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NEW DRUG DISCOVERY AND DEVELOPMENT

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ABSTRACT

The establishment of a novel drug is still a costly, prolonged, difficult, and inefficient process with a high attrition rate of new therapeutic discovery. This approach can cost pharmaceutical companies an average $2.6 billion and 10–15 years of research and development. Drug design is the innovative process for the discovery of new medications, involves the design of new therapeutic entities that are complementary in shape and charge to the molecular target with which they interact and bind. A traditional approach is one of the oldest methods for finding new drugs of natural origin, involves the investigation of medicinal substances of plant, animal, or mineral origin in their crude or unprepared state. On the other hand, ultra-high-throughput drug screening and combinatorial chemistry-based development are being heavily employed to reduce the cost and the time of early drug discovery. The present review article will look deeper into the key concepts of drug discovery, drug development and clinical stages of the drug discovery. Our main objective of the review is to assist scientists whose research may be related to drug discovery and development to shape their research report in a way that relevantly places their findings into the drug discovery and development process, hence supporting effective and translation of preclinical research to humans.

KEYWORDS: Drug discovery, Clinical researches, clinical trials, phases of clinical trials, Investigational drug, and Generic drug.

INTRODUCTION

Historical perspective

A few hundred years ago, until the late 1800s, most drugs were derived from herbs, fungi, and other natural sources or extraction of ingredients from botanical sources. The illustrated substances had known therapeutic properties that were discovered by trial and error method. In the late 1800s, pharmaceutical research progress from the application of plants and fungi to the highly technical procedures. The beginning of pharmacology where physicians and chemists start to study how to isolate molecules of organic substances known to have therapeutic benefits and test them to establish which molecules showed the desired effects.[1]

The first synthetic drug Aspirin was produced in 1897, by Felix Hoffman. In the 1950s produced several advances and discoveries for modern medicine. DNA-based advancement was the discovery of recombinant DNA technology in the 1970s.

Structure of DNA discovered in 1953 that gave rise to greater understanding of viruses. In the 1970s, scientists developed recombinant DNA technology and initiate cloning molecules. Development in molecular biology and virology provided awareness in the late 1980s and early 1990s in the research of HIV.

The understanding of growth, replication of virus and how it act on the body give rise to the development of peptide anagoges, non-nucleosides and nucleosides designed to target HIV. While the introduction of drug-resistant viral strains made treatment more difficult and challenging, Scientists early understand combinations of medications were the answer. The strategies such as bioinformatics, combination chemistry and molecular modelling were used to produce modernize generation drugs.

Recently together with the cellular biology, microbiology state-of-the art research includes enzyme-based molecular synthesis, chemical biology, recombinant biomolecules and stem cell research some additional pharmaceutical advances are made possible.[2]

In the traditional or classical method of drug development process medicinal chemists necessitate modification of bioactive molecule from natural products from the early 1930s, drug discovery concentrated on screening natural products and isolating the active ingredients for treating diseases. The active ingredients are normally the synthetic version of the natural products. These synthetic versions, called new chemical entities (NCEs), have to go through many iterations and tests to ensure they are safe, potent, and effective.[3]

Drug development is the method of introducing a new drug molecule into clinical practice. The process of drug discovery and development involves a combination of numerous disciplines and interests starting from a simple process of identifying an active compound. The main objective of drug development is to find a therapeutically effective compound for curing and treating disease. Identification of candidates, synthesis, characterization, confirmation, optimization, sampling, and assays for therapeutic efficacy are all part of this method.

Once a compound has been shown to be effective in these experiments, it will continue the drug development phase prior to clinical trials. To produce a medication that is healthy, reliable, and satisfies all regulatory criteria, the modern drug production process must go through many phases.

The discovery of a new chemical entity that modifies a cell or tissue function is the first step in the drug development process. The chemical agent can be considered to be a therapeutic entity when it exhibit effectiveness, selectivity and must be free from toxicity and also having good bioavailability.[4] One of the essential justification of the present article is that the procedure is simply too drawn-out, sophisticated, and expensive for several individuals to prevent it.

Due to large R&D and clinical trial costs, drug research and production is a costly process. A single new drug molecule takes nearly 12-15 years to grow from the moment it is discovered to the time it is available on the market for treating patients and an investment of about $1 billion is needed. A million molecules are tested on average, but only one is investigated in late-stage clinical trials and then made available to patients. This article offers a short description of how new medicines are found and produced.[5-6] A successful medication is estimated to cost between $900 million and $2 billion in research and development. The cost of the thousands of errors is included in this figure: Just one compound out of every 5,000-10,000 that join the investigation and production pipeline is approval.[4,7]

Drug research is a multifaceted procedure that entails identifying a drug chemical that is therapeutically useful in the treatment and control of a disease. Usually, researchers discover potential medicines by gaining new insights on a disease mechanism that enable researchers to devise a medication to reverse or avoid the disease's impact.[4]

The goal of the present review is discuss the whole process, from target identification through clinical trials and post-approval monitoring for the development of a new drug. The present review assist the scientists whose research may be associated with new drug discovery and development to shape their research report in a manner that appropriately places their findings within the drug discovery and development process and thereby lead effective translation of preclinical research to humans.

Drug Development Process

The processes of drug development essentially proceed through different stages with the goal to produce safe and effective drug product, and has surpassed each and every regulatory requirements [Fig.1][8]. There are mainly five important steps in the U.S. drug development process, along with many phases and stages within each of them. The five steps are –

- Step 1: Discovery and Development
- Step 2: Preclinical Research
- Step 3: Clinical Development
- Step 4: FDA Review
- Step 5: FDA Post-market Safety Monitoring.

