Phase-0: A General Overview

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A B S T R A C T

Submitted: 16/05/2013 **Accepted: 02/09/2013**

Development of a new drug molecule is very long and expensive operation. Out of 9000 to 10,000 compounds, one (on average) will actually reach to the market. In 2004, the US Food and Drug Administration (FDA) introduced its "Critical Path" document highlighting the serious discordance between major advances in science and technology and limited or stagnated new drug development and offer examples of newer methodologies that might be incorporated early in the drug development process to increase the efficiency of bringing a new therapeutic agent to the bedside. For this reason, the FDA issued a new Exploratory IND Guidance in 2006, to allow for such studies often called as phase 0 clinical trials which are also called as Human Micro-dosing Studies. Micro-dosing methodology is referred to as a new viable "tool" in the drug development toolbox. In micro-dosing studies extremely low, non-pharmacologically active doses of the drug are used to define the agent's pharmacokinetic profile in humans. In phase 0 clinical trial, animal studies can be avoided with compounds having unsuitable pharmacokinetic profiles, greatly save the investment, shorten development timeline and improve the efficiency and success of subsequent trials. The patients included in the trials are expected to be treated with better effective and more safe, efficacious drugs.

Keywords: Phase 0, micro-dosing, investigational new drug, drug discovery and development

Introduction

The discovery, development, and registration of a pharmaceutical agent is an immensely expensive operation and represents a rather unique challenge. For every 9000 to 10,000 compounds specifically synthesized or isolated as potential therapeutics, one (on average) will actually reach the market. This process is illustrated diagrammatically in Figure 1. Each successive stage in the process is more expensive, making it of great interest to identify as early as possible those agents that are likely not to go the entire distance, allowing a concentration of effort on the compounds that have the highest probability of reaching the market.[1]

Scientists and doctors are continually looking to find the best ways to diagnose and treat disease. This means that they work together to:

- Develop new diagnostics and treatments and test their effects in people.
- Test a new use of an existing diagnostic or treatment in people, look at new combinations of existing treatments or change the way they are given in order to make them more effective or to reduce side effects.
- Compare the effectiveness of existing diagnostics and treatments in people.

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Fig. 1: Development of new drug molecule

Time (in Years)		No. of new drug Molecule
16	Product approved for market	1
15		
14	FDA Review	2
13	NDA Filed	
12		
11	Phase III Clinical Trails	6
10		
9	Phase II Clinical Trails	8
8		
7	IND Filed / Phase I Clinical Trails	250
6	Proposed for preclinical Development	400
4		
2	New Compound from research	
0	"Discovery	5000-100000

- See which diagnostics and treatments are the most cost-effective.

This form of testing is called a clinical trial because it scientifically tests the diagnostic or treatment in people.[2]

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.[3]

Phases of clinical trial

In broad terms, the types of trials conducted in human subjects may be divided into four phases.

A) Phase-1 B) Phase-2 C) Phase-3 D) Phase-4

These phases represents the stages, for example, the development of a new drug which requires early dose findings & toxicity data in man, indications of potential activity, comparisons with a standard to determine efficacy and then post marketing trials.[4] Currently, only 10 per cent of investigational new drug (IND) applications to the Food and Drug Administration (FDA) result in clinically approved agents, and in oncology it is only 5 per cent. This is a very serious problem, since the development of a new agent is a lengthy and expensive process and many of these agents fail relatively late in that process. The fact that an increasing proportion of IND agents is molecularly targeted, which suggests testing the agent for effectiveness against the target by means of a PD (pharmacodynamics) assay very early in the drug development process. This is particularly useful and important since the pre-clinical tests of such effectiveness are often misleading, yielding both false positive and false negative results.[5]

