CHAPTER 1

Newer Paradigms in Drug Development

OVERVIEW

INTRODUCTION

Drug discovery is the process of identifying a new drug molecule from the library of various drug candidates screened. After a new drug molecule is discovered, it undergoes various stages of preclinical and clinical testing to become a commercial drug product, this process is called drug development. Huge costs ranging from $ 150 million to several billion are spent to bring a new drug to market. Average time in developing a new drug that reaches market ranges from 10-15 years. Apart from being increasingly expensive and time consuming, pharmaceutical innovation is highly inefficient. Of the total 10,000 candidate compounds screened, only 1 drug molecule succeeds in reaching the market (Figure 1.1). Hence it becomes extremely important for different phases of drug development to be executed in an efficient and effective way to reduce high attrition rates.

APPROACHES TO DRUG DISCOVERY

In ancient times, most drugs were discovered ***serendipitously*** as an observation of potential of certain plant extracts or chemicals to exert physiological or functional alterations in animals

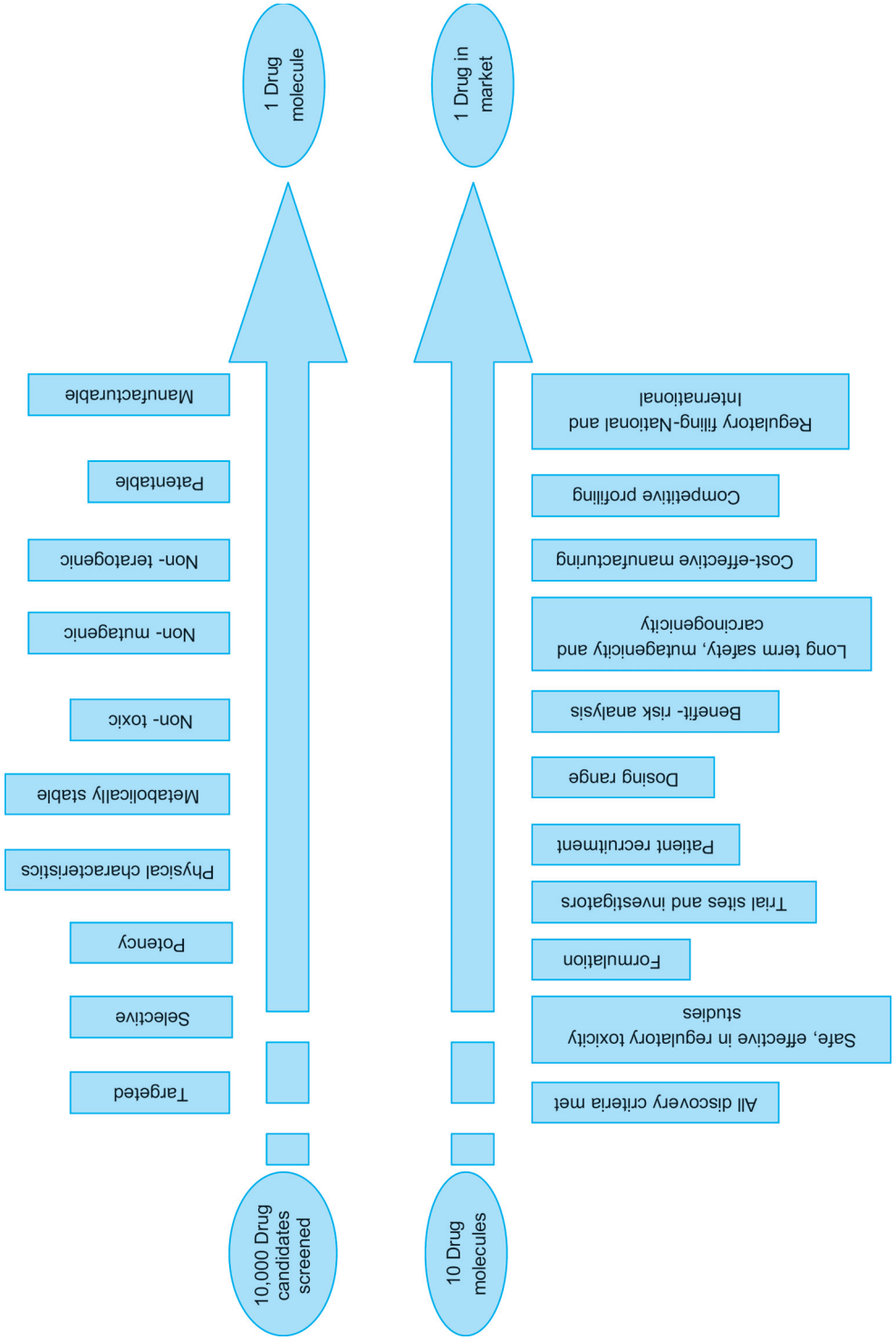


Figure 1.1 Drug discovery and development process.

or humans. Later came the era of ***classical or forward pharmacology***, also called phenotypic drug discovery (PDD). In classical pharmacology, the process of drug discovery moved from functional studies to repeated screenings, towards genomic research (i.e. drug to gene). Various steps involved in classical pharmacology have been outlined in Figure 1.2.

