International Journal of Pharmacognosy and Pharmaceutical Research

ISSN Print: 2664-7168
ISSN Online: 2664-7176
Impact Factor: RJIF 8
IJPPR 2024; 6(2): 08-20
www.pharmacognosyjournals.com
Received: 14-05-2024
Accepted: 13-06-2024

Parth Patel
Student of Pioneer Pharmacy College, Vadodara, Gujarat, India

Dr. Vaishali Sharma
Professor, Pioneer Pharmacy College, Vadodara, Gujarat, India

Dr. DB Meshram
Principal of Pioneer Pharmacy College, Vadodara, Gujarat, India

Corresponding Author:
Dr. Vaishali Sharma
Professor, Pioneer Pharmacy College, Vadodara, Gujarat, India

A review on drug design and development

Parth Patel, Dr. Vaishali Sharma and Dr. DB Meshram

DOI: https://doi.org/10.33545/26647168.2024.v6.i2a.72

Abstract
Drug design is a complex pharmaceutical science with a long history. Gradually, drug design has been transformed into a coherent and well-organized science with a solid theoretical background and practical applications. Now, drug design is the most advanced approach for drug discovery. It utilizes the innovations in science and technology and includes them in its wide-ranging arsenal of methods and tools in order to achieve the main goal: discovery of effective, specific, non-toxic, safe and well-tolerated drugs. Medicinal chemistry is facing new challenges in approaching precision medicine. Several powerful new tools or improvements of already used tools are now available to medicinal chemists to help in the process of drug discovery, from a hit molecule to a clinically used drug. Among the new tools, the possibility of considering folding intermediates or the catalytic process of a proteinase a target for discovering new hits has emerged. In addition, machine learning is a new valuable approach helping medicinal chemists to discover new hits. Other abilities, ranging from the better understanding of the time evolution of biochemical processes to the comprehension of the biological meaning of the data originated from genetic analyses, are on their way to progress further in the drug discovery field toward improved patient care. The present review aims to capture some of the most important milestones in the development of drug design, to outline some of the most used current methods. Without pretending to cover fully the wide range of drug design topics, the review introduces the reader to the content of Molecules' Special Issue "Drug Design-Science and Practice".

Keywords: Drug design, drug discovery and development, drug target, preclinical research

Introduction
A drug is a foreign molecule that affects biological processes and is used to prevent, diagnose or treat a disease. Drugs can be of natural origin or produced synthetically. The ideal drug should have a specific action, be safe, non-toxic, without side effects or as few as possible, be chemically and metabolically stable, be synthetically feasible, be soluble in water in therapeutic concentrations in order to avoid precipitation in the blood stream, be soluble in lipids as well, in order to be able to cross the lipid membranes and distribute around the body, and finally, be a unique molecule.

Developing a new drug from an original idea to the launch of a finished product is a complex process which can take 12-15 years and cost in excess of $1 billion. The idea for a target can come from a variety of sources including academic and clinical research and from the commercial sector. It may take many years to build up a body of supporting evidence before selecting a target for a costly drug discovery program. Once a target has been chosen, the pharmaceutical industry and, more recently, some academic centres would have streamlined a number of early processes to identify molecules which possess suitable characteristics to make acceptable drugs.

The process of drug discovery and development consists of three main stages: drug discovery, preclinical development and clinical trials. The drug discovery starts with the finding of a hit molecule. A hit is a molecule that elicits a desired activity in a screening assay. Then, the structure of this molecule is optimized in terms of improving affinity and selectivity, reducing toxicity, improving water and lipid solubility, improving ADME properties in general and converting the hit molecule into a lead molecule. The further optimization of the lead molecule delivers the fascinating path of drug discovery shares many features with a very complex and multidimensional maze, in which the medicinal chemist starts from the chemical space, more than 10^{60} small drug-like molecules of which only about 10^8 of have been synthesized so far, and has to find the way to the drug at the centre of the maze. A further intriguing property of this maze is that the walls and the centre keep moving with time. Obviously, the maze is the body, with its barriers and transporters, and the centre is the target site for a drug, which we call a receptor in its extensive sense.

The present review aims to capture some of the most important milestones in the development of drug design, to outline some of the most used current methods and to sketch the future perspective according to the author's point of view. Without pretending to cover fully the wide range of drug design topics, the review introduces the reader to the content of *Molecules'* Special Issue "Drug Design-Science and Practice".

Target

A "target" is produced within the pharmaceutical industry. Generally, the "target" is the naturally existing cellular or molecular structure involved in the pathology of interest where the drug-in-development is meant to act. However, the distinction between a "new" and "established" target can be made without a full understanding of just what a "target" is. This distinction is typically made by pharmaceutical companies engaged in the discovery and development of therapeutics [19].

"Established targets" are those for which there is a good scientific understanding, supported by a lengthy publication history, of both how the target functions in normal physiology and how it is involved in human pathology. This does not imply that the mechanism of action of drugs that are thought to act through a particular established target is fully understood [20]. Rather, "established" relates directly to the amount of background information available on a target, in particular functional information. In general, "new targets" are all those targets that are not "established targets" but which have been or are the subject of drug discovery efforts. The majority of targets selected for drug discovery efforts are proteins, such as G-protein-coupled receptors (GPCRs) and protein kinases.

Future trends in drug design

Any advance in science and technology finds immediately its application in medicine, in pharmacy, in drug discovery and development. Investments in drug design are worthwhile because as better is designed a given drug candidate during the experimental stage, as less likely is for the drug to fail in the late stages where the tests are more expensive, especially in the clinical trials. The COVID pandemic forced us to rethink how to accelerate the timelines of discovery and development of drugs and vaccines. New, effective, and less costly methods for drug discovery are required and AI has the potential to provide them. AI is able to gather and analyse large amounts of data in a short time, to select appropriate targets and complimentary ligands, to design tests and to perform them. The ultimate goal of the future drug design is to be able to design and develop a specific, non-toxic, effective and patient-tailored drug over a period of several hours. Although this goal seems fantastic at the moment, it is completely achievable in the near future.

When evaluating the potential of drug design and development approaches, one needs to remember that the field faces increasing challenges for a number of reasons including, but not limited to the ever-expanding regulatory burden, the shrinking pool of remaining new druggable therapeutic targets, and the increasing but unrealistic public expectation that there should be no side effects or abuse potential not to mention the problems of managing the needed highly multidisciplinary and collaborative research and development (R&D) work [16].

Among challenges, one needs to mention the importance of achieving an adequate balance between maximizing the desired local activity and minimizing the undesired systemic toxicity: (Soft drug) SDs have to be sufficiently stable to reach their intended targets/receptors and produce their desired effects while remaining sufficiently fragile to not cause unwanted systemic side effects. Several SD designs failed in the end because the metabolic degradation was too fast and acceptable activity could not be achieved. For ester-containing drugs, including SDs and prodrugs, a further challenge is that esterase activities vary strongly among species as well as among organs and tissues. This must be considered during preclinical evaluations, especially because rodents tend to hydrolyse much faster than humans (At least for aliphatic esters) [17].