In 2004, the US Food and Drug Administration (FDA) introduced its "Critical Path" document highlighting the serious discordance between major advances in science and technology and limited or stagnated new drug development. Despite advances in many scientific disciplines pertaining to drug discovery and development, the registration of new chemical entities (NCEs) has declined. "The medical product development process is no longer able to keep pace with scientific innovation. Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path.[6] This "Critical Path" document and a subsequent exploratory investigational new drug (IND) guidance[6,7] challenge this discordance and offer examples of newer methodologies that might be incorporated early in the drug development process to increase the efficiency of bringing a new therapeutic agent to the bedside**.** In addition, other regulatory agencies such as the European Medicines Agency have also supported the use of new methodologies in drug development.[8] For this reason, the FDA issued a new Exploratory IND Guidance in 2006, to allow for such studies as small first in man trials, conducted at dose levels and administration schedules not expected to result in significant clinical toxicity, and generally restricted to at most approximately one week per patient. Conducting studies under this guidance requires substantially less pre-clinical toxicology work than that required for standard IND phase 1 studies. Therefore, phase 0 studies can be administered while the toxicology studies preparatory to filing a standard IND are being conducted, and they will not postpone the time until the phase 1 trial can be initiated.[5] Phase 0 trials bridge the region between the traditional preclinical and clinical testing phases and allow researchers to develop a better understanding of variables such as pharmacokinetics, pharmacodynamics and target localization of a new compound, or a series of related compounds before undertaking phase 1 trials.[9]

Micro-dosing methodology is referred to as a new viable "tool" in the drug development toolbox. In micro-dosing, extremely low, non-pharmacologically active doses of drug are used to define the agent's pharmacokinetics profile in humans.[10] Investigational New Drug (IND) Studies Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies.[11] A micro-dose is defined as the lesser of: **(a)** $1/100^{th}$ of the dose calculated to yield a pharmacological effect based on in-vitro and in-vivo primary pharmacodynamic data or **(b)** a dose of 100 mg. Therefore, by definition, micro-dosing will only provide information on pharmacokinetics.[12]

Objectives of Phase 0 trial

The objective of Phase 0 trials conducted under an exploratory IND can involve:

1) Pharmacodynamic characteristics of candidate drugs

2) Modulation of a molecular target (i.e. change in gene or protein expression)

3) Selection for lead candidate by evaluations of analogs and

4) Agent pharmacokinetics (PK).[13]

Role of FDA in phase 0 trial

According to the FDA a phase 0 is designed to take place very early in phase 1, involves very limited human exposure receiving only sub-therapeutic dose and this means the patients (study subjects enrolled) produce a pharmacologic response rather than the toxic effect, and the risk involved is less than conventional phase 1 trials in which administration continues if there is evidence of clinical benefit and thus phase 0 trials lack even therapeutic intent. Ultra-sensitive AMS (accelerator mass spectrometry) has made it possible to undertake clinical studies in man using extremely low drug doses to obtain early PK and ADME (Absorption, Distribution, Metabolism, Excretion) data.[14]

Designing of Phase 0 trial

By design, phase 0 trials portend lower risks to human subject than traditional phase 1 trials. As such, fewer preclinical supporting data are required prior to conducting a phase 0

trial. The initial agent dose depends in part on the stated trial objectives, but should not be greater than 1/50th of the no-observed-adverse-effect level (NOAEL) estimated from animal toxicology testing. Validated pharmacodynamic assays, ideally with low variability in the molecular target, are suitable for application to phase 0 trials if the investigational agent can reasonably be expected to demonstrate target modulation at a non-toxic dose. Standard operating procedures for tissue collection and bio-specimen handling should be defined in advance and revised as necessary based on results of the phase 0 trial. Chemoprevention agent development is uniquely challenged by the need to identify widely acceptable, minimally toxic compounds (even when chronically administered) that favorably affect carcinogenesis when measured against surrogate biomarkers, rather than direct cancer endpoints. Methods to identify bio-available, pharmacodynamically active candidates earlier in the drug development cycle would offer clear advantages with respect to process efficiency, resource utilization and other parameters. Natural products (or derivatives thereof) represent an attractive source for chemoprevention agent discovery and, given their oftentimes demonstrated favorable safety profile at standard doses, provide an excellent opportunity to explore potential benefits gained through the phase 0 trial paradigm.