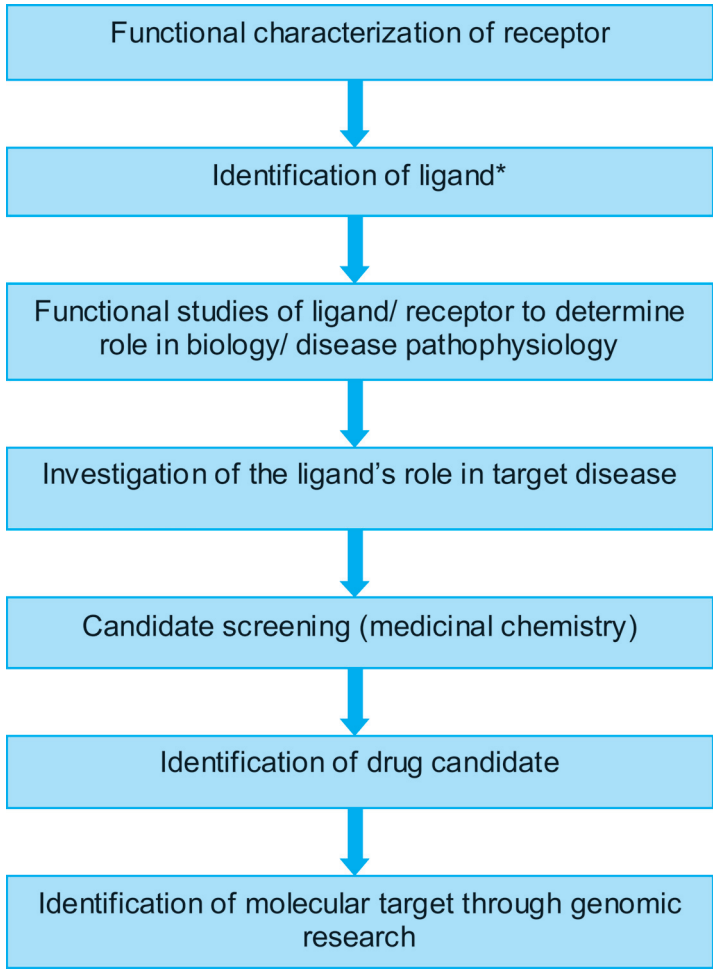


Figure 1.2 Drug discovery steps in classical or forward pharmacology.

***Approaches for ligand identification: (1) *random screening for biological activity of natural sources,* (plants, animals, minerals, microorganisms), *libraries of previously discovered chemical entities, peptides, nucleic acids or other organic molecules*; (2) *random or targeted chemical synthesis* like synthesizing chemical analogues of natural or synthetic compounds having well- defined pharmacological activity; (3) *rational designing of a new drug molecule on the basis of biologic mechanisms and structure of receptor* e.g. computer-assisted design (CAD), combinatorial chemistry, QSAR (Quantitative structure activity relationship) analysis, molecular modeling, biotechnology etc.**

Figure 1.3 illustrates an example of the discovery of tamsulosin by classical approach.

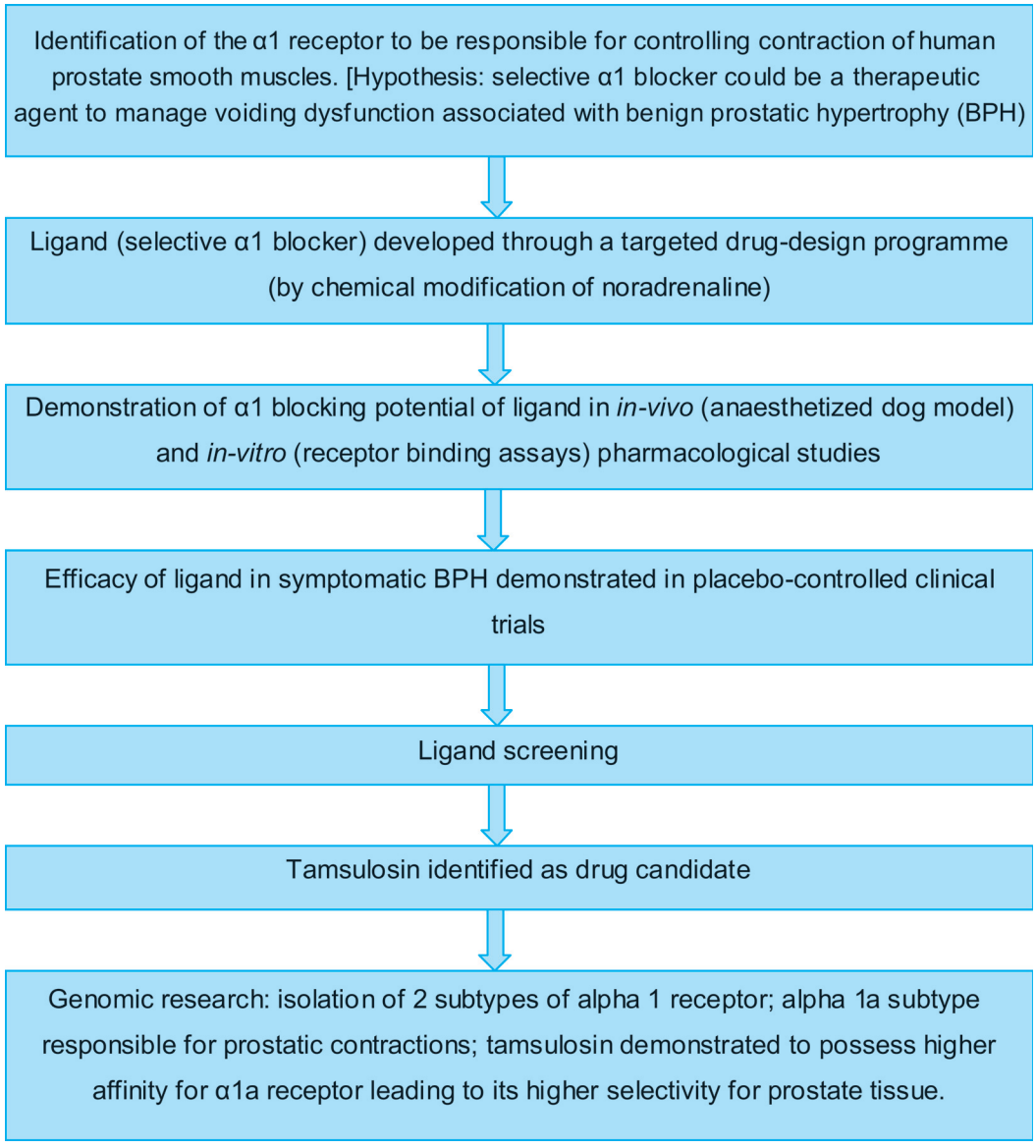


Figure 1.3 History of discovery of tamsulosin by classical pharmacology approach.

Nowadays, most of the drug discovery is carried out by ***reverse pharmacology***, also called target based drug discovery (TDD). In reverse pharmacology, drug discovery process starts with genomic research followed by repeated screenings and finally functional studies (i.e. gene to drug). The stepwise approach followed in reverse pharmacology is depicted in figure 1.4.

