International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1080-1087 www.ijprajournal.com ISSN: 2249-7781

Clinicalresearch: A prominent drug development

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Submitted: 12-01-2023 Accepted: 24-01-2023

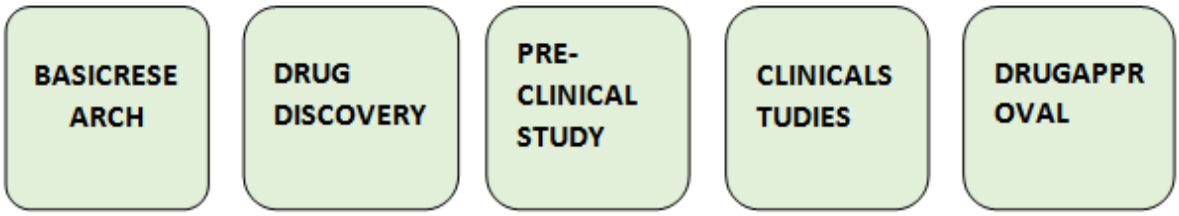
ABSTRACT: Clinical research has produced significant medical improvements and breakthroughs that have raised our standard of living as a whole.To assure the efficacy and safety of novel medications, clinical trials are a crucial component of the drug discovery process.Clinical research involves development ofnovel treatments for disease, new methods to diagnose disease, new ways to prevent disease. It includes pharmacodynamics ,pharmacokinetics, absorption, distribution, metabolism and excretion studies and toxicity testing.If preclinical studies show that the therapy is safe and effective, clinical trialsare started.Clinical trial phases include Phases 0, I, II, III and IV clinical trials and are steps in the research to evaluate whether an intervention will be beneficial or detrimental to humans.

Keywords: Clinical Research,Phases,Single Blind Trial, Double Blind Trial, New Drug Application, Investigational New Drug

I. INTRODUCTION:

Clinical Trials

The World Health Organization (WHO) defines a clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes [1]. The process of drug development is divided typically into three major steps are drug discovery , Pre-clinical Studies and Clinical Studies [2].



Overview of drug development –

The US Food and Drug Administration (FDA) has defined and regulated the overall path to drug research and approval for many years.Safety has historically been its primary focus, followed by efficacy. If preclinical Studies show that the therapy is safe and effective, a drug sponsor or sponsor-investigator can submit an investigational new drug (IND) application. After approval, the drug is studied and if demonstrated safe and efficacious in the intended population, The drug sponsor can then submit New Drug Application (NDA) to the FDA. After an extensive review by the FDA that often involves a recommendation by an external committee, the FDA determines whether the therapeutic can he granted an indication and marketed. After final approval, the drug can continue to be studied in phase IV trials, in which safety and effectiveness for the indicated population is monitored[3].

Pre-Clinical Studies-

If preclinical studies show thatthe therapy is safe and effective ,clinical trials are started.The four possibleoutcomes are 1) The new treatment has a large beneficial effect and is superior to standard treatment 2) the new treatment is equivalent to standard treatment, 3) the new treatment is neither clearly superior nor clearlyinferior to standard treatment, or 4) a new treatment is inferior to standard treatment.Pre-clinical investigations include animal studies and evaluations of drug production and purity.Animal studies explore : 1) the drug safety in doses equivalent to approximated human exposures 2) pharmacodynamics (ie, mechanisms of action, and the relationship between drug levels and clinical

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response), and 3) pharmacokinetics (ie, drug absorption, distribution, metabolism, excretion, and potential drug-drug interactions). This data must be submitted for IND approval if the drug is to be further studied in human subjects [4].After synthesizing identifying a prospective compound, it is tested on animals to expose the whole pharmacological profile. Experiments are generallyperformed on a rodent (mouse, rat, guinea pig. hamster, rabbit) and then on a larger animal (cat, dog, monkey). As the evaluation progresses unfavourable compounds get rejected at each step, so that only a few out of thousands reach the stage when administration to man is considered.

The following types of tests are performed.

1. Screening tests: These are simple and rapidly performed tests to indicate presence or absence of a particular pharmacodynamic activity that is sought for, eg.analgesic or hypoglycaemic activity.

