Clinical Research – A Basic Understanding

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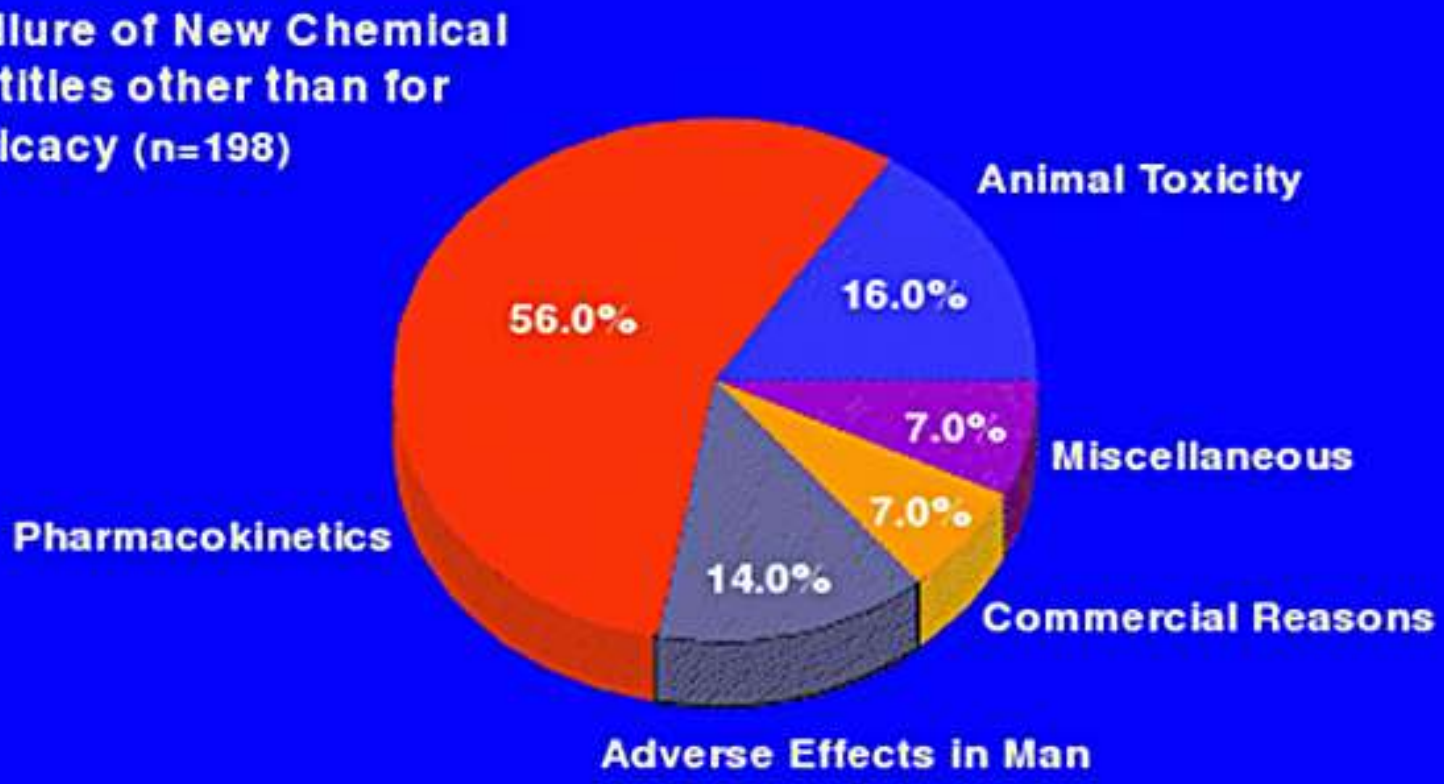
Definition for drug according to US Food, Drugs and Cosmetics act

- A substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication recognized or defined by US Food, Drug and Cosmetic Act.
- A drug can be chemical, biologic, synthetic or non synthetic

- Drug discovery is the process by which drugs are identified and / discovered.
- Drug development is a process which takes a drug from initial discovery to the pharmacy shelves.
- The entire drug discovery and development process takes an average of 12 – 15 years to complete and costs around ~$950 million
- About 75% (~$700 million) of this cost is attributable to failure during development
- 90% of all drug development candidates fail to make it to the market.