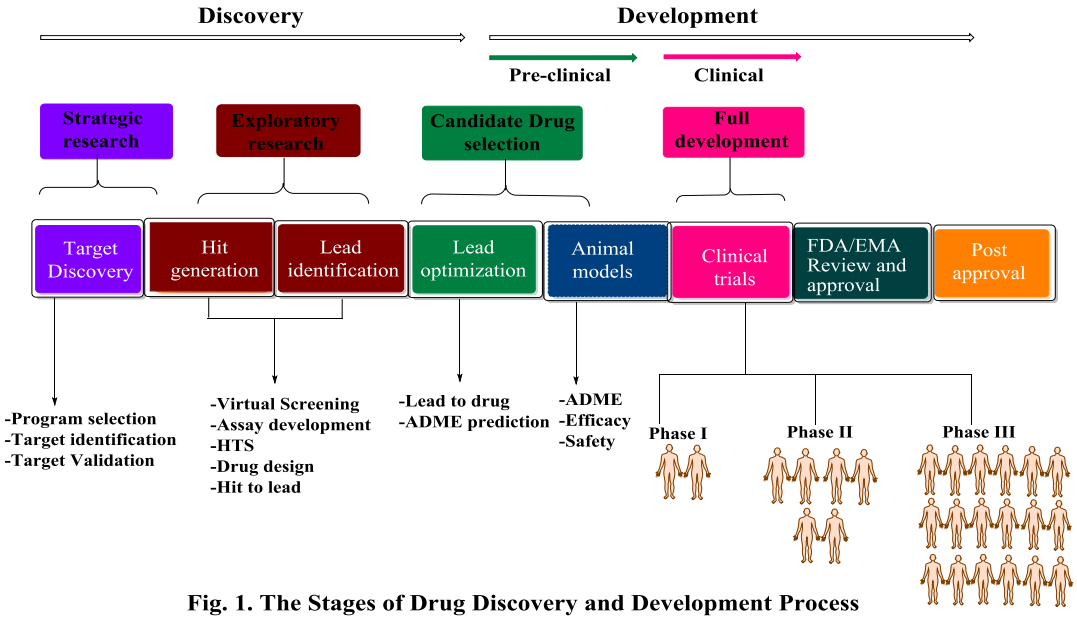

Fig. 1. The Stages of Drug Discovery and Development Process

Step 1: Discovery and Development

Drug discovery is the process in which new medications are discovered, it involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Historically, drugs were discovered through identifying the active ingredient from traditional remedies or by chance discovery.[9]

New drug discovery include the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity, effectiveness, metabolic stability, potency, and oral bioavailability. When a drug satisfies all of these necessities have been identified, it will start the process of drug development prior to clinical trials [Fig.2].[10]

The present modern drug discovery entails screening hits, medicinal chemistry, and optimization of hits to decrease the possible side effects (improve the selectivity and affinity of the drug). fficacy or potency, metabolic stability (half-life), and oral bioavailability are also improved in this step of the drug development process.[11] once researchers identify a promising compound for development; they conduct experiments to gather information on.[12]

- The method of absorption, distribution, metabolism, and excretion.
- Possible mechanisms of action and its potential benefits.
- Its best dosage.
- The best rout of drug administration.
- Toxic effects (Side effects or adverse events).
- The way in which it affect differently on different groups of people such as by gender, race, or ethnicity.
- Interaction with other drugs.
- Its efficacy as compared with similar drugs.

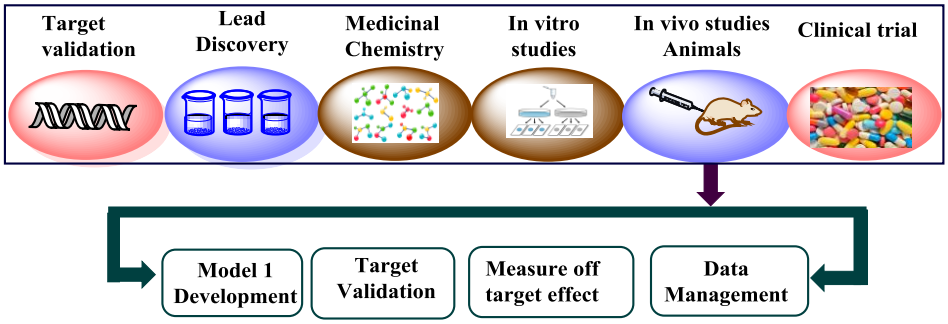

Fig. 2. Drug development process

Target identification and validation

Target identification finds a gene or protein (therapeutic agent) that plays a significant role in disease [**Fig.3**][13]. The term druggability employ in drug discovery is to describe the biological target (like protein) bind to a drug, subsequently the binding of the drug to a druggable target necessary change the activity of the target with a therapeutic benefit to the patient. If the activity of the target can be modify by the therapeutic, whether it may be a small molecule drug or biologic proteins and nucleic acids are both examples of biological targets[14] after identification of the target followed by characterization of the molecular mechanisms addressed by the target. A molecular target must be safe, effective and pass clinical and industrial requirement.[15]

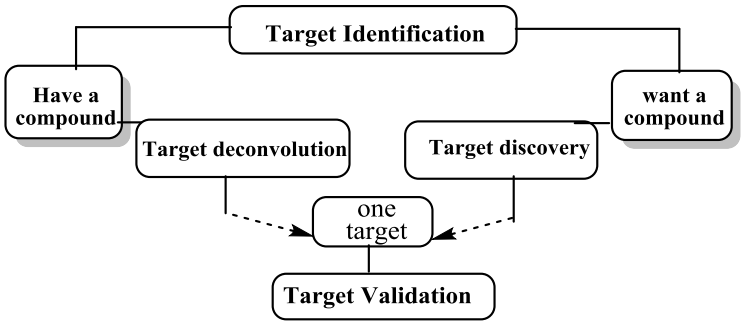

Fig.3. An overview of target deconvolution vs target discovery.

Understanding of target characteristics, such as protein / nucleic acid sequence features, structural properties, proteomic profiles, pathway affiliation and roles, and tissue-distribution patterns is useful for a molecular dissection and mode of action of the drug and for envisage elements to direct objective discovery and drug plan.[6,17]

A good goal is one that is efficient, secure, and meets clinical and commercial criteria. Goal recognition

methods may be based on concepts from molecular biology biochemistry, genetics, biophysics, or other areas.[15]

Characteristics of a promising drug target [14]

- The target has pronounced role in the pathophysiology of a disease.
- The expression of target is not evenly distributed throughout the body.
- A target has suitable 3D-structure to assess druggability.
- The target is easily 'assayable' to allow high-throughput screening (HTS).
- The target adverse effects, toxicity profile can be predicted using phenotypic data.
- The suggest target has a favorable intellectual property (IP) status.

