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DRUG DISCOVERY AND DEVELOPMENT

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ABSTRACT

The process of drug discovery aims to find a compound that can be used to treat and cure diseases. It involves identifying potential candidates, synthesizing, characterizing, validating, optimizing, and screening them for therapeutic efficacy. Once a promising compound is identified, it goes through a rigorous drug development process that includes clinical trials and regulatory approvals to ensure it is safe and effective. This process is lengthy, complex, and expensive, requiring the consideration of multiple biological targets for every new medicine. New research tools may be necessary to investigate these targets. It takes around 12-15 years and a billion dollars to develop a marketable medicine. On average, only one out of a million screened molecules makes it to late-stage clinical trials and is made available to patients. This article provides an overview of the drug discovery and development process.

KEYWORDS: Drug Discovery, Validation, Optimization, Screening, Clinical Trials etc.

INTRODUCTION

Discovering a new drug is a complex process that involves finding a chemical that can effectively treat a specific disease. Researchers use their understanding of the disease to design a medicine that can stop or reverse its effects. This involves identifying potential drug candidates, synthesizing and characterizing them, and screening for therapeutic effectiveness. If a molecule shows positive results in these investigations, it moves on to the drug development process, which includes clinical trials. However, drug discovery and development is an expensive process due to the high costs of research and clinical trials. It can take up to 15 years from discovery to market availability, with an average cost of $900 million to $2 billion per drug. For every 5,000 to 10,000 compounds investigated, only one

ultimately gains approval. Despite the challenges, success in drug discovery requires the best scientific minds, advanced laboratory technology, and project management skills, as well as persistence and good fortune. The end result of this process is hope, faith, and relief for billions of patients.

Stages of drug discovery and development include: - (As shown in figure no.1)

1. Target Identification
2. Target Validation
3. Lead Identification
4. Lead Optimization
5. Product Characterization
6. Formulation and Development
7. Preclinical Research
8. Investigational New Drug
9. Clinical Trials
10. New Drug Application
11. Approval

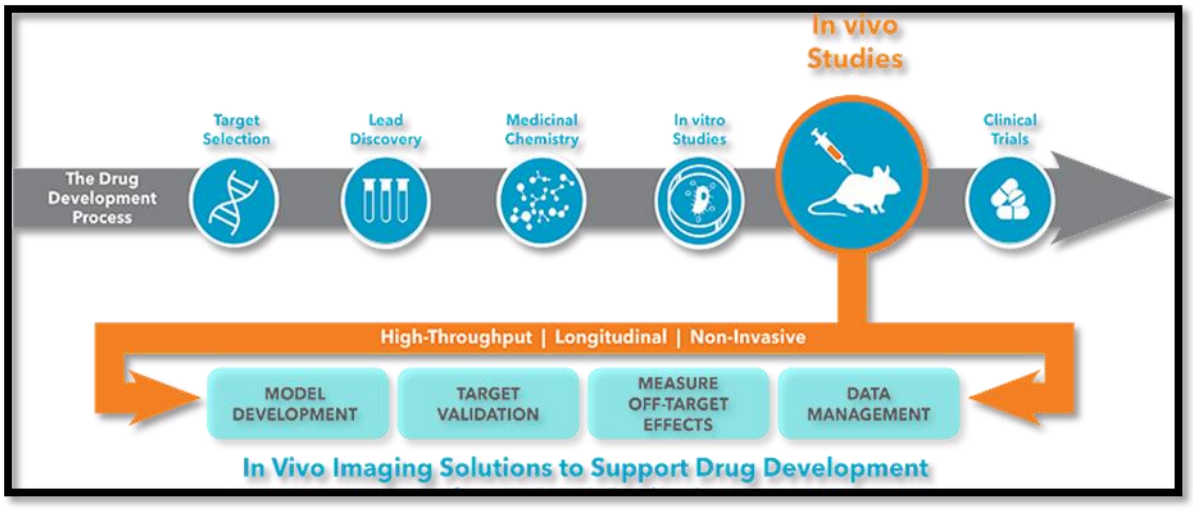

Figure No. 1: Stages of Drug Discovery and Development.

Target Identification

The initial step in discovering a drug involves identifying the biological origin of a disease and its potential targets for intervention. The process of target identification begins with determining the function of a possible therapeutic target, such as a gene, nucleic acid or protein, and its role in the disease. This is followed by characterizing the molecular

mechanisms that are addressed by the target. The ideal target should be effective, 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 related disciplines.