Regarding the future of SDs, it is encouraging that there are many new projects initiated relatively recently, and more than a few will certainly lead to new clinically approved drugs. Some of the more intriguing one include soft JAK inhibitors, ROCK inhibitors, phosphodiesterase 4 (PDE4) inhibitors, TRPV1 modulators (Soft capsaicin analogues), HAD Cinhibitors, immune-modulators (e.g., soft cyclosporine and tacrolimus analogues), cytokine modulators (e.g., IL-5 inhibitors and TLR7 agonists), S1PR1 inhibitors (Soft fingolimod analogues), cannabinoids, and many others [18].

Types

Drug design, often referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the biomolecular target with which they interact and therefore will bind to it. Drug design frequently but not necessarily relies on computer modelling techniques. This type of modelling is sometimes referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the biomolecular target is known as structure-based drug design. In addition to small molecules, biopharmaceuticals including peptides and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed.

These several approaches are frequently utilised in the creation of pharmaceuticals

1. Mechanism-based drug design;
2. drug design based on structure
3. Ligand-based drug design
4. Receptor Based drug design
5. Computer based drug design

A. Drug design based on mechanisms: When the disease process is comprehended at the molecular level and the target molecule (s) are determined, drugs may be carefully developed to interact with target molecules in a way that disrupts the disease.

B. Structure-based Drug Design: This is one of the first methods in drug development.
- Contributed to the development of a new medicine. Calculations are used to learn more about the structural dynamics and electronic characteristics of ligands.
- Drug design based on structure may be loosely classified into two types.

1) Ligand-based.
2) Based on receptor.

1. Drug design based on ligands
- In the first category, ligands for a specific receptor are sought after.
- Several hundred ligand candidates are examined.
- This process is typically known as ligand-based drug design.
- The process of synthesising novel lead compounds is more efficient.

2. Based on receptor: Ligand molecules are built up within the confines of the binding pocket by assembling small pieces in a stepwise manner. These pieces can either be individual atoms or molecular fragments. The key benefit of such a method is that novel structures not contained in a nay database, can be suggested.

C. Ligand-based drug design
Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target. In other words, a model of the biological target may be built based on the knowledge of what binds to it, and this model in turn may be used to design new molecular entities that interact with the target. Alternatively, a quantitative structure-activity relationship (QSAR), in which a correlation between calculated properties of molecules and their experimentally determined biological activity, may be derived. These QSAR relationships in turn may be used to predict the activity of new analogy [39].

D. Receptor Based drug design
E. Computer based drug design
Techniques of drug design
1) X-Ray crystallography:
- Starting place for getting knowledge from mechanism drug design.
- Discover the structural details of molecules.
- Offers the vitally necessary coordinates required for the data processing by computer modelling systems.

2) Comparative protein modelling, sometimes referred to as homology modelling
Building atomic-resolution models of the target and a similar homologous protein's experimental three-dimensional structure.

Docking
- Docking seeks to match two molecules as closely as possible.
- It entails locating the proper key for the lock. Determine, given two biological compounds.
- The two molecules' ability to decide.

Goal
Being able to do a search on a database of molecular structures and get a list of all the molecules that can talk to the structure in the search.

Drug design with the help of computers may be used at any of the following stages of drug discovery:
1. Hit identification using virtual screening (structure- or ligand-based design)
2. Hit-to-lead optimization of affinity and selectivity (Structure-based design, QSAR, etc.)
3. Lead optimization of other pharmaceutical properties while maintaining affinity

In order to overcome the insufficient prediction of binding affinity calculated by recent scoring functions, the protein-ligand interaction and compound 3D structure information are used for analysis. For structure-based drug design, several post-screening analyses focusing on protein-ligand interaction have been developed for improving enrichment and effectively mining potential candidates:
- Consensus scoring [33, 34]
- Selecting candidates by voting of multiple scoring functions
- May lose the relationship between protein-ligand structural information and scoring criterion
- Cluster analysis [35, 36]
- Represent and cluster candidates according to protein-ligand 3D information
- Needs meaningful representation of protein-ligand interactions.

Ideally, the computational method will be able to predict affinity before a compound is synthesized and hence in theory only one compound needs to be synthesized, saving enormous time and cost. The reality is that present computational methods are imperfect and provide, at best, only qualitatively accurate estimates of affinity. In practice it still takes several iterations of design, synthesis, and testing before an optimal drug is discovered. Computational methods have accelerated discovery by reducing the number of iterations required and have often provided novel structures [37, 38].

Drug development process
The development of a pharmaceutical product requires a broad spectrum of scientific expertise to lead it through a complex pathway from discovery through characterization of quality, efficacy, and safety, which are the hallmarks of a successful drug product. A company must be highly proactive in setting targets for appraising and selecting a compound that has the highest probability of success. In addition, the compound and its therapeutic use must be consistent with the research and marketing goals of the company in order to leverage existing resources and experience. To ensure scientific and commercial success, it is critical to understand the drug development process

(Scheme 1) and the myriad tasks and milestones that are vital to a comprehensive development plan. Although Scheme 1 looks straightforward, the discovery and development of new medicines is a long, complicated process. It can take up to fifteen years to develop one new medicine from the earliest stages of discovery to the time the drug is available for treating patients.

The development of a pharmaceutical product requires a broad spectrum of scientific expertise to lead it through a complex pathway from discovery through characterization of quality, efficacy, and safety, which are the hallmarks of a successful drug product. A company must be highly proactive in setting targets for appraising and selecting a compound that has the highest probability of success. In addition, the compound and its therapeutic use must be consistent with the research and marketing goals of the company in order to leverage existing resources and experience. To ensure scientific and commercial success, it is critical to understand the drug development process (Scheme 1) and the myriad tasks and milestones that are vital to a comprehensive development plan.

Although Scheme 1 looks straightforward, the discovery and development of new medicines is a long, complicated process. It can take up to fifteen years to develop one new medicine from the earliest stages of discovery to the time the drug is available for treating patients.

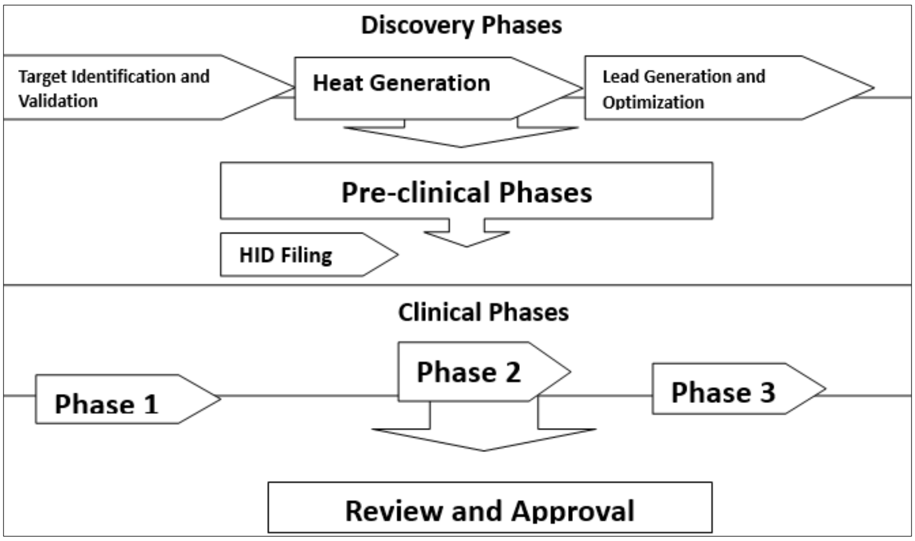
The development of a pharmaceutical product requires abroad spectrum of scientific expertise to lead it through a complex pathway from discovery through characterization of quality, efficacy, and safety, which are the hallmarks of a successful drug product.

