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The Phases of Drug Discovery and Development

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Abstract:

Finding a therapeutically effective molecule for the treatment and cure of illness is the goal of drug development. The selection of candidates, synthesis, characterisation, validation, optimization, screening, and tests for therapeutic effectiveness are all parts of this process. A molecule will start the medication development process prior to clinical trials after it has demonstrated its importance in these studies. A new medication must go through a number of phases of development in order to be produced that is both safe and efficient and meets all regulatory standards. One overarching theme of our article is that the procedure is sufficiently drawn out, expensive, and complex that numerous biological targets must be taken into account for every new drug that is eventually approved for clinical use. Additionally, new research tools may be required to examine each target.

It takes time and effort to develop a drug that can be sold. From the time of discovery until the treatment is licenced, it takes roughly 12 to 15 years and costs about US $1 billion. A million molecules are typically tested, but only one is examined in advanced clinical trials and ultimately made available to patients. An overview of the procedures for discovering and developing novel drugs is given in this article.

Keywords — Clinical studies, target discovery and validation, lead optimization, new medication.

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INTRODUCTION

Drug discovery is a complex process that entails finding a medication molecule that is therapeutically effective in managing a clinical condition. New insights into the a disease process that enable investigators to develop a therapy to prevent or oppose the effects of the illness are often how researchers discover new pharmaceuticals. The detection of drug targets, biosynthesis, characterization, screening, and tests for therapeutic effectiveness are all parts of the drug development process. A compound will start the process of medication development after clinical trials when these studies yield favorable results. Due to the high costs of research and development and clinical trials, developing new drugs is a costly process. The development of a single new medicinal molecule from scratch takes around 12–15 years. For each effective medicine, the average cost of research and development will likely range from $900 million to $2 billion. The cost of the tens of thousands of failures is included in this sum: One finally receives clearance for every 5,000–10,000 molecules that enter the inquiry and development pipeline. These numbers defy belief, but a basic knowledge of the R&D process helps to clarify the reason why so many molecules fail as well as why it requires such a big effort and a long time to deliver one drug to patients. To succeed, you'll need a lot of money, the brightest brains in science and reasoning, cutting-edge technology and labs, and multidimensional project management. It also requires luck and tenacity. In the end, the process

of medication development gives billions of sufferers comfort, hope, and relief.

Drug development and discovery stages include:

- Identification of the Target-
- Target confirmation
- Identification of Lead
- lead optimization
- Characterization of the Product
- Development and Formulation
- Preclinical Testing
- The Procedure for Investigational New Drugs (IND)
- Clinical Study
- New Drug Application (NDA)
- Approval

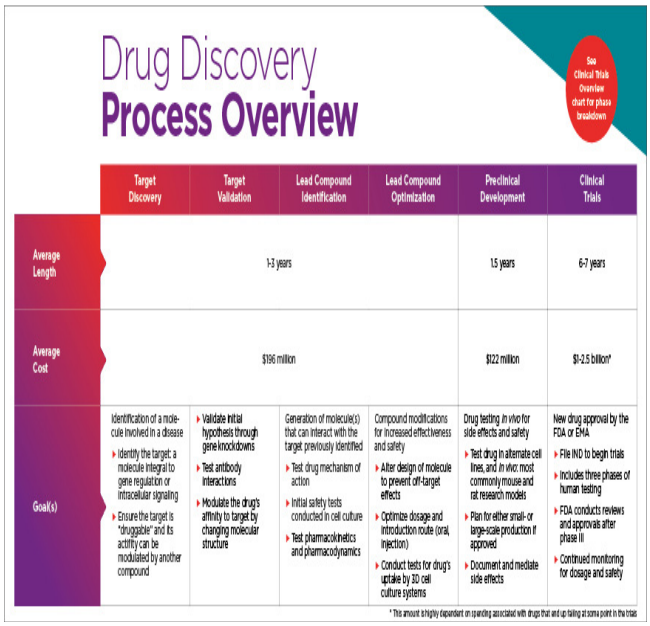

Fig. 1stages in the process of discovering and developing drugs

Identification of the Target-

Identification of a disease's biological cause and possible intervention targets is the first stage in the development of a medication. Identifying a potential therapeutic target's (gene, nucleic acid, or protein) function and contribution to the illness is the first step in the target discovery process. The molecular mechanisms that the target targets are then characterized when it has been identified. A good target should be effective, safe, suit clinical and business needs, and be druggable. Principles from molecular genetics, biochemistry, genomics, biophysics, or other fields may form the foundation for target identification strategies.

