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DRUG DISCOVERY AND CLINICAL EVALUATION OF NEW DRUG

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ABSTRACT:

Natural products (NPs) have provided the source for the majority of FDA-approved agents and continue to be one of the major sources of inspiration for future drug discovery. The R&D thrust in the pharmaceutical sector today is focused on development of new drugs, innovative/indigenous processes for known drugs, development of NP-based drugs through investigation of leads obtained from the traditional systems of medicine as well as other resources. Present review describes natural products (NPs), semi-synthetic NPs and NP-derived compounds that have been registered, undergoing registration or in clinical development since 1998 till June 2010 by disease area i.e. infectious (bacterial, fungal, parasitic and viral), immunological, cardiovascular, neurological, inflammatory and related diseases and Oncology. This review also highlights the recently launched natural product-derived drugs, new natural product templates and late-stage development candidates.

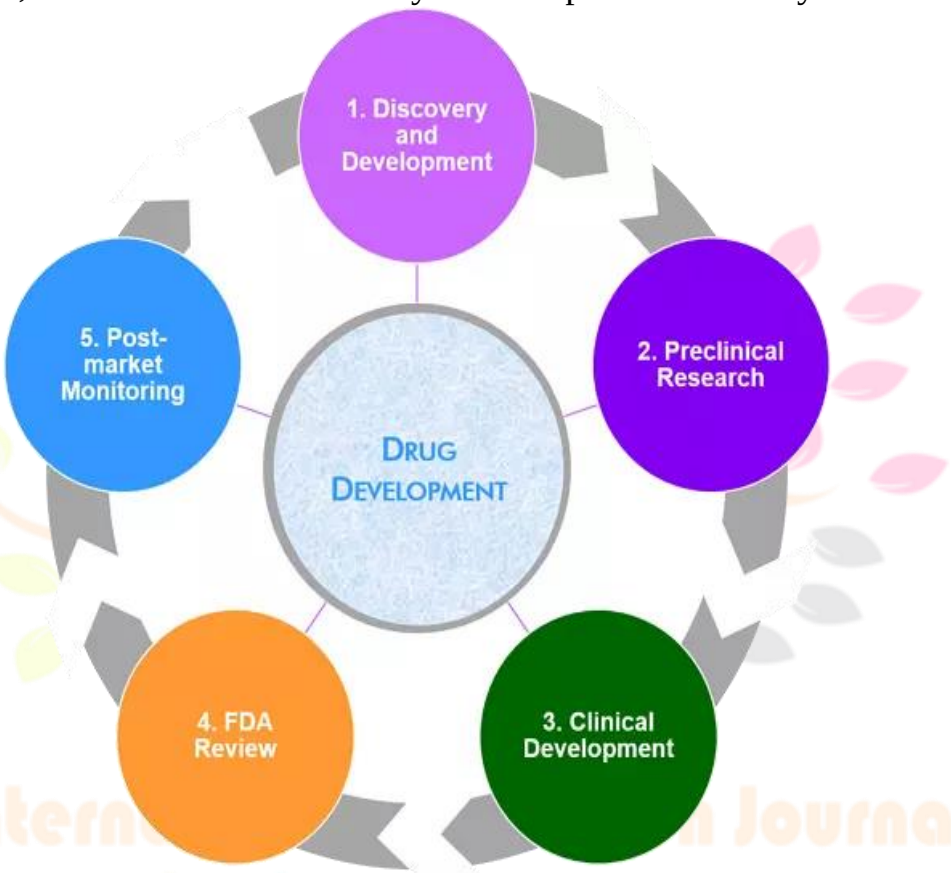
Keywords: Drug discovery, pre-clinical evolution, In vitro, In vivo, Development and Approval process, Phase of clinical trial conclusion, etc

Introduction:

Drug discovery is a varied process, which involves identification of a drug chemical therapeutically useful in treating and management of a disease condition. Typically, new drug find out through the new vision by the researchers. Disease processes that permit investigator to design aur making medicine to stop over the effect of disease. Firstly new drug find out and get trials in animals by the in vitro and in Vivo process in clinical evolution was gate by the new drug

1. Drug Discovery:

Drug discovery is the process to which likely new medicines are identify by the process of clinical trial. It was a wide range of scientific disciplines including biology, chemistry and pharmacology. In the past most drugs have been discovered at their identifying the active ingredient from tradition remedies for by the discovery. A new approach has been to a understand how disease and infections are control at the molecular and physiological level and target specific on this knowledge. The process of drug discovery in was the identification of candidate, synthesis, characterization and assay for therapeutic efficiency.



