Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Review Article

HUMAN MICRO DOSING STUDIES (PHASE 0): A NOVEL APPROACH IN CLINICAL RESEARCH

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DOI: 10.7897/2277-4572.03196
Published by Moksha Publishing House. Website www.mokshaph.com

Received on: 07/12/13 Revised on: 10/01/14 Accepted on: 05/02/14

ABSTRACT
Micro dosing or Phase 0 clinical trial is a breakthrough in drug development, where sub therapeutic dosages of various investigational products are administered under necessary safety conditions to minimal number of volunteers in order to obtain an early pharmacokinetic profile of the product. This important important bioanlaytic tool benefits patients as well as the pharmaceutical industry by bringing out new effective molecules faster and reducing the attrition rates at later clinical trial phases. This review encompasses the concept of micro dosing from its inception to its practical approaches till date in clinical research. The concept has evolved over the last decade from merely pharmacokinetic assessments to wider perspectives like drug-drug, drug-food interactions, bioavailability, oncology, metabolic profiling and use in vulnerable populations etc. which are discussed in this article. In future, micro dosing might emerge to be the standard predictive tool for human pharmacokinetics over alternative method and may continue to provide benefits that aren't fully realized up to date.
Keywords: Micro dosing, Phase 0, Clinical trials, Drug Development, Pharmacokinetics

INTRODUCTION

Drug development has always been an extremely dynamic field. Dating back from the prehistoric era to the 21st century, mankind has never ceased the relentless pursuit to discover newer drugs and therapies to treat various maladies. The essential process of drug development is highly valued by the pharmaceutical industry, despite being expensive, laborious and time consuming. Traditional drug development requires 10-15 years from initial lead discovery to filing a new drug application, for marketing the drug. The cost estimates usually range between $800 million and $1.8 billion[1]. However, a vast majority of these compounds (90 %) in clinical development fail during later stages of human clinical trials: Only 20 new drugs were approved in 2005, compared with 36 in 2004 and 53 in 1996[2]. Thus, a major impetus for Phase 0 in drug development was a clogged drug pipeline.

Problems with Conventional Drug Development

Modern era has witnessed a paradigm shift, from conventional medical therapy to the advent of biotechnology, nanotechnology, biomarker assays, receptor level digital drug designing and molecular targeting in drug discovery. However, despite these advances in biomedical research and simultaneously, high investments to develop a new drug, the last decade was marked by stagnation in the field of new drug discovery. There was an urgent need to improve efficiency and success rates of clinical trials. A range of pre-clinical trials: *in-vitro* and *in-vivo* animal screening, of the investigational product (IP) are performed on suitable models for observing the general as well as organ specific effects, toxicology profiles, adverse reactions etc. deriving an effective and safe dose. These dose values (from preclinical studies) are extrapolated to obtain the human dose. This method is nonspecific, crude and cannot be relied completely[3]. However, the pharmaceutical industry heavily depends on the preclinical biology. The lack of predictive animal model was also attributed for the high failure rate of drug molecules, once they enter various phases of human trials. Moreover, enforcement of stringent laws regarding use of animals for preclinical testing; prompted researchers and the pharmaceutical industry to explore better modalities to obtain various parameters of the newly discovered molecules. Currently there are 4 phases in clinical trials (Figure 1): Phase I evaluates dose kinetics, equivalence and safety in healthy volunteers, Phase II evaluates mechanism of action, safety and efficacy (first in patient trials), Phase III assess the drug safety and efficacy in a large number of patient volunteers (usually multi centric) and Phase IV addresses post marketing surveillance of the drug. During the past decade, failure or attrition rates of the IP in clinical trials were highest during Phase II (62 %), Phase III (45 %) and significant at the time of registration (23 %)[4]. Late failure indicated wastage of resources, money and time. This alarming attrition rate prompted the US regulatory agency called the Food and Drug Administration- FDA to analyze the situation and publish an executive summary in 2004 called 'Critical Path Initiative (CPI)', detailing the current issues in new drug development and probable initiatives to be taken to tackle the rise in attrition rates. One of the parameter observed for failure of new drug, during the evaluation, was lack of human pharmacokinetic profiling; if the concentration of the drug in humans is too less it can cause therapeutic failure and if it's too much, it can cause toxicity. Given this situation, administering sub pharmacological doses of the new molecule to fewer human volunteers for a short time period allowed early understanding of *in vivo* Pharmacokinetic (PK) and Pharmacodynamics (PD) profiling which would ameliorate the need for future failure in clinical trials. Regarding this, FDA released guidelines on human exploratory IND studies in 2006. Thus a new approach in clinical trials called as Phase 0 or 'Micro Dosing' (MD) study came into existence[5].

