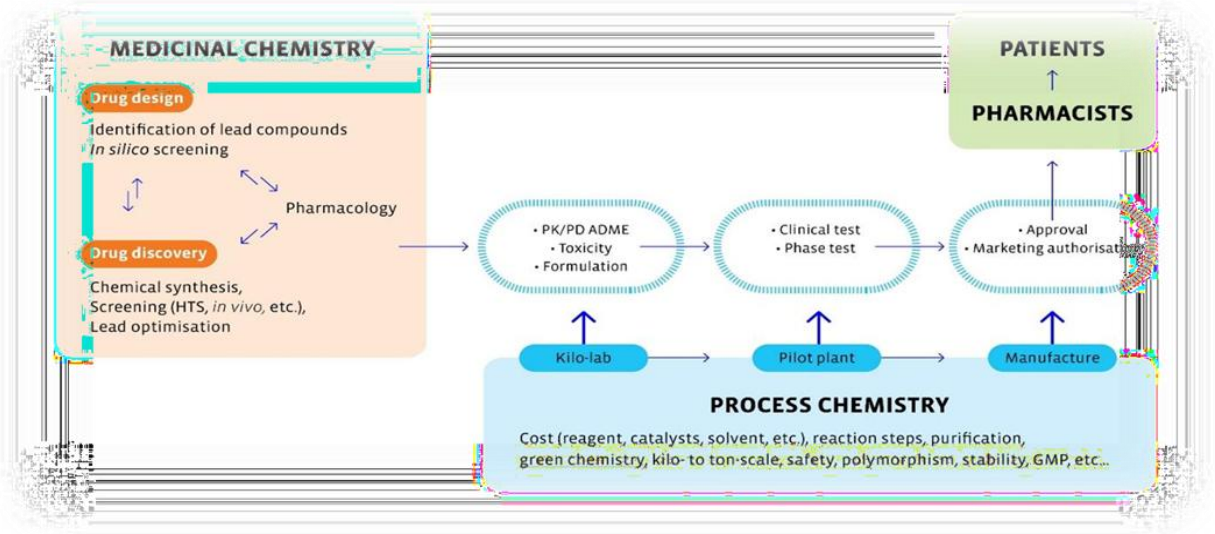
I. INTRODUCTION

Drug design and discovery play a vital role in the development of new medicines that improve human health. It is a process of identifying and designing chemical compounds that can interact specifically with biological targets such as enzymes, receptors, or nucleic acids to produce a desired therapeutic effect. Modern drug design integrates knowledge from medicinal chemistry, pharmacology, molecular biology, and computational sciences to create safer and more effective drugs.

Traditionally, drugs were discovered through trial and error methods, but with the advancement of technology, the process has become more scientific and systematic. The introduction of Computer-Aided Drug Design (CADD) and Structure-Based Drug Design (SBDD) has made it possible to visualize the interaction between a drug and its target at the molecular level. These tools help in predicting the biological activity of new compounds even before synthesis, saving both time and resources.

One of the best examples of successful drug design is Atorvastatin, a cholesterol-lowering drug belonging to the statin class. It was designed by studying the enzyme HMG-CoA reductase, which is responsible for cholesterol biosynthesis in the liver. By understanding the enzyme's structure, scientists were able to design Atorvastatin molecules that fit precisely into its active site, blocking the enzyme's action and thereby reducing cholesterol levels in the blood.

The study of Atorvastatin in this domain helps to understand the principles of rational drug design, QSAR, molecular docking, and ADMET properties. It also provides insight into how small structural modifications can improve drug activity, stability, and safety. Thus, drug design represents a bridge between theoretical research and practical drug development, guiding scientists in the discovery of new and effective therapeutic agents.



II. BASIC PRINCIPLE OF COMPUTER-AIDED DRUG DESIGN

Meaning:

Computer-Aided Drug Design (CADD) is a modern technique used to design and develop new drug molecules with the help of computer software.

It allows scientists to predict how a molecule will behave in the body and how strongly it will bind to a biological target (like an enzyme or receptor).This saves time, money, and experimental effort in drug discovery.

Basic Principle:

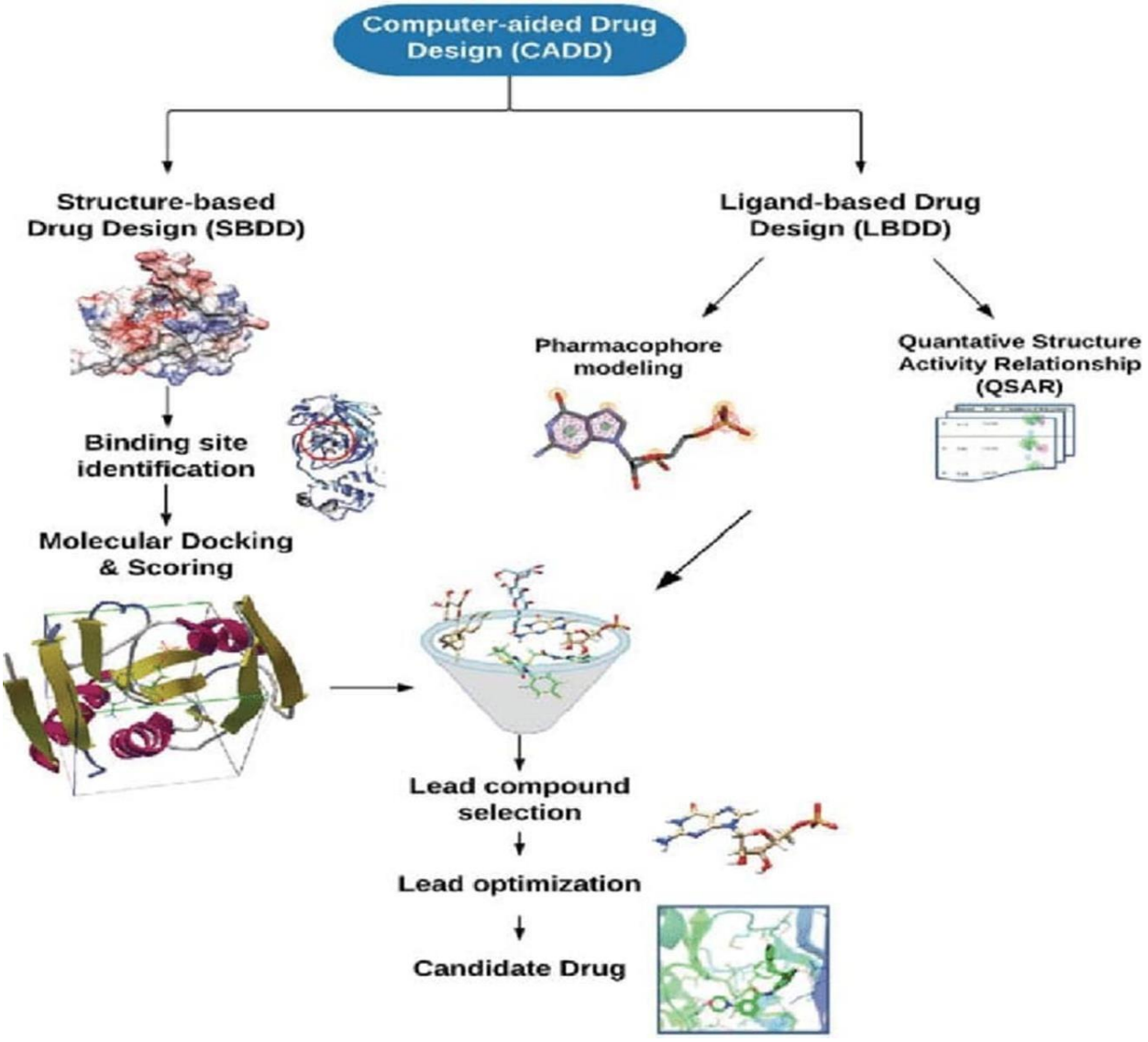
The main principle of CADD is based on the relationship between the structure of a molecule and its biological activity.

By using computer simulations, researchers can visualize:

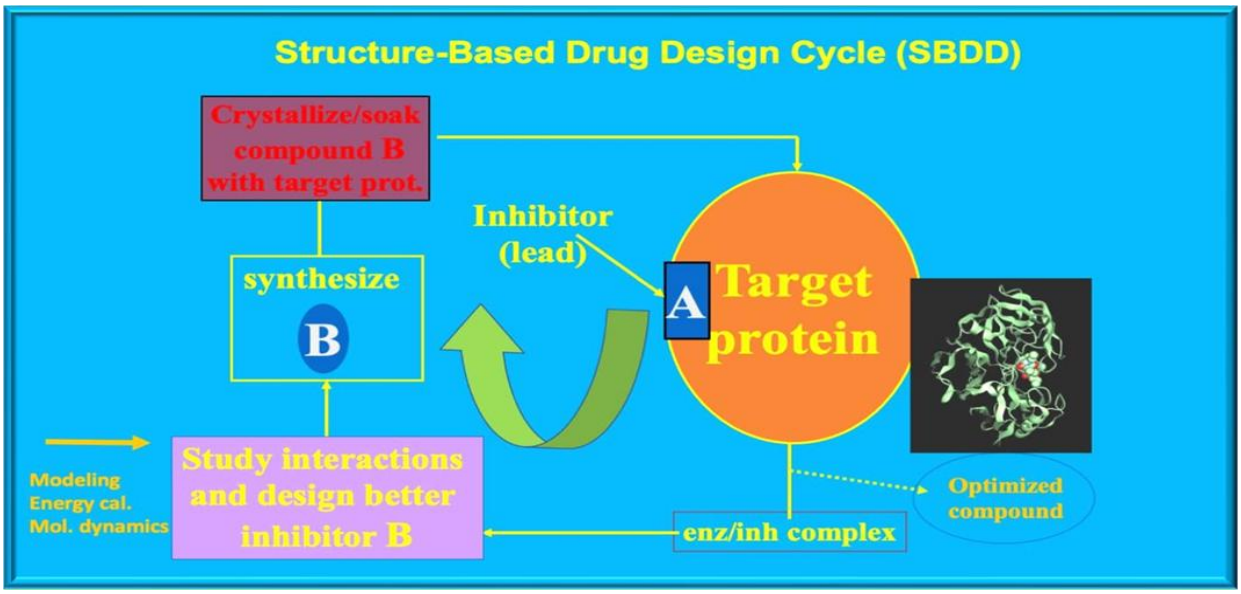
- How a drug fits into the target site (like a key into a lock).
- Which parts of the molecule are responsible for activity.
- How small chemical modifications can improve potency, selectivity, or reduce side effects.