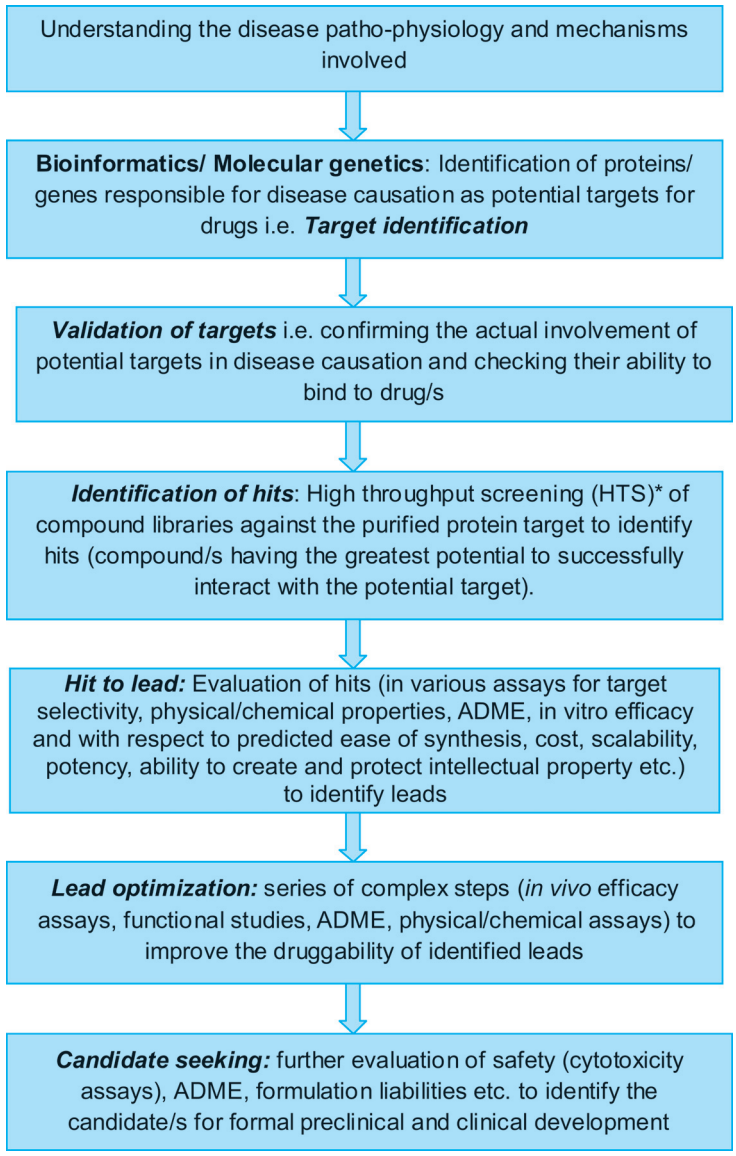


Figure 1.4 Steps in the process of drug discovery by reverse pharmacology.

***High throughput screening (HTS): HTS is the process by which large compound libraries are screened for activity against biological targets by means of automation, miniaturized assays, automated robotic techniques and highly sensitive detectors. A key component of HTS is micro-titer plate with 96 (or multiples of 96) wells containing test items. Compared to conventional screening methods, HTS has been demonstrated to be 1,000 times faster and utilizing 1 millionth cost allowing efficient and less time consuming screening.**

Drug discovery through reverse pharmacology approach takes about 2-3 years on an average which is time effective as compared to classical pharmacology approach which usually takes more than 5 years to discover a new drug molecule.

CRITICAL PATH INITIATIVE

"Critical Path Initiative" was launched by the US Food and Drug Administration (FDA) in 2004 with an aim to enhance the efficiency of drug development process by the adoption of certain modern scientific technologies. Critical Path has been defined as the whole process of new drug molecule identification and its development through various stages till it is launched as a therapeutically active drug product (Figure 1.5).

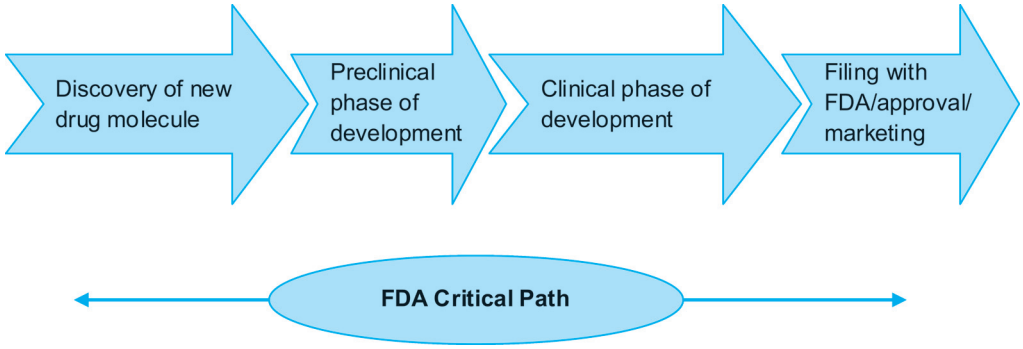


Figure 1.5 The FDA Critical Path for development of new medicinal products.

During its path to marketing, a new candidate drug emerging out of the drug discovery phase has to go through rigorous series of evaluations for its potential efficacy and safety. Besides, it should also be amenable to production on a large scale. Figure 1.6 represents various activities in different dimensions which need to be successfully completed along the critical path.

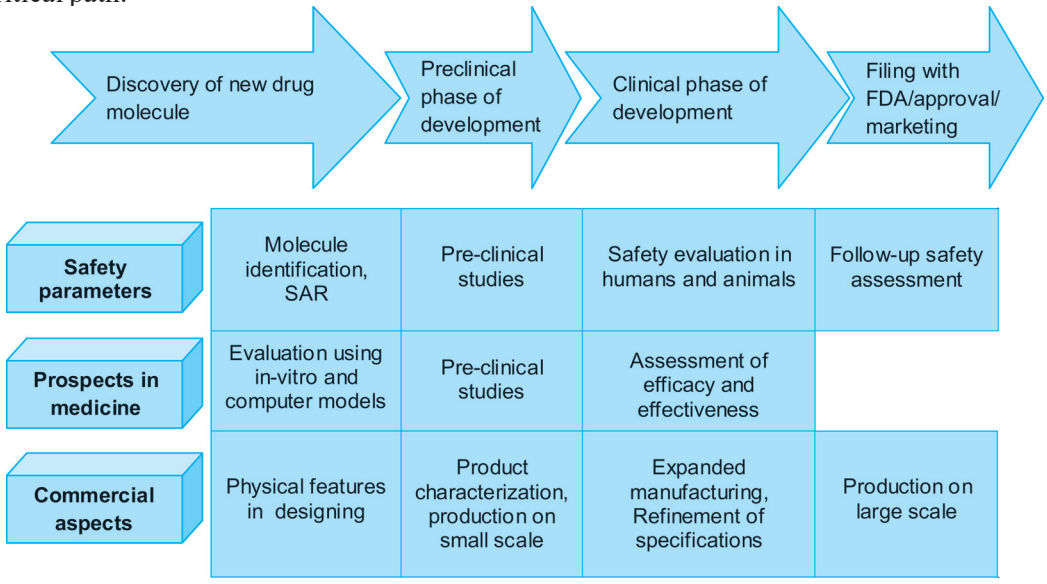


Figure 1.6. Activities in three dimensions in the Critical Path (SAR: Structure Activity Relationship).