Micro Dosing

The concept of Micro Dosing existed from past 10-15 years but its application was enforced only after the Paraxel Tragedy at London in 2006, where a life threatening multi organ failure occurred during the first-in-human (Phase 1)

trail of TGN1412, an experimental monoclonal antibody, in 6 healthy male volunteers. The diagnosis was Cytokine Release syndrome due to the dosage of the drug administered after a series of calculations and dose extrapolation from preclinical studies. This amounted to be the maximal immune stimulatory dosage for humans, thereby causing the reaction and residual complications. Hence leading to the realisation that species specificity of action may not reproduce intended effect or predict "on target" toxicity in humans and can provide misleading PK and PD results[6]. Hence, recommendation for an alternative initial dose-setting assessment for certain novel agents was put forward leading to Micro Dosing studies, in very few human volunteers to analyze absorption, distribution, metabolism, excretion of drugs and to calculate dose related parameters from the pharmacokinetic values obtained *in vivo*. These are Exploratory IND (investigational new drug) studies conducted early in Phase I (hence, the term Phase 0) involving limited human exposure and have no therapeutic or diagnostic intent. Micro dosing is defined as the 'use of 100 mcg of candidate drug or less than $1/100^{th}$ of the pharmacological dose determined from animal models and *in-vitro* systems using the test substance" (a dose of drug that is 1 % of the pharmacologically active dose, up to a maximum of 100 µg). In addition to this FDA has suggested a maximum micro dose of less than 30 nano moles for protein products. Minute quantity of the drug, neither intending to produce pharmacological response nor any toxicity, when administered to humans provide useful pharmacokinetic data early in drug development. However, ultrasensitive and high technical analyzers, like HPLC coupled with Accelerated mass spectroscopy (AMS) or tandem mass spectroscopy, capable of detecting picograms to femtograms range of the drug in body fluids, are required for analysis. Also, the compounds must be isotopically labeled with C14 but the low dose won't cause any significant adverse events[3]

Design

By design, Phase 0 trials portend lower risk to subjects than phase I trials by using sub pharmacological dosages to understand pharmacological disposition towards candidate compounds. The initial dose depends on the stated trial objective, but should not be greater than $1/50^{th}$ of the no-observed-adverse-effect level (NOAEL) estimated from animal toxicology testing. Investigational new drug is exposed to limited number of patients or volunteers (10 -15) for a limited duration (7 days or less) and dose (in the range of one 100^{th} of the dose required to yield a pharmacologic effect of the test substance) and are conducted before the conventional phase I dose-escalation, safety and tolerance studies. Since Phase 0 trials involve only small number of patients, the tissue samples require precise and reproducible assay procedures and innovative statistical methodology to demonstrate significant results. Analyzers like AMS enable this by providing qualitative and quantitative assays of target materials in humans, to obtain pharmacokinetic characteristics and metabolic profiling of candidate compounds. Standard operating procedures for tissue collection and bio-specimen handling for further trials should be defined in advance and revised as necessary based on results of the phase 0 trial. The application of micro dosing has been extended from merely drug development to absolute bioavailability, mass balance studies, evaluation of drug interactions, drug metabolism etc. Phase 0 for oncology trials in development is uniquely challenged by the need to identify widely acceptable, minimally toxic compounds that favorably affect carcinogenesis when measured against surrogate biomarkers, rather than direct cancer endpoints. An example for a well-established phase 0 trial is of ABT-888, a poly ADP-ribose polymerase (PARP) inhibitor, because of which the drug was able to move quickly into combination studies, bypassing the traditional phases of clinical trial[9].

