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To Study On The Drug Discovery On The Basis Of Pharmaceutical Software.

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ABSTRACT

This article provides a brief overview of the processes of drug discovery and development. Our aim is to help scientists whose research may be relevant to drug discovery and development to frame their research report in a way that appropriately places their findings within the drug discovery and development process and thereby support effective translation of preclinical research to humans. Software based drug discovery and development methods have major role in the development of bioactive compounds. structure-based drug design, structure-based virtual screening, ligand interaction and molecular dynamics are considered to be powerful tool for investigation of pharmacokinetic and pharmacodynamic properties of drug, and structural activity relationship between ligand and its target. An awareness of these issues allows the early implementation of measures to increase the opportunity for success. As editors of the journal, we encourage submission of research reports that provide data relevant to the issues presented.

Keywords: Drug discovery, Docking, Structural activity relationship, Molecular modelling.

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INTRODUCTION

Drug discovery is a process in which we are identified of a drug chemical therapeutically useful in treatment and diagnosis of a disease condition. Typically, discoverer find out new drugs through new visions into disease process that permit discoverer to design a medicine to stopover or contrary the effects of the disease.[1] Implementation of these techniques can decrease the numbers of animals needed in the discovery and preclinical stages of drug discovery, help for trouble-free to handle huge data, and improve the accuracy of study results [2],[3]. The process of drug discovery includes the identification of drug candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Drug discovery and development is an expensive process due to the high budgets of R&D and clinical trials. It takes almost 12-15 years to develop a single new drug molecule from the time it is discovered when it is available in market for treating patients.[4] Drug discovery plays an important role for the growth of any pharmaceutical industry and also to the society, as newer and safe drugs are launched in the market with the view to improve the therapeutic value and safety of the agents.[5]

History

The idea that the effect of a drug in the human body is mediated by specific interactions of the drug molecule with biological macromolecules, (proteins or nucleic acids in most cases) led scientists to the conclusion that individual chemicals are required for the biological activity of the drug. This made for the beginning of the modern era in pharmacology, as pure chemicals, instead of crude extracts of medicinal plants, became the standard drugs. Examples of drug compounds isolated from crude preparations are morphine, the active agent in opium, and digoxin, a heart stimulant originating from Organic chemistry also led to the synthesis of many of the natural products isolated from biological sources.

Historically, substances, whether crude extracts or purified chemicals were screened for biological activity without knowledge of the biological target. Only after an active substance was identified was an effort made to identify the target. This approach is known as classical pharmacology, forward pharmacology,[6] or phenotypic drug discovery.[7] The goal of a drug discovery program is to deliver one or more candidate molecules, each of which has sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug-like properties so that it can be entered into human testing. Most discovery programs seek to produce more than one candidate molecule.

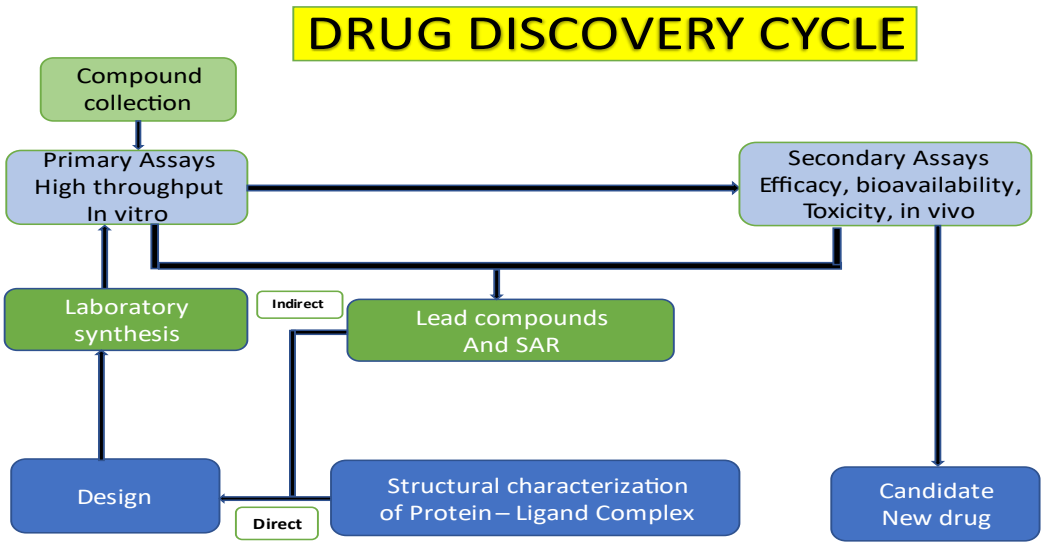

Figure 1: Drug Discovery Cycle

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

Figure 2: Stages of drug discovery and development process

Table 1. Software and computer-based programs used during new drug discovery and development.

