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"DRUG DEVELOPMENT: STAGES OF DRUG DISCOVERY AND DEVELOPMENT PROCESS"

Prof.Diksha Gupta[1]*, Swara Suryarao[2], Harshraj Suryawanshi[2], Ujjwala kumari[2],Dr.Rajesh Oswal[3]

*Assistant Professor, Department of Pharmaceutics[1], Students[2], Principal[3]

Genba Sopanrao Moze College of Pharmacy Wagholi Pune,412207, Maharashtra.

ABSTRACT:

Drug discovery is the process aimed at identifying therapeutically useful compounds for the cure and treatment of disease. This process includes candidate identification, synthesis, characterization, validation, optimization, screening, and testing of therapeutic efficacy. Once these studies demonstrate the compound's importance, the drug development process begins prior to clinical trials. The drug development process must go through several stages to produce a drug that is safe, effective and meets all regulatory requirements. A common theme of our articles is that the process is so lengthy, complex and expensive that many biological targets need to be considered for any new drug that will ultimately be approved for clinical use. New research tools may need to be evaluated to explore new targets. The journey from initial discovery to marketed drug is a long and arduous task. From discovery to approved drug takes about 12 to 15 years and requires an investment of about $1 billion. On average, one million molecules are screened, but he only one will be investigated in late-stage clinical trials and ultimately delivered to patients. This article provides a brief overview of the processes involved in drug discovery and development.

Keywords: Clinical Trials, Lead optimization, New Drug Application, Preclinical research.

I.INTRODUCTION:

The development of new drugs is very complex, costly and risky. Its success is highly dependent on an intense collaboration and interaction between many departments within the drug development organization, external investigators and service providers, in constant dialogue with regulatory authorities, payers, academic experts, clinicians and patient organizations. Within the different phases of the drug life cycle, drug development is by far the most crucial part for the initial and continued success of a drug on the market.[1,2]

The average cost for research and development for each efficacious drug is likely to be $900 million to $2 billion. This figure includes the cost of the thousands of failures: For every 5,000-10,000 compounds that enter the investigation and development pipeline, ultimately only one attains approval. These statistics challenge imagination, but a brief understanding of the R&D process can explain why so many compounds don't make it and why it takes such a large, lengthy effort to get one medicine to patients. [3] The Success requires immense resources the best scientific and logical minds, highly sophisticated laboratory and technology; and multifaceted project management. It also takes persistence and good fortune. [4] Eventually, the process of drug discovery brings hope, faith and relief to billions of patients. [5]

The discovery of a new chemical entity that modifies a cell or tissue function is but the first step in the drug development process. Once shown to be effective and selective, a compound which is to be discovered must be completely free of toxicity, should have good bioavailability and marketable before it can be considered to be a therapeutic entity.[6]

II.STAGES OF DRUG DISCOVERY AND DEVELOPMENT INCLUDE:

- Target identification
- Target validation
- Lead identification
- Lead optimization
- Product characterization
- Formulation and development
- Preclinical research
- Investigational New Drug Application (INDA)
- Clinical trials
- New Drug Application

- FDA Review
- Approval

Stages of drug discovery and development:

