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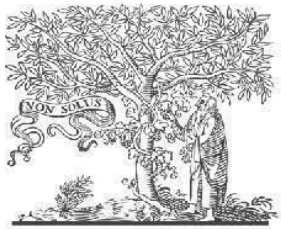

ELSEVIER SSRN

IJIEMR Transactions, online available on 31st December 2022. Link

https://ijiemr.org/downloads.php?vol=Volume-11&issue=issue12

DOI:10.48047/IJIEMR/V11/ISSUE12/371

Title: "EXPLORING DRUG DISCOVERY AND DEVELOPMENT: A PHARMACEUTICAL PERSPECTIVE"

Volume 11, ISSUE 12, Pages: 2435- 2440

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EXPLORING DRUG DISCOVERY AND DEVELOPMENT: A PHARMACEUTICAL PERSPECTIVE

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ABSTRACT
The journey from conceptualizing a drug to its market entry is a highly intricate process, spanning approximately 5-10 years with costs reaching $1.7 billion. Inspiration for new drug developments can arise from various sources such as market needs, emerging diseases, academic and clinical research, and the commercial sector. Once a target for discovery is identified, pharmaceutical companies or associated academic institutions embark on early-stage processes to pinpoint chemical molecules possessing the desired characteristics for the intended drugs. This review delves into essential aspects of drug discovery, development, and the clinical stages involved in bringing a drug to market.

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

INTRODUCTION
The development of new drugs is an immensely costly, risky, and intricate process. Its success hinges on effective collaboration among various departments within drug development companies, external researchers, service providers, and ongoing engagement with payers, academic experts, clinicians, regulatory bodies, and patient organizations. Drug development stands as the pivotal phase in the lifecycle of a drug, crucial for its initial and sustained success in the market [1,2].

Drug development is a multidisciplinary endeavor that begins with identifying an active molecule and spans numerous disciplines and domains of interest. Merely identifying a novel chemical entity that alters cellular or tissue function does not conclude the process of developing new drugs. To be recognized as a therapeutic entity, a chemical must demonstrate efficacy, selectivity, safety, good bioavailability, and commercial viability [3].

Objectives of Drug Discovery and Development [4]

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

The entire process of discovering and developing a drug, from inception to commercialization, typically spans five to ten years and costs approximately $1.7 billion to complete effectively [6–8]. This journey through drug discovery and development encompasses several stages [9–13]:

Drug Discovery Period [14-20]

1. Initiation of drug discovery program
2. Utilization of combinatorial chemistry
3. Identification of lead compound series
4. Synthesis of additional compounds
5. Identification of New Chemical Entities (NCEs)

Drug Development & Registration Period [21-24]

1. Establishment and initiation of Investigational New Drug (IND) plan
2. Filing of IND
3. Initiation of clinical studies
4. Preparation and submission of New Drug Application (NDA)
5. Drug launch into the market

Drug Discovery and Development

Drug Discovery

Drug discovery researchers typically identify new pharmaceuticals by:

- Investigating disease processes in-depth, motivating the search for new treatments to mitigate or reverse their effects [31, 32].
- Conducting extensive testing of chemical compounds to identify potential therapeutic properties across various diseases.
- Addressing unforeseen side effects associated with current therapies [33–38].
- Exploring new technologies that enhance drug delivery to specific body parts or facilitate genetic modifications [39–41].

Thousands of chemical compounds may initially qualify as candidates for medical therapy. However, only a select few show promise after initial screening and require further investigation [42–45].

Drug Development

Following the discovery of a promising molecule, scientists conduct tests to explore:

- Its potential benefits and modes of action.
- Pharmacokinetics: how it is absorbed, distributed, metabolized, and excreted.
- Optimal dosage and administration routes.
- Variations in efficacy based on demographic factors like gender, ethnicity, or age.
- Interactions with other drugs and therapies.
- Side effects, often referred to as toxicity.

- Comparative effectiveness against existing treatments.

Preclinical Research

Preclinical investigations assess whether a drug has potential hazards to human health before human trials commence. These studies are conducted:

- **In Vitro:** Using controlled laboratory environments without animal subjects [52–55].
- **In Vivo:** Conducted directly on animal models [56, 57].

Preclinical studies, though not extensive in scope, must provide detailed data on dosage levels and toxicity profiles [58]. Following preclinical testing, scientists evaluate the results to determine if the drug is suitable for human trials [59, 60].

Key experiments in preclinical investigations include:

- Single-dose toxicity.
- Repeated-dose toxicity.
- Safety pharmacology.
- Genotoxicity.
- Carcinogenicity.
- Reproductive toxicity [61–65].

Clinical Research

While preclinical research offers foundational safety insights, clinical trials are essential for understanding how a drug interacts within the human body [66]. Clinical research involves human subjects in phases known as:

- Investigational New Drug Application (INDA), a prerequisite for initiating clinical trials [67–70].
- **Phase I–IV Clinical Trials:** These phases sequentially assess safety, dosage, efficacy, and side effects in increasing numbers of human subjects.

Phase Studies in Drug Development

Phase 1 (First in Humans)

Trial Design:

- **Patients:** 20 to 100 normal healthy volunteer subjects in a single center.
- **Duration of Study:** Short-term, ranging from 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 Effects**
3. **Tolerability, Side Effects, and Toxicity at Different Doses**
4. **Early Evidence of Efficacy**
5. **Safety Evaluation – Identification of Potential Toxicities and Optimal Dosage Range**

Percentage of Drugs Advancing to Next Phase: Approximately 70% [86].