2. Tests on isolated organs, bacterial cultures, etc : These also are preliminary tests to detect specific activity, such as antihistaminic, antisecretory, vasodilator,antibacterial, etc.

3. Tests on animal models of human disease : Such as kindled seizures in rats, spontaneously geneticallyhypertensive rats, experimental tuberculosis in mouse, alloxan induced diabetes in rat or dog, etc.

4. Confirmatory tests and analogous activities: Compounds found active are taken up for detailed study by more elaborate tests which confirm and characterize the activity. Other related activities, eg. antipyretic and anti-inflammatory activity in an analgesic are tested.

5. Systemic pharmacology: Irrespective of the primary action of the drug, its effects on major organ systems such as nervous, cardiovascular, respiratory, renalare worked out. Mechanism of action, including additional mechanisms, eg adrenergic blockade, calcium channel blockade, nitro-vasodilatation, etc. in a ß adrenergicblocker antihypertensive, are elucidated.

6. Quantitative tests: The dose-response relationship. maximal effect and comparative potency/efficacy withexisting drugs is ascertained.

7. Pharmacokinetics: The absorption, volume of distribution, metabolism, excretion, pattern of tissue distribution and plasma half-life of the drug are quantified.

8. Toxicity tests: The aim is to determine safety of the compound in at least 2 animal species, one rodent and onenonrodent, eg mouse/ rat and dog by oral and parenteral routes.

PHASES OF CLINICAL TRIALS:

PHASE 0	MICRODOSING STUDIES
PHASE I	HUMAN PHARMACOLOGY AND SAFETY
PHASE II	THERAPEUTIC EXPLORATORY PHASE
PHASE III	THERAPEUTIC CONFIRMATORY PHASE
PHASEIV	POST MARKETING SURVEILLANCE

PHASE 0 STUDIES:

It is also called as Human microdosingstudies,exploratory Investigational New Drug, pre-phase I studies.The Food and Drug Administration announced in January 2006 the launch of the exploratory Investigational New Drug (IND), also known as phase o clinical trials, in an effort to speed the discovery of new medications.Doses are subtherapeutic and patients are monitored by the clinical researcher and involve about 10 to 15 individuals. The duration of dosing in an exploratory IND study is expected to be limited (eg.7 days). Early in the drug development process, phase "O" trials provide a chance to generate significant pharmacokinetic and pharmacodynamics (PD) data for patients[6]. Only the most promising compounds are included in phase "O" clinical trials for further research due to which sponsors reduces the excessive cost, time and human volunteers. [7].

Need of phase 0 clinical trial

These studies help in eliminating candidate therapies before they reach Phase I studies .These trials were developed to shorten the critical path for drug development, to explore pharmacokinetic and pharmacodynamic profiles of IND's in humans, to help in accelerating

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identification of promising drugs, and to reduce development time and costs[8].

Limitations of phase 0 clinicaltrials

It include lack of therapeutic intent, motivation of patients to participate, may delay or exclude patients from other clinical trials that may have therapeutic intent, microdosing pharmacokinetics and relationship to therapeutic dose, and availability of sensitive analytical methods[9].

Classification of phase 0 clinical trials

The phase 0 clinical trials are categorised into three major types such as:

(i) Determination of drug pharmacokinetics (microdose Trials).
(ii) Determination of pharmacologically significant doses of drug
(iii) Determination Drugs mechanism of action.

(i) Determination of drug pharmacokinetics (microdose Trials).

These phase 0 studies strictly investigate pharmacokinetics, which helps to further establish the data relating to various pharmacokinetics factors including bioavailability. Drug distribution and metabolism of the medication or its metabolites.

(ii) Determination of pharmacologically significant doses of drug

The aim of these phase 0 studies is to specifically establish the dosage regimen for a molecular target compound or a biomodulator that is used in accordance with other medications. This phase 0 trial can be used to determine the administration sequence and dose range for additional combination investigations but cannot be used to determine the maximum tolerated dose.

(iii) Determination Drugs mechanism of action.

