**St Peter’s Institute of Pharmaceutical Sciences**

**Course : Bachelor of Pharmacy**

**Subject : Pharmaceutical Regulatory Science**

**Subject Code:** **BP804ET**

**STAGES OF DRUG DISCOVERY**

**Targeted Discovery**

In vitro research was performed to determine the targets involved in certain diseases in the first step. Targets are usually cells that include genetic control or intracellular signaling, such as nucleic acid sequences or proteins. In order to determine which target to focus on research efforts, one needs to make sure that the molecule is “druggable” - that its function can be repaired by exogenous compounds.

**Target Validation**

After a possible selection of target, researchers must demonstrate that they are involved in the progression of a given disease and that its function can be controlled. Conducting targeted and accurate validation tests is focused on the success of drug development in the following phases.

**Lead Compound Identification**

Lead Compoundidentification is a process of identifying or creating a combination that can work with a pre-selected target. Investigators may conduct experimental studies to identify natural products that may be regenerated as drugs. Alternatively, artificial combinations can be created that will target the predicted target while not interfering with other cellular processes. In addition to testing the effectiveness of the drug, initial safety tests were performed on cell cultures. Both the pharmacokinetics and pharmacodynamics of the drug are also tested - how it is metabolized and how it affects the various functions of the body, respectively.

**Lead Optimization**

Once a compound has been discovered, it needs to be optimized showing its efficacy and safely. The structure of the molecules that are formed can be altered to prevent binding outside the target, making them less likely to interact with the molecules outside the target. For this, the total dose and various routes of administration are tested on cell culture platforms.

This phase also includes pre safety tests before doing in multi-vivo animal models in the next stage of development. Animal species such as mice and rats can be used in this phase, but some safety tests are first performed in vitro.

**Preclinical Drug Development**

The preclinical-drug phase includes testing on animal models to determine if the drug is safe for human testing and to be effective. Specifically, the side effects of the drug need to be considered and monitored.

In order to progress from this stage to clinical trials, the FDA requires extensive testing data. To date, companies have spent an estimated $ 500 million on R&D. Since the next stages of development will cost more than double that amount, it is important that pre-clinical testing can be as accurate in determining the possible success of the drug as possible.

Types of mammals, such as knockers or genetically modified rats, are used in this category. While the probability of drug performance in phase III clinical trials is only 12%, a development company is expected to scale-up if drug is found to be successful.

**Advancing to Clinical Trials**

Application for New Drug Investigation (IND)

Prior to the start of the clinical trial, an application for Investigational New Drug (IND) must be submitted to the FDA. This document should include:

• Animal and toxicological study data

• Manufacturing information

• Clinical protocols for proposed human trials

• Information from any previous human research

• Details of the principal investigator(s)

The FDA then conducts a comprehensive review of the IND, and, after 30 days, may respond in one of two ways:

1. IND approval and the beginning of the clinical trial

2. Suspend until further information is available, or complete suspension of the investigation

Due to the nature of the drug development process and the cost of research to date, it is not uncommon for IND to be submitted and canceled by the FDA. In many cases, the FDA recommends the improvement in the development of a proposed clinical trial procedure and allows for the release of IND.

**Clinical Trials**

**Phase I Clinical Trials**

During the first phase of clinical trials, a new drug is tested in 100 or fewer healthy patients to obtain drug-related safety.

This phase also includes testing of carcinogenicity in animal models of mice, particularly the Tg rasH2 rat, which is used to predict carcinogenic chemical potential. This mouse model carries human c-Ha-ras oncogene in addition to the endogenous Ha-ras oncogene of mouse. The presence of a human copy of this gene puts the model at greater risk of developing a tumor after exposure to cancer-causing chemicals in humans. This model reduced the time associated with carcinogenicity testing from two years to six months.

**Phase II Clinical Trials**

During phase II, the number of patients increases to the 100-500 group and the effectiveness of the drug is studied. These patients have a disease for which a new drug attempts to cure. Adverse events, side effects, and efficiency are all tested in this category.

**Phase III Clinical Trials**

In a Phase III trial, researchers studied a drug group of about 1,000-5,000 patients to produce statistical data. Only 12% of drugs pass through this phase, as it is the key to determining the safety and effectiveness of a new drug. If the drug is able to pass this stage, the information obtained from a larger group of patients provides the basis for future labelling.

**FDA review and approval**

After successful clinical trials, the New Drug Application (NDA) is submitted to the FDA for review and approval. The purpose of this document is to show whether clinical trials have proven the safety and efficacy of a drug, and whether it is suitable to go to market. More information is needed, including information about all stages and subjects, clinical outcomes, safety measures, and possible interactions with other medications. The review process can take anywhere from six to ten months. Once the drug is approved at this stage, the labelling process begins, which is the development of determining the information associated with all prescription drugs in the US.

**Post-Approval Research & Monitoring**

Post-approval monitoring is done by pharmaceutical companies while their drug is on the market. Other data obtained in this category are unintended side effects, interactions with other drugs, potential alternative use, and dosage modification.

**References**

1. Thorne N, et al. (2010). “Apparent activity in high-throughput screening: origins of compound-depedent assay interference”. Curr Opin Chem Biol. June ; 14(3): pp 315–324.
2. [Adel H Karara](https://pubmed.ncbi.nlm.nih.gov/?term=Karara+AH&cauthor_id=20097935)[1](https://pubmed.ncbi.nlm.nih.gov/20097935/#affiliation-1), [Timi Edeki](https://pubmed.ncbi.nlm.nih.gov/?term=Edeki+T&cauthor_id=20097935), [James McLeod](https://pubmed.ncbi.nlm.nih.gov/?term=McLeod+J&cauthor_id=20097935), [Alfred P Tonelli](https://pubmed.ncbi.nlm.nih.gov/?term=Tonelli+AP&cauthor_id=20097935), [John A Wagner](https://pubmed.ncbi.nlm.nih.gov/?term=Wagner+JA&cauthor_id=20097935)(2010). “PhRMA survey on the conduct of first-in-human clinical trials under exploratory investigational new drug applications” J Clin Pharmacol. Apr; 50 (4): pp 380-91.