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Steps in the process of new drug development

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Abstract
This review determines the various stages of drug discovery, pre-clinical trials and clinical trials. This process involves the identification of chemical compound, synthesis, characterization, validation, optimization, screening and assay for therapeutic efficacy. Once a new drug target or promising molecule has been identified the process of moving from the science laboratory to the pre-clinical to clinical trials have been discussed in this article. The main aim of this process is identifying the chemical compound which is therapeutically useful in treating and curing the disease. The most common steps in the development of a new drug are discovery or synthesis of a potential new drug compound or elucidation of a new drug. Once a chemical compound has shown its therapeutic efficacy in these investigations, it will initiate the process of drug development earlier to clinical trials. The drug development from initial idea to the market is a very complex process which can take upto 5 to 10 years and cost of $17 billion. Due to high budget of research & development and clinical trials drug discovery process is the most expensive. The average time taken for the drug discovery is almost 12 - 15 years to develop a single new compound and enter into market.

Keywords: Target identification, lead optimization, lead compound, preclinical trials, clinical trials and post marketing surveillance.

Introduction
Drug discovery initially starts with the identification of a drug compound which is therapeutically used in treatment and management of the disease through different stages as shown in figure 1[1]. It is a long term, expensive and complicated process. It involves mainly two phases, first is stringent test and optimization of the selected chemical compound [2, 3]. Drug discovery and development follows two different approaches namely structured based drug discovery and target based drug discovery. In structure based drug discovery the biological profile is identified and then it is refined and developed further. Where as in target based drug discovery the drug target is identified [4, 5].

Different stages of drug development
1. Drug target identification.
2. Target validation.
3. Identification of Lead compound & Lead optimization.
4. Product characterization.
5. Formulation &development.
6. Pre-clinical trials.
7. The investigational new drug application.
8. Clinical trials.
9. Drug approval and marketing.

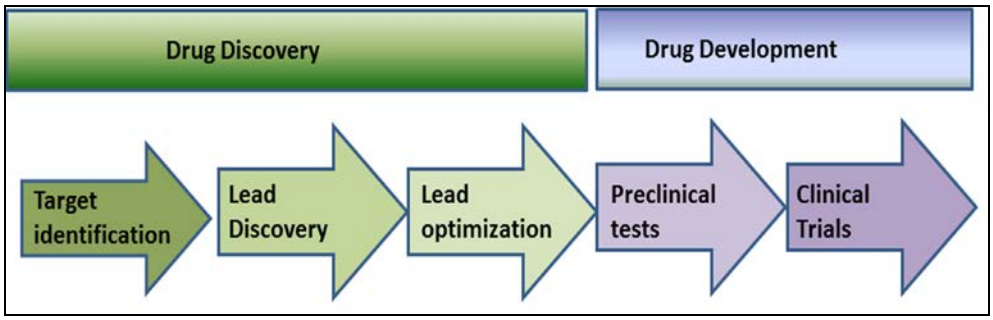

Fig 1: The drug development process.

Target identification
Target identification is the first step in the drug development process. It can be defined as the possible reason for a particular disorder as well as the phenotype of the disease. This target may be the naturally existing cellular or molecular structure involved in the pathology of the disease [4].

Approaches for target identification [1].
1. Data mining based bio informatics.
2. Genetic association.
3. Expression profile.
4. Pathway and phenotypic analysis.
5. Function screening.

Target validation
Target validation is another step in the drug discovery process. In this stage we undergo validation process because there is no clinical trial option. So obtaining target from target discovery is needed to undergo validation process.
Target validation can be done in two key steps first is to perform the experiment to confirm the reproducibility by using the different techniques like study of existing drugs, biochemical suppression, microarray DNA, affinity chromatography and expression cloning. And in second step we need to introduce the variation to ligand target environment by chemical genomics by means of chemical approaches against the genome encoding protein [6].

Identification of lead compound and lead optimization
In the lead identification we need to identify the lead compound which shows drug like properties. Where as in lead optimization we need to optimize the lead compound with respect to receptor target of interest so, that it may enter in to the drug development phase [6].

Product characterization
In product characterization if the drug molecule shows the maximum therapeutic efficacy, then it must be characterized in terms of molecule size, shape, strength and weakness, toxicity and biological activity. Early stages of pharmacokinetic and pharmacodynamic studies are helpful to characterize the mechanism action of the drug compound [7].

Formulation and development
In this stage the physiochemical properties of active pharmaceutical ingredients are determined to produce stable and optimal dosage form in specified administration route.

Preclinical studies
Preclinical studies mainly involves both the *in vitro*, *in vivo* and trials on animal population. Information about the dosing and toxicity levels is obtained from these studies. After the pre-clinical trials researchers review their findings and decide whether the drug can be tested in people [8].

Various types of experiments conducted during these pre-clinical studies include
1. Single dose toxicity studies.
2. Repeated dose studies.
3. Safety pharmacology studies.
4. Genotoxicity studies.
5. Carcinogenicity studies.

