Original Article

A Review On Drug Discovery And Development

Manouchehr Khanipour[1]*, Mina Shahraki Mohammadi[2]

[1]*Intern, Department of Pharmacy Practice, Karnataka College of Pharmacy, Bangalore, India.E-mail:khanipour1989@yahoo.com

[2]Intern, Department of Pharmacy Practice, Cherran`s College of Pharmacy, Coimbatore, India
E-mail: minashahraki91@gmail.com

***Corresponding Author:** Manouchehr Khanipour

*Intern, Department of Pharmacy Practice, Karnataka College of Pharmacy, Bangalore, India. E-mail: khanipour1989@yahoo.com
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Abstract

Developing and discovery of a new drug for treating a disease is costly and needs up to 14 year's research and testing. Proper procedure necessitates a stepwise approach along with well documentation. Normally the work starts with target identification and validation. Optimization, discovery of lead compounds and testing on animals in pre pre-clinical phase are different stages which need to be followed by clinical studies and assessing the drug candidates on humans. Approximately every one to ten drug candidates may have a chance to be marketed. After marketing, development still continues by evaluation and study of adverse reactions or finding new action of drugs which was not recognized before. In this research, all mentioned steps briefly have been reviewed.

Key words: Lead compound, hit discovery, clinical phase, pre-clinical phase, and adverse reaction.

INTRODUCTION

Developing a new drug has a significant share in health system expenditure. Developing and discovery of a new medicine approximated between $314 million to $2.8 billion[1]. During covid pandemic Pfizer company claimed to have invested $2 billion for developing covid Vaccine[2]. This complicated process has different stages and phases. Time for regular discovery and development of a new agent, from starting point to getting approved by authority takesup to 14 years[3].
Drug discovery and development is a process in which new therapeutic agent for treating specific disease by applying different models will be identified. These models can be listed as computational, experimental, translational, and clinical[4]. Pre clinical, clinical and post marketing studies are different stages of development of drug. Today this process has been affected by artificial intelligent.

Stepwise Development

Generally stages of drug development and discovery can be listed as research stage, lead discovery, preclinical development, clinical development, FDA approval, post marketing studies.Identifying and discovery of a new drug initiates by recognizing a biological target. Biological target includes variety of option from enzymes to receptors or binding molecules[5]. It is clear, this work need deep knowledge of pharmacology, toxicology and biochemistry.

Target identification

Most important feature of a target is being drug-able. Hughes et al in principle of early drug discovery use this term as important criteria for a target. They believe drug able target can be reached by molecules for producing biological response. This response plays role in efficacy of drug[6].
There are three different approaches to identify target of drugs and small molecules. Direct biochemical approach, genetic interaction approach and computational inference approach. Direct method is based on labelling and biochemical affinity[7]. Genetic interaction approach emphasizes on suppression or stimulating genetic materials. Computational approaches can be called as Computer-aided drug discovery. These methods use structure base or ligand based systems[8]. Yang gives special credit to data mining which means use of bio information to identify and weighing importance of targets. This information can be directed from literatures, gen data, patents and etc [6].

Target validation:

After identification of target, it needs to be validated. In this step, by using different methods researchers try to verify and understand the therapeutic effect of target [9]. Without validation, target cannot be studied further in development process. Target validation has different aspects which include monitoring the capacity of target, defining metric method as marker for assessing target, screening for finding hits [10].
High-throughput screening (HTS) is a way to identify lead compound from other candidates and ignoring weak and false targets. HTS involves screening of the all candidatesby using thetarget or in anassay system, to see whether the activity is relevant to the target [11].

Validation can be done also by variety of techniques. Antisense tool which uses RNA like compounds, transgenic animals for observing effect of drug, tissue restriction and knockout method, monoclonal antibodies and recently chemical genomics are example of these techniques and tools [6].

Lead discovery

After target identification and validation, it is time for hit or lead discovery. National Cancer Institute defined lead compound as a chemical substance that revealsproperty for treating a disease and can be developed as a new drug or medicine.Lead between other candidates has more benefits and less harm.Discovering a hit or lead is the first step in developing a new medicine [12]. Lead discovery is based on screening and so different methods of screening can be used. Imaging study at molecular level such CT, MRI, PET and SPECT are functional in this process [13]. For improving study multimodal methods such as photo-acoustic imaging (PAI) [14] and bioluminescence optical imaging (BLI) [15]also developed. After screening, usually one or more compounds go to next step for assessing optimization. In optimization candidates are evaluated as drug like compound [13]. Focusing on ADME, safety and efficacy are main parameters in this process [16]. Final goal in lead discovery should be selection a lead substance with ideal properties to be developed as a drug [13].

