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A REVIEW ON THE STAGES OF DRUG DISCOVERY & DRUG DEVELOPMENT PROCESS

[1]Mr. Prashant D. Rathod, [2]Mr. Mukesh M. Nikhade, [3]Mr. Nayan D. Chaudhari, [4]Mr. Gajanan V. Jadhao, [5]Mr. Avinash B. Gore

[1]B. Pharmacy, [2]M. Pharmacy (Pharmacology), [3]B. Pharmacy, [4]B. Pharmacy, [5]B. Pharmacy

Jagadambha Institute of Pharmacy And Research, Kalamb , Maharashtra, India.

Abstract:

Drug discovery is the process of identifying a compound therapeutically useful in the treatment and cure of disease and therapeutic efficacy tests. Once a compound proves its worth in these studies, it begins the drug development process before clinical trials. It takes about 12 to 15 years from discovery to an approved drug and requires an investment of about $1 billion. On average of the million molecules are screened, but they only one is explored in the late stages of clinical trials and is finally available to patients. This article provides a brief outline of the processes involved in the discovery and development of new drugs. This testing is done on cells (in vitro) and animals (in vivo) to study metabolism and to produce a product that is safe and meets all regulatory requirements. It may be a protein receptor that is related to a disease state, so it is important to know how the disease occurs at the molecular, cellular and genetic level. Once a target is identified, the next step is how the target plays a role in the disease process. The development and discovery of a new drug to treat a disease is expensive and requires up to 14 years of research and testing. Proper procedure requires a step-by-step approach along with well documentation. The work usually begins with target identification and validation. Optimization, lead compound discovery, and preclinical animal testing are the various stages that must be followed by clinical trials and evaluation of drug candidates in humans. This review article will cover the key concepts of drug discovery, drug development and the clinical phases of drug discovery.

Key words: Lead optimization, clinical phase trial, target validation, target identification, Investigation new drug.

INTRODUCTION

The development of a new drug has a significant share in the expenditure of the healthcare system. The development and discovery of a new drug ranged between $314 million and $2.8 billion [1]. During the covid pandemic, Pfizer claimed to have invested $2 billion in the development of a covid vaccine [2]. This complicated process has different stages and phases. The time for the regular discovery and development of a new agent, from start to approval by the authority, takes up to 14 years [3]. the development of new drugs is very complex, expensive and risky. Its success is highly dependent on intensive collaboration and interaction between every department within the drug development organization, the external researchers and Purchase, in continuous dialogue with regulators, academics, healthcare provider and patient organizations. Within the different phases of the drug life cycle, drug development is by for the very important part for the initial and continued success

of a drug in the market [4,5]. The drug discovery process involves a combination of many disciplines and interests. from a simple process of identifying the active compound. The discovery of a new chemical entity that modifies the function of a cell or tissue is only the first step in the drug development process. Once proven to be effective and selective, the compound to be discovered in must be fully non-toxic, in the good bioavailability, and to be marketable before it can be considered the therapeutic entity [6]. The drug discovery process involves identifying drug candidates, synthesis, characterization, screening and tests of therapeutic efficacy. When a molecule uses its satisfactory results in these studies, it begins the process of drug development after clinical trials. Drug discovery and development is an expensive process due to high budgets for research and development and clinical trials. The development of a single molecule of a new drug takes almost 12–15 years from the time it is discovered to when it is available on the market for treating patients.[7]. Average research and development costs for each effective drug are likely to be between $900 million and $2 billion. This number includes cost of the thousands of failures: For in the whole lot 5,000–10,000 compounds that enter the investigation and drug development process, only one ultimately wins approval. These statistics defy the imagination, but a brief understanding of the research and development process can explain why it is such a large and lengthy effort to get a single drug to patients.[8]. Success requires vast resources, the best scientific and logical minds, highly sophisticated laboratory and technology; and multifaceted project management. It also requires persistence and luck.[9]. the drug discovery process brings hope, faith, and relief to billions of patients.[10].