Problem: Drug Discovery Challenge



T. Kennedy, DDT 2(10) 1997

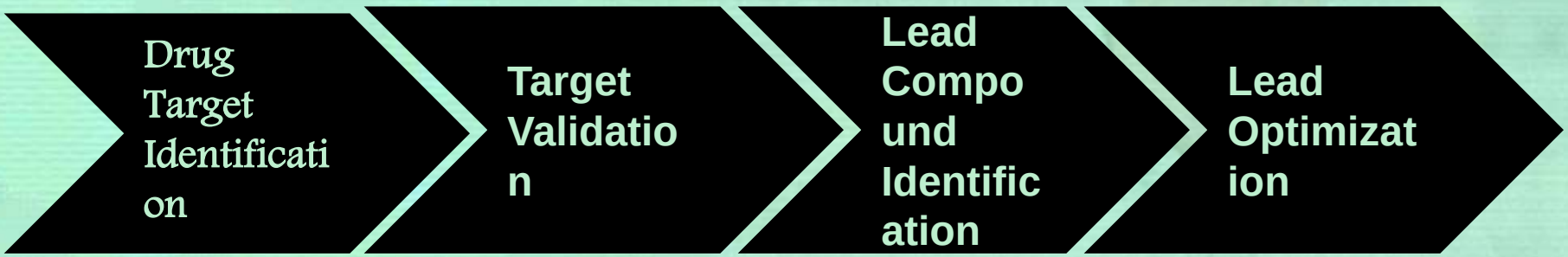
- New Drug development is divided to 4 phases
  1. **Drug Discovery**
  2. **Pre clinical development**
  3. **Clinical Trial**
  4. **Post approval**

Drug Discovery

- In past most of the drugs were discovered by
  - Identifying the active ingredients from traditional medicines
  - Serendipitous discovery
- Later the trend was to alter the structure of existing molecules and make them more active
  - i.e. SAR
- Most modern approach
  - Understand how a disease is controlled at molecular and physiologic levels and target that entities

- Why to extract active ingredients from plants?
  - Plants even though they are effective may contain more than 400 chemicals.
  - eg : Quinine (Antimalarial) from Cinchona bark.
- Serendipitous discovery
  - Penicillin by Alexander Fleming
- Altering the structure of compounds
  - Nalorphine from Morphine
- Target specific molecules
  - Levodopa for Parkinson's disease

Drug discovery process can be summarized as



Drug Target Identification

- "target" is the naturally existing cellular or molecular structure involved in the pathology of interest that the drug-in-development is meant to act on.
- It has been estimated that 10 genes contribute to multifactorial disease
- These disease genes are linked to another 5-10 genes in physiologic circuits
- If these number is multiplies with number of known diseases there are ~5000 – 10000 potential drug targets

- Current therapy is based upon less than 500 molecular targets
  - 45% of which are G-protein coupled receptors
  - 28% are enzymes
  - 11% are hormones and factors
  - 5% ion channels
  - 2% nuclear receptors
- New techniques for target identification are
  1. Genomics
  2. Bioinformatics
  3. Proteomics
- **Genomics**
- Evolved from 2 independent advances

a) **Automation** – resulting in a significant increase in the number of experiments that could be constructed in a given time. (eg. DNA sequencing)

a) **Informatics**– the ability to transform raw data into meaningful information by applying computerized techniques for managing, analyzing, and interpreting data.

- the identification of new biological targets has benefited from the genomics approach
- Sequencing of microbial genomes will enable the identification of novel drug targets, especially when comparing to the human genome
- **Bioinformatics**
- identification of novel drug targets is now feasible by systematically searching for paralogs (related proteins within an organism) of known drug targets (eg. may be able to modify an existing drug to bind to the paralog).

