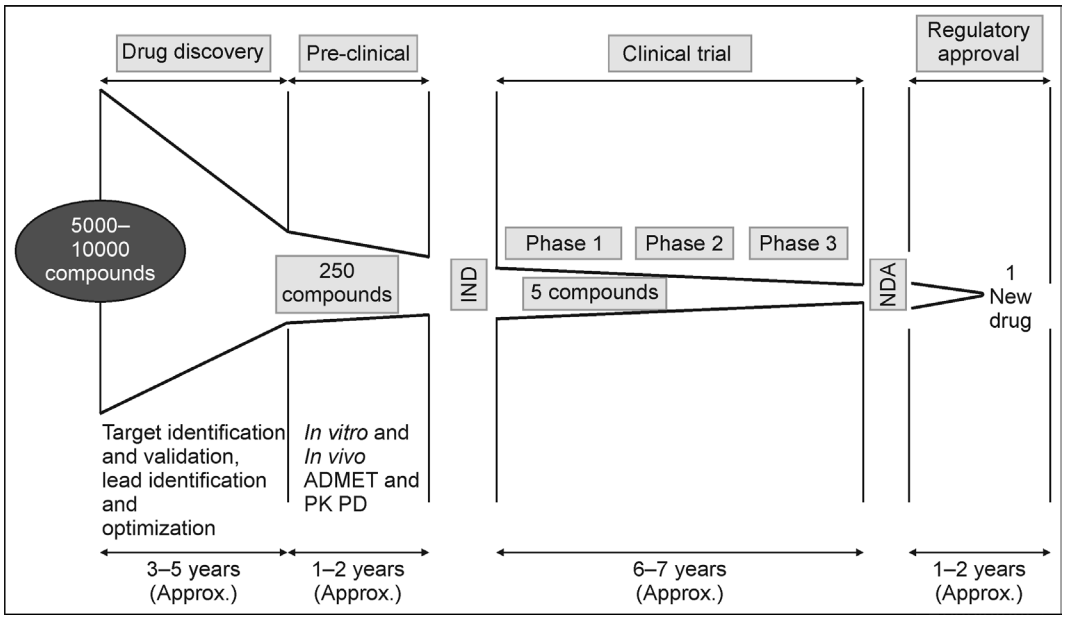


**Fig. 1.1:** New drug developmental process

250 of the 5,000–10,000 drug candidates found during the drug discovery phase will pass the first hurdle and enter the pre-clinical stage. Of this 250, only about 5 will reach the clinical trials phase and usually only one will get the approval from the regulatory bodies (**Fig. 1.1**).

From the moment a molecule is identified to the completion of a clinical trials, it can take up to 16 years on average. Drug development costs remain high, driven by the expense of failure. The drug candidates entering clinical trials will have a more than 90% chance of failing during the drug development process, due to unforeseen human side effects or inadequate efficacy. The regulatory processes have also become stricter, resulting in several obstacles a new medication must overcome to reach the market. After rofecoxib and a number of other well-known medications were withdrawn due to safety concerns, the regulatory bodies across the world have started giving greater emphasis to preapproval safety appraisals and augmented their dependence on post-approval procedures to screen drug safety and efficacy. **Table 1.1** summarizes the challenges in development of new drug.

**Table 1.1:** Some of the challenges in development of new drug

| |
|---|
| Between 5,000 and 10,000 novel compounds are assessed during the drug development stage for each medication that eventually reaches the market |
| Drug candidates have more than 90% chance of failing during the drug development process, due to unforeseen human side effects or inadequate efficacy |
| From the moment a molecule is identified to the completion of a clinical trial, it can take up to 16 years on average |
| Increase in drug development cost, driven by the expense of failure |
| Regulatory processes have become stricter with greater emphasis on preapproval safety appraisals and post-marketing surveillance |

## PROCESS OF NEW DRUG DEVELOPMENT

### Target Identification and Validation

The first step in the process of developing a novel medicine is target identification and validation, which also serves as the foundation for many processes aimed at further selecting and identifying the targets of human illnesses. A target is a general phrase that may be used to describe a wide range of biological things, such as proteins, genes, and RNA. Target identification is the method of sensing the direct molecular target. Please note that every target may not be equally capable of affecting the course of a disease (*see* **Fig. 1.1**).

