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Phase 0 Trial

# Phase 0 Clinical Trial: Hope Through Research

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This paper Development of a drug molecule has always been a long and an exclusive process. From preclinical to clinical testing, it takes almost 10-15 years with an expense of almost US$2 Billion. It has been observed that serious challenges faced by researchers resulting in highest rate of failure in development of new drug molecules in clinical research. Seeing these grievances, the US FDA in 2004 introduced a "Critical Path "document highlighting the major decline of the drug development process despite having new advances and technology in biomedical research and the majors to improve the quality and effectiveness of overall drug discovery and development process. Thus, in 2006 a new guidance was issued on Exploratory IND studies by US FDA which is called phase 0 clinical study. It uses the concept of micro dosing. Minimum 30-40% of drugs fail in phase 1 trial due to unfavorable pk and pd. Micro-dosing is a new toolkit used in the drug development process and includes low or minute intake of molecules hardly to show any pharmacological effect when administered by participants and thus, helps in evaluating pk profiles. It shows no therapeutic effect, so chances of adverse reactions are also low. It acts as a bridge between preclinical and clinical study and can be beneficial in reducing extensive use of animal testing. Human screening is conducted to enroll few healthy participants for minimal no. of 7 days for the conduction of phase 0 trial. With recent technology, research and development and advancement, micro dosing has become more and more revolutionary and is emerging as the dormant challenge to be enormously used in more and more drug development process and make a shift to the process in a positive direction. The First emerging development of phase 0 trial can be witnessed in successful oncology trial in patients with progressive malignancies. Results proved to show a good and a well-tolerated bioavailability, and a desirable pharmacokinetics and biochemical data and hence this evidence can be used further to guide the development process and improve the drug development scenario.

**Keywords:** Amide, Exploratory IND, Micro Dosing, Drug Development, Phase 0 Trial, Pharmacokinetics, Pharmacodynamics

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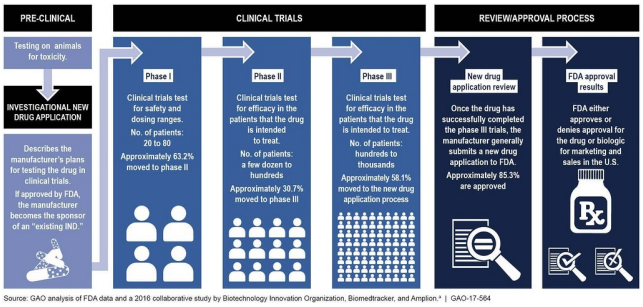
# Introduction

The process of drug discovery and development and gaining approval for selling a drug is a long, arduous and an expensive process. Drug development process is nevertheless, not an easy step to adhere to. It is bringing a novel drug from "bed to bench side". It takes a long and tedious process of approximately 10 -15 years with a very low rate of approval. Drug development process comprises pre-clinical and clinical phases (see figure 1).Before a drug is administered by participants it must go through rigorous experimental evaluation to determine whether it is safe, effective at treating the condition it was developed for, and to ascertain Maximum Tolerated Dose (MTD) and correct defined dosage form or mode of administration. Selected and shortlisted candidates undergo a series of investigation starting with in vitro with different models for enzyme catalytic activity, toxicity testing, receptor binding etc. Which further undergo to test safety and efficacy in in-vivo model.



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

The process of drug development is very expensive and time consuming, making it of prodigious curiosity to identify the agents that are likely not to go the entire distanceas early as possible, allowing an attention of finding the compounds that have the maximum likelihood of reaching the market. [1]

The data of pharmacokinetics and pharmacodynamics (PDs) properties of the product gathered through various studies done in humans and animals, determines the assortment of an effective and suitable dose in humans. Pharmacodynamics and pharmacokinetic data attained from studies done in animals may not at all times be predictive of human Pharmacokinetics and Pharmacodynamics, which results the process of drug development expensive and complicated.[2]

Research Scientists and physicians are constantly look for the greatest ways to make the diagnose process and treatment better.

