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REVIEW ON DRUG DISCOVERY AND DEVELOPMENT

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ABSTRACT

Drug discovery is a process which aims at identifying a compound therapeutically usefulin curing and treating disease. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. Once a compound has shown its significance in these investigations, it will initiate the process of drug development earlier to clinical trials. New drug development process must continue through several stages in order to make a medicine that is safe, effective, and has approved all regulatory requirements. One overall theme of our article is thatthe process is sufficiently long, complex, and expensive so that many biological targets must be considered for every new medicine ultimately approved for clinical use and new research tools may be needed to investigate each new target. From initial discovery to a marketable medicine is a long, challenging task. It takes about 12 - 15 years from discovery to the approved medicine and requires an investment of about US $1 billion. On an average, a million molecules screened but only a single is explored in late stage clinical trials and is finally made obtainable for patients. This article provides a brief outline of the processes of new drug discovery and development.

KEYWORDS: Drug discovery, drug development, clinical trials.

INTRODUCTION

The process of finding a medicine that is chemically therapeutically beneficial in the treatment and management of a disease condition is known as drug discovery. Researchers typically discover novel medications by developing fresh insights into the pathophysiology of an illness, which enables them to create medications that countract or stop the consequences of the illness. Drug candidates are identified, synthesised, characterised, screened, and assayed for therapeutic efficacy as part of the drug development process. Following cliical trials, a molecule will begin the process of medication development if it yields favourable results from these investigations. The process of finding and developing new drugs is costly since R&D and clinical trial expenses are so large. A novel medicine molecule must be developed over a period of approximately 12 to 15 years, starting from discovery and ending with commercial availability for patient treatment. The typical price of development and research The estimated cost for each effective medication ranges from $900 million to $2 billion. This sum accounts for the thousands of failed attempts: In the end, just one compound out of every 5,000–10,000 that enters the pipeline for research and development is approved. These figures defy belief, but a quick review of the R&D process can help explain why so many compounds fail to find a market and why it requires such a significant amount of time and resources to get one medication into patients. To achieve success, one needs a plethora of resources, the sharpest minds in science and reasoning, extremely advanced lab and technology, and diverse project management. It also requires luck and perseverance. Ultimately, the drug discovery process gives billions of patients comfort, hope, and trust[1,2,3,4]

DRUG DISCOVERY

Typically, researchers discover new drugs through:

- New research into a disease process that encourages the scientists to discover a newproduct to stop or reverse the effects of the disease
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases
- Existing treatments that have unanticipated effects
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material

At this stage, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.[5,6,7,8,9,10]

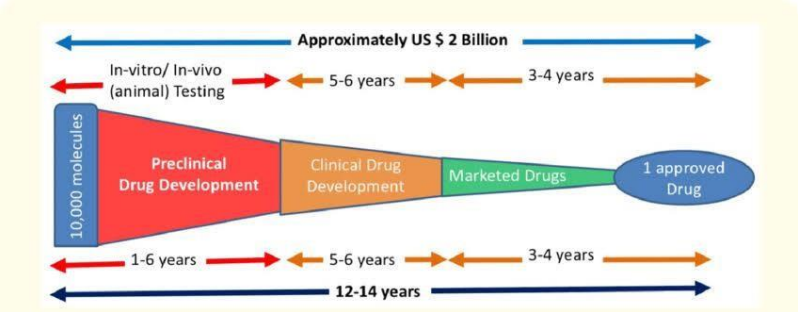

Fig. no. 1: Drug Discovery process.[11]

DRUG DEVELOPMENT

Once researchers identify a promising compound for development, they conduct experiments to gather information

- How it is absorbed, distributed, metabolized, and excreted
- Its potential benefits and mechanisms of action
- The best dosage and best way of administration
- Side effects (often referred to as toxicity)
- How it affects different groups of people (such as by gender, race, or ethnicity) differently
- How it interacts with other drugs and treatments
- Its effectiveness as compared with similar drug[12,13]

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
- Clinical trials
- New Drug Application
- Approval

