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A REVIEW - DRUG DISCOVERY & DEVELOPMENT

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ABSTRACT
Drug discovery is the process of identifying and characterizing molecules with the potential to safely modulate disease, with a goal to bring medicines that can improve the lives of patients. It is a lengthy and resource intensive process, that requires close cooperation across multiple disciplines. Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery.

KEYWORDS: Drug discovery; Drug development; Clinical research; Clinical trials.

INTRODUCTION

Drug development is a term used to define the entire process of bringing a new drug or device to market. It is an integrated, multidisciplinary endeavor that includes drug discovery, chemistry and pharmacology, nonclinical safety testing, manufacturing, clinical trials, and regulatory submissions. Drug discovery is the process through which potential new therapeutic entities are identified, using a combination of computational, experimental, translational, and clinical models The process of drug discovery involves a combination of many disciplines and interests starting from a simple process of identifying an active compound. 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.

Objectives of Drug Discovery & Development

- Recognize the investigational drug success rates by stages.
- Define Pre-clinical studies
- Define Investigational New Drug Application – Phase I, Phase II, Phase III studies
- Define New Drug Application
- Define Phase IV studies

Investigational Drug Success

Discovery/Screening: 5000-10,000
Enter Preclinical Testing: 250
Enter Clinical Testing: 5

Periods In Drug Discovery In Development Process

The process of drug discovery and development consists of three main stages: drug discovery, preclinical development and clinical trials. The drug discovery starts with the finding of a hit molecule. A hit is a molecule that elicits a desired activity in a screening assay.[5,6]

Drug Discovery Period[14-20]

- Initiate drug discovery program
- Combinatorial chemistry
- Lead compound series identification
- Additional compounds are made
- NCE' s identified

Drug Development & Registration Period[21-24]

- IND plan established & initiated
- IND filed
- Clinical studies initiated
- NDA prepared & submitted
- Drug launched into the market

Drug Marketing & Line Expansion[25-30]

- Post-Marketing surveillance initiated
- New clinical indications pursued
- New dosage forms and formulations developed
- Actidities conducted to support marketing

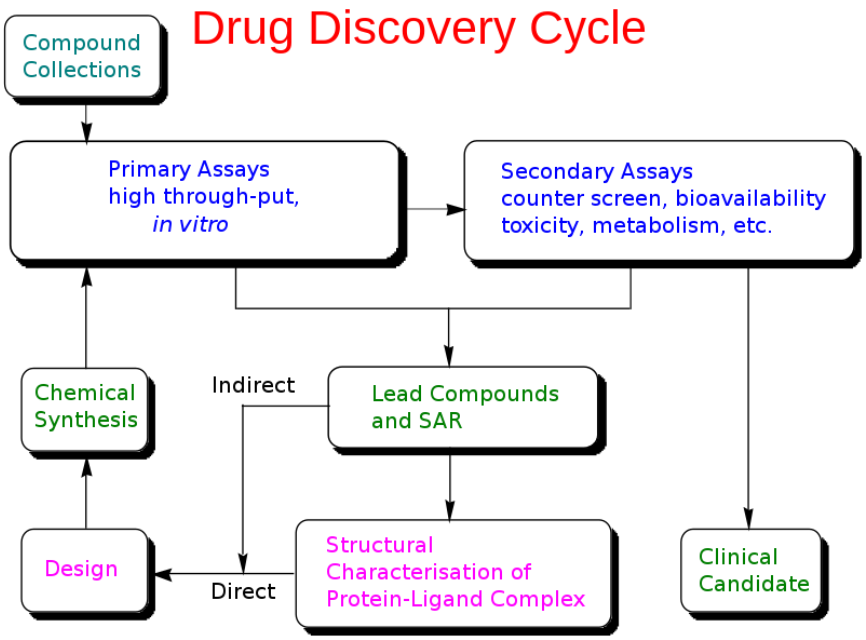
Drug Discovery and Development

Drug Discovery

Typically, researchers discover new drugs through:

- New research into a disease process that encourages the scientists to discover a new product to stop or reverse the effects of the disease.[31,32]
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases
- Existing treatments that have unanticipated effects.[33-38]
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.[39-41]

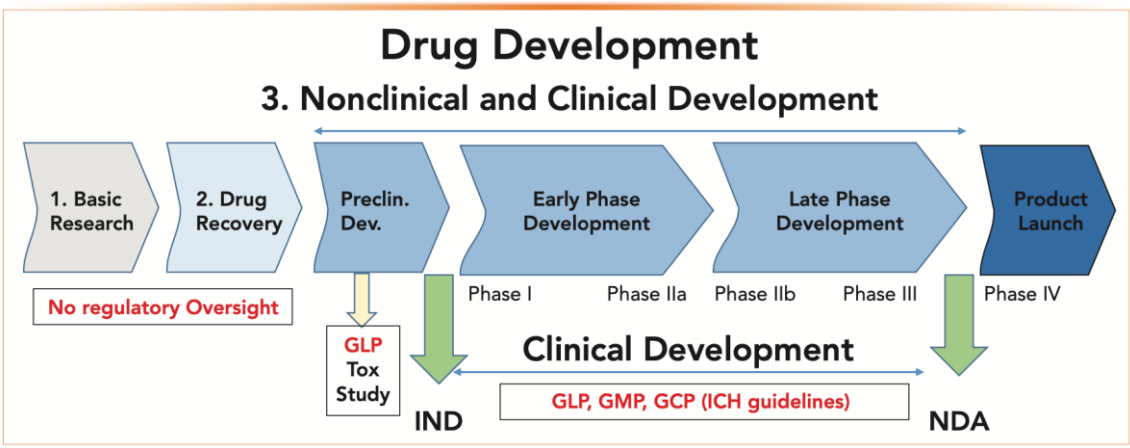
At this stage, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study.[42-45]