It is apparent that they continuously making effort together develop new ways to diagnose disease and find better treatment to cure diseases to improve the quality of the life of patients.[3]

**Clinical Trials:** The systematic examination in human volunteers in an intention to identify and verify the clinical, pharmacokinetic and pharmacodynamic and other pharmacological properties of product undergoing investigation, and to identify any unintended harmful drug reactions resulted by a product under investigation, and to study the product under investigation with the intention to ensure its efficacy as well as safety can be referred as clinical trial[4]

Individual voluntarily take part in these clinical trials. The different phased of Clinical trials are done to test medical interventions including therapeutic medicine, other cell and biological products, vaccines, surgical interventions, diagnostic procedures, devices, behavioral therapies and other preventive interventions [5]. Clinical trials are conducted in four phases; phase I, phase II, Phase III, and Phase IV

The phases include first safety testing followed by efficacy testing and then comparison of the molecule with existing medicine followed up by post marketing. At present, it has been observed that only 10 percent of all the IND's (investigational new drug application) to the Food and Drug Administration (FDA) result in successfully completed clinically approved agents, and in the area of oncology it is found only to be 5 per cent. This is a very challenging, since the drug development process is lengthy and highly expensive process.

Consequently, new methods, plans and equipment are being adopted for the drug discovery and development process to be quicker and more efficient and accurate. Thus, the proposal of phase 0 was brought forward for the advancement in clinical trial process.

**Exploratory Investigational New Drug (IND) Studies and Regulatory Guidelines**

Also referred as "Phase 0 trial", "Pre phase 1 trial", "Proof of Concept trial" or a "Pilot study".

Seeing the challenges faced in the drug development process the US FDA in 2004 introduced "Critical Path "document highlighting

The major declination of drug development process despite having new advances and technology in biomedical research. The objective of this step is to provide a better insight and an perceptive knowledge base to result the drug development process much more well-organized and efficient, the US FDA issued Guidance on Exploratory IND Studies, in 2006.[7]

The objective of this guidance which was drafted CDER (Center of Drug evaluation and Research) is to elucidate and differentiate preclinical and clinical methods, as well as other approaches should be followed during planning of exploratory studies in humans, as well as the studies ofrelated drugs or products used in therapeutic purpose, under an investigational new drug application (IND)[8].The guidelines also elucidate the features and the objectives of studies of the product under investigation. Briefly, they are known as studied conducted in early phase(Phase I) of clinical development in a very limited number of subjects specifically on healthy human volunteers.

Similarly in 2003 a paper on non-clinical safety studies (released by EMA) to support human clinical trials using micro dosing method (CPMP/SWP/2599/02/). In 2006 EMA published another paper recommending the development of some standard guideline explaining what non-clinical information are obligatory to be comprised in a clinical trial for an early phase study in humans. The guidance provided by EMA envisioned to allow for suppleness of different approaches, as well as those delineated in the EU Micro dose guideline [9]. EMA familiarized the likelihood of a abridged preclinical safety package for micro-dosing clinical studies. As defined by EMA, micro dosing studies has a significant role in the evaluation of human plasma PK studies. Additionally, it can also contribute in receptor selectivity profile of investigational drugs as early as possible in the pre-clinical phase of drug development. Hypothetically, micro dose studies in human can result in an early choice with respect to differentiating between promising, effective and unsuitable molecules for future development.[10]

Later in 2009 ICH international guideline was released where ICH M3 depicts guidance on clinical safety pharmacological studies for human pharmaceuticals CPMP/ICH/286/95.

**Phase 0**

It is a first in human trial exposure with a very a smaller number of volunteers usually 10-12. A very low non- toxic dose is given for a minimum of 7 days. In the initial phase of testing, the human volunteer chosen are usually healthy rather than people suffering from the disease the drug is intended for.