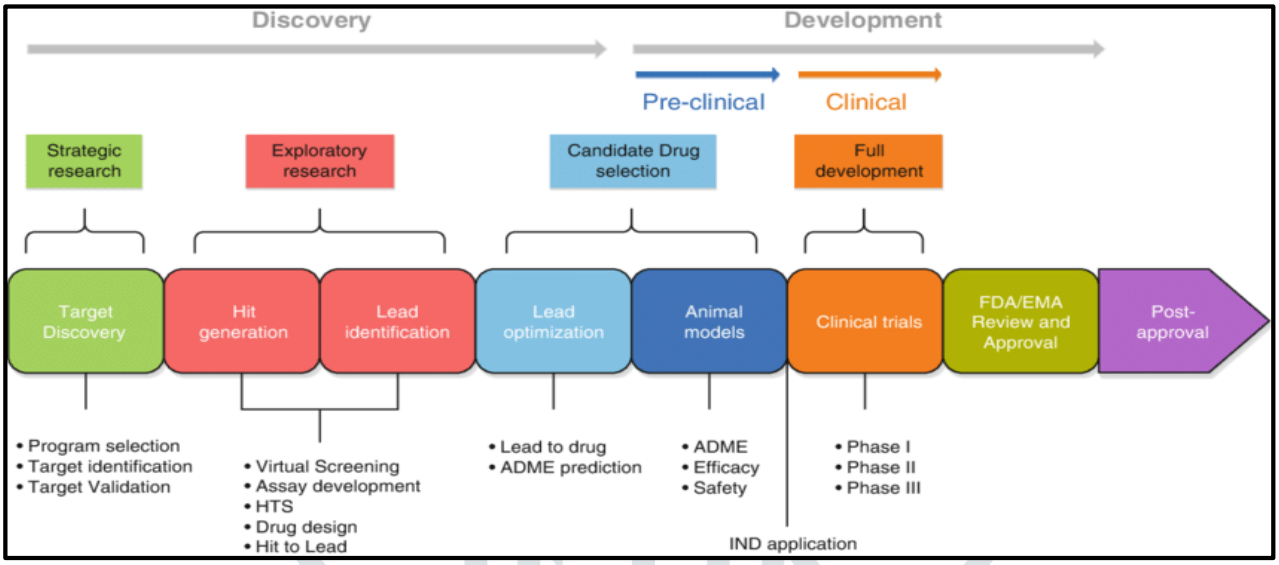

fig 1: Stages of drug discovery

2.1 Target Identification

The first step in the discovery of a drug is identification of the biological origin of a disease, and the potential targets for intervention. Target identification starts with isolating the function of a possible therapeutic target (gene/nucleic acid/protein) and its role in the disease.[7]

The Target identification defines the possible causes of a particular disorder, as well as the path or phenotype of the disease. Targets are the specific components naturally existing cellular or molecular structure involved in the pathology which are responsible for disease; they may be receptors, enzymes, nucleic acids, hormones, ion channels etc. Target selection by the pharmacist depends on the disease on which he focused. Presently, G-protein coupled receptors (GPCR) are the predominant families addressed and more than 600 genes encoding GPCR have been identified. In humans, GPCR are responsible for about 30 disease including Diabetes insipedus, hypo and hyperthyroidism, retinis pigmentosa, several fertility disorders and even carcinoma [8] . Approximately, 150 GPCRs found in human have unknown function [9] . For the identification of target, In Silica approach is widely used, it's a computer based technique to study the specific chemical responses in the body or target organism and tailoring combination of these to fit a treatment profile[10] .

The techniques used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines.[11]

Approaches:

• Data mining using bioinformatics — identifying, selecting and prioritizing potential disease targets

• Genetic association — genetic polymorphism and connection with the disease

• Expression profile — changes in mRNA/protein levels

• Pathway and phenotypic analysis — In vitro cell-based mechanistic studies

• Functional screening — knockdown, knockout or using target specific tools.[12]

2.2 Target Validation

New target validation is the basis of completely new drug exploration and the initial step of drug discovery. New drug target validation might be of great help not only to new drug research and development but also provide more insight into the pathogenesis of target related diseases [13].

The target validation process might include six steps:

1. Discovering a biomolecule of interest.

2. Evaluating its potential as a target.

3. Designing a bioassay to measure biological activity.

4. Constructing a high-throughput screen.

5. Performing screening to find hits.

6. Evaluating the hits.

The drug discovery process starts with the identification or growing evidence of, biological targets that are believed to be connected to a particular condition or pathology. Information supporting the role of these targets in disease modulation can come from a variety of sources .[14]

Target validation is the process of demonstrating the functional role of the identified target in the disease phenotype. Whilst the validation of a drug‘s efficacy and toxicity in numerous disease-relevant cell models and animal models is extremely valuable – the ultimate test is whether the drug works in a clinical setting.[15]

2.3 Lead Identification

A chemical lead is defined as a synthetically stable, feasible, and drug like molecule active in primary and secondary assays with acceptable specificity, affinity and selectivity for the target receptor. This requires definition of the structure activity relationship as well as determination of synthetic feasibility and preliminary evidence of in vivo efficacy and target engagement.

Characteristics of a chemical lead are:

• SAR defined

• Drug ability (preliminary toxicity, hERG)

• Synthetic feasibility

• Select mechanistic assays

• In vitro assessment of drug resistance and efflux potential

• Evidence of in vivo efficacy of chemical class

• PK/Toxicity of chemical class known based on preliminary toxicity or in silico studies

In order to decrease the number of compounds that fail in the drug development process, a drug ability assessment is often conducted. This assessment is important in transforming a compound from a lead molecule into a drug. For a compound to be considered druggable it should have the potential to bind to a specific target; however, also important is the compound‘s pharmacokinetic profile regarding absorption, distribution, metabolism, and excretion. Other assays will evaluate the potential toxicity of the compound in screens such as the Ames test and cytotoxicity assay.[16]

2.4 Lead Optimization

Lead optimization is the process by which a drug candidate is designed after an initial lead compound is identified. The process involves iterative series of synthesis and characterization of a potential drug to build up arepresentation of in what way chemical structure and activity are related in terms of interactions with its targets and its metabolism.