Types of CADD Approaches : CADD Technologies can be classified into two main categories

1. Structure -based approaches
2. Ligand -based approaches



III. STRUCTURE-BASED DRUG DESIGN (SBDD)



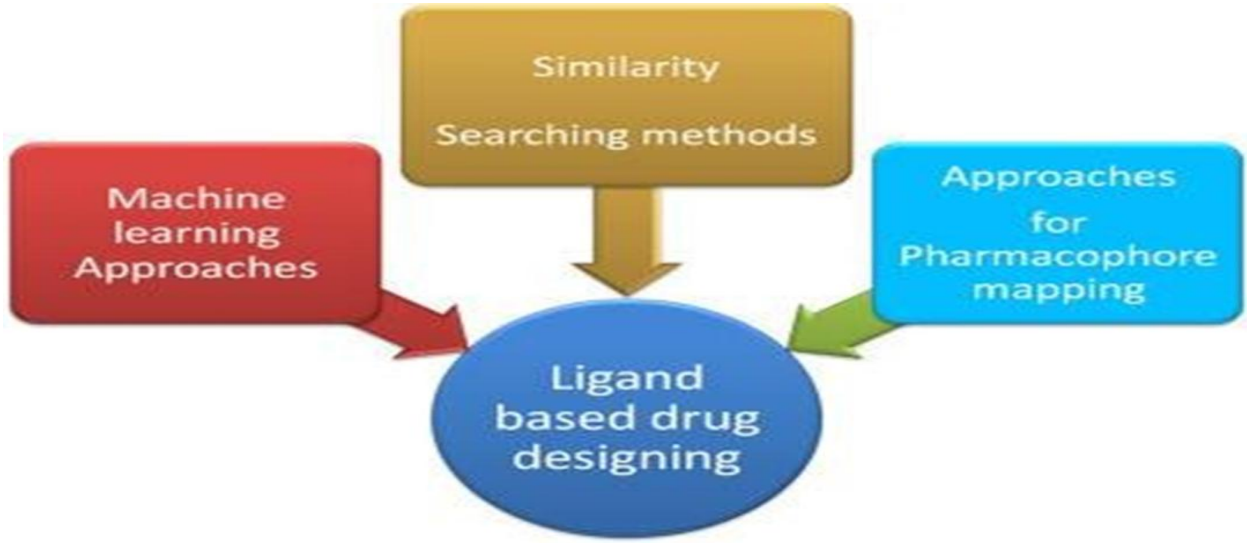
Structure-based drug design uses the 3D structure of the biological target (usually a protein or enzyme) to design molecules that can bind effectively to it.

The process involves:

1. Target Identification & Structure Determination – using X-ray crystallography or NMR.
2. Docking Studies – testing how well potential drug molecules (ligands) fit into the active site.
3. Interaction Analysis –studying hydrogen bonds, hydrophobic interactions, and electrostatic forces.
4. Optimization – modifying the molecule to improve binding affinity and selectivity.
5. Synthesis & Validation – synthesizing optimized compounds and testing biologically.

This approach helps in designing drugs like Atorvastatin, where computer modelling predicts strong binding to the enzyme HMG-CoA reductase (the target for cholesterol synthesis inhibition).

2□Ligand-Based Drug Design (LBDD)



Ligand-based drug design is used when the 3D structure of the target protein is not known Instead, it relies on the structures and activities of known active compounds (ligands) to design new drugs.
Main steps:

- Analyse the chemical features common among active compounds.
- Use computational tools to predict new molecules with similar features.
- Apply QSAR (Quantitative Structure–Activity Relationship) and pharmacophore modelling to optimize potency.

