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Review Article

NEW DRUG DEVELOPMENT: A REVIEW

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Abstract: Drug development is a highly complex, tedious, competitive, costly and a commercially risky process. From the synthesis/identification of the new molecule to its marketing as a new drug, the process takes at least 20 years with an investment of millions of dollars. New Drug development involves drug discovery, preclinical development, clinical development and post approval process. Due to an increase in the attrition rate of new drugs in clinical research, the USFDA (US- Food and Drug Administration) has released the Critical Path Initiative & the Critical Path Opportunity programs to tackle the issues involved in new drug failure. Phase 0 and Adaptive clinical trials are such initiatives taken to ensure that more molecules have drug approvals for marketing. This review highlights the various processes involved in new drug development.

Key**words:** Drug discovery, Preclinical development, Clinical development.

INTRODUCTION

Science and Technology has always been on track aiding in the enhancement of the Quality Of Life of Human population. The changes happening over the few years in the Drug manufacturing industry has been quite dramatic. Sponsor companies are investing billions of dollars into their drug manufacturing research projects. Out of thousands of chemical compounds that are possible new drug candidates, only few will qualify for Clinical research.[1] The attrition rate in Clinical development for Phase I is 23%, for Phase II is 62% & for Phase III it is 45%. These numbers shows how stringent and important is the New Drug Development practice.

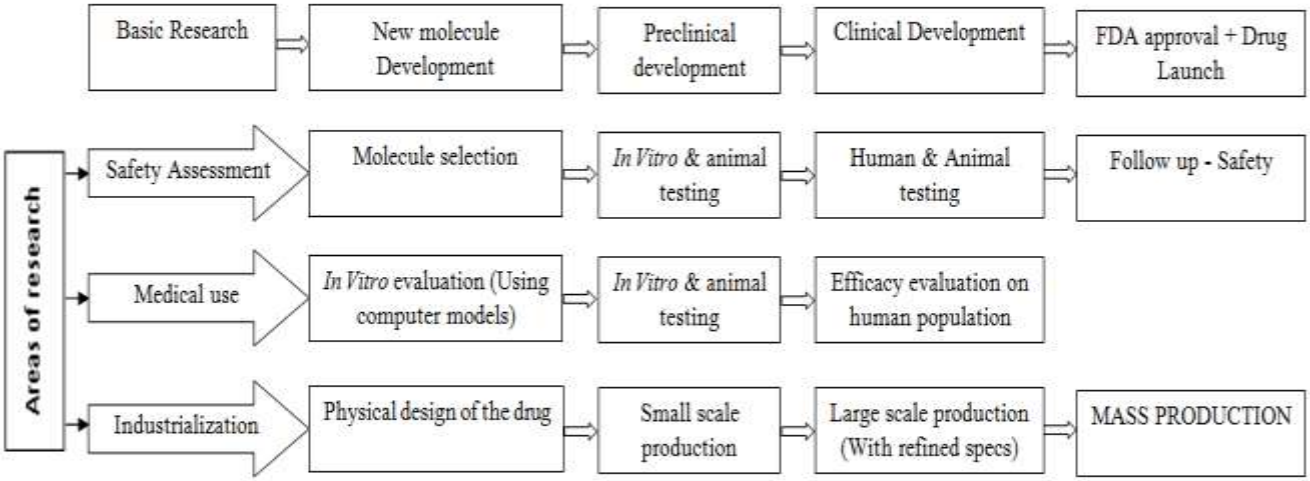

Figure 1: FDA's "Critical Path Initiative" (CPI) project

To mitigate these risks, the USFDA came up with the "Critical Path Initiative" (CPI) project to guide the new drug development process. The CPI was launched in the year 2004 as a result of the FDA's report on "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products".[2] It was designed to expand the gap between the scientific discoveries towards the cure of diseases with the use of innovative treatment methodologies. The report highlights the need to update all the technical and scientific tools to help in evaluating the safety and efficacy of medical products. New Drug Development involves four stages namely Drug discovery, Pre Clinical Development, Clinical Development and the Post approval process.

