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SHORT COMMUNICATION

# An overview of drug drug development process

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**Abstract:** Drug design, sometimes referred to as just rational design or rational drug design. It is described as the form of molecules to predict how they will mix with other molecules or bind to cell receptors. Candidate identification, synthesis, characterisation, validation, optimisation, screening, and tests for therapeutic efficacy are all steps in this process. In order to create a medication that satisfies all regulatory standards and is safe and effective, the new medication's creation method must proceed through multiple stages. Prior to conducting clinical trials, the medication development process starts as soon as these investigations show how important the chemical is. To create a medication that satisfies all legal, regulatory, and safety standards, it must pass multiple stages of development. One recurring topic in our writings is that For any new medicine that is eventually approved for clinical usage, a number of biological targets must be taken into consideration due to the lengthy, intricate, and costly procedure. To explore new targets, it can be necessary to examine new research tools. It takes a lot of time and effort to go from a drug's initial discovery to its commercialization. A $1 billion investment is needed throughout the course of twelve to fifteen years, from drug research to approval. Only one of the one million molecules that are screened on average will be studied in advanced clinical trials and eventually given to patients. An overview of the procedures involved in finding and developing novel drugs is given in this article.

**Keywords:** Clinical studies; preclinical studies; target validation; lead optimisation; novel drug discovery

## 1. Introduction

The process of finding possible new therapeutic entities through the application of computation, experimental, translated, and clinical models is known as drug discovery. Even with the breakthroughs in biotechnology and our knowledge of biological systems, the process of finding novel therapeutics is still exceedingly time-consuming, expensive, challenging, and inefficient, and it still results in few new therapeutic discoveries. The creative process of creating novel drugs using a biological target's information is known as drug design. Drug design, in its most basic form, is the creation of compounds that complement the target molecules that they interact and bind to in terms of charge and shape. In the big data era, bioinformatics methods and computer modelling techniques are often, but not always, used in drug creation. Apart from tiny molecules, Pharmaceuticals, and particularly therapeutic antibodies, represent a growingly significant class of pharmaceuticals. Significant progress has also been made in computational approaches for enhancing the stability, selectivity, and affinity of these protein-based therapies [1]. Preclinical research on animal and cell models, as well as human clinical trials, are all part of the process of developing and discovering new drugs. Afterward, the drug must receive regulatory approval before being put on the market. The process of finding new drugs entails identifying screening hits, optimising medicinal chemistry, and increasing the affinity, selectivity, efficacy, potency, metabolic stability, oral bioavailability, and reduction of side effects. The process of creating the medicine will move on to clinical testing once a molecule that satisfies each of these requirements has been identified.

The process of finding a medicine that is chemically therapeutically beneficial in the management and treatment of a disease condition is known as drug discovery. Preclinical research on animal and cell models, as well as human clinical trials, are all part of the process of developing and discovering new drugs. Afterward, the drug must receive regulatory approval before being put on the market. The process of finding new drugs entails identifying screening hits, optimising medicinal chemistry, and increasing the affinity, selectivity, efficacy, potency, metabolic stability, oral bioavailability, and reduction of side effects. Before conducting clinical trials, a molecule that satisfies all of these criteria will be determined, and the drug development process will start [2]. 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 organisations. Drug development

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is by far the most important component of the many stages of the drug life cycle for the initial and ongoing success of a drug on the market [3]

Researchers typically discover novel medications by developing fresh insights into the pathophysiology of an illness, which enables them to create medications that counteract or stop the consequences of the illness. Drug candidates are identified, synthesised, characterised, screened, and assayed for therapeutic efficacy as part of the drug development process. Following clinical trials, a molecule will begin the process of medication development if it yields favourable results from these investigations. The process of finding and developing new drugs is costly since R&D and clinical trial expenses are so large. A single new medicine molecule must be developed over a period of around 12 to 15 years from the moment it is discovered to the point when it can be sold to treat patients[4]. The efficacy and tolerance of the medication candidates must be demonstrated in cultures of cells and animals before any kind of human testing is conducted on them. The candidates will not be given the opportunity to advance if they prove to be toxic or hazardous. In order to save time and money, as well as to adhere to more ethical standards, the utilisation of models of animals for testing can be curtailed during this phase. Other models that adhere to the 3Rs specifications and are more affordable for researchers include Zebrafish. In the piece that follows, we will go into more detail on this subject.