Target Deconvolution vs Target Discovery

The retrospective identification of the molecular targets that control observed phenotypic responses is known as target deconvolution. It is important for explaining the biological mechanisms of disease and will also incredibly aid rational drug design and involves exposing cells, isolated tissues, or animal models, to small molecules to decide whether a particular candidate molecule exerts the desired effect.[18] Although various animal models can be used for the characterization of small molecules and small-scale drug screening approaches, use of mammalian cells is often favored due to their similarity with high-throughput screening (HTS) and more noteworthy physiological importance.

Target discovery

In the target discovery, drug targets are previously established prior to lead discovery starts therefore; target discovery is the foundation of target-based screening.[19] The role of the drug targets in a disease process is investigated, then this drug target is used to design applicable systems-based assays and huge compound libraries are screened in search of a 'hit' – a candidate drug.[18-20]

Target Validation

Target validation process demonstrates the functional role of the identified target in the disease phenotype and shows that a molecular target is directly involved in a disease process, and that modulation of the target is likely to have a therapeutic effect [Fig.4][21]

The practice of certifying the expected molecular target likes a gene, enzyme, or nucleic acid of a small molecule called as target validation. The most important criteria for target validation are to demonstrate the functional role of the specified target in the disease phenotype. It is important to validate a medication's effectiveness and toxicity in a variety of disease-relevant cell and animal models, the ultimate measure is whether the drug performs in a therapeutic setting.[14-22]

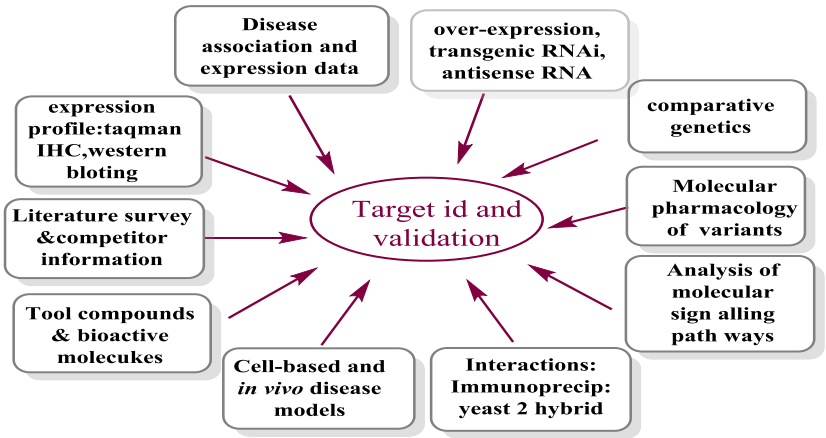

Fig.4. Target validation process

Target validation includes

- To find out the structure activity relationship (SAR) of the analogs of the small molecule. Make a drug-resistant mutant of the assumed target.
- Knockdown or over expression of the presumed target.
- Observe the studied signaling systems downstream of the expected target.

The target validation can be divided into two steps:

- **Reproducibility:** After a drug target has been identified, whether by a specific method or a literature review, the first step is to repeat the procedures to ensure that it can be successfully reproduce.
- **Introduce variation to the ligand (drug)-target-environment**. Affinity of the drug should be modulated to the target by modulating the activity of the drug molecule. Effect of drug should or should not, alter by varying the cell or tissue type. Presence of mutation in the binding domain of protein target should consequently results in to modulation or loss of ligand (drug) activity.[23]

Lead Identification

A chemical lead is a stable, viable, and drug-like molecule that is active in primary and secondary assays with suitable specificity, affinity, and selectivity for the target receptor. This necessitates the establishment of the structure-activity relationship, as well as the assessment of synthetic viability and tentative proof of in vivo effectiveness and target interaction.

Characteristics of a chemical lead are

- SAR defined
- Drug ability (preliminary toxicity, hERG)
- Synthetic feasibility
- Select mechanistic assays
- In vitro assessment of drug resistance and efflux potential
- Evidence of in vivo efficacy of chemical class
- PK/Toxicity of chemical class known based on preliminary toxicity or in silica studies

Lead Optimization

After identifying an initial lead molecule, the method of lead optimization is used to design a drug candidate. The procedure entails an iterative sequence of synthesis and characterization of a possible drug in order to construct a model of how chemical structure and function are associated in terms of interactions with targets and metabolism. The hits from hit-to-lead high-throughput screening experiments are then optimized to find interesting compounds in the early stages of drug development. As the final step of early stage drug development, potential leads are tested for a variety of properties, including selectivity and binding mechanisms.

The aim of lead optimization is to keep beneficial properties in lead compounds while enhancing lead structure flaws. To build a pre-clinical drug candidate, lead compounds (small molecules or biologics) must have their chemical structures modified to increase target specificity and selectivity. The parameters of pharmacodynamics and pharmacokinetics, as well as toxicological properties, are both assessed. To precisely describe the compound and determine the route of optimization, labs must collect data on its toxicity, potency, durability, and bioavailability.

Rapid methods for narrowing down the list of drug candidates for downstream selectivity profiling and further investigation are needed by drug discovery researchers. Drug metabolism and pharmacokinetics (DMPK) screens with high throughput have been an integral aspect of lead optimization, allowing for improved interpretation and estimation of in vivo pharmacokinetics utilizing in vitro studies. Chemical changes to the structure of candidate drugs are made by optimization in order to make potential drugs with higher potency and safety profiles.

Pharmaceutical and biopharmaceutical drug research laboratories are increasingly using automated screening technologies. The identification and quantification of metabolites is achieved using mass spectrometry. MALDI imaging is a vital tool for easily and reliably testing drug candidates and their metabolites in tissue structure. Furthermore, in the pharmaceutical industry, NMR Fragment-based Screening (FBS) has been a commonly used tool for the detection and optimization of lead molecules in selective screening campaigns.[24,25]

Product Characterization

If a new drug molecule displays promising therapeutic action, its scale, form, strength, vulnerability, application, toxicity, and biological activity are all assessed. The early stages of pharmacological science are useful for evaluating the compound's mode of action.[26]

***Formulation and Development [Fig.5]*[27]**

Pharmaceutical formulation is a stage of drug production in which the physicochemical properties of active pharmaceutical ingredients (APIs) are studied in order to create a bio-available, safe, and ideal dosage type for a given administration path.[28]

