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Comprehensive Review on Drug Discovery and Development Process

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ABSTRACT:
Drug discovery is the systematic procedure of identifying a chemical compound that possesses therapeutic properties for the purpose of healing and treating diseases. This process involves the identification of candidates, the synthesis, characterization, validation, optimization, screening, and testing to assess the therapeutic effectiveness. After a molecule has proven its significance in these investigations, it will initiate the process of developing medication. Preclinical development precedes clinical testing. The process of developing a new drug must advance through several stages in order to create a medication that is both safe and effective, and that meets all regulatory requirements. The essay highlights the lengthy, difficult, and costly nature of producing new medicines. It underscores the need to consider various biological targets for each authorized treatment. In addition, it may be important to employ novel research instruments in order to investigate each novel objective. The process of developing a commercial medicine from early discovery is time-consuming and demanding. The process of developing a new pharmaceutical, from its initial discovery to its approval, usually spans a period of 13 to 15 years and requires an investment of around $1 billion. Usually, a million molecules undergo screening, but only one is chosen for further clinical trials and ultimately becomes accessible to patients. This article provides a succinct summary of the processes involved in the identification and creation of new pharmaceuticals.

1. Introduction

Drug discovery is a complex process that entails identifying a chemically therapeutic medicine for treating and managing a disease. Researchers usually discover novel drugs by gaining fresh insights into the illness process, enabling them to develop a drug to prevent or counteract the consequences of the disease. Drug discovery involves identifying potential drugs, synthesizing them, characterizing them, screening them, and testing their therapeutic effectiveness. Once a chemical demonstrates satisfactory results in these investigations, it will proceed to drug development following clinical trials. Drug discovery and development is costly because of the substantial resources required for research and development as well as clinical trials. It typically takes approximately 13-15 years to produce a new drug molecule from its discovery to its availability on the market for patient treatment. The typical expenditure for research and development of each effective drug is estimated to range from $800 million to $1.5 billion. This statistic encompasses the expenses incurred due to several failures. Out of 4,000-10,500 chemicals that go through inquiry and development, just one receives approval. The complexity of the research and development process explains why many

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compounds fail and why it is a time-consuming endeavor to bring a single drug to patients. Success necessitates abundant resources, top scientific and logical brains, advanced laboratory technologies, and comprehensive project management. Persistence and good fortune are also required. Ultimately, the drug discovery process instills hope, faith, and relief in billions of patients. [1,2]

2. Process steps of drug discovery and development:

- Objective Identification
- Objective Validation
- Direct Identification
- Direct Optimization
- Product Characterization
- Formulation Development
- Preclinical Research
- Invenstigational New Drug
- Clinical Trials
- New Drug Application
- Approval