- Using gene expression microarrays and gene chip technologies, a single device can be used to evaluate and compare the expression of up to 20000 genes of healthy and diseased individuals at once.
- **Proteomics**
- It is a large scale study of proteins, particularly their structure & functions
- The word "proteome" is a blend of "**prote**in" and "gen**ome**“
- It is becoming increasingly evident that the complexity of biological systems lies at the level of the proteins, and that genomics alone will not suffice to understand these systems.
- Therefore, the analysis of proteins (including protein–protein,protein–nucleic acid, and protein–ligand interactions) will be utmost importance to target discovery

Target Validation

- Involves demonstrating that a particular target is relevant to the disease being studied through complicated experiments in both living cells and in animal models of disease.
- Since strong interactions between a protein and its ligand are characterized by a high degree of complementarity, knowledge of the protein three dimensional structure will enable the prediction of "druggability" of the protein.
- **Lead Compound identification**
- Compounds are mainly identified using random (screening) or rational (design) approaches.

1. **High-throughput Screening**
   - Used to test large numbers of compounds for their ability to affect the activity of target proteins.

- Uses robotics, data processing and control software, liquid handling devices, and sensitive detectors and it allows a researcher to quickly conduct millions of biochemical, genetic or pharmacological tests.
- **Structure Based Drug Design**
- Three dimensional structures of compounds from virtual or physically existing libraries are docked into binding sites of target proteins with known or predicted structure.
- Once hits have been identified via the screening approach, these are validated by re-testing them and checking the purity and structure of the compounds.

Lead Optimization

- Leads are characterized with respect to pharmacodynamic properties such as efficacy and potency *in vitro* and *in vivo*, physiochemical properties, pharmacokinetic properties, and toxicological aspects in order to obtain compounds with suitable properties to become a drug.

Preclinical Studies

- Involve *in vitro* studies and trials on animal populations.
- Wide ranging dosages of the compounds are introduced to the cell line or animal in order to obtain preliminary efficacy and pharmacokinetic information.
- designed primarily to assess the safety and viability of new molecular entities.
- Prior to clinical studies, the sponsor needs evidence that the compound is biologically active, and both sponsor and the FDA need data showing that the drug is reasonably safe for initial administration to humans.

Clinical Trials/Study

- Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Phases of Clinical Trials

- **Phase 0**
  - A recent designation for exploratory, first-in-human trials.
  - also known as human micro dosing studies and are designed to speed up the development of promising drugs.
  - Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics
- **Phase I**
  - a small group of healthy volunteers (20-80) are selected to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of a therapy.

- normally include dose ranging studies so that doses for clinical use can be set/adjusted.
- There are three kinds of phase I trials
  - **Single Ascending Dose (SAD) studies**– a small group of patients are given a single dose of the drug and then are monitored over a period of time. If they do not exhibit any adverse side effects, the dose is escalated and a new group of patients is given the higher dose.
  - **Multiple Ascending Dose (MAD) studies**– a group of patients receives multiple low doses of the drug, while blood (and other fluids) are collected at various time points and analyzed to understand how the drug is processed within the body.
  - **Food effect**– designed to investigate any differences in absorption caused by eating before the dose is given.

Phase 1 CLINICAL TRIALS [STAGE 3]

Begins after 30 days of filing IND.

Drug given to 20-100 healthy volunteers

-Duration could vary from 1 month to 1 year.

-Cost could vary from $100K to $1000K

Following is studied here :

-Drug absorption/Metabolism in human.

-Effect on organs and tissues.

-Side affect of different dosages.

Thus early evidences on effectiveness are achieved.

Proceed to next Stage.

80% of drugs fail the Phase I clinical trial.

- **Phase II**
  - performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients.
  - Phase II studies are sometimes divided into Phase IIA and Phase IIB
    - Phase IIA is specifically designed to assess dosing requirements.
    - Phase IIB is specifically designed to study efficacy.

