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DRUG DEVELOPMENT PROCESS

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Abstract: Drug discovery is a procedure that tries to find a therapeutically beneficial chemical for curing and treating disease. Identification of candidates, synthesis, characterization, validation, optimization, screening, and tests for therapeutic efficacy are all part of this process. Once a molecule has been proven to be significant in these studies, it will begin the medication development process prior to clinical trials. To create a medicine that is safe, effective, and meets all regulatory standards, the new drug development process must go through numerous stages. One of the main points of our article is that the process is long, complicated, and expensive enough that multiple biological targets must be considered for any new treatment that is eventually approved for clinical use, and new research methods may be required to investigate each new target. It takes a long time and a lot of effort to turn a discovery into a commercial medicine. It takes roughly 12 to 15 years from discovery to licensed drug, and an expenditure of about $1 billion is required. A million molecules are screened on average, but only one is investigated in late-stage clinical trials and eventually made available to patients. This article gives a quick overview of how new drugs are discovered and developed.

Index Terms **- Drug discovery , Development , Validation, Optimization , Screening.**

I. INTRODUCTION

Drug discovery is a multidimensional process that include identifying a drug molecule that is therapeutically useful in the treatment and management of a disease. Typically, researchers discover novel medications by developing new perspectives on a disease process that allow researchers to construct a medicine to counteract or stop the disease's symptoms. The identification of drug candidates, synthesis, characterization, screening, and assays for therapeutic efficacy are all part of the drug development process. Following clinical trials, if a molecule achieves favorable findings in these investigations, it will begin the process of medication development. Due to the high costs of R&D and clinical trials, drug discovery and development is a costly process.[(1)]

A single new medicine molecule takes almost 12-15 years to develop from the moment it is discovered to the time it is accessible on the market for treating patients. For every 5,000-10,000 compounds that join the research, Success necessitates vast resources, including the best scientific and logical brains, cutting-edge labs and equipment, and multidimensional project management. Persistence and good fortune are also required. Drug discovery eventually offers hope, faith, and relief to billions of sufferers[(2)]

II. STAGES OF DRUG DISCOVERY

stage 1: Target identification:

Target identification is the first and key step in the drug discovery channel. A drug target is the specific binding site for drug in vivo through which it exerts action. Usually, drug target refers to a single biomolecule.[(4)]

A drug target can be an established drug for which there is good scientific Know-how which is supported by publications that describe both how the target behaves in normal physiology and how it is involved in human pathology There are many drugs targeting established drug targets. A drug target can also be potential drug targets which are biomolecules whose functions are not fully understood and which lack drugs targeting them.[(5)]

A drug target has any of the following characteristics

1. the drug targets can be a biomolecule(s) such as a protein that could exist in solitary or complex forms.
2. The biomolecules have specific locations or sites that match with the other, the drug
3. The structure of biomolecules may change when it binds to drugs. The changes in structure are usually reversible.
4. Various physiological responses occur when the structure of a biomolecule changes, causing the cell, organ, tissue, or body condition to be regulated.[(5)]

Stage 2: Target Validation:

Target validation is the basis for new drug exploration in the process of drug discovery. Target validation helps to new drug research and development and to provide more insight into the pathogenesis of target-related diseases. (6)

The target validation process includes

1 Discovery of the biomolecule of interest

2. Evaluation of its potential as a target.

3. Designing a bioassay to measure its biological activity.

4. Constructing a high-throughput screening method. [6]

Stage 3: Lead Discovery

Leads can also be obtained by molecular modelling assisted by 3D computer graphics, which allows the development of structures based on new and pre-existing molecules to increase desired features while eliminating undesirable properties to develop highly selective targeted compounds. A combinatorial chemistry wherein unplanned mixing and matching of large numbers of chemical building blocks to produce libraries of all possible combinations can also be attempted to get leads. This technique generates billions of compounds, screened by high-throughput screening (HTS), meaning thousands a day. [3]