Ways to find Disease targets

- Bioinformatics Data Mining
- Genetic Association Studies
- Expression Profiling
- In Vitro Studies
- Functional Screening

Target Validation

The process of target validation involves confirming the expected molecular target, such as a gene, protein, or nucleic acid, of a small molecule. This process 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, and monitoring the known signaling systems downstream of the presumed target. The goal of target validation is to demonstrate the functional role of the identified target in the disease phenotype. While testing a drug's efficacy and toxicity in disease-relevant cell models and animal models is valuable, the ultimate test is whether the drug works in a clinical setting.

Target Validation can be divided into two steps

1. **Reproducibility**

When a potential drug target is found, either through a particular method or by reviewing existing research, the initial step is to replicate the experiment to ensure its success. The process of validating the target involves various techniques, such as affinity chromatography, expression cloning, protein microarrays, reverse transfected cell microarrays, biochemical suppression, siRNA, DNA microarrays, system biology, and analyzing existing medication.

2. **lead Identification**

A chemical lead is a molecule that is synthetically stable, feasible, and drug-like. It should be active in both primary and secondary assays, and have acceptable specificity, affinity, and selectivity for the target receptor. To achieve this, the structure activity relationship needs to

be defined, and synthetic feasibility and preliminary evidence of in vivo efficacy and target engagement should be determined.

Characteristics of a chemical lead are

- SAR defined
- Drug ability (preliminary toxicity, hERG)
- Synthetic feasibility
- Select mechanistic assays
- In vitro assessment of drug resistance and efflux potential
- Evidence of in vivo efficacy of chemical class
- PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

To prevent a large number of compounds from failing during the drug development process, an assessment of their drug ability is often conducted. This assessment is crucial in turning a lead molecule into a drug. A compound can be considered druggable if it has the potential to bind to a specific target and if it also has a good pharmacokinetic profile in terms of absorption, distribution, metabolism, and excretion. Additional assays, such as the Ames test and cytotoxicity assay, can also be used to evaluate the potential toxicity of the compound.

Lead Optimization

Lead optimization involves designing a drug candidate after identifying an initial lead compound. Potential leads are evaluated for selectivity, binding mechanisms, and other properties to identify promising compounds. Researchers alter the chemical structures of lead compounds to enhance target specificity, selectivity, and other properties. They rely on high throughput DMPK screens to improve drug potency and safety. Drug discovery labs use automated systems like mass spectrometry and MALDI imaging to detect and evaluate drug candidates and metabolites in tissues. NMR Fragment-based Screening is also widely used to optimize lead molecules in targeted screening campaigns.

Product Characterization

When a new drug molecule exhibits promising therapeutic activity, it must undergo product characterization to determine its size, shape, strength, weakness, use, toxicity, and biological activity. This process is particularly useful in the early stages of pharmacological studies as it helps to characterize the mechanism of action of the compound.

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 preformulation studies the following parameters are evaluated

- Solubility in different media and solvents.
- Dissolution of the active pharmaceutical ingredient (API).
- Accelerated Stability Services under various conditions.
- Solid state properties (polymorphs, particle size, particle shape etc.).
- Formulation services and capabilities.
- Formulation development of new chemical entities (NCE).
- Optimization of existing formulations.
- Process development for selected dosage forms.
- Novel formulations for improved delivery of existing dosage forms.
- Controlled release and sustained release formulations.
- Self-emulsifying drug delivery systems.
- Colloidal drug delivery systems.
- Sub-micron and Nano-emulsions.

Preclinical Trials

The process of developing drugs involves pre-clinical research, which includes testing the drug's safety and effectiveness in animal species before testing on humans. Regulatory authorities must approve pre-clinical trials to ensure they are conducted safely and ethically. Only drugs that are confirmed to be safe and effective will receive regulatory approval. The International Council for Harmonization (ICH) has established guidelines for pre-clinical drug development. (As shown in figure No.2).