Phase 0 trials are designed primarily to evaluate the pharmacodynamic and/or pharmacokinetic properties of selected investigational agents prior to initiating more traditional phase 1 testing. One of the major objectives of phase 0 trials is to interrogate and refine a target or biomarker assay for drug effect in human samples implementing procedures developed and validated in preclinical models. Thus, close collaboration between laboratory scientists and clinical investigators is essential to the design and conduct of phase 0 trials.[14]

Ethics in phase 0 trial

The ethics of doing phase 0 trials must also be considered carefully. These trials have no therapeutic intent and often will require significant invasive procedures. They have finite treatment duration and, theoretically, are not in the range of efficacious dosing. Fewer toxicology data are necessary, so there is some concern that this limited toxicology will be insufficient and not well defined in every drug scenario to maximize patient safety. The patient must be made aware of the investigational nature of these studies, the lack of therapeutic intent, and the limited toxicology and safety testing. There is a responsibility on the part of the investigator to advocate for the patient's ability to be treated after his or her phase 0 experience, either with conventional treatment or on another clinical trial, in as timely a fashion as possible. Thus, during the design of a phase 0 study additional patient treatment strategies must be taken into account and possibly incorporated into the actual trial.

The necessary end points of the phase 0 trial must be defined in real time so that there is minimal delay for subsequent treatment intervention. Therefore, significant multidisciplinary input from biostatisticians, clinicians, and basic and translational scientists in the design process is required to best protect the patient. Who benefits from the use of phase 0 trials? By incorporating this innovative tool to potentially expedite a new drug to clinic, the hope is that the main beneficiary will eventually be the patient population at large. Even if the phase 0 trial identifies the drug as not being of therapeutic worth, the patient population may benefit through the minimization of study participants recruited to subsequent trials on the critical path. The sponsor of the compound may realize the benefits of a phase 0 trial the most.[15] There should be an expectation that exploratory trial results will either be published or committed to a publicly accessible electronic database. Such a policy is admittedly unlikely to find political traction. Nevertheless, studies pursued with no intention of disseminating results that is, trials conducted purely for commercial ends are inconsistent with the value requirement for clinical research. One compromise might be permitting sponsors a reasonable delay before posting results.[16] However, FDA supports the conduct of phase 0 trials. Phase 0 trials in oncology related studies raise important ethical concerns that have received little attention in recent years. The question arises it is ethical to enroll a subject in human micro-dosing that offers them no potential clinical benefit and further concern focuses on the inclusion of terminally ill and the consequently vulnerable cancer subjects in this type of trial.[17]

Data needed to justify micro-dosing approach

The potential value of the micro-dosing approach has been recognized by many pharmaceutical companies but taken on board only by few due to the lack of data justifying the approach. It is therefore imperative that a body of knowledge is built to convince the pharmaceutical industry of the merits of human micro-dosing as a science driven approach to drug development.[18]

Advantages of phase 0 trial

First of all, micro dosing requires minute quantities of the drug for safety testing. A micro dose is so small that when administered to human subjects, it is not intended to produce any pharmacologic action; hence, the risk of adverse events is less. A smaller toxicology package is required. As per the regulatory requirement, animal studies, at least in one species are required to establish microdose in humans, but at a much reduced level. Further, if human screening of compounds is

done earlier in the drug development process, fewer animal studies are required before phase 1 clinical trial. Thus, further animal studies can be avoided with compounds having unsuitable pharmacokinetic profiles.[10] Pharmacokinetic data for initial dose selection can be generated in 4 to 6 months from obtaining preliminary toxicology data in animals.[19] This pharmacokinetics data can further be used 1) to help in selection of the ideal candidate drug 2) obtain the first in man dose of that selected drug 3) Establish the tentative pharmacological dose[10] and 4) calculate the potential cost of goods for a drug that is expensive to manufacture, the pharmacological dose could be so great that the drug becomes uneconomical to produce. 5) Select the best species for long-term toxicological studies from microdose metabolite profiling data.[20]

Results from Phase 0 trials can also highlight any undesirable PK or PD properties, such as poor bioavailability or the lack of target modulation, supporting the decision to eliminate an agent from the clinical development pipeline and saving resources in the process. Thus, Phase 0 trials offer a mechanism that allows for the early assessment and expeditious development of promising agents as well as deprioritisation of agents unlikely to provide clinical benefit. Phase 0 trials with PD end-points require allocation of extensive re-sources early in the drug development process, but could potentially compress the overall development timeline by allowing earlier informed go/no go development decisions, improve the success rate (defined as number of agents that are approved for standard clinical use), and save valuable patient resources.[21]

