Microdosing: Concept, Application and Relevance

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Abstract

The use of microdose pharmacokinetic studies as an essential tool in drug development is still to catch on. While this approach promises potential cost savings and a quantum leap in efficiencies of the drug development process, major hurdles still need to be overcome before the technique becomes commonplace and part of routine practice. Clear regulations in Europe and the USA have had an enabling effect. The lack of enabling provisions for microdosing studies in Indian regulation, despite low risk and manifest relevance for the local drug development industry, is inconsistent with the country’s aspirations to be among the leaders in pharmaceutical research.

Keywords: Microdosing, Phase 0, Exploratory IND, Bioanalysis, AMS, ISCR.

The Concept

Microdosing is a concept that has been talked about for over a decade. The concept assumes that key pharmacokinetic (PK) parameters of a new chemical entity (NCE) that is being sought to be developed as a drug can be measured or estimated in PK studies that use very small “micro” doses of the investigational product. Since such low doses are unlikely to have any pharmacodynamic effects and would be too small to cause any major side effects after a single dose, it should be possible to undertake such studies in humans without having to complete the whole range of classical toxicology studies at therapeutically effective doses that are mandated prior to regular Phase 1 trials. Guidelines issued by the EMEA and the US FDA in 2004 and 2006, respectively, have provided recognition to the concept and legitimacy to the conduct of such studies.

What is a microdose? Published guidelines define a microdose to be at 1/100th of the expected pharmacological dose provided it is no more than 100 ìg or 30 n Mol. Studies using such a microdose are called microdosing studies. Guidelines in Europe and USA now permit such studies in human subjects very early in the drug development process. The preclinical toxicology required is minimal and hence these studies can be used as a candidate selection tool to effectively eliminate drug candidates that show sub-optimal human PK before spending time and effort in the kind of extensive toxicology that is required prior to regular Phase 1 trials. Guidelines issued by the EMEA and the US FDA in 2004 and 2006, respectively, have provided recognition to the concept and legitimacy to the conduct of such studies.

Whether these advantages can actually be captured by extensive use of microdosing studies depends, however, on whether the PK results from a microdosing study will indeed predict the results of a full-dose PK study. This is by no means a certainty. Various practical issues can vitiate results and make the outcome of a microdosing study very different from that of a conventional full-dose PK study. Oral dosing with partially acid-labile compounds can result in a much smaller proportion of a microdose reaching the systemic circulation than with a full dose, thus showing much poorer absorption than would actually be the case for therapeutically effective doses. The same effect may result from partial first-pass metabolism. In other words, the fidelity of 1st order pharmacokinetics may not be entirely reliable at doses in the microgram range. Moreover, high affinity, low-capacity tissue

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binding can play havoc with the predictability of PK using microdoses. The CREAM study did indeed through up many of these issues despite showing that for many drug candidates microdosing may be sufficiently predictive of full-dose PK.

Thus, while the evaluation of results of a microdosing study requires finesse and expert interpretation, these studies may prove valuable in a number of scenarios such as early PK screening of the program pipeline, early development of a delivery system, generation of data for PK/PD modeling, obtaining early PK data in special populations for candidate selection, screening for pharmacogenomic variations, inputs for toxicology and conventional Phase 1 dose selection, and human 14C mass balance studies.

**Application**

How would one go about conducting a human microdosing study? Once the cohort of compounds for candidate selection has been determined, animal PK data and allometric scaling methodology would have to be used to determine the possible human therapeutic dose. A 14-day single-dose toxicity study would have to be carried out in one animal species to meet regulatory toxicology requirements for human microdosing. A microdosing CTA or exploratory IND would have to be submitted. If required, 14C-labeled drug may have to be obtained. Dosing and bioanalytical methods would have to be standardized and validated. The study would have to be meticulously designed to dose and obtain bioanalytical samples for appropriately screened and consented volunteers. And, finally, samples would be analyzed and the results reported.

