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Drug Discovery and Development Process: A Review of Current Methodologies

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ABSTRACT :

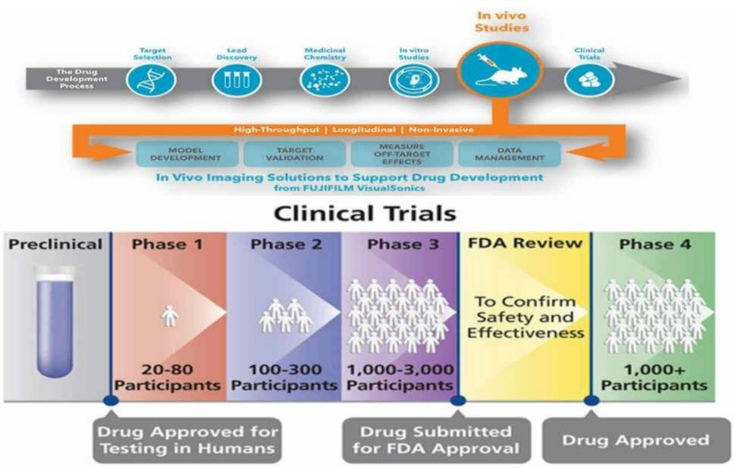
Drug development is a highly regulated and multifaceted process aimed at translating scientific discoveries into safe and effective medicines. It begins with the identification and validation of therapeutic targets, followed by the discovery of potential compounds such as small molecules, biologics, or gene therapies. The journey from an initial idea to market entry is lengthy, often taking 5–10 years and costing around $1.7 billion. Sources of new drug ideas include emerging diseases, market needs, academic research, and the commercial sector. Once a target is selected, pharmaceutical industries and research centers work to identify and optimize candidate molecules with desirable characteristics. Preclinical studies, clinical trials, and regulatory review ensure safety, efficacy, and quality. This review highlights the essential stages of drug discovery and development, balancing innovation with rigorous evaluation to address unmet medical needs.

KEYWORDS: Clinical Trials, Drug Development, Therapeutic targets, Validation, New Drug Application, Regulatory Review.

INTRODUCTION

The goal of the intricate, multidisciplinary, and strictly controlled process of drug research and development is to find and introduce novel medications to the market. With the ultimate goal of guaranteeing safety and efficacy, it incorporates biology, chemistry, pharmacology, and clinical sciences. Because it requires a great deal of research, preclinical examination, and multi-phase clinical trials, the process usually takes 12 to 15 years and costs close to $1 to $2 billion. Only one of thousands of evaluated compounds is frequently approved, underscoring the enormous rates of research attrition. Target identification, lead molecule discovery, and optimization to enhance pharmacokinetics and biological activity are the first steps in the process. Before being approved by regulatory bodies such as the FDA or EMA, promising compounds go through preclinical research and then undergo rigorous human clinical trials.
Drug creation, in spite of the expense and difficulties, is a testament to human ingenuity and perseverance, providing millions of patients throughout the world with hope and medicines
that can change their lives. (1)

The process of developing new drugs is time-consuming, costly, and heavily regulated; it can take anywhere from 12 to 15 years and cost billions of dollars. Improvements in artificial intelligence, biotechnology, and genetics have increased efficiency despite high failure rates, opening the door for more individualized and focused treatments. In the end, drug research and discovery are still essential for enhancing global health and meeting unmet medical needs.
Target identification, target validation, lead identification, lead optimization, product characterization, formulation and development, preclinical research, investigative new drug, clinical trials, new drug application, and approval are some of the phases of drug discovery and development.



Identification of the Target The first and most important stage in the drug development process is target identification, which aims to identify molecules (genes, proteins, nucleic acids, or receptors) that are important in the progression of disease and that medications can affect. It connects disease pathways to possible druggable targets, laying the groundwork for successful treatment development.