A company must be highly proactive in setting targets for appraising and selecting a compound that has the highest probability of success. In addition, the com-pound and its therapeutic use must be consistent with the re-search and marketing goals of the company in order to lever-age existing resources and experience. To ensure scientific and commercial success, it is critical to understand the drug development process and the myriad tasks and milestones that are vital to a comprehensive development plan. Although Scheme 1 looks straightforward, the discovery and development of new medicines is a long, complicated process. It can take up to fifteen years to develop one new medicine from the earliest stages of discovery to the time the drug is available for treating patients.

Drug Development Phases There are three major phases in drug development: (i) Pre-discovery/discovery phase; (ii) pre-clinical phase; (iii) Clinical and development phase. After the compound is on the market, a possible “post-marketing” phase is also considered.

Drug Impurity It is usually a long way from the very early synthesis of an API molecule to the successful submission for registration of a new drug. Many hurdles have to be taken and many pitfalls may arise. One of the well-known complications in this respect may be the gradual change of the route of drug synthesis during development and therefore the possible change in the impurity profile. Such a change may have major consequences, in particular for the interpretation of toxicological and clinical studies [1]. The presence of impurities in APIs can have a significant impact on the quality and safety of drug products. The International Conference on Harmonization (ICH) guidelines [2, 3] achieved a great deal in harmonizing the definitions of impurities in new drug substances.

Given table below shows a brief summary of different phases of drug development along with the main objective of each phase and the approximate time it takes.



Scheme 1: Schematic representation of the drug development process

Analytical Techniques

From the beginnings of official pharmaceutical analysis, the aim of including assay methods in compendial monographs has been to characterize the quality of bulk drug materials by setting limits for their API content. The analytical techniques used in drug analysis are listed in Table 4 based on recent editions of European Pharmacopoeia (EP) [5] and United States Pharmacopoeia (USP) [6].

There are mainly 15 Analytical Techniques those are given below:

1. Titrimetric Methods
2. High Performance Liquid Chromatography
3. Gas Chromatography
4. Capillary Electrophoresis
5. Thin Layer Chromatography
6. High Performance Thin Layer Chromatography
7. Flow Injection Analysis

8. UV-Visible Spectrophotometry
9. Derivative Spectrophotometry
10. Fluorimetry
11. Near-Infrared Spectroscopy
12. Nuclear Magnetic Resonance Spectroscopy
13. Mass Spectrometry
14. Electrochemical Methods
15. Kinetic Methods

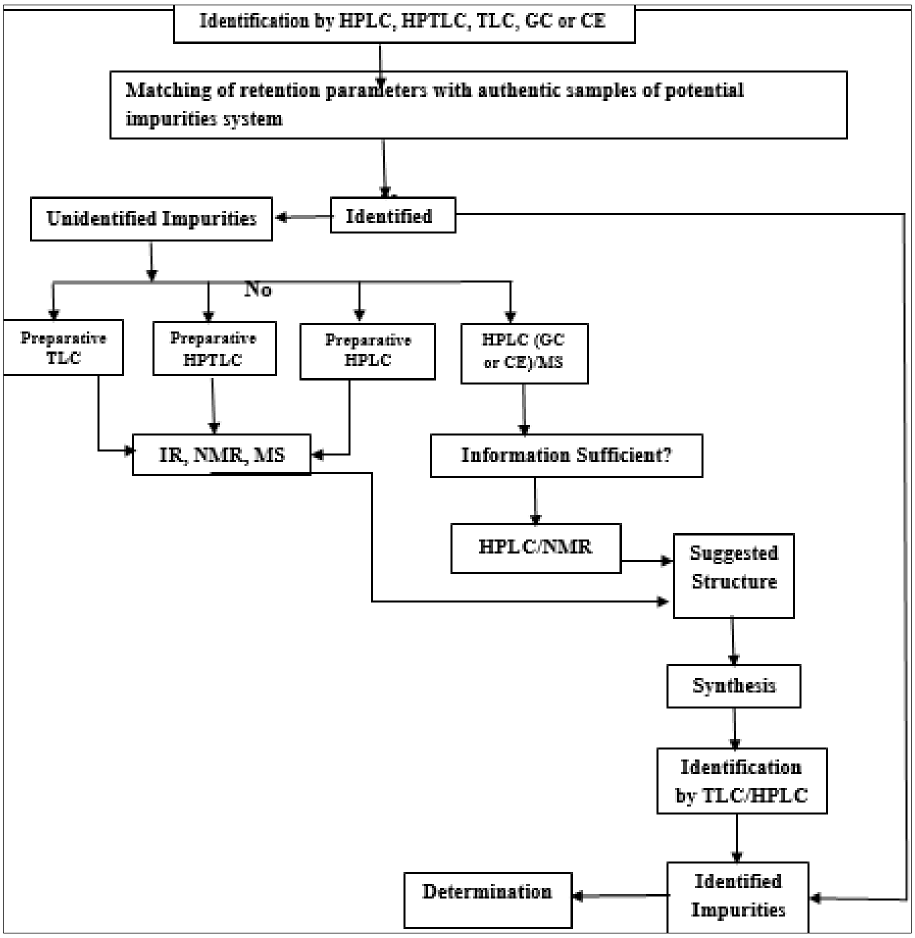


Fig 1: Proposed chart for profiling drug impurity.

Table 1: Drug Discovery and Development Process

	Discovery			**Pre-Clinical**		**Clinical**				**Review & Approval**
	Target ID & Validation	**Hit Generation**	**Lead Optimization**			**Phase 1**	**Phase 2**	**Phase 3**		
Years	1-2	1-2	1-2			1-2	1-2	2-3		1-2
Purpose	Chose a "drugable" target and establish its involvement in the disease	Find a compound that can act on the target and alter	Make "lead" compound more effective and safer	Determine efficacy and safety in animal models	IND: Obtain approval to test in human	Determine what the safe dose is (20-100 healthy volunteer)	Evaluate the candidate drug's effectiveness and examine the possible short-term side effects (100- 500 patient volunteers)	Verify the candidate drug's effectiveness and examine the possible long-term side effects (1000-500 0 patient volunteers)	NDA: Apply for New Drug Application	FDA reviews results of all testing to determine if the drug can be approved for patients to use

How to build a new designer drug?

In the beginning, it is a basic requirement to know what features an "ideal" drug should fulfil the following criteria's: [7]

- Must be safe,
- Should be well absorbed orally and bioavailable,
- Metabolically stable and with a long half-life,
- Nontoxic with minimal or no side pharmaceutical effects,
- Should have selective distribution to target tissues.