I. Drug discovery [3]

The Drug discovery process involves identifying a particular diseased condition and studying the modality of treatment for the disease in question. If a new molecule is available for a particular disease state, the aim is to cure the

ailment in a better/faster way than the current medications available. Drug discovery has 4 steps namely, Target selection, Lead identification, Lead optimization and Pharmacological profiling.

1. Target selection:

A target could either be a protein, RNA or a gene that is effective, safe and 'druggable'. Druggable targets are those which are 'drug molecule friendly' and responds on *In Vitro* and *In Vivo* measurement. Targets are classified into two groups namely, established targets and new targets. The targets that have an established ground with regards to its functioning and are supported by research publications are categorized as established targets. A 'new target' is not 'established' yet, but is usually a part of the drug discovery crusade, an upcoming ideology that needs more research. This includes most of the newly identified proteins, receptors, enzymes etc.

2. Lead identification:

A lead is a chemical or a series of chemicals that has the ability to bind to a target. To get the right lead for a target, a large number of probable chemical entities need to be tested. This is usually done by high-throughput screening aided by data processing software and highly sensitive detectors.

3. Lead optimization (Lead-Target Interaction):

The identified lead molecule is tested for ADMET (Adsorption, Distribution, Metabolism, Excretion and Toxicity). Once the lead is proven for nil toxicity and mutagenicity, it is a potential lead compound. A continuous screening of these lead compounds, with subsequent tweaking in its chemical structure to fit more to the desired lead-target action will help in optimizing lead molecules.

4. Pharmacological profiling

The Pharmacological profiling helps in measuring the effectiveness of the lead compound by assessing key parameters like EC/IC 50, pA_2, Hill slope values etc which in turn aids in estimating the dosage range, dose regimen and mode of drug delivery. The preclinical studies play a very important role in the Pharmacological profiling.

II. <u>Pre-clinical development (PCD)</u>

The Pre-clinical development spaces the gap between drug discovery and clinical development. PCD includes pharmacology studies, toxicity studies, pharmacokinetic studies, reproduction toxicity, genotoxicity and carcinogenicity. Other studies involving phototoxicity, Immunotoxicity, juvenile animal toxicity and abuse liability may be conducted on a case-by-case basis.

The goal of PCD include characterization of new molecule toxic effects with respect to target organs, dose dependence, relationship to exposure & when appropriate, potential reversibility. The information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse effects. It also plays a vital role for Investigational New Drug (IND) towards getting an approval from the regulatory authority.

1. Toxicity studies[4]

Toxicity studies are of two types namely, single dose toxicity and repeated dose toxicity studies.

In Single dose toxicity studies, otherwise known as Acute Toxicity**,** two rodent species are chosen. Equal numbers of male and female animals are used. The number of animals should be at least 5 and the duration is 14 days. The route of administration should include both parenteral and the route intended to be used in humans. It helps to define the Maximum Tolerated Dose (MTD) & the Maximum Feasibility Dose (MFD).

In Repeated dose toxicity studies(Dose ranging studies), usually two species of mammals, one of which is a non rodent (equal numbers of male and female animals) is chosen based on its similarity to humans with respect to the PK profiling including biotransformation. The sample size of the treatment group should allow a meaningful scientific interpretation of the data generated, however ethical considerations and practical aspects are also of importance. The route of Administration of the new molecule should be the same route as intended for humans. The duration of administration depends on the duration of the proposed therapeutic use in humans. When toxicity studies of more than three months duration are required, the general recommendation is to do a repeated dose toxicity study of two or four weeks duration thus making it a dose-finding study for a longer term investigation. The frequency of administration should be determined on case to case basis, taking account of the intended clinical dosing regimen and the toxicological, PK/PD profile of the new molecule. The dose levels should include a low-dose that is enough to produce a PD effect/desired therapeutic effect; a high-dose for enabling the identification of target organ toxicity or other non-specific toxicity, or until limited by volume of dose and an intermediate-dose which is the geometric mean between the high-dose & low-dose.