Drug Development

Once researchers identify a promising compound for development, they conduct experiments to gather information on[4650]:

- 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



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

The two types of preclinical research are

- In Vitro: These experiments are conducted outside the animals in controlled laboratory conditions
- In Vivo: These experiments are conducted inside the animals

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug can be tested in people The various experiments conducted during these studies include

- Single dose toxicity studies
- Repeated dose studies
- Safety pharmacology studies
- Genotoxicity studies
- Carcinogenicity studies
- Reproductive toxicity studies

Clinical Research

Clinical research is the study of health and illness in people. There are two main types of clinical research: observational studies and clinical trials. Read and share this infographic (PDF, 317K) to learn why researchers do different kinds of clinical studies. Observational studies monitor people in normal settings. While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body "Clinical research" refers to studies, or trials, that are done in people. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins

Investigational New Drug Application

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)

Designing Clinical Trials

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific study plan, called a protocol that is developed by the researcher or manufacturer Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives Then they decide:

Clinical trial design is an important aspect of interventional trials that serves to optimize, ergonomise and economize the clinical trial conduct. The purpose of the clinical trial is assessment of efficacy, safety, or risk benefit ratio. Goal may be superiority, non-inferiority, or equivalence.

- Who qualifies to participate (selection criteria)
- How many people will be part of the study
- How long the study will last
- Whether there will be a control group and other ways to limit research bias
- How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- How the data will be reviewed and analyzed

Clinical trials follow a typical series from early, small-scale Phase 1 studies to late-stage, large scale Phase 3 studies

Phase Studies

Phase 1 (First in Humans)

Trail Design

Patients: 20 to 100 normal healthy volunteer subjects in a single center with no benefit to the subjects.

Duration of study: Short – Days to several weeks or months

Type of study: Open label (No Placebo or comparative agent), uncontrolled, single or multiple doses

Purpose

- Mechanism of action (ADME) and PK/PD studies
- Pharmacological effect
- Tolerability, side effects and toxicity at different doses
- Early evidence of efficacy
- Evaluates safety – Identify most likely potential toxicities and most likely dosage range Percentage of Drugs that Move to the next Phase 70%

Phase 2 (Therapeutic Exploratory)

Trail Design

Patients: several hundred (100-300) patients with the targeted disease/condition.

Length of Study: Several months to 2 years

Purpose: Efficacy and side effects

Type of study: Randomized, placebo or active control, parallel double blinded study, single or multiple doses, multicenter

Phase II trials, also referred to as "therapeutic exploratory" trials, are usually larger than phase I studies, and are conducted in a small number of volunteers who have the disease of interest

Purpose

- Dose range finding (Minimum and maximum effective dose)
- Effectiveness for the treatment of the disease or condition for which the drug is intended to use
- Maximum Tolerated Dose (MTD)
- Common short time side effects and risks
- Pharmacokinetics

Percentage of Drugs that Move to the Next Phase 33

Phase 3 (Therapeutic Confirmatory) – Pivotal Trails

Trail Design

Patients: Several 1000 to 3,000 patients with the targeted disease/condition

Length of Study: 1 to 4 years

Type of study: Randomized, placebo or active control, parallel double blinded study, multicenter

Purpose

- Effectiveness (Large scale)
- Effectiveness (Large scale)
- Relative risk/benefit relationship
- Long term safety information – common side effects, drug interactions, age/rate/gender differences
- Dosing (for labeling)
- Assessment of safety and efficacy

Percentage of Drugs that Move to the Next Phase 25-30%

After completing the phase III trails the application is filed with the concerned regulatory bodies seeking permission for marketing and after the regulatory bodies grant the required approval, the product is launched into the market

Phase 4 (Post-Marketing Therapeutic Use)

Trail Design Patients: Several hundred to thousand patients with the disease/condition.

Type of study: Randomized, Placebo or active control, Multicenter

Purpose

- Perform Quality of Life Trails (QOL) trails
- Perform pharmacoeconomic trails – Is the drug more effective that other available treatments
- Collection of long term safety information – Epidemiological studies for safety and additional surveillance for unexpected or rare adverse effects
- Add line extensions – New dosage forms and formulations

CONCLUSION

New drugs are an important part of modern medicine with the emergence of diseases. A few decades ago, a disease such as peptic ulcers was an indication for major surgery The advent of new pharmacologic treatments and introduction of novel medications have reduced the serious complications of peptic ulcer disease. Similarly, thanks to many new antiviral medications with which the outlook for HIV-infected patients has improved. It is important that physicians understand the process of drug discovery and development Understanding the process can promote innovation, help physicians assess new products, underline the importance of reporting adverse drug events and provide physicians with the information to educate patients about participating in a clinical trial

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