Cost of developing new drug

The cost of drug development is the full cost of bringing a new drug to market from drug discovery through clinical trials to approval [8]. Typically, companies spend tens to hundreds of millions of U.S. dollars on drug development. One element of the complexity is that the much-publicized final numbers often not only include the out-of-pocket expenses for conducting a series of Phase I-III clinical trials, but also the *capital costs* of the long period (10 or more years) during which the company must cover out-of-pocket costs for preclinical drug discovery. Additionally, companies often do not report whether a given figure includes the capitalized cost or comprises only out-of-pocket expenses, or both.

In an analysis of the drug development costs for 98 companies over a decade, the average cost per drug developed and approved by a single-drug company was $350 million. But for companies that approved between eight and 13 drugs over 10 years, the cost per drug went as high as $5.5 billion [9].

A new study in 2020 estimated that the median cost of getting a new drug into the market was $985 million, and the average cost was $1.3 billion, which was much lower compared to previous studies, which have placed the average cost of drug development as $2.8 billion [10].

Development: kinetics, drug disposition, safety, biomarkers, and efficacy

A biological target, even one with validating data, will only be useful for drug development if it is possible to make molecules that affect the target in a way that could be well tolerated and therapeutically useful. Furthermore, those molecules must be shown to have properties enabling them to act like a medicine when given to people. The molecules must have pharmacokinetic (PK) properties that enable there to be a predictable and consistent relationship between the dose of the drug given, exposure of the drug at the proposed site of action, and the binding of the drug to the target of therapeutic interest. The preclinical and later clinical studies needed to determine these PK properties of a proposed medicine are extensive and are particularly complex for CNS targets because of the blood-brain barrier. Fortunately, advances in medicinal chemistry and biological PK modelling have reduced the number of molecules entering clinical development with unsatisfactory PK properties [11].

Indeed, this represents an area in which the identification of a problem, unsatisfactory PK/bioavailability, has resulted in implementation of effective strategies to remedy a significant cause of drug development failures. During 1991, unsatisfactory PK/bioavailability properties of experimental drugs represented the most significant cause of attrition, accounting for approximately 40% of drug development failures. By 2000, however, this cause of attrition had fallen to less than 10% [12].

The appreciation that previously successful drugs typically have physicochemical and structural properties within certain ranges, and the application of this knowledge when considering the synthesis of new chemical entities, as proposed by Chis Lipinski in his “rule of five”, has positively impacted the development of both systemic and CNS drugs.

These studies should provide information on the emergence of adverse effects as compound dose is increased and provide guidance on compound-specific monitoring that might be needed in early clinical studies. Serious, irreversible adverse effects observed in these studies within some multiples of the projected efficacious dose are likely to prevent further development of the compound. Compound failure rates due to toxicity before human testing are relatively high, and account for as much as 30% of drug attrition occurring during the clinical stage of development, emphasizing the need to have backup compounds for targets that are well validated and of high strategic importance.

As indicated in Fig.2, only about 1 in 8 compounds entering clinical development in the pharmaceutical industry is eventually approved for marketing. As noted, the success rate is much lower for diseases such as AD. The recent review mentioned previously found that 244 compounds entered clinical development for AD between 2002 and 2012 with only one of them (Memantine-an N-methyl-D-aspartate receptor antagonist and symptomatic, rather than disease progression, drug) achieving regulatory approval; this is a failure rate of 99.6%. Even with the extraordinarily high failure rate in this disease, companies have continued to invest because the unmet medical need is great and there are scientifically plausible targets to pursue. Most (78%) of the 413 clinical trials (244 unique molecules) conducted of potential medicines for AD between 2002 and 2012 were supported by the pharmaceutical industry [15].

The Drug Development Process: It’s Long, Expensive and Risky

	Target to Hit	Hit to Lead	Lead Optim	Non-Clinical	Phase 1	Phase 2	Phase 3	Sub to Launch
# per Launch	24.3	19.4	14.6	12.4	8.6	4.6	1.6	1.1
P(TS)	80%	75%	85%	69%	54%	34%	70%	91%
Cycle time (yrs)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5
Cost/launch ($mil)	$94	$166	$414	$150	$273	$319	$314	$48
P(TS)AD[1]					28%	8%	1.8%	100%

Adapted from: SM Paul et al. Nature Reviews: Drug Discovery, 2010.
Costs are capitalized based on 11% cost of capital and in 2010 dollars.

[1]Adapted from: JA Cummings et al. Alz Res & Therapy, 2014.

Fig 2: A diagram of the stages of drug discovery and development with estimates of cost and duration.

Strategies for improved success in the drug discovery and development process: Several strategic approaches to enhance efficiency in the drug discovery and development process have been proposed, adopted, and exploited to varied extent in the pharmaceutical research and development (R&D) projects. They include exploitation of genomics and proteomics, the complementarity of phenotypic and target-based screening platforms, expanding the use of existing drug molecules through repurposing and repositioning, use of collaborative research, exploring under-served therapeutic areas, outsourcing approach, and pharmaceutical modelling and artificial intelligence.

Repurposing and repositioning of existing drug molecule

Drugs that have been developed for a specific therapeutic application may in the course of their clinical use potentially reveal beneficial effects in other therapeutic areas outside the scope of their original indications. These molecules may, therefore, be evaluated for use in the new diseases areas without requiring structural modifications (Drug repurposing). Alternatively, the drugs may require alteration of the primary molecular structure to accentuate a desirable side activity while diminishing the primary effect (Drug repositioning). The two approaches have the potential to resuscitate/rescue previously abandoned molecules as well as expanding the therapeutic applications of drugs in current use. Examples of successful applications of drug repurposing and repositioning are given in Table 2. They include the drug miltefosine which was developed in the 1980s as an antitumor agent but abandoned due to dose-limiting gastrointestinal side effects. The drug was refocused as an antileishmanial drug with significant success. Other potential applications for its use as an anti-infective agent have been established with the latest, being its use in the treatment of granulomatous amoebic encephalitis [21-25].

Table 2: Examples of successfully repurposed drugs.

Drug	Original indication	Repurposed indication
Zidovudine	Anticancer	Antiretroviral
Miltefosine	Anticancer	Leishmaniasis
Sildenafil	Pulmonary arterial hypertension	Erectile dysfunction
Thalidomide	Sedative	Erythema nodosum and multiple myeloma
Sirolimus	Immunosuppressant	Lymphoproliferative syndrome
Bupropion	Antidepressant	Smoking cessation aid
Rituximab	Anticancer	Rheumatoid arthritis
Raloxifene	Osteoporosis	Breast cancer
Gabapentin	Antiseizure	Post herpetic neuralgia
Eflornithine	Cancer	Hirsutism
Minoxidil	Antihypertensive	Alopecia
Pramipexole	Parkinson's disease	Restless leg syndrome

Sildenafil is another classic example of successful drug repurposing. Although primarily researched for and originally launched into the market for treatment of pulmonary arterial hypertension secondary to patent ductus arteriosus, sildenafil and other phosphodiesterase type 5 inhibitors are best known for their repurposed clinical indication, namely the management of erectile dysfunction. Similarly, drug repositioning was efficiently applied in the R&D of antidiabetic sulfonylureas from sulfonamide antibiotics where the hypoglycemic effect was enhanced while diminishing the antibacterial effect through systematic structural modifications. The key advantage of drug repurposing and repositioning is the faster development time since the pharmacokinetics and toxicological data as well as other pertinent information regarding the molecules are already available with resultant huge economic savings. Repurposing remains a viable approach to availing medicines for protozoan diseases and helminthic diseases. Many experimental drugs that were abandoned due to development issues or efficacy shortfalls could be resuscitated through repurposing/repositioning. Approaches to repurpose or reposition existing drugs include experimental screening and in silico approaches with the latter utilizing data of existing drugs to identify new molecule with the potential clinical application.