Sr. No.	Software name	Major use
A. Pharmacokinetic parameters		
1	DDDPlus	Dissolution and disintegration study
2	GastroPlus	In-vitro and in vivo correlation for various formulations
3	MapCheck	Compare dose or fluency measurement
B. Ligand interactions and molecular dynamic		
4	AutoDock	Evaluate the ligand-protein interaction
5	Schrodinger	Ligand-receptor docking
6	GOLD	Protein-ligand docking
7	BioSuite	Genome analyzing and sequence analyzing
C. Molecular modeling and structural activity relationship		
8	Maestro	Molecular modeling analysis
9	ArgusLab	Molecular docking calculations and molecular modeling package
10	GRAMM	Protein-protein docking and protein-ligand docking
11	SYBYL-X Suite	Molecular modeling and ligand based design
12	Sanjeevini	Predict protein-ligand binding affinity
13	PASS	Create and analysis of SAR models
D. Image analysis and Visualizers		
14	AMIDE (A Medical Image Data Examiner)	Medical image analysis in molecular imaging
15	Discovery Studio® Visualizer	Viewing and analyzing protein data
16	Imaging Software Scge-Pro	Cytogenetic and DNA damage analysis
17	Xenogen Living Image Software	In vivo imaging display and analysis
E. Data analysis		
18	GeneSpring	Identify variation across set of samples and for correction method in samples
19	QSARPro	Protein-protein interaction study
20	REST 2009 Software	Analysis of gene expression data

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.[8] Identification of the target is followed by characterization of the molecular mechanisms addressed by the target. An ideal target should be efficacious, safe, meet clinical and commercial requirements and be ‗druggable '. The techniques used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines.[9]

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.[10]

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 a representation of in what way chemical structure and activity are related in terms of interactions with its targets and its metabolism. In initial drug discovery, the resulting leads from hit-to-lead high throughput screening tests undergo lead optimization, to identify promising compounds. Potential leads are evaluated for a range of properties, including selectivity and binding mechanisms during lead optimization, as the final step in early-stage drug discovery. The purpose of lead optimization is to maintain favourable properties in lead compounds, while improving on deficiencies in lead structure. In order to produce a pre-clinical drug candidate, the chemical structures of lead compounds (small molecules or biologics) need to be altered to improve target specificity and selectivity. Pharmacodynamic and pharmacokinetic parameters and toxicological properties are also evaluated. Labs must acquire data on the toxicity, efficacy, stability and bioavailability of leads, in order to accurately characterize the compound and establish the route of optimization.[11]

Preclinical Testing

Pre-clinical research in drug discovery process involves evaluation of drug ‗s safety and efficacy in animal species that conclude to prospective human outcome. The pre-clinical trials also have to acquire approval by corresponding regulatory authorities. The regulatory authorities must ensure that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective. ICH has established a basic guideline for technical necessities of acceptable preclinical drug development.[12]

Pharmacokinetic studies are very important to make known the safety and efficacy parameters in terms of absorption, distribution, metabolism and excretion. These studies give information on absorption rate for diverse routes of administration, which helps in selection of dosage form, distribution, rate of metabolism and elimination; which governs the half-life of the drug. Half-life of the drug clarifies the safety outline of the drug which is the obligatory for a drug to get approved by regulatory agencies. The drug distribution mechanism elucidates the therapeutic effectiveness of the drug as it depends on the drugs bioavailability and its affinity. Drug metabolism provides the probability of through phases of biotransformation process and formation of drug metabolites. It also helps in understanding the reactions as well as enzymes involved in biotransformation. [13]

Clinical Research

Clinical trials are conducted in people (volunteer)and intended to answer specific questions about the safety and efficacy of drugs, vaccines, other therapies, or new methods of using current treatments. Clinical trials follow a specific study protocol that is designed by the researcher or investigator or manufacturer. As the developers design the clinical study, they will consider what they want to complete for each of the different Clinical Research Phases and starts the Investigational New Drug Process (IND), a process they must go through before clinical research begins. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives.[14]

Then, they decide:
• 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.

