A review on advancement in drug discovery and drug development

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Abstract- **This article provides a brief overview of process of drug discovery and development. The process of drug discovery and development has undergone spreading changes over the years. Introduction of several novel technologies in drug target identification and validation. Drug discovery and drug development is a very complex process which requires a lot time to discover and develop a new drug. Drug discovery is a process aimed at identifying a drug compound which have therapeutic use in curing and treating a disease or disorder. The process of drug discovery involves the identification of a drug, synthesis, characterization, screening and assay for therapeutic efficacy. Drug discovery and drug development is an ideal process for discovery of new drug, innovative default, mainly focus on actual process that's drug target identification as well as validation is done lead optimization and identification this both process come under a long and expensive drug discovery and development procedure. Clinical trials involves some orderly organized phases, which evaluate the developed drug on the basis of safety and efficacy .If drug passed all the phases of clinical trail it ready to approved by food and drug administration (FDA) and then it is ready for bring to the market. Developing a new drug is a tedious and expensive undertaken, Despite promising discoveries and multibillion dollar investment for new drug development is quietly undergoing crisis.**

Keywords: **Drug discovery, drug development, target validation, target identification, lead discovery, lead optimization, pre-clinical trial, clinical trail.**

INTRODUCTION:
Drug discovery is intricated process which involved identification of a drug chemicals to find out therapeutic use in treating and management of various disease conditions. Drug discovery and drug development is a very complex process which requires a lot time to discover and develop a new drug. Drug discovery is a process aimed at identifying a drug compound which have therapeutic use in curing and treating a disease or disorder. The process of drug discovery involves the identification of a drug, synthesis, characterization, screening and assay for therapeutic efficacy. Drug discovery and development is an extravagant process due to the high budgets of R&D, pre-clinical and clinical trials (1). The approximately cost for research and development for each efficacious and safe drug is likely to be $900 million to $2 billion (2). Drug discovery and drug development is an ideal process for discovery of new drug, innovative default, mainly focus on actual process that's drug target identification as well as validation is done lead optimization and identification this both process come under a long and expensive drug discovery and development procedure. The Success requires endless resources the best scientific and logical minds, highly advanced laboratory and technology; and multifaceted project management. It also takes constant and good fortune (3).
History of drug discovery
a)   Early drug discovery till 19th century :
Early drug discovery till 19th century in which natural products have been discovered and still are the most important source of drugs or drug precursors. Drug discovery has a long history that dates back to early days of human development. In those days, drugs were used for physical remedies and also connected with religious and spiritual relief. These drugs were discovered and identified through error and trial experimentation and observation of human and animals that how they responded to use of such products (4).
b)   Modern drug discovery in 19th century:
Modern drug discovery consisted of a set of limited developments beginning in the early years of the nineteenth century. The middle age from around 400 to 1500 , plagues scourge many part of Europe. Disease such as leprosy, tuberculosis, smallpox, scabies and bubonic plague were beyond control and many people gave away lives to these diseases. Introduction new techniques for separating individual components in extracts paved way for availability of single entity drugs (4) A typical example is quinine, Quinine was isolated in 1823 (5). Several other molecules were also development and synthesis into commercial entities during this century. Till late nineteenth century, the focus of drug research was on evaluation and testing existing natural (6).
c)   Current drug discovery:
Development of the modern pharmaceutical industry dates back to the beginning of the 20th. There were many development made in physiology, anatomy medical treatment, surgery including hygiene, sanitation and public health (4). Until the middle of the twentieth century, serendipity methods of discovering new drugs were followed, leading to the discovery of several successful drugs such as Benzodiazepines meprobamate and chlorpromazine (7).