Methods:

i) Finding, choosing, and ranking targets that are important to the condition
ii) Research on genetic variations and how they relate to illnesses
iii) Examination of alterations in the expression of proteins or mRNA (omics research)
iv) Cellular processes and signaling pathways studied in vitro
v) Functional validation with target-specific techniques (e.g., CRISPR, siRNA) or knockdown/knockout
vi) Using AI and bioinformatics to examine huge biological datasets(2)

- **Verification of the target**

The target must be confirmed when it has been located. Researchers employ a variety of techniques in this step to confirm and comprehend the target's therapeutic effect. The target cannot be investigated further in the development process without verification. Monitoring target capacity, establishing a metric approach as a marker for target evaluation, and screening for hits are some of the components that make up target validation. One technique for separating a lead molecule from additional candidates and ignoring weak and erroneous targets is high-throughput screening, or HTS. HTS entails evaluating each applicant against a target or within a test system to determine whether the action is pertinent to the target. Numerous methods can also be used for validation.

These methods and tools include the tissue restriction and knockout approach, transgenic animals to detect pharmacological effect, antisense tools that use RNA-like chemicals, monoclonal antibodies, and, more recently, chemical genomics.

Methods:-

i) Genetic methods: To evaluate the functional role, use siRNA and CRISPR knockout and knockdowm-techniques.

ii) Pharmacological methods: Employing antibodies, agonists, or selective inhibitors Biochemical methods: investigating signalling cascades, binding interactions, and protein activity

iii) Assays based on cells: Assessing phenotypic changes in response to target modification Animal models: In vivo confirmation of the disease's target relevance

- Identification of leads

A synthetically stable, practical, and drug-like molecule that exhibits appropriate specificity, affinity, and selectivity for the target receptor in primary and secondary testing is referred to as a chemical lead. Determining the synthetic feasibility, defining the structure-activity connection, and obtaining initial proof of in vivo efficacy and target engagement are all necessary for this. (3)

A chemical lead's characteristics include:

- SAR defined
- Drug ability (preliminary toxicity, hERG)
- Synthetic feasibility
- Select mechanistic assays
- In vitro assessment of drug resistance and efflux potential
- Proof of the chemical class's in vivo effectiveness.
- The chemical class's PK/toxicity is known from in silico research or preliminary toxicity.

A drug ability assessment is frequently carried out to reduce the number of compounds that fail during the medication development process. When turning a chemical from a lead molecule into a medication, this evaluation is crucial. A chemical must have the ability to bind to a particular target in order to be deemed druggable; nevertheless, the compound's pharmacokinetic profile—which includes its absorption, distribution, metabolism, and excretion—is also crucial. The Ames test and the cytotoxicity assay are two other tests that will assess the compound's possible toxicity in screening. (4)

- **Take the lead in optimization**

The process of designing a drug candidate after identifying an initial lead molecule is known as lead optimization. A hypothetical medication is synthesized and characterized iteratively in order to illustrate the relationship between chemical structure and activity, interactions with targets, and metabolism. Hit-to-lead optimization is used in early drug discovery to find interesting compounds from the leads obtained from high-throughput screening testing. During lead optimization, the last phase of early drug discovery, potential leads are assessed for a variety of characteristics, such as selectivity and binding processes. Lead optimization aims to improve the lead structure's shortcomings while maintaining the advantageous qualities of lead compounds.

The chemical structures of the lead compounds (small molecules or biologics) must be changed to increase target specificity and selectivity in order to create a preclinical therapeutic candidate. Additionally assessed are toxicological characteristics as well as pharmacodynamic and pharmacokinetic aspects. To properly define the molecule and create an optimization path, laboratories need to gather information on the lead's toxicity, potency, stability, and bioavailability. (5)

- Features of the product

Size, form, potency, weakness, use, toxicity, and biological activity are characteristics of a novel pharmacological molecule that exhibits promise therapeutic efficacy. Pharmacological research in its early phases is assisting in the characterization of the compound's mode of action.