Preclinical Research

A clinical trial is a research investigation when a new treatment is first given to humans, with or without a disease, to establish if the drug is safe and effective at treating the disease.

Clinical trials, also known as clinical development or clinical studies, are research investigations that specifically involve human volunteers.

They are set up to establish the effectiveness and safety of new treatments including:

- Drugs
- Drug combinations
- Other forms of therapy such as surgery
- Preventative medicines such as vaccines

Before testing a drug in people, researchers must find out whether it has the potential to cause serious harm to humans. The preclinical studies are conducted on animal models under laboratory conditions [41].

The two types of preclinical research are:

- **In Vitro:** These experiments are conducted outside the animals in controlled laboratory conditions [42, 43]
- **In Vivo:** These experiments are conducted inside the animals [44, 45].

The various experiments conducted during these studies include [46, 47]:

- Single dose toxicity studies
- Repeated dose studies
- Safety pharmacology studies
- Genotoxicity studies
- Carcinogenicity studies
- Reproductive toxicity studies

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 [48, 49]:

- 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 analysed

Clinical trials follow a typical series from early phase 0, small-scale Phase 1 studies to late-stage, large scale Phase 3 studies:

Phase Studies:

Phase 0

- Usually, trials go straight to Phase I but sometimes a Phase 0 study will be run.
- Phase 0 involves a very small group of people who are given a very small dose of a drug.
- Phase 0 is looking to see:
- If the drug reaches its target, for example, a cancer?
- how the drug behaves in the body
- How target cells in the body respond to the drug, for example cancer cells.
- The main aim of Phase 0 is to speed up the development of promising new drugs. Testing some drugs in very small doses in humans gives a clearer idea of drug-target interactions than Doing the same in model organisms.

Phase 1 (First in Humans)

Trail Design [50, 51]:

- **Patients:** 20 to 100 normal healthy volunteer subjects in a single centre 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

Purpose

- Mechanism of action (ADME) and PK/PD studies
- Pharmacological effect
- Tolerability, side effects and toxicity at different doses
- Early evidence of efficacy
- Evaluates safety - Identify most likely potential toxicities and most likely dosage range Percentage of Drugs that Move to the next Phase 70% [52]

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, multicentre [53].

Purpose

- Dose range finding (Minimum and maximum effective dose).
- Effectiveness for the treatment of the disease or condition for which the drug is intended to use
- Maximum Tolerated Dose (MTD)
- Common short time side effects and risks
- Pharmacokinetics

Percentage of Drugs that Move to the Next Phase 3

Phase 3 (Therapeutic Confirmatory) - Pivotal Trails

Trail Design [54, 55].

- Patients: Several 1000 to 3,000 patients with the targeted disease/condition.
- Length of Study: 1 to 4 years
- Type of study: Randomized, placebo or active control, parallel double blinded study, multicentre

Purpose [92]

- Effectiveness (Large scale)
- Relative risk/benefit relationship
- Long term safety information - common side effects, drug interactions, age/rate/gender differences
- Dosing (For labelling)
- Assessment of safety and efficacy

Percentage of Drugs that Move to the Next Phase 25-30%
After completing the phase III trials 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 [56, 57]
Phase 4 (Post-Marketing Therapeutic Use)
Trail Design [58]

- **Patients:** Several hundred to thousand patients with the disease/condition.
- **Type of study:** Randomized, Placebo or active control, Multicentre

Purpose [59]

- Perform Quality of Life Trails (QOL) trails
- Perform pharmacoeconomic trails, Is the drug more effective that other available treatments
- Collection of long-term safety information, Epidemiological studies for safety and additional surveillance for unexpected or rare adverse effects
- Add line extensions, New dosage forms and formulation

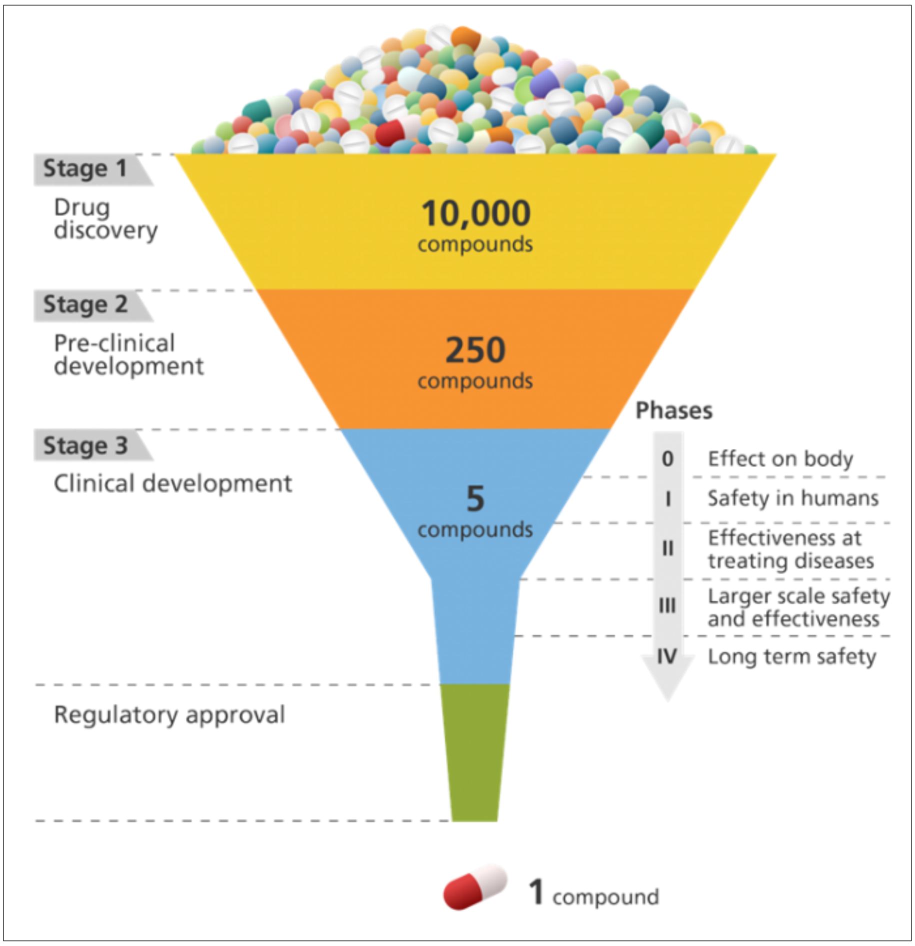


Fig 3: An illustration showing the different stages involved in developing a drug