d)   Naming of new drug
 Every drug has it's proprietary or brand name. During R&D process a new pharmaceutical drug is given an generic name or International Non proprietary Name(IIN). Non proprietary names are intended for use in pharmacopeia, labeling, product information and advertising.Non proprietary name is basis for product name for example generics (4).
  Stages of drug discovery
Across the pharmaceutical industry there are several authorized processes that must be undergone before the final sale of a drug can begin on the market. Following are the different stages which are required to get approval of new drug for market authorization from Food and Drug Administration(FDA)
1.   Target identification
2.   Target validation
3.   Lead identification
4.   Lead optimization
5.   Product characterization
6.   Formulation and development
7.   Preclinical research
8.   Investigational New Drug
9.   Clinical trials
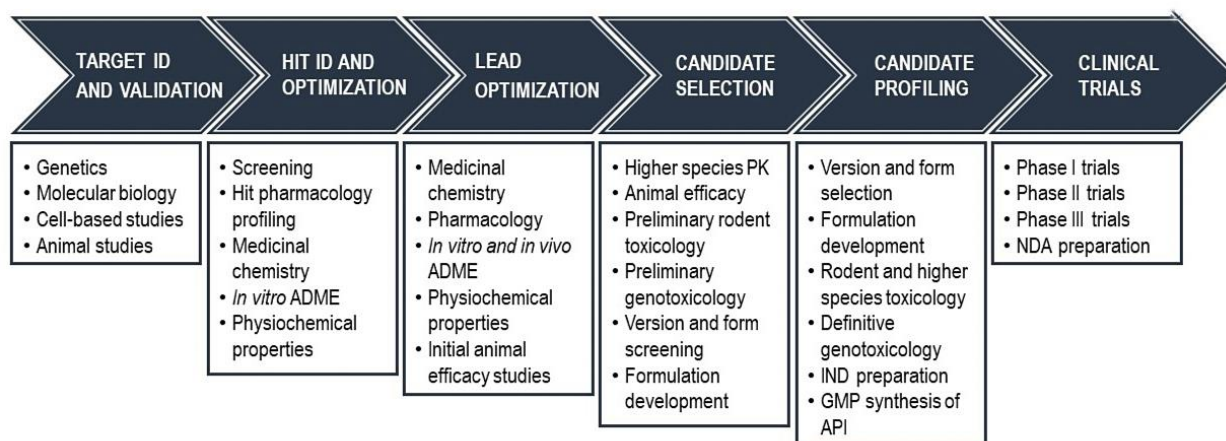10.   New Drug Application & approval (8).

Figure No.1: Stages of drug discovery

1.Target Identification
Target identification begins with separating the function of a possible therapeutic target and its role in the disease. An ideal target should be safe, efficacious, meet clinical and commercial requirements and be _druggable'.The techniques used for target identification may be based on principles of molecular biobiophysic,genetics, biochemistry, biology or other disciplines (9).
A specific drug target might have the following features:
▪ The drug target is a biomolecule(s), normally a protein that could exist in single or complex form
▪ The biomolecules have special sites that match other drug.
▪ The bimolecular structure might change when the biomolecule binds to drug and the changes in structure normally are reversible.
▪ The physiological responses due to changes in structure play a major role in complex regulation of companies functions of cells that exerts therapeutic effect.
▪ Structure of the biomolecule might change over the duration of the pathological process.
▪ Small molecules binding to the biomolecules are drugs (10).
2.Target validation
Target validation is the process of indicating the functional role of the identified target in this disease phenotype (11). New drug validation is the basis of investigation of new drug and the starting step of drug discovery. Target validation helps in research and development of new drug. The drug discovery process starts with the identification or develop evidence of, biological targets that are believed to be associated to a particular condition or pathology
The target validation process include
• Discovery of a desired biomolecule.
• Evaluation of it's ability as target.
• Design a bioassay to calculate it's biological activity.
• Constructing a high-throughput screen.
• Performing screening to find hits.

• Evaluating the hits (12).

3 .Lead discovery

Once drug targets have been identified and validated, identification of a suitable chemical moiety exploring interaction with the target is initiated. Identification of small molecule modulators and developing them into high-content lead series are key activities of contemporary drug discovery (13) Molecules displaying better interactions are called "hits". Most commonly, hit compounds are derived from high-throughput screening (HTS). In the next step, from the "hits", compounds with pharmaceutical properties such a low toxicity, membrane permeability, genotoxicity, etc. are recognized. These compounds are often called ''leads' (14,15)
Characteristics of a chemical lead are :
• SAR defined
• Drug capacity
• Synthetic viability
• Select mechanistic assays
• PK/Toxicity based on preliminary toxicity or in silico studies (16).

