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Drug discovery and development- a pharmaceutical review

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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.

Keywords: Drug discovery; Drug development; Clinical research; Clinical trials

I. INTRODUCTION:

New drug development is an extremely expensive, dangerous, and complex process. Its success is largely reliant on the close coordination and interaction of numerous departments within the drug development company, outside researchers, and service providers, as well as ongoing communication with payers, academic experts, clinicians, regulatory bodies, and patient organizations. Drug development is, without a doubt, the most important component of the various stages of the drug life cycle for the initial and ongoing success of a drug on the market [1,2].

Drug development is a multidisciplinary process that starts with the identification of an active molecule and encompasses many different disciplines and areas of interest. The process of developing new drugs does not end with the identification of a novel chemical entity that alters the function of a cell or tissue. Before a chemical is deemed a therapeutic entity, it must first be proven to be efficacious and selective, then be absolutely devoid of toxicity, have good bioavailability, and be commercially viable [3].

Objectives of Drug Discovery and Development [4]

- Identify the stages of exploratory medicine success rates.
- Describe preclinical research.
- Describe Phase I, Phase II, and Phase III investigations for investigational new drug applications.
- Explain the New Drug Application
- Describe Phase IV research.

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 and Development:

It is estimated that the entire process of finding and developing a medicine, from conception to commercialization, takes five to ten years, and it costs approximately $1.7 billion to complete effectively [6–8]. The process of finding and developing new drugs goes through several stages, which are [9–13].

Drug Discovery Period [14-20]
1) Initiate drug discovery program
2) Combinatorial chemistry
3) Lead compound series identification
4) Additional compounds are made
5) NCE' s identified

Drug Development & Registration Period [21-24]
1) IND plan established & initiated
2)IND filed
3) Clinical studies initiated
4) NDA prepared & submitted
5) Drug launched into the market.

Drug Marketing & Line Expansion [25-30]
1) Post-Marketing surveillance initiated
2)New clinical indications pursued
3)New dosage forms and formulations developed

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4)Activities conducted to support marketing.

Drug Discovery and Development :

Drug Discovery:

Medication Discovery Researchers typically find new pharmaceuticals by:

• Investigating a disease process in greater detail, which motivates scientists to find a novel product to halt or reverse the consequences of the condition [31, 32].

• Extensive testing of chemical compounds to identify potential protective properties against a wide range of illnesses

• Current therapies have unforeseen side effects [33–38].

• New technologies, such as those that offer improved methods for directing medical supplies to certain bodily parts or for modifying genetic material [39–41].

Thousands of chemicals could be suitable candidates for medical therapy development at this point. Only a few molecules, meanwhile, appear promising after preliminary testing and demand more research [42–45].

Drug Development:

After discovering a molecule that shows promise for development, scientists run tests to learn more about [46–50]:

• Its possible advantages and modes of action;

• How it is distributed, digested, eliminated;

• The ideal dosage and mode of administration;

• How it affects different groups of people differently (based on factors like gender, color, or ethnicity);

• How it interacts with other drugs and therapies;

• Side effects, which are frequently referred to as toxicity;

• How effective it is in comparison to comparable drugs.

Preclinical research:

Preclinical Investigations Researchers must determine whether a medicine has the potential to seriously damage humans before testing it on humans. Preclinical research is carried out in a lab setting using animal models [51]. There are two categories for preclinical research:

• In Vitro: In controlled laboratory settings, these studies are carried out without the use of animals [52–55].

• In Vivo: The research is carried out on the animals themselves [56,57].

Preclinical investigations are typically not very large. But these studies need to give specifics about dosage and levels of toxicity [58]. Following preclinical testing, scientists evaluate their results and determine if a medicine is suitable for human testing [59, 60].

Among the numerous experiments carried out for these investigations are [61–65]: Study types include:

Single-dose toxicity,
Repeated-dose toxicity,
Safety pharmacology,
genotoxicity,
Carcinogenicity, and
Reproductive toxicity.