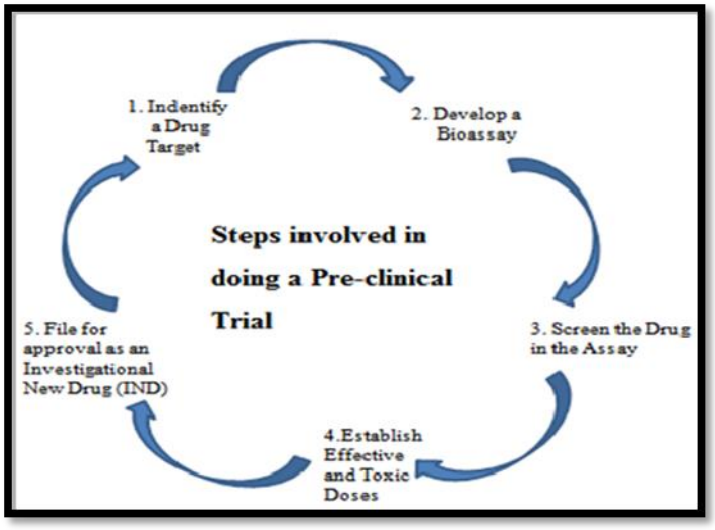

Figure No. 2: Steps in Preclinical Trials.

Pre-clinical trials can be conducted through two methods.

1. **Pharmacology: -** Pharmacology examines the drug's Pharmacokinetic and Pharmacodynamics parameters and explores unwanted pharmacological effects in animal models. Pharmacokinetic studies are vital as they provide information on absorption rates and help determine dosage form, distribution, metabolism, and elimination.
2. **Toxicology: -** Toxicology studies evaluate the drug's toxicological effects through in-vitro and in-vivo testing. The appropriate animal species must be selected for toxicity study as many drugs are species-specific.

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

Investigational New Drug

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

Clinical Trials

Clinical trials test drugs, vaccines, and treatments for safety and effectiveness. Researchers create a study plan, analyze existing information, and follow a protocol. (As shown in figure No.3) Then, they decided.

Selection criteria for participants

- Number of people take part of the study.
- Duration of study.
- Dose and route of administration of dosage form.
- Assessment of parameters.
- Data collection and analysis.

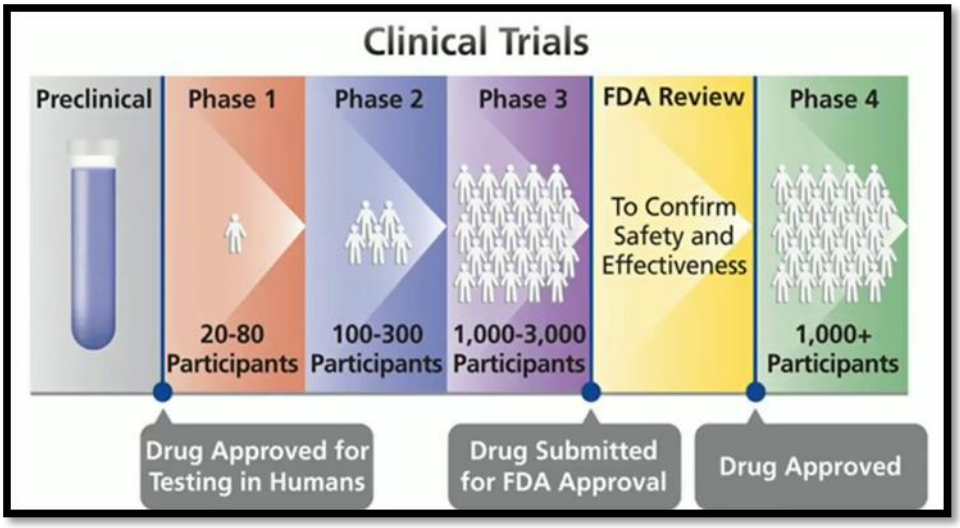

Figure No. 3: Phases of Clinical Trials.

Phase 0.

Phase 0 involves investigative trials that are conducted in accordance with FDA guidelines and are the first to be conducted on humans. These trials are also known as human micro dose studies, where a single sub-therapeutic dose is given to 10 to 15 volunteers to collect pharmacokinetic data or help with imaging specific targets without exerting pharmacological actions. Pharmaceutical companies conduct Phase 0 studies to determine which of their drug candidates has the best pharmacokinetic parameters in humans.

Phase 1.