4. Lead optimization

Lead optimization is the process that initiate with a compound show a potential biological activity and confirm with best Lead component. The aim of lead optimization is to maintain favorable properties in lead compounds, while improving errors in lead structure. Leads are characterized with respect to pharmacodynamics properties such as efficacy and potency in vitro and in vivo, pharmacokinetic Properties, Physiochemical properties, and toxicological aspects (17).

5.Product Characterization

The molecule is characterized by its size, shape, weakness, strength, use , toxicity and biological activity after showing a promising therapeutic activity The drug product is categorized according to its route of administration.

6.Formulation and Development

Formulation of a product is a stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a bioavailable, stable , safe and maximum dosage form for a specific administration route.
During pre-formulation studies the following characteristics are evaluated:

- Solubility in different media and solvents
- Dissolution of the active pharmaceutical ingredient(API)
- Formulation development of new chemical entities(NCE)
- Formulation services and capabilities
- Controlled release and sustained release formulations
- Sub-micron and nano-emulsions
- Self-emulsifying drug delivery systems
- Optimization of existing formulations
- Colloidal drug delivery systems
- Accelerated Stability Services under various conditions
- Process development for selected dosage forms.

7.Preclinical Research

Preclinical development include developing a method on large scale synthethesis,drug delivery, carcinogenic studies, animal safety studies, Elimination and metabolism studies and dose ranging studies in animals.The pre-clinical trials also have to perform by corresponding regulatory authorities. The regulatory authorities must ensures that trials are conducted in safe and social way and would give approval for only those drugs which are approved to be safe and effective. ICH has established a basic guideline for technical requirement of acceptable preclinical drug development (16).

8.Investigational New Drug (IND) Application

A Pre -IND assessment can be organized with the FDA to calculate multiple issues:

- The design of animal research, which is required to lend support to the clinical studies
- The intended protocol for conducting the clinical trial
- ▪The chemistry, manufacturing, and control of the investigational drug
- Drug developers must file an Investigational New Drug Application to FDA before commencement clinical research

In the IND application, developers must include:
▪ Preclinical and toxicity study data
▪ Drug manufacturing information
▪ Clinical research protocols for studies to be conducted
▪ Previous clinical research data (if any)
▪ Information about the investigator/ develop (18).

9.Clinical trials :

The Clinical trail defines as any experiments on human being for the assessment of effectiveness of new drug or combinations of drugs, new approaches of surgery or radiography or technique to improve the diagnostic procedure of disease to improve the quality of life of patient. Clinical trials follow a specific study protocol that is designed by the researcher or investigator or manufacturer (19).