Phase 2 (Therapeutic Exploratory)

Trial Design:

- **Patients:** Several hundred (100-300) patients with the targeted disease/condition.
- **Length of Study:** Several months to 2 years.

- **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 Treating the Targeted Disease or Condition**
3. **Maximum Tolerated Dose (MTD)**
4. **Common Short-term Side Effects and Risks**
5. **Pharmacokinetics**

Percentage of Drugs Advancing to Next Phase: Approximately 33% [89].

Phase 3 (Therapeutic Confirmatory) – Pivotal Trials

Trial Design:

- **Patients:** Several thousand (1000 to 3000) 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:

1. **Effectiveness (Large-scale)**
2. **Relative Risk/Benefit Relationship**
3. **Long-term Safety Information – Common Side Effects, Drug Interactions, Age/Race/Gender Differences**
4. **Dosing (for Labeling)**
5. **Assessment of Safety and Efficacy**

Percentage of Drugs Advancing to Next Phase: Approximately 25-30%. Upon completion of Phase III trials, the application is filed with regulatory bodies for marketing approval. Upon approval, the product is launched into the market [93-95].

Phase 4 (Post-Marketing Therapeutic Use)

Trial Design:

- **Patients:** Several hundred to thousand patients with the disease/condition.
- **Type of Study:** Randomized, placebo or active control, multicenter.

Purpose:

1. **Quality of Life Trials (QOL)**
2. **Pharmacoeconomic Trials – Comparison with Other Treatments**
3. **Collection of Long-term Safety Information – Epidemiological Studies**
4. **Additional Surveillance for Unexpected or Rare Adverse Effects**
5. **Line Extensions – New Dosage Forms and Formulations** [96, 97].

Problem Identification in Phase 3 Trials

Bit opertin

Problem Identified in Phase 3 Trial: Lack of Efficacy

- Despite statistically significant results in reducing symptoms of schizophrenia in Phase 2, bitopertin failed to improve negative symptoms of schizophrenia in Phase 3 trials.

Background on Schizophrenia:

- Schizophrenia is a chronic brain disorder characterized by abnormal interpretation of reality, including positive symptoms like hallucinations and delusions, negative symptoms such as social withdrawal and lack of motivation, and cognitive symptoms affecting memory and concentration.
- Treatment typically involves lifelong use of antipsychotic medications, including typical and atypical types that block dopamine pathways. Atypical antipsychotics are preferred for long-term management due to fewer movement-related side effects but may still cause weight gain, increased cholesterol, and other issues.

Mechanism of Bitopertin:

- Bitopertin increases glycine availability in the synapse, proposing a novel approach to treating schizophrenia.
- A placebo-controlled, double-blind study spanning eight weeks and involving over 320 patients worldwide showed a significant 25% reduction in negative symptoms compared to placebo.

Phase 3 Studies:

- Three subsequent Phase 3 studies evaluated bitopertin's efficacy and safety in over 1800 patients for one year or more.
- Despite promising Phase 2 results, two Phase 3 studies did not show statistically significant improvement in negative symptoms when bitopertin was added to conventional treatments compared to placebo.

Iniparib

Product: Iniparib

- **Sponsor:** Sanofi
- **Purpose:** Add-on treatment for "triple negative" breast cancers.

Problem Identified in Phase 3 Trial: Lack of Efficacy

- Despite promising Phase 2 results on tumor response and survival rates, adding iniparib to established chemotherapy regimens in Phase 3 trials did not improve overall survival.

Background on Triple Negative Breast Cancer:

- Triple-negative breast cancer is a subtype that lacks three specific receptors, making it aggressive and challenging to treat with standard therapies.

Iniparib in Preclinical and Phase 2 Testing:

- In preclinical testing, iniparib showed strong activity by enhancing the effects of standard chemotherapy on metastatic triple-negative breast cancer cells.
- Phase 2 trials with 123 patients demonstrated significant improvements in tumor response and overall survival without increasing toxicity.

Phase 3 Trial Results:

- Iniparib was tested in 519 patients with metastatic triple-negative breast cancer.
- The trial did not identify significant safety concerns, but adding iniparib to standard chemotherapy did not result in improved overall or progression-free survival compared to chemotherapy alone.
- Overall survival was 11.1 months for patients receiving standard chemotherapy and 11.8 months for those receiving chemotherapy plus iniparib, indicating no substantial benefit from adding iniparib in Phase 3 testing.

CONCLUSION

Emerging diseases continually underscore the pivotal role of new medications in modern medicine. Conditions that once necessitated extensive surgery, like gastric ulcers, have seen a transformative decrease in significant side effects due to advancements in pharmaceutical therapies and innovative drugs [98]. Similarly, the prognosis for HIV-positive patients has markedly improved with the introduction of numerous novel antiviral drugs.

Understanding the drug discovery and development process is paramount for healthcare professionals [99]. Familiarity with this process not only fosters innovation but also aids in the evaluation of new products, underscores the importance of reporting adverse drug events, and equips physicians to inform and guide patients considering participation in clinical trials.

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