2. Pharmacology studies

The pharmacology studies are categorized into two groups, the Safety pharmacology and Pharmacodynamic studies (PD). The core battery of safety pharmacology studies includes the assessment of drug effects on cardiovascular, central nervous and respiratory systems, and should generally be conducted before human exposure. Whereas, the PD studies (*In Vivo* and/or *In Vitro*) are intended to investigate the mode of action and/or effects of the new molecule in relation to its desired therapeutic target.

3. Pharmacokinetics

The Pharmacokinetics (based on absorption, distribution, metabolism and excretion) studies are conducted in test species to understand the *In Vitro* biochemical information relevant to potential drug interactions that should be made available before exposing large numbers of humans to the study medication or treating them for long duration. Pharmacokinetics studies are generally conducted prior to Phase III Clinical study.

4. Local tolerance studies

This is done to evaluate the local tolerance resulted by the intended therapeutic route as a part of the general toxicity studies.

5. Carcinogenicity studies [5]

`The objectives of carcinogenicity studies are to identify tumorogenic potential in animals and to assess the relevant risk in humans. Any cause for concern derived from laboratory investigations, animal toxicology studies, and data in humans leads to the need for carcinogenicity studies. The practice of requiring carcinogenicity studies in rodents was instituted for new molecules that were expected to be administered regularly over a substantial part of a patient's lifetime. Since carcinogenicity studies are time consuming and resource intensive, they should only be performed when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential.

Factors considered for carcinogenicity testing are:

i. Duration & Exposure

Carcinogenicity studies should be performed for a new molecule whose expected clinical use is continuous for at least 6 months. For new molecules used frequently in an intermittent manner in the treatment of chronic or recurrent conditions, carcinogenicity studies are generally needed. The carcinogenicity studies may also need to be considered for certain delivery systems which may result in prolonged exposures.

ii. Cause for concern

Carcinogenicity studies may be recommended for some new molecules if there is a concern about their carcinogenic potential. A few instances would be, where in a previous demonstration of carcinogenic potential in the product class that is considered relevant to humans, a structure-activity relationship suggesting carcinogenic risk, an evidence of pre-neoplastic lesions in repeated dose toxicity studies or a long-term tissue retention of parent molecule or its metabolite(s) resulting in local tissue reactions or other pathophysiological responses.

iii. Carcinotoxicity

Unequivocally Carcinotoxic compounds in the absence of other data are presumed to be trans-species carcinogens, implying a hazard to humans. Such molecules need not be subjected to long-term carcinogenicity studies.

iv. Indication and patient population

When carcinogenicity studies are required they usually need to be completed before submitting application for marketing approval. However, completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population.

v. Route of exposure

The route of exposure in animals should be the same as the intended clinical route when feasible.

6. Genotoxicity/Mutagenicity studies [6]

Genotoxicity tests can be defined as the *In Vitro* and *In Vivo* tests designed to detect molecules that induce genetic damage directly or indirectly by various mechanisms. These tests should enable hazard identification with respect to damage to DNA and its fixation.

`It is clear that no single test is capable of detecting all relevant genotoxic agents. Therefore, the approach is to carry out a battery of *In Vitro* and *In Vivo* tests for Genotoxicity. Such tests are complementary rather than representing different levels of hierarchy.

The standard test battery is appropriate to assess Genotoxicity in a bacterial reverse mutation test. This test has been shown to detect relevant genetic changes and the majority of genotoxic rodent carcinogens. The DNA damage considered to be relevant for mammalian cells and not adequately measured in bacteria should be evaluated in mammalian cells. Several mammalian cell systems are in use: Systems that detect gross chromosomal damage (*In Vitro* tests for structural and numerical chromosomal aberrations), Systems that detect primarily gene mutations, and a System that detects gene mutations and clastogenic effects (mouse lymphoma tk assay). An *In Vivo* test for genetic damage should usually be a part of the test battery to provide a test model in which additional relevant factors (ADME) that may influence the genotoxic activity of a compound are included. An *In Vivo* test for chromosomal damage in rodent hematopoietic cells tests the chromosomal damage in rodents which could either be an analysis of chromosomal aberrations in bone marrow cells or an analysis of micronuclei in bone marrow or peripheral blood erythrocytes.