For every effective medication, research and development expenses range from $900 million to $2 billion on average. This sum accounts for the thousands of failed attempts: In the end, just one compound out of every 5,000–10,000 that enters the pipeline for research and development is approved. These figures defy belief, but a quick review of the R&D process can help explain why so many compounds fail to find a market and why it requires such a significant amount of time and resources to get one medication into patients. The greatest logical and scientific minds, advanced lab and technology, vast resources, and diversified project management are all necessary for success. It also requires luck and perseverance [5] Millions of patients eventually find healing, hope, and faith thanks to the drug research process.

Important preclinical phases of the drug discovery process will be examined in this study, starting with the initial target selection and validation. This review's main focus is on general strategies and factors to be taken into account while developing analytical techniques for the identification, quantification, and separation of active pharmaceutical ingredients (APIs), which can be used for a variety of purposes across the drug development lifecycle. The review also covers the problems and criteria that need to be taken into account while validating analytical techniques, as well as clinical and pre-clinical research that determines a drug's safety and effectiveness in the human body..

## 2. Drug Development Process

### 2.1. Research and Development of Drugs

The process of finding and developing new medications is very time-consuming and expensive. R&D decisions in the research-based pharma sector have significant long-term effects, and changes in the public policy or market may take years to fully manifest. Therefore, it is crucial to keep analysing the elements and trends in the price tag of pharmaceutical innovation from the perspectives of industry and policy. Drug development is a costly, drawn-out, and gradual process that starts with the identification of a promising target and ends with the finished drug. Finding a chemical in the human body that has the required impact and proving its quality, safety, and effectiveness in treating patients are the ultimate goals. The aforementioned prerequisites guarantee that the authorised drug enhances the patient's quality of life by treating their ailment and preventing it from leading to unintended consequences. It also implies that this is an especially expensive and drawn-out procedure. A new medication currently costs about US$800 million to bring to market; this figure increases every five years. The US Food and Drug Administration (FDA) estimates that it takes an experimental medication an average of 12 years to go from the bench to the market[6]. Optimising a medication's qualities related to distribution, absorption, metabolism, elimination, and toxicity (ADMET) is the most challenging aspect of the entire drug discovery process. When developing a medication, the ADMET profile is crucial.

#### *2.1.1. Absorption*

The medicine needs to pass through the cell membrane in order to enter the systemic circulation, regardless of the absorption site. One of two main mechanisms—passive (basic) diffusion or carrier-mediated membrane transporters—can be responsible for this. Passive diffusion is the medication absorption process that occurs most frequently. The process by which a medication enters the bloodstream from its administration site is called absorption

*2.1.2. Distribution*

A medication can travel throughout the body after it is absorbed into the bloodstream. This process is classified as reversible and distributed. Volume of distribution (Vd), which can be obtained after intravenous (IV) injection, is the amount of substance that would have been available for the drug to disseminate everywhere in the body were it at the same concentration as in blood. Drug levels in plasma are monitored over time and a measured dose is given

*2.1.3. Metabolism*

The medication takes a while to metabolise. Through the kidneys and bile, drugs are either eliminated from the body unaltered or they may experience chemical alterations that facilitate their more straightforward excretion. This intricate process, which involves transporters and metabolising enzymes and has physiological ramifications for pharmacological and toxic effects, might be very important in drug design in order to more effectively find better therapeutic compounds. The body uses a complex biotransformation process called metabolism to change the structure of medications into new molecules called metabolites. This process is carried out by a variety of metabolising enzymes

*2.1.4. Excretion*

The medication does not secrete easily. Drug excretion is essentially the body's method of getting rid of drugs. The kidneys eliminate the majority of medications, but there are other ways as well, like through lungs, milk, tears, sweat, skin, or saliva.