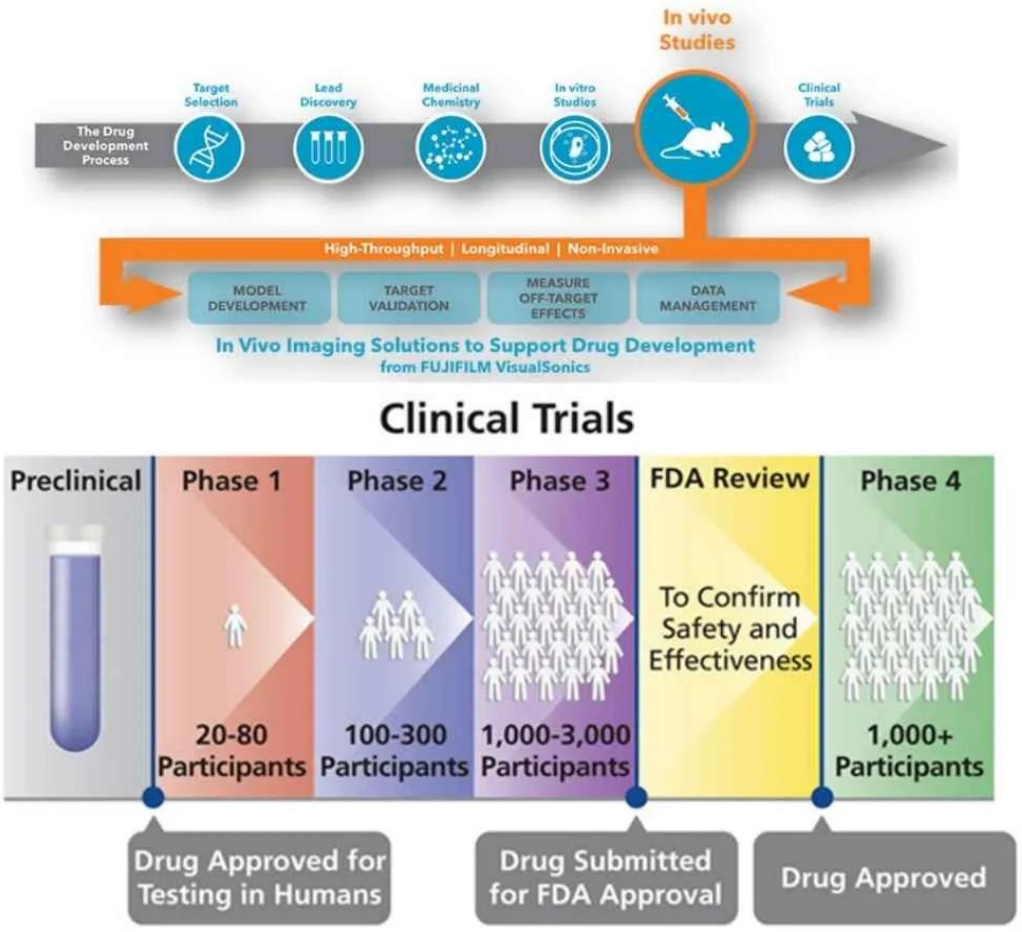

Fig 1: Process Steps of Drug Discovery and Development [1]
Credit for the figure: Deore, AB, Dhumane JR, Wagh HV, Sonawane RB, The Stages of Drug Discovery and Development Process. Asian Journal of Pharmaceutical Research and Development. 2019.

2.1 Objective Identification

The first step in drug discovery entails determining the biological origin of a disease and prospective targets for therapeutic intervention. The process of objective identification commences with the assessment of the function of a prospective therapeutic target, which can be a gene, nucleic acid, or protein, and its role in the disease. Once the objective has been identified, the molecular mechanisms associated with it are thoroughly defined.

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An optimal objective should possess efficacy, safety, meet both clinical and commercial requirements, and be susceptible to pharmacological targeting. Objective identification procedures can utilize concepts from several fields such as molecular biology, biochemistry, genetics, biophysics, or other relevant disciplines. [1,2,3,4,5]
Strategies:

- Identifying, selecting and prioritizing potential disease objectives
- Genetic polymorphism and connection with the disease
- Changes in mRNA/protein levels
- In vitro cell based mechanistic studies
- Functional screening

2.2 Objective Validation

Objective validation is the procedure of verifying the predicted molecular target, such as a gene, protein, or nucleic acid, of a small molecule. Objective validation encompasses the examination of the structure-activity relationship (SAR) of small chemical analogs, generation of a drug-resistant mutant of the target, manipulation of the target's expression levels, and observation of the signaling pathways linked to the target. [1,2]
Objective validation is the procedure of proving the functional significance of the selected target in the illness manifestation. Validating a drug's effectiveness and safety in many disease-specific cell and animal models is valuable, but the ultimate test is its performance in a clinical context.
Objective validation can be divided into two essential processes. [1,2,6,7,8]
Reproducibility: After identifying a pharmacological target, whether through a specialized technique or literature research, the initial step is to replicate the experiment to verify its reproducibility. The objective validation process encompasses various techniques, including affinity chromatography, expression-cloning, protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, systems biology, and investigation of existing drugs. [1]

Enhance the diversity to the ligand (drug)target environment: [1]
1. Genetic modification of certain genes in a controlled environment Suppressing the gene using shRNA, siRNA, or miRNA, eliminating the gene using CRISPR, and introducing new genes through viral transfection of mutant genes.
2.Antibodies bind strongly to the target and prevent additional interactions.
3.Chemical methods targeting protein synthesis encoded in the DNA.