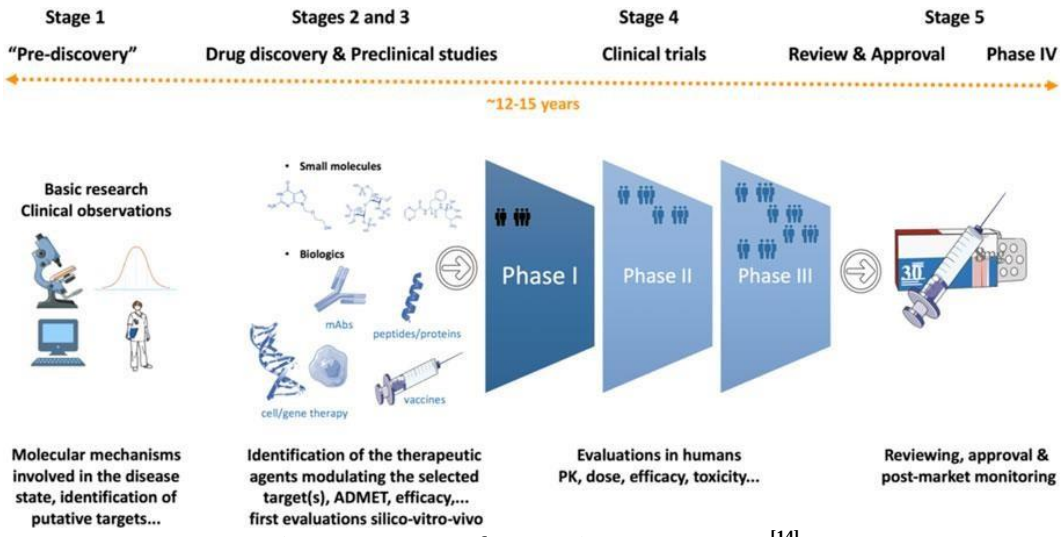

Fig. no. 2: Stages of Drug Discovery Process.[14]

TARGET IDENTIFICATION

Finding a disease's biological cause and possible intervention targets is the first stage in the drug discovery process. The first step in target identification is determining the function and contribution of a potential therapeutic target (gene, nucleic acid, or protein) to the illness. Characterization of the molecular pathways the target addresses comes after target identification. In addition to being safe, effective, and meeting clinical and commercial objectives, an ideal target should also be "druggable." Target identification methods might be derived from concepts in molecular biology, biochemistry, genetics, biophysics, or other fields.[15]

TARGET VALIDATION

Validation of the target Target validation is the procedure used to certify the intended molecular target, such as a small molecule's gene, protein, or nucleic acid. The process of target validation involves identifying the structure-activity relationship (SAR) of the small molecule's analoguesand creating a drug-resistant.

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.

Target validation can be broken down in to two key steps.[16]

REPRODUCIBILITY

Once a drug target is identified, whether it be via a specific technique or from review of literature, the first step is to repeat the experiment to confirm that it can be successfully reproduced. The target validation technique includes affinity chromatography, expression- cloning, protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, system biology and Study of existing drugs.[17,18]

LEAD IDENTIFICATION

Finding the Lead A synthetically stable, workable, drug-like molecule that exhibits appropriatespecificity, affinity, and selectivity for the target receptor and is active in primary and secondaryassays is referred to as a chemical lead. To achieve this, the structure-activity relationship must be defined, the synthetic feasibility must be established, and there must be some indication ofin vivo efficacy and target engagement. A chemical lead's characteristics 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

Lead optimization: The process of designing a drug candidate after the identification of an initial lead chemical is known as lead optimisation. In order to provide a picture of how chemical structure and activity are associated in terms of interactions with targets and metabolism, a prospective medication is put through an iterative series of synthesis and characterization steps.

Drug discovery researchers require quick ways to reduce the number of drug candidates chosen for downstream selectivity profiling and additional research. Drug metabolism and pharmacokinetics (DMPK) screens with high throughput have become a crucial component oflead optimisation because they make it easier to comprehend and forecast in vivo pharmacokinetics using in vitro experiments. Through optimisation, chemical alterations to the structure of candidate medications are made in order to create new pharmaceuticals with higher potencies and safety profiles.[19]

PRODUCT CHARACTERIZATION

Any novel pharmacological molecule that exhibits potential therapeutic efficacy is identified by its size, shape, strength, weakness, application, toxicity, and biological activity. Early pharmacological research phases are useful for characterising the compound's mechanism of action.