Stage 4: Lead optimization:

Lead optimization is a procedure that begins with the identification of a compound that has the potential to have a biological effect and ends with the selection of the best compound. Molecules are chemically modified and described to produce molecules with desirable qualities, which are then converted into drugs. Physiochemical qualities, pharmacokinetic properties, and toxicological elements of leads are optimized in vitro and in vivo for efficacy and potency[7]

Stage 5: Pre-clinical and Clinical Development:

Companies use stylized statistics to illustrate the risks in preclinical research, such as that on average, only one in every five thousand compounds that enters drug discovery to the stage of preclinical development becomes an approved drug[8]

Clinical trials are organized by the National Institutes of Health (NIH) into 5 different types:

1. Treatment trials: This trial tests the experimental treatments or a new combination of drugs.

2. Prevention trials: This trial looks for ways to prevent a disease or prevent it from recuring.

3. Diagnostic trials: This trial finds better tests or procedures for diagnosing a disease.

4. Screening trials: This trial tests methods of detecting disease.

5. Quality of life trial: This study looks into ways to improve the comfort and quality of life for those who have a chronic illness[12]

III. PRE-CLINICAL STUDIES

Preclinical development, also known as nonclinical studies, is a stage of drug development that occurs before clinical trials (human testing) and collects essential feasibility, iterative testing, and drug safety data, generally in laboratory animals.[9]Preclinical studies are used to determine a starting, safe dose for first-in-human studies and to assess the product's potential toxicity, which often includes new medical equipment, prescription medications, and diagnostics.[8]

The pre-clinical development includes developing a method of large-scale synthesis, animal safety studies, carcinogenicity tests, drug delivery, elimination and metabolism studies , drug formulation experiments, a dose-ranging studies in animals. At this stage, wide range dosages of the potential drugs are introduced to the cell line or animal to get preliminary effectiveness and pharmacokinetic information[8]

IV. CLINICAL STUDY

• A clinical study is a research project that uses human volunteers (also known as participants) to further medical knowledge. Clinical trials (also known as interventional studies) and observational studies are the two basic forms of clinical investigations.[10]

• Clinical trials are human research studies that are used to assess a medicinal, surgical, or behavioral intervention. They are the most common technique for researchers to determine whether a novel treatment, such as a new medicine, diet, or medical equipment (such as a pacemaker), is safe and effective in humans. A clinical trial is frequently performed to determine whether a new treatment is more successful than the current treatment and/or has fewer negative side effects.[10]

• Clinical studies are often carried out in stages that build on one other. Each phase is intended to provide answers to specific questions. Knowing the clinical trial's stage is crucial since it might give you a sense of how much is known about the medicine being investigated. [12]

PHASE 0 CLINICAL TRIALS -Despite the fact that phase 0 studies are conducted in humans, they are not the same as the other stages of clinical trials. The goal of this phase is to assist the drug approval process go more quickly and smoothly. Researchers may use phase 0 trials to see if the medications do what they're supposed to do. This could save time and money that would otherwise be spent on later-phase experiments. .Phase 0 studies use only a few small doses of a new drug in a few people known as micro dosing study [(11)]

PHASE I CLINICAL TRIALS -Phase I studies of a new drug are usually the first that involve people. Phase I studies are done to find the highest dose of the new treatment that can be given safely without causing severe side effects. Study participants ranges from 20-100 healthy volunteers. .It determine safety and dosage.[(13)]

PHASE II CLINICAL TRIALS: A phase II clinical study is conducted if a new medication is found to be safe in phase I clinical trials and to see if it works in specific forms of cancer. The advantage that doctors seek is determined by the treatment's purpose. It could indicate that the cancer is shrinking or disappearing. Study participants are up to several 100 people with disease and length of study is up to several months to 2 years .Determine efficacy and side effects [(14)]