*2.1.5. Toxicity*

The medications might not impact every other cell or tissue. Adverse drug reaction is another name for drug toxicity (ADR).When a patient has taken too many pharmaceuticals or when drugs mix with other drugs to cause negative side effects including decreased oxygen levels, respiratory suppression, and eventually death, the drugs turn into toxins [7].

Three different factors have an impact on medication development costs:

- Number of chemicals synthesised: Out of the 5,000–10,000 compounds that were examined, only one medication is commercialised.
- Nature of the lead molecule: Preparing the lead molecule using a costly method will result in a high production cost.
- New drug standards: There has been a significant increase in the requirements that regulatory bodies demand before releasing a medicine into the market. Every medicine required roughly $350 million during the discovery stage. $150 million more was spent on the Food and Drug Association's Phases I, II, and III. This raises the total to almost $500 million for each medication made available to customers.

It is important to know the following ideal features of a drug molecule.

- Drugs need to be efficient and safe.
- The medication needs to be long-acting, metabolically stable, and have good bioavailability.
- The medication ought to be safe and have few to no adverse effects.
- The drug should be distributed selectively to the disease state or target tissues.

Stages of drug discovery and development include.

- Target identification
- Target validation
- lead identification
- lead optimization
- Product characterization and Formulation and development
- Preclinical research
- Investigational New Drug
- New Drug Application
- Clinical trials
- Approval

**2.2. Identification of targets**

Target Identification: The first step in the discovery of a drug is determining the biological cause of a disease and the potential targets for intervention. This involves determining the function of a potential therapeutic target (gene, nucleic acid, protein) and its role in the disease. Characterising the molecular mechanisms that the target addresses is the next step after identifying the target; an ideal target should be safe, effective, meet clinical and commercial requirements, and be 'druggable.' The methods used for target identification may be based on concepts from molecular biology, biochemistry, genetics, biophysics, or other disciplines.[8]

Approaches used for identification of targets:

- Data mining using bioinformatics — identifying, selecting and prioritizing potential disease targets
- Genetic association — genetic polymorphism and connection with the disease
- Expression profile — changes in mRNA/protein levels
- Pathway and phenotypic analysis — In vitro cell-based mechanistic studies
- Functional screening — knockdown, knockout or using target specific tools.

### 2.3. Target validation

The process of certifying the intended molecular target, such as a small molecule's gene, protein, or nucleic acid, is known as target validation. Target validation entails the following procedures: establishing the structure activity relationship (SAR) of the small molecule's analogues; producing a drug-resistant mutant of the putative target; over- or knock-expressing the putative target; and keeping an eye on the established signalling systems that are downstream of the putative target .In The process of proving the selected target's functional significance in the illness manifestation is known as target validation. A drug's ability to function in a clinical context is the final test, even if it is highly valuable to validate a drug's toxicity and efficacy in a variety of disease-relevant cell models and animal models [8].

Two essential steps comprise the target validation process.

Reproducibility: Whether a pharmacological target is found by a particular technique or a review of the literature, the first step in ensuring its successful replication is to repeat the experiment. The target validation techniques encompass a range of methods such as system biology analysis, affinity chromatography, expression-cloning, protein microarray, reverse transfected cell microarray, biochemical suppression, siRNA, DNA microarray, and drug discovery [10].Give the ligand (drug) some variety .The intended setting:

- Target gene alteration (in vitro) genetic engineering using CRISPR to wipe out genes, shRNA, siRNA, and miRNA to knock down genes, and viral transfection of mutant genes to knock in genes
- Strong affinity antibodies that bind to the target and prevent further interactions
- Chemical methods for genomic encoding protein through chemical genomics [11]

