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Microdosing in Translational Medicine:

Pros and Cons

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Executive Summary

The pharmaceutical industry's productivity crisis has set the wheels turning in the minds of many drug development experts. The quest for new strategies that would make the pathway from discovery to pharmacy shelves quicker, more predictable, and cheaper has already generated a huge number of proposals that, however, tend to fall into only a few categories.

One major point is that the extrapolation of animal data to humans contains an element of unpredictability that no amount of *in vitro* testing and advanced software has been able to circumvent. This concerns not so much safety but rather basic issues such as bioavailability, pharmacokinetics (PK), and pharmacodynamics (PD). In contrast to the late-stage failures and post-approval market withdrawals, early-stage failures are usually not publicized and surrounded with drama. However, they contribute significantly to the write-offs that pharmaceutical companies currently accept as a part of the cost of drug development.

Microdosing: Human Trials with Trace Drug Concentrations

As the saying among pharmacologists goes, the rat is not a good human—which is to say, there is just no real surrogate for early-stage human data, no matter how many laboratory animals you sacrifice in whatever ways. In the heroic times of medicine, drug developers used to test their invention on themselves before applying it to patients. This would be mostly meaningless today because, given the current regulatory framework, it would not yield data that would be accepted in support of initiating regular trials. However, another option has now been formally adopted and endorsed by the world's major regular bodies: *human microdosing*.

The concept of microdosing calls for the administration of an investigational compound to healthy human volunteers in doses at least two orders of magnitude lower than those that, based on animal studies, would have a pharmacological effect in humans. There is also a fixed-ceiling dose (100 µg) that must not be exceeded. After the European Agency for the Evaluation of Medicinal Products (EMEA) took the lead in July 2003 by implementing its Guideline on Microdosing, the U.S. Food and Drug Administration not only followed suit in January 2006, but (as a part of FDA's Critical Path Initiative) came forth with an Exploratory Investigational New Drug Guideline that goes beyond microdosing in its efforts to offer drug developers more innovative ways to investigate their candidate molecules.

The incentives offered by the FDA and EMEA guidelines, though not exactly identical, are considerable. In preparation for a microdosing study, the set of preclinical safety studies mandatory for initiating a conventional Phase I study can be replaced by a single-dose toxicity study with a two-week observation period in only one mammalian species; the choice of species must be justified based on comparative *in vitro* biological activity and metabolism data. It should use intravenous administration and the intended clinical route.

In Europe, genotoxicity studies must be performed, but abridged versions of the mutation tests are acceptable if the investigational compound belongs to a chemical class for which no particular concern exists in this respect. The FDA went beyond that by waiving the requirement for genotoxicity testing as well—a move that has drawn criticism. Most European ethics committees find it unacceptable. Moreover, the FDA's Exploratory IND Guideline has relaxed the Good Manufacturing Practices requirements for clinical supplies manufactured for microdosing studies: These do not need to be process-validated. It is sufficient to manufacture them according to Good Laboratory Practices.

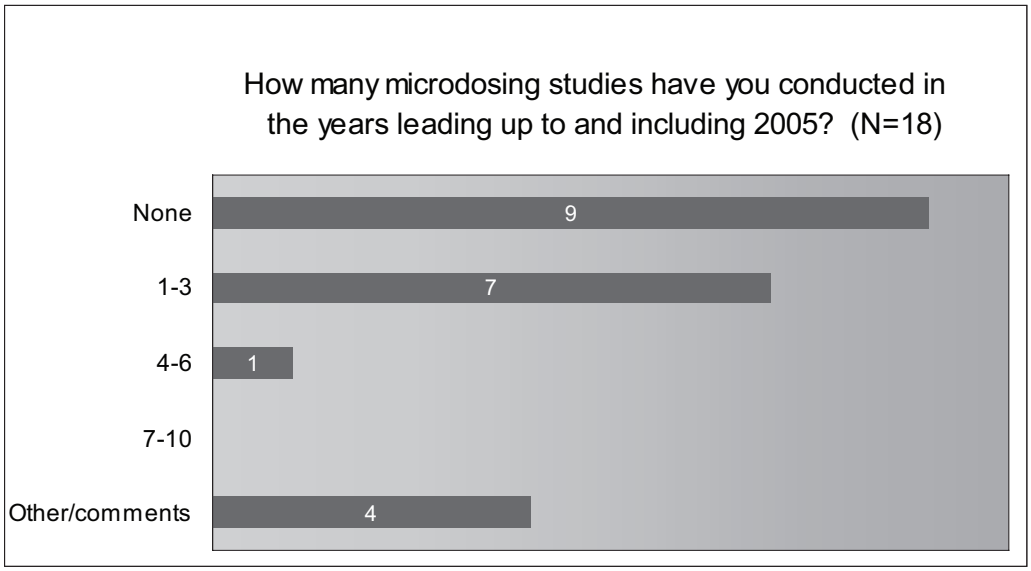
So far, a Cautious Reception from the Industry…

Although these regulatory outlines were interactively developed with industry representatives, pharmaceutical companies did not actually respond enthusiastically. This is understandable for a simple reason: In today's extremely competitive environment, developers tend to avoid everything that might complicate or delay the advance of a new candidate—which is exactly what could happen while developers and regulators are still on a learning curve with respect to a new modality.