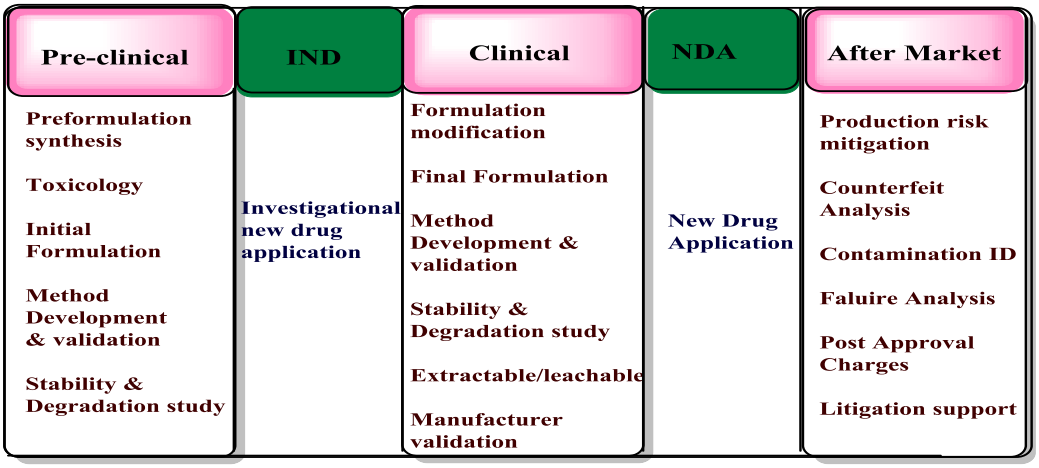

Fig.5. Formulation and Development Process

During pre-formulation studies the following parameters are evaluated

- Solubility in different media and solvents.
- Dissolution of the active pharmaceutical ingredient (API)
- Accelerated Stability Services under various conditions
- Solid state properties (polymorphs, particle size, particle shape etc
- Formulation services and capabilities
- Formulation development of new chemical entities (NCE)
- Optimization of existing formulations
- Process development for selected dosage forms
- Novel formulations for improved delivery of existing dosage forms
- Controlled release and sustained release formulations
- Self-emulsifying drug delivery systems
- Colloidal drug delivery systems
- Sub-micron and nano – emulsions

Step 2: Preclinical Research

In the drug discovery process, once a lead compound is found, drug development begins with preclinical research to assess a drug's safety and effectiveness in animal models before forecasting a human outcome. Researchers determine whether it has the potential to cause serious harm, also called toxicity. The two types of preclinical research are: In Vitro and In Vivo:

Preclinical studies give information on dosing and toxicity levels. When preclinical testing done then researchers evaluate their results and conclude that whether the drug should be tested in peoples. Researchers determine the following about the drug:

- Absorption, distribution, metabolization, and excretion information
- Potential benefits and mechanisms of action
- Best dosage, and administration route
- Side effects/adverse events
- Effects on gender, race, or ethnicity groups
- Interaction with other treatments
- Effectiveness compared to similar drugs

Obtaining permission from the relevant regulatory authorities is also required. The regulatory authorities must ensure that trials are performed in a safe and ethical manner, and only certain medicines that have been shown to be safe and successful will be approved. The International Conference on Harmonization (ICH) has developed a specific framework for the technological requirements of appropriate preclinical drug production.[29,30]

General pharmacology and Toxicology

The primary objective of the preclinical research is to decide a starting, safe dose for first-in-human study and determine the potential toxicity of the product, which commonly encompass new scientific devices, prescription drugs, and diagnostics. Pharmacology is concerned with the drug's pharmacokinetic and pharmacodynamic parameters. Unwanted pharmacological effects must be investigated in appropriate animal models and monitored in toxicological experiments. Pharmacokinetic trials are crucial for assessing the safety and effectiveness of a drug's absorption, delivery, metabolism, and excretion parameters. The half-life of a drug clarifies the drug's safety profile, which is required for a drug to be accepted by regulatory agencies. Since it is based on the drug's bioavailability and affinity, the drug delivery process elucidates the therapeutic efficacy of the device.[31]

Preclinical Toxicology Testing and IND Application

This stage of preclinical testing analyzes the bioactivity, safety, and efficacy of the formulated drug product. It is critical to a drug's eventual success and, as such, is scrutinized by many regulatory entities. In the preclinical research of the development process, plans for clinical trials and an Investigative New Drug (IND) application are prepared. Main stages in the preclinical toxicology testing include:

Acute Studies

The main goal of acute toxicity studies is to evaluate the effects of a drug when administered in a single dose or in multiple doses during a period of 24 h in two mammalian species (one nonrodent). Acute toxicity studies: Data from acute toxicity studies helps to provide information for repeated dose studies in animals and Phase I studies in humans.

Repeated Dose Studies

The major aim of the repeat-dose toxicity studies is to regulate the adverse effects of the compounds when administered to the experimental animals frequently for a period of time. Depending on the duration of the studies, repeated dose studies may be referred to as sub acute, sub chronic, or chronic.

Genetic Toxicity Studies

Genetic toxicology studies are conducted to assess that the drug compound is mutagenic or carcinogenic. Ames test conducted in bacteria to detect genetic changes. DNA destruction is examined in tests utilizing mammalian cells, for example, the mouse micronucleus test. The Chromosomal Aberration Test and comparative method distinguish the destruction at the chromosomal level.

Reproductive Toxicity Studies

Reproductive toxicology is the study of the occurrence, causes, manifestations, and sequence of adverse effects of exogenous agents on reproduction. Generally, reproductive toxicity research should be finished before a drug can be given to female in the youngster bearing age.

Carcinogenicity Studies

Carcinogenicity test is the prolonged rodent carcinogenicity bioassay defined in Organization for economic cooperation and development (OECD) test guideline. The main objective of this test is "to examine test animals for greater part of their life span for the development of neoplastic lesions throughout or after exposure to numerous doses of a test substance with a proper route of administration. The carcinogenicity study is normally necessitated only for drugs meant for chronic or recurring conditions. The process is lengthy, expensive, and should be design early in the preclinical process.

Toxicokinetic Studies

Toxicokinetics study related with what the body does with a drug whilst given a comparatively higher dose relative to the therapeutic dose. The purpose of the TK is to correlate the results of toxicity (not therapeutic efficacy) with a correspondent level of exposure to an experimental drug compound. TK study determine the results of toxic doses of the drug and assist to estimate the clinical margin of safety.

