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**Research**

# Risk and opportunities in development of new drug

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## Abstract

Drug discovery is a process which aims at identifying a compound therapeutically useful in curing and treating disease. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. Once a compound has shown its significance in these investigations, it will initiate the process of drug development earlier to clinical trials. New drug development process must continue through several stages in order to make a medicine that is safe, effective, and has approved all regulatory requirements. Drug Regulatory Affairs refers to all aspects within the pharmaceutical process on drug discovery and research which also deals with many risks and opportunities of drug development and they have subject to different degrees of regulations of different countries such as India, USA, Europe. The pharmaceutical law frame is used as guidelines on covering Quality, Safety and Efficacy of a drug as well as Health Authorities' attitudes and requirements are employed for the correct pathway of pharmaceutical needs and have a great influence on the drug development process and had success through it. The role of Regulatory affairs professionals deals with all these aspects to get a desired result of drug development. The health authorities are framed to guide and analyse the drug which fulfils the appropriate quality and efficacy.

**Keywords:** Drug discovery, pharmaceutical drug,

## INTRODUCTION

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. It includes preclinical research on microorganisms and animals, filing for regulatory status, such as via the United States Food and Drug Administration for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug.[1,2] The entire process – from concept through preclinical testing in the laboratory to clinical trial development, including Phase I–III trials – to approved vaccine or drug typically takes more than a decade.[3,1,2,4]

**AIM AND OBJECTIVES**

- The ultimate goal of drug development is to bring a new compound with proven therapeutic effect to the market. In this context, the transition from preclinical research to clinical stages marks a critical turning point, as it nears the new medicinal product to the market.
- The drug development process could be substantially improved if rigorous randomized trials become the first rather than the last step in the process of discovery of new, effective drugs and if randomization permeates testing at all stages. Both for animals and for humans, more, not fewer, randomized trials are needed.
- Drug development is often a lengthy and expensive process. Extensive preclinical testing via in vitro and animal experimentation aims to select drugs most likely to work in humans.
- The goal of a preclinical drug discovery program is to deliver one or more clinical candidate molecules, each of which has sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug-like properties so that it can be entered into human testing.

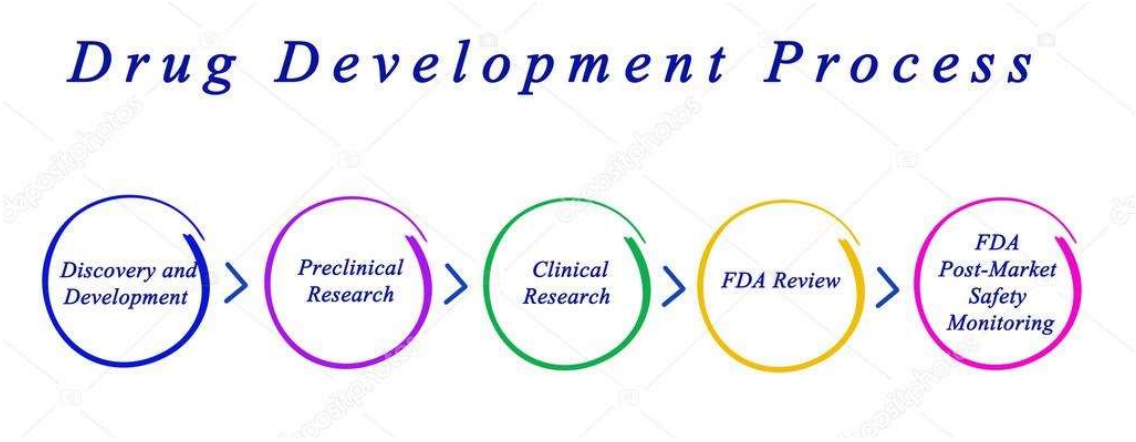


**Fig 1 : Drug Development Process**

**New chemical entity development**

Broadly, the process of drug development can be divided into preclinical and clinical work.

**Pre-clinical**

New chemical entities (NCEs, also known as new molecular entities or NMEs) are compounds that emerge from the process of drug discovery. These have promising activity against a particular biological target that is important in disease. However, little is known about the safety, toxicity, pharmacokinetics, and metabolism of this NCE in humans. It is the function of drug development to assess all of these parameters prior to human clinical trials. A further major objective of drug development is to recommend the dose and schedule for the first use in a human clinical trial ("first-in-human" [FIH] or First Human Dose [FHD], previously also known as "first-in-man" [FIM]).