For molecules giving negative results, the completion of this standard test battery, performed and evaluated in accordance with current recommendations will usually provide a sufficient level of safety to demonstrate the absence of genotoxic activity. Molecules giving positive results in the standard test battery may, depending on their therapeutic use, need to be tested more extensively. Furthermore, molecular techniques to study mechanisms of Genotoxicity in the standard battery systems may be useful for risk assessment.

7. Reproductive toxicity/Teratogenicity studies [7]

The aim of reproductive toxicity studies is to reveal any effect of one or more active molecule(s) on mammalian reproduction. For this purpose, both the investigations and the interpretation of the results should be related to all other pharmacological and toxicological data available to determine whether potential reproductive risks to humans are greater, lesser or equal to those posed by other toxicological manifestations.

The combination of studies selected should allow exposure of mature adults and all stages of development from conception to sexual maturity. To allow detection of immediate and latent effects of exposure, observations should be continued through one complete life cycle, that is, from conception in one generation through conception in the following generation. For convenience of testing, this

integrated sequence can be subdivided into three stages namely, Premating to conception (adult male and female reproductive functions, development and maturation of gametes, mating behavior, fertilization), Conception to implantation (adult female reproductive functions, pre-implantation development, implantation), Implantation to closure of the hard palate (adult female reproductive functions, embryonic development, major organ formation), Closure of the hard palate to the end of pregnancy (adult female reproductive functions, fetal development and growth, organ development and growth), Birth to weaning (adult female reproductive functions, neonate adaptation to extrauterine life, pre-weaning development and growth) and Weaning to sexual maturity (post-weaning development and growth, adaptation to independent life, attainment of full sexual function).

i. Criteria for animal selection

The animals used must be well defined with respect to their health, fertility, fecundity, prevalence of abnormalities, embryofetal deaths and the consistency to display from study to study. Within and between studies, animals should be of comparable age, weight and parity at the start; the easiest way to fulfill these criteria is to use animals that are young, mature adults at the time of mating with the females being virgin.

ii. General recommendations concerning treatment

The selection of dosages is one of the most critical issues in design of the reproductive toxicity study. The choice of the high dose should be based on data acquired from all available studies (pharmacology, acute and chronic toxicity and kinetic studies). Another factor is the route and frequency of administration, which should be similar to those intended for human usage. The usual frequency of administration is once daily but consideration should be given to use either more frequent or less frequent administration taking kinetic variables into account. It is preferable to have some information on kinetics before initiating reproductive studies since this may suggest the need to adjust choice of species, study design and dosing schedules.

iii. Proposed study designs

The most probable option can be equated to a combination of studies for effects on the fertility and early embryonic development, pre- and postnatal development, including maternal function and the embryo-fetal development

8. Immunotoxicity studies [8]

Evaluation of potential adverse effects of the new molecule on the immune system should be incorporated into standard drug development. Toxicity to the immune system encompasses a variety of adverse effects which include suppression or enhancement of the immune response. Suppression of the immune response can lead to decreased host resistance to infectious agents or tumor cells. Enhancing the immune response can exaggerate autoimmune diseases or hypersensitivity.

The initial screen for potential Immunotoxicity involves standard toxicity studies (STS). Data from rodent and non-rodent studies from early short term to more chronic repeat-dose studies should be taken into consideration.

The data from STS should be evaluated for signs of immunotoxic potential. A few signs that should be taken into consideration includes, Hematological changes such as leukocytopenia/leukocytosis, granulocytopenia/ granulocytosis, or lymphopenia/ lymphocytosis; Alterations in immune system organ weights and/or histology; Changes in serum globulins that occur without a plausible explanation, such as effects on the liver or kidney, can be an indication that there are changes in serum immunoglobulins; Increased incidence of infections; Increased occurrence of tumors can be viewed as a sign of immunosuppression in the absence of other plausible causes such as genotoxicity, hormonal effects, or liver enzyme induction.