### Lead Identification

Potential lead compounds are synthesized when therapeutic targets are determined. These compounds may be found in nature, found through high-throughput screening of sizable chemical libraries, or created by synthesizing analogues of existing compounds that have been shown to be successful in treating specific diseases. Modern robots and computer technology have made it possible for high-throughput screening to evaluate enormous "libraries" of chemical compounds. "Virtual screening," also known as "in silico screening," is another technique for identifying leads. It is characterized as "selection of compounds by evaluating their desirability in a computational model."

### Lead Optimization

As soon as a preliminary lead compound is recognized, lead optimization should be done to collect additional data on test drug effectiveness, safety and molecule mechanism. The lead compound might be having some shortcomings or unfavorable properties. Therefore, it is essential to improve the lead compound. To put it succinctly, the process of optimization involves creating a number of compounds based on the similarity principle, assessing their overall structure-activity relation, and optimizing their physical, chemical, and biological characteristics.

### Preclinical Studies

In order to determine if an agent is suitable and safe for testing in people, preclinical research is conducted utilizing both *in vitro* and *in vivo* experiments, including cellular and animal models. *in vitro* biochemical or cellular tests are used to confirm the potency and selectivity of lead compounds that pass screening. Subsequently, *in vitro* functional biochemical and pharmacological testing is usually conducted, succeeded by *in vitro* pharmacodynamic and pharmacokinetic testing. To find out the likely safety profile, we need to finish the pilot toxicological study. The "lead" becomes a "candidate" and is proposed for progression to the clinical testing if all preclinical test results has met the basic selection requirements.

### Investigational New Drug (IND) Application

If a product has a promising profile, an IND application delineating the available pre-clinical data along with manufacturing data, must be filed with the regulatory body before moving on to the subsequent stage. An IND filing is necessary to get permission for clinical testing in humans. An IND should incorporate following information:

- Data from animal toxicology and pharmacology tests

- Manufacturing data in order to confirm that the sponsor can satisfactorily manufacture and steadily supply the drug
- Trial protocol detailing the trial design of initial phase.

### Clinical Trials

Clinical trials encompass the next stage. Clinical trials are defined as a type of research that studies interventions on human subjects and evaluates their efficacy and safety. Phase I trials aim to determine the safety as well as optimal dosage of the intervention in a small group of healthy subjects. Phase II trials investigate the agent's efficacy and adverse effects in a patient population with the disease. Phase III and IV trials further characterize the agent's efficacy and safety. Phase III studies are done on larger number of patient populations and are usually multi-centric, and are often conducted just before a new treatment gets marketing approval. Phase III trials are considered the benchmark to establish the efficacy of a novel intervention compared to standard intervention. After a new medication is approved, phase IV studies are carried out and it furnishes extra-data about the safety of the drug when it is being prescribed during clinical practice. Lets understand in brief about these phases of clinical trials.

#### *Phase I Trials*

The first time the novel medication given to a human volunteer is when phase I begins. Apart from cytotoxic medications (i.e. cancer therapies), which are evaluated in patients without initially requiring testing in healthy volunteers, this phase often involves healthy volunteers. This phase's objective is to assess the tested drug's pharmacodynamic and pharmacokinetic effects, as well as its safety, tolerability, and maximum tolerated dosage (MTD).

Volunteers for phase I trials run the danger of misinterpreting the study's goal as therapeutic. Modifications to the informed consent procedure might help refute some of these myths while preserving sufficient enrollment numbers. Phase I studies are often carried out in specially designed phase I centers (these are research facilities connected to teaching or general hospitals and staffed by medical professionals with experience conducting these kinds of investigations). These units offer complete resuscitation facilities. In an inpatient environment, study subjects are usually closely watched for signs of medication toxicity.