Example: Designing new β-blockers based on the structure–activity relationship of propranolol.

IV. DRUG DISCOVERY CYCLE

Introduction:
Drug discovery is the process of identifying new potential drug molecules that can be used to cure or manage diseases. It involves scientific understanding of disease mechanisms, identification of biological targets, screening of potential molecules, and optimizing them to develop a safe and effective therapeutic agent. The process is time- consuming, complex, and requires an integrated approach involving biology, chemistry, and computer-aided techniques.
o Two Major Approaches in Drug Discovery:
1. Phenotypic Drug Discovery (PDD):

Phenotypic drug discovery is one of the oldest and most traditional methods. In this approach, compounds are screened based on their ability to produce a desired effect on a cell, tissue, or organism — without knowing the exact molecular target at the beginning.
This approach focuses on observing the phenotype (the visible biological response).

Example: Discovery of Penicillin by Alexander Fleming was a result of observing bacterial cell death, even though the molecular mechanism was unknown at that time.

Another example is Aspirin, which was discovered for its pain-relieving effects long before its mechanism (COX enzyme inhibition) was understood.
Advantages:

- Can discover novel mechanisms and unexpected targets.
- Useful when the disease biology is poorly understood.

Disadvantages:
- Difficult to optimize molecules without knowing the specific target.
- High time and cost due to broad experimental testing.

2. Rational (Target-Based) Drug Discovery (RDD):

Rational drug discovery is a modern, scientific, and systematic approach that begins with identifying and understanding a specific biological target such as an enzyme, receptor, or protein that plays a key role in disease development.
After target identification, molecules are designed or selected to specifically interact with that target to modify its activity.
Example:

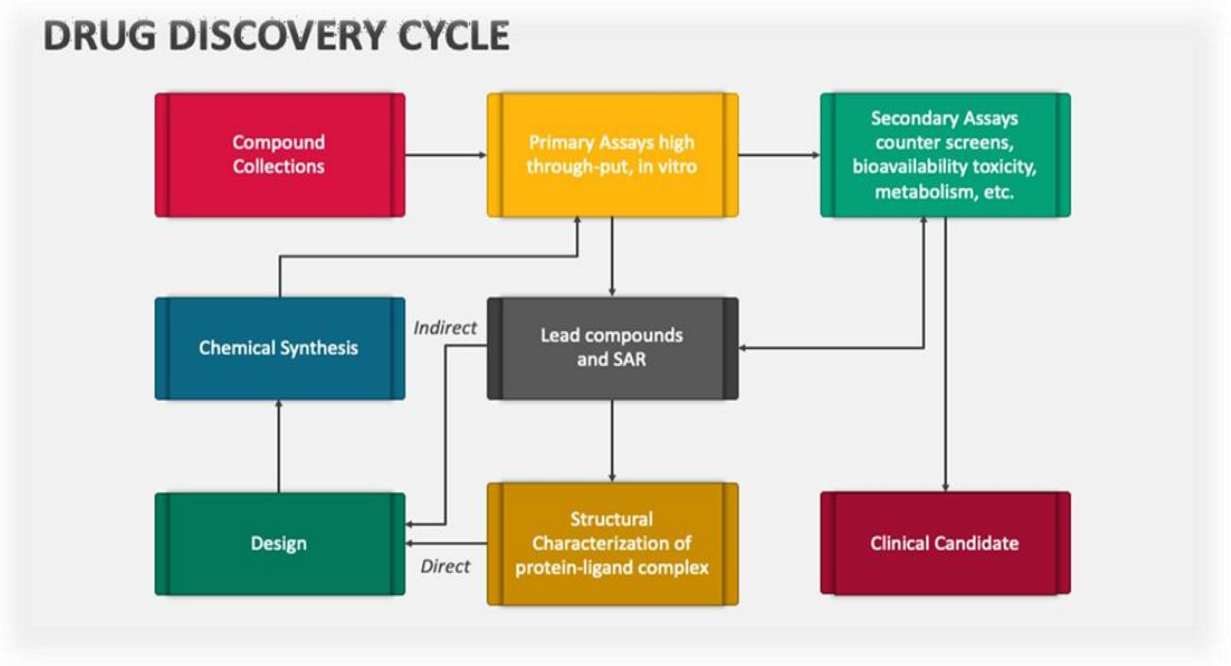
- Atorvastatin (Lipitor) was developed using rational design to inhibit the enzyme HMG-CoA reductase, which reduces cholesterol biosynthesis.
- Captopril was designed based on the active site of the angiotensin-converting enzyme (ACE).

Advantages:
- More predictable and efficient compared to phenotypic methods.
- Supports computer-aided drug design (CADD), molecular modeling, and docking techniques.

