



INVITED ARTICLE

MICRODOSING: A PHASE 0 CLINICAL TRIAL

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Abstract

The process of new drug development requires extensive non-clinical safety testing in order to generate sufficient data to move to clinical development and then for market entry. Not only clinical development, but also non-clinical safety and pharmacology testing are time consuming, costly and require lot of resources. Many-times, after clearing non-clinical safety and pharmacology testing, the drug candidate may fail to demonstrate desired pharmacokinetic in clinical development phase. Suboptimal pharmacokinetic is one of the reasons for failure of the drug in demonstrating desired clinical efficacy and safety in later clinical development phase. Therefore, it is very important to have idea of pharmacokinetic of the drug candidate in human at least to make early “go/no-go” decision during development in order to reduce the time and cost of development. Microdosing is a new technique to obtain human pharmacokinetic information before the usual expensive clinical phase of drug development starts. Microdose studies uses less than 1/100th of the dose calculated to yield a pharmacological effect of the drug and hence, risk to trial subject is very less in microdose studies and it can be initiated early after completing limited non-clinical studies. It uses highly sensitive and specific analytical methods for estimating drug and metabolite concentrations in picogram to fentogram range. Experience of various drug developers with microdose studies so far suggests that microdosing is a better tool for predicting human pharmacokinetics early and may be helpful in order to make early “go/no-go” decision in drug development.

Keywords: *Microdosing, Phase 0 Clinical trial, drug developement*

Introduction

Drug development is a scientific endeavor and is highly regulated because of legitimate public health concerns. Drug development process involves integration of different expertise, conduct of many experiments and involvement of lot many resources, considerable time and significant cost. It takes about 2 to 12 years for a new drug for development [1] and the cost of a new drug development range from USD\$92 million to USD\$883.6 million [2]. During the drug development process, many animals are used for experiments and during clinical trials, many human subjects are exposed to the drug at various dose. Even after spending lot of resources, time, cost and experimentation on animals and humans; the drug may fail to provide desired clinical efficacy and safety. Only one in 10,000 compounds ever reaches the market and of those, only one in three ever recaptures its development costs [1]. There are many reasons for failure of the drug candidate during drug development or after market entry. They are Poor pharmacokinetic (39%), Lack of efficacy (30%), Animal toxicity (11%), Adverse effects in man (10%), Commercial reasons (5%), Miscellaneous (5%) [3,4] and are appeared at different stage of drug development or sometimes after market entry of the drug. Hence, at each stage of drug development, the developer needs to make “go/no-go” decision based on available information. On one side, it is good to make “go” decision at each stage of development based on the available data, but on other side, it is highly

desirable to identify limiting factor (if any) as early as possible so as to make earliest “no-go” decision with the drug candidate in order to save time, money and efforts. The drug development phase which tests the drug’s performance in humans is call clinical development. The drug’s fate, eventually the developer’s fate, depends upon the performance of the drug in target population (humans) during clinical development and then in market use. Hence, it is very important to have data of drug’s performance in humans as early as possible in order to make “go/no-go” decision.

Microdosing

Microdosing is a new technique to study new drug especially for human pharmacokinetic before the usual expensive clinical development phase starts. A microdose is defined as less than 1/100th of the pharmacological (predicted) dose of a test drug candidate or a maximum dose of $< 100 \mu\text{g}$. Due to differences in molecular weights as compared to synthetic drugs, the maximum dose for protein products is d^{30} nanomoles to be said as microdose [5]. Studies using such a microdose are called microdose studies. In microdose studies, sub-pharmacological doses of prospective drug candidates are administered to human subjects in order to obtain pharmacokinetic and if possible some pharmacodynamic information (e.g. mechanisms of a drug action). European and USFDA guideline now permit microdosing studies in human subjects very early in the drug development process. The preclinical

toxicology data required for microdosing studies are minimal and hence these studies can be used as a drug candidate selection tool to effectively eliminate drug candidates that show sub-optimal human pharmacokinetic before spending time and effort in the kind of extensive toxicology that is required prior to conventional Phase 1 and other conventional clinical pharmacokinetic studies for such drug candidates. The term “Phase 0” is therefore used to refer to such microdose studies.