Phase 2 CLINICAL TRIALS [STAGE 4]

Drug given to 100 - 300 patient volunteers

-Duration could vary from 1 year to 2 years.
-Cost could vary from $10 - $100 million.

Following is studied here :

-Drug effectiveness in treating the disease.
-Short term side effects in patients

Less than 1/3rd of INDs survive phase 2

Proceed to next Stage.

- **Phase III**
  - randomized controlled multicenter trials on large patient groups (300–3,000 or more)
  - Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

Phase 3 CLINICAL TRIALS [STAGE 6]

FDA consulted before beginning phase 3

Drug given to 1000-3000 patient volunteers

-Duration could vary from 3 years to 4 years.
-Cost could vary from $10 - $500 million

Following is studied here :

-Safety of Drug [Benefits v/s risk analysis]
-Long term side effects in patients

Proceed to next Stage.

- Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life.
- **Phase IV**
  - also known as **Post Marketing Surveillance Trial**.
  - Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold.

Market Launch/Phase 4

Drug is launched to the Market

Additional post marketing testing of patients to

-support the use of the approved indication.

-Finding new therapeutic opportunities

-Extending use of the drug to different classes of patients like children

Marketing of a Drug

- After Phase III all drug remains in the market for 4 years as New Drug.

Trial Design

- Trial Designs
  - Parallel group Study
  - Cross over study
  - Titration Designs
  - Cluster Randomization designs

Need For A Good Design

- Trial set up is achievable
- Subject recruitment at time
- Trial completed at time
- Result generated at time
- Dossier preparation in time

Parallel Group Study

- Patient/arm is administered to one and only one treatment procedure, in a random fashion.

Test Arm →

Control Arm →

Basically of two types

I. **Group comparison (parallel group)**–

compares 2 or more treatments, most common in confirmatory trials

e.g. treatment grp v/s control grp

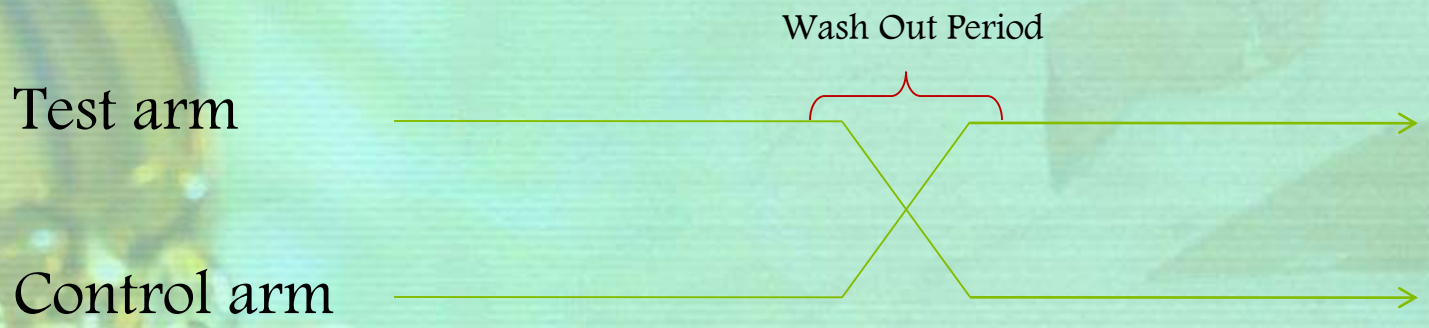
II. **Matched pairs parallel design**–

– complete block design with a block size of 2

– Patient is matched with another of similar prognostic characteristics

Cross over study

- Each arm receives more than one treatment at different dosing periods.
- Patients in each arm receives all treatments under investigation.
- It allows a within-patient comparison between treatments.



Titration study

The dose are tittered for the subject

Why titration study?

-To expose the patients only to the amount of dose they need

- To provide a conservative and cautious approach in investigating the dose-response relationship, and finally the therapeutic window.