2.3 Direct Identification

A chemical lead refers to an artificially created molecule that is stable, functional, and similar to a medicine. It exhibits activity in both primary and secondary tests, demonstrating suitable specificity, affinity, and selectivity for the intended receptor. This entails establishing the relationship between the structure and activity, evaluating the possibility of synthesis, and offering preliminary evidence of effectiveness and target interaction in living organisms. Chemical lead characteristics:

- SAR Defined
- Drug ability
- Synthetic feasibility
- Select mechanistic assay
- In vitro assessment
- Evidence of in vivo efficacy
- Pharmacokinetic/Toxicity of chemical class known based on preliminary toxicity

Drug ability assessments are frequently carried out to reduce the occurrence of failed compounds in the medication development process. This assessment is vital for the transformation of a substance from a primary molecule into a medicinal drug. In order to be considered druggable, a molecule must have the capacity to selectively attach to a specific target. Equally important is the compound's pharmacokinetic profile, encompassing absorption, distribution, metabolism, and excretion. Further examinations will evaluate the potential detrimental impacts of the chemical by employing techniques such as the Ames test and cytotoxicity assay. [1,2,9,10,11]

2.4 Direct Optimization

Direct optimization is the process of developing a therapeutic candidate after identifying an initial lead chemical. The approach is an iterative process of synthesizing and examining a potential medication in order to gain insight into the relationship between its chemical structure, activity, and interactions with its

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targets and metabolism.

In the initial phases of drug discovery, leads obtained from high throughput screening tests undergo lead optimization in order to identify promising molecules. In the process of lead optimization in the early stages of drug discovery, promising leads are evaluated based on many characteristics, including selectivity and binding mechanisms. Lead optimization seeks to maintain favorable attributes in lead compounds while improving any deficiencies in the lead structure. In order to develop a pre-clinical treatment candidate, it is necessary to modify the chemical structures of lead compounds, whether they are small molecules or biologics, in order to improve the specificity and selectivity towards the target. Pharmacodynamic, pharmacokinetic characteristics, and toxicological properties are evaluated. Laboratories must collect data on the toxicity, efficacy, longevity, and bioavailability of prospective substances in order to thoroughly assess them and identify areas for enhancement.[1,2,12,13,14,15]

Researchers in drug discovery require quick ways to limit down the selection of drug candidates for subsequent selectivity profiling and additional analysis. High-throughput DMPK screens are crucial for lead optimization, aiding in the comprehension and forecasting of in vivo pharmacokinetics through in vitro experiments. To create more potent and safer medications, chemical adjustments are made to the structure of prospective drugs through optimization.

Automated screening technologies are becoming vital in pharmaceutical and biopharmaceutical drug development laboratories. Mass spectrometry is utilized to identify and measure metabolites. MALDI imaging is a crucial method for quickly and precisely assessing drug candidates and their metabolites in tissue structure. NMR Fragment-based Screening (FBS) is a commonly used approach in the pharmaceutical industry for identifying and refining lead molecules in targeted screening efforts. [1,2,16,17,18]

2.5 Product Characterization

When a new drug molecule demonstrates potential therapeutic effects, it is analyzed based on its size, shape, potency, limitations, application, toxicity, and biological properties.

Initial phases of pharmacological research are beneficial for understanding the compound's mechanism of action. [19,20]

2.6 Formulation and Development

Pharmaceutical formulation is a critical phase in medication development where the physical and chemical characteristics of active pharmaceutical ingredients (APIs) are analyzed to create a dosage form that is bioavailable, stable, and suitable for a particular route of administration. [1,2,21]

During the preformulation studies the following parameters are evaluated:

- Solubility in different solvents and media
- Dissolution of API
- Accelerated stability studies under different conditions
- Solid state properties
- Formulation capabilities
- Formulation development of new chemical entities (NCE)
- Optimization of existing formulations
- Process development for targeted dosage forms
- Novel formulations for improved delivery of existing dosage forms
- Controlled release and sustained release formulations