## 3. Identification of lead

A synthetically stable, workable, drug-like molecule that exhibits appropriate specificity, affinity, and selection for the target receptor and is active in primary and secondary assays is referred to as a chemical lead. To achieve this, the structure-activity relationship must be defined, the synthetic feasibility must be established, and there must be some indication of in vivo efficacy and target activation. Qualities of a chemical lead include:

- SAR terminology
- Pharmacological potential (HERG, preliminary toxicity)
- Viability of synthesis
- Use specific mechanistic tests
- Evaluation of medication efflux potential and resistance in vitro
- Proof of the chemical class's effectiveness in vivo
- Based on preliminary toxicity or in silico investigations, the PK/toxicity of a class of chemicals is known.

A medication ability evaluation is frequently carried out in an effort to reduce the amount of compounds that fail throughout the drug development process. Making a chemical into a medication requires this evaluation in order to convert it from a lead molecule. In order for a chemical to be classified as druggable, it must possess the ability to attach to a particular target. Additionally, the compound's pharmacokinetic profile pertaining to its absorption, distribution, metabolism, and excretion should be taken into consideration. Ames test and cytotoxicity assay are two further assays that will assess the compound's possible toxicity in screens [12]

### 3.1. Lead candidate optimization

The process of designing a drug candidate after the identification of an initial lead chemical is known as lead optimisation. In order to develop a picture of how chemical structure and function are associated in terms of interactions with targets and metabolism, a prospective medication is subjected to an iterative set of synthesis and characterization steps. Lead optimisation is performed on the leads obtained from hit-to-lead screening assays in the early stages of drug discovery in order to find interesting compounds. As the last stage of early stage drug discovery, potential leads are analysed for a variety of characteristics, such as selectivity and binding mechanisms, during lead optimisation. Maintaining advantageous characteristics in lead compounds while addressing structural flaws in lead is the aim of lead optimisation. The chemical composition of principal compounds (small molecules or biologics) must be changed to increase target specificity and selectivity in order to generate a pre-clinical therapeutic candidate. Toxicological characteristics as well as pharmacodynamic and pharmacokinetic aspects are assessed. To precisely characterise the molecule and determine the course of optimisation, laboratories need to gather data on the toxicity, effectiveness, stability, and bioavailability of leads[13].

The procedure entails a series of iterative steps in the synthesis and characterisation of a possible drug to develop a presentation of the relationship between the chemical structure and function with regard to interactions with targets and metabolism. Chemical transformation of the hit structure is used to achieve this optimisation; changes are selected by using structure-activity analysis (SAR) and, if structural knowledge of the target is available, structure-based design.

### 3.2. Product characterization

Any novel pharmacological molecule that exhibits potential therapeutic efficacy is identified by its size, shape, power, weakness, application, toxicity, and biological activity. Early pharmacological research phases are useful for characterising the compound's mechanism of action.

### 3.3. Formulation and development

In order to create a bioavailable, stable, and ideal dosage form for a particular administration route, the physicochemical characteristics of active pharmaceutical ingredients (APIs) are characterised during the pharmaceutical formulation stage of drug development [14].

After discovering a molecule that shows promise for development, scientists run tests to learn more about:

- Its possible advantages and modes of action.
- How it is distributed, metabolised, eliminated?
- The ideal dosage and mode of administration.
- Adverse consequences, which are sometimes called toxicity.
- How it differs in its effects on other groups of individuals (based on factors like gender, race, or ethnicity)?
- How it works with other medications and medical procedures?
- How effective it is in comparison to comparable drugs?