Clinical research:

Preclinical research provides basic safety answers, but it cannot replace investigations into how a medicine will interact with the human body [66]. Human subjects are used in studies or trials referred to as "clinical research." The Investigatory New Drug Process (IND), which must be completed before clinical research can start, will be started by the developers after they have decided what they aim to achieve for each of the several Clinical Research Phases [67–70].

Investigational New Drug Application:

Once the preclinical studies demonstrate success, the product is submitted to the INDA and, if approved, moved on to the Phase I–Phase IV clinical research trials [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:

1) Who qualifies to participate (selection criteria)
2) How many people will be part of the study
3) How long the study will last
4) Whether there will be a control group and other ways to limit research bias
5) How the drug will be given to patients and at what dosage

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6) What assessments will be conducted, when, and what data will be collected
7) 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:
1) Mechanism of action (ADME) and PK/PD studies
2) Pharmacological effect
3) Tolerability, side effects and toxicity at different doses
4) Early evidence of efficacy
5) 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:
1) Dose range finding (Minimum and maximum effective dose) [88].
2) Effectiveness for the treatment of the disease or condition for which the drug is intended to use
3) Maximum Tolerated Dose (MTD)
4) Common short time side effects and risks
5) 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]
1) Effectiveness (Large scale)
2) Relative risk/benefit relationship
3) Long term safety information – common side effects, drug interactions, age/rate/gender differences
4) Dosing (for labeling)
5) 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]
1) Perform Quality of Life Trails (QOL) trails
2) Perform pharmacoeconomic trails – Is the drug more effective that other available treatments
3) Collection of long term safety information – Epidemiological studies for safety and additional surveillance for unexpected or rare adverse effects
4) Add line extensions – New dosage forms and formulations.

Case studies:
Phase 3 Trials Showing a Potential Experimental Therapy's Lack of Efficacy
1.Bitopertin:[101-104]
Product -Bitopertin
Sponsor-Roche
Purpose- Add-on treatment of schizophrenia

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Problem identified in phase 3 trial- Lack of efficacy

Divergent results in phase 3 trial -Despite statistically significant results in reducing the symptoms of schizophrenia in phase 2, in phase 3 trialsBitopertin failed to improve the negative symptoms of schizophrenia.

Schizophrenia is a chronic brain disorder in which people abnormally interpret reality and features three symptom categories: positive, negative and cognitive. Positive symptoms include hallucinations and delusions, while negative symptoms may include social withdrawal, lack of motivation, and reduced emotional reactivity. Cognitive symptoms include problems with memory and concentration.

Schizophrenia typically requires lifelong treatment with antipsychotic medications,which come in two types: typical and atypical. Both types block the brain's dopamine pathway, but atypical antipsychotics are less likely to cause certain undesired side effects (e.g., movement problems), making them useful for long-term management of patients with schizophrenia. However, atypical antipsychotics are still associated with undesirable side effects such as weight gain, increased cholesterol, and movement disruption.

Like dopamine, glycine is a neurotransmitter that has been implicated in the schizophrenia disease process. Over the past years, researchers have noted that people with schizophrenia have a decreased level ofglycine in their blood and cerebrospinal fluid.Bitopertin increases the availability of glycine in the synapse (the connection between nerve cells), suggesting a novel approachin the treatment of schizophrenia. A placebo-controlled, double-blind, eight week study randomized over 320 patients across 66 sites worldwide. The study found a statistically significant 25% reduction in negative symptoms among those patients who received the drug compared to those who received placebo.

Three subsequent double-blind, placebo-controlled phase 3 studies evaluated the efficacy and safety of bitopertin when added to conventional drugs in patients with negative symptoms ofschizophrenia. These studies together followed over 1800 patients for one year or more, and measured improvement in a patient's negative symptoms compared to symptoms before treatment began. However, results from two of these phase 3 studies found no evidence of a statistically significant improvement in negative symptoms over baseline in patients who received bitopertin add-on therapy compared to those who received placebo.

2.Iniparib[105-109]

Product -Iniparib

Sponsor- Sanofi

Purpose -Add-on treatment of "triple negative" breast cancers

Problem identified in phase 3 trial- Lack of efficacy

Divergent results in phase 3 trial -Despite promising phase 2 results on both tumor response and Survival, in the phase 3 trial adding iniparib to an established Chemotherapy regimen did not improve survival.