In Phase-I

- Rising single-dose design
- Rising single-dose cross over design e.t.c

Standard titration design (phase-II)

- To characterize the dose response relationship which defines the *Therapeutic range* of the Test drug

Therapeutic window = MTD – MED

- **Forced Titration (Dose Escalation) study**

– Used when drug is unlikely to be effective at lower dose

– Safety is in concern.

- **Optional titration study**

– A modified titration design with a concurrent placebo-controlled group where subjects are titrated until they show a well-characterised favorable/unfavourable response.

Randomization

- The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
- The main advantages are
  1. Randomization removes the potential of bias in the allocation of participants.
  2. Tends to produce comparable groups, prognostic factors and other characteristics at the time of randomization will be on an average evenly distributed between the intervention and control arms
  3. Validity of statistical tests of significance is guaranteed.

Methods of Randomization

- **Fixed Allocation (Static)Randomization**
  - Simple Randomization
  - Blocked Randomization

- **Adaptive (Dynamic)Randomization**
  - Baseline Adaptive Randomization
  - Response Adaptive Randomization

Blinding

A procedure in which one or more trial related parties in the trial are kept unaware of, which treatment the subjects receive in a clinical trial.

- **Single Blinding**- subjects being unaware

- **Double Blinding**- both the subject and the investigator are unaware

- **Triple Blinding**- A study in which the statistical analysis is carried out without knowing which treatment patients received, in addition to the patients and investigator also being unaware.

Ethics Committee

- Rights, Safety and Well-being
  - A body constituted of medical and non-medical members whose responsibility is to ensure the protection of rights safety and well-being of human subjects, to provide public assurance of that protection, by reviewing or approving trial protocol, suitability of investigators, facilities and methods and materials used in obtaining informed consent of trial subjects

    ICH-GCP E6 1.27

Ethics Committee Submission

- What?

  Submission of relevant study documents for review and approval.

- Study documents

  Trial Protocol with date and version no:

  - Title with signature of PI as attestation for conducting the study.
  - Clear research objectives and rationale.
  - Inclusion and exclusion criteria.
  - Precise description of methodology, including sample size with its justification, type of study design, intended intervention, dosage of drugs, route of administration, duration of treatment and details of invasive procedures, if any.
  - Plan to withdraw or withhold standard therapies in the course of research.
  - Statistical plan.

- Safety of proposed intervention.
- An account of management of risk and injury in case of research involving more than minimal risk.
- An account of storage and maintenance of all data.
- Plans for publication of results.
- A statement on probable ethical issues and steps taken to tackle the same.

- Inform Consent Form in English and/or vernacular languages (including back translations) and Patient information sheet.
- IB with date and version number.
- Subject recruitment procedures.
- Insurance policy/compensation for participation and for SAE.
- CRFs

- Investigator’s Undertaking.
- Agreement to comply with national and international GCPs.
- Current CV of PI.
- Details of funding agency/sponsor and fund allocation.
- Statement of relevant regulatory clearances.
- For international studies, details about foreign collaborators and documents for review by DCGI.
- For exchange of biological material in international collaborative study an MoU/ Material Transfer Agreement between the collaborating partners.
- A statement of Conflict-of-interest (COI), if any.

- Why?
  - Regulatory requirement
  - Needed for initiation of site.
- When?
  - After site selection and before site initiation.
- Who?
  - Responsibility of Investigator.

Informed Consent

- A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Placebo

- is a simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient.
- **placebo effect**

Terminologies

- **Case Report Form (CRF)**
  - A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
- **Sponsor**
  - An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
- **Contract Research Organization (CRO)**
  - A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

- **Investigator**
  - A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.
- **Impartial Witness**
  - A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

- **Protocol**
  - A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.
- **Monitoring**
  - The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
- **Multicentre Trial**
  - A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

- **Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**
  - Any untoward medical occurrence that at any dose:
    - - results in death,
    - - is life-threatening,
    - - requires inpatient hospitalization or prolongation of existing hospitalization,
    - - results in persistent or significant disability/incapacity,
    - - is a congenital anomaly/birth defect
- **Adverse Drug Reaction (ADR)**
  - all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

Thank You.....