2. Development and Approval process:

A) .Development :

Firstly drug can be send to the company to test it .The Company then sends CDER the evidence from these tests to prove the drug is safe and effective for its intended use. Before a drug can be tested in people, the drug company performs laboratory and animal tests to discover how the drug works and whether it's likely to be safe and work well in humans.

B). FDA approval:

FDA approval of a drug means 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.

Clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval.
FDA reviews reports of problems with prescription and over-the-counter drugs, and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues**.**

3**. Pre-clinical evaluation:**
Before testing a drug in human body or animal body research must find out whether it has side effects to harm human and animal body. The preclinical studies are conducted on animal models under laboratory conditions there are two types of pharmaceutical testing.

In Vitro :
- Clinical trial outside the animal or human body.

In Vivo :
-clinical trial conduct inside the body.

The various experiment have been conducted during studies such as-

1. Single dose toxicity studies.

2. Repeated dose studies.

3. Genotoxicity studies.

4. Reproductive toxicity study.

Phases of Clinical Trial
All new drugs are labelled as Investigational New Drugs (NDs) by UDFDA. All INDs undergo vanous stages of development. Clinical trials have been classically divided in to four phases as described below. In addition phase 0 has been added in recentyears

Phase 0

Phase 0 has been added by USFDA from 2006 guidance on exploratory IND studies. Phase O trials are known as human micro dosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug behaves in human subjects as was expected from pre clinical studies. Distinctive features of phase 0 trials include administration of sub-therapeutic doses to a small number of subjects (10:15) to gather preliminary data on pharmacokinetics of the drug Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Based on information from phase studies, a decant regarding progress of the drug in next phases is taken. 3.2 Phase I Phase I trials were formerly called as first-in-humans studies. Normally, a small group of 2-100 healthy volunteers are recruited into phase I trial. These trials are conducted in a clinical trial clinic, where the subject can be observed by a full time statt.

The subject who receives the drug is usually observed until several half-lives of the drug have passed. This phase is designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a drug. Normally, phasettras include dose-ranging, also called as dose escalation studies, so that the best and safest dose can be identified Normany, phase I trials include dose ranging, also called as dose escalation studies so that the best and safest dose can be identified. The tested range of doses is usually a fraction of a dose which causes harm in animal testing Although phase I trials are conducted on healthy volunteers, there are some circumstances when clinical patients are used for phase tin such cases where treatment is likely to make healthy individuals patients of terminal cancer or HIV are used for the trial in addition to terminal patients, patients who have been already tried and failed to improve on existing standard therapies may also participate in phase 1 trials Volunteers are paid a variable inconvenience fee for their participation in phase I trial in addition, their health insurance premium is paid by the sponsor of the that. Before beginning phase I trial the sponsor must rube nit an IND application to FDA detailing the preliminary data on the drug gathered from cellular models and animal studies.
Three types of studies are included in phase I trials single ascending dose, multiple ascending dose and the effect of food

Phase II

Once a dose range of doses is determined the next goal is to evaluate whether the drug has any biological activity or effect in human beings. Phase II trials are performed on a relatively larger group as compared to phase I trials. Normally, 100-300 patients are included in phase II studies Genetic testing is common, especially when there is evidence of venation in metabolic rate of the drug When the development process for an IND tails, it is inually during phase il trials. Convenienty, phase il trials can be divided in to two sub categories: phase A and phase Phase A studies are plot studies designed to demonstrate clinical efficacy of biological activity. It can be termed as "proof of the concept studies Phase studies find the optimum dose at which the drug shows the biological activity with minimal side effects. They are also termed as 'definite dose finding studies. Occasionyphase land phase II may be combined to test both efficacy and toxicity. Phase II studies historically have recorded lowest success rate. In 2010, the percentage of phase II trials that have proceeded to phase III was 18% During 2006-2015, only 37% of developmental drugs advanced from phase ll to phase II