Breast cancer is the most common cancer in women.Triple-negative breast cancer is a subtype of breast cancer that is aggressive and difficult to treat. It is called triple-negative because the cancer cells do not over-express three different receptors; the cancer could otherwise be treated by chemotherapies and/or agents targeted to the receptors.

Iniparib showed strong activity in preclinical testing, enhancing the effects of standard chemotherapy on triple-negative metastatic breast cancer cells.In phase 2 testing, 123 patients with metastatic

triple-negative breast cancer were randomized to receive either standard chemotherapy or standard chemotherapy plus iniparib. Adding iniparib to a standard chemotherapy regimen significantly improved tumor response and overall survival, without increasing toxicity. Despite promising phase 2 results, iniparib was not shown to be effective in phase 3 testing. Five hundred nineteen patients with metastatic triple-negative breast cancer were randomly assigned to receive either standard chemotherapy regimen or the standard regimen plus iniparib.

The phase 3 trial did not identify any significant safety concerns, but the addition of iniparib to the standard regimen did notdemonstrate any improvement in overall or progression-free survival.Overall survival of the patients receiving standard chemotherapy was 11.1 months, versus 11.8 months for those also receiving iniparib.

3. Capsaicin Topical Patch (Qutenza) [110-117]

Product -Capsaicin topical patch (Qutenza)

Sponsor- NeurogesX

Purpose -Treatment of HIV-associated nerve pain

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Problem identified in phase 3 trial- Lack of efficacy

Divergent results in phase 3 trial- Despite demonstrated efficacy in a related condition and positive clinical results in a proof of concept study, in an RCT pain control was similar in the Qutenza and control groups.

Many HIV patients experience a burning-type of pain, often in the feet or hands, as a result of nerve damage. Called HIV-associated distal symmetric polyneuropathy (HIV-DSP), it is the most common nerve complication of HIV infection, affecting over 50% of patients.

Qutenza is made from capsaicin, the pungent component that makes chili peppers hot. Capsaicin acts on certain pain receptors in the skin by desensitizing nerve endings, resulting in analgesia and pain relief. In 2009, FDA approved Qutenza (8% patch) as a medicated skin patch for pain relief in patients with post-herpetic neuralgia, a painful complication following shingles.

Researchers also studied the efficacy of capsaicin in a related intended use, painful HIV-DSP. An open-label pilot study assessed the efficacy and safety of NGX-4010 (capsaicin 8% patch) in twelve patients with HSV-DSP.Following a single 60-minute NGX-4010 application, these patients were followed up for 12 weeks. The majority of these patients reported a significant reduction in pain, prompting the researchers to proceed to a large, controlled clinical trial.

In two similarly designed RCTs, 800 patients with HIV-DSP were randomized to receive NGX-4010 or a 0.04% concentration control patch. This low concentration control patch was considered too weak to actually treat HIV-DSP, but strong enough to cause the localized skin reactions thatare common with capsaicin so that patients would not know to which group they had been assigned.

While the initial study found significant pain relief with NGX-4010 over 12 weeks of treatment compared to controls, these findings were not replicated in the second study.In 2012, a FDA Advisory Committee analyzed the two controlled trials and agreed that there was no substantial evidence of effectiveness for Qutenza in treating HIV-DSP.Advisory Committee did not recommend the approval of Qutenza, and FDA did not approve the drug.

II. CONCLUSION:

As diseases emerge, new medications play a critical role in modern medicine. A few decades ago, a condition like gastric ulcers would have required significant surgery [98]. The significant side effects of peptic ulcer disease have decreased with the development of new pharmaceutical therapies and the introduction of innovative drugs. Similarly, the prognosis for HIV-positive patients has improved as a result of numerous novel antiviral drugs. Physician comprehension of the drug discovery and development process is crucial [99]. Knowing the procedure can encourage creativity, assist medical professionals in evaluating novel products, emphasize the significance of reporting adverse medication events, and give doctors the knowledge they need to advise patients about taking part in clinical trials [100].

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