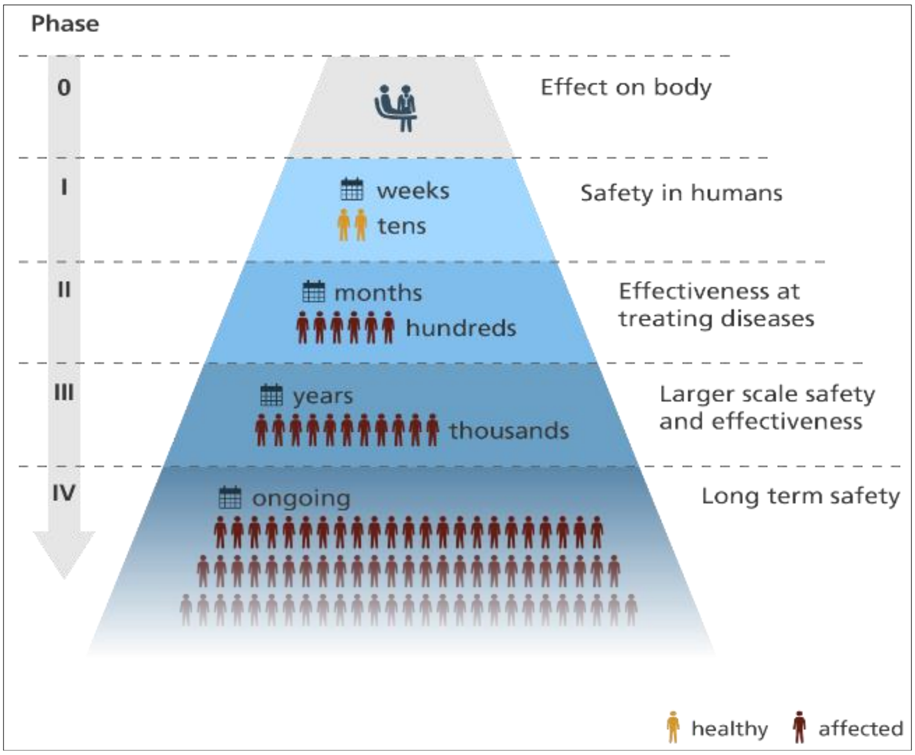


Fig 4: A flow diagram to show the different phases in a clinical trial

Factors to be consider during drug design

Especially in the part of older drug discovery where high sensitivity and rapid sample throughput is momentary and where samples are pooled or "cocktailed" ranked as dosing or analysis. Several factors are considered while making any chemical compound as a drug. When an entry of drug molecule is observed in the micro level of inner part of the body, it can able to alternate the biological pathway which affected human health also. So while making a new drug researcher should consider many case and effect which are mentioned below Especially in the part of older drug discovery where high sensitivity and rapid sample throughput is momentary and where samples are pooled or "cocktailed" ranked as dosing or analysis.

Several factors are considered while making any chemical compound as a drug. When an entry of drug molecule is observed in the micro level of inner part of the body, it can able to alternate the biological pathway which affected human health also. So while making a new drug researcher should consider many case and effect which are mentioned below Especially in the part of older drug discovery where high sensitivity and rapid sample throughput is momentary and where samples are pooled or "cocktailed" ranked as dosing or analysis. Several factors are considered while making any chemical compound as a drug. When an entry of drug molecule is observed in the micro level of inner part of the body, it can able to alternate the biological pathway which affected human health also. So while making a new drug researcher should consider many case and effect which are mentioned below Especially in the part of older drug discovery where high sensitivity and rapid sample throughput is momentary and where samples are pooled or "cocktailed" ranked as dosing or analysis. Several factors are considered while making any chemical compound as a drug.

When an entry of drug molecule is observed in the micro level of inner part of the body, it can able to alternate the biological pathway which affected human health also. So while making a new drug researcher should consider many case and effect which are mentioned below Especially in the part of older drug discovery where high sensitivity and rapid sample throughput is momentary and where samples are pooled or "cocktailed" ranked as dosing or analysis. Several factors are considered while making any chemical compound as a drug. When an entry of drug molecule is observed in the micro level of inner part of the body, it can able to alternate the biological pathway which affected human health also. So, while making a new drug researcher should consider many cases and effect which are mentioned below:

Safety and Efficacy

Human life is very costly as it never gets by any form and newly coming unwanted particles in the human body totally change their lifestyle. When an unwanted particle enters through the Gastrointestinal System or any mode, it may affect their immune system. Hence, it's very important to design and formulate a new drug molecule which should not intercept the functioning of the body. Drug companies seeking to sell a drug in the world must first test it. This test is obtained by various ways like a LIMIT TEST or ASSAY TEST. After successful completion of all these analysis drug manufacture may approach CDER (Centre for Drug Evaluation and Research) to certify safe and granted for human consumption. A team of CDER statisticians, chemists, pharmacologists, and other scientists gives their own thoughts in the company's work and proposed labelling.

Drugs should be well absorbed orally and bioavailable

Drugs that we take inside human body have the capacity to degrade it. So, the ultimate goal is to prepare drugs in such a way that after all degradation the quantity, or % which required in body got that. Bioavailability is the part of the administered drug that encounters the systemic circulation in a chemically unchanged form. For instance, if 500 mg of a drug is administered orally and 50 mg of this drug is absorbed unchanged, then the bioavailability is 0.1. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, one can measure the area under the curve (AUC). This curve reflects the extent of absorption of the drug. Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection.

Metabolic stability and half-life

Metabolic stability refers to the exhibition of compounds to bioactive in the reference of selecting and/or designing drugs with favourable pharmacokinetic properties. As we know that every drug has their own life in term of pharmaceutical effect inside the body and the main role of a pharmacist is to discover a new drug which has a long stability. But due to environmental conditions, these drugs may degrade easily. Since these factors plays a vital role in defining the pharmacological and toxicological profile of drugs. Optimization of metabolic stability is a crucial part of the drug discovery process because the ADME profile of the drug will be evaluated based on the scope and depth of the metabolic stability issues.

Non-toxicity and minimal side effects

Targeted drug delivery, is al so known as SD D (smart drug delivery), is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. So, the priority is to design drugs in such a manner that it only effects on the active site and not affect the rest parts of the body. For instance, Paracetamol (Acetaminophen) is a pain reliever and a fever reducer and work on the active site where the actual pain occurs, but beside it, it also blocks the COX 2 hormones which are produced by the pancreas to rebuild or reproduces the inner layer of the stomach. As a result, when we access paracetamol, it produces side effect as ulcer, so the goal should produce the drugs that have minimum side effect [26].