Phases of clinical trial:
1.	Phase 0 Clinical trial
2.	Phase 1 Safety and dosage
3.	Phase 2 Efficacy and side effects
4.	Phase 3 Safety and adverse drug effect monitoring
5.	FDA review
6.	Phase 4 Post-Market drug safety monitoring
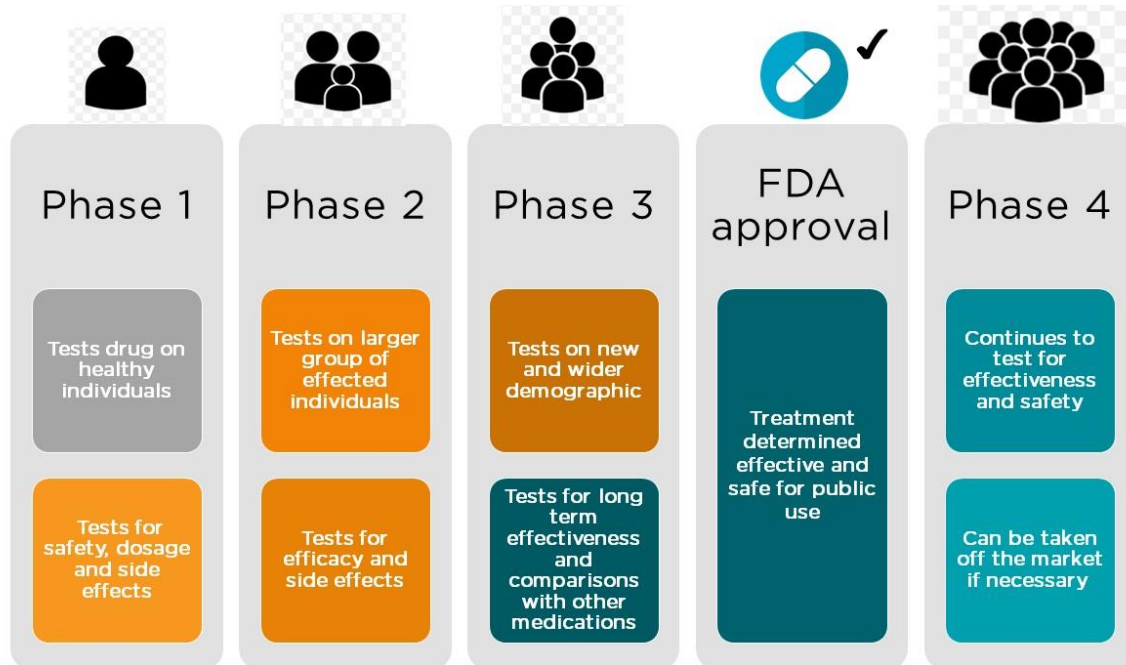
Figure No 2 : Phases of clinical trials

**1.	Phase 0 clinical trail:**
Phase 0 trial Besides termed as human micro dose studies, they have sings phase 0 trials besides termed as human micro dose studies, they have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific targets without showing pharmacological actions. Pharmaceutical industries perform Phase 0 Studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans (21).

**2.	Phase 1 clinical trail : safety and dosage**
Phase 1 clinical trail are the first test of a drug with a lesser number of healthy human sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific target without showing pharmacological action. Pharmaceutical industries perform phase 0 studies to pick which of their drug applicant has the preeminent pharmacokinetic parameters in human. *Volunteers.*

**3.	Phase 2: Efficacy and side effects**
Phase II trials are conducted on larger groups of patients (few Hundreds) and are aimed to determine the efficacy of the drug and to ensure the Phase I safety assessments. These trials aren't enough to confirm whether the drug will be Therapeutic. Phase 2 studies provide with additional safety data to the researchers.

**4.	Phase 3 Safety and adverse drug effect monitoring**
A drug developer must include all about a drug starting from pre- clinical data to Phase 3 trial data in the NDA. Developers must include reports on all studies, data, and analysis. Beside with clinical trial outcomes, developers must include:
•	Proposed labeling
•	Safety updates
•	Drug abuse information
•	Patent information Institutional review board compliance information
•	Directions for use
•	Data collection and analysis (20))

**5.	FDA Review**
Once FDA obtains a complete NDA then FDA team of review may require about 6 to 10 months to take a pronouncement on whether to approve the NDA.This is denotedas Labeling. In other the cases, FDA have need of additional studies. At this situation,

the developer can choose whether to continue further development or not. If a developer distresses with an FDA decision, There are tools for official appeal (22).

6.   Phase 4: Post-Market Drug Safety Monitoring

Phase IV studies may be required by regulatory authorities or may be undertaken by the promoting company for competitive purposes or other reasons. Therefore, the true illustration of a drug's safety essentially requires over the months and even years that markup a drug's lifespan in the market. FDA reviews reports of problems with prescription and OTC drugs, and can decide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions (23).

10.New Drug Application & approval

Developers must include reports on all studies, data, and analysis Beside with clinical trial outcomes, developers Must include
• Proposed labeling
• Safety updates
• Drug abuse information
• Patent information
• Institutional review board compliance information
• Directions for use (24).

CONCLUSION:

Drug Discovery and development are among most important translational science. Every clinical trail has a protocol or action plan, for conducting the trail. . Each study answers scientific questions and tries to find better ways to prevent, screen, diagnose or treat disease. A key goal of drug discovery campaign is the recognition of new molecular entities that may be value in the treatment of diseases that qualify as presenting unmet medical needs.

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