Various strategies described in FDA Critical Path Initiative which can be incorporated during the drug development process include:

- Novel strategies like modeling and simulation.
- Identification and validation of new biomarkers.
- Streamlining clinical trials.
- Embracing adaptive designs in clinical trials. (For detailed discussion on adaptive designs, kindly refer to the chapter on "Designs used in clinical trials").
- Clinical trial modernization.

MODELING AND SIMULATION

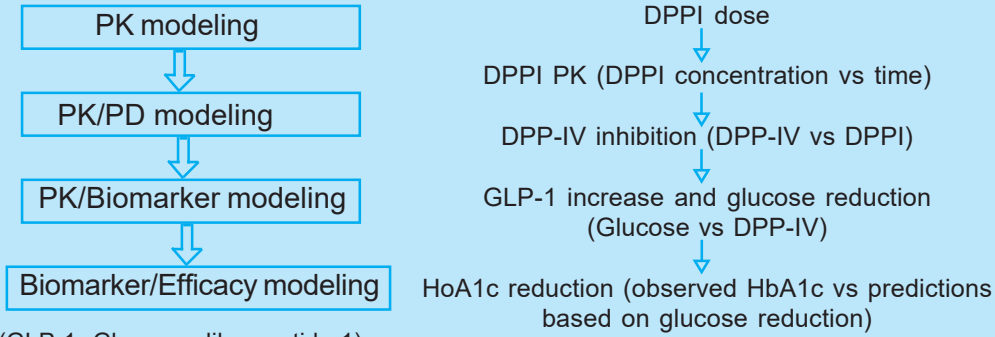
As addressed in the critical path initiative, adoption of model-based approaches has great potential in increasing the efficiency of drug development process. Modeling is the process of building mathematical constructs/models by using available data, information and knowledge to describe the aspects of a system. Simulation is building upon these models by incorporating random variability in an attempt to understand its long-term impact.

Uses of modeling and simulation

- The advanced developments in the field of modeling and simulation are helpful in determining a dose and dosage regimen which attains the desired clinical benefit and has minimal disagreeable side effects. In this context, biological and pharmacological modeling are usually applied. *Biological modeling* is the application of various genetic, biochemical, physiological and pathological processes involved in the underlying disease condition and its pharmacotherapy. *Pharmacological modeling* provides guidance on clinical trial design, appropriate dose selection and drug development approach. An example of a case scenario using modeling for dose regimen selection is given in box 1.1.
- Modeling and simulation techniques can be applied to understand the dose and time relationship of efficacy and toxicity endpoints.
- Combined with Bayesian methods, these techniques have been extremely helpful in providing a persistent surge of knowledge across various drug development phases. For instance, the data from preclinical studies can be utilized to build models and predict clinical parameters in advance.
- Modeling also enables the utilization of external information to determine variables of interest in the population. For instance, values of safety parameters at baseline from data can be incorporated with information from external sources to increase the efficiency of detection of safety signals.

Box 1.1 Case scenario: Modeling for dose selection of a DPPI (Dipeptidyl peptidase–IV inhibitor) in diabetes mellitus.

In this case, a number of mathematical models can be linked to study different measures in the sequence of events occurring after DPPI administration, to predict the effect of altering dose or dosage regimen of DPPI on clinical end-point as estimated by glycosylated hemoglobin (HbA1c), a surrogate marker of efficacy.



(GLP-1: Glucagon like peptide-1)

Input: PK (Pharmacokinetic) data, biomarker data and outcome data
Output: Predictions of clinical outcomes for different dosing regimens

Modeling and simulation hold crucial importance in various stages of the drug development process (Table 1.1).

Table 1.1 Role of modeling and simulation in different stages of drug development.

Preclinical development

- Development of mechanism based models
- Evaluation of potency, efficacy and intrinsic activity in -vivo
- Compartmental modeling
- Development of biomarkers/ surrogates and pre-clinical models for efficacy and safety parameters
- Refinement of dosage form and dosage regimen
- Extrapolation of data from preclinical studies to humans
- Allometric scaling

Clinical development

- Selection of initial dose /dose escalation
- Description of dose-concentration-response relationships
- Evaluation of dosage forms and administration pathways
- In vivo estimation of active metabolites
- Study food effects, gender based effects
- Drug-drug/ drug-disease interactions
- Evaluation of drug analogues
- Disease progression models
- Population PK/PD
- Simulations to predict PK/PD
- Trial forecasting
- Post marketing PK/PD

PHARMACOMETRICS

This is the scientific discipline which relies on the application of mathematical models built on the basis of disease, biology, pathophysiology, and pharmacology for quantification of various interactions between pharmacological therapies and patients. Different models in pharmacometrics on the basis of their application include "exposure–response models," "disease models," "trial execution models" etc.

Pharmacokinetic–Pharmacodynamic Modeling (PK–PD modeling) or Exposure–Response Modeling

This approach is based on mathematical models linking the drug's pharmacokinetics (PK) i.e. concentration-time relationship to its pharmacodynamics (PD) i.e. relationship between effective concentration at target site and magnitude of effect. The integrated PK-PD models, thus obtained, provide an illustration of the entire time course of the effect intensity after administration of a given dosing regimen. Many softwares are available for PK-PD modeling e.g. Phoenix, Winnolin, Pmetrics, etc.

Translational PK-PD modeling

This approach employs the integration of data from in-silico, in vitro, and animal or in-vivo preclinical studies with models constructed on the basis of mechanism to predict the effects of new therapies in humans and across various biological levels (Figure 1.7). Such translational models have various applications in drug development process like identification of lead molecules and their optimization, estimation of starting dose for first in man studies, selection of designs of exploratory and proof-of-concept clinical trials of new drugs and their combinations.