This optimization is accomplished through chemical modification of the hit structure, with modifications chosen by employing structure-activity analysis (SAR) as well as structure-based design if structural information about the target is available. [17]

2.5 Product Characterization

When any new drug molecule shows a promising therapeutic activity, then the molecule is characterized by its size, shape, strength, weakness, use, toxicity, and biological activity. Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

2.6 Formulation and Development

Pharmaceutical formulation is a stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a bioavailable, stable and optimal dosage form for a specific administration route

2.7 Preclinical Research

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm to humans. The preclinical studies are conducted on animal models under laboratory conditions [18].

The two types of preclinical research are:

• *In Vitro*: These experiments are conducted outside the animals in controlled laboratory conditions [19-22].

• *In Vivo*: These experiments are conducted inside the animals.[23-24]

Experiment are generally performed on a rodent (mouse, rat, guinea pig, hamster, rabbit) and then on a larger animal (cat, dog, monkey). As the evaluation progresses unfavourable compounds get rejected at each step, so that only a few out of thousands reach the stage when administration to man is considered.

The following types of tests are performed;

1. Screening tests.

2. Tests on isolated organs, bacterial cultures, etc.

3. Tests on animal models of human disease.

4. Confirmatory tests and analogous activities.

5. Systemic pharmacology.

6. Quantitative tests.

7. Pharmacokinetics.

8. Toxicity tests.[25]

2.8 The Investigational New Drug Application (INDA)

INDA is applied after the Preclinical studies show success and if the INDA submission is accepted the product is further forwarded to the clinical research studies (Phase I - Phase IV studies).[26]

2.9 Clinical Research

A clinical trial is a research study that tests a new medicaltreatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease.[27]

Clinical trial phases are steps in the research to determine if an intervention would be beneficial or detrimental to humans and include Phases 0, I, II, III, IV, and V clinical studies.[28-29]