Due to the unforeseen risks, very less amounts of dose of the drug are utilized for minimal durations usually of less than seven days, to curtail any adverse side effects that the subject can get exposed to and get harmed. Minimal doses that were considered to be nontoxic in the animal model studies are used. The objective of Phase 0 trial is not to test the therapeutic benefit but to find out whether the drug behaves as expected in humans subjects and to obtain preliminary information regarding various parameters like what the drug carry out changes into the body and what the body does to the drug, target binding affinity, receptor binding property, enzyme catalytic activity etc. [2]

It creates a bridge between preclinical and clinical studies for better understanding of the drug compound. This phase helps in ranking the drug and making a selection among the drug candidates for the Phase 1 clinical trial. Thus, reducing cost and time and improving the efficiency of the drug development process.

Micro-dosing is a new toolkit used in the drug development process. It includes low, non-pharmacologically active doses of drugs that are used to identify and evaluate pk profiles in humans. A micro-dose of an investigational product is considered as the lesser of: (a) 1/100 of the dose which can result a pharmacological result based on the preliminary data obtained from in-vitro and in-vivo studies. [11]

**Some Important Definition**

**A. Volume of distribution:** "A pharmacokinetic parameter that would represent the amount of drug present in the body(tissue) at the same concentration as in the plasma."

Volume of Distribution (L) = Amount of investigational product in the body (mg) / Plasma concentration of drug (mg/L) Thus, higher the volume of distribution, more the distribution to other tissue.

**B. Single Ascending Dose(SAD):** The participants during research usually a small group of healthy volunteers are provided with the single dosing of drug molecule and are monitored well over a period of time to evaluate the PK and safety of the drug molecule.

If no adverse effect is found and the data aligns as per protocol then the group of subjects are provided with the advanced dose.

This will not be stopped until pre-defined safety levels are achieved, or unacceptable noxious effects start showing up.

**C. Multiple Ascending Dose(MAD):** MAD evaluates the parameters like pharmacokinetics (PK) and pharmacodynamics (PD) of multiple doses of the drug, determining its safety and MTD (Maximum tolerated dose).

A squad of healthy volunteers/patients/participants administered with multiple low doses of the drug, and at different period of time, samples (of blood and other fluids) are collected and analyzed well to get the facts related to processing of the drug within the body.

**D. o-Observed-Adverse-Effect-Level (NOAEL)**
Amount of a substance or highest concentration, that causes no noticeable adverse effect or any changes in morphology, growth, development, functional activity or lifespan of the target under specifed conditions of exposure during experiment.It is well illustrated in animal toxicity studies and marks a safe starting dose in human subjects.

**Objective of phase 0 trial included the following:**

- Evaluate the pharmacokinetics
- Pharmacodynamic of candidate drug
- Selection of the lead candidate from the compound library
- Amplification of the molecular target

Important features required considered while designing Phase 0 trials:

- Corroboration for linear Pharmacokinetic of the investigational drug;
- Accessibility of a sensitive biomarker assay;
- Required infrastructure, enthusiastic, competent and professional study team;
- Accessibility of a measurable Pharmacodynamic result at minimal doses;
- Readiness of appropriate study subjects.

**Difference between phase 0 and phase 1**

The phase I clinical trial usually done on human volunteers is to identify the MTD (maximum tolerated dose) of the selected compound. The goal is mainly about target modulation. As a significance of this, dosingand dose escalation studies are significantly limited in Phase 0 trials. Basically, the phase 0 studies are proposed to provide alternative solutions in the drug discovery and development process. In the traditional Phase I studies carried out for oncologic investigational productand other different therapeutic areas, the preliminary safety pharmacology studies are done to assess the effects of a new drug on the central nervous system, cardiovascular system, and respiratory system. These can be conducted as a part of in-vivo studies in selected animal model. Single-dose acute toxicology studies are obligatory in two mammalian species to decideand distinguish the toxic and safe doses [7]. The basic difference between phase 0 and phase 1 is summarized in the figure shown below