FORMULATION AND DEVELOPMENT

In order to create a bioavailable, stable, and ideal dosage form for a particular administration route, the physicochemical characteristics of active pharmaceutical ingredients (APIs) are characterised during the pharmaceutical formulation stage of drug development.

DURING PREFORMULATION STUDIES THE FOLLOWING PARAMETERS AREEVALUATED

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

PRECLINICAL TESTING

Trials Pre-clinical research is a step in the drug development process that evaluates a medicine's safety and effectiveness in animal models before it is potentially applied to humans.The respective regulatory bodies must also approve the pre-clinical investigations. Only medications that have been proven to be both safe and effective will be approved by regulatorybodies, who also have an obligation to oversee the conduct of trials in an ethical and safe manner. An essential set of guidelines for the technical requirements of appropriate preclinicaldrug development has been established by ICH.[20]

THE INVESTIGATIONAL NEW DRUG PROCESS (IND)

Drug developers must file an Investigational New Drug application to FDA before commencement clinical research. In the IND application, developers must include: • Preclinicaland toxicity study data • Drug manufacturing information • Clinical research protocols for studies to be conducted • Previous clinical research data (if any) • Information about the investigator/ developer.[21,22]

CLINICAL RESEARCH

Clinical trials are carried out on volunteers and are designed to provide targeted answers regarding the efficacy and safety of medications, vaccines, other therapies, or novel approaches to utilising existing treatments. Clinical trials adhere to a particular study protocol that the manufacturer, investigator, or

researcher designs. clinical research, they will take into account the tasks they wish to accomplish for every phase of the clinical research process and initiate the Investigational New Drug Process (IND), which is a procedure they have to go through prior to starting clinical research. Prior to starting a clinical trial, scientists formulate study questions and objectives by reviewing available data on the medication. Next, they make a decision.[23]

Selection criteria for participants

- Number of people take part of the study
- Duration of study
- Dose and route of administration of dosage form
- Assessment of parameters
- Data collection and analysis

