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Review Article

The process of drug discovery and development consists of many stages.

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Abstract

The primary goal of the drug discovery process is to identify a chemical molecule that has therapeutic properties and has the potential to be used in the treatment and potential eradication of illnesses. The approach involves many stages: candidate identification, synthesis, characterization, validation, optimization, screening, and research to evaluate therapeutic efficacy. Once a chemical has shown its efficacy in this research, the process of drug development will begin prior to clinical trials. A treatment that satisfies all regulatory standards and is safe and effective has to undergo through multiple stages of the new drug development process. Our article's main thesis is that the procedure is so long away intricate, and costly that any new medication that is eventually approved for clinical usage must take into account a variety of biological targets, and it may be necessary to develop new research instruments in order to examine each new target. The journey from initial discovery to a marketable drug is a lengthy and arduous procedure. A substantial investment of about US $1 billion is required, and the process from discovery to obtaining an approved drug typically takes between 12 and 15 years. On average, one million compounds are screened, but only one is thoroughly explored at a later stage. The drug undergoes rigorous phase clinical trials before being made accessible to patients. This article provides a comprehensive description of the processes involved in the identification and creation of new pharmaceutical compounds

INTRODUCTION

Discovering a medication that has therapeutic value for treating and managing a medical condition is the first step in the complex process of drug discovery. Researchers often uncover innovative pharmaceuticals by gaining new understanding of the biology of a disease, enabling them to develop pharmaceuticals that may prevent or impede the progression of the condition.[1] The drug discovery process involves many processes, including the identification, synthesis, characterisation, screening, and testing of potential drug candidates for their medicinal effectiveness. If the results of clinical studies are satisfactory, a chemical will proceed with the process of drug development. The process of identifying and cultivating novel medications is expensive due to the elevated expenses associated with research and development as well as clinical trials.[2] The timeline for the development of a novel pharmaceutical compound usually spans around 12-15 years', beginning with its discovery and concluding when it is commercially ready for patient treatment. The average research and development costs for each efficacious treatment typically vary from $900 million to $2 billion. This amount encompasses the expenses incurred by the many failures.

Ultimately, only one chemical out of every 5,000–10,000 that undergoes research and development is given approval. These figures are astonishing, but a closer analysis of the research and development (R&D) process may explain why many compounds fail to reach the market and why it requires a significant investment of time and money to produce a single medicine that really helps patients.[3] Success requires abundant resources, highly skilled scientists and logicians, state-of-the-art laboratories and equipment, and comprehensive project management. Determination and serendipity are also essential.[4] The medication development process ultimately leads to the recovery, optimism, and belief of millions of patients.[5].

- The stages involved in the process of drug discovery and development are as follows:
- Identification of the target and confirmation of the target
- Identification of leads and optimization of leads.
- Characterization of the product
- Creation and advancement
- Preclinical research refers to the stage of scientific investigation that occurs before testing on humans. It involves conducting experiments and studies on animals or in vitro models to gather data and assess the level of safety and effectiveness of a possible treatment or intervention. The term Novel Medication Medical experiments
- Submission of a New Drug Application and subsequent approval