Preclinical study

After basic research, target identification and validation, lead and hit discovery and optimization, final candidates will be selected and proceed to preclinical phase of drug development and discovery. In this phase, substances are supposed to test and study in animals. In this stage, pharmacokinetics, pharmacodynamics, toxicity, mechanism of action, possible adverse reaction, normal dose are being assessed.Generally, pre clinical phase has two types namely in vitro and in vivo. These studies which are necessary before test of drug in human include the acute and repeated dose toxicity studies, the reproductive toxicity studies, the genotoxicity and carcinogenicity studies and safety pharmacology studies [17].
For toxicity study, two or more animal species should be tested to identify safe dose of candidate substances [18]. In case of serious side effect study will be stopped. This failure of study accounts about 30% of all cases [19]. It is estimatedonly 1 in 8 candidateproceeds to next stage and passes pre clinical phase [20].
These animal phasestudies are not much large but need to be informative about safe range and toxicity. This is noteworthy to mention principle of good clinical practice must be followed in all steps of this phase [21].

Clinical study

Completion of pre clinical study is start of testing compound on human. This phase is known as clinical since candidate will be studied on human subject for first time. In this stage both healthy and patient subject will be exposed to medication in different series of stages. Pharmacokinetic properties of lead compound and its safety in first phase, assessing efficacy of drug and finding dose with relation to response in second phase will be evaluated. Third phase of clinical trial which is most costly phase is conducted to confirm efficacy and safety of product in large population and cohort [22]. Unlike first phase in clinical stage, in2nd and 3rd phases, participants are patients with the disease which drug is intended to be developed.
Clinical phase of drug development needs specific design and protocol which discuses about inclusion and exclusion criteria of participants, duration, compensation, way of collection and analyzing of data and etc.
Investigators after designing the study need to submit Investigational New Drug Application (IND) to FDA. In phase I, about 20 to 100 healthy volunteers will be participated. About 70% of lead compounds pass this phase and proceed to 2nd phase. In second stage, hundreds of people with same disease are included and rate of success is about 33%. The large scaled study with thousands of patients with same condition and disease is last phase of clinical study to develop new drug [21].
Drug candidate has to show safety and efficacy in the target cohort and people. It is clear that benefits of drug have to overcome its side effects. Every one to ten candidates proceeds to market and included in post marketing studies for identifying those effects which not revealed in during pre clinical and clinical investigation[22].

Table 1: Details of different stages in clinical study

	Phase I	Phase II	Phase III
Participants	20 – 100 healthy	Several hundred	Several thousand
Duration	Months	Months to 2 years	2 to 4 years
Purpose	Safety and dosage	Efficacy-side effect	Efficacy and monitoring adverse effects
Rate of success	70%	30%	10%

Adopted from Food and Drug Administration (FDA)[21]

Post marketing study

Post marketing study (PMS) is the 4th stage of development of a drug. In fact efficacy of drug is supposed to be assessed in very large population and above boundaries and limitations of previous phases. This phase is non experimental which means no intervention is allowed and is based on observational studies [23].

PMS is done by different methods, mainly spontaneous reporting system which is handled by medical professionals. Since during premarketing studies there are some limitations such as fewer participants, less duration, time and budget, post marketing study seems a must.Apart from these reasons, additional knowledge about drug and patient interest only can be gained after marketing [23]. Another noteworthy point is about involvement of female in clinical phases which can effect on study. Recently, it has been found in clinical phase of drug development, enough number of female participants has been enrolled. This fact may lead to poor understanding of female mechanism about drug [24]. These barriers will be considered during PMS.

For value of PMS we can refer to some drug removal from market. Thalidomide is one of the famous drugs which removed from market after a thalidomide disaster in 1960s. It was indicatedand approved to use for the treatment of nausea during pregnancy. It was found as causation of birth defects in many new born infants [25].

CONCLUSION

Discovery and development of new drug, is an expensive procedure which takes time up to 14 years. It starts by identification and validation of target in body and followed by lead discovery, pre clinical and clinical studies. Due to some limitations during development of new drug during different phases, the process needs to be continued even after marketing. Different stages of drug discovery and development concentrates on specific purpose which will be used as a source of data for next phases. Developing artificial intelligence has huge effects on drug discovery process and may accelerate it.

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