In addition, drug development must establish the physicochemical properties of the NCE: its chemical makeup, stability, and solubility. Manufacturers must optimize the process they use to make the chemical so they can scale up from a medicinal chemist producing milligrams, to manufacturing on the kilogram and ton scale. They further examine the product for suitability to package as capsules, tablets, aerosol, intramuscular injectable, subcutaneous injectable, or intravenous formulations. Together, these processes are known in preclinical and clinical development as chemistry, manufacturing, and control (CMC).

Many aspects of drug development focus on satisfying the regulatory requirements for a new drug application. These generally constitute a number of tests designed to determine the major toxicities of a novel compound prior to first use in humans. It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g., the skin if the new drug is to be delivered on or through the skin). Such preliminary tests are made using in vitro methods (e.g., with isolated cells), but many tests can only use experimental animals to demonstrate the complex interplay of metabolism and drug exposure on toxicity.[5]

The information is gathered from this preclinical testing, as well as information on CMC, and submitted to regulatory authorities (in the US, to the FDA), as an Investigational New Drug (IND) application. If the IND is approved, development moves to the clinical phase.

**Clinical phase**

**Clinical trials involve three or four steps[6]**

Phase I trials, usually in healthy volunteers, determine safety and dosing.

Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of patients having the disease targeted by the NCE.

Phase III trials are large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients with the targeted disease. If safety and efficacy are adequately proved, clinical testing may stop at this step and the NCE advances to the new drug application (NDA) stage.

Phase IV trials are post-approval trials that are sometimes a condition attached by the FDA, also called post-market surveillance studies.

The process of defining characteristics of the drug does not stop once an NCE is advanced into human clinical trials. In addition to the tests required to move a novel vaccine or antiviral drug into the clinic for the first time, manufacturers must ensure that any long-term or chronic toxicities are well-defined, including effects on systems not previously monitored (fertility, reproduction, immune system, among others).[7,8]

If a vaccine candidate or antiviral compound emerges from these tests with an acceptable toxicity and safety profile, and the manufacturer can further show it has the desired effect in clinical trials, then the NCE portfolio of evidence can be submitted for marketing approval in the various countries where the manufacturer plans to sell it.[4] In the United States, this process is called a "new drug application" or NDA.[4,7]

Most novel drug candidates (NCEs) fail during drug development, either because they have unacceptable toxicity or because they simply do not prove efficacy on the targeted disease, as shown in Phase II–III clinical trials.[4,7] Critical reviews of drug development programs indicate that Phase II–III clinical trials fail due mainly to unknown toxic side effects (50% failure of Phase II cardiology trials), and because of inadequate financing, trial design weaknesses, or poor trial execution.[9,10]

A study covering clinical research in the 1980–90s found that only 21.5% of drug candidates that started Phase I trials were eventually approved for marketing.[11] During 2006–15, the success rate of obtaining approval from Phase I to successful Phase III trials was under 10% on average, and 16% specifically for vaccines.[12] The high failure rates associated with pharmaceutical development are referred to as an "attrition rate", requiring decisions during the early stages of drug development to "kill" projects early to avoid costly failures.[12,13]

**Risks In Development Of New Drug**

Drug development became reconciled to twice the challenge of high price and pressure in appraise.

To abstain from the absence of awareness on business viewpoint may lead to extant medical demand unsatisfied, medical companies and more others take holders were examine the pathways to enhance the effectiveness of drug development[15]. The reason for disengage of a new drug development action was shortage of clinical efficacy. Simultaneously, attenuation values are more in clinical Phase II, hence it comprise the initial proof for pharmacodynamic mode of action of the molecule. Accordingly, most of the organisation in new drug research and development won't drained on making of some molecules in market which leads to failure[14]. The cause for lack of success would be numerous like incorrect option of goal, impotence to catch suitable compounds to unpredicted toxicity and absence of efficacy in clinical trials. Drug discovery can be stopped for reasons primarily based on science like

- Routine policy changeover in medical industry,
- Changeover in medicine rules and regulation,
- Conditions for regulatory approval,
- Successfull competitor or fragile cognitive possessions.
- Medicines which are approved by the constitutional domination made unsuccessful economy.

Risks are associated with the science aspects of the new project as well as the afore-mentioned plan, legislation and business risks.