Methods:

- Bioinformatics-based data mining
  — selecting, ranking, and identifying possible disease targets
- Genetic correlation
  — modifications to mRNA/protein levels.
- Analyzing phenotypic and pathway data.
  — Mechanistic research using in vitro cells
- functional assessment
  — employing target-specific tools, knockdown, or knockout techniques

Target confirmation-

A tiny molecule's intended molecular target, such as a gene, protein, or nucleic acid, is verified by a method called target validation. Determine the structure activity relationship (SAR) of small molecule analogues, create a drug-resistant mutant of the assumed target, overexpress or knockdown the assumed target, and monitor the known signalling pathways downstream of the assumed target are all examples of target validation techniques.

Target validation is the process of proving the functional significance of the chosen target in the illness manifestation. The final measure of a drug's effectiveness is whether it works in a clinical environment, even if it is incredibly useful to validate its efficacy and toxicity in multiple disease-relevant cell models and animal models.

Target validation consists of two essential processes.

Reproducibility: The first step after identifying a pharmacological target—whether via the use of a specific technology or through a literature review—is to repeat the experiment to ensure that it can be effectively replicated. Affinity chromatography, expression-cloning, protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, system biology, and examination of already available medications are all components of the target validation approach.

Adjust the ligand (drug)-target environment to be more variable

- **Genetic manipulation of target genes** (in vitro), including viral transfection of mutant genes, shRNA, siRNA, and miRNA gene knockdown and knockout as well as CRISPR gene knockin.

- **Antibodies**
  engaging with the target strongly and preventing more interactions

- **Chemical genomics**
  Chemical defences against proteins encoded by the genome

Identification of Lead-
A chemical lead is a molecule that can be synthesised that is stable, practical, and drug-like and that exhibits adequate specificity, affinities, and selectivities for the target receptor in primary and secondary tests. The structure-activity connection must be defined, the viability of the synthetic process must be determined, and there must be some early proof of the effectiveness and target engagement in vivo. Among a chemical lead's characteristics are:

- defining SAR
- Medication efficacy (hERG preliminary toxicity)
- synthetic viability
- Particular mechanistic tests
- Proof of in vivo efficacy of chemical class, as determined by preclinical toxicity or in silico research, and in vitro assessment of drug resistance and efflux potential.

A drug ability evaluation is frequently carried out in order to reduce the number of molecules that fail in the medication development process. In order to turn a chemical from the a lead chemical into a medication, this evaluation is crucial. A substance must have the capacity to bind to a particular target in order to be regarded as druggable; nevertheless, the substance's pharmacokinetic profile with relation to absorption, distribution, metabolism, and excretion is also crucial. In other tests, such as the Ames test and cytotoxicity assay, the compound's potential toxicity will be assessed.

Lead Optimization-
Following the identification of a primary lead chemical, a pharmaceutical candidate is created via the lead optimization procedure. A putative medication is put through an iterative procedure for synthesis and characterization to see how its chemical structure and activity relate to the interactions with its targets and metabolism**.** In the early stages of drug discovery, the hit-to-lead high throughput screening test results go through lead optimization to find interesting compounds. At the last stage of early stage drug discovery, potential leads are assessed for a variety of characteristics, such as selectivity and binding mechanisms,

during lead optimization. Lead optimization aims to preserve advantageous features in lead compounds while addressing structural flaws. Lead compounds (small molecules or biologics) must have their chemical structures changed in order to increase target specificity and selectivity in order to create a pre-clinical therapeutic candidate. Toxicological characteristics as well as pharmacodynamic and pharmacokinetic aspects are assessed. To correctly define the molecule and determine its bioavailability, labs must collect data on the toxicity, effectiveness, stability, and bioavailability of leads.

The pick of active compounds for this downstream selectivity profile and additional research has to be whittled down quickly by drug discovery researchers using these methodologies. Lead optimization has benefited from the development of high throughput DMPK (metabolism and pharmacokinetics) screens, which make it easier to comprehend and predict in vivo pharmacokinetics using in vitro experiments. Chemical alterations to the structure of prospective pharmaceuticals are made through optimization in order to create new medications with greater potencies and safety profiles.

Drug discovery laboratories for the pharmaceutical and biopharmaceutical industries are increasingly relying on automated screening methods. Metabolites are found and quantified using mass spectrometry. A crucial method for quickly and reliably assessing active compounds and associated metabolites in tissue structure is MALDI imaging. The pharmaceutical sector has also used NMR Fragment-based Screening (FBS) as a frequently used technique for the identification and improvement of lead compounds in focused screening campaigns.

Characterization of the Product

The size, shape, strength, weakness, usage, toxicity, and biological activity of any novel drug molecule that has a prospective therapeutic action are used to describe the molecule. Early pharmacological research is useful for describing the compound's mode of action.