Drug Targets

A biomolecular target (Most commonly a protein or a nucleic acid) is a key molecule involved in a particular metabolic or signalling pathway that is associated with a specific disease condition or pathology or to the infectivity or survival of a microbial pathogen. Potential drug targets are not necessarily disease causing but must by definition be disease modifying. In some cases, small molecules will be designed to enhance or inhibit the target function in the specific disease modifying pathway. Small molecules (For example receptor agonists, antagonists, inverse agonists, or modulators; enzyme activators or inhibitors; or ion channel openers or blockers) will be designed that are complementary to the binding site of target. Small molecules (Drugs) can be designed so as not to affect any other important "off-target" molecules (Often referred to as anti-targets) since drug interactions with off-target molecules may lead to undesirable side effects. Due to similarities in binding sites, closely related targets identified through sequence homology have the highest chance of cross reactivity and hence highest side effect potential [27-30].

Most commonly, drugs are organic small molecules produced through chemical synthesis, but biopolymer-based drugs (Also known as biopharmaceuticals) produced through biological processes are becoming increasingly more common. In addition, mRNA-based gene silencing technologies may have therapeutic applications [31, 32].

Pharmacokinetics of drug design

- Drugs must be polar - To be soluble in aqueous conditions to interact with molecular targets
- Drugs must be 'fatty' - To cross cell membranes to avoid rapid excretion
- Drugs must have both hydrophilic and lipophilic characteristics
- Many drugs are weak bases with pKa 's 6-8.

Drug designing methods

Most important/critical step involved during drug designing is computation part i.e., a computational tool which increases the effectiveness of drug molecule inside the body by making it more precise, and pharmaceutically active. Salient features of such drug design software include [40].

Affinity Automated, flexible docking

- Applies the free energy of the ligand/receptor complex to spontaneously discover the optimal binding modes of the ligand to the receptor (Energy-driven method) through AutoDock (Automated Docking of Flexible Ligand to Receptors),
- It comprises of three distinct computer programs, including (i) AutoDock - performing ligand docking to a set of grids with the targeted protein, ii) Auto Grid for pre-calculating the atomic affinities, and (iii) Auto Tors set up will be treated as movable in the ligand,
- Deliver a programmed process for forecasting the interactions of ligand - biomolecular target and helps to narrow the conformational opportunities and identify the suitable structures,
- Applies a Monte Carlo (MC) simulated annealing (SA) technique for the exploration with an extraordinary energy estimation using grid-based molecular affinity potentials,
- Reported as a potential approach for docking a flexible ligand into the binding site of a static protein. Application of flexible docking includes virtual screening, protein-protein docking, combinatorial library design, X-ray crystallography, SBDD, and biochemical mechanism studies.
- SBDD (Structure-based drug design) program build to aid the design of combinatorial libraries,
- Prediction of the software is applied to find out nanomolar inhibitor Cathepsin Ds

Approaches for drug designing

The various approaches used in drug design include the following.

1. Random screening of synthetic compounds or chemicals and natural products by bioassay procedures.
2. Novel compounds preparation based on the known structures of biologically active, natural substances of plant and animal origin, i.e., lead skeleton.
3. Preparation of structural analogs of lead with increasing biological activity and
4. Application of bio isosteric principle.

The current trend in the drug design is to develop new clinically effective agents through the structural modification of lead nucleus. The lead is a prototype compound that has the desired biological or pharmacological activity but may have many undesirable characteristics, like high toxicity, other biological activity, insolubility or metabolism problems. Such organic leads once identified, are easy to exploit. This process is rather straightforward. The real test resides with the identification of such lead real test resides with the identification of such lead bioactive positions on the basic skeleton of such leads.

Conclusion

Drug design, regularly referred to as rational drug layout or tritely rational layout, is the imaginative procedure of locating new medicines primarily based totally at the expertise of a organic goal. Clinical improvement, additionally referred to as scientific trials, includes trying out the drug on human volunteers to offer greater records approximately by the stop of the scientific improvement phase, maximum of the investigational new capsules will had been removed at the grounds of protection and effectiveness. Its protection and effectiveness. The last purpose of drug improvement is to convey a brand-new compound with confirmed healing impact to the market.
New drugs are an important part of modern medicine with the emergence of diseases. The advent of new pharmacologic treatments and introduction of novel medications have reduced the serious complications of peptic ulcer disease. Progress in the medicinal chemistry field, we need, in addition to new targets, a more accurate description of their different conformations and possibly of the evolution of the target structure with time during the biological process. This, combined with the knowledge of the genetic variants of the targets, will lead to an increased number and precision of the "magic bullets" that are drugs, and allow the progress of precision medicine. Understanding the process can promote innovation, help physicians assess new products, underline the importance of reporting adverse drug events and provide physicians with the information to educate patients about participating in a clinical trial. [60]

Reference

1. Bauer M, de Leede L, Van Der Waart MV. Eur J Pharm Sci. 1998;6:331-335.
2. International Conference on Harmonization (ICH). Impurities in New Drug Substances, ICH Guideline Q3A (R); c2002.
3. International Conference on Harmonization (ICH). Impurities in New Drug Substances, ICH Guideline Q3B (R); c2002.
4. Raghu MS, Basavaiah K, Prashanth KN, Vinay KB. Int. J Anal Chem. 2013;2013:697651.
5. European Directorate for the Quality of Medicines. The European Pharmacopoeia. 4th Ed. Strasbourg: Council of Europe; c2002.
6. United States Pharmacopeial Convention. The United States Pharmacopoeia. 27th Ed. Rockville, MD: The USP Convention Inc.; c2004.
7. FDA. Centre for Drug Evaluation and Research - Drug Safety Priorities. 2017.
8. Sertkaya A, Wong HH, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United