Disadvantages:
- Requires detailed knowledge of the disease target.
- May miss new mechanisms or off-target

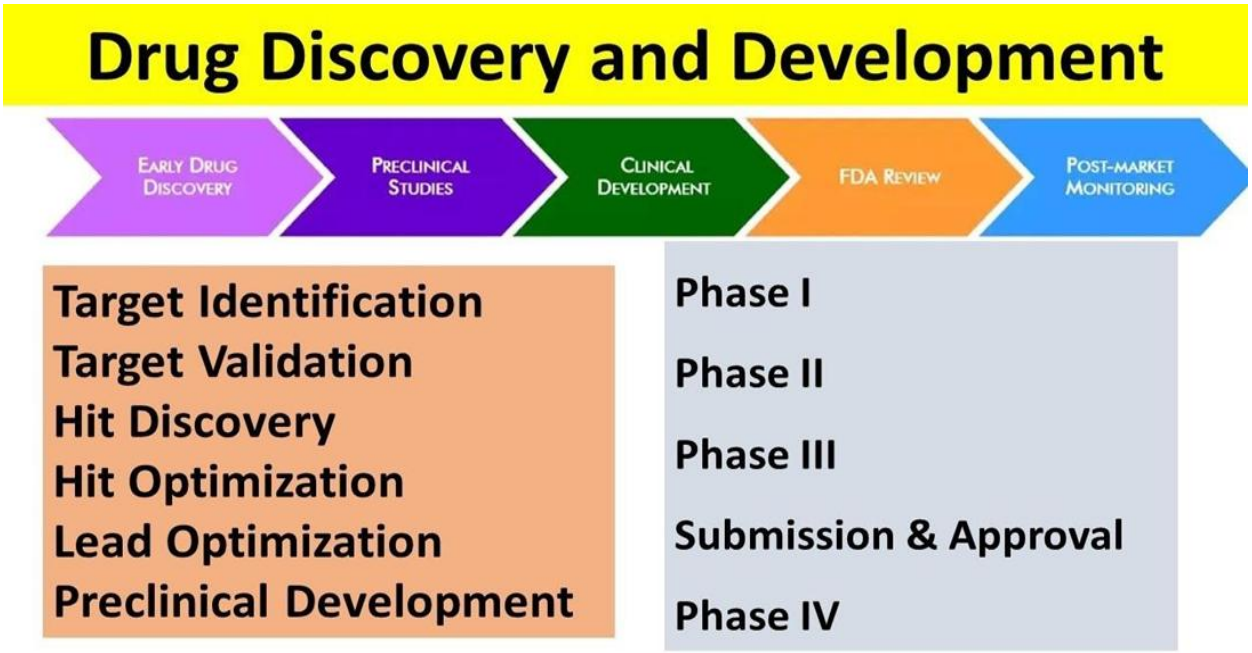
effects that could be beneficial.

"Both these approaches form essential parts of the overall Drug Discovery Cycle, which involves several systematic steps — from target identification to clinical development."



The drug discovery cycle represents the process of identifying, designing, testing, and developing a new drug molecule. It starts with compound screening, followed by biological testing, optimization of lead compounds, and ends with clinical evaluation and approval. This cycle ensures that safe, effective, and specific drug candidates reach the market.

V. STAGES OF DRUG DISCOVERY AND DEVELOPMENT



Following are the different stages which are required to get approval of a new drug for market authorization from the Food and Drug Administration (FDA):

1. Target Identification
2. Target Validation
3. Lead Identification
4. Lead Optimization
5. Product Characterization
6. Formulation and Development
7. Pre-Clinical Studies
8. Investigational New Drug (IND)
9. Clinical Trials
10. New Drug Application (NDA) & Approval

1. Target Identification

Every year thousands of molecules are discovered through high-throughput screening which helps in identifying suitable biological targets. By interaction with these targets, potential drug molecules are assessed. Lead compounds are further screened after assessment and then checked for their pharmacological properties and activities to develop safe and effective medicine.

The first step in drug discovery is the identification of the biological origin of a disease and potential molecular targets for intervention. Target identification begins with isolating the function of a possible therapeutic target such as a gene, nucleic acid, or protein, and understanding its role in the disease process.

Identification of targets is followed by characterization of the molecular mechanisms addressed by that target. The ideal drug target should be efficacious, safe, meet clinical and commercial requirements, and be druggable.

The techniques used for target identification are based on the principles of molecular biology, biochemistry, genetics, biophysics, or other related disciplines.

2. Target Validation

Target validation is the process by which the expected molecular target—such as a gene, protein, or nucleic acid—is confirmed to be directly involved in a disease process. This step certifies that modulating the target with a drug can produce the desired therapeutic effect.

It includes determining the structure–activity relationship (SAR) of analogs of the small molecule and monitoring the known signaling systems downstream of the presumed target. The validation ensures that the target selected is relevant, safe, and can yield measurable pharmacological effects.