To measure drug concentration in microdose studies, ultrasensitive analytical methods like Accelerator Mass Spectrometry (AMS) and Positron Emission Tomography (PET) are used. AMS is the most sensitive analytical method being used in microdosing study using radiolabeled substance. AMS differs from other forms of mass spectrometry in that it accelerates ions to extraordinarily high kinetic energies before mass analysis. The special strength of AMS among the mass spectrometric methods is its power to separate a rare isotope from an abundant neighboring mass. AMS measures individual atom of the isotope and not radioactive decay events, this makes AMS highly sensitive than conventional Liquid Scintillation Counting and upto 100000 times more sensitive than liquid chromatography mass spectrometry (LC-MS). In studies using high performance liquid chromatography-AMS, limits of detection of 0.0008 dpm/fraction have been reported. Using AMS, drug developer can generate human pharmacokinetic data of drug candidate using microliter or milligram quantities of sample and minute

levels of ^{14}C tracer, which is virtually undetectable and of nanocurie level of radioactivity [6,7]. PET is 3-dimensional imaging technique using radioactive tracer to label drug. PET can be used to study pharmacodynamic information like receptor selectivity, receptor occupancy profile etc. ^{11}C or ^{18}F are generally used for radiolabeling which generate images using gamma cameras and can be used to study distribution of labeled drug candidate in body in real time including penetration in central nervous system, cross of blood brain barrier etc [6-8]. Sometimes, liquid chromatography coupled with tandem mass spectrometry (LC-MS-MS) is also used in microdose studies. Below are some of the advantages and limitation of microdosing technique (Table 1).

Microdosing technique is significant technological advancement in the field of clinical development which generates some human pharmacokinetic and pharmacodynamic data to improve and speed-up drug development process. It greatly helps in generating early pharmacokinetic data to make early “go/no-go” decision in order to save cost, time and efforts. Lappin and Garner [9] had reviewed literature comparing pharmacokinetics at a microdose with a therapeutic. They concluded that of the 18 drugs reported, 15 demonstrated linear pharmacokinetics within a factor of 2 between a microdose and a therapeutic dose. There are currently a total 35 compounds where microdose and therapeutic dose data have been compared (oral, intravenous, human and animal) [10]. Of these 35 compounds (human and

animal), 27 tested orally showed scalable pharmacokinetics between a microdose and a therapeutic dose (79%) and 100% of

those tested intravenously [10]. Reference of microdosing has been included in guidelines of ICH [5], the European

Table 1.: Advantages and limitations of microdosing technique

Advantages	Limitations
<ul style="list-style-type: none"> • It helps to generate human pharmacokinetic data early in order to make “go/no-go” decision early for the drug candidate. • It requires minute quantities of the drug substance for study. • It reduces cost of drug development phenomenally. • It reduces time of drug development significantly. • As it helps to take “go/no-go” decision early and hence, it reduces unnecessary exposure of human volunteers to new drug candidates for phase I studies if the drug candidate is not have desired human pharmacokinetic properties. • It requires smaller toxicology package for initiation in human. • It helps to avoid unnecessary exposure of animals for additional toxicology studies for non-promising drug candidates. • The microdose can be administered via any route of drug administration for study. • It involves minimal risk to the volunteers due to extremely low dose. 	<ul style="list-style-type: none"> • Because it uses very less does of the drug, the predictive accuracy of microdosing has limitation and microdose studies cannot replace traditional pharmacokinetic studies to establish pharmacokinetic of the drug candidate. • It has limitation in case the drug candidate has dose dependent dissolution and absorption characteristics, have non-linear pharmacokinetic and pharmacokinetic properties are influenced by enzyme saturation, transporter saturation, binding site saturation, dose dependent drug distribution, tissue saturation or any other dose dependent factor etc. and may lead false positive or false negative conclusions. • It requires radiolabeling of test drug, which further add to regulator and ethical clearance. • It requires AMS and PET set-up, which itself is a big capital investment. • It does not give any direct therapeutic or efficacy evaluation of the drug candidate. • As it uses very less dose than predicted pharmacologically active dose, it does not give any therapeutic benefit to the volunteer.

- Data of microdose studies are helpful in establishing likely pharmacological dose and thereby determining the first dose for the subsequent phase-1 study.
- Data of microdose studies are helpful in selection of best animal species for long term toxicology studies.
- It may be an attractive approach for the study of new and existing drugs in vulnerable populations (children, pregnant women, elderly, hepatically and renally impaired), who are routinely excluded from clinical trials due to safety concerns.

- Experience with microdosing studies are emerging; and as of today, it has been used for BDDCS (Biopharmaceutical Drug Disposition and Classification System) class 1 drug only. No information exists for experience with other BDDCS class drugs.

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