States. Clin Trials. 2016;13(2):117-26. DOI: 10.1177/1740774515625964. PMID 26908540.
9. Herper M. The cost of creating a new drug now $5 billion, pushing Big Pharma to change. Forbes, Pharma & Healthcare. 2013 Aug 11. Available from: https://www.forbes.com
10. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. JAMA. 2020;323(9):844-53. PMID 32125404. DOI: 10.1001/jama.2020.1166.
11. Shaffer CL. Defining neuropharmacokinetic parameters in CNS drug discovery to determine cross-species pharmacologic exposure-response relationships. Annu Rep Med Chem. 2010;45:55-70.
12. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov. 2004;3:711-7115.
13. Center for Drug Evaluation and Research (CDER), U.S. FDA. General Principles of Validation. Washington: U.S. FDA; c1987.
14. Wegscheider H. Validation of analytical methods. In: Guenzler H, editor. Accreditation and Quality Assurance in Analytical Chemistry. Berlin: Springer Verlag; c1996.
15. Cummings J, Morstof T, Zhong K. Alzheimer's disease drug development pipeline: few candidates, frequent failures. Alzheimers Res Ther. 2014;6:37-44.
16. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov. 2012;11(3):191-200.
17. Egan TD. Is anesthesiology going soft? Trends in fragile pharmacology. Anesthesiology. 2009;111(2):229-230.
18. Aprile S, Serafini M, Pirali T. Soft drugs for dermatological applications: recent trends. Drug Discov Today. 2019;24(12):2234-2246.
19. Rask-Andersen M, Almén MS, Schiöth HB. Trends in the exploitation of novel drug targets. Nat Rev Drug Discov. 2011 Aug;10(8):579-5790. DOI: 10.1038/nrd3478.
20. US Food and Drug Administration. The drug development process: Step 1, Discovery and development; c2018 Jan 4. Available from: https://www.fda.gov
21. Pushpakom S, Iorio F, Eyers PA, *et al*. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2018;18:41-58. Doi:10.1038/nrd.2018.168.
22. Cha Y, Erez T, Reynolds IJ, *et al*. Drug repurposing from the perspective of pharmaceutical companies: drug repurposing in pharmaceutical companies. Br J Pharmacol. 2018;175:168-180. DOI: 10.1111/bph.13798.
23. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov. 2004;3:673-683. DOI: 10.1038/nrd1468.
24. Charlton RL, Rossi-Bergmann B, Denny PW, Steel PG. Repurposing as a strategy for the discovery of new anti-leishmanials: the state-of-the-art. Parasitology. 2018;145:219-236. DOI: 10.1017/S0031182017000993.
25. Sindermann H, Engel J. Development of miltefosine as an oral treatment for leishmaniasis. Trans R Soc Trop Med Hyg. 2006;100-120. DOI: 10.1016/j.trstmh.2006.02.010.
26. Kelder J, Grootenhuis PD, Bayada DM, Delbressine LP, Ploemen JP. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. Pharm Res. 1999;16:1514-1519.
27. Dixon SJ, Stockwell BR. Identifying druggable disease-modifying gene products. Curr Opin Chem Biol. 2009 Dec;13(5-6):549-555.
28. Imming P, Sinning C, Meyer A. Drugs, their targets and the nature and number of drug targets. Nat Rev Drug Discov. 2006 Oct;5(10):821-834.
29. Anderson AC. The process of structure-based drug design. Chem Biol. 2003 Sep;10(9):787-797.
30. Recanatini M, Bottegoni G, Cavalli A. In silico antitarget screening. Drug Discov Today Technol. 2004 Dec;1(3):209-215.
31. Wu-Pong S, Rojanasakul Y. Biopharmaceutical Drug Design and Development. 2nd Ed. Totowa, NJ: Humana Press; c2008.
32. Scomparin A, Polyak D, Krivitsky A, Fainaro SR. Achieving successful delivery of oligonucleotides - From physico-chemical characterization to *in vivo* evaluation. Biotechnol Adv. 2015 Apr;33(6):1294-1309.
33. Liang S, Meroueh SO, Wang G, Qiu C, Zhou Y. Consensus scoring for enriching near-native structures from protein-protein docking decoys. Proteins. 2009 May;75(2):397-403.
34. Oda A, Tsuchida K, Takakura T, Yamaotsu N, Hirono S. Comparison of consensus scoring strategies for evaluating computational models of protein-ligand complexes. J Chem Inf Model. 2006;46(1):380-391.
35. Deng Z, Chuaqui C, Singh J. Structural interaction fingerprint (SIFt): A novel method for analyzing three-dimensional protein-ligand binding interactions. J Med Chem. 2004 Jan;47(2):337-344.
36. Mari S, Aizawa M, Zhang J, Fukuzawa K, Mochizuki Y, Iwasawa Y, *et al*. VISCANA: visualized cluster analysis of protein-ligand interaction based on the ab initio fragment molecular orbital method for virtual ligand screening. J Chem Inf Model. 2006;46(1):221-230.
37. Singh J, Chuaqui CE, Boriack-Sjodin PA, Lee WC, Pontz T, Corbley MJ, *et al*. Successful shape-based virtual screening: the discovery of a potent inhibitor of the type I TGFβ receptor kinase (TβRI). Bioorg Med Chem Lett. 2003 Dec;13(24):4355-4359.
38. Becker OM, Dhanoa DS, Marantz Y, Chen D, Shacham S, Cheruku S, *et al*. An integrated in silico 3D model-driven discovery of a novel, potent, and selective amidosulfonamide 5-HT1A agonist (PRX-00023) for the treatment of anxiety and depression. J Med Chem. 2006 Jun;49(11):3116-3135.
39. Tropsha A. QSAR in Drug Discovery. In: Reynolds CH, Merz KM, Ringe D, editors. Drug Design: Structure- and Ligand-Based Approaches. 1st ed. Cambridge, UK: Cambridge University Press; c2010. p. 151-64.
40. Mandal S, Moudgil MN, Mandal SK. Rational drug design. Eur J Pharmacol. 2009;625:90-100.
41. Baumeister AA, *et al*. On the exploitation of serendipity in drug discovery. Clin Exp Pharmacol; c2013, 3.

42. Cheng SB. The nervous system: an ideal therapeutic target for anti-schistosomal drug discovery. Trop Med Surg; c2013, 1.
43. Pomin VH. Current status of fucanomics and galactanomics in drug discovery and glycomics. J Glycobiol. 2013;2:104.
44. Cheng F, Vijaykumar S. Applications of artificial neural network modeling in drug discovery. Clin Exp Pharmacol; c2012, 2.
45. Deshmukh R. Modeling and simulation in drug discovery and development. J Bioequiv Availab. 2012;4:27-28.
46. Yang Z, Marotta F. Pharmacometabolomics in drug discovery & development: applications and challenges. Metabolomics; c2012, 2.
47. Gonzalez-Sabin J. Natural products: back to the future in drug discovery. Biochem Pharmacol (Los Angel). 2012, 1.
48. Panda AK. Ayurveda treatment outcomes for osteoarthritis. J Homeop Ayurv Med; c2015, 4.
49. Jayram H, *et al*. Ayurvedic regimen in hemorrhagic ovarian cyst without peritoneal bleeding: A case report. J Homeop Ayurv Med. 2014;3:164.
50. Panda AK. Complementary and alternative medicine is mother medicine. Altern Integr Med; c2013, 3.
51. Aliev G, *et al*. Mitochondria specific antioxidants and their derivatives in the context of the drug development for neurodegeneration and cancer. Drug Des. 2013;2:103.
52. Sun L. Peptide-based drug development. Mod Chem; c2013 Appl, 1.
53. Amin A, Lowe L. Plant-based anticancer drug development: Advancements and hurdles. J Gastroint Dig Syst; c2012, 2.
54. Akkol EK. New strategies for anti-inflammatory drug development. J Pharmacogenomics Pharmacoproteomic; c2012, 3.
55. Luisa BM, *et al*. Challenges faced in the integration of pharmacogenetics/genomics into drug development. J Pharmacogenomics Pharmacoproteomics. 2012;3:108.
56. Ansari R. Defining the role of single nucleotide polymorphic (SNP) in drug development and toxicity. J Drug Metab Toxicol; c2012, 3.
57. Khan A, Khan AU. Biomarker discovery and drug development: A proteomics approach. J Proteomics Bioinform. 2012;5:5-6.
58. Sang N. Biochemistry, drug development and open access. Biochem Pharmacol. 2011, 1.
59. Nicolson TJ, *et al*. The post-transcriptional regulator EIF2S3 and gender differences in the dog: implications for drug development, drug efficacy, and safety profiles. J Drug Metab Toxicol. 2010;1:101.
60. Dev Bukhsh Singh. Success, limitation and future of computer-aided drug designing. Transcr Open Access; c2014, 4.