Experimental methods such as gene knockout, RNA interference (RNAi), antisense oligonucleotides, and CRISPR/Cas9 genome editing are often employed to confirm target involvement.

3. Lead Identification

A chemical lead is defined as a synthetically stable, feasible, and drug-like molecule that exhibits biological activity in primary and secondary assays with acceptable specificity, affinity, and potency.

Lead identification involves screening large libraries of compounds using biochemical or cell-based assays to discover molecules that can interact with the validated target.

There are two main approaches:

- High-Throughput Screening (HTS): Automated testing of thousands of compounds against the target.
- Virtual Screening: Computer-based screening using molecular docking and computational chemistry methods.

After identification, the leads are subjected to biological evaluation, synthesis, and ADME (Absorption, Distribution, Metabolism, and Excretion) studies to ensure their suitability for optimization.

4. Lead Optimization

In this stage, the chemical structure of the identified lead is systematically modified to improve its potency, selectivity, and pharmacokinetic profile. Lead optimization focuses on:

- Improving efficacy and minimizing toxicity.
- Enhancing metabolic stability and bioavailability.
- Reducing off-target interactions.

Medicinal chemists modify functional groups, create analogs, and study Structure–Activity Relationships (SAR) to find the best optimized lead. Computational modeling and molecular

dynamics simulations are used to predict activity and improve performance before animal testing.

Lead Compound
↓
Structure Modification
↓
SAR (Structure–Activity Relationship) Studies
↓
Optimization of Pharmacokinetics & Toxicity
↓
Optimized Lead (Drug Candidate)

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.

6. Formulation and Development

Pharmaceutical formulation is a crucial stage of drug development in which the physicochemical properties of the active pharmaceutical ingredient (API) are evaluated and optimized to produce a bioavailable, stable, and effective dosage form suitable for the intended route of administration.

During pre-formulation and formulation studies, the following parameters are generally assessed:

- Solubility of the API in different solvents and media
- Dissolution behavior and rate of the drug
- Stability studies under accelerated and long-term storage conditions
- Solid-state characterization including polymorphism, particle size, and crystal shape
- Compatibility of the API with excipients
- Optimization of formulation composition to achieve desired drug release
- Development of new dosage forms and process optimization
- Novel formulation approaches for improved delivery, such as:
- Controlled and sustained-release formulations
- Self-emulsifying drug delivery systems (SEDDS)
- Colloidal, sub-micron, and nano-emulsion systems
- For Atorvastatin, formulation development especially important due to its low aqueous solubility and variable bioavailability. Hence, techniques such as solid dispersions, nano-formulations, and lipid-based carriers are often explored to enhance its solubility, stability, and therapeutic performance.

7. Pre-Clinical Studies

Preclinical studies involve the in vitro (test tube or cell culture and in vivo (animal) testing
of optimized compounds before human trials. The purpose is to evaluate safety, efficacy, pharmacokinetics (ADME), and toxicity.

These studies are divided into two parts:
Pharmacodynamics (PD): Understanding the mechanism of action and therapeutic effects.

Pharmacokinetics (PK): Studying absorption, distribution, metabolism, and excretion of the compound.

Toxicological studies determine the safe dose, potential organ damage, and carcinogenicity. Only the compounds that pass these tests are submitted for clinical trials

In case of In silico ; In silico drug design uses computer-based tools to design and analyse drug molecules before laboratory testing. It helps predict how a drug like Atorvastatin interacts with its target enzyme (HMG-CoA reductase) using molecular docking and ADMET studies, saving time and cost in drug discovery.

8. Investigational New Drug (IND)

Before a new drug can be tested in humans, the sponsor (usually a pharmaceutical company or research team) must submit an Investigational New Drug (IND) application to the regulatory authority such as the U.S. Food and Drug Administration (FDA) or the Central Drugs Standard Control Organization (CDSCO) in India. The IND application provides evidence that the drug is safe for initial testing in humans and that the proposed clinical study design is scientifically sound and ethical.

Key Components of an IND Application:

1. Preclinical Data: Results of animal studies showing safety, toxicity, and pharmacological effects.
2. Chemistry, Manufacturing, and Control (CMC) Information: Details of drug composition, formulation, purity, and manufacturing process.
3. Clinical Trial Protocols: The plan for human testing—study design, dosage, number of participants, and safety monitoring methods.
4. Investigator's Brochure: Information for clinical investigators about the drug's pharmacology and previous research findings.
5. Regulatory and Ethical Approvals: Institutional Ethics Committee (IEC) or Institutional Review Board (IRB) approvals ensuring patient safety and informed consent.