Step 3: Clinical trial and Research

Clinical research refers are the experiments, studies, or trials, that are carried out on individuals (volunteers) to address particular concerns about the safety and effectiveness of medications, vaccines, other therapies, or alternative ways of using existing treatments.

When the researchers plan the clinical study, they'll examine what they need to perform for every of the distinctive Clinical Research Phases and start the Investigational New Drug Process (IND), a process they should undergo earlier than clinical studies begins. Before beginning clinical trials, drug developers must submit an Investigational New Drug proposal to the FDA.[32]

In the IND application, developers must include.

- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical study protocol for **research** to be conducted
- Previous clinical research data (if any)
- Information about the investigator/ developer

Before starting a clinical trial, experts look over previous knowledge about the drug and come up with testing questions and objectives.[33, 34] After that they decide (1) Selection criteria for participants (2) Number of people take part of the study (3) Duration of study (4) Dose and route of administration of dosage form (5) Assessment of parameters (6) Data collection and analysis.

Types of Trials

Timeline of Clinical Trials (605 BC - 1986 AD) • 605 - 562 BC: King Nebuchadnezzar II performed the first clinical trial 537: It was by chance surgeon Ambrose Pare, Turning Point Emerged the Nuremburg Code.[35]

- Open Label Trial- patients and Investigator both be aware of the full detail of treatment.
- Single Blind- only Investigator have the detail knowledge of the treatment.
- Double Blind- none of the two Investigator and patients is aware of the treatment detail. Triple Blind- Investigator, Patients and statistician are blinded.

Phases of Clinical Trials

Generally there are three stages to accomplish the clinical trial method earlier than a sponsor can submit their treatments to the FDA for examination to be bought at the market. The trials at each phase have a different purpose and ensure that the treatment is safe and effective for use by the public. Different Phases of Clinical Trials are:

- In Phase I trials, small group of healthy people (20 - 50) the first time to evaluate its safety, determine a safe dosage range.
- In Phase II trials, group of patients (100 – 300) effective and evaluate its safety
- In Phase III trials, crowd of patients (1000 – 3000) effectiveness, screen adverse effects, analyze it to usually used treatments, and used safely.
- In Phase IV trials, post marketing studies drug's risks, benefits and optimal use.

Phase-0 clinical trial

Phase-0 applies to first-in-human (FIH) trials that are performed in compliance with FDA regulations. Phase 0 experiments, also known as human micro dose tests, include offering single sub-therapeutic doses to 10 to 15 participants and presenting pharmacokinetic evidence or assisting in imaging particular targets without triggering pharmacological results. Pharmaceutical firms conduct Step 0 trials to assess which of their drug candidates has the best human pharmacokinetic parameters.

Advantages

- Less chances of adverse effects
- Short duration
- Less no. of volunteers
- Reduced cost of development Reduced drug development time

Limitations

The study was primarily focused on PK criteria, rather than effectiveness and protection. Phase 0 experiments do not test agents with distinct kinetic properties between micro-dose and maximum dose. Agents with nonlinear PKs have little utility. Since laboratory parameters are small and costly, researchers must rely on BA/BE laboratories.

Phase I Clinical trial (Safety and dosage phase)

Phase I clinical trial associated with examination of experimental drug or therapeutics in a small group of individuals for the first time by the researchers. The researchers evaluate the treatment's safety, determine a

safe dosage range, and identify side effects. Phase I studies are used to evaluate pharmacokinetic parameters and tolerance, generally in healthy volunteers. These studies include initial single-dose studies, dose escalation and short-term repeated-dose studies. The trial monitors for potential "serious adverse events"— that is, any toxic, undesirable, or unwanted effect that causes death or danger to health, like a disability or permanent damage, birth defect, heart attack, or other serious medicinal effects.

Consequently in the Phase 1 trial, the results are collected, analyzed, and submitted to the FDA for permission to proceed to Phase 2 Clinical Trials. Although, if the results show that the treatment was related to one or more serious adverse effects, then the FDA might not give permission to proceed to Phase 2.

Phase II Clinical Development (Therapeutic Exploratory)

Phase II clinical studies are small-scale trials takes place with few hundred of volunteers (100 to 300) who have the disease and are intended to evaluate the drug's effectiveness as well as the patient's ability to survive the Phase I safety tests. In Phase II clinical trial volunteers divide in to different treatment groups, where each group can receive different doses or delivery of the treatment. Normally, one is control group" that gets either the standard drug, if an alternative form of treatment previously present in the market for that disease, or a "placebo" remedy, like a sugar tablet or safe injection that doesn't include the treatment. The additional groups that received the distinct kinds of treatment are compared to the contro groups. However, if the effects now no longer suggests greater than the current standard of care or maybe prompted acceleration of the disease or different unexpected severe adverse effect, the FDA might not permit to previous Phase 3. Normally, testing of that remedy is discontinued or "drops out" of the jogging for making it to the market.

Phase III Clinical Trial

Phase III Clinical studies are large-scale clinical trials for safety and efficacy large number of participants. Phase 3 trials will be performed to assess whether a substance has an intervention value to a certain group of individuals. These trials, also known as pivotal studies, include 300 to 3,000 participants.

The aim of phase III clinical trials is to evaluate how the new medication works in comparison to existing medications for the same condition. After accomplishment of the Phase 3 Clinical Trials, the health of the patients who received the different types of treatment are compared to the control groups. If investigators demonstrate that the medication is at least as safe and effective as others already on the market, the FDA will usually approve the medication.

Phase IV clinical trials: Post-Market Drug Safety Monitoring

After the approval of FDA medications, Phase IV clinical trial takes place. This phase involves thousands of participants and can last for many years. After certification, these experiments are also known as post-marketing monitoring, which includes pharmacovigilance and ongoing logistical assistance. Investigators use this phase to get more information about the medication's long-term safety, effectiveness, and any other benefits. In Phase 4 trials, a number of observational methods and evaluation trends are used to evaluate the feasibility, cost-effectiveness, and safety of an experiment in a real-world environment.

The FDA examines evidence of prescription and over-the-counter drug problems and may decide to apply warnings to dose or practice records, as well as other incidents with more severe adverse drug, reactions.[36]

Step 4: FDA Drug Review (approval process)

At the end of NDA, the FDA has 60 days to conclude whether to record it so it very well may be surveyed. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness. The FDA reviews information that goes on a drug's professional labelling (information on how to use the drug).