Stages of drug discovery and development include:

- Target identification
- Target validation
- lead identification
- lead optimization
- Product characterization
- Formulation and development
- Preclinical research
- Investigational New Drug
- Clinical trials
- New Drug Application
- FDA Review
- FDA Approval
- Post-Market Drug Safety Monitoring [Phase-IV]

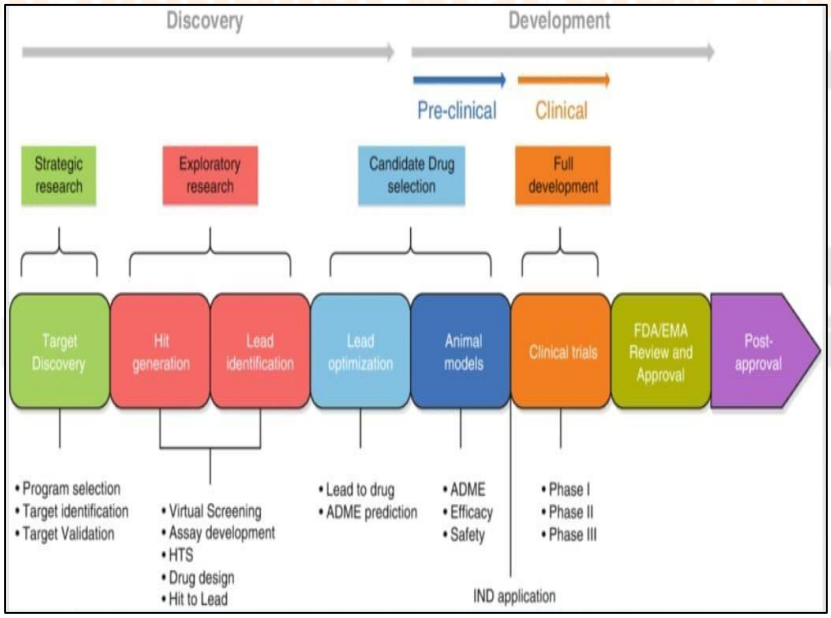

Figure 1.1 The process of drug discovery and drug development

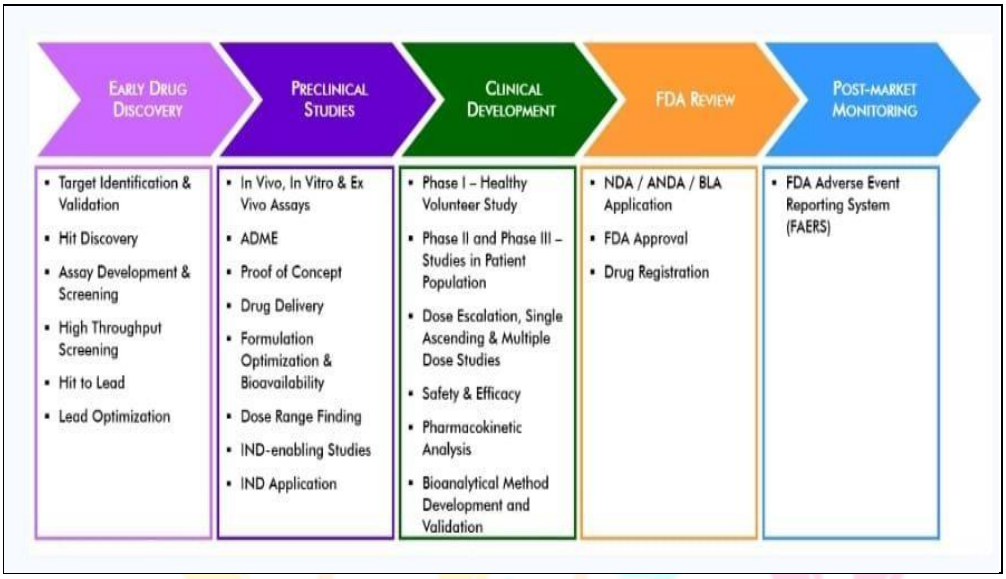

Figure 1.2 The Stages of drug discovery and development process

Target identification

The first step in drug discovery is to identify the biological origin of the disease and potential targets for intervention. Target identification begins with isolating the function of a potential therapeutic target (gene/nucleic acid/protein) and its role in disease. target identification can be based on the principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines [11].

Approaches:

- identification, selection and prioritization of potential disease targets
- genetic polymorphism and association with disease
- changes in mRNA/protein levels
- In vitro study of cellular mechanism
- knockdown, knockout or use of target-specific tools [12].