Creation and development

The phase of medication development known as pharmaceutical formulation involves characterizing the physicochemical characteristics of active pharmaceutical ingredients (APIs) in order to produce a dosage form that is stable, bioavailable, and ideal for a particular mode of administration.

Preformulating studies assess the following parameters:

- Solubility in different mediums and solvents;
- Dissolution of the active pharmaceutical ingredient (API);
- Accelerated stability services under different conditions
- Solid phase characteristics (such as polymorphs, particle size, shape, etc.)
- Formulation services and capacities

New formulations for enhanced distribution of current dosage forms; process development for specific dosage forms; optimization of current recipes; and creation of new chemical entity (NCE) formulations (6)

Submicron and nano emulsions; self-emulsifying drug delivery systems; colloidal drug delivery systems; formulations with controlled and extended release

Preclinical studies

Scientists must ascertain whether a medicine has the potential to seriously injure people before testing it on them. Preclinical research is carried out in lab settings using animal models.

Preclinical research comes in two varieties:

- In Vitro: These studies are conducted in a controlled laboratory setting without the use of animals.
- In vivo: These tests are carried out on living things.

Preclinical research is typically quite brief. All things considered, these studies must offer comprehensive data on dosage and toxicity levels. Scientists evaluate the results of preclinical research before determining whether the medication is suitable for human testing.

These investigations involve a number of experiments, such as repeated dosage studies, pharmacological safety studies, genotoxicity studies, carcinogenicity studies, reproductive toxicity studies, and investigative new drug research.

Before starting clinical testing, drug developers must submit an application to the FDA for an investigational new drug. Data from preclinical and toxicology studies; information about drug manufacture; clinical research protocols for the studies to be conducted; any prior clinical research data; and details about the investigator or developer must all be included in the IND application.(7)

Clinical trials

The purpose of clinical trials, which are carried out on volunteers, is to provide specific answers regarding the approaches efficacy and safety of medications, vaccines, other therapies, or novel to the use of existing treatments. Clinical trials adhere to a particular study protocol created by the manufacturer, researcher, or both. Developers think about what they want to accomplish for each of the several stages of clinical research when they design a clinical trial. They also start the investigational new drug (IND) process, which is a prerequisite for the start of clinical research. Prior to initiating a clinical trial, researchers create the research problem and objectives by reviewing prior data on the medicine.

They then determine the following:

- Selection criteria for participants;
- Number of participants;
- Study duration Dosage and dosage form administration technique; parameter evaluation; Gathering and analysing data (8)

Clinical trial in phase 0

Phase 0 refers to first-in-human (FIH) investigative investigations carried out in compliance with FDA regulations. Other than those known as human microdose studies, phase 0 investigations involve giving 10 to 15 volunteers individual subtherapeutic doses in order to obtain pharmacokinetic data or help image particular targets without pharmacological action. Phase 0 investigations are carried out by the pharmaceutical industry to determine which of its drug candidates exhibit superior human pharmacokinetic properties.

Phase 1: Dosage and Safety

The initial testing of a medication using fewer healthy human subjects is known as a phase I trial. Typically, 20 to 80 healthy volunteers with a disease or condition participate in Phase 1. Patients are typically only utilized when the drug's mechanism of action suggests that healthy individuals will not tolerate it. Researchers will, however, perform phase 1 trials on individuals with this kind of diabetes if a new medication is created for use in this population.
Phase 1 studies collect data on pharmacodynamics in the human body under close observation.
Based on information from animal research, scientists modify the dosing schedule to ascertain the acute adverse effects and the amount of the medicine that the body can handle. Researchers are looking into the mechanism of action, adverse effects that come with increasing dosages, and efficacy data as the Phase 1 study progresses. The design of phase 2 investigations requires this. Nearly 70% of medications advance to the next stage. (9)

Phase 2: Side effects and effectiveness

Phase II trials are carried out on larger patient populations (hundreds) with the goal of assessing the drug's efficacy and resilience to Phase I safety assessments. These are therapeutic tests. Researchers can obtain more safety data from phase 2 studies. Researchers utilize this information to create new phase 3 research procedures, improve their research methodology, and hone their research topics. Roughly one-third of medications advance to the next stage. Finding therapeutic dosages for big phase III trials is the main function of phase II clinical trials.