Development and Formulation

Pharmaceutical formulation is a phase of medication research when the physicochemical characteristics of active pharmaceutical ingredients (APIs) are studied in order to create a bioavailable, stable, and ideal dose form for a particular delivery route**.**

Preformulation studies investigate the following variables:

Solubility in various mediums and solvents

- The active pharmaceutical ingredient (API) dissolving;
- Services for accelerated stability under diverse circumstances.
- Solid state characteristics (polymorphs, particle size, particle shape etc.)
- Capabilities and services for formulation
- New formulations for improving the delivery of existing dosage forms include controlled release and sustained release formulations, self-emulsifying drug delivery systems, colloidal drug delivery systems, sub-micron and nano-emulsions, process development for specific dosage forms, and novel formulations.

Preclinical Testing-

Pre-clinical research is used to assess a drug's effectiveness and safety in animal species with an eye towards potential human outcomes. The relevant regulatory authorities must also approve the pre-clinical trials. The regulatory authorities must make sure that clinical studies are carried out

in a safe and ethical manner and will only approve medications that have been proven to be both effective and safe. A fundamental set of technical requirements for approved preclinical drug development has been defined by ICH.There are two methods for doing pre-clinical trials: general pharmacology and toxicology. The pharmacodynamic and pharmacokinetic characteristics of drugs are the subject of pharmacology. Exploring adverse pharmacological effects in appropriate animal models and keeping an eye on them in toxicological investigations are crucial. To determine the safety and effectiveness characteristics in terms of absorption, distribution, metabolism, and excretion, pharmacokinetic studies are crucial.These studies provide data on the rate of absorption for various routes of administration, which aids in dosage form selection and the regulation of the drug's half-life through distribution, metabolism, and excretion rates. The medicine's half-life explains its safety profile, which is a requirement for a drug to receive regulatory agency approval. The medicine's bioavailability and affinity are determined by the drug distribution mechanism, which explains how successful the drug is as a treatment. The possibility of going through stages of the biotransformation process and producing drug metabolites is provided by drug metabolism. Understanding the processes and enzymes are involved in biotransformation is also aided by this.

In-vitro and in-vivo tests can be used to conduct toxicological studies on the substance, which assess its toxicological effects. To examine the direct impact on cell proliferation and phenotypic, in-vitro experiments can be carried out. Toxicological effects can be determined qualitatively and quantitatively by in-vivo research. In order to properly investigate animal toxicity, it is crucial to choose the right species because many medications are spec-specific. Studies conducted in animals to assess pharmacological and toxicological effects, including mechanism of action, are frequently used to support the rationale for the product's proposed usage in clinical trials.

The Procedure for Investigational New Drugs (IND)-

Before starting clinical research, drug companies are required to submit an investigational new drug application to the FDA. Developers must include the following in the IND application:

- Data from preclinical and toxicology studies
- Details on drug production.
- procedures for conducting clinical research studies
- Data from earlier clinical research (if any)
- Information regarding the researcher or creator

Clinical Study-

Clinical trials are performed on volunteers and are designed to provide specific answers concerning the security and effectiveness of medicines, vaccines, other therapies, or novel ways to administer existing medications. Clinical trials adhere to a particular research protocol that has been created by the manufacturer, investigator, or researcher. Developers must start the Investigational New Drug Procedure (IND) before clinical research can commence, and as they plan the clinical study, they will think about what they want to accomplish for each of the many Clinical Research Phases. Prior knowledge about the medication is reviewed by researchers to create study questions and objectives before a clinical trial starts. They then choose:

- Participants' eligibility requirements
- A number of participants in the research
- Study period length
- The dosage and method of administering the dosage form
- parameter evaluation
- Gathering and analysing data

phase 0 of a clinical study-

Phase 0 includes exploratory, first-in-human (FIH) studies that are carried out in

accordance with FDA regulations. The single subtherapeutic doses are administered to 10 to 15 volunteers in phase 0 trials, which are also known as human microdose studies. These trials provide pharmacokinetic data or aid in the imaging of certain targets without causing pharmacological effects. The pharmaceutical industry conducts Phase 0 investigations to determine which of their medication candidates has the best human pharmacokinetic parameters.

Phase 1: Dosage and safety

The initial evaluation of a medicine is done in phase I studies, which use fewer healthy human participants. Phase 1 typically involves 20 to 80 healthy volunteers who have the illness or condition. Patients are often only utilised when a drug's mechanism of action indicates that healthy individuals will not tolerate it. Nonetheless, researchers carry out Phase 1 studies in patients with that particular form of diabetes if a new medication is recommended for use in diabetic patients. Studies in the first phase, which document the effects of pharmacodynemics on the human body, are highly watched. To determine what dosage of a medicine the body can take as well as its acute adverse effects, researchers modify the dosing regimen based on data from animal studies. As a Phase 1 study progresses, scientists learn more about the drug's mechanism of action, the adverse effects that come with dose increases, and its efficacy. For the planning of Phase 2 investigations, this is essential. Almost 70% of medications move on to the following stage.