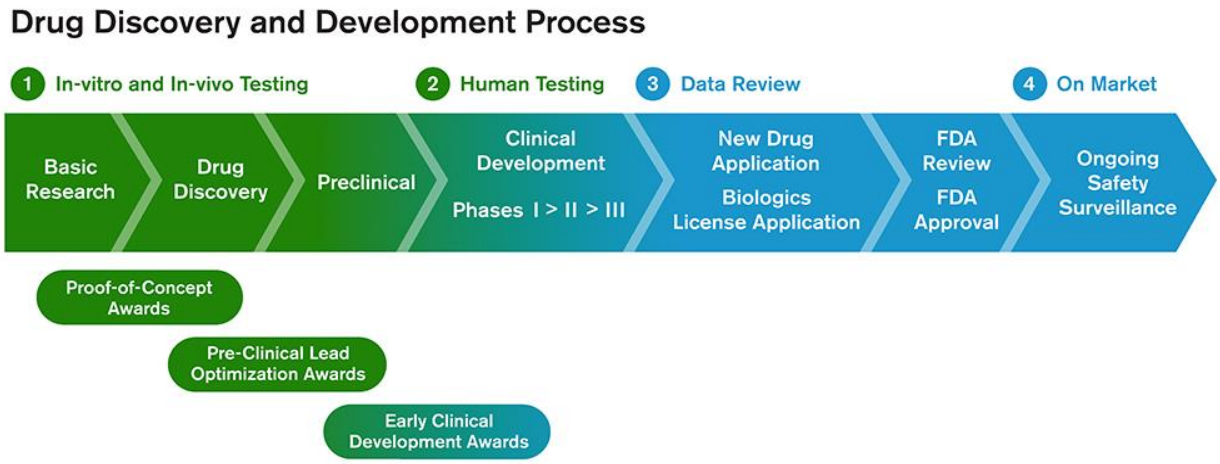

Figure **1** drug research and development process consist of many stages.

Target identification

The first phase of pharmaceutical development involves the identification of the fundamental biological process responsible for a disease and prospective targets for therapeutic intervention.

The first phase of target identification is determining the function and influence on the disease of a potential therapeutic target, such as a gene, protein, or nucleic acid.[6].

The molecular pathways associated with the target are defined after the target has been identified. A target that satisfies clinical and commercial objectives, is safe, effective, and druggable is the perfect candidate.

The fundamental concepts of molecular biology, biochemistry, genetics, and biophysics, along with other related sciences, may provide the basis for target identification processes.[7]

Approaches:

- Utilizing bioinformatics to extract, analyze, and appraise possible disease targets
- Genetic association: the relationship between a genetic variation and the illness
- Expression profile: changes in the amounts of mRNA and proteins
- Pathway and phenotypic analysis Mechanistic investigations based on in vitro cells
- Functional screening involves the use of target-specific tools or techniques to achieve knockdown or knockout.[8]

Target Validation

Target validation is the procedure of confirming the precise molecular target, such as a gene, protein, or nucleic acid, that a small molecule is designed to interact with. Target validation encompasses several methodologies, such as examining the structure-activity relationship (SAR) of small chemical analogs and generating a drug-resistant mutant of the target in question., the manipulation of the suspected target's

expression levels (either overexpression or knockdown), and monitoring established signaling pathways downstream of the suspected target.[9].

Target validation involves confirming the functional significance of the selected target in the development of the condition. While it is indeed beneficial to assess a drug's toxicity and effectiveness using several cell and animal models relevant to the condition, the ultimate evaluation lies in its performance in a clinical setting. [10]

The target validation process consists of two primary components.

Reproducibility (The ability to replicate)

Once a pharmacological target has been identified, either by a specific approach or by reviewing existing in literature, the first stage involves repeating the experiment in order to validate its findings. its successful execution. The strategies for validating the target are as follows: System biology is the study of the existing information and its analysis.

The words stated include pharmaceuticals, protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, affinity chromatography, and expression-cloning. [11,12]

Add diversity to the ligand-target (drug) environment

- In vitro genetic modification of target genes
  knocking in genes (viral transfection of mutant genes), knocking out genes (CRISPR), and knocking down genes (shRNA, siRNA, and miRNA).
- Antibodies
  demonstrating a pronounced inclination towards the target and inhibiting any more contacts
- Chemical genetics
  chemical methods to target proteins that encode genomes [13]

Identification of Lead

A chemical lead refers to a molecule that closely resembles a drug, has strong stability during synthesis, and demonstrates appropriate specificity, affinity, and selectivity for the target receptor during primary and secondary testing. Therefore, it is necessary to clarify the connection between the structure and activities., evaluation of the feasibility of synthesis, first data on the effectiveness in living organisms, and confirmation of the interaction with the target. The features of a chemical lead are as follows:

- Explanation of SAR (Synthetic Aperture Radar)
- Assessment of drug compatibility (her, first toxicity)
- The feasibility of synthetic
- Select mechanistic assays
- The toxicity of a chemical class is determined via preclinical toxicity studies or in silico investigations. Proof of the effectiveness of the chemical class in living organisms
- Assessment of drug resistance and the ability to expel substances in a controlled laboratory setting