Industry Perspectives

Micro dosing eliminates an agent very early in clinical development because of poor PD (pharmacodynamic) or PK (pharmacokinetic) properties like poor bioavailability, rapid clearance or lack of target effect in humans. It helps in ranking potential drug candidates depending on their success rates and also determines first dosing of the investigational drug for Phase 1 studies. This is a boon to the industry by allowing early modifications in the design and decision making concerning further clinical development of an agent and it helps saving resources. It also helps in predicting whether the mechanism of action observed in non-clinical models can be obtained in humans. For example, researchers will be able to tell if the drug is entering the bloodstream as it should or interacting with a certain enzyme as anticipated. In addition, micro-dosing can elect the best animal species for long-term toxicological studies from micro-dose metabolite profiling data[7]. Another objective of phase 0 trials is to refine a target or biomarker assay using human tissue samples for drug effect in implementing procedures developed and validated in preclinical models. For example, it was found out from theory and preclinical studies that tumor PARP inhibition was the target for ABT-888 and by performing phase 0 trials scientists had an opportunity to evaluate PARP inhibition in human peripheral blood mononuclear cells as well as in human tumors and therefore, the discovery of a validated assay even before initiation of phase I trials. Phase 0 trials holds significant promise as an analytical tool[8]. It will also help in the drug repurposing and pharmacogenomics activity by expediting the initial work.

Ethical Issues

Potential issues in ethics could be due to the fact that that Phase 0 has no therapeutic intent which could pose a threat to enrollment and concerns about availability of patients for study. Regarding the Informed Consent Process, the Institutional Ethics committee review and input, there is a need to clearly explain the rationale for the study and define the limited treatment and follow up period. Reviewers are skeptical on the need for Pre- and post-treatment tissue biopsies as well as abstaining the patient volunteers (in case of oncology trials) from other trials or therapies. Phase 0 requires a non-clinical assay development laboratory including preclinical animal models which is again a concern for animal ethics committees. Micro dosing requires dedicated human tissue PK/PD laboratory, capable of real-time analysis and a Clinical team with expertise in conduct of early phase trials which is again a concern in developing countries. Phase 0 trials in oncology related studies raise questions regarding ethical aspects of enrolling subjects 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[10]

Regulatory Concerns

Regulatory agencies have not made Phase 0 mandatory in drug development. However, detailed pharmacokinetics of a drug is an important regulatory requirement and this can be achieved by micro dosing, which require very minute quantity of radiolabelled drug to the subject without causing any significant risk. Furthermore, Phase 0 trials are allowed to be initiated under the Food and Drug Administration Exploratory Investigational New Drug guidance with less preclinical toxicity data than usually required for traditional first-in-human studies. Phase 0 trials offers no therapeutic benefit, which may impede patient enrollment, particularly if invasive procedures like biopsies are required. The challenges are not in surmountable; however, well-designed and executed phase 0 trials are feasible and have great potential for improving the efficiency and success of subsequent trials, particularly those evaluating molecularly targeted agents[11].

Merits of Phase 0 Trials (Figure 2)

Phase 0 utilises the smallest dose possible with which no adverse reactions are expected. It brings down the time taken to develop new chemical entities. It reduces expense and overall cost of the trial by selecting the best drug candidate. It is estimated that Phase 1 trial requires 1.5 to 3 million USD but phase 0 requires only 0.3-0.5 milion USD[12]. Phase 0 can reduce number of patients for Phase 1 trials, thereby reducing the exposure to unwanted drug. It helps in reducing number of animals and preclinical experiments upto an extent[13,14]. Small quantity of the test drug is only required which can be prepared as per good manufacturing and laboratory practice guidelines and this can be administered via any route. It can also be administered in vulnerable population like pediatric, geriatric, pregnancy, patients with renal and hepatic impairement, to understand the pharmacokinetic parameters in them. It helps in Detection of endogenous biomarkers. It benefits oncology, by reducing the number of subjects exposed to toxic effects of chemotherapeutic agents. Pharmacokintetic data is obtained early: 6 months compared to 18 months in Phase 1. When appropriately and intelligently used, micro dosing can offer potential to aid in drug candidate selection which benefits the pharmaceutical industry