In order to evaluate a drug's pharmacodynamic effect, this phase 0 trial investigates how a drug's mechanism of action and eff
icacy are related.In the field of cancer therapy, these phase 0 studies are particularly important for the assessment of the chemotherapeutic medicines (molecular targeted)[10].

PHASE I STUDIES:

A Phase I clinical study assesses the optimal manner to deliver a medicine, its frequency and dose, the maximum tolerated dose (MTD), and adverse effects. The assessments of pharmacokinetics, pharmacodynamics, and tolerability is done.This phase assess the safety of the drug.This is first in human study.Trials usually involve 20 to 100 patients and are monitored by a clinical researcher. Patients are checked to see if they are responding to the medication and dosages are elevated if there are no serious side effects[11].

Types of phase I studies

Phase I trial are of the following three types:

1.SAD (Single Ascending Dose)

Small group of subjects given single dose of drug and observed for a period.Pharmacokinetic data is in line with predicted safe values, the dose is increased in a new group of subjects. Dose escalation is continued till Maximum Tolerated Dose (MTD) is reached.

			Single Ascending Dose		
Subject Cohort	Week 1	Week 2	Week 3	Week 4	Week 5
Cohort 1	05 mg				
Cohort 2		10 mg			
Cohort 3			20 mg		
Cohort 4				50 mg	
Cohort 5					100 mg

Single Ascending Dose [12]

2.MAD (Multiple Ascending Dose)

A group of subjects receives multiple low doses of drug and observed for a period.Samples of blood and other body fluids are collected at various time points and analysed.This phase investigates thepharmacokinetics and pharmacodynamics of the drug in order to check safety and tolerability.

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Multiple Ascending Dose					
Subject Cohort	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**
Cohort 1	**20 mg**	**40 mg**	**60 mg**	**80 mg**	**100 mg**
Cohort 2	**40 mg**	**60 mg**	**80 mg**	**100 mg**	**120 mg**
Cohort 3	**60 mg**	**80 mg**	**100 mg**	**120 mg**	**140 mg**
Cohort 4	**80 mg**	**100 mg**	**120 mg**	**140 mg**	**160 mg**
Cohort 5	**100 mg**	**120 mg**	**140 mg**	**160 mg**	**180 mg**

Multiple Ascending Dose [12]

3.Food Effects:

To evaluate the specific influence of food consumption on the absorption of the medicine, food effect studies are carried out. Typically, two equal doses of the medicine are administered to volunteers in these experiments, one after fasting and one after meals.

PHASEII STUDIES:

Phase II trials, also known as therapeutic exploratory trials, are carried out in a small number of volunteers who have the disease of interest. They are usually larger than phase I studies. They may also be created to provide information crucial to the formulation of phase III trials. They are designed to assess safety, pharmacokinetics, and pharmacodynamics Including choosing the optimal dosages, dosage intervals, administration routes, and endpoints[13].

These studies, which involve bigger cohorts (between 100 and 300 patients), are carried out to evaluate the effectiveness of the medication and to carry out ongoing safety evaluations. The clinical researcher administers therapeutic doses that were identified during Phase I while keeping an eye on the patients. Trials are frequently held in a setting with multiple institutions. Phase II may be further divided into Phase IIA, which are pilot clinical trials to assess efficacy and safety in selected populations with the disease or condition to be treated, diagnosed, or prevented (objectives may include dose-response, type of patient, frequency of dosing, or other identifiers of safety and efficacy), and Phase IIB, which are the most rigorous trials intended to demonstrate efficacy. In this Phase II, the development process typically fails when the drug is discovered not to work as planned or to have toxic effects[14].

Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "blinded" which means that neither the patients nor the researchers know who has received the experimental drug. This allows researchers to provide the pharmaceutical company and the FDA with comparative information about the relative safety and effectiveness of the new drug. About one-third of experimental drugs successfully complete both Phase I and Phase II studies.