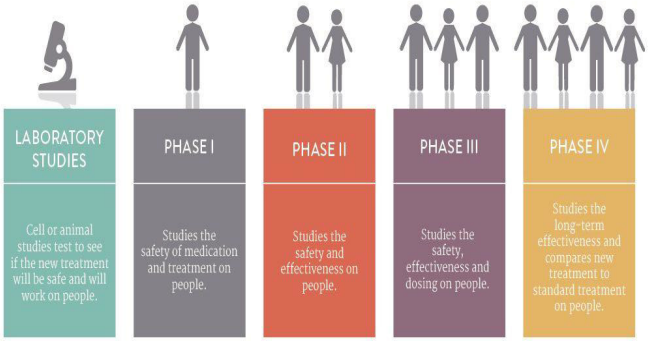

Fig. 2 Phases of clinical studies are shown in

Phase 2: Efficacy and side effects-

Phase II studies are done on bigger patients groups (few hundred) and are meant to examine the effectiveness of the medicine and to outlast the Phase I safety tests. The drug's potential for therapeutic benefit cannot be determined by these studies alone. Phase 2 trials provide researchers more information on safety. This data are used by researchers to establish new Phase iii research procedures, develop research techniques, and revise their research topics. A third or so of medications move on to the subsequent stage.

Clinical investigations in Phase II play a key role in determining therapeutic dosages for the extensive Phase III research.

Phase 3: Therapeutic confirmatory

To demonstrate if a product offers a specific group of individuals an action benefit or not, researchers are planning Phase 3 trials. These trials, which occasionally go by the name of pivotal studies, involve 300 to 3,000 individuals. The majority of the safety data comes from phase 3 research. The earlier study could not have been able to find fewer frequent adverse effects. Nevertheless, because phase 3 trials involve a greater number of volunteers and last longer, the findings are more likely to reveal persistent or unusual adverse effects. Drugs go on to the following stage of clinical study

in around 25–30% of cases. An application to sell a drug may be submitted by the pharmaceutical industry if a drug's safety and efficacy for the intended use have been established via prior testing, preclinical research, and clinical trials. the Food and Drug Administration.

New Drug Application (NDA)

A chemical molecule's whole history is detailed in an NDA (New Drug Application). Its goal is to confirm that a medicine is both safe and effective for the population being researched. The NDA must contain all information regarding a medicine, from preclinical research to Phase 3 trial results. Reports on all investigations, data, and analysis must be included by developers. Together with the results of clinical trials, developers must also provide:

- The suggested labelling
- Updates to safety
- Information about substance abuse
- Information about patents
- Information about institutional review board compliance
- Application guidelines

FDA Review

After receiving a comprehensive NDA, the FDA team of reviewers may need between 6 and 10 months to decide whether to approve the NDA. If the FDA receives an incomplete NDA, the FDA review panel will reject the NDA.

Working with the developer to update the prescription information is crucial if the FDA rules that a medicine has been shown to be safe and effective for the intended use. Labeling is used to describe this. Labeling preciselydefines the reason for approval and directionhow to use the medicine. Yet, problems still need to be resolved before the medicine can be licenced for commercialization. In other situations, the FDA needs further research. The developer now has the option of continuing or stopping future development. A developer has options for formal appeal if they are upset with an FDA decision.

Phase 4: Postmarketing surveillance

When the FDA has authorised a medicine or device, phase 4 studies are carried out. These studies are also acknowledged as post-approval monitoring that includes pharmacovigilance and ongoing technical assistance. In Phase 4 trials, a variety of observational techniques and evaluation patterns are employed to gauge the effectiveness, viability, and safety of an intervention in real-world contexts. Phase IV studies may be needed by regulatory agencies (such as a change in labelling or an action plan for risk management or reduction) or may be carried out by the sponsoring firm for other factors such as competition. A drug's actual safety must thus be demonstrated throughout the weeks, months, and often even years that make up its shelf life. FDA evaluates reports of adverse medication reactions and may decide to increase dosage precautions as a result.

CONCLUSION

The pharmaceutical industry is dealing with complicated and difficult problems, as is evident to those who are engaged in and interested in the art and science of drug development. Mobilizing the appropriate scientific community to integrate and advance the process through collaborative and transdisciplinary activities that would

include both academic and industry entities is, in fact, both wise and opportune. More welcoming and open-access information and resources, especially for academic researchers, are required as academic-industrial relationships are developed and strengthened in order to support their discovery and development of drugs research efforts.

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