A drug effectiveness assessment is often performed to reduce the incidence of compounds that prove to be ineffective in the pharmaceutical development process. This evaluation is crucial for the conversion of a primary chemical compound into a pharmaceutical substance. For a molecule to be deemed druggable, it must possess the ability to bind to a particular target. However,

it is also important to examine the compound's pharmacokinetic profile, which includes its absorption, distribution, metabolism, and excretion. During the screening procedure, the potential toxicity of the molecule will be assessed using other tests, such as the cytotoxicity assay and the Ames test.[14]

Lead Optimization

Lead optimization is the process of developing a potential drug candidate after the discovery of a lead molecule. A stepwise approach including the synthesis and characterization of a potential medicine is used to determine the association between a drug's chemical structure and its activity in terms of interactions with targets and metabolism. During the first stages of drug development, the method of lead optimization is used to identify promising molecules. This entails the process of improving the leads obtained from hit-to-lead high throughput screening research. During the lead optimization phase, the early-stage drug development process involves a comprehensive examination of prospective leads to assess their selectivity and binding mechanisms.

The goal of lead optimization is to maintain favorable attributes in lead compounds, while improving shortcomings in the lead structure. To develop a pre-clinical therapy candidate, it is essential to alter the chemical structures of lead compounds, regardless of whether they are small molecules or biologics. This modification is done to improve the specificity and selectivity of the target. Assessments are carried out to ascertain the toxicological characteristics, as well as the pharmacodynamic and pharmacokinetic aspects. To precisely identify the chemical and choose the path for enhancement, laboratories need to gather data on the toxicity, effectiveness, durability, and capacity to be absorbed by the body of possible candidates.[15].

Drug discovery researchers want effective techniques to reduce the number of drug candidates chosen for further selectivity profiling and additional exploration. Drug metabolism and pharmacokinetics screens, often referred to as high throughput DMPK screens, are presently a necessary component of lead optimization. They enhance the comprehension and forecasting of in vivo pharmacokinetics by using in vitro experiments. Optimization is used to perform chemical alterations on potential drug structures, leading to the development of novel medications with improved effectiveness and safety characteristics.

Pharmaceutical and biopharmaceutical companies are increasingly using automated screening methods into their drug development facilities. Mass spectrometry is a method that may be used to identify and measure metabolites. MALDI imaging is an essential technology for efficiently and precisely assessing pharmacological candidates and their metabolites inside tissue structure.

Furthermore, the pharmaceutical sector often uses NMR Fragment-based Screening (FBS) as a method to enhance and reveal primary compounds in focused screening initiatives.[16]

Product characterization

In order to achieve the best degree of therapeutic effectiveness, the drug molecule must be characterized in terms of its dimensions, configuration, potency, vulnerability, toxicity, and biological functionality. Early stages of pharmacokinetic and pharmacodynamic research may assist in characterizing the mechanism of action of the medicinal

molecule.
Any potential therapeutic molecule in a new medicine is characterized based on the characteristics of the substance include its dimensions, configuration, strength, susceptibility, application, harmfulness, and physiological impacts.

The early phases of pharmacological research are crucial for elucidating the compound's mechanism of action.

Formulation and development

This step involves determining the physiochemical characteristics of the active medicinal components to develop a reliable and optimal formulation for the chosen method of drug delivery.

Pre formulation studies involve the evaluation of the following parameters:

• Dissolvability in different solvents and media
• API dissolution • Accelerated stability testing under different circumstances
• Particle size, shape, and polymorphism properties in the solid state
• Services and capacities for formulation
• The creation of novel chemical entities through formulation (NCE)
• Enhancement of current formulas
• Development of specific dosage form processes
• Innovative formulations to enhance the dose forms currently in use
• Pharmaceutical preparations with regulated and prolonged release
• Self-emulsifying drug delivery systems
• Systems for administering colloidal drugs
• Nano emulsions and submicron ones

Preclinical Testing

During the pre-clinical phase of drug research, the medicine's safety and efficacy are evaluated in animal models in order to forecast its impact on humans. The preclinical studies must also get approval from the appropriate regulatory organizations. The regulatory agencies are responsible for ensuring the ethical and safe conduct of studies and for granting approval only to pharmaceuticals that have shown both safety and efficacy. ICH has produced a crucial set of criteria for the technical prerequisites of suitable preclinical drug development.[17]