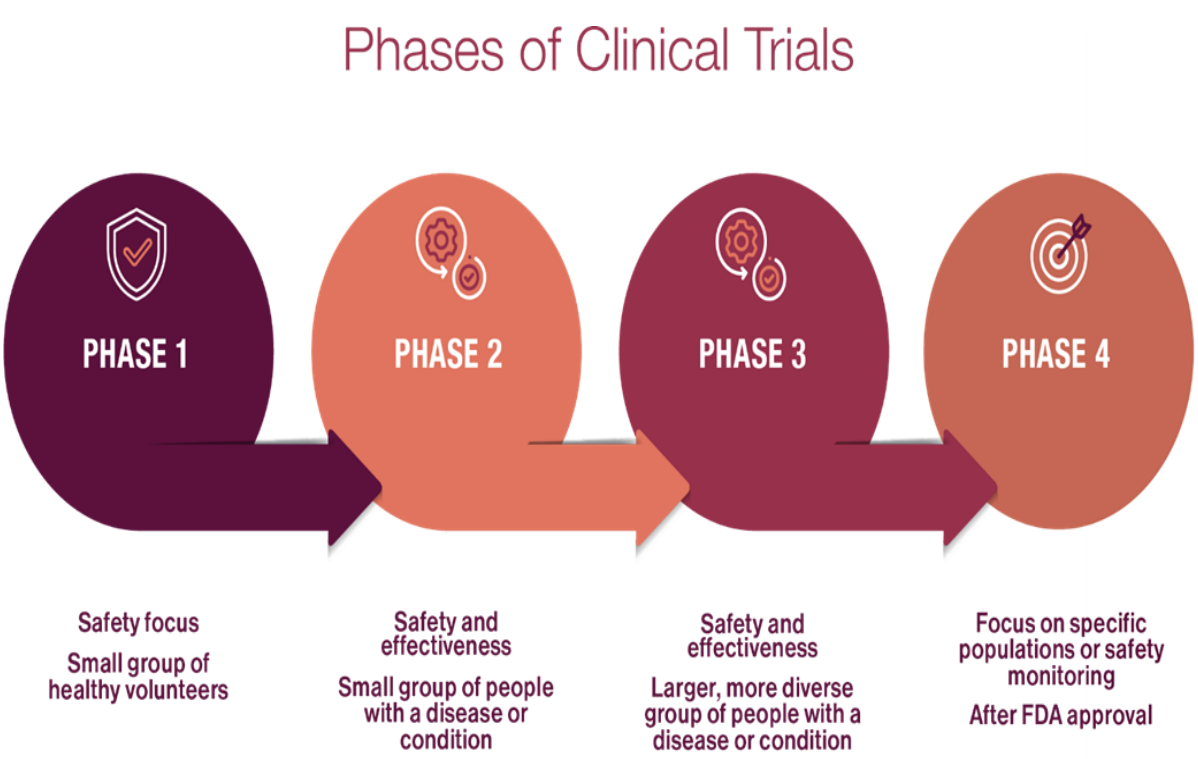
Purpose of IND:

The main purpose of filing an IND is to obtain permission to begin clinical trials in humans after demonstrating sufficient safety in preclinical testing. Once approved, the IND becomes active, and the clinical development of the drug can proceed in Phase I trials.

9. Clinical Trials

After obtaining approval for the Investigational New Drug (IND), the drug enters the clinical trial phase, where it is tested on human volunteers to evaluate its safety, efficacy, dosage, and side effects.

Clinical trials are conducted in four main phases (I–IV) under strict regulatory and ethical supervision.



1. Phase I – Safety and Dosage Studies

- Conducted on a small group (20–100) of healthy volunteers.
- Main aim: To determine the safe dosage range, pharmacokinetics, and pharmacodynamics of the drug.
- Also helps identify any immediate side effects or toxicity.

2. Phase II – Efficacy and Side Effect Studies

- Conducted on a larger group (100–300) of patients who have the disease.
- Main aim: To evaluate the effectiveness of the drug and further assess safety.
- Helps to determine optimal dose and refine dosage regimen.

3. Phase III – Large-Scale Efficacy and Monitoring

- Involves a large population (1,000–3,000 patients) in multiple centers.
- Aim: To confirm therapeutic effectiveness, monitor adverse effects, and compare the new drug with standard treatments.
- Successful completion leads to submission of a New Drug Application (NDA) for marketing approval.

4. Phase IV – Post-Marketing Surveillance

- Conducted after the drug is approved and marketed.
- Aim: To detect long-term side effects, rare adverse reactions, and assess real- world effectiveness.
- Provides ongoing data for drug safety monitoring.

VI. PURPOSE OF CLINICAL TRIALS:

Clinical trials ensure that the drug is safe, effective, and beneficial for human use. Each phase builds upon the results of the previous stage to move the drug closer to regulatory approval and commercial production.

10. New Drug Application (NDA) & Approval

After successful completion of all four phases of clinical trials, the sponsor (usually a pharmaceutical company) prepares and submits a New Drug Application (NDA) to the regulatory authority such as the U.S. FDA or CDSCO (India) for

permission to market the drug.
The NDA contains comprehensive data proving that the drug is safe, effective, and manufactured under quality standards.