Phase III

This phase is designed to assess the effectiveness of the IND, Phase III studies are randoned controlled multicentre trials on a large patient groups ranging from 300-3000
These studies are aimed at being the definitive assessment of effectiveness of the drug Phase ill trials are the most expensive. time-consuming and dimcuittrusis to design and run, especially in chronic diseases Phase il trials of chronic diseases often haveashort follow-up period of evaluation, relative to the penod of time during which intervention might be used in clinical practice Phase II studies are also called as 'pre-marketing phase During this stage sub groups of patients like those having hepatic, renal oncardiac failure may also be exposed with appropriate modification in dosages if proof about adequate safety is available, then paediatric and geriatric patients may also be included. In case of paediatric patients, a separate clinical study is suggested byregulatory authority
It is expected that at least two successful phase bemonstrating drugs safety and efficacy are necessary in order to obtain approval from approprite regulatory agencies like USFDA EMA

etc. Once a drug has proved satisfactory in phase il tras the trial results are usually combined in to alge document containing comprehensive description of the methods and results human and animas studies, manufacturing procedures formulation details and shelf life. This collection of information makesup the regulatory submission which is provided for review to appropriate regulatory authorities in different countries. The regulatory authorities review the submission, and if found appropriate, give approval for marketing the drug to the sponsor By 2010, about 50% of the INDs fail during phase il trials or are rejected by national regulatory agencies. An estimate of phase Altrials depends on various factors, therapeutic area being studied and types of clinical procedures as key drivers. It is indicated that, phase studies may cost about $20 million (130 crores), and phase lit studies $53 million (345 crores)

Phase IV

By the end of phase studies after review, regulatory authorities provide marketing permission to the sponsor Thus, a plus V tries also known as post marketing surveillance toal/contatorytriat Phase IV tras move surveilance of safety and ongoing technical support of a drug Phase IV studies may be required by regulatory authorities or may be undertaken by the supporting company for competitive or other reasons. The safety surveilance is designed to detect any are of long-term adverse effects ver a much larger patient population and longer time period than was possible sung the phase Hill dinical trans if an adverse drug effect is rare, then it may be detected ey in phase studies. The minimum time perod mandatory for phase Vctricaltha Hot two years Dang this penod, if a serious adverse reactions lerved, then the ine of drug may be appropriately restricted the advise actions to senous probably coming death, then the ding may be withdraws from the market dung phase IVstudes The ante process of developing new drug thaplechnicalyesearch to marketing can take 12:11 years and may cost over 51 bilin 6500 crore Thee of pocene of drug cepires 20 years after its registration.
The figures inficate big financial skindevnicong a new drug.

Table 2.5: Summary of trial phases

Sr. No.	Phase	Primary goal	Dose	Typical number of participants
1.	Pre-clinical	Testing of drug in animals to gather efficacy, toxicity and pharmacokinetics	Unrestricted	Not applicable (*in-vitro* and *in-vivo* only)
2.	Phase 0	Pharmacokinetics, oral bioavailability and half-life	Very small, sub-therapeutic	10 healthy volunteers