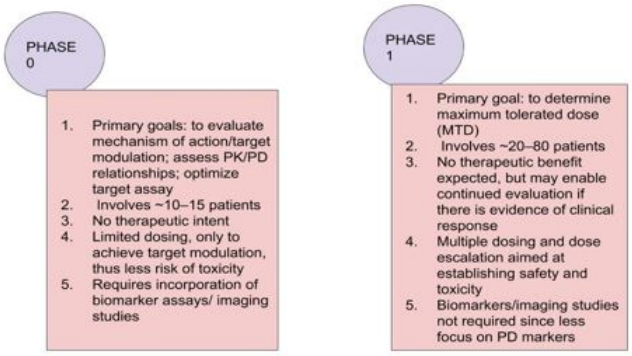



**Figure 2: Overview for phase 0 and phase 1**

**Ethical Consideration in Phase 0**

- Ethics must be followed in all the phases for the smooth functioning of the trial. Negligence in the ethics led to misconduct. A proper protocol must be designed stating complete details about the trial and approval must be taken by the regulatory bodies.
- Volunteers enrolled for the trial must be made clear that it has no therapeutic intent or chance of benefit. Researchers need to be upfront in discussing the goal and objective of these type of studies, as well as to develop knowledge base regarding the potential benefit

- on the development of the drug under investigation with prospective volunteers participating in the nontherapeutic nature of Phase 0 trials[2]
- This ethical consideration of imparting a micro dose administration with no expected benefits is much less challenging in chemoprevention studies.[14]
- Informed consent process must be performed thoroughly and every detail must be well explained to volunteers about the nature, lack of therapeutic intent, safety testing and limited toxicology study.
- Clear description of foundation for the study— This should be the obligation of the researcher to advice the subjects for their ability to participate after phase 0. While developing the design of phase 0 studies, parallel patient treatment planning is to be planned and should be included in real study.[15]
- Determining the treatment as well as follow-up duration— The crucial end points of the 'phase 0' studies should be precise and defined as per real time.
- For every participant, a proper plan is essential for overall clinical care combined with participation in phase 0 trial and if the product is found to be beneficial and helpful, participants of phase 0 should be allowed to participate in later phase studies.
- Using comparatively much lower doses in additional to greater safety margin, the likelihood of adverse effects is anticipated to be much lesser; however, close monitoring and acceptable medical care similar to other clinical trials is required.

**Advantage of Microdosing**

- Helps to establish drug - drug interaction relationship. The pharmacokinetics of an investigational product administered as a micro dose before as well as post administration of a pharmacologically active dose of a suitable inhibitor or inducer of a selected enzyme is compared.
- Helps in measurement of drug concentration at the site of action and also shows metabolic profile of the drug to ascertain preliminary data on metabolism of a candidate.
- It allows the selection of promising compounds at a early stage for further development of the drug before the traditional phase 1 trial and also accelerates the drug development by focusing only on promising compounds.
- All studies done using micro dosing needs lesser amount of the investigational drug for testing the safety of the drug. A micro dose is so small that whenever it is administered to subjects, it is not thought to produce any pharmacologic action; hence, the risk of united noxious effect is less. As per the requirement of regulatory bodies, animal studies at least in one species are vital to establish micro dose in human subjects, but at a very decreased level.
- The intrinsic toxicological low risk of micro dose permit pharmacokinetics studies to be completed in vulnerable populations like children, elderly people, pregnant women, hepatically and renally impaired populations who are not allowed to participate in clinical trials due to safety and ethical concerns.
- Outcomes of Phase 0 trials highlight any unwanted and unfavorable properties, such as poor bioavailability or the problem of target modulation. The phase 0 trial help in taking a decision to reject an agent from the clinical development pipeline thereby saving resources in the overall process. The cost involved in conducting phase 0 trial is comparatively very less as compared to traditional phase 1 trial. Phase 1 may cost around US$ 1.5-3.0 million, whereas in the study using micro-dose, the cost used to be reduced to approximately US$ 0.3 - 0.5 million.[2]