Contents of NDA:
1. Preclinical and Clinical Data: Complete results from all studies showing safety and efficacy.
2. Drug Composition and Manufacturing: Information on formulation, manufacturing site, and process validation.
3. Labelling Information: Proposed packaging, prescribing information, and usage instructions.
4. Safety Updates: Adverse event reports from clinical trials.
5. Regulatory and Quality Compliance Documents.

Evaluation Process:
The regulatory authority reviews the NDA to ensure the drug meets safety, efficacy, and quality requirements.
Expert committees may conduct additional reviews or request more data.

If approved, the drug is granted a marketing authorization, allowing it to be sold and prescribed.

Post-Approval Monitoring:
Even after approval, the drug undergoes Phase IV (post-marketing surveillance) to monitor rare side effects and long-term safety.
Example:

For Atorvastatin, the NDA submission included extensive data on its lipid-lowering efficacy and safety profile, leading to its approval for managing hypercholesterolemia.

VII. FDA REVIEW AND APPROVAL

Once the New Drug Application (NDA) is submitted, it undergoes a thorough evaluation by the Food and Drug Administration (FDA). The purpose of this review is to ensure that the drug is safe, effective, and of high quality before it reaches the public.
The FDA review is a critical step in the drug development process, where all preclinical and clinical data, manufacturing details, labelling information, and proposed usage are examined in detail.

Steps in FDA Review Process:
1. Filing Review:
The FDA first checks whether the NDA is complete and acceptable for full review. If accepted, the review clock (usually 10 months for standard review or 6 months for priority review) begins.
2. Scientific Review:
Teams of experts analyse data from preclinical and clinical studies. They evaluate:

- Safety profile (toxicology, side effects, adverse events)
- Efficacy (how well the drug works)
- Dosage form and administration
- Labelling accuracy (information for doctors and patients)
- Chemistry, Manufacturing, and Controls (CMC) data

3. Facility Inspection:
The FDA inspects the manufacturing facility to ensure Good Manufacturing Practices (GMP) are followed, ensuring quality and purity of the drug.

4. Advisory Committee Review (if needed):
Sometimes, the FDA seeks advice from an independent committee of experts who review the data and provide recommendations.

5. Decision Phase:
After reviewing all evidence, the FDA may:
Approve the drug (if benefits outweigh risks)
Request additional studies or data
Reject the application if serious issues are found

6. Post-Approval Requirements:
Even after approval, the FDA may require Phase IV (post-marketing) studies to monitor long-term safety and real-world effectiveness.

Purpose of FDA Review

✅ Protect public health by ensuring only safe and effective drugs reach the market.

✅ Confirm that the drug labelling provides accurate information for safe use.

✅ Maintain quality standards in manufacturing and distribution.

VIII. POST-MARKETING SURVEILLANCE (PHASE IV STUDIES)

After a new drug receives regulatory approval and enters the market, it continues to be monitored through post- marketing surveillance, also known as Phase IV clinical trials.

This stage ensures that the drug remains safe, effective, and of high quality when used by a large and diverse population in real-life conditions.

Objectives of Post-Marketing Surveillance:

1. To detect rare or long-term adverse drug reactions (ADRs) that may not appear during earlier clinical trials.
2. To evaluate the drug's performance, effectiveness, and safety in real-world conditions.
3. To identify drug–drug or drug–food interactions.
4. To monitor prescribing patterns and patient compliance.
5. To collect feedback for potential label updates or dosage adjustments.

Methods of Post-Marketing Surveillance:

- Spontaneous Reporting System (SRS): Healthcare professionals report ADRs to pharmacovigilance center.
- Prescription Event Monitoring (PEM): Continuous monitoring of prescriptions to assess drug performance.
- Cohort Studies and Registries: Long-term studies conducted in patients using the drug.
- Pharmacovigilance Programs: Conducted by companies and regulatory agencies to maintain ongoing safety data.

Example – Atorvastatin:
After Atorvastatin was launched, post-marketing studies monitored side effects like muscle pain, liver enzyme elevation, and rare myopathy cases. Such data helped in updating safety warnings and ensuring proper patient use.

IX. CONCLUSION

Drug design and development is a systematic and multidisciplinary process that transforms a chemical molecule into a safe and effective therapeutic agent.
In our study on Atorvastatin, various stages were explored — from computer-aided drug design (CADD) and in silico modeling, to preclinical testing, clinical trials, and regulatory approval.
Atorvastatin acts as a potent HMG-CoA reductase inhibitor, effectively reducing cholesterol synthesis and preventing cardiovascular diseases.
Through this project, we understood how scientific, computational, and regulatory approaches come together to ensure the development of a safe, effective, and high-quality medicine for public health.

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