Target verification

Once the target is identified, it needs to be verified. In this step, researchers use different methods to verify and understand the therapeutic effect of the target. Without verification, the target cannot be studied further in the development process. Target validation has various aspects that include monitoring target capacity, defining a metric method as a marker for target evaluation, screening to find hits. High- throughput screening (HTS) is a way to identify a lead compound from other candidates and ignore weak and false targets. HTS involves screening all candidates with a target or in a test system to see if the activity is relevant to the target [13]. Validation can also be done by various techniques. Antisense tool that uses RNA-like compounds, transgenic animals to observe drug effect, tissue restriction and knockout method, monoclonal antibodies and more recently chemical genomics are examples of these techniques and tools [14].

Lead of identification

A chemical lead is defined as a chemically stable, feasible and drug-like molecule active in primary and secondary assays with acceptable specifically, correlation and selectivity for the target receptor. This requires definition of the structure-activity relationship, as well as determination of artificial feasibility and primary evidence of in vivo efficacy and target engagement. The properties of chemical lead are:

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

To reduce the number of compounds that fail in the drug development process, drug potency evaluation is often performed. This evaluation is important in the transformation of a compound from a lead molecule to a drug. To be considered a drug, a compound should have the potential to bind to a specific target; however, distribution, metabolism and excretion are also important. Other tests will evaluate the potential toxicity of the screening compound, such as the Ames test and the cytotoxicity test [15].

Lead optimization

The Lead optimization is process by which a drug candidate is designed after an original lead compound is identified. The process involves an iterative series of syntheses and characterizations of a potential drug to create a representation of how chemical structure and activity relate to interactions with its targets and its metabolism. In initial drug discovery, resulting leads from high-throughput screening tests undergo hit-to-lead optimization to identify promising compounds. Potential leads are evaluated for a number of properties, including selectivity and binding mechanisms during lead optimization, the final step in prematurely stage drug discovery. The purpose of lead optimization is to preserve the beneficial properties of lead compounds while improving the deficiencies in the lead structure. In order to produce a preclinical drug candidate, the chemical structures of the lead compounds (small molecules or biologics) need to be altered to improve target specificity and selectivity. Pharmacodynamic and pharmacokinetic parameters and toxicological properties are also evaluated. Laboratories must obtain data on the toxicity, potency, stability, and bioavailability of the lead in order to accurately characterize the compound and establish an optimization path [16].

Product characteristics

When some unique new drug molecule shows promising therapeutic activity, the molecule is characterized by its size, shape, potency, weakness, use, toxicity, and biological activity. Early stages of pharmacological studies are helping to characterize the compound's mechanism of action

Formulation and development

Pharmaceutical formulation is the stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized in order to create a bioavailable, stable and optimal dosage form for a specific route of administration [17].

The following parameters are evaluated during preformulating studies

- Solubility in various media and solvents
- Dissolving the active pharmaceutical ingredient (API)
- Accelerated stability services under various conditions
- Properties of the solid phase (polymorphs, particle size, particle shape, etc.)
- Formulation services and capabilities
- Development of new chemical entity (NCE) formulations
- Optimization of existing recipes
- Process development for selected dosage forms
- New formulations for improved delivery of existing dosage forms
- Formulation with controlled and extended release
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Submicron and nano emulsions

Preclinical research

Before testing a drug on humans, scientists must determine whether it has the potential to cause serious harm to humans. Preclinical studies are performed on animal models in laboratory conditions [18].

There are two types of preclinical research:

- In Vitro: These experiments are performed outside animals in controlled laboratory conditions.
- In vivo: These experiments are performed inside animals [19].

Preclinical studies are usually not very extensive. all the sum, these studies need provide detailed information on dosage and toxicity levels. After preclinical testing, scientists review their findings and decide whether the drug can be tested in humans [20].

Various experiments conducted during these studies include

- Single dose toxicity studies
- Repeated dose studies

• Pharmacological safety studies
• Genotoxicity studies
• Carcinogenicity studies
• Reproductive toxicity studies

Investigational New Drug Process (IND)

Drug developers must file an Investigational New Drug application with the FDA before beginning clinical research. In the IND application, developers must include:
• Data from preclinical studies and toxicity studies
• Information on pharmaceutical production
• Clinical research protocols for studies to be conducted
• Data from previous clinical research (if any)
• Investigator/developer information [21].