Changes in these parameters could reflect immunosuppression or enhanced activation of the immune system. Immunosuppression is usually reflected by reduced values of immune parameters, whereas immunoenhancement is usually reflected by increased values. However, these relationships are not absolute and can be inverted in some cases.

III. Clinical development

"The purpose of clinical research is to create knowledge needed to improve health care. Without such knowledge, action for health care may be impossible, wasteful, expensive or harmful because it will have no logical or empirical basis." To get the best out of a Clinical research, it is very important that a proper design is given before its execution. Clinical Research can be classified into two different groups namely, Descriptive and Analytical.

Descriptive studies are the first scientific "toe in the water" approach towards a new disease or the area of research. It is "concerned with and designed only to describe the existing distribution of variables, without regards to causal or other hypotheses". It includes Case reports, Case series, Correlation study, Drug Registries, Cross-sectional & Longitudinal studies.

Analytical studies are conducted in situations where information is already available for the disease under study. These studies are done to test the cause-effect relationship and are usually dependant on developing new data [9]. There are two sub groups under analytical studies namely, observational studies and interventional studies. The observational studies include Case control & Cohort studies.

A randomized controlled trial (RCT) is an intervention type of Clinical study and is often used to test the efficacy and/or effectiveness of various types of medical intervention within a patient population. RCT also provides an opportunity to gather information about adverse effects, such as drug reactions.

The key distinguishing feature of any RCT is Randomization and Blinding. Randomization is the process by which the study population, after assessment of eligibility and recruitment, but before the intervention to be studied begins, is randomly allocated to receive one or other of the alternative treatments under study. Whereas, Blinding is the process by which the study participants, care givers or the outcome assessors are prevented from knowing which type of intervention the subject is receiving **(10).**

Designs in RCT

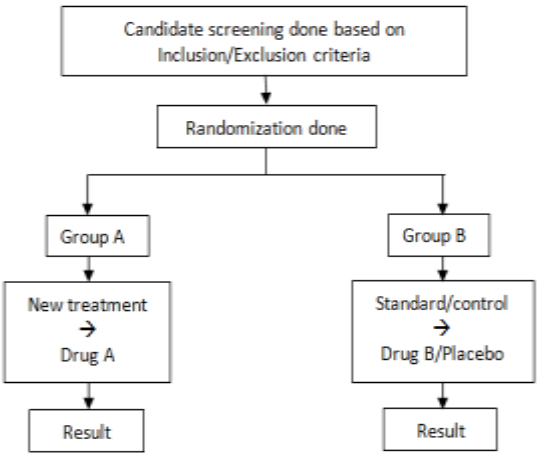

Figure 2 – Parallel Design RCT

The most common design in RCT is the parallel group design in which subjects are randomized to one of two or more arms, each arm being allocated a different treatment. These treatments will include the investigational product at one or more doses, and one or more control treatments, such as placebo and/or an active comparator. The assumptions underlying this design are less complex than for most other designs. However, there may be additional features of the trial that complicate the analysis and interpretation (e.g. covariates, repeated measurements over time, and interactions between design factors, protocol violations, dropouts and withdrawals).