PHASE III CLINICAL TRIALS: Before being approved for general use, treatments that have been shown to work in phase II clinical trials must pass a third phase. Phase III clinical studies assess the novel treatment's safety and effectiveness against the current standard of care. Study participants are up to 300-3000 volunteers who have disease and length of study is 1 to 4 years.[(14)]

PHASE IV CLINICAL TRIALS: In phase IV studies, drugs that have been approved by the FDA are generally monitored for a long time. Even after thousands of patients have been exposed to a new therapy, not all of the treatment's side effects may be known.it is the practice of monitoring safety of drug after it has been released in the market[(15)]

V. INVESTIGATIONAL NEW DRUG (IND) APPLICATION

The filing of an Investigational New Drug (IND) application is the initial stage in the drug review process. The application to the US Food and Drug Administration (US FDA) for an exemption to send the product to investigators throughout the state has been submitted. To qualify for this exemption, the company must submit the required information via the IND. INDs are divided into two categories:

1. Commercial - For companies looking to have a new medicine approved for marketing.
2. Non-commercial (research) - for companies submitting Investigator IND, Emergency Use, and Treatment INDs. [(17)]

VI. NEW DRUG APPLICATION (NDA)

The NDA application is the formal proposal to the FDA by drug sponsors, like as biotech and pharmaceutical corporations, to authorize a new pharmaceutical for sale and marketing. Since 1983, every new drug or therapy has required approval of a New Drug Application (NDA) before being commercialized in the United States.[(18)]

The NDA documentation is expected to detail the drug's entire history, such as what happened during clinical trials, what the medicine's ingredients are, the conclusions of animal research, how the drug acts in the body, and how it is produced, processed, and packed.[(17)]

Once the FDA has reviewed the NDA, it issues one of the below mentioned three action letters:

- Approval Letter – This letter confirms that the drug has been approved.
- Approvable Letter – This letter shows that the drug will be authorized eventually, but that it will need to be corrected due to a few flaws such as labelling revisions.
- Not Approvable Letter - Indicates that the medicine will not be approved and provides a list of reasons why. [(17)]

Objectives of NDA

- Whether the medicine's proposed labelling (package insert) is acceptable and what it should include
- Whether the drug is safe and effective in its proposed usage, and whether the drug's advantages exceed the hazards
- Whether the production procedures and quality control measures employed to maintain the drug's identity, strength, quality, and purity are sufficient to maintain the drug's identity, strength, quality, and purity. [(16)]

VII. TIME REQUIRED FOR DEVELOPING NEW DRUG

Drug development takes a long time since a candidate drug is reviewed by regulatory authorities in numerous countries at every step of development before being released on the market. A new drug can take anywhere from 12 to 15 years to create, according to PhRMA (Pharmaceutical Research and Manufacturers of America, a pharma industry trade organization in the Americas). Preclinical testing takes roughly six and a half years. Phase-I trials last around 1.5 years; Phase-2 trials last about 2 years; Phase-3 trials last about 3.5 years; and regulatory body assessment and approval takes about 1.5 years. Once the prospective drug has been approved for use as a medication. It may be subjected to additional Phase-IV trials to gather more safety and effectiveness information.(17)

VIII. DRUG DEVELOPMENT COST ACCORDING TO STUDIES

The cost of medication development has been estimated to be anywhere from $314 million and $2.8 billion, according to the report. Olivier Wouters, an assistant professor of Medicine Policy at the London School of Economics and Political Science, Martin McKee, a professor of European Public Health at the London School of Hygiene & Tropical Medicine, and Jeroen Luyten, an associate professor of the Faculty of Medicine at the Leuben Institute for Healthcare Policy's Department of Public Health and Primary Care, were the authors. (16)

Drug development costs for therapeutic domains with five or more medications ranges from $765.9 million for central nervous system treatments to $2.7716 billion for cancer and immunomodulating drugs, according to the median estimates.(16)

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