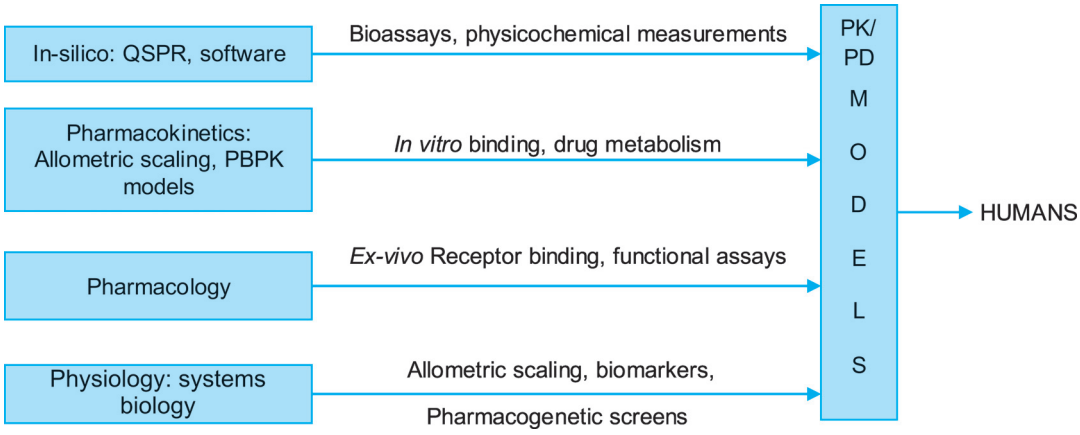


Figure 1.7 Components of PK-PD models for translating pre-clinical data to clinical pharmacology data (QSPR- Quantitative structure PK/PD relationships; PBPK-Physiologically based pharmacokinetic).

MODEL BASED DRUG DEVELOPMENT (MBDD)

It is defined as the development and implementation of pharmacological and statistical models from preclinical and clinical data to predict efficacy and safety of pharmacological interventions with an aim to enhance decision-making in the drug development process. MBDD employs the integration of mathematical as well as statistical approaches to build, validate and apply drug exposure-response and pharmacometric models along with disease models to enhance the quality and efficiency of drug development program.

MBDD is a relatively newer concept embracing the whole drug development process from discovery of a new molecule to its launch as a commercial product. It involves model-based data analysis and simulation at discrete isolated events throughout the development process. MBDD provides a data-driven model framework enhancing the meticulous establishment of a scientific knowledgebase by means of continuously integrating knowledge gained through the development program, and serving as a valuable decision-making tool.

Traditional vs. Model Based Drug Development

As discussed previously, the traditional/ conventional process of drug development makes use of modeling and simulations through different phases of drug development; hence it can be termed as "model- aided drug development". However, the concept of MBDD is quite distinct. Table 1.2 enlists the key differences between model-aided and model-based drug development.

CLINICAL TRIAL SIMULATION (CTS)

CTS is the utilization of simulation techniques like Monte-Carlo simulation in drug development program with an aim to increase the probability of getting favorable results in clinical trials. CTS makes it possible to test varying scenarios simultaneously, predicting potential end results for each and finally choosing the most suitable study design. Prior to study conduct, testing different methodologies by means of such simulation techniques can help increase the chances of success in clinical trials. It also facilitates pooling of data from different sources like prior studies with same drug and external data which may serve as an informative tool to attain superior decision-making. Hence, simulation plays important role in guiding development strategy by clarifying how various study designs influence outcome and probability of success (Table 1.3).

Challenges for CTS

- ✓ Relatively new concept; there is a need for good understanding of the concept and its uses.
- ✓ Requires extensive trainings for pharmacokineticists as well as clinical pharmacologists.
- ✓ Need to educate the pharmaceutical community regarding the applications and limitations of simulation.
- ✓ Willingness of pharmaceutical industry to adopt and consider simulation technology as a component of drug development process.

Table 1.2 Comparison of model-aided drug development with model based drug development.

Model aided drug development	Model based drug development
Models are largely empirical	Both empirical and mechanistic models are developed and applied
Model function formats are driven by observed trend in data	Function formats are elucidated by underlying treatment, disease condition and pathophysiological mechanisms involved
Difficulties in linking models across experiments, response types, developmental stage and compounds	Models include a good knowledge, data and scientific background from various applicable aspects and are regularly upgraded.
Model quality is restricted by data quality and quantity	Rich prior knowledge alleviates the dependence on data quality and quanity
Limited predictability for future studies	Predictability is the major parameter for model's performance
Models are mostly developed in PK/PD during late stages of drug development	Models in different disciplines are developed at various preclinical and clinical development stages of drug development
Models (PK/PD) are used for quantifying response levels in exposure, biomarkers & end points, sources of variation and covariate effects.	Models are used for characterizing candidate attributes, disease mechanisms, competitor knowledge and trial management strategies.
Models are used to confirm decisions	Models facilitate quantitative decisions
The focus of models is on few individual attributes.	Models reflect all known attributes
Models generally do not influence the decision making process.	Models are developed prospectively and are a necessity for decision making

Table 1.3 Applications of Clinical Trial Simulations in various phases of drug development.

Phase I

- Estimation of starting/ initial dose for administration in humans
- Prediction of pharmacokinetic parameters in multiple-dose study from data of single-dose study
- Influence of any drug interactions on pharmacodynamics and pharmacokinetic parameters
- Potential effect of renal and/or hepatic disorder on pharmacodynamics and pharmacokinetic parameters

Phase II/III

- Dose selection for Phase II/III trials
- Estimation of number of subjects required to attain an acceptable power
- Dosage required to achieve therapeutic concentration at target site
- Choice of statistical test to achieve maximum power under test conditions
- Differentiation of alternative clinical trial designs

Phase IV

- Comparability of drug to other competing products in market
- Influence of any drug interactions on pharmacodynamics and pharmacokinetic parameters

- ✓ Need to have superior biomarkers/ surrogates for drug effect.
- ✓ Depends on a good background knowledge of the link between pharmacokinetics and pharmacodynamics.
- ✓ Better understanding of compliance patterns.
- ✓ Doubtful financial benefit.
- ✓ Cost effectiveness of techniques and beneficial results not guaranteed.

QUANTITATIVE PHARMACOLOGY

This is a multidisciplinary avenue in drug development program which depends on the collaboration of associations between pathological disorder, attributes of pharmacological treatment, and individual variation in response across different drug developmental phases. It involves a continual quantitative integration of data through different phases of drug development.