The FDA assesses the services where the medication will be produced as a component of the approval process. FDA evaluators will confirm the application or issue an overall reaction letter. The process of FDA drug review involves.[37]

- Every member of the review team regulates a full review of his or her section of the application. Such as, the medical officer and the statistician review clinical data, while a pharmacologist reviews the data from animal studies. Between every technical regulation described the team , there is also a supervisory review.
- FDA inspectors travel to clinical study sites to conduct a routine inspection. The Agency searches for proof of fabrication, manipulation, or with finding of data.
- The project management collects every individual reviews and different informations, for example, the assessment report, into an "activity package." This document turns into the record for FDA survey.
- The review team issues a recommendation, and a senior FDA official makes a decision.[38]

Reviewing Applications

Once a new drug application is filed, an FDA review team--medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts--evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. No drug is absolutely safe; all drugs have side effects."Safe" in this sense implies that the advantages of

the drugs seem to offset the known dangers. The analysts examine the investigation study results and searches for potential issues with the application, for example, shortcomings of the examination plan or investigations. Reviewers determine whether they agree with the sponsor's results and conclusions, or whether they need any additional information to make a decision.[37] FDA approval of a drug indicate that data on the drug's effects have been reviewed by CDER, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population. The drug approval process includes.[39]

Analysis of the target condition and available treatments

Reviewers of FDA examine the condition or illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug's risks and benefits.

For instance, a drug designed to treat patients with a serious disease for which no other medication available might be considered to have benefits that offset the dangers regardless of whether those dangers would be considered unsuitable for a condition that isn't perilous.

Assessment of benefits and risks from clinical data

Reviewers of FDA evaluate clinical benefit and risk information submitted by the drug maker, taking into consideration any uncertainties that may result from imperfect or incomplete data.

Mostly, the agency suppose that the drug producer will submit results from two well defined clinical trials, to be certain that the discoveries from the primary trial are not the findings of possibility or predisposition. In specific cases, particularly if the disease is uncommon and different trials may not be attainable, persuading proof from one clinical trial might be sufficient. Proof that the drug will help the objective population ought to offset any dangers and vulnerabilities.

Strategies for managing risks

All medicines have risks. Risk management programmed includes an FDA-approved drug label, which clearly describes the drug's benefits and risks, and how the risks can be detected and managed.

Accelerated Approval

An Accelerated approval is given to for some new drugs serious and life-threatening illnesses that lack satisfactory treatments. This allows an NDA to be approved before measures of effectiveness that would usually be required for approval are available.[39]

An oral treatment for patients with a life-threatening form of cancer called chronic myeloid leukemia (CML) Gleevec (imatinib mesylate), received accelerated approval.

The drug was likewise established under the FDA's orphan drug program, which gives financial impetuses to patrons for manufacturing drugs that treat uncommon illnesses. The action of the Gleevec is to blocks enzymes that play a role in cancer growth.

The agreement depended on results of three huge Phase 2 investigations, which showed the drug could significantly diminish the degree of harmful cells in the bone marrow and blood.[37]

Step 5: Investigational New Drug (IND)

An Investigational New Drug (IND) is another synthetic or natural element or substance that has not been established for promoting as a medication in any country**.**

When a drug comes to this point, the pharma company submits an application to get the consent of the Food and Drug Administration (FDA) to begin these trials.

The workplace of medication regulator general (India) [DCG (I)] receive agreement of production/ import of new medication for marketing in the country. This office is likewise answerable for award of consent to lead clinical preliminaries of new medications as well as Investigational New Drugs.[40,41]

Application of the Investigational New Drug (IND)

Pharmacology and Toxicology Studies of animal: Gathering of adequate information from preclinical investigations to allow an appraisal with regards to whether the product is logically alright for beginning testing in humans. Also included any previous experience with the drug in humans (often foreign use).

Manufacturer Information: Information's related with the structure, producer, stability, and controls utilized for production of the drug and the drug product. This information is assessed to ensure that the company manufacture sufficient batches of the drug and has the proper controls in place to do so safely.

Clinical Protocols and Investigator Information: complete procedures for proposed clinical examinations are expected to decide whether the underlying trial will expose human subjects to unnecessary risks. This also includes the qualifications of the clinical investigators professionals who will oversee the administration of the compound.[42]

Classification of Investigational New Drugs (INDs)

Investigational New Drugs (INDs) categories in to two types: commercial and research. The big difference between these two categories is who does the application filing.

Commercial IND

This category is sought by a company that wants to test a drug in order to bring it to market. Business INDs are recorded by organizations to get marketing consent for

another medication. Any company can register for this IND, whether it's a large pharma or Biotech Company, as well as a nonprofit organization (NPO), such as a cancer research group.

Research IND

The non-commercial or research IND is the step investigators require to run tests on an existing drug. Analysts require approval when they need to test supported drug that are now available in the market. Testing may include new dosages or new applications for these drugs.

The greater parts of INDs are petitioned for non-business examination and are of three fundamental sorts: Investigator IND, Emergency Use IND, and Treatment IND. The application process is generally simpler than that of a commercial IND because testing is normally done by a smaller group of people and in one location.

Investigator's IND

It is completed by a practitioner who initiates and performs an examination as well as administers and dispensing the IP. A physician may send a research IND to recommend testing an unapproved drug or an approved drug for new indications or in a different patient group.[43]

Emergency Use IND

This IND enables FDA to approve the use of an experimental drug in an emergency situation where an IND is not required under -21 CFR Sec 312.23 or Sec 312.34. It may also be used for patients who do not follow the requirements of an established research protocol or for patients who do not have access to an appropriate study protocol.[44]

Treatment IND

Expanded Access IND is another name for it. This IND will be used to apply new medications that have shown efficacy in clinical trials for critical and life-threatening disorders whilst the final clinical work is being completed and the FDA review is being completed (21 CFR 312.34).[45]

The New Drug Application (NDA) is the vehicle by which medication supports officially recommend that the FDA endorse another drug available to be purchased and advertising.

Some 30% or less of initial drug candidates proceed through the entire multi-year process of drug development, concluding with an approved NDA, if successful.[46]

The objectives of the NDA are to give adequate data to allow FDA analysts to build up the total history of the drug. Various facts for the application are.