Two methodologies exist for performing pre-clinical trials: toxicology and general pharmacology. Pharmacology primarily concerns itself with the pharmacokinetic and pharmacodynamic properties of medicines.
Studying unforeseen pharmacological effects in appropriate animal models and properly monitoring them is crucial in toxicological research.
Pharmacokinetic studies are essential for evaluating the safety and efficacy of absorption, distribution, metabolism, and excretion processes. These studies provide insights into the rate at which medications are assimilated via various methods of delivery. This information helps determine the appropriate dosage form, distribution, metabolism rate, and elimination rate, all of which influence the drug's half-life. The half-life of a pharmaceutical is crucial in determining its safety profile, since it is a prerequisite for regulatory authorities to provide authorization for a drug. The distribution route of a medicine is determined by its bioavailability and affinity, which in turn affects the drug's therapeutic effectiveness. Drug metabolism has a crucial role in influencing the likelihood of advancing through various stages of the biotransformation process and producing

drug metabolites. Moreover, it enhances the comprehension of enzymes and their mechanisms.[18]

Toxicological research of drugs may be conducted using both in vitro and in vivo testing procedures to evaluate their harmful effects. To evaluate the immediate impact on cellular development and properties, it is possible to carry out in-vitro tests. The toxicological consequences may be evaluated by in-vivo experimentation., which allows for both qualitative and quantitative determination. Selecting the appropriate animal species for toxicity research is of utmost importance due to the species-specific nature of many drugs. Clinical studies sometimes use in-vivo research to evaluate the pharmacological and toxicological characteristics of a drug, including its mechanism of action, in order to support its proposed use.[19]

Investigational New Drug Process (IND)

Prior to initiating clinical research, drug researchers are required to submit an Investigational New Drug application to the FDA.[20]". Developers are required to include the following components within the IND application:
Alternatively
Pharmaceutical producers must submit an Investigational New Drug application to the Food and Drug Administration (FDA) before starting clinical studies. The IND application requires developers to provide the following: • Preclinical data and toxicity study results • Information on drug manufacturing • Clinical research methods for the specific investigations • Data from previous clinical research, if available • Details about the researcher or developer.[21]

Clinical Research

The purpose of conducting clinical trials on voluntary volunteers is to gather detailed information about the efficacy and safety of new medications, vaccines, therapies, or ways of administering existing treatments. Manufacturers, investigators, and researchers adhere rigidly to a predetermined study procedure while conducting clinical studies.

Figure 2Phases of clinical trials

The developers will initiate the Investigational New Drug Process (IND), a prerequisite for commencing clinical research. They will strategize the objectives to be accomplished in each of the many Clinical Research Phases while designing the clinical trial. Prior to the start of a clinical trial, scientists' study available data on the medication to create research inquiries and targets.[22] Then they make a decision:

- Participants' selection criteria
- Total participants in the research
- How long the study took
- Dose and mode of dose form administration
- Parameter evaluation
- Compiling and analyzing data [23]

Clinical trial in phase 0(zero phase)

Phase 0 encompasses initial studies conducted on human subjects, according to the rules set out by the FDA. Phase 0 trials, sometimes referred to as human micro dosage studies, serve the purpose of obtaining pharmacokinetic data or facilitating the imaging of specific targets, all while avoiding any pharmacological effects. The procedure entails the giving of individual sub-therapeutic dosages to a group of 10 to fifteen volunteers. Pharmaceutical businesses execute Phase 0 examinations to ascertain the drug candidate with the most favorable human pharmacokinetic properties.[24]

Clinical trials in phase 1 (one phase): - Safety and dosage

Phase I studies are the first round of drug testing and include a smaller sample of healthy individuals. In Phase 1, a group of healthy people with the specified disease or condition (usually between 20 and 80 people) are enrolled. In cases when a drug's action mechanism suggests it may not be well-tolerated by healthy individuals, patients are often summoned. Any time a potential new medication for diabetic patients is being considered, phase 1 studies are carried out on people who have that particular kind of diabetes. Phase I studies collect data on the pharmacodynamics in the human body and are closely monitored. Researchers ascertain the tolerable dosage of a medicine and its immediate adverse effects by modifying the dosing schedule using data obtained from animal experiments. During the Phase 1 study, scientists gather information regarding the treatment's efficacy, its mode of action, and any potential adverse effects associated with dose escalation. It is crucial to consider this while planning Phase 2 investigations. Approximately 70% of medications reach the subsequent stage.