Phase 0 clinical trial

Phase 0 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.[15]

Phase 1: Safety and dosage

Phase I trials are the first tests of a drug with a lesser number of healthy human volunteers. In most cases, 20 to 80 healthy volunteers with the disease/condition participate in Phase 1Patient are generally only used if the mechanism of action of a drug indicates that it will not be tolerated in healthy people. However, if a new drug is proposed for use in diabetes patients, researchers conduct Phase 1 trials in patients with that type of diabetes. Phase 1 studies are closely monitored and collect information about Pharmacodynemics in the human body. Researchers adjust dosage regimen based on animal study data to find out what dose of a drug can tolerate the body and what are its acute side effects. As a Phase 1 trial continues, researchers find out research mechanism of action, the side effects accompanying with increase in dosage, and information about effectiveness. This is imperative to the design of Phase 2 studies. Almost 70% of drugs travel to the next phase.

Phase 2: Efficacy and side effects

Phase II trials are conducted on larger groups of patients (few hundreds) and are aimed to evaluate the efficacy of the drug and to endure the Phase I safety assessments. These trials aren't sufficient to confirm whether the drug will be therapeutic. Phase 2 studies provide with additional safety data to the researchers. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols. Around 33% of drugs travel to the next phase. Most prominently, Phase II clinical studies aid to found therapeutic doses for the large-scale Phase III studies.

Phase 3: Efficacy and adverse drug reactions monitoring

Researchers plan Phase 3 studies to prove whether a product deals an action benefit to a specific people or not. Sometimes known as pivotal studies, these studies comprise 300 to 3,000 volunteers. Phase 3 studies deliver most of the safety data. The previous study might not able to detect less common side effects. But phase 3 studies are conducted on large no. of volunteers and longer in duration, the results are more probable to detect long-term or uncommon side effects. Around 25-30% of drugs travel to the next phase of clinical research. If a drug developer has data from its previous tests, preclinical and clinical trials that a drug is safe and effective for its intended use, then the industry can file an application to market the medicine. The FDA review team comprehensively inspects all submitted data on the drug and makes a conclusion to approve or not to approve it.[16]

Phase 4: Post-Market Drug Safety Monitoring

Phase 4 trials are conducted when the drug or device has 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 assessment patterns used in Phase 4 trials 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. Therefore, the true illustration of a drug 's safety essentially requires over the months and even years that mark up a drug's lifespan in the market. FDA reviews reports of complications 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.[17]

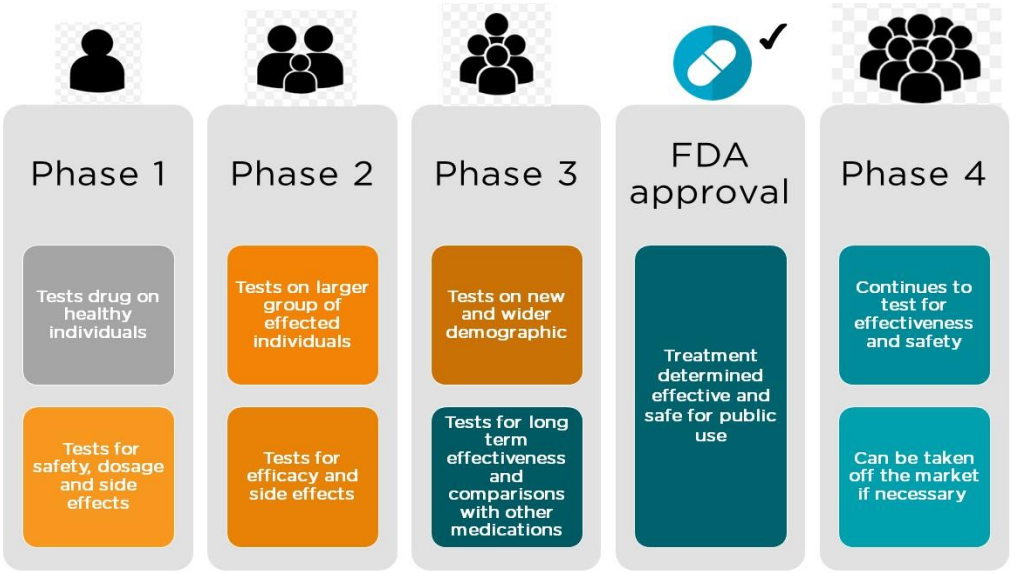

Figure 3: Phases of Clinical Trials

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.[18] Beside with clinical trial outcomes, developers must include:

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

CONCLUSIONS

Many more approaches like metabolomics, genomics, proteomics also compliment well with the other techniques so that more target specific agents can be discovered with more accuracy. The review on metabolomics shall explain more in detail (Martis, et al., 2011b). Drug discovery is yet more to be explored, even more than that explored till date. The findings of the human genome project have added more understanding to the target identification. Nature has made all the provisions for curing a disease or disorder, human efforts of finding is what is required. Exploring natural sources which is ill-explored should be effective done as nature is source of countless chemicals which could lead to a successful drug candidate.

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