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From Idea to Medicine: The Comprehensive Stages of Drug Discovery and Development

Prof. (Dr.) Mohd. Wasiullah[1], Prof. (Dr.) Piyush Yadav[2], Assistant Professor Sushil Yadav[3*], Kishan Kumar[4]

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ABSTRACT:
Drug discovery and development is a complex, multidisciplinary process that transforms an initial scientific idea into a safe and effective therapeutic agent. This review provides a comprehensive overview of the key stages involved in this process, including target identification and validation, hit discovery, lead optimization, preclinical testing, clinical development (Phases I–III), regulatory approval, and post-marketing surveillance (Phase IV). Each stage plays a critical role in ensuring the efficacy, safety, and quality of new drugs. Target identification focuses on selecting disease-relevant biological molecules, while lead discovery and optimization involve the design and refinement of compounds with therapeutic potential. Preclinical studies assess pharmacological properties and toxicity profiles, which inform the progression to clinical trials. Clinical development evaluates the drug in human populations to confirm its safety and effectiveness. Regulatory agencies review data from all stages before granting marketing authorization. Post-marketing surveillance continues to monitor long-term effects and rare adverse events. Understanding this comprehensive pipeline is essential for advancing innovations in pharmaceutical science and improving public health outcomes.

Keyword: Drug Discovery, Drug Development, Preclinical Trial, Clinical Trial, Regulatory approval etc.

I. INTRODUCTION:

Drug discovery is a complex and multi-discovery step process that involves identifying new chemical compounds with therapeutic potential for treating or managing diseases. Researchers typically discover new drugs by gaining novel insights into disease mechanisms, which help to design compounds that can halt or reverse the condition's effects. The drug discovery process includes identifying potential drug candidates, synthesizing and characterizing them, and conducting screenings and assays to evaluate their therapeutic efficacy. Once a compound demonstrates promising results, it enters the drug development phase, which leads into clinical trials. This entire process is costly, largely due to the significant investment required for research and development aswell as clinical testing. On average, it takes approximately 12 to 15 years for a newly discovered drug to reach the market and become available to patients.

Stages of Drug Discovery and Development Process:-There are the various stages involved in obtaining market authorization for a new drug from the Food and Drug Administration.

(A). DRUG DISCOVERY:

1. TargetIdentification: The initial stage in drug discovery involves identifying the biological cause of a disease and determining potential targets for intervention. This process begins with isolating the function of a potential therapeutic target, such as a gene, nucleic acid, or protein, andunderstanding its role in the disease.The process begins with the identification of the target, followed by an examination of the molecular mechanisms that the target influences. An ideal target should be effective, safe, clinically relevant, commercially viable, and "**druggable.**" Techniques for identifying targets can draw on a variety of fields, including molecular biology, biochemistry, genetics, biophysics, and other related disciplines.

Approaches of Target Identification

Data mining with bioinformatics:	Identifying, selecting, and prioritizing potential disease targets
Genetic association:	Exploring genetic polymorphisms and their connection to disease
Expression profiling:	Analyzing changes in mRNA and protein levels

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Pathway and Phenotypic analysis:	Conducting in vitro cell-based mechanistic studies
Functional screening:	Using knockdown, knockout, or target-specific tools

2. Target Validation: Target validation is the process of confirming the molecular target of a small molecule, which could be a gene, protein, or nucleic acid. This process involves several key steps, like determining the structure-activity relationship (SAR) of molecule analogs, creating drug-resistant mutants of the suspected target, manipulating the target through knockdown or over expression, and observing the known signaling pathways that are activated downstream of the target.

Reproducibility: After identifying a drug target, whether through a specific technique or literature review, the first step is to replicate the experiment to ensure it can be consistently reproduced. Target validation techniques include affinity chromatography, expression cloning, protein microarrays, reverse transfected cell microarrays, biochemical suppression, siRNA, DNA microarrays, systems biology, and the study of existing drugs.

Introduce variation to the ligand (drug)-target-environment:

- Genetic manipulation of target genes (in vitro), including gene knockdown (shRNA, siRNA, miRNA), gene knockout (CRISPR), and gene knock-in (viral transfection of mutant genes).
- Antibodies that interact with the target at high affinity, blocking further interactions.
- Chemical genomics, utilizing chemical approaches to target genome-encoded proteins.[9]

3. Lead Identification:A chemical lead compound is a basic moiety of drug molecules which is a synthetically stable, feasible, and drug-like molecule that demonstrates activity in primary and secondary assays, with acceptable specificity, affinity, and selectivity for the target receptor.