PHASE III STUDIES:

Phase III trial also referred as therapeutic Confirmatory, Comparative efficacy or pivotal trial.These are the most thorough and rigorous kind of clinical research investigations into new treatments. These are "pre-marketing phase" of clinical studies. These studies are typically the most expensive and time-consuming. The trials could be challenging to plan and carry out. Trial designs have included randomised controlled trials (parallel design), uncontrolled trials (single treatment), historical controls, no-randomized concurrent trials, factorial designs, and group designs. Large groups (100 to 3000 subjects) are recruited. And kept an eye on by the personal physician and clinical researcher. Phase III clinical trials can be separated into Phase IIIA trials, which are conducted after the efficacy of the medication has been established but before regulatory submission of a New Drug Application (NDA) or other dossier, and Phase III B which are conducted after submission of an NDA but before approval and launch.Here the drug is tested in large number of patients at several centers to includePatient with different genetic makeup. This is done to generalize the results of the study toVariable genetic and ethnic groups. If the drug is found to be safe and effective in these trials, then another application is filed with FDA (New Drug Application or NDA) to market the drug. If approval is granted,the drug is marketed.[15].

PHASE IV STUDIES:

Phase IV trials are also referred as "therapeutic use" , post marketing Surveillance trials .Once the drug is approved,the FDA may require that a sponsor conduct a Phase IV trial as a stipulation for drug approval.These are performed on FDA approved drugs to: 1.Identify less common

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adverse reactions, 2.Evaluate Cost and drug effectiveness in disease.

Pharmaceutical companies have several goals:

(1) to compare a drug with other drugs already on the market;

(2) to monitor a drug's long-term efficacy and impact on a patient's quality of life; and

(3) to assess the cost-effectiveness of a drug therapy in comparison to other existing and new therapies. A medication or device may be withdrawn off the market as an outcome of a phase IV study, or usage restrictions may be placed on the product depending on the study's findings[16].

Types of Clinical Trials:

1.Treatment Trials:

Test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

2.Prevention Trials:

Look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

3.Diagnostic Trials:

Conducted to find better tests or procedures for diagnosing a particular disease or condition.

4.Screening trials:

Test the best way to detect certain diseases or health conditions.

5.Quality of life:

Trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness[17].

Clinical Trial Design:

1.Open-Label Trials

2. Blind Trial

a.Single Blind Trial

b Double Blind Trial

c.Triple Blind Trial

1.Open Label Trials:

Open-label trials and conventional blinded studies differ significantly in key ways. In an open-label experiment, both the researchers and the trial subjects are fully aware of the treatment groups they are assigned to and the treatments they will receive. Open-label trials are performed to compare various therapies or learn more about the long-term effects of novel medications and therapies.

2.Blind Trials:

Today, the majority of research are what are referred to be "blind trials." To avoid bias and improve the quality of the information acquired on treatment success, blind trials anonymize the treatments and control groups. The group to which a patient will be assigned is kept a secret.

a.Single Blind Trial:

In a single-blind trial, the researcher knows the details of the treatment but the patient does not. Because the patient does not know which treatment is being administered (the new treatment or another treatment) there might be no placebo effect. In practice, since the researcher knows, it is possible for him to treat thepatient differently or to subconsciously hint to the patient important treatment- related details, thus influencing the outcome of the study.

b.Double Blind Trial:

In a double-blind trial, one researcher allocates a series of numbers to 'new treatment' or 'old treatment. The second researcher is told the numbers, but not what they have been allocated to. Since the second researcher does not know, he cannot possibly tell the patient, directly or otherwise, and cannot give in to patient pressure to give him the new treatment. In this system, there is also often a more realistic distribution of sexes and ages of patients. Therefore double-blind (or randomized) trials are preferred, as they tend to give the most accurate results.

c.Triple Blind Trial:

Some randomized controlled trials are considered triple- blinded, although the meaning of this may vary according to the exact study design. The most common meaning is that the subject, researcher and person administering the treatment (often a pharmacist) are blinded to what is being given. Alternately, it may mean that the patient. Researcher and statistician are blinded. The team monitoring the response may be unaware of the intervention being given in the control and study groups. These additional precautions are often in place with the more commonly accepted term "double blind trials", and thus the term "triple-blinded" is infrequently used. However, it connotes an additional layer of security to prevent undue influence of study results by anyone directly involved with the study.[18]