Phase 3: Tracking the medication's efficacy and adverse effects

Phase 3 tests are being planned by the researchers to demonstrate whether the substance offers tangible advantages for particular individuals. Between 300 and 3,000 people participate in these investigations, which are also referred to as pivotal studies. The majority of the safety data comes from phase 3 research. It's possible that less frequent side effects were missed by earlier research. Many people are the subjects of phase 3 investigations. The findings are more likely to show long-term or less frequent adverse effects if the participants and duration are longer. About 25–30% of medications advance to the next stage of clinical trials.
The industry can seek to sell a medicine if the drug developer provides evidence from preclinical, clinical, and prior testing that the drug is safe and effective for its intended application. Before deciding whether or not to approve the drug, the FDA's review team thoroughly examines all of the evidence that has been presented. (10)

- **Application for a new drug**

A drug molecule's complete story is told in a New Drug Application (NDA). Its goal is to confirm that the medications are safe and effective for the intended use in the test subjects. The NDA must contain all of the drug's information, including preclinical and Phase 3 trial data. Reports of all investigations, data, and analysis must be included by developers.
Information on drug abuse, patent information, Institutional Review Board compliance information, suggested labeling, security upgrades, and usage instructions.

- **FDA evaluation**

The FDA's review team decides if the NDA is complete after receiving it. The review panel may reject the NDA submission if it is not comprehensive. The review team has six to ten months to determine whether to approve the medicine if it is finished.(11)

Drug safety monitoring after marketing (Phase IV)

Post-marketing surveillance trials are another name for this stage. They are carried out following regulatory approval of the medication or device for sale to consumers. At this point, pharmaceutical companies have multiple objectives:

1. evaluate the medication against other currently available medications;
2. track the medication's long-term efficacy and influence on the patient's quality of life; and
3. assess the cost-effectiveness of pharmacological therapy in relation to other established and novel medicines.

Phase 4 studies could result in the drug or device being taken off the market, and depending on the study's conclusions, the product might be registered for usage.

- **FDA Clearance**

The FDA must next collaborate with the applicant to create and approve the prescribing instructions if it finds that a medication has been demonstrated to be both safe and effective for its intended use. "Marking" is the term for this. The labeling explains the rationale behind approval and the optimal way to utilize the medication. But before a medication is authorized for sale, lingering problems frequently need to be fixed. The FDA occasionally asks the developer to respond to inquiries based on available information. In other situations, the FDA demands more research. (12)The developer can now choose whether or not to carry out

additional work. Formal appeal procedures are available if the developer disagrees with the FDA's decision. (13)

CONCLUSION

The multi-stage, intricate process of drug discovery and development turns scientific discoveries into treatments that can save lives. Every stage guarantees that only the safest and most effective drugs progress, starting with target identification and validation and continuing through lead discovery and optimization, preclinical research, and clinical trials.
Drug development and discovery are the innovative processes of discovering novel treatments based on biological target knowledge. Every success is based on countless failures. Drug discovery is the process of identifying potential new therapeutic entities using a combination of clinical, translational, experimental, and complementary models. New insights into human biology and disease are creating exciting new opportunities for breakthrough medications.

Despite being expensive, time-consuming, and heavily regulated, the procedure is nonetheless necessary to meet unmet medical requirements and enhance patient outcomes. Modern drug development is becoming more effective, accurate, and creative with the combination of genetics, bioinformatics, artificial intelligence, and sophisticated screening tools.
In the end, this process from lab to market demonstrates how science, technology, and regulation work together to deliver innovative medications to patients all around the world.

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