The characteristics of a chemical lead include:

- Defined Structure-Activity Relationship (SAR)
- Drugability (preliminary toxicity, hERG)
- Synthetic feasibility.
- Selection of relevant mechanistic assays.
- In vitro assessment of drug resistance and efflux potential.
- Evidence of in vivo efficacy for the chemical class.

To reduce the number of compounds that fail during the drug development process, a drugability assessment is often performed. This assessment is crucial for transforming a lead molecule into a viable drug. For a compound to be considered druggable, it must have the potential to bind to a specific target.

4. Lead Optimization: Lead optimization is the process of optimize (refining) a drug candidate after an initial lead compound has been identified. This process involves a series of iterative cycles of synthesis and characterization to better understand how the chemical structure relates to the compound's activity, its interaction with targets, and its metabolism. During early-stage drug discovery, leads generated from hit-to-lead high-throughput screening are subjected to lead optimization to identify the most promising candidates. These potential leads are evaluated for various properties, including selectivity and binding mechanisms, as part of the final stage of early drug discovery. The goal of lead optimization is to preserve the favorable attributes of the lead compounds while addressing any weaknesses in their structure.

5. Product Characterization: When a new drug molecule demonstrates promising therapeutic activity, it is characterized by its size, shape, strength, weaknesses, uses, toxicity, and biological activity. Early-stage pharmacological studies play a crucial role in understanding the compound's mechanism of action.

In this steps involves detail information of any new like- physical, chemical, size, shape, strength, uses, pharmacological study, and toxicity etc.

Then decided the drug product characterization is a betterment for human use.

(B) DRUG DEVELOPMENT:

1. Formulation and Development: Pharmaceutical formulation is a stage in drug development where the physicochemical properties of active pharmaceutical ingredients (APIs) are analyzed to create a bioavailable, stable, and optimal dosage form tailored for a specific route of administration.

2. Pre-Clinical Research: Before a drug is tested on humans, researchers must determine if it could potentially cause serious harm on human beings.

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Preclinical studies are carried out using animal models in controlled laboratory environments.There are three types of preclinical research:

- **In Vitro:** These experiments are performed outside of animals in controlled laboratory environments.
- **In Vivo:** These experiments are carried out inside living animals.
- **In Silico:** In Silico studies in preclinical testing refer to computer-based simulations and models used to predict the effects of a drug or treatment.

The Preclinical trials are conducted in two ways: General pharmacology and Toxicology. **Pharmacology** focuses on the pharmacokinetic and pharmacodynamic properties or study of a drug. It is crucial to assess any undesirable pharmacological effects in appropriate animal models and monitor them through toxicological studies. Pharmacokinetic studies are essential for determining the safety and efficacy of a drug, specifically in terms of absorption, distribution, metabolism, and excretion (ADME). These studies provide valuable data on the absorption rate for different routes of administration, which aids in selecting the correct dosage form. They also reveal the drug's distribution, metabolism rate, and elimination, which influence the drug's half-life. The half-life is a key indicator of a drug's safety profile, which is required for regulatory approval. The drug's distribution mechanism helps determine its therapeutic effectiveness, as it is dependent on bioavailability and its affinity for target sites.

Toxicological studies of a drug can be conducted through both in-vitro and in-vivo testing to assess its toxic effects. In-vitro studies are used to examine the direct impact of the drug on cell proliferation and phenotype. In-vivo studies, on the other hand, help in the qualitative and quantitative assessment of toxicological effects.

3. Investigational New Drug Application:

Before beginning clinical research or trial, drug developers must submit an Investigational New Drug (IND) application to the FDA for starting of clinical trial of any new biological drug product on human being.The IND application must include the following:

- Preclinical and toxicity study data.
- Information on drug manufacturing.

Flow chart of IND Process:

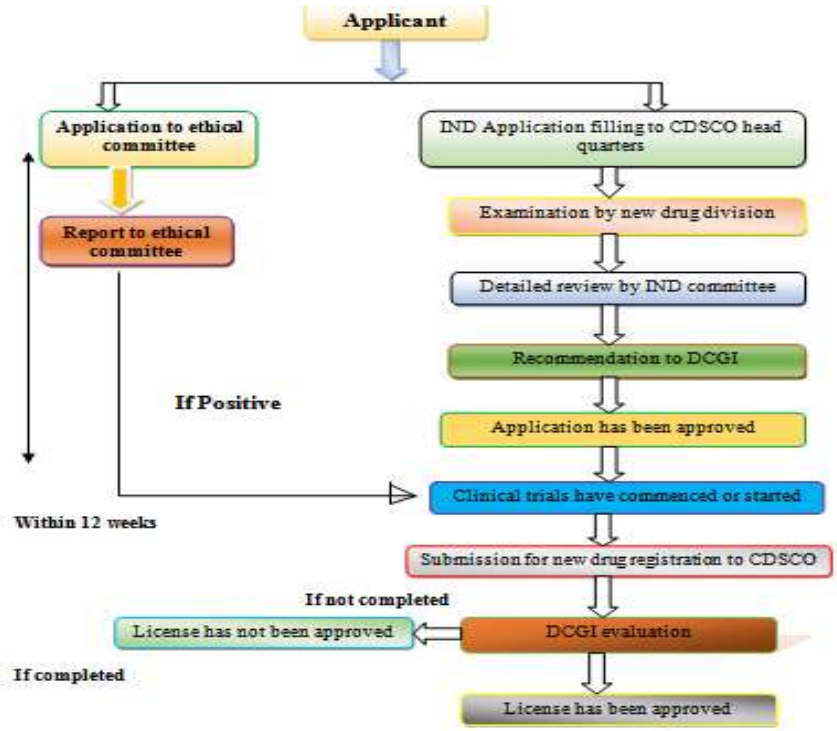

Fig.1.1: Flow chart of Investigational New Drug Application (IND) process

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4.1 CLINICAL STUDIES:

Clinical trials involve volunteers and are carried out to test the safety and effectiveness of new drugs, vaccines, treatments, or new ways of using current ones. These trials follow a plan created by the researcher or manufacturer. When designing a clinical trial, the developers think about what they want to achieve in each stage of the research and start the Investigational New Drug (IND) process, which is required before the trial begins. Before the trial starts, researchers review all available information about the drug to help form the research questions and goals.

There are followings phases involves in clinical trials-

Phase 0 [Microdose study]:

Phase 0 involves investigative, first-in-human (FIH) trials are conducted according to FDA guidelines. This trials is also known as human microdose studies, administer single, sub-therapeutic doses to 10 to 15 volunteers. They provide pharmacokinetic data or assist in imaging specific targets without producing pharmacological effects. Pharmaceutical companies conduct Phase 0 studies to identify which of their drug candidates shows the best pharmacokinetic properties in humans.

Phase 1 [Safety and dosage]:

Phase I trials are the first tests of a drug involving a small number of healthy human volunteers, typically 20 to 80 participants. These trials are usually conducted with healthy individuals unless the drug's mechanism of action suggests it may not be safe for healthy people. For example, if any new drug is intended for diabetes patients, Phase 1 trials are conducted with patients who have diabetes. These trials are closely monitored to gather information on how the drug behaves in the human body (pharmacodynamics). Researchers use data from animal studies to adjust the drug's dosage and determine the highest dose the body can tolerate, as well as its acute side effects. This information is crucial for designing Phase 2 studies. Approximately 70% of drugs move on to the next phase.

Phase 2 [Efficacy and side effects]:

Phase II trials are conducted on largest groups of patients, they are involves about 100-300 to evaluate the drug's efficasy and confirm the safety findings from Phase I. While these trials provide valuable information, they are not enough to confirm if the drug will be fully therapeutic. Phase II studies also offer additional safety data that researchers use to refine their research questions, improve study methods, and design new protocols for Phase III trials. Around 33% of drugs move on to the next phase. Most importantly, Phase II trials help determine the appropriate therapeutic doses for large-scale Phase III studies.

Phase 3 [Efficacy and adverse drug reactions monitoring]:

Researchers design Phase 3 studies to determine whether a product provides a meaningful benefit to a specific group of people. It referred to as pivotal studies, these trials involve 300 to 3,000 or 1000 to 5000 volunteers. Phase 3 studies provide the majority of safety data, as earlier studies may not detect rare side effects. Since Phase 3 studies are conducted with a larger number of participants and over a longer duration, they are more likely to uncover long-term or uncommon side effects. Around 25-30% of drugs move on to the next phase of clinical research. If the data from preclinical and clinical trials show that a drug is safe and effective for its intended use, the developer can submit an application to market the drug. The FDA review team carefully examines all the submitted data before making a decision to approve or reject the drug.

New Drug Application (NDA):

A New Drug Application (NDA) provides a complete overview of a drug molecule. Its purpose is to confirm that the drug is safe and effective for its intended use in the people who were studied. The drug developer must include all relevant information, from preclinical data to Phase 3 trial results, in the NDA. Developers are required to submit reports on all studies, data, and analyses conducted.