2.7 Preclinical Research

Preclinical research in drug development evaluates the safety and efficacy of a medication in animal species to anticipate prospective outcomes in humans. Preclinical trials necessitate clearance from regulatory authorities before proceeding to clinical trials. Regulatory authorities have the responsibility to guarantee that studies are done in a manner that prioritizes safety and ethics. They will only grant approval for drugs that have been demonstrated to be both safe and effective. The International Council for Harmonisation (ICH) has established a basic benchmark for the technical specifications necessary for successful preclinical drug development. [1,22,23]

Pre-clinical research can be conducted using two different approaches. Pharmacology is concerned with the study of how medications are absorbed, distributed, metabolized, and excreted in the body (pharmacokinetics), as well as how they interact with the body to produce their effects (pharmacodynamics). Conducting thorough investigations into harmful

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pharmacological effects using suitable animal models and closely monitoring them is of utmost importance in toxicological research. Pharmacokinetic studies are essential for assessing the safety and efficacy attributes. Absorption, distribution, metabolism, and excretion (ADME) studies provide data on absorption rates for various routes of administration, aiding in the selection of dose form, distribution, metabolism rate, and elimination, which determine the drug's half-life. The drug's half-life is a crucial factor in determining its safety profile and is a need for regulatory approval. The medicine's distribution mechanism explains how effective the drug is based on its bioavailability and affinity. Drug metabolism involves the likelihood of passing through stages of biotransformation to produce drug metabolites. It also aids in comprehending the processes and enzymes involved in biotransformation. [1,22,23]

Toxicological investigations of the medicine can be conducted by in vitro and in vivo tests to assess its toxicological effects. In-vitro investigations can be conducted to examine the direct impact on cell growth and characteristics. Studies can be conducted in living organisms to assess both the qualitative and quantitative toxicological effects. Since many medications are particular to certain species, it is crucial to choose the right animal species for toxicity studies. In-vivo studies are commonly utilized to assess the pharmacological and toxicological effects, as well as the mode of action, to provide evidence for the intended clinical usage of a product. [1,22,23]

2.8 Investigational New Drug Application (IND)

Drug developers need to submit an Investigational New Drug application to the FDA before starting clinical trials. Developers must include:

- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical research methods
- Previous clinical research data in the IND application

  Details regarding the investigator/developer

2.9 Clinical Research

Clinical trials are carried out in volunteers to address particular inquiries regarding the safety and effectiveness of medications, vaccines, other treatments, or innovative approaches to using existing remedies. Clinical trials adhere to a defined study protocol created by the researcher, investigator, or manufacturer. During the development of the clinical study, the developers will plan the objectives for each Clinical Research Phase and initiate the Investigational New Drug Process (IND) as a prerequisite before commencing clinical research. Researchers analyze previous data on the medicine to formulate research inquiries and goals before commencing a clinical trial. Subsequently, they make a decision: [1]

- Participant eligibility criterion
- Participant count in the study
- Study duration
- Dosage amount and method of administration
- Evaluation of parameters Collecting and analyzing data

Phase 0 Clinical Trial

Phase 0 involves first exploratory trials in humans that adhere to FDA regulations. Phase 0 trials, often known as human micro dose studies, involve administering single sub-therapeutic doses to 10 to 20 volunteers to collect pharmacokinetic data or aid in imaging specific targets without causing pharmacological effects. Pharmaceutical companies conduct Phase 0 studies to determine which of their drug candidates have the most favorable pharmacokinetic properties in people.

Phase 1: Safety and Dosage

Phase I trials are initial studies of a medicine involving a small group of healthy human volunteers. Typically, Phase 1 involves the participation of 20 to 80 healthy volunteers with the disease/condition. Patients are often only administered a medicine if its mechanism of action suggests that it would not be well-tolerated by healthy individuals. Yet, when considering a new medicine for diabetic patients, researchers carry out Phase 1 trials specifically in individuals with diabetes. Phase 1 studies are constantly monitored to gather information on Pharmacodynamics in the human body. Researchers modify the dosage schedule according to data from animal studies to determine the body's tolerance to a medicine and its immediate negative effects. During a Phase 1 trial, researchers investigate the mechanism of action, side effects related to dosage escalation, and effectiveness of the treatment. It is crucial for the design of Phase 2 investigations. Approximately 72% of medications progress to the next level. [1]

Phase 2: Efficacy and Side Effects

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Phase II trials involve bigger groups of patients, often a few hundred, to examine the drug's effectiveness and confirm the safety findings from Phase I. The trials are inadequate to confirm the drug's medicinal potential. Phase 2 studies offer researchers additional safety data. Researchers utilize this data to enhance research inquiries, formulate research methodologies, and create new Phase 3 research protocols. Approximately 34% of medicines progress to the next level.