Clinical trials

Clinical trials are conducted on people (volunteers) and are designed to answer specific questions about the safety and effectiveness of drugs, vaccines, other therapies, or new methods of using current treatments. Clinical trials follow a specific study protocol designed by the investigator or investigator or manufacturer. When developers design a clinical trial, they consider what they want to complete for each of the different phases of clinical research and begin the investigational new drug (IND) process, the process they must go through before clinical research can begin. Before starting a clinical trial, researchers review previous information on the drug to develop research problem and objectives. They then decide:

- Criteria for selecting participants
- Number of people perform in the study
- Length of study Dosage and method of administration of the dosage form
- Assessment of parameters
- Data collection and analysis

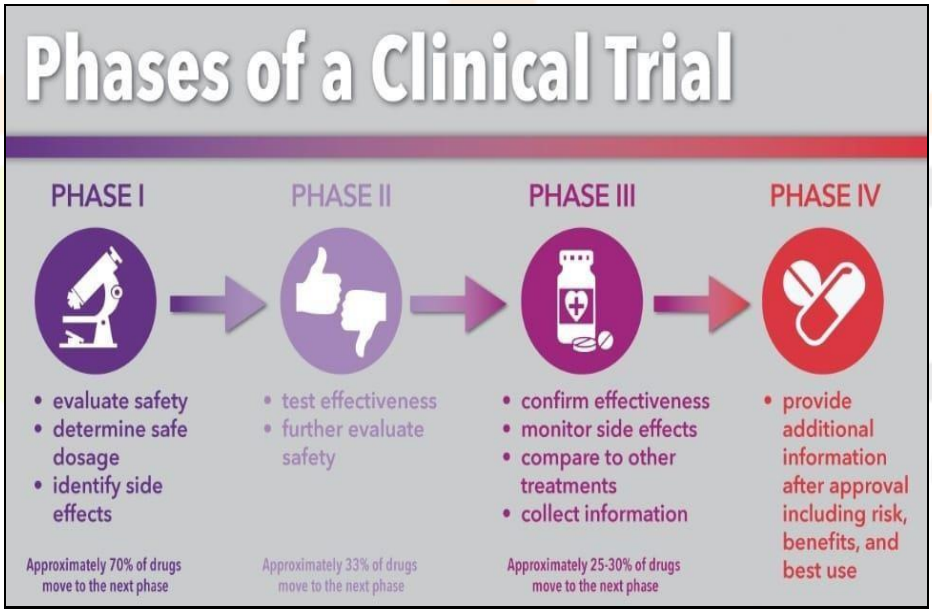

Figure 2.1 Clinical Trials

Phase 0 clinical trial

Phase 0 implies investigational, first-in-human (FIH) studies that are conducted according to FDA guidelines. Phase 0 studies, other than those referred to as human micro dose studies, have individual subtherapeutic doses administered to 10 to 15 volunteers and provide pharmacokinetic data or assist in imaging specific targets without pharmacological action. The pharmaceutical industry conducts phase 0 studies to select which of their drug candidates have superior pharmacokinetic parameters in humans [22].

Phase 1: Safety and Dosage

Phase I trials are the first tests of a drug with a smaller number of healthy human volunteers. In most cases, Phase 1 involves 20 to 80 healthy volunteers with a disease/condition. Patients are generally used only if the mechanism of action of the drug indicates that it will not be tolerated by healthy people. However, if a new drug is designed for use in patients with diabetes, researchers will conduct phase 1 trials in patients with this type of diabetes. Phase 1 studies are carefully monitored and gather information on pharmacodynamics in the human body. Scientists adjust the dosage regimen based on data from animal studies to determine how much of the drug the body tolerates and what its acute side effects are. As the Phase 1 study continues, researchers are investigating the mechanism of action, side effects accompanying dose increases, and efficacy information. This is necessary for the design of phase 2 studies. Almost 70% of drugs go to the next phase.

Phase 2: Efficacy and side effects

Phase II studies are conducted on larger groups of patients (several hundred) and aim to evaluate the drug's effectiveness and withstand Phase I safety evaluations. These tests are therapeutic. Phase 2 studies provide researchers with additional safety data. Researchers use this data to refine research questions, develop research technique, and design new phase 3 research protocols. About 33% of drugs go on to the next phase. Phase II clinical trials primarily help to find therapeutic doses for large phase III trials.