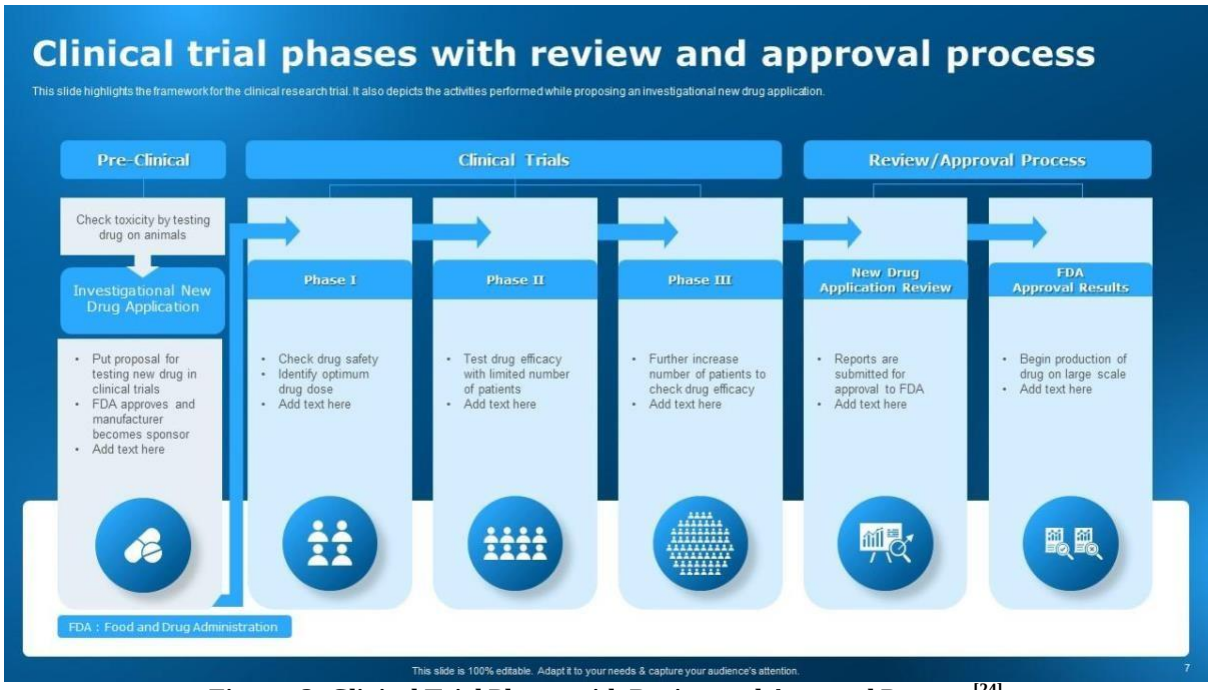

Fig. no. 3: Clinical Trial Phases with Review and Approvel Process.[24]

PHASE 0 CLINICAL TRIAL

Implicates investigative, first-in-human (FIH) trials that are conducted according to FDA guidelines. 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 exerting pharmacological actions. Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans.[25]

PHASE 1 CLINICAL TRIALS

Dosage and safety Drugs are first tested in phase I trials, which involve fewer healthy human participants. Phase 1 typically involves 20 to 80 healthy volunteers with the illness or condition. Patients are often only utilised when a drug's mode of action suggests that healthy individuals won't be able to tolerate it. Researchers do Phase 1 trials on individuals with that kind of diabetes, nevertheless, if a new medication is suggested for use in diabetics.

PHASE 2 CLINICAL TRIALS

Results and adverse reactions Phase II trials are carried out on larger patient populations (few hundreds) with the goal of assessing the drug's effectiveness and enduring the Phase I safety evaluations. There is insufficient evidence from these trials to determine if the medicine will be therapeutic. Researchers receive new safety data from phase 2 investigations. These data are used by researchers to build new Phase 3 research protocols, research methods, and research topics. 33% of medications make it to the next stage. The most significant contribution from Phase II clinical investigations is the discovery of therapeutic dosages for the extensive PhaseIII research.

PHASE 3 CLINICAL TRIALS

Monitoring for side effects and efficacy of medication Phase 3 studies are planned byresearchers to demonstrate whether or if a product offers a particular group of people an actionbenefit. These studies, which involve 300–3,000 people, are sometimes referred to as pivotal studies. The majority of the safety data are provided by phase 3 trials. Less frequent adverse effects might not have been identified by the prior investigation. However, because phase 3 studies involve a larger number of participants and last longer, it is more likely that long-termor unusual side effects may be found in the data. Roughly 25–30% of medications advance to the next stage of clinical investigation.

NEW DRUG APPLICATION

A New Drug Application (NDA) expresses the full story of a drug molecule. Its purpose is toverify 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.[26] Beside with clinical trial outcomes, developers must include:[26]

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information

FDA REVIEW

Following receipt of a completed NDA, the FDA team responsible for review may need up to six months to decide whether to approve the NDA. When the FDA receives an incomplete NDA, the FDA review team will reject the NDA. Working with the developer to update prescribing information is crucial if the FDA decides that a medicine is safe and effective for its intended purpose. We refer to this as labelling. The grounds for approval and instructions on how to take the medication are clearly defined on the label. Nonetheless, there are still problems that need to be resolved before the medication is authorised for sale. The FDA requires more research in other situations.[27]

PHASE 4: POST-MARKET DRUG SAFETY MONITORING

Trials are conductedwhen the drug or devicehas been approved by FDA. These trials are also recognized as post-marketing surveillance involving pharmacovigilance and continuing technical support after approval. There are numerous observational strategies and assessmentpatterns used in Phase 4trials to evaluate the efficacy, cost-effectiveness, and safety of an involvement in real-world settings. Phase IV studies may be required by regulatory authorities (e.g. change in labelling, risk management/minimization action plan)or may be undertaken by the sponsoring company for competitive purposes or other reasons. FDA reviews reports of complications with prescription and OTC drugs, and candecide to add precautions to the dosage or practice information, as well as other events for more serious adverse drug reactions.[28]

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