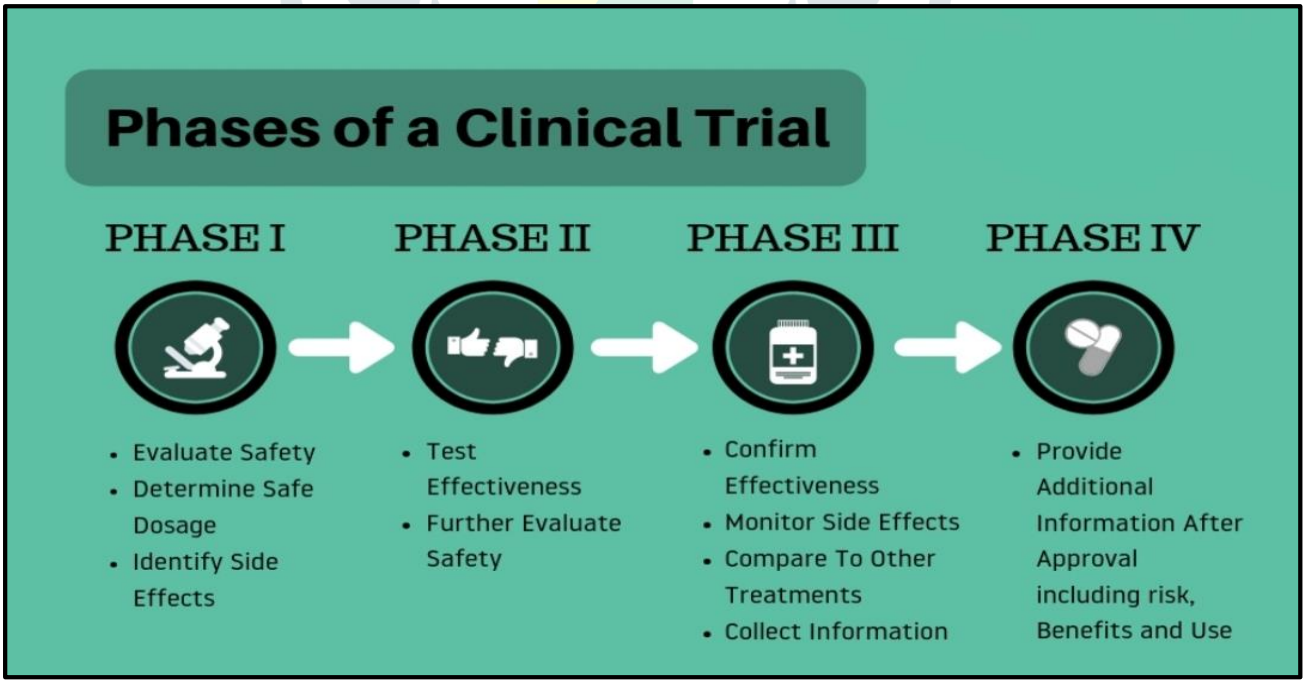

fig 2: phases of clinical trials

Without clinical trials, researchers cannot properly determine whether new medicines developed in the laboratory or by using animal models are effective or safe, or whether a diagnostic test works properly in a clinical setting.[30-32]

Types of Cinical Trial:

1. Treatment trials

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

2. Prevention trials

Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

3. Diagnostic trials

Conducted to find better tests or procedures for diagnosing a particular disease or condition.

4. Screening trials

Test the best way to detect certain diseases or health conditions.

5. Quality of Life

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.[33]