Demerits of Phase 0 Trials

Micro dosing doesn't offer any therapeutic benefit to the volunteer or patient because sub therapeutic doses are administered. For the same reason, obtaining motivated volunteers for the study design is a problem. These studies cannot predict exact clinical response as with the therapeutic dosage. Moreover, there is not enough evidence to predict human reaction to micro dose because many studies have not been done so far. Strict caution should be taken when micro dosing is done for drugs employing nonlinear kinetics or complex pharmacokinetic mechanisms. Absorption process is dependent on rate and extent of dissolution. Many drugs require transporters, enzymes and receptor sites, which may get saturated with therapeutic dose, but with micro dose most compounds dissolve rapidly yielding rapid and often extensive absorption. Hence stability and dissolution differences in micro dosing and therapeutic level could pose a problem in interpreting results. AMS and other analyzers used for Phase 0 trials are expensive and hard to maintain. Radiotracer assays are limited in specificity. Currently, only few biomarkers are available for predicting the activity. Another major drawback is that micro dosing cannot replace the dose escalation, safety, tolerance studies and the impact of drug on the targeted disease.

Applications of Micro Dosing

Over the last decade, micro dosing has proved its major strengths like improved safety, reduced financial burden on Pharmaceutical companies, and time to developmental decisions[15]. Currently there are 35 compounds where micro dose and therapeutic dose data have been compared out of which 27 tested orally showed scalable pharmacokinetics between a micro dose and a therapeutic dose (79 %) and 100 % of those tested intravenously[16]. Present ICH M3 guideline, permits human micro dosing based on a single dose toxicity study in any one animal model, followed by 14 days observation, preferably in the intended route of administration along with an in vitro target receptor data[17]. The toxicity study dose should be 1000 times the human micro dose so that the resulting safety data justifies the administration of a maximum of 100 µg of drug. Although the emphasis has been on pharmacokinetic prediction there are other applications of micro dosing that are emerging. Micro dosing helps in predicting drug-drug interactions[18] and food-drug interaction before the drug enters Phase 1 clinical trials[19]. It can also assess polymorphisms associated with drug transporters[20], especially in genetically diverse populations. Likewise, it is a boon for vulnerable population who are excluded from routine clinical trials like children, pregnant women, elderly, hepatic and renally impaired. It helps to obtain necessary pharmacokinetic data with a low dose of the candidate drug but without toxicity. Incorporating an intravenous micro dosing study into pharmacokinetic simulations we get reliable values with good predictability since intravenous data is a fundamental pharmacokinetic parameter to assess clearance and volume of distribution[21]. It also helps obtain preliminary data on the metabolism of a drug candidate. This is termed metabolic profiling[22]. In future, combination of microdosing and modelling may lead to more reliable predictions in new drug development. Phase 0 trials are uncommon in India as of today, but it can be performed with ease with our improved biomedical research infrastructure, adequate support and funding from the respective agencies and with necessary training in handling the sophisticated instruments required. The strengths and advantages of this new approach will continue to grow. This is important in providing valuable information regarding safety during therapeutic development for the vulnerable population[23]. However, it is necessary to understand the concept thoroughly, get adequate training, identify the challenges and address them early, for the universal adoption of micro dosing in routine clinical trials[24].