IDENTIFICATION AND VALIDATION OF NEW BIOMARKERS

The development of newer biomarkers has been identified as one of the highest priorities in the field of drug development. Various innovative technologies like genomics, proteomics, metabolomics, gene expression assays using animal or whole cell systems and advanced imaging methods bear huge potential for developing new biomarkers which can have utility in reflecting the health or disease state at molecular level. These technologies can also be used to compare the effects of new drug candidate to other drugs in its class or other groups of drugs used for similar indications. The newer biomarkers are particularly helpful in improving diagnosis, defining subsets of disease showing differences in response to treatment, defining individual variations in the drug targets at molecular level, and predicting drug response at an early stage. For example, molecular assays employing assessment of target status within tumor cells can be exploited to anticipate response to a targeted molecule like transtuzumab, imatinib etc. In this context, the role of upcoming technologies like metabolomics and toxicogenomics in drug development has been discussed below.

PHARMACOMETABOLOMICS

Metabolomics (metabonomics) is the quantitative measurement of how the living systems respond dynamically to multiple parameters including external stimuli or genetic modification. It studies all small molecular metabolites (whether intermediates and/or obtained as final products of various cellular processes) present in cells, tissues, or organs and hence provides a detailed overview of the metabolic state of an individual.

Pharmacometabolomics, initially termed "Pharmacometabonomics" is defined as the process of predicting a drug's or xenobiotic's outcome (e.g. efficacy or safety) in an individual on the basis of a mathematical model using metabolite signatures prior to intervention. It is a novel approach combining the application of chemo-metrics and metabolite profiling to create models and predict various parameters like drug targets, pharmacodynamics, pharmacokinetics and toxicity on individual as well as population basis.

Pharmacometabolomics complements proteomic, genomic, transcriptomic and epigenomic "systems biology" approaches to new drug development and helps in an extensive and comprehensive understanding of effects of drugs by keeping into consideration both intrinsic (e.g. age, gender, genetic makeup, ethnicity) and extrinsic (e.g. environment factors like diet, lifestyle, use of other medications, gut microbiome) factors determining interindividual variation in drug response (Figure 1.8).

Pharmacometabolomics provides a constructive and economical approach to assess drug efficacy and toxicity and might prove to be instrumental in making personalized medicine practical and realistic from scientific as well as financial perspectives.

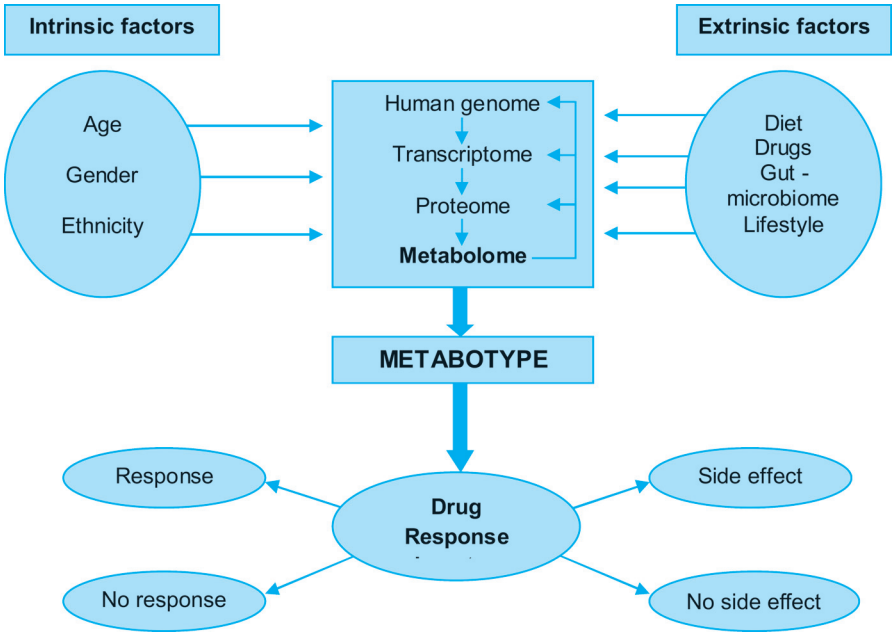


Figure 1.8 Pharmacometabolomic approach for drug response phenotyping.

Role of Pharmacometabolomics in drug development

- *Reducing inter-individual variation in clinical trials: Metabolic profiling to evaluate response phenotype.*

In clinical drug development, the major role of pharmacometabolomics is to reduce inter-individual variability in response to therapy by differentiating patients into responder or non-

responder groups. Pharmacometabolomics identifies various characteristics of response to drug or xenobiotic interventions on the basis of individual's metabotype. The "metabotype" is the entirety of person's characteristics which govern disease heterogeneity and response to therapy. In addition to reflecting the individual's constitution and disease impact, it also takes into consideration the product of exposure to environmental factors and effects of any concurrent or past treatments that have influenced the organism. Metabotype, hence, provides a distinctive and holistic profiling of an individual's constitution. Metabotype signatures at baseline (prior to drug exposure) and post exposure to therapeutic intervention can have potential applications in defining mechanisms involved in producing variation in therapeutic response.

- *Prediction of therapeutic outcomes: identification of biomarkers*

A major advantage of pharmacometabolomics is a quicker, more reliable and efficient prediction of therapeutic outcomes. This application relies on successful identification and utilization of metabolomic components as intermediate biomarkers or surrogate end points of long term or delayed clinical outcomes such as toxicity, remission, mortality etc.

Challenges for Pharmacometabolomics

- The cornerstone of pharmacometabolomics is the need to accurately identify and quantify the small metabolites at cellular, molecular, tissue or organ level.
- Dependence on proper maintenance and accurate calibration of equipments used in analyses and computations e.g. mass spectrometry, nuclear magnetic resonance (NMR).
- In order to confirm the results of pharmacometabolomics, there should be large enough sample size of selected cohorts.
- Special emphasis needs to be given to the statistical methodologies to avoid false positive/ negative results in metabolomics and allied experiments.

Despite the challenges, pharmacometabolomics holds great promise to improve future drug discovery and development process by providing individual-specific information about drug efficacy and toxicity, revealing new insights into pharmacokinetics and pharmacodynamics, discovery of new biomarkers, identifying novel therapeutic targets and playing a critical role in the movement towards personalized medicine.