Various steps involved in the doing pre-clinical trials are
1. We need to identify the drug target.
2. Develop a bioassay.
3. We need to screen the drug in the assay method.
4. We need to establish effective and toxic doses.
5. And finally we need to file an application for the approval of investigational new drug (IND) [9].

The Investigational New Drug (IND) Process
It is an application which is filed to the FDA to start the clinical trials in humans. If the drug was found to be safe and effective from pre-clinical trials. A sponsor will submit the IND application to the FDA [9]. And there will be a pre IND meeting with FDA to discuss the various issues like
1. The design of the pre-clinical trials.
2. The intended protocol of the clinical trial.
3. The chemistry, manufacturing and control of the investigational drug.
4. Clinical trials

Clinical trials
Clinical trials can be defined as the systemic study of a new drug or an investigational new drug in healthy human volunteers to generate data to determine the safety, efficacy and toxicity of a new drug in order discover a new molecule. The clinical trials have classified as follows like phase 0, phase 1, phase 2, phase 3, phase 4 and finally phase 5 as shown in figure 2 and all these phases of clinical will be discussed below [10, 11].

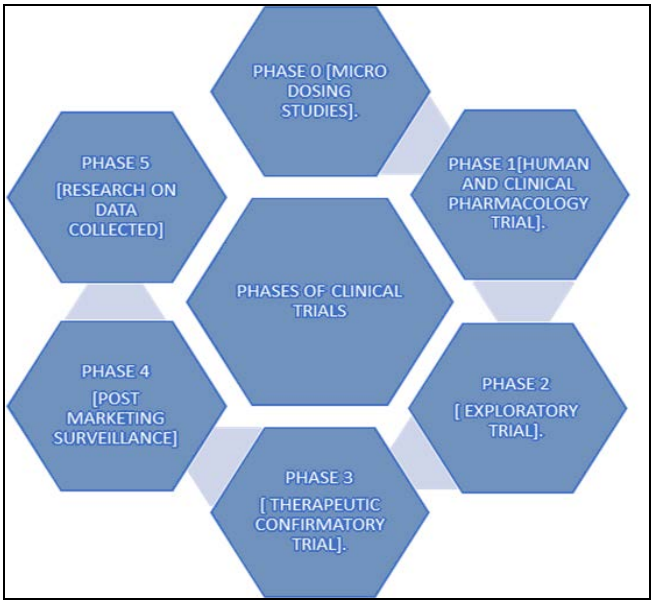

Fig 2: Phases of Clinical Trials [12].

Phases of clinical trials
Phase 0
These are also called as micro dosing studies, here a very small dose is administered to the healthy volunteers. As the dose is only 100 microgram so, safety and efficacy cannot be known. Phase 0 studies are used for ranking the drug candidate in order to decide the pharmacokinetic parameters on humans for the further development.

Phase 1: Clinical Trial
This phase is also called as human and clinical pharmacology. It is the first step in clinical trials in which 20-80 group of healthy volunteers will be selected. The main purpose of this stage is to estimate the safety, tolerance, pharmacokinetic and pharmacodynamic properties and success rate is 70%. Duration of the study is days to several weeks and months. Different kinds of phase 1 clinical trials are SAD and MAD [13].

Sad: is single ascending dose studies in which small group of human subjects are selected and a single dose of the drug tested for a particular period of time.

Mad: is multiple ascending dose studies. It gives information about the pharmacokinetic and pharmacodynamic properties of the multiple doses of the drug.

Phase 2: Clinical Trials
This phase is also called as therapeutic exploratory. In this phase we are going to select 100-300 group of healthy volunteers to estimate the safety in the longer participants. Duration of the study is several months to years. We can determine both the safety and efficacy and also maximum tolerated dose, common short time side effects and risk. Phase 2 clinical trials are divided in to Phase II A and Phase II B. Phase II A will determine how much drug should be given and Phase II B will determine the how well the drug works at the prescribed dose. Phase 2 clinical trials are performed at universities and hospitals and success rate is 33%.

Phase 3: Clinical Trials
These trials are randomized controlled multicenter trials on a large patient groups 300-3000. The main purpose of this study is to compare the safety and efficacy of new treatment against the current treatment because to select the better treatment. Duration of this study is 1 to 4 years. It is time consuming, expensive, difficult to design and perform. Success rate is 25 to 30%.

Phase 4: Clinical Trials
Phase 4 clinical trials also called as post marketing surveillance or pharmacovigilance. These are primarily used for observational purpose not for non-experimental nature. In which the patient population selected is not fixed and it consists of all types of patients. This phase is performed by sponsoring company or any regulatory authority to find a market for the new drug. The purpose of this study to detect the rare adverse reactions in particular diseased condition people. Duration of this phase is approximately 10 to 18 years.

Phase 5: Clinical Trials
Phase 5 clinical trial is also called as translational research or field research. It refers the effectiveness and community based research studies. In this phase dose and monitoring of patients are not required. It is particularly performed for test generalization mechanism to a large sample [11].

Drug approval and marketing.
The formulation developed is submitted for approval to regulatory bodies like CDSCO in India, USFDA in US etc for approval for marketing.

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