# Limitations

- The limitations of micro-dosing studies can be related to metabolism and solubility of substance. There are various progressions inside the body which include involvement of the use of specialized transporters enzymes as well as binding sites and these can be concentrated like the pharmacokinetic properties of drug agent is diverse at the advanced therapeutic dose than those are seen with the micro-dosing studies. Further the compounds required to be soluble so that it can pass through the cell membranes and act as expected within the body. It is seen that

- most of the compound dissolve very fast at micro-dosing level, resulting rapid and usually fast absorption. However, at advanced therapeutic doses, many of the compounds reveal limited solubility. Thereby absorption becoming more reliant on the rate and amount of dissolution, which is not possible to be predicted by micro-dosing.
- A lot of studies are not performed to clearly indicate whether the drug reaction to the body is similar when used as a micro dose and in its pharmacological dose. It may result as false positive (when the compound is accepted as a micro dose but is rejected when used as its pharmacological dose). It may also result in false negative (compound being rejected).
- Since phase 0 trial has got no therapeutic benefit or any diagnostic care so it might become challenging to recruit volunteers.
- For examination of the data there is a requirement of ultrasensitive equipment like PET(positron emission tomography) and AMS (accelerator mass spectrometry) are applied to examine the concentration of the targeted molecule. Both these tools are scarcely available and become a troublesome. For both these tools drug must be labeled at metabolically sites.[6]

**Indian Scenario:** Regulatory amendments supporting the early phases of clinical trial (phase I) and micro-dosing trial would result in enhancement of the science of early clinical development. It will help in reducing the time and cost of drug development thereby contributing to advancement in drug development process in the country. This would certainly bring India into the mainstream of drug development research. It can play a crucial role for global drug development in the recent future.

In India, there are many pharmaceutical organizations which are thriving to develop or compete with other companies at global level by discovering and developing new and promising drug molecules. Regrettably, still in Indian regulation there is no provision for phase 0 studies or other simar studies. The study evaluating the toxicity which are included in phase I studies are apparently more required in India as compared to other countries worldwide. So, the early clinical development trials are mostly conducted in outside India.

As a result, the companies in India are lacking behind on in identifying and selecting the drug candidate through microdosing studies.

A proposal for the amendment in the clinical trial regulation to include phase 0 trial in the process was circulated by The Indian Society for Clinical Research (ISCR) in 2007– 2008.

The change in the regulation would have added flavor to the drug development process. It has allowed pharmaceutical fast growth and rapid advancement and development in the whole process and would have led India to be recognized and plays very significant role in the Drug Discovery and Development process.

**Indian Scenario:** Phase 0 trial helps in improving the effectiveness of the drug discovery and development process and saves time, effort and cost. It is advisable to perform a micro dosing trial before entering in the traditional phase 1 trial since it helps in ranking the drug and making a selection among the drug candidates, thus hastening the drug development process. It creates an opportunity for small biotech companies for speedy development of their own molecule and become the pioneer of the arena.

In the race of scientific technology and development, the concept of micro dosing is considered as one of the most "viable tool ". Micro-dosing is a new toolkit used in the drug development process which includes low and minute intake of active doses of drugs that are used to identify and evaluate pk and pd profiles in humans. It not only provides proof of concept but also helps in reducing or getting rid of the targeted molecules which may be discarded in the later stage of the drug development process therefore saving time and cost.

With recent technology and research and development and advancement, micro dosing has become more and more enlightened and has the prospective to be widely used in more and more drug development process and make a shift to the process in a positive direction. Phase 0 yet need to be clearly defined since the exact role and implication is virtual and can be made real by gathering more and more data by performing phase 0 trial. It is recommended to take the advantage of the initiative provided by US FDA and take the drug development process reach up to the notch.

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