- Information of the Patent and manufacturing
- Drug safety and effectiveness for its proposed uses when used as directed
- Reports on the outline, submission and conclusions of finished clinical trial by the Institutional Review Board's
- Drug susceptibility to abuse
- Proposed labeling (package insert) and directions for use

1. Exceptions to this process include voter driven initiatives for medical marijuana,[47] in certain states.
2. Medications for which NDAs are submitted will have effectively gone through a few clinical trials.
3. As such, drugs that reach the NDA phase typically have a high probability of securing FDA approval.

Classification of drugs in NDA

The Center for Drug Assessment and Research (CDER) categorizes experimental drug applications based on the type of drug and the planned use.[48]

Type 1 — New Molecular Entity A Type 1 New Molecular Entity (NME) is an active ingredient that not have any active moiety and has been previously approved by the Agency in an application submitted under section 505 of the Act3 or has been previously marketed as a drug in the United States. Enantiomer or a racemic mixture is a new molecular entity only when neither has been previously approved or marketed.

A Type 2 — New Active Ingredient A Type 2 new active ingredient (NAI) include those products whose effective part has been previously accepted or promoted in the United States, however whose specific salt, ester, or noncovalent derivative of the unmodified parent atom has not been accepted by the Agency or marketed in the United States, either alone, or as a portion of a combined product.

Type 3 — New Dosage Form A Type 3 NDA is for another measurement type of a functioning ingredient that has been approved or place on the market in the United States by something very similar or another candidate yet in an alternate dose form. The sign for the drug item shouldn't be equivalent to that of the all around promoted drug product.

Type 4 — New Combination: A Type 4 or New Combination NDA is for novel drug-drug combination of at least two active components. An advantage for another drug-drug combined product might have more than one classification code if minimum one ingredient of the mixture is a NME or another active component.

Type 5 — New Formulation or Other Differences A Type 5 or New Formulation or Other Differences NDA is for a product, other than a new dosage form, that differs from a product already approved or marketed in the United States (e.g., new indication, new applicant, new manufacturer).

Type 6 — New Indication or Claim, Same Applicant A Type 6 or New Indication or Claim, Same Applicant NDA used for an NDA received prior to July 27, 2009,5

in accordance a drug product that copies a drug product previously consider or promoted in the United States by a similar candidate, then again, actually it is expected for another sign or guarantee (same functioning moiety or mixture of functioning moieties, same salt(s), ester(s), or other noncovalent derivative(s), same method of administration, and same preparation method (counting all ingredients utilized in the production method whether they are available in the final dose form).

Type 7 — Previously Marketed But Without an Approved NDA A Type 7 NDA is a drug product that incorporate an active moiety that has not been previously approved in an utilization, although has been marketed in the United States. This catagorization applies just to the main NDA consent for a drug product including these active moieties.

Type 8 — Rx to OTC A Type 8 NDA is a drug product planned for over-the-counter (OTC) marketing that contains an active ingredient that has been approved previously or advertise in the United States only for release of product by prescription.

Type 9 — New Indication or Claim, drug not being advertises under type 9 NDA after approval. A Type 9 NDA is intended for another evidence or demand for a drug product that is as of now being inspected under an alternate NDA (the "parent NDA") and the candidate doesn't mean to market this medication item under the Type 9 NDA after approval.

Type 10 — New Indication or Claim, Drug to be promoted under type 10 NDA after approval. A Type 10 NDA is for a drug that is a copy of a drug product that is the matter of either a forthcoming or approval NDA, and the candidate expects to market the drug under this different Type 10 NDA after approval.

P***rocess of NDA***

The regulatory process for New Drug Applications (NDA) requires sufficiently preclinical evidence to check the efficacy of the drug and justify the initiation of clinical trials. In 2001, the Drug Administrative Law was updated to include premarket testing, clearance of experimental drug formulations, and a prohibition on drug adulteration.[49]

Abbreviated New Drug Application (ANDA)

Conventional drug applications are mentioned as Abbreviated New Drug Application.

- Pharmaceutical organizations should concede ANDAs and accept FDA's endorsement prior to advertising new conventional drug as indicated by 21CFR 314.105(d).
- Once approved, an applicant can manufacture and market generic drug to provide safe, effective and low cost alternative of innovator drug product to the public.
- Generic drug applications are entitle "abbreviated" as they are normally not need to incorporate preclinical and clinical data to establish safety and effectiveness. Instead conventional applicants should scientifically illustrate that their product is acts in the similar way as the innovator drug.
- A generic drug is comparable to Innovator drug I dosage form, strength, route of administration, quality, performance and intended use.
- Measuring the time it takes for a generic drug to enter the bloodstream in 24-36 healthy volunteers is one way to show bioequivalence. The amount of active ingredients in the body and the time it takes for them to enter the bloodstream should be equivalent to that of the Innovator medication.
- The WAXMAN-HATCH ACT, also known as the WAXMAN-HATCH ACT, defined the use of bioequivalence as a basis for accepting generic drug drugs in 1984. Because of this act, generic drugs are less expensive without the need for unnecessary and redundant clinical trials.

Somehow applicants indicate that a generic drug acts similarly as the innovator drug is to quantify the time it takes the conventional medication to come to the Blood stream in healthy volunteers.

This evidence of "bioequivalence" gives the rate of absorption, or bioavailability, of the conventional medication, which can then measure up to that of the innovator drug. To be supported by FDA, the conventional version should convey similar measure of active components into a patient's circulatory system in a similar measure of time as the innovator drug.[50]

Investigation of medicinal products dossier (IMPD)

The IMPD is the fundamental, for approval of clinical trials by the qualified in the EU.

- The Clinical Trial Directive came in power blending the laws, guidelines and regulatory arrangements of the Member states identifying with the execution of GCP in the lead of clinical trial on therapeutic product for human use.
- The regulations presented an orchestrated strategy for the approval to play out a clinical report in any of the EU Member States.
- Furthermore, it outlines the documents that must be sent to the Ethics Committee, as well as the IMPD that must be accepted by the responsible authority. A dossier is a series of documents relating to a single individual, case, or subject. As an exception- Health history of the patient Medicinal medication dossier: a file containing comprehensive information on a specific substance.[51-52]

Innovator/ Brand-Name Drug

A drug with a brand name and a copyright (which means it can only be manufactured and marketed by the corporation that owns the patent) When a brand-name drug's patent rights terminates, conventional duplicates of the drug might be sold if the FDA approved.[53]

Generic-Drugs

"A medication that is identical to a brand/innovator drug in dose size, potency, administration route, quality and execution attributes, and arranged use," as indicated by the explanation.