Phase II clinical investigations primarily help establish therapeutic dosages for the extensive Phase III research. [1,4,22,23]

Phase 3: Efficacy and Adverse Drug Reactions

Researchers are planning Phase 3 studies to determine whether a product provides a therapeutic advantage to a specific group of individuals. Pivotal studies, also known as pivotal trials, involve a participant pool ranging from 300 to 3,000 individuals. Phase 3 trials provide the majority of safety information. The prior study may have been unable to identify rare adverse effects. Phase 3 studies, which involve a significant number of participants and longer duration, are more likely to identify rare or long-term negative effects. Approximately 26-30% of medicines progress to the subsequent step of clinical testing.

Once a drug developer has data from earlier preclinical and clinical trials confirming the safety and efficacy of a drug for its intended use, the company can submit an application to commercialize the medicine. The FDA review panel thoroughly examines all supplied data on the drug and decides whether to approve it or not. [1,2,3,27,28]

New Drug Application

A New Drug Application (NDA) provides a comprehensive account of a drug molecule. The objective is to confirm the safety and efficacy of a medicine for its intended usage in the subjects under study. A drug developer must include comprehensive information on a drug, ranging from preclinical research to Phase 3 trial results, in the New Drug Application (NDA). Developers are required to provide reports for all investigations, data, and analysis conducted. In addition to clinical trial outcomes, developers must include:

- Proposed labelling
- Safety updates
- Drug abuse information
- Patent information
- Compliance information
- Direction for use

FDA Review

Once the FDA receives a comprehensive New Drug Application (NDA), the FDA review team may take approximately 6 to 12 months to make a decision on whether to approve the NDA. If the FDA receives an incomplete New Drug Application (NDA), the FDA review panel will reject the NDA.

Once the FDA determines that a medicine is safe and effective for its intended purpose, it is crucial to collaborate with the developer to update the prescribing instructions. This is referred to as "labeling." Precise labeling establishes the criteria for approval and provides guidance on the drug's usage. However, there are still unresolved difficulties that need to be addressed before the medicine can be licensed for marketing. In other instances, the FDA requires additional investigations. The developer has the option to decide whether to proceed with future development or not in this scenario. Developers have methods available for official appeal if they are dissatisfied with an FDA judgment. [2,3,29]

Phase 4: Post Market Drug Safety

Phase 4 trials are carried out after FDA approval of the medicine or device. These trials are known as post marketing surveillance, which includes pharmacovigilance and ongoing technical support post-approval. Various observational methodologies and evaluation patterns are utilized in Phase 4 studies to analyze the effectiveness, cost-effectiveness, and safety of an intervention in real-world situations. Phase IV studies may be mandated by regulatory agencies for purposes such as updating labeling or implementing risk management strategies. Alternatively, they may be initiated by the sponsoring corporation for competitive reasons or other motivations. Hence, accurately assessing a drug's safety necessitates monitoring its longevity in the market across months and years. The FDA examines complaints of difficulties associated with prescription and over-the-counter pharmaceuticals. Based on this information, the FDA may choose to include additional precautions in the dosage or usage instructions, as well as take other measures in response to more severe adverse drug reactions. [1,4,8,30]

3. Conclusion and Author's Perspective

Drug discovery and the development of new medicines are lengthy processes that have been accomplished.

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Pharmaceutical businesses dedicated to research prioritize improving scientific knowledge and developing new medications for patients. Enhanced support from government and organizations can aid in the development of safer and more cost-effective drugs.

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Declarations / Conflict Of Interest

None

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