The first stage of testing a new drug is Phase 1 trials, which involve a small group of healthy human volunteers ranging from 20 to 80 participants. If the drug's mechanism of action

suggests that it may not be well-tolerated by healthy individuals, patients with the targeted disease/condition may also participate. For example, if a new drug is intended for diabetes treatment, Phase 1 trials may include patients with diabetes. During Phase 1 studies, researchers closely monitor the pharmacodynamics of the drug in the human body, adjusting the dosage regimen based on animal study data to determine the appropriate dose and potential acute side effects. Over the course of the trial, researchers gather information about the drug's mechanism of action, any accompanying side effects with increasing dosage, and its effectiveness, which is vital for designing Phase 2 studies. Approximately 70% of drugs move on to the next phase after Phase 1 trials.

Phase 2.

Phase 2 trials involve studying larger groups of patients to evaluate drug efficacy and confirm safety assessments from Phase 1. They provide safety data for researchers to refine research questions and design protocols for Phase 3 studies. Only about 33% of drugs proceed to Phase 3. Phase 2 studies establish therapeutic doses for larger-scale Phase 3 studies.

Phase 3.

Phase 3 studies involve up to 3,000 volunteers and focus on determining the safety of a product. If a drug is deemed safe and effective, the developer can apply for FDA approval. The FDA reviews all submitted data to determine if approval should be granted.

New Drug Application

The purpose of a New Drug Application (NDA) is to provide a comprehensive report about a drug molecule, verifying its safety and effectiveness for its intended use. To create an NDA, drug developers must include all relevant information about the drug, from preclinical data to Phase 3 trial data. This includes detailed reports on all studies, data, and analysis conducted.

In addition to clinical trial results, developers must also include

- Safety updates.
- Information on drug abuse.
- Patent details.
- Details regarding compliance with institutional review board regulations.
- Instructions on how to utilize the product.

FDA Review

The FDA takes around 6 to 10 months to approve a complete NDA, but an incomplete one will be rejected. If a drug is deemed safe and effective, the developer must update its labeling information. Sometimes additional studies are required before approval, and developers can appeal an FDA decision. (As shown in figure no.4).

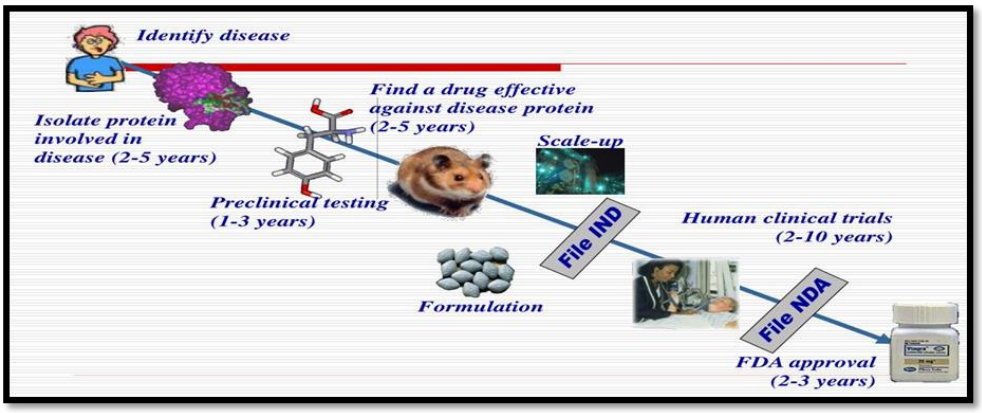

Figure No 4: Development of Drug.

Phase 4

Phase 4 trials occur after FDA approval of a drug or device. They are also referred to as post-marketing surveillance and require pharmacovigilance and ongoing technical support. Phase 4 trials utilize various observation techniques and assessment patterns to assess the safety, efficacy, and cost-effectiveness of the drug/device in real-world settings. Regulatory authorities may require Phase 4 studies due to changes in labeling or risk management plans, while the sponsoring company may undertake them for competitive reasons or other purposes. The true evaluation of a drug's safety requires monitoring over months or even years in the market. FDA reviews reports of complications with prescription and OTC drugs and can add precautions or additional safety information in response to serious adverse drug reactions.

CONCLUSION

Drug discovery aims to cure diseases by identifying, synthesizing, characterizing, validating, optimizing, and screening compounds for therapeutic efficacy. Promising compounds undergo a rigorous drug development process, including clinical trials and regulatory approvals. This process is lengthy, complex, and expensive, requiring consideration of multiple biological targets and the use of new research tools. It takes 12-15 years and a

billion dollars to develop a marketable medicine. Only one out of a million screened molecules makes it to late-stage clinical trials and is made available to patients.

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