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Drug Discovery & Development - A Review

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Review Article

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ABSTRACT

The development of a drug from an initial idea to its entry into the market is a very complex process which can take around 5-10 years and cost $1.7 billion. The idea for a new development can come from a variety of sources which include the current necessities of the market, new emerging diseases, academic and clinical research, commercial sector, etc... Once a target for discovery has been chosen, the pharmaceutical industries or the associated academic centres work on the early processes to identify the chemical molecules with suitable characteristics to make the targeted drugs. This review article will look into the key concepts of drug discovery, drug development and clinical stages of the drug discovery.

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 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 [3].

OBJECTIVES OF DRUG DISCOVERY & DEVELOPMENT [4]

• 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 [5]

Discovery/Screening: 5000-10,000
Enter Preclinical Testing: 250
Enter Clinical Testing: 5
Approved by Regulatory Bodies: 1

PERIODS IN DRUG DISCOVERY IN DEVELOPMENT PROCESS

It is roughly estimated that it takes around 5-10 years for the complete drug discovery and development process and for its introduction into the commercial market and its costs around $1.7 Billion for the complete process to proceed successfully [6-8]. The various periods/phases in drug discovery and development process are [9-13]

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
- Activities 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 [46-50]:
• 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 [51].

The two types of preclinical research are:
• In Vitro: These experiments are conducted outside the animals in controlled laboratory conditions [52-55].
• In Vivo: These experiments are conducted inside the animals [56,57].

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels [58]. After preclinical testing, researchers review their findings and decide whether the drug can be tested in people [59,60].

The various experiments conducted during these studies include [61-65]:
• Single dose toxicity studies
• Repeated dose studies
• Safety pharmacology studies
• Genotoxicity studies
• Carcinogenicity studies
• Reproductive toxicity studies

Clinical Research

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 [66].

"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 [67-70].

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) [71].

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 [72-75].

Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives [76]. Then they decide:

• 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 [77-80].

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 [81-85].

 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% [86]

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 [87].

Purpose:
- Dose range finding (Minimum and maximum effective dose) [88].
- 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 [89]

Phase 3 (Therapeutic Confirmatory) – Pivotal Trails

Trail Design:

Patients: Several 1000 to 3,000 patients with the targeted disease/condition [90,91].
Length of Study: 1 to 4 years
Type of study: Randomized, placebo or active control, parallel double blinded study, multicenter
Purpose [92]
- 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 [93-95].

Phase 4 (Post-Marketing Therapeutic Use)

Trail Design [96]

Patients: Several hundred to thousand patients with the disease/condition.
Type of study: Randomized, Placebo or active control, Multicenter

Purpose [97]

- 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 [98]. 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 [99]. 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 [100].

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