Phase 3: Monitoring the drug's effectiveness and side effects

The researchers are planning Phase 3 studies to show whether or not the product has actionable benefits for specific people. These studies, sometimes known as pivotal studies, involve 300 to 3,000 volunteers. Phase 3 studies provide most of the safety data. Previous studies may not be able to detect less common side effects. Phase 3 studies are conducted on large numbers. volunteers and of longer duration, the results are more likely to reveal long-term or less frequent side effects. Approximately 25-30% of drugs go into the next phase of clinical research. If a drug developer has data from its previous tests, preclinical and clinical studies that the drug is safe and effective for its intended use, the industry can apply to market the drug. The FDA's review team comprehensively reviews all submitted data about the drug and makes a decision whether to approve or not to approve it [23].

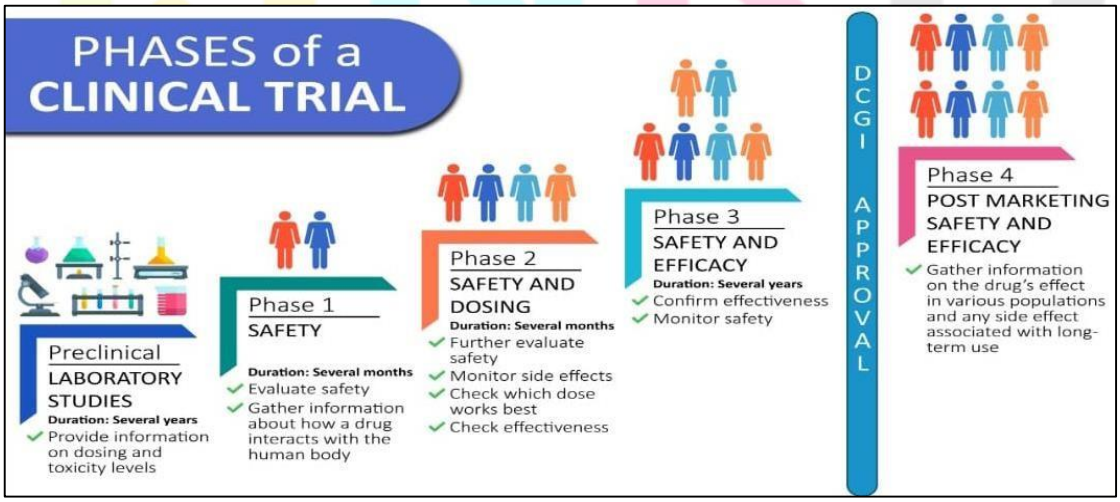

Figure 2.2 Phases of Clinical Trials

New drug application

A New Drug Application (NDA) tells the whole story of a drug molecule. Its purpose is to verify that the drugs safe and effective for its proposed use in the subjects being tested. A drug developer must include everything about the drug in the NDA, from preclinical data to Phase 3 study data. Developers must include reports of all studies, data, and analyses.

• Proposed labeling

• Security updates

• Information on drug abuse

• Patent information

• Institutional Review Board compliance information

• Instructions for use [24].

FDA review

Once the FDA receives the NDA, the review team determines whether it is complete. If incomplete, the review team may reject the NDA submission. If complete, the review team has 6 to 10 months to decide whether to approve the drug.

FDA approval

In cases where the FDA determines that a drug has been exhibited to be safe and effective for its conscious use, it must then work with the applicant to develop and clear the prescribing information. This is called "marking". The labeling corrects and objectives describes the basis for approval and how best to use the drug. However, remaining issues often need to be resolved before a drug can be approved for marketing. Sometimes the FDA requires the developer to answer questions based on existing data. In other cases, the FDA requires additional studies. In this point, the developer can decide whether to continue further development or not. If the developer take issue with the FDA's decision, there are formal appeal mechanisms.

Post-marketing drug safety monitoring (Phase IV)

This phase is also called Post Marketing Surveillance Trials. They are performed after the drug or device has been approved for consumer sale following regulatory approval. Pharmaceutical companies have several goals at this stage:
1. compare the drug with other drugs already on the market;
2. monitor the long-term effectiveness of the drug and the impact on the patient's quality of life; and
3. determine the cost-effectiveness of drug therapy compared to other available and new therapies. Phase 4 studies may lead to the drug or device being withdrawn from the market, use registrations may be placed on the product depending on the findings of the study [25].

CONCLUSION

Drug discovery and Drug devlopment be the creative process of finding new remedies base on knowledge of Biological target. drug discovery be the process by which potential new therapeatic entities are identified using a combination of compotationl, experimental, translational, and clinical models, every success is built on many, many previons failures, advances in understanding of human biology and disease are opening up exicting new possibilities for break throgh medicines.

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