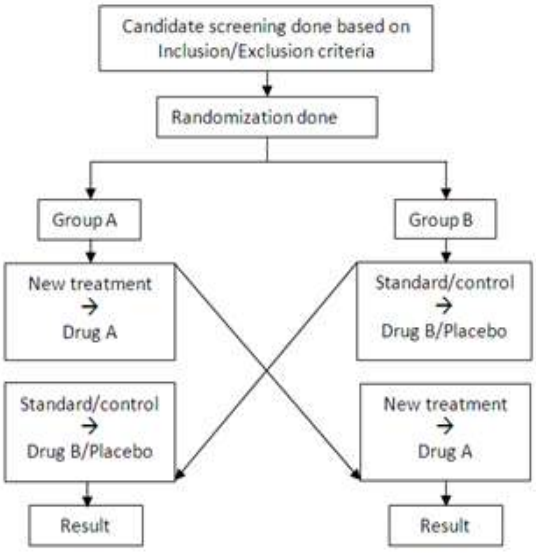

Figure 3 – Crossover Design RCT

In the crossover design, each subject is randomized to a sequence of two or more treatments, and hence acts as its own control for treatment comparisons. This simple maneuver is attractive primarily because it reduces the number of subjects and usually the number of assessments needed to achieve a specific power, sometimes to a marked extent. The cross over design depends upon the treatment group within the study population. For example, in 2×2 crossover design, each subject receives each of two treatments in randomized order in two successive treatment periods, often separated by a washout period.

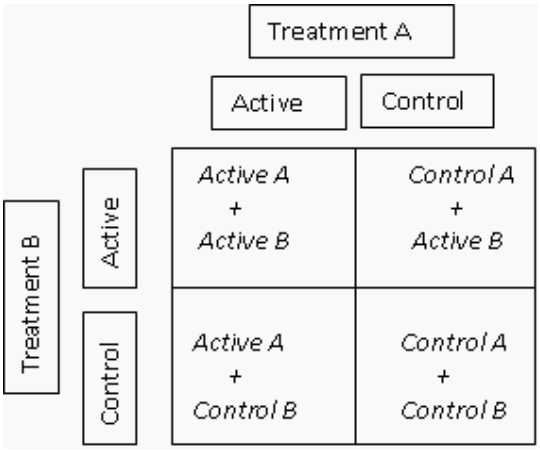

Figure 4 – Factorial Design RCT

In a factorial design two or more treatments are evaluated simultaneously through the use of varying combinations of the treatments. For example, in a 2×2 factorial design in which subjects are randomly allocated to one of the four possible combinations of two treatments, A and B, these are: A alone; B alone; both A and B; neither A nor B (figure 3). In many cases this design is used for the specific purpose of examining the interaction of A and B. The statistical test of interaction may lack power to detect an interaction if the sample size was calculated based on the test for main effects. This consideration is important when this design is used for examining the joint effects of A and B, in particular, if the treatments are likely to be used together.

Design Options in RCT

The purpose of a Design option in RCT is to determine the effectiveness of the new drug on accordance to the standard therapy, to analyze the risk benefit ratio and for continuous comparative assessment.

The design options are as follows

1. Superiority RCT is carried out when its primary objective of the trial is to show that the response of the investigational product is superior to a comparative agent (active or placebo control).

2. Equivalence RCT is carried out when the primary objective of the trial is to show that the response to two or more treatments differs by an amount which is clinically unimportant. This is demonstrated by showing the true treatment difference is likely to lie between a lower and an

upper equivalence margin of clinically acceptable differences.

3. Non-Inferiority RCT is carried out when the primary objective of the trial is to show that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control).

IV. Phases in clinical trials (0-III)

Phase 0/ Microdosing [11]

Phase 0, also known as Microdosing, is a novel approach incorporated in NDD paradigm. USFDA introduced Phase 0 in its CPI release. The Pharmacokinetics of the molecule is one of the reasons responsible for the attrition in NDD. Too low concentration leads to failure in efficacy and too high concentration leads to toxicity. To manage this, Phase 0/Microdosing method was developed to address issues pertaining to PK and drug metabolism.

The concept of Microdosing involves the use of extremely low, non-pharmacological active doses to define the Pharmacokinetic profile of the medication in human subjects. Microdosing means use of less than $1/100^{th}$ of the dose calculated to yield a pharmacological effect of the test molecule to a maximum dose of <100 micrograms. Thus, Microdosing allows the selection of drug candidates more likely to be developed successfully and also determines the first dose for subsequent Phase 1 clinical trial.

The advantages of Microdosing involve the use of minute quantities of drug, which is not intended to produce any pharmacological effect in humans. It reduces/replaces the extensive animal testing of new molecules for kinetics. The cost of conducting Microdosing studies is phenomenally less as compared to Phase 1. This also may be useful in discovery of endogenous biomarkers, which would assist in the quantitative evaluation of the in-vivo effects of drugs.