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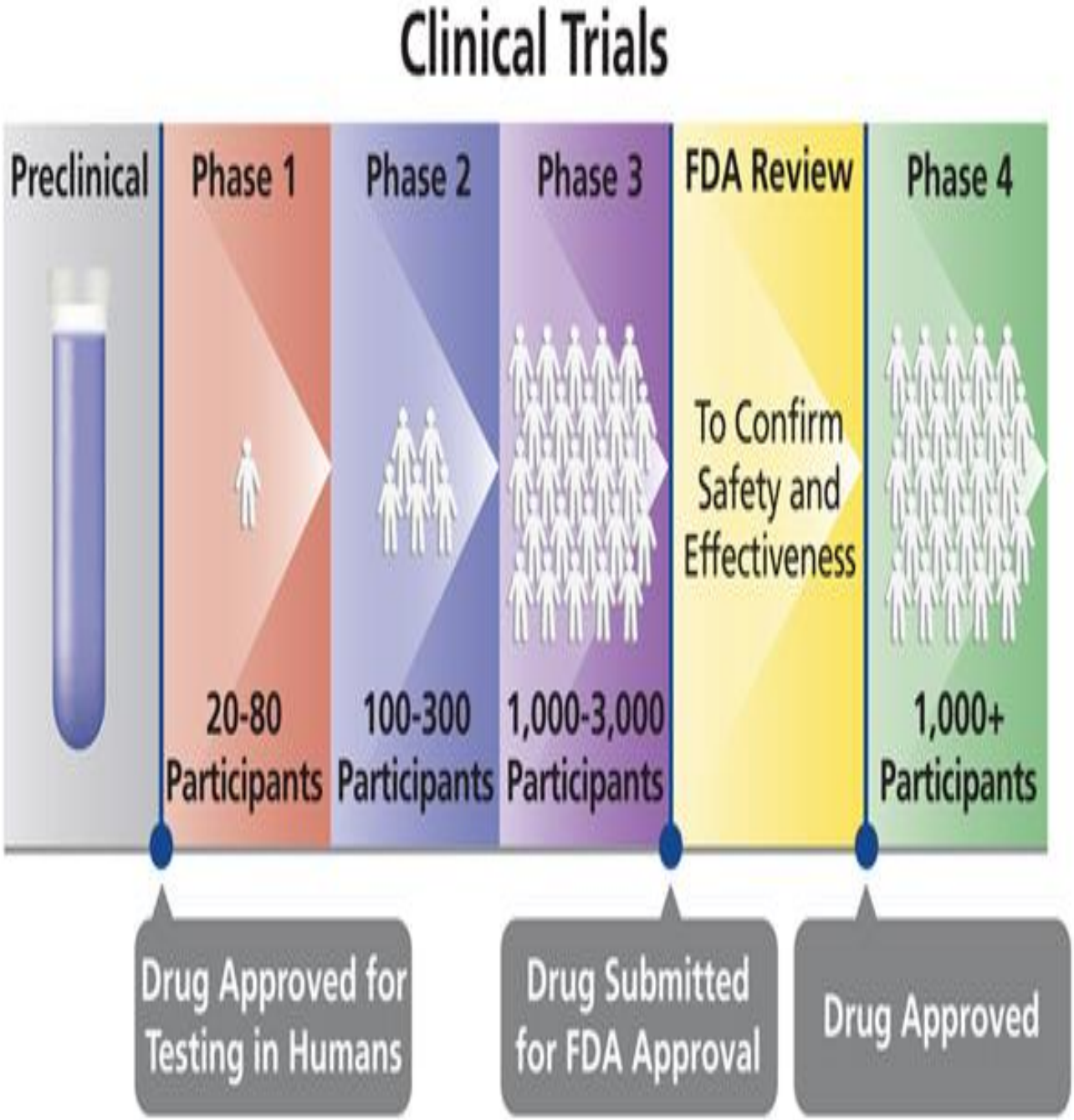
3.	Phase I	Testing on healthy volunteers for dose-ranging	Sub-therapeutic with ascending doses	20-100 healthy volunteers (cancer patients for anti-cancer drugs)
4.	Phase II	Testing of drug on patients to assess efficacy and side effects	Therapeutic dose	100-300 patients with specific diseases
5.	Phase III	Testing on patients to assess efficacy, effectiveness and safety	Therapeutic dose	300-3000 patients of diverse sub-groups
6.	Phase IV	Post-marketing surveillance-watching drug use in public	Therapeutic dose	Anyone seeking treatment from physician



Preclinical evaluation phase (animal studies) :
Major areas are: Pharmacodynamic studies in vivo in animals, In vitropreparation Absorption, distribution, elimination studies (pharmacokinetics) Acute,sub acute, chronic toxicity studies (toxicity profile), Therapeutic index (safety & efficacy evaluation)

5). CONCLUSION:

The above review hasgiven the information about discovery of drug & pre- clinical trials on the side effect animal or human body. Also Introduce the clinical phases.

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