In addition to clinical trial results, drug developers are required to include the following information in their submission:

- Proposed labeling
- Updated safety data
- Information related to potential drug abuse
- Patent details
- Documentation of compliance with institutional review board (IRB) requirements
- Clear directions for proper use of the drug.

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Flow chart of NDA Process:

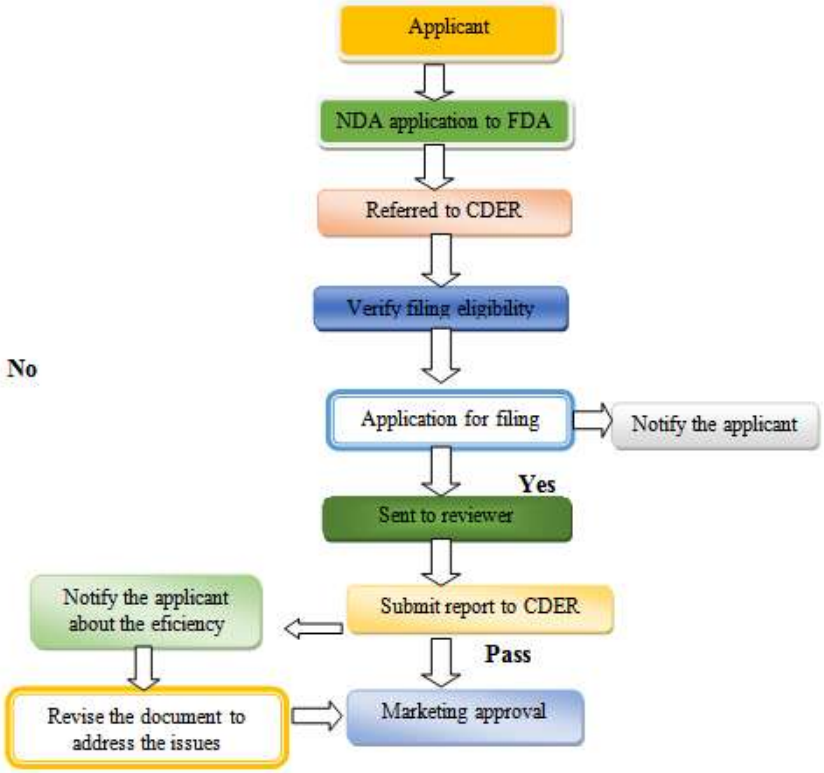

Fig.1.2: Flow chart of New Drug Application(NDA) Process

FDA Review: Once the FDA receives a complete NDA, the review team may require 6 to 10 months to make a decision on whether to approve it. However, if the FDA receives an incomplete NDA, the review team will reject it.Once the FDA determines that a drug has been shown to be safe and effective for its intended use, it is important to collaborate with the developer to update the prescribing information, known as "labeling." Labeling clearly outlines the basis for approval and provides guidance on how to use the drug. However, there may still be remaining issues that need to be addressed before the drug can be approved for marketing.

Phase 4 [Post-Market Drug Safety Monitoring]:

Phase 4 trials are conducted after a drug or device has been approved by the FDA. These trials are also known as post-marketing surveillance, it focus on pharmacovigilance and ongoing technical support following approval. Phase 4 trials use various observational strategies and assessment methods to evaluate the efficacy, cost-effectiveness, and safety of a drug in real-world settings. Regulatory authorities may require Phase 4 studies, such as for labeling changes or risk management plans, or the sponsoring company may undertake them for competitive reasons or other purposes. Therefore, a true understanding of a drug's safety requires monitoring over the months and even years it remains on the market. The FDA reviews reports of complications related to prescription and OTC drugs and may decide to update dosage instructions, add precautions, or implement other measures in response to serious adverse drug reactions.

II. CONCLUSION:

The comprehensive stages of drug discovery and development represent a highly intricate and multi-phase process designed to ensure the safety, efficacy, and market readiness of new pharmaceutical compounds. Starting from basic research, where potential drug targets are identified, the process moves through stages such as drug screening, preclinical testing, clinical trials, and regulatory approval. Each stage is carefully designed to minimize risks, optimize drug performance, and meet regulatory standards. The complexity of this process involves rigorous testing, patient safety considerations, and considerable investment of time and resources.

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Ultimately, successful drug development results in innovative therapies that can transform healthcare by offering new treatments for diseases, but the journey from concept to market is long and involves collaboration among researchers, regulatory bodies, and healthcare providers.

Drug discovery and development is a complex, multidisciplinary process that aims to identify and create new pharmaceutical agents to treat diseases effectively. It involves several critical phases, from the initial discovery of potential drug candidates to the clinical trials and eventual commercialization.

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