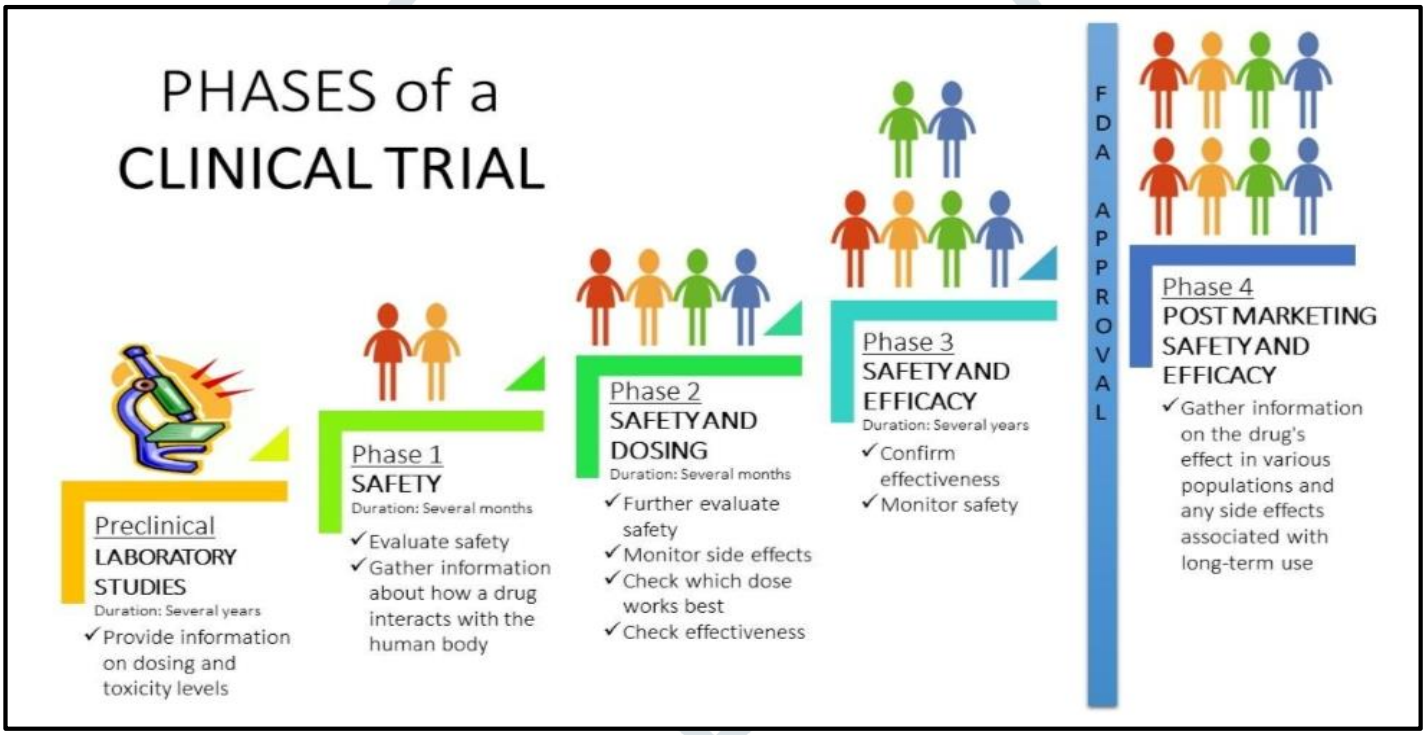

fig 3: phases of clinical trials

Phase 0 : Clinical trial

According to the FDA a phase '0' is designed to carry out before in phase 1, it has very limited human exposure receiving only sub-therapeutic dose and this means the volunteer produces a response (Pharmacological Action) than the toxic effect with less risk compared to conventional clinical trials in phase 1 in which administration continues if clinical benefit which means even phase '0' trials don't have any therapeutic intention. With the ultra-sensitive accelerator mass spectrometry (AMS) it was possible to carry out clinical trials in human using small dose to obtained pharmacokinetic data.[34-36]

Phase 1: Safety and dosage

A Phase 1 clinical trial evaluates the best way to administer a drug, its frequency and dose, the maximum tolerated dose (MTD), and side effects. Tolerability, pharmacokinetics, and pharmacodynamics are evaluated. These studies determine, most importantly, if the treatment is safe. Trials usually include 20 to 100 patients and are monitored by the clinical researcher. Doses are increased if there are no severe side effects and patients are tested to determine if he or she is responding to the therapy. These escalation dose studies are used to determine the best and safest dose that can be administered and is a fraction of the dose that caused harm during animal testing. Unnecessary exposure of subjects to subtherapeutic doses while maintaining safety and rapid accrual is the primary goal of Phase I trial.[37]

Phase 2: Efficacy and side effects

This is conducted by physicians who are trained as clinical investigators, and involve 100–500 patients selected according to specific inclusion and exclusion criteria. The primary aim is establishment of therapeutic efficacy, dose range and ceiling effect in a controlled setting. Tolerability and pharmacokinetics are studied as extension of phase I. The study is mostly controlled and randomized, and may be blinded or open label. It is generally carried out at 2–4 centres. The candidate drug may get dropped at this stage if the desired level of clinical efficacy is not obtained.[38]

Phase 3: Efficacy and adverse drug reactions monitoring

Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

2.10 New Drug Application

A New Drug Application (NDA) expresses the full story of a drug molecule. Its purpose is to verify that a drug is safe and effective for its proposed use in the people studied. A drug developer must include all about a drug starting from preclinical data to Phase 3 trial datain the NDA. Developers must include reports on all studies, data, and analysis.[39]

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.[40]

2.11 FDA Review

Once FDA receives an NDA, the review team decides if it is complete. If it is not complete, the review team can refuse to file the NDA. If it is complete, the review team has 6 to 10 months to make a decision on whether to approve the drug.

2.12 FDA Approval

In cases where FDA determines that a drug has been shown to be safe and effective for its intended use, it is then necessary to work with the applicant to develop and refine prescribing information. This is referred to as “labeling.” Labeling accurately and objectively describes the basis for approval and how best to use the drug.

Often, though, remaining issues need to be resolved before the drug can be approved for marketing. Sometimes FDA requires the developer to address questions based on existing data. In other cases, FDA requires additional studies. At this point, the developer can decide whether or not to continue further development. If a developer disagrees with an FDA decision, there are mechanisms for formal appeal.

Phase 4: Post-Market Drug Safety Monitoring

This phase is also called as Post Marketing Surveillance Trials. They are conducted after a drug or device has been approved for consumer sale after approval regulatory authority. Pharmaceuticals companies have several objectives at this stage:

1. to compare a drug with other drugs already in the market;

2. to monitor a drugs long-term effectiveness and impact on a patient’s quality of life; and

3. to determine cost-effectiveness of the drug therapy relative to other available and new therapies. Phase 4 studies can result in a drug or a device being a taken off the market registrations of use could be placed on the product depending on the findings in the study.[41-43]

III. CONCLUSION

The drug discovery and development process is a long and complicated process. Before any newly drug is placed on the market, it must undergo extensive testing. The discovery and development of new medicines is a long, expensive and complicated process. Each success is built on many, many prior failures. Advanced in understanding human biology and disease are opening up exciting

new possibilities for breakthrough medicines. At the same time, researchers face great challenges in understanding and applying these advances to treatment of disease. This possibilities will grow as our scientific knowledge expand and become increasingly complex.

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