As Dr. Neil Gibson, CSO at OSI Pharmaceuticals has stated, "We have yet to use microdosing and this in part reflects [uncertainty] that the answers that will be obtained will relate to the dose used. For instance, in oncology we already know that for certain drugs the PK in normal human volunteers is not always predictive of PK in cancer patients." Another industry contact has stated that "nobody wants to be a pioneer as long as it is not clear how—and at what cost—potential discrepancies between microdosing and conventional human data would be resolved."

The exhibit below, from CHA's Microdosing Survey (April 2006), gives some indication of the extent of microdosing activities in the life science industry:

Survey Results: Microdosing Studies in 2005



Source: Cambridge Healthtech Associates, © 2006. Sample included individuals in clinical pharmacology, DMPK, and translational medicine. Respondents who have conducted studies represented a mix of CROs, large pharmas, and biotech companies.

The table below compares the conventional approach to first-time-in-human testing with the microdose approach:

Upsides and Downsides of Microdosing vs. Conventional Pathway to First-in-Human Milestone

	Conventional Approach	Microdosing Approach
Time and cost from selection of preclinical candidate to finalized first-time-in-man study	12 – 18 months $1.5 to $3.0 million	5 - 8 months $0.3 – 0.5 million
Minimum amount of compound required and qualification	Approx. 100 grams (GMP qualified for Phase I)	Less than 100 milligrams in GLP quality only
Predictive power for pharmaco-kinetic parameters at pharmacol-ogically effective doses	Definite	Generally good if mass effects and/or protein binding make no significant contributions
Need for ^{14}C labeled compound for first-time-in-man study	No	Yes (if AMS is used) No (if LC/MS/MS is used)
Available options for outsourcing	Huge number of certified preclinical and clinical-stage CROs and analytical laboratories in all major pharmaceutical markets	Use of AMS requires certification of clinical CRO for ^{14}C work; analytics restricted to a handful of highly specialized providers
Standardization and degree of establishment of regulatory path	Firmly established and inter-nationally harmonized through ICH guidelines; few if any variations possible	Very new – authorities and developers are on a learning curve; U.S. and European regulations not identical in some points

Source: Cambridge Healthtech Associates

…Which is Expected to Give Way to Broad Acceptance

This current attitude should not be overestimated. It reflects not a basic conservativism but rather cautiousness in a typical situation where industry is expected to provide the regulators with hard information concerning the validity and utility of a new approach. By 2010 we believe that microdosing will already have gained a secure foothold at the interface between the preclinical and early clinical stages of drug development.

Microdosing is primarily seen as a tool to help focus limited development resources on the most promising candidates—that is, to use it as an advanced screening method on humans. The objective in

this setting is to ensure the early but well-founded elimination of candidate compounds that would otherwise be discontinued only after a regular Phase I study would have revealed bioavailability or PK problems. Although the cost of the microdosing trial would be added to the development cost of each candidate that (based on microdosing results) is advanced into conventional trials, the fact that unworthy or problematic candidates can be reliably eliminated from development with comparatively minimal spending of time and resources will be found to be a huge benefit.

Examples of more innovative modalities in which human microdosing can be used strategically include:

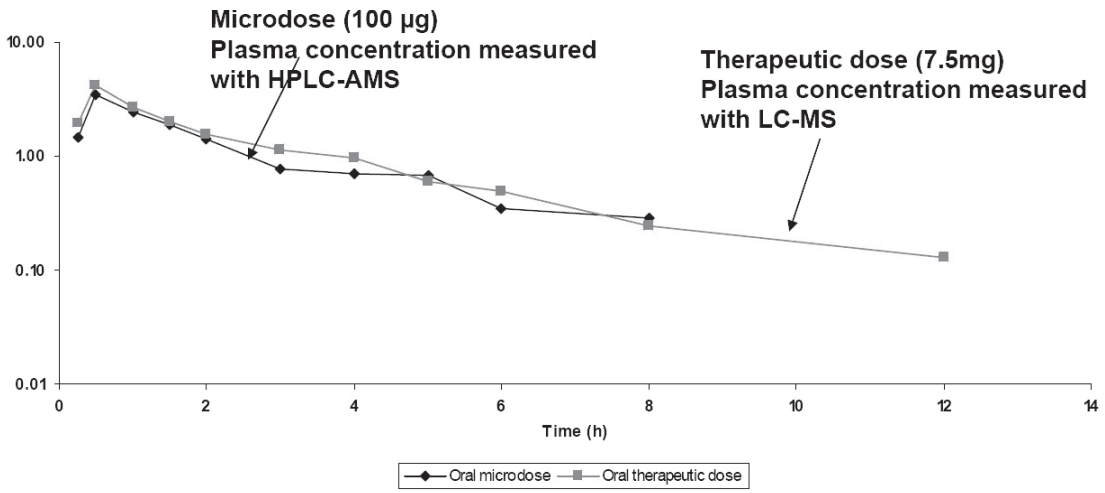
- ***Early Supportive Data for Drug Delivery*** If the developer is forced to work with a class of candidates that is problematic in the PK and bioavailability context, microdosing studies can be designed to guide and accelerate formulation development.

- ***Synergy with* in silico *Approaches*** Microdosing could be integrated into an iterative process where human *in vivo* data are systematically fed back into PK/PD software for its fine tuning to provide the calibration that is needed for *in silico* virtual screening.

- ***Synergy with