**Figure 1 Bioanalytical Techniques for Microdosing Studies**

| HPLC/AMS (Accelerator Mass Spectrometry) | LC/MS/MS (Liquid Chromatography/Mass Spectrometry) |
|-----------------------------------------|-----------------------------------------------|
| • Requires 14C labeled drug              | • Uses conventional analytical methods         |
| • Sensitivity from pg to ag range        | • Sensitivity is low ng to pg range             |
| • Useful for low BA, high Vd sub drugs  | • Suitable for mid-high BA, low Vd sub drugs   |
| • Measures parent drug + metabolites    | • Provides accurate levels for parent drug     |
| • Parent drug can be estimated using HPLC, and compared to total 14C to study metabolism | • Metabolism cannot be studied without measuring metabolites |
| • Administered dose and non-specific binding to dosing apparatus can be easily measured by scintigraphy | • Non-specific binding to dosing apparatus has to be separately estimated |
| • Equipment and drug cost is high       | • Costs are comparable to conventional PK studies |
| • Radiation exposure rules may apply    | • Only drug development regulations apply      |
| • Vendor oligopoly affects feasibility  | • Significant equipment and method optimization is required, limiting availability of capabilities |

Predictably, bioanalysis in microdosing studies has been a challenge. The sensitivity required to detect very small quantities of drug in circulation could earlier only be obtained with the use of Accelerated Mass Spectrometry (AMS). The sensitivity of this method is in the picogram to attogram range, and AMS still continues to be more sensitive than the most sensitive LC/MS/MS machines, although the latter are fast catching up. The use of AMS is therefore still unavoidable for drug series that show low bioavailability and/or high volume of distribution. A drawback of the AMS system is that it measures total 14C and therefore cannot distinguish parent drug from metabolites. Hence an additional HPLC step is required to determine the parent to metabolite ratio. However, radiolabeling facilitates the use of scintigraphy to measure non-specific binding of the drug to dosing apparatus that, for such small doses, may need to be accounted for if the results are to be valid. The equipment and drug labeling costs with AMS are high and vendor oligopoly affects feasibility of conducting microdosing studies using this method. Moreover, radiation exposure rules may apply and radiopharmaceutical regulations may occasionally be an additional hurdle to jump over.

In recent years LC/MS/MS has grown in sensitivity to a level where microdose studies with most drugs, especially if they have good bioavailability and a relatively low volume of distribution, may now be feasible using conventional analytical techniques. Accurate parent drug levels can be measured without the need for additional filters, and radiolabeling-related complications are eliminated. Incremental costs are low since the equipment is generally used for a variety of purposes – not just microdosing studies. However, significant effort in method optimization may be required to reach the desired levels of sensitivity. Additional disadvantages relate to the fact that non-specific drug binding to the dosing apparatus has to be separately estimated and it is not possible to study metabolism unless key metabolites are also analyzed and estimated.

There are similarities and differences in the regulations governing microdosing currently in place in the European Union and in the United States. While both guidances define a microdose in a similar manner, the US FDA guidance, published later, permits repeated doses for up to 7 days. Both require one toxicology study in a single mammalian species at multiple dose levels, with the highest dose inducing
minimal toxic effects. But the EMEA guidance requires the use of the IV route in addition to the intended route of administration, a separate genotoxicity study, and a 1000x safety margin if no toxic effects are elicited with the highest doses, while the FDA guidance requires only one route of administration and a 100x safety margin. Overall, the US regulation is more flexible, allowing more innovative use of the microdosing tool.

Status in India

While several Indian companies are now competing with their worldwide peers to discover and develop new drugs, there is no concept of Phase 0 or any other equivalent of an Exploratory IND in Indian regulation. Indeed, the toxicology requirements for conventional Phase 1 studies are more demanding in India than elsewhere in the world, pushing early clinical development abroad. Indian companies will therefore be at a disadvantage if and when they require microdosing studies to help them make choices among candidate drug molecules or to help with other aspects of decision-making in the course of running a drug development program. The poor state of development of Phase 1 expertise in the country implies that India will continue to be exclude herself from developing scientific expertise not only in innovative approaches such as microdosing but also from the opportunity to make a mark in the science of early clinical development, the most challenging frontier in the journey of drug candidates from bench to bedside.

In 2007-08 the Indian Society for Clinical Research (ISCR) proposed a change in regulation that would allow the regulators to recognize and permit microdosing studies in India. The proposal would align Indian regulations with the most progressive ones anywhere in the world. The Drugs Technical Advisory Board unanimously approved the proposal together with other far-reaching amendments in regulation. The proposals were, nevertheless, disregarded by the government due to non-technical sensitivities that surround clinical research and drug development in India. Since then, regulatory reform in drug development science has stagnated.

Regulatory change enabling Phase 1 and microdosing studies would open the door to the science of early clinical development, setting the stage for rapid growth and scientific advancement in pharmaceutical development in the country, bringing India into the mainstream of pharmaceutical research and laying the foundation for a possible central role for the country in global drug development in the not-too-distant future.

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