TOXICOGENOMICS

Toxicogenomics is the discipline that studies relationship between the structure and function of genome (the cellular complement of genes) and undesired biological effects of exogenously administered agents. Toxicogenomics, as a new risk assessment tool during the drug development

program, can prove to be strongly instrumental in increasing our knowledge of the molecular mechanisms (gene and protein expression) and DNA polymorphisms involved in the manifestation of efficacy and toxicity of xenobiotics,

The major principle behind toxicogenomics (TGx) is that "compounds having identical toxicity mechanisms and consequences should perturb the transcriptome in a similar manner and these perturbations could be exploited to serve as biomarkers predicting downstream toxicity outcome." Figure 1.9 shows a flowchart explaining the concept of toxicogenomics.

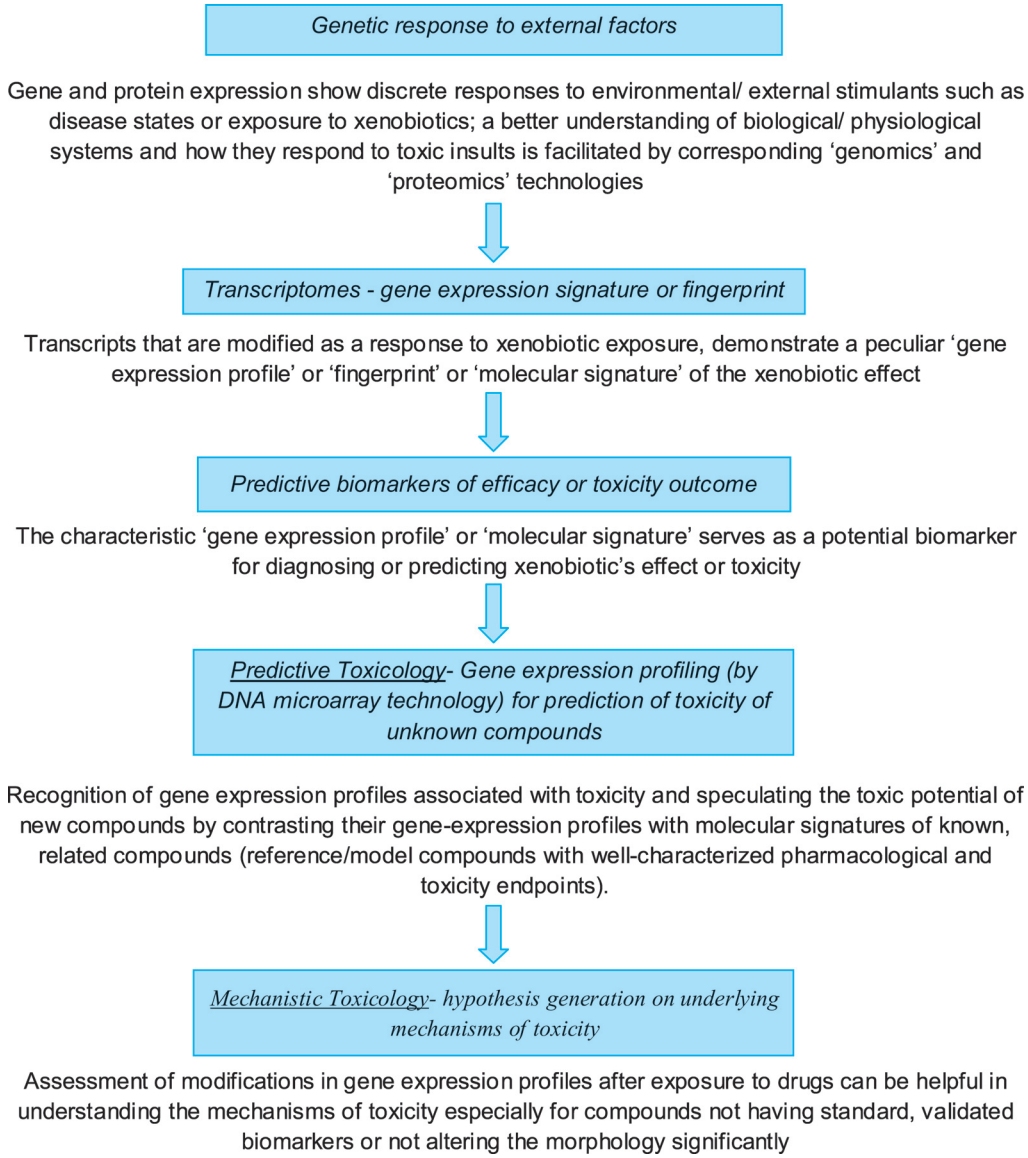


Figure 1.9 The concept of Toxicogenomics.

TGx is the unique combination of conventional toxicology with emerging "omics" technologies like genomics and bioinformatics. For the implementation of TGx as a predictive tool, it is absolutely essential to have a prior knowledge of patterns of gene expression involved in manifestation of toxicity. Hence, this approach hinges on the accessibility of a standard gene expression database.

The application of global gene expression analysis in TGx has provided considerable quantity of data on already recognized toxicants like hepatotoxins in animal models, allowed classification of compounds according to their mechanism of toxicity and helped in understanding cellular pathways involved in activation of macrophages, proliferation of peroxisomes, causation of oxidative stress or formation of reactive metabolites etc. In recent times, the applications TGx have expanded to evaluate the nephrotoxic, genotoxic and testicular toxicity potential of compounds as well.

Advantages of Toxicogenomics

- TGx serves as a substantial tool for classifying compounds and for detecting novel, functional, responsive and specific markers for the toxicity mechanisms under consideration.
- Higher sensitivity of toxicogenomics (gene expression profiling and predictive biomarkers) than the conventional toxic endpoints, thereby increasing the clinical prediction of toxicity.
- Enables the rapid development of newer compounds with good safety profile while bringing down the cost involved and need for animal experiments.
- Gene expression analysis techniques, by enhancing our knowledge of the molecular mechanisms leading to toxicity, provide a deeper understanding of species-specific factors responsible for response to drugs. This will in turn facilitate a more accurate extrapolation of data across species e.g extrapolation of disease conditions in man from observations in animals.