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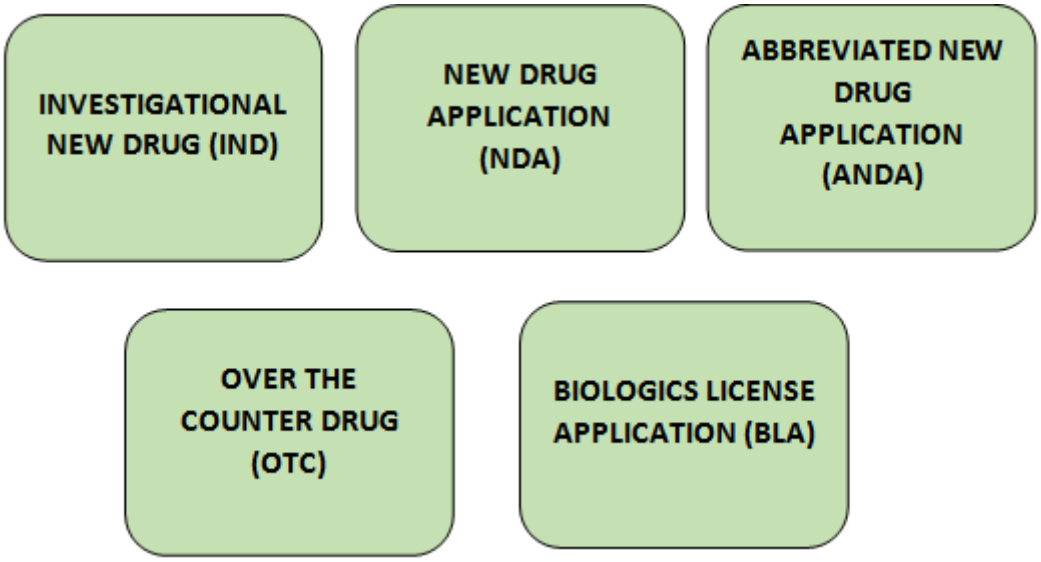
Types Of Regulatory Application:

The FDA has five common application types: Investigational New Drug (IND),New Drug Application (NDA), Abbreviated New Drug Application (ANDA), Over-the-Counter Drug (OTC) and Biologics License Application (BLA).



1.Investigational New Drug Application (IND):

It's an application filed to the FDA in order to Start clinical trials in humans if the drug was Found to be safe from the reports of Preclinical Trials. A firm or institution, called a Sponsor, is Responsible for submitting the IND application.

2.NEW DRUG APPLICATION(NDA):

If clinical studies confirm that a new drug is Relatively safe and effective, and will not pose Unreasonable risks to patients, the manufacturer Files a New Drug Application (NDA), the Actual request to manufacture and sell the drug In the United States.

3.Abbreviated New Drug Application (ANDA):

It's an application made for approval of Generic Drugs. The sponsor is not required to Reproduce the clinical studies that were done for the original, brand name product. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product[19].

4.OVER THE COUNTER DRUGS (OTC):

Over-the-counter (OTC) drugs play an increasingly vital role in America's health care system. OTC drug products are those drugs that are available to consumers without a prescription. There are more than 80 therapeutic categories of OTC drugs, ranging from acne drug products to weight control drug products. As with prescription drugs, CDER oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks[20].

5.Biologics License Application (BLA):

Biological products are approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires a firm who manufactures a biologic for sale in interstate commerce to hold a license for the product. A biologics license application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical affects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product.