The active ingredients should be the same as in the initial formulation. In terms of pharmacokinetic and pharmacodynamic properties, generic drugs are similar or within an appropriate bioequivalent spectrum to their brand-name counterparts, according to the FDA.[54,55]

A generic drug is a pharmaceutical drug that is not branded but is similar to a branded or reference listed drug in terms of dosage, administration quality and performance.[56] The word may likewise apply to any medication promoted under its chemical name without publicizing, or to the synthetic cosmetics of a drug instead of the brand name under which the medication is sold.[57]

Despite the fact that they may not be related with a specific organization, generic drugs are normally concern with government ordinance in the nations where they are distributed. According to the description the active ingredients should be the same as in the initial formulation. In terms of pharmacokinetic and pharmacodynamic properties, generic drugs are similar or within an appropriate bioequivalent spectrum to their brand-name counterparts, according to the FDA.[52,53]

Generic Drug Approval Process

1962 Kefauver-Harris Drug Amendments Act

This amendment was the first to mandate drug companies to show the FDA that a medication is safe and effective before selling it.[58]

Drug Price Competition and Patent Term Restoration Act (1984) - (Hatch-WaxmanAct)

- Approve approach to advertise conventional forms of brand-name drugs (Without Proving Clinical Trial).
- Reducing the expense related with the approval of a conventional medication.
- Allowing early-experimental use.
- compensating generic drug companies for time spent from the patent term due to regulatory approval formalities (allowed brand-name manufacturers to extend their patent protection for up to 5 years for new products)
- Motivating the generic drug manufacturers Legislative History.
- The FDA's Generic Drugs Division is in charge of reviewing ANDAs and authorizing prescription label ads.
- The FDA's Office of Generic Drugs operates a website at http://www.fda.gov.org that features additional material for generic drug suppliers, including a flow map depicting the ANDA review process. It also explains how the FDA assesses the consistency, protection, and effectiveness of generic drug drugs prior to marketing clearance.
- Brand name drug product, applicable chemistry and manufacturing data, and suitablr labeling.
- Promoters of generic drugs are not needed to undergo nonclinical animal toxicity trials or costly clinical effectiveness and safety studies that are required for novel drug applications.
- The ANDA contains data which is then submitted to FDA's Center for drug evaluation and research for the generic drugs.
- FDA approved conventional drugs should greet the similar inflexible standard as the innovator drug.

To be approved by the FDA, a generic drug product must contain the same active ingredient as an approved drug product, though the inactive ingredients can differ. Be equal in strength, dosage type, administration pathway, indications, bioequivalence, and batch requirements." Licensed drug products with clinical equivalence by the FDA the orange book contains evaluations and lists of all licensed brands, both innovator and generic.[59]

Generic drug approval process in India

CDSCO (Central drugs standard control organization) under the ministry of health and family welfare is responsible for approval new drugs clinical trials and licensing of drugs. Drugs are regulated in India both central and state level through the CDSCO.

Drug regulatory agencies permit the licenses at the state level. The regulation of drugs, medical devices and biological products in India is distributed with in various ministries.[60]

There are basically two regulatory bodies which direct the drug approval, advertising, production, standards and drug cost in India. [Fig.6].[61]

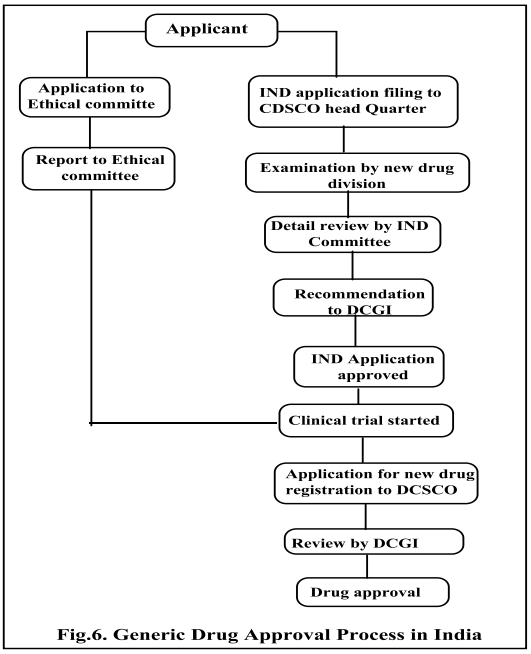

Fig.6. Generic Drug Approval Process in India

DISCUSSION

The drug discovery crusade is the identifications of new molecular entities that may be of value in the treatment of diseases that competent as presenting unmet medical needs. The traditional method of drug discovery and development process suffers from a high attrition rate. Modern method of drug development can provide new insights that could never be realized using the older and established methodologies.

Over the last three decades there has been a remarkable increase in the cost and timeline of delivering new drugs for clinical use. In spite of increased investments, expenditure in research support by pharmaceutical companies and technological advances in the scientific tools available, efforts to increase the number of molecules coming through the drug development channel have largely been fruitless. Not more than 1% of drugs in the discovery and development pipeline will reach the marketplace.

As per the requirement of safe and efficacious pharmaceutical medications, technological solutions will be of increasing interests that reduce barriers to clinical success instead of simply shifting obstructions and necessitating new compromises in the discovery and development process. For the discovery of safe and effective drug critically depends upon experimental approaches capable of providing high-impact information on the biological effects. New technologies in the drug discovery and development can serve as valuable enablers and potentially contribute to reducing the current, unacceptably high rates of compound clinical failure.

CONCLUSION

New Drug development process is an expensive and risky affair and involves lot of money and time. A drug before reach to a patient, it must go through meticulous testing to determine whether it is safe, effective at treating the condition it was developed for, and to find out the correct dosage and appropriate route of administration. Drug discovery and development process provide more scientific knowledge of any compound, how this compound is beneficial for human being, what is the mechanism of action, more about the drug dosage form, and also therapeutic benefit more than of harm Full effect or side effect. Drug development process results in very significant increase in the therapeutic index and can move into a more informed and rational phase aimed at optimizing drug design for targeted system of body.

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