**Types Of Risk Factors**

In account of drug development, two major types of risks can be distinguished below:

1. Technical risks
2. Translational risks.

**Technical Risk**

Technical risks can be defined as the lead of inability to findout and adequately characterize the appropriate compound which encounter the needed outline to label selected goal[16].

Technical risks will come under the following on,

- The absence of appropriate assays,
- Unable to produce suitable materials or bioreagents ,
- Lack of selectivity toward the target,
- Unsuitable pharmacokinetics,
- Toxicity of the developed molecules.

**Translational Risks**

Translational risk are those liable for inappropriate clinical efficacy for which the molecules having another sensible ideal profile. This absence of potency can be the result of the incorrect selection of goal, implementation of proposed structure that are not divining for people illness, or non-success of the particle to capture the aim in the clinical circumstances[16,17].

Collection of Translational risks results in drug development as follows:

- Aim surmise depend upon incorrect qualification.
- Absence on outgrowth connection: inessential passage, counter regulation in elimination or suppression.
- Insubstantial comprehension of biology and pathophysiological procedure infection.
- Pre diagnosis proposed structure which anticipated for diagnosis circumstances.
- Inadequate anthropoid proof.
- Absence of biological markers to describe the commitment and therapy success.
- Impotence to recognise the correct sick patient for treatment.
- No additive to current treatment.

**Opportunities In Development Of New Drug**

The key points of opportunities in development of new drug are listed:

- The molecular medicine method can be used for new drug development by knowing the basic pathophysiology of disease in order to examine and evaluate drug targets.
- Using exploratory drugs as clinical study, to recognise and confirm a target in healthy human people, this can guide the examiners to take decision go on or not to go.
- Appearance of tools and technologies based on scientific advantage basis that are applicable to the field today such as variation and competition are needed.
- Transporting the standard paradigm or pattern of drug screening to one that needs more careful preclinical and clinical experiments can increase the chance of finding out the right targets and process.
- Human constitution will inform the drug discovery. If drug development starts in humans first and then confirming in animal models can lead to more beneficial drug development.
- On account of difficulty and heterogeneity of patients, greater the importance on multiple procedures using combined therapies may reflect in an increased number of prospicious drugs.
- The academia, industry, and government can help to de-risk the research by public-private partnerships and extension of precompetitive space.
- Enlarging quality and apportion of preclinical data will help to enhance reproducibility and build up the new drug development pipeline

**Regulatory Affairs In Product Management**

RA professional guides the company in planning and skilfully in higher amount. They starts from innovation of drug to modelling, trading and post trading planning. They guide the pharmaceutical companies in account of legal and technical needs at all stages[18,19].


**Fig 2: Overview of Regulatory Affairs in Pharmaceutical Industries**

**Regulatory Affairs In Clinical Trials**

RA professional advices on the basis of laws, fundamentals and guidelines to divisions of medical industry. They develop a policy for clinical trials in basis of regulatory bodies for approval of new molecule which prevents from approval delay. They make data on risks and opportunities of drug or medicine and delivers to the constitutional agencies, medical and health organisation and public[23].

**Regulatory Affairs In R&D**

Fundamental organisation plays important action in R&D to develop the drug in advantage of technical and constitutional developments to expedite at time to market. They make adaptive clinical trial and get fast approval from regulatory bodies and avoid danger in task to get rapid progess of new medicine and also helps to decrease high-cost fault and time lags[20].

**Process Of Drug Approval**

The drug approval procedure includes, appeal to perform clinical trial and appeal to the regulatory authority for marketing authorization of new drug. The procedure will be same for all countries, where they will summit the information regarding quality, safety and efficacy of drug to regulatory authorities. Although the fee, review process and time of clinical trials and marketing authorization requisition will vary. This process will prevent the duplication work on research and development of new drugs. Hence conformation of drug approval procedure is done by ICH or WHO at global level[21]. The regulatory agency for INDIA and USA is a single agency which is CDSCO and USFDA[24].

The Drug patronage in the India, USA, Europe, are the greatest provocation in this world. The basic purpose of the rules and regulation governing medicines in major countries is to protect public health. There is a law that recommends the drugs to be discovered, developed, tested, trailed, and manufactured in conformity to the guidelines for safety and patient health[22].