## 4. Research before clinical trials

Pre-clinical research is a step in the drug development process that evaluates a medicine's safety and effectiveness in animal models before it is potentially applied to humans. The respective regulatory bodies must also approve the pre-clinical investigations. Only medications that have been proven to be both safe and effective will be approved by regulatory bodies, who also have an obligation to oversee the conduct of trials in an ethical and safe manner. A foundational set of guidelines for the technical requirements of appropriate preclinical drug development has been established by ICH. There are two methods for carrying out the pre-clinical trials: both toxicology and general pharmacology. The pharmacokinetic and pharmacodynamic aspects of drugs are the focus of pharmacology. Investigating undesired pharmacological effects in appropriate animal models and keeping an eye on them in toxicological research are crucial. To determine the safety and efficacious parameters pertaining to absorption, distribution, metabolism, and excretion, pharmacokinetic studies are crucial. These studies provide data on the rate of absorption for various routes of administration, which aids in the choice of dose form, distribution, rate of metabolism, and rate of elimination—all of which affect the drug's half-life. The medicine's half-life provides clarity on its safety profile, which is a requirement for regulatory agencies to authorise a drug. Given that the drug's bioavailability and affinity depend on it, the drug distribution mechanism clarifies the drug's therapeutic efficacy. The possibility of passing through stages of the biotransformation process and the creation of drug metabolites is provided by drug metabolism. It also aids in comprehending the enzymes and processes involved in biotransformation [15].

### 4.1. Investigational New Drug

A request will be made to the FDA to begin human clinical studies in the event that the results of preclinical trials indicate that the medicine is safe. To support the need for human drug testing, the IND application must include excellent quality pre-clinical data. IND applications are filed for clinical trials that are applied to around 85% of medications. The IND application must be submitted by an organisation known as a Sponsor. To discuss a number of topics, a Pre-IND evaluation can be scheduled with the FDA:

- The way that research on animals is designed, which is necessary to provide backing for clinical studies.
- The planned clinical study procedure.
- The investigational drug's chemistry, production, and quality control.

## 5. New drug application

An investigational new drug (IND) application can be filed by a drug sponsor or sponsor-investigator if a drug shows promise in pre-clinical testing. The pre-clinical drug information and data, investigator credentials, and a request for an exception from federal statutes that forbid the interstate transportation of unapproved medications are all included in this comprehensive application. Following approval, the medication is investigated, and the drug sponsor may then file a New Drug Application (NDA) with the FDA if it is shown to be safe and effective in the target demographic. The FDA decides whether to issue an indication and begin marketing a treatment after a thorough assessment that frequently includes a proposal from an outside committee. The medication can be investigated further in phase IV trials following final approval, when the safety and efficacy for the target population are tracked. Under the International Conference on Harmonisation of Technical Standards for Regulation of Pharmaceuticals for Human Use (ICH), attempts have been made to standardise this approval procedure throughout the United States, Europe, and Japan in order to expedite the examination and endorsement of foreign medication data [16].

### 5.1. Clinical experiments

Clinical trials are carried out on volunteers and are designed to provide targeted answers regarding the efficacy and safety of medications, vaccines, other therapies, or novel approaches to utilising existing treatments. Clinical trials adhere to a particular study protocol that the manufacturer, investigator, or researcher designs. When designing a clinical trial, developers take into account the requirements of each of the Clinical Research Phases and initiate the Investigational New Drug Process (IND), which is a prerequisite for starting clinical research. Prior to starting a clinical trial, scientists create study questions and objectives by reviewing available data about the medication. Next, they make a decision:

- The study's duration, the number of participants, and the participant selection criterion
- The dosage form's amount and method of administration
- Evaluation of the parameters
- Gathering and analysing data.