Challenges for Toxicogenomics

- Technical validation i.e. issues like data comparability and use of standardized methods. For this, various areas like quality control, gene annotations, and data analysis need to be carefully addressed.
- Questionable significance of the findings in biological and toxicological fields due to lack of clear knowledge of any relationship between gene expression and causation of dose-dependent toxicity at present.
- Inability to predict the idiosyncratic adverse drug events.

However, appropriate utilization of toxicogenomics, along with current technologies like proteomics and metabolomics could offer a huge competitive advantage to drug discovery and development industry.

STREAMLINING CLINICAL TRIALS

One of the major critical path priority for the FDA as well as other stakeholders is streamlining and improving the predictive value of clinical trials. The strategies recommended for streamlining the clinical trials include:

- ✓ Design, use and interpretation of active controlled trials, i.e. trials designed to show that a product candidate is not inferior to an existing treatment (rather than superior to placebo as in traditional trial design).
- ✓ Need for transparent rules on deciding the time points to make amendment/s in clinical trial protocol on the basis of results from early or interim data.
- ✓ Application of adequate statistical techniques to increase the reliability of pre-clinical data.
- ✓ Appropriate approaches to handle missing data from subjects lost to follow up.
- ✓ Better methods for evaluating multiple end-points in a single trial.
- ✓ Development of consensus trial designs for specific therapeutic areas.
- ✓ Enhancing the methodologies to measure drug responses in subjects e.g. evaluation of pain and other subjective endpoints.
- ✓ Standardization of forms and methods for recording and reporting clinical trials data.

CLINICAL TRIAL MODERNIZATION

This area as included in critical path initiative comprises

- ❖ Establishment of standard guidelines for handling and managing the data in clinical trials. In this context, the Clinical Data Interchange Standards Consortium (CDISC) has contributed significantly in standardizing the data management. An initiative of CDISC called Clinical Data Acquisitions Standards Harmonization (CDASH) is actively involved in this process and has laid standards for drafting case report forms.
- ❖ Use of automatic techniques during the process of clinical trials and data management;
- ❖ Enhancing the quality management systems;
- ❖ Implementation of modern technologies to facilitate oversight of the trial process by regulatory authorities.

ARTIFICIAL INTELLIGENCE IN CLINICAL TRIALS

Artificial Intelligence (AI), also called machine intelligence, is the ability of a machine or computer or computer- controlled robot to imitate intelligent human behavior such as speech recognition, statistical learning, image processing, translation between languages, processing natural languages, motion and manipulation, pattern recognition, decision-making etc. In other words, it is mechanical intelligence in contrast to natural intelligence exhibited by man and other animals.

The goal of AI is to develop systems and softwares which can function independently and intelligently like human brain. Crucial elements for AI are:

- huge amounts of data,
- advanced algorithms, and
- high performance processors

AI has become an integral component of many industries e.g. automotives (driverless cars), video games, military (lethal autonomous weapons) etc.

Applications of AI in clinical trials

Artificial intelligence and allied technologies e.g. machine learning (ML) and natural language processing (NLP) are increasingly making their way into clinical trials. The existing applications of AI and emerging technologies in clinical trials include:

Patient recruitment. A major challenge faced by clinical trial industry is patient recruitment. It is reported that around 80 percent trials fail in meeting the recruitment timelines while one third of Phase 3 trials are terminated due to recruitment challenges. Also. patients are unable to find appropriate clinical trials in the absence of recommendations from physicians and difficulty in navigating the clinical trial databases (e.g. clinicaltrials.gov).

AI can help address this issue by extracting pertinent information from medical records and comparing it to the inclusion/ exclusion criteria of ongoing trials, thus identifying more effectively and efficiently the appropriate patients for enrollment.

Clinical trial design. AI algorithms and deep learning techniques can help in designing protocols making the clinical trials more intelligent in a number of ways:

- Analyzing historical operational data
- Measuring drug responses
- Predicting site performance
- Monitoring trial risks preemptively
- Centralized trial monitoring
- Enabling voice assisted technologies
- Enabling virtual trials
- Monitoring adherence to therapy
- Providing additional predictive data to determine outcomes, patient drop out etc.

Applying these AI driven techniques and predictive algorithms, risks associated with trials can be mitigated well in advance which would be helpful to enhance the clinical trials success rates.

Clinical trial optimization. The AI-machine learning (ML) models can prove to be helpful in predicting which patients are at risk of dropping out of clinical trials by utilizing the real world evidence (RWE) from medical claims, prescription and other data. This would allow the clinical personnel to intervene and take appropriate steps to preserve trial validity.

Patient centric clinical trial designs. AI-enabled trial management technologies like digital reporting applications, wearable devices, telehealth, smart phone applications etc. are changing the conduct of clinical trials in a number of ways:

- patients can send feedback on their symptoms and manage intake of medications.
- patients can share information with researchers reducing the frequency of visits to trial sites.
- create opportunities for patients to respond immediately to symptomatic or biometric changes.
- automatic and continuous communication of patient- specific trial data to investigators and clinical trial databases etc; this in turn ensures data integrity by eradicating delays in transfer, eliminating transcription errors and reducing the incomplete/missing data.

Hence, such patient centric clinical trial designs allow real time engagement of patients in their own care which in turn can profoundly benefit in improving patient adherence and persistence in trials.

Table 1.4 enlists some AI softwares along with their applications.

Table 1.4 Examples of various AI softwares and their applications.

Name of software	Applications
Antidote (2010) London, England	*Patient recruitment*: uses machine learning (ML) to connect patients to medical research studies through its clinical trial matching platform
Deep 6 AI (2015) Pasadena, California	*Patient recruitment*: uses natural language processing (NLP) to better match patients to clinical trials
Trials.AI (2015) San Diego, California	*Clinical trial design:* uses NLP to help researchers manage clinical trial workflows in an efficient manner
Bullfrog AI (2017) Annapolis, Maryland	*Clinical trial design:* uses platforms which conduct data mining to identify correlations and patterns with large, complex data and generates predictive models
Brite health (2015) Palo Alto, California	*Clinical trial optimization:* uses an algorithm trained on millions of clinical data points; identifies the key markers correlating with patient

Hence, AI offers potential in solving many major challenges encountered by clinical trial industry by assisting and augmenting human intelligence, maximizing patient recruitment and retention, leveraging data, improving clinical trial designs, making predictions of trends, risks and outcomes etc. By improving data quality, reducing trial durations and cutting sky- rocketing costs of developing new drugs, AI can accelerate new drug development. AI applications hold huge promise in dramatically shortening the time to market life saving drugs.