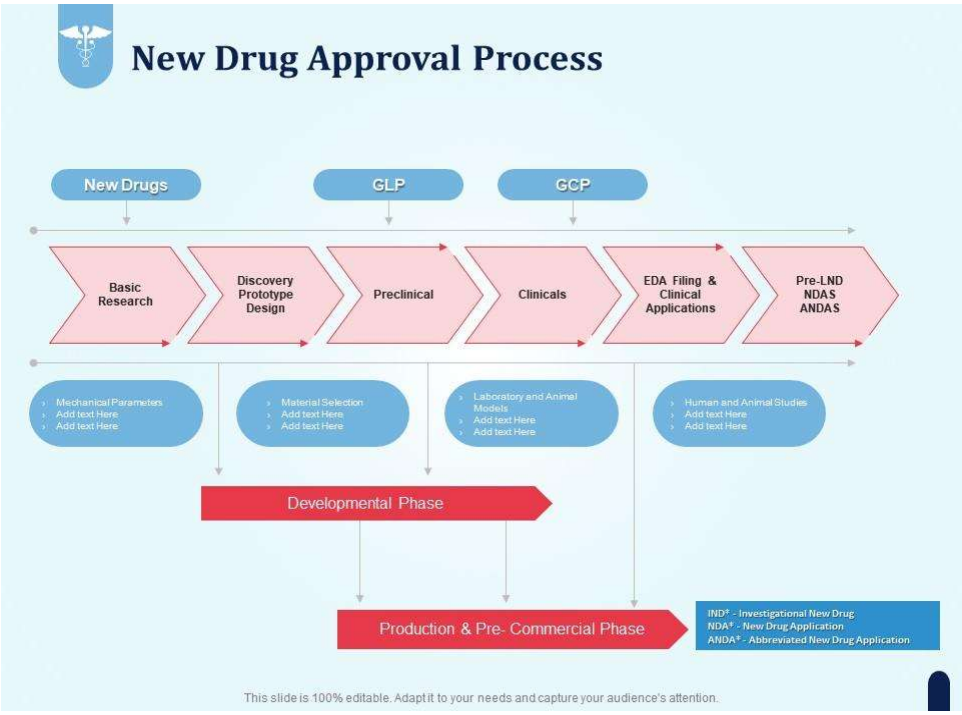


**Fig 3: New Drug Approval Process**

**The Drug Development Process[25]**

**Discovery and Development**

**Discovery**

Typically, researchers discover new drugs through:

- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.
- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments that have unanticipated effects.
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.

At this stage in the process, 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.

**Development**

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

- How it is absorbed, distributed, metabolized, and excreted.
- Its potential benefits and mechanisms of action.
- The best dosage.
- The best way to give the drug (such as by mouth or injection).
- Side effects or adverse events that can often be 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 drugs.

**Preclinical Research**

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are:

- In Vitro
- In Vivo

FDA requires researchers to use good laboratory practices (GLP), defined in medical product development regulations, for preclinical laboratory studies. The GLP regulations are found in 21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies. These regulations set the minimum basic requirements for:

- study conduct
- personnel
- facilities
- equipment
- written protocols
- operating procedures
- study reports
- and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product

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 should be tested in people.

**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. "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.

On this page you will find information on:

- Designing Clinical Trials
- Clinical Research Phase Studies
- The Investigational New Drug Process
- Asking for FDA Assistance
- FDA IND Review Team
- Approval

**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:

- 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.

## CONCLUSION

The FDA's mission is to facilitate the premarket review and evaluation of INDs and NDAs. A central theme over the past few years has been a standardized approach to evidence-based review and evaluation. The FDA emphasizes the Quality Risk Management approach to design of studies by providing oversight and objective review of risk-benefit analysis that guides the use of new drug products by providing patients organized data and appropriate labeling information in support of the new drug's intended clinical use.

The development of new drug is associated with many risks and benefits. But degrading the risk with new techniques and regulations will help the pharmaceutical company to work on research and development of new drug. This will helps the patient quality of life for growing population. They trusted the new drug development with fundamentals will simultaneously can be organised for all drugs which shows the correct structure for dispatching new drug to trade in a sensible duration with sustainable care. The proper management of fundamental activities are hence, considerable economic importance for the new drug development.

Understanding the nature of a risk is a precondition for a good response. Therefore, Risk Assessment facilitates the creation of more realistic project plans. Optimistic planning is the main reason for project failure.

Every year, the U.S. pharmaceutical industry develops a variety of new drugs that provide valuable medical benefits. Many of those drugs are expensive and contribute to rising health care costs for the private sector and the federal government. Policymakers have considered policies that would lower drug prices and reduce federal drug expenditures. Such policies would probably reduce the industry's incentive to develop new drugs.

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