### 5.2. Types of clinical trials

#### *5.2.1. Treatment trials*

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

#### *5.2.2. Prevention trials*

Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes

#### *5.2.3. Diagnostic trials*

Conducted to find better tests or procedures for diagnosing a particular disease or condition

#### *5.2.4. Screening trials*

Test the best way to detect certain diseases or health conditions

#### *5.2.5. Quality of life*

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness

### 5.3. Phases of clinical trials

#### *5.3.1. Phase 0*

Phase 0 implicates investigative, first-in-human (FIH) trials that are conducted according to FDA guidelines. Phase 0 trials besides termed as human micro dose studies, they have single sub-therapeutic doses given to 10 to 15 volunteers and give pharmacokinetic data or help with imaging specific targets without exerting pharmacological actions. Pharmaceutical industries perform Phase 0 studies to pick which of their drug applicants has the preeminent pharmacokinetic parameters in humans [17]

#### *5.3.2. Phase 1*

In general, 20 to 80 healthy volunteers with the disease or condition participate in Phase I trials, which are the first tests of a drug with a smaller number of human volunteers. Patients are typically used only when a drug's mechanism of action suggests that it will

not be tolerated in healthy individuals; however, if a new drug is proposed for use in diabetes patients, researchers conduct Phase 1 trials in patients with that type of diabetes. Phase 1 studies gather data on pharmacodynamics in the human body and are subject to strict monitoring. To determine the maximum dosage of a medication that the body can withstand and its acute side effects, researchers modify the dosing schedule based on data from animal studies. Researchers learn more about the effectiveness of the drug, its mechanism of action, and the side effects that come with increasing its dosage as a Phase 1 trial progresses. The design of Phase 2 investigations requires this. Nearly 70% of medications advance to the next stage

*5.3.3. Phase 2*

Phase II trials are carried out on larger patient populations (few hundreds) with the goal of assessing the drug's effectiveness and enduring the Phase I safety evaluations. These trials are insufficient to determine if the medication will be effective. Researchers receive new safety data from phase 2 investigations. These data are used by researchers to build new Phase 3 research protocols, research methods, and research topics. 33% of medications make it to the next stage. The most significant contribution from Phase II clinical investigations is the discovery of therapeutic dosages for the extensive Phase III research

*5.3.4. Phase 3*

Phase 3 studies are planned by researchers to demonstrate whether or if a product offers a particular group of people an action benefit. These studies, which involve 300–3,000 people, are sometimes referred to as pivotal studies. The majority of the safety data are provided by phase 3 trials. Less frequent adverse effects might not have been identified by the prior investigation. However, because phase 3 trials involve a larger number of participants and last longer, it is more likely that long-term or unusual adverse effects may be found in the data. Roughly 25–30% of medications advance to the next stage of clinical investigation. An industry can submit an application to commercialise a medication if a drug developer provides evidence from preclinical and clinical trials, as well as from past testing, that the drug is safe and effective for the intended use. The FDA review team carefully examines all of the data that has been presented on the medication before deciding whether or not to approve it [18]

## 6. FDA Review and approval

The review team at FDA determines if an NDA is complete after receiving it. The review committee has the right to decline filing the NDA if it is incomplete. Once it is finished, the review panel will have six to ten months to decide whether to approve the medication. The FDA collaborates with the applicant to create and improve prescribing information if it finds that a medicine has been demonstrated to be safe and effective for the intended use. This is known as "labelling." Labelling provides a clear and impartial explanation of the drug's approval process and recommended usage.

However, before the medication is authorised for sale, there are frequently unresolved matters to be attended to. FDA will occasionally ask the developer to respond to inquiries using data that is already available. The FDA demands more research in other situations. The developer now has the option of proceeding with additional work or not. There are procedures for formally appealing FDA decisions, should a developer disagree.

## 7. Conclusion

In conclusion, drug design, encompassing candidate identification, synthesis, validation, optimization, screening, and therapeutic efficacy testing, is a multifaceted process crucial for developing medications that meet rigorous regulatory standards. The journey from initial discovery to commercialization is lengthy, intricate, and resource-intensive, with a staggering investment of $1 billion over twelve to fifteen years. The exploration of new biological targets and the use of advanced research tools are vital components in this endeavor. The review provides an overview of the intricate procedures involved in the discovery and development of novel drugs, emphasizing the challenges and investments required for the successful translation of scientific findings into clinically approved medicines.

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