Clinical trials in phase 2 (Two Phase) Efficacy & Side effect

Phase II studies include doing tests on a larger group of patients, often a few hundred, in order to evaluate the drug's efficacy and confirm the safety findings from Phase I. These studies are inadequate to ascertain the therapeutic efficacy of the medicine. Researchers get new safety data from phase 2 tests. This information is crucial for the development of new research protocols, methodology, and subjects for Phase 3 studies. About a third of all medications advance to the next stage.

In order to establish the therapeutic dosages for large-scale Phase III research, phase II clinical trials are essential.[25]

Clinical trials in phase 3 (Third Phase): - Monitoring of adverse drug reactions and efficacy

To determine if a product offers an action advantage to a certain group of people or not, researchers plan Phase 3 studies. Known as key studies at times, 300–3,000 people participate in these trials. Most safety data are provided by phase 3 trials.

It's possible that less common adverse effects were missed by the earlier study. However, phase 3 studies are longer-lasting and involve a larger number of volunteers, increasing the likelihood that long-term or unusual side effects will be identified.
Just over a quarter of all drugs make it to the next round of clinical trials.
Drug researchers may submit an application to sell a medication if they have proof from prior testing, clinical trials, and preclinical investigations. showing the medicine is risk-free and works as expected. Before deciding whether to approve or reject the drug, the FDA review committee carefully looks over all of the evidence that has been presented.

NDA (New Drug Application)

The comprehensive account of a therapeutic molecule is conveyed in a new drug application (NDA). The objective is to verify the safety and efficacy of a medicine for its intended usage in the research participants. A drug researcher must include all pertinent information in the New Preclinical data, results of Phase 3 studies, and any other relevant information for a drug's New Drug Application (NDA). All data, research, and analyses must be reported by developers.[26]
Developers also need to consider the following in addition to clinical trial results:
• This suggested labeling
• Updates on safety
• Information about drug misuse
• Details about patents
• Details on adherence to institutional review board (IRB) regulations
• Usage instructions

FDA Review
The FDA review team typically requires a period of six to ten months to make a determination about the approval of a New Drug Application (NDA) after they have received a fully completed application. If the FDA receives an NDA that is not complete, the FDA review team will refuse to accept the paperwork. After a drug has been shown to be safe and effective for its intended use, the FDA must work with the developer to update the prescription information. The term "labeling" describes this process well. There are clear instructions on how to provide the medicine and specific standards for its approval on the label.
Nevertheless, the drug cannot be authorized for commercial distribution until all outstanding difficulties are resolved. The Food and Drug Administration has mandated further studies in a wide variety of other cases. At this point, the developer may decide to keep working on it or stop. There are formal channels for developers to use if they are dissatisfied with an FDA decision.[27]

Clinical trial in phase 4 (Fourth phase): -

Phase 4 studies are carried out after a drug or device has been approved by the FDA. Research like this, which evaluates the efficacy and safety of the authorized product while providing ongoing technical support, is often called post-marketing surveillance. During Phase 4 studies, a range of observational methods and assessment strategies are used to assess the safety, cost-effectiveness, and efficacy of an intervention in real-world settings. Phase IV studies may be conducted for the purpose of gaining a competitive edge or for many other reasons. They may also be required by regulatory agencies, such as for making revisions to product labels or implementing risk management and reduction strategies. Consequently, obtaining an accurate assessment of a drug's safety often requires monitoring its effects for an extended period, sometimes spanning many months or even years, in order to determine its long-term viability. The FDA investigates reports of problems with both prescription and over-the-counter medications and has the option to include warnings on the appropriate dose or use. They may also include extra information

about more serious adverse reactions to the drugs.[28]

CONCLUSION

It takes a lot of time and complexity to find and develop new drugs. New drugs have to go through a rigorous testing process before they are released onto the market. A protracted, costly, and difficult process goes into finding and developing new medications.

Every triumph arises from a plethora of earlier setbacks. Modern insights into human biology and illness are creating novel and intriguing opportunities for ground-breaking therapeutics. However, comprehending and utilizing these developments for illness treatment present significant obstacles for researchers. As scientific understanding expands and becomes more sophisticated, these possibilities will increase.

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