Further, the cost of conducting a microdose study is phenomenally less, as compared to a full Phase 1 study. A conventional phase 1 study may cost about US$ 1.5 to 3.0 million, whereas in the micro-dosing approach, the cost drops to about US$ 0.3 - 0.5 million. Human micro-dosing promises to be a significant analytical tool. In future, as research methods and technology involved in Phase 0 trials become more sophisticated, human micro-dosing may be applied to a number of drugs that could potentially be administered consequently. Additionally, micro-dosing could be useful in the discovery of endogenous biomarkers, which would assist in the quantitative evaluation of the in vivo effects of drugs.[10]

Disadvantages of phase 0 trial

Patients in a phase zero trial get only too small portion of the investigational new drug and such small doses could give results there are not relevant to the later real-world one. The laboratory and other parameters are very limited and very expensive hence many phase 0 trial researchers have to depend on BA/BE labs involved in use sensitive instrument in detecting the test articles at micro-dose level in the matrix of the study subjects.[14] Participation in a Phase 0 trial might delay or exclude the patient from other clinical trials that may have some, although little, therapeutic intent. Although the total duration of a patient's participation in a Phase 0 trial is short and is expected to last no longer than 1 week, not only the preparation for a subsequent clinical study may be delayed but also a wash-out period may need to be taken into consideration. These issues may significantly impair patient recruitment, thus influencing the feasibility of Phase 0 trials.[25]

Limitations of phase 0 trial

1) A micro-dose may not be able to predict the behavior of a clinical dose of the drug.[10]

2) Use of micro-dosing commonly raised by skeptics is the potential for poor predictability of pharmacokinetic information obtained with a micro-dose versus a therapeutic dose due to the occurrence of nonlinear absorption or disposition.[22]

3) Further, AMS (accelerator mass spectrometry) and PET (positron emission tomography) are applied to analyze the concentration of the drugs in low picogram to femotgram range when micro-dose is used. These radiotracer assays have the disadvantages of short tracer half-life and limited specificity (as assay may include metabolites also). Both for PET and AMS, the drugs must be labeled at metabolically stable sites.

4) The limitations of micro-dosing relate to compound metabolism and solubility of compound. Many processes within the body involve the use of specialized transporters enzymes and binding sites, which can be saturated such that the pharmacokinetic profile is very different at the higher therapeutic dose than seen with the micro-dose. Further the compounds must be soluble to pass across the cell membranes and act within the body. Most compounds dissolve rapidly at micro-dose levels, yielding rapid and often extensive absorption However, at higher therapeutic doses, many compounds exhibit limited solubility. This means, absorption becomes more dependent on the rate and extent of dissolution, which cannot be predicted by micro-dose. Thus, it has been suggested that the dose of 100 micrograms may be too low to achieve the full potential of micro-dosing.[10]

5) Agents with different kinetic characteristics between micro-dose and full-dose are not well evaluated by Phase 0 trials. In addition, the range of resources required for the pre-clinical and clinical aspects of Phase 0 studies, particularly those evaluating target or biomarker effects, is not available for most sponsors.

6) Some institution cannot afford to a dedicated PD assay development laboratory and staffs who have the necessary expertise in biomarker analytic assay development and validation, as well as the facilities for clinical human tissue PD and PK studies that can be done in real time, all of which are necessary when Phase 0 trials are to be conducted.

7) The concept and efficiency of conducting Phase 0 trials is not widely accepted by the pharmaceutical industry because

some of companies have not knowledge about Phase 0 trials or they doubt whether Phase 0 clinical trials would really save greatly investment, shorten development timeline and increase probability of successful drug development.[23]

8) Te acquisition of information does not guarantee that it will actually be used. For example, if negative results found during the course of a phase 0 study would not change the commitment of the developer to proceed or would not even alter the course of development, there is no role for phase 0, and a traditional phase 1 is the more likely choice.[24]

CONCLUSION

Due to Phase 0 clinical trial human screening of compounds is done earlier in the drug development process so fewer animal studies are required before phase 1 clinical trial. Thus, further animal studies can be avoided with compounds having unsuitable pharmacokinetic profiles and pharmacokinetic data for initial dose selection can be generated in 4 to 6 months from obtaining preliminary toxicology data in animals. Phase 0 trials can greatly save the investment, shorten development timeline and improve the efficiency and success of subsequent trials, particularly those for the development of molecularly targeted agents.

Phase 0 trials have the potential to shift drug development process towards a positive direction; and it is hoped that, on the cumulative side of future, by means of these trials patient community could expected to be treated better in short span of time with effective and more safe, efficacious drugs.

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