Phase I testing involves a variable number of subjects, often between 20 and 80. Usually, Phase I takes a year or two to finish. The relevant regulatory body and an ethical committee must approve phase I studies. As mentioned above, before beginning Phase I clinical trials, an Investigational New Drug (IND) application must be filed to the regulatory body. This application summarizes the existing preclinical and manufacturing facts and provides guidance to the investigators.

**Phase 0 Trials**

Phase 0 trial uses few small doses of new interventions in a very few subjects to select the best drug candidate from those interventions, which can further be tested on later phases of clinical trial on large number of subjects. Phase 0 studies are conducted before the phase 1 trial and are also known as micro dosing study. In a phase 0 study, a sub-pharmacologically active dose of medication is administered to the small number of subjects, but it has no therapeutic intent. It basically tries to collect human pharmacokinetic/pharmacodynamic data to identify the most promising drug candidate for additional research.

### *Phase II Trials*

Evaluating the medication's pharmacokinetics, safety, and dosage range in healthy subjects is the initial stage in determining its efficacy and safety in the intended population. Phase II studies evaluate multiple dosage regimens, proof of concept, efficacy and safety in individuals suffering from the ailment under investigation. Phase II trials are bigger than phase I trials and involve about 100–300 patients with the condition of interest. They are also frequently called "therapeutic exploratory" trials. In addition to testing pharmacokinetics, pharmacodynamics, and safety, they may also be made to address issues related to phase III trial preparation, such as figuring out the best dosages, frequency of doses, modes of administration, and outcomes. They could also provide early proof of the efficacy of the medication. However, the small number of study subjects along with limited power to establish efficacy and safety supports the necessity of a subsequent phase III trial.

Phase IIa and Phase IIb are the two major divisions of phase II. In Phase IIa trials (also known as the "proof of concept." study) a small patient cohort is evaluated for the treatment (often confined to a single high/maximum tolerated dose level).

After the proof of concept, phase IIb entails conducting dose-ranging studies (testing many dosage levels in the target population) to identify the lowest effective or non-effective dose and the optimal dose to go to the next phase based on safety and clinical efficacy. Phases IIa and IIb are occasionally integrated into a single, sizable research.

### *Phase III Trials*

Phase II studies that demonstrate safety and efficacy pave the way for phase III trials (also known as a "therapeutic confirmatory," "comparative efficacy," or "pivotal trial"). These large-scale trials, which may require months or years, are meant to collect data that will be utilized in the risk vs benefit analysis. This is the final stage of medication development before registration.

The sponsor should have a high degree of confidence in the medication's safety and efficacy in the intended patient group and the dosage range to be studied before starting an expensive phase III study. Depending on the indication, phase III trials can include thousands of patients (typically 300–3,000), so a large enough database (with at least 80% power to identify statistically significant differences) can be created to evaluate the safety and efficacy profile and enable accurate drug labelling.

Phase III studies are largely engineered and structured to test the hypothesis of efficacy; concurrently, adverse events are recorded to evaluate the drug's benefit-risk potential. Phase III studies are required to adhere to stringent regulatory and statistical requirements and they serve as the foundation for the prescription information (package insert).

### *New Drug Application (NDA)*

An NDA incorporating the data collected in stages 1 through 3 is submitted for regulatory authority evaluation. An NDA encapsulates all of the pre-clinical data along with clinical efficacy and safety data. On an average, new drug application, or "NDA," may take up to fifteen months to review. Nonetheless, an expedited (accelerated) review may be authorized in situations with extremely high unmet medical need or in fields without adequate therapies (such as cancer and HIV). A biologic license application, or "BLA," is filed in place of an NDA if the new medication is a biologic.

*Phase IV Trials*

A sponsor may be required by the regulatory body to carry out a phase IV study as a condition of marketing authorization. Phase IV trials of observational, non-interventional nature mandated by the regulatory authority to verify the safety and efficacy of marketed medications in real-world settings are called post-marketing surveillance (PMS) studies.

Finding any unusual or chronic adverse events in a wider patient group is made easier with the use of post-marketing safety surveillance. Apart from overseeing safety, post-marketing surveillance studies aid in the systematic gathering of clinical data concerning a drug's usage over a broad range of patients, providing information that would not have been obtained in phase III trials.