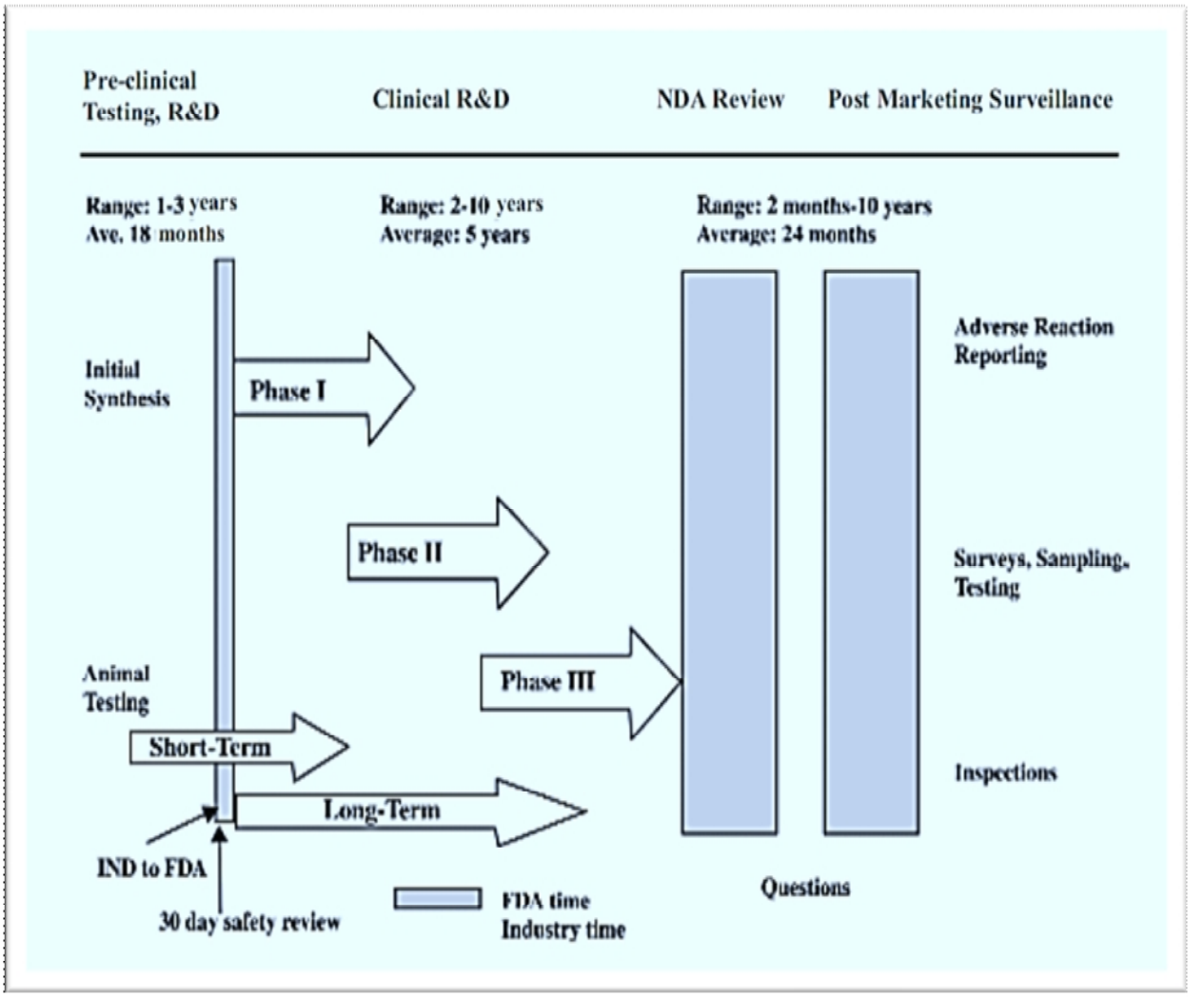

Figure 1: New Drug Development Timeline

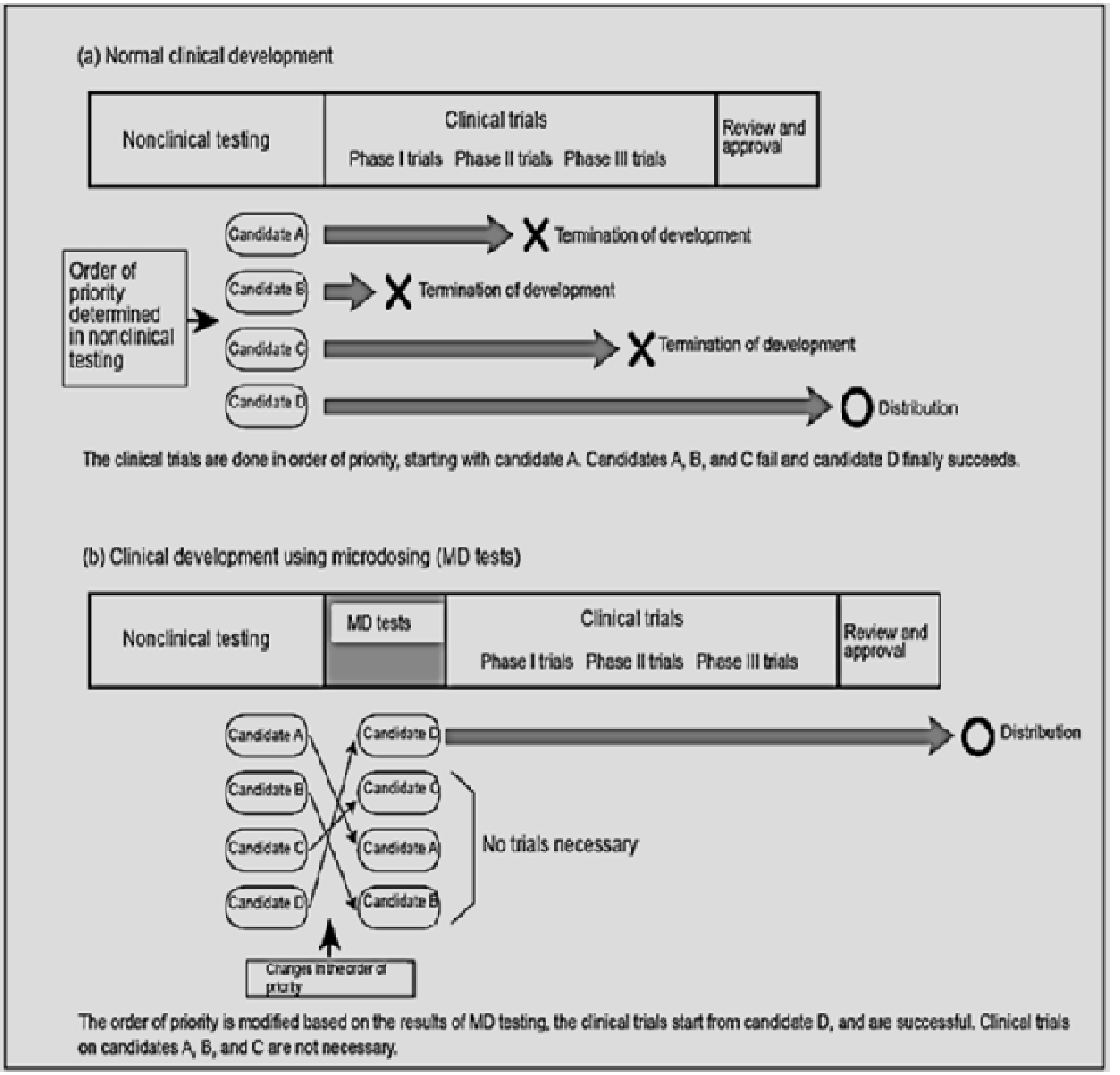

Figure 2: Advantage of Mirodosing over normal clinical development

CONCLUSION

It is presumed that micro dosing might replace customary animal to human dose scaling. Hence, there is a urgent necessity in systematically authenticating this breakthrough approach in the field of drug development with an aim to reduce animal experiments, help patients, pharmaceutical industry and mankind as a whole.

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Source of support: Nil, Conflict of interest: None Declared

QUICK RESPONSE CODE	ISSN (Online) : 2277 –4572
	Website http://www.jpsionline.com

How to cite this article:
Aravind Aiswarya, V R Manohar. Human micro dosing studies (Phase 0): A novel approach in clinical research. *J Pharm Sci Innov*. 2014;3(1):4-9 http://dx.doi.org/10.7897/2277-4572.03196