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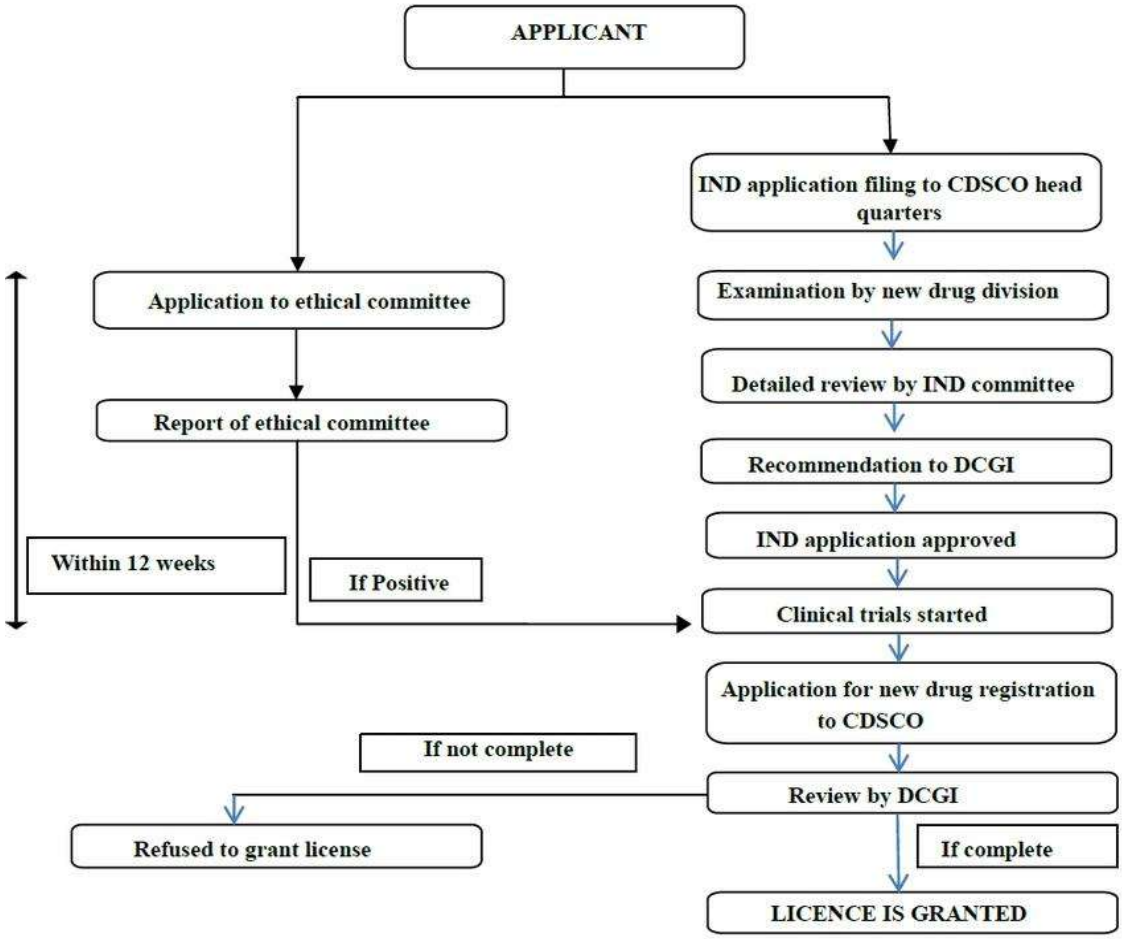
Drug Approval Process In India:



When a company in India wants to manufacture/import a new drug it has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it has to conduct clinical trials inaccordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.

But a provision is there in Rule 122A of Drugs and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public health he may grant permission for import of new drugs basing on the data of the trials done in other countries. Similarly there is another provision in Rule 122A which saysthat the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries.

Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required.

Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant. Should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials.

Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may require pharmacokinetic studies. (Bioequivalence studies) first to show that the data generated in Indian population is equal to

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data generated abroad and then require him to proceed withPhase III trials.

In summary, the exact requirements of Clinical trials may change from case to case and depend on the extent to which licensing authority is satisfied about its safety and efficacy.

The process of approval of new drug in India is a very complicated process, which should meet necessary requirements along with NDA to FDA. The need of the present work is to study and document the requirements for the process of approval of new drug in India with emphasis on clinical trials as per Drugs Control department, Government of India.

II. CONCLUSION:

The overall conclusion of the present article found that it is essential to describe the clinical research, how it was conducted and what clinical trial phases are. To understand the drug therapy that is required to pass through multiple phases before coming to market and the importance of safety and health of a population. The various regulatory bodies that ensure all experimental studies should be conducted ethically. It is essential to maintain the highest quality and standard in drug safety and efficacy evaluation parameters as it directly links with wellbeing of the population.

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