Consequently, observational studies known as "post-marketing surveillance" trials are conducted on regulatory-approved medications in order to: (1) detect less frequent adverse responses; and (2) assess the efficacy of the medication under conditions, demographics, or dosages that are either substantially similar to or dissimilar from the original research population.

The data demonstrates the limits of pre-marketing (e.g. phase III) trials, since roughly 20% of drugs have received new black box warnings during the post-marketing trials and about 4% of pharmaceuticals had to be discontinued due to safety reasons. As demonstrated by the cases of rofecoxib, cerivastatin, and other drugs, harmful effects found during phase IV studies may result in the drug's removal from the market.

Therefore, all pharmaceutical products that has been post-marketed are required to comply with post-marketing surveillance. Following approval, the pharmaceutical developers will also submit periodic safety update reports (PSURs) on the new medication. The comparison of different phases of clinical trials is given in **Table 1.2**.

**Table 1.2:** Comparison of different phases of clinical trials

| Phase of the trial | Subjects | Number of subjects tested | Purpose of this stage | Also referred as |
|---|---|---|---|---|
| Phase I | Healthy volunteers Except for cytotoxic medications, which are tested on patients | 20–80 | Evaluate the safety, tolerability, maximum tolerated dose (MTD), pharmacodynamic and pharmacokinetic effects of the tested drug | First in Human (FIH) studies |
| Phase II | In the target patient population | 100–300 | Evaluate multiple dosage regimens, proof of concept, efficacy and safety in individuals suffering from the ailment under investigation | Therapeutic exploratory trials |
| Phase III | In the target patient population | 300 to thousands | Efficacy and safety | "Therapeutic confirmatory," "Comparative efficacy," or "Pivotal trial" |
| Phase IV | Patients with target disease as well as new age groups, gender etc. | Several thousands (usually >10,000) | 1. To identify less common adverse reactions by long term safety surveillance, and<br>2. To evaluate drug effectiveness in patient populations | "Post-marketing surveillance" trials |

## KEY LEARNING POINTS

- Between 5,000 and 10,000 novel compounds are assessed during the drug development stage for each medication that eventually reaches the market.
- From the moment a molecule is identified to the completion of a clinical trials, it can take up to 16 years on average.
- Drug development costs remain high, driven by the expense of failure. The drug candidates entering clinical trials will have a more than 90% chance of failing during the drug development process, due to unforeseen human side effects or inadequate efficacy.
- Target identification and validation serve as the starting point for the process of developing novel drugs and as the foundation for other operations aimed at further selecting and identifying the targets of human illnesses.
- Potential lead compounds are synthesised when therapeutic targets are determined.
- As soon as a preliminary lead compound is recognized, lead optimization should be done to collect additional data on test drug effectiveness, safety and molecule mechanism.
- In order to determine if an agent is suitable and safe for testing in people, preclinical research is conducted utilizing both in vitro and in vivo experiments, including cellular and animal models.
- The "lead" becomes a "candidate" and is proposed for progression to the clinical testing if all preclinical test results has met the basic selection requirements.
- If a product has a promising profile, an IND application delineating the available pre-clinical data along with manufacturing data, must be filed with the regulatory body before moving on to the subsequent stage. An IND filing is necessary to get permission for clinical testing in humans.
- Broadly 'clinical trial' can be defined as any study in human subjects envisioned to determine or confirm the efficacy and/or safety of one or more investigational intervention(s).
- Phase I, II, III, and IV are the four stages of clinical trials.
- Phase I clinical studies aim to ascertain the optimal dosage and safety of a medication in a limited number of human volunteers who are healthy.
- Phase II studies evaluate multiple dosage regimens, proof of concept, and efficacy in individuals suffering from the ailment under investigation.
- Phase III studies are done on a relatively bigger patient populations compared to phase II studies and are often conducted right before NDA submission is done.
- Phase IV drug trials are conducted after the approval of the medication and furnish further data about the safety of the drug.

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