The limitations of Microdosing are, it can't clarify whether the body's reaction to a particular molecule is similar, when used as microdose and in its pharmacological dose. The accuracy of PK parameter of drugs having non-linear kinetics is of concern. Also, he rate & extent of dissolution can't be predicted at Microdosing level.

Estimation of 1st Dose in Humans [12]

The estimation of the first dose in humans is an important element to safeguard subjects participating in first-in-human studies. All of the relevant nonclinical data, including the pharmacological dose response, the pharmacological/toxicological profile, and pharmacokinetics, should be considered when determining the recommended starting dose in humans.

In general, the No Observed Adverse Effect Level (NOAEL) determined in nonclinical safety studies performed in the most appropriate animal species gives the most important information. The proposed clinical starting dose will also depend on various factors including PD, particular aspects of the molecule and the design of the clinical trials

Phase I/First In Humans study (FIH) [13]

The Phase I, also known as the 'First In Humans Study', is done on Healthy human volunteers, except for trials which include development of drugs for AIDS and cancer treatment. The study is done on a small group, usually ranging from 20 to 100 volunteers. Phase 1 studies are designed as open labeled, baseline controlled or even a blinded study to validate the study observation.

The aim of Phase I is to assess the safety & tolerability, Pharmacokinetics, Pharmacodynamics (PK/PD) of a drug. Once the drug is administered to the volunteer, a tolerable dose range that could support a clinical study could be extracted, which will also help in determining an expected adverse drug reaction. The Pharmacokinetics study is conducted understand the ADME mechanism of the administered drug. This will provide information on the drug-drug interactions. A Pharmacodynamics assessment is done to study the physiological and biochemical activity of the drug.

Phase II/THERAPEUTIC EXPLORATORY [13]

Phase II, also known as Therapeutic exploratory studies, estimates the efficacy of the new treatment. The main objective of this phase is to determine the biological activity of the drug and see if it has any sufficient scope of succeeding.

Phase II studies are done on patient volunteers specific to the study treatment. The end point is to determine the dose range and medical regimen that would be used in the Phase III trials.

Phase II trials are done in 2 stages

a. Phase IIa: A pilot study is conducted to assess the efficacy and safety of the drug on a selected population where the patients belongs into the category of 'to be treated', 'to be diagnosed' or 'to be prevented'. The focus is to understand the dosage frequency and the dose-response.

b. Phase IIb: A pivotal study /properly controlled Clinical trials to evaluate the safety and efficacy of the study drug
This Phase is carried out on patient population ranging from 100 – 300 for around 1 to 2 years.

Phase III/THERAPEUTIC CONFIRMATORY(13):

Also called as the Therapeutic confirmatory phase, the study is usually done on a larger population (1000-3000) and often they are randomized controlled multi-centric studies. The objective is to assess the effectiveness of the study drug compared to that of the standard care of treatment.

This phase stands as the basis for the marketing approval (NDA – New Drug Application) of the drug. The scope of the phase could be expanded to explore the dose-response relationship, study the effect of the drug on different stages of the disease.

There are two stages in Phase III, namely Phase IIIa and Phase IIIb.

Phase IIIa: designed for Pilot studies to compare the drug with a placebo or another comparator drug. The objective is to get statistical data which will give a significant enough evidence to prove the safety and efficacy of the study drug which is needed for NDA approval. This stage is done on a long term basis on a larger population, and on diverse study group.

Phase IIIb: designed as a pivotal study to support the publications and product claims rather than regulatory submissions. This is done post the regulatory submission for NDA and pre product approval and market launch. The stage can provide vital information to the sponsors about the Quality of life, the marketing and also evaluation that need to be done for Phase IV studies.

Adaptive Clinical trials [14]

An adaptive Clinical Trial is defined as a design that allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. The purpose is to make clinical trials more flexible, efficient and fast. Due to the level of flexibility involved, these trial designs are also termed as "flexible designs."

FDA for industry defines adaptive design clinical trials as "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."

Types of adaptive clinical Trials:

1. Allocation rule: defines how the subjects will be allocated to different arms in a trial and comprises response. Ex: adaptive randomization and covariate adaptive allocation.
2. Sampling rule: defines how many subjects will be sampled at the next stage. Ex: Sample size re-estimation design (both blinded and unblinded) and drop-the-loser design.
3. Stopping rule: defines when to stop the trial. Ex: Group sequential design and adaptive treatment-switching design.
4. Decision rule: comprises changes not covered under the other three categories and consists of hypothesis-adaptive design and change the primary end-point or statistical method or patient population design. The following table shows the comparison between Conventional and Adaptive Clinical trials.

Table 1: Comparison between conventional & adaptive clinical trials

Features	Conventional trial	Adaptive design
Design	More rigid	Flexible
Treatment arms	Maximum two or three	Many simultaneously
Hypothesis	Test the hypothesis under consideration	Fit data into a hypothesis
Modifications	Not allowed without protocol amendments	Pre-specified allowed
Phases	Phases I–II are well defined	Can be seamless phase 2/3 design
Statistical analysis	Use routine frequentists methods	Use complicated Bayesian approach
Organization	Much simple	Complicated, requiring simulations
Interim analysis	Not a routine	Done routinely and frequently
Role of IDMC	More once trial/phase is over	Proactive role throughout the trial
Regulatory view	Well endorsed	Still speculative

The advantages of Adaptive clinical trials are, there is flexibility to react to unanticipated events and options exist to introduce any new doses, changes end-points. The credibility of results is well maintained and it ensures that the sponsor investment on the unsuccessful drug is minimal and can more quickly reassign resources to alternatives drugs within their pipelines. Since the potential modifications are approved before hand by regulatory authorities and ethics committee, there is no need of protocol amendments.

There are certain limitations though; the Bayesian approach for statistical analysis is a compulsion rather than a choice. The type 1 errors are difficult to control and the Ad-hoc analysis based on unblended data may jeopardize the credibility of the study. Also, there is a risk of developing a tendency to conduct adaptive trials

at an early stage, which may jeopardize the overall study findings.

V. Post Approval process [15]

Also known as Post Marketing Surveillance, the Phase IV study starts following the approval of the drug for marketing. With comparison to global diseased population, the number of people undergoing a Clinical trial is minimal, implicating the possibility of occurrence of rare adverse events, drug-drug interactions within the general population. The PMS helps to assess the safety and efficacy of the new drug in the 'real world' practice.

There is no definite timeframe for PMS, and once a drug is seen to fail the PMS due to unexpected, untoward Serious Adverse Events, the licensing authority has the reservations to withdraw the drug from the market.

Table 2: Various phases of Clinical Trials and their objectives

Human Pharmacology	**a.** Study tolerance **b.** Define PK and PD **c.** Study the Drug metabolism **d.** Study the drug activity **e.** Study Drug interactions
Therapeutic Exploratory	**a.** Estimate the drug dosage for subsequent studies **b.** Provide the basis for endpoint methodologies
Therapeutic Confirmatory	**a.** Confirm efficacy **b.** Establish a safety profile **c.** Asses the benefit risk relationship for regulatory requirements **d.** Establish the dose response relationship
Therapeutic use	**a.** Refine understanding of benefit/risk relationship in general population **b.** Identify less common ADR **c.** Redefine dosing recommendations

Conclusion

NDD is a process which applies to drugs/products to be used on human subjects. Drug discovery is a multidisciplinary process. Preclinical development bridges the gap between drug discovery and clinical development. NDD is a costly affair which has the highest attrition rate and the new molecule may fail at any phase. The Pharma/ Sponsor companies have intensified their work process to improve their productivity and cost containment towards yielding better results. By understanding the NDD process and the USFDA's Critical path initiative, companies can improve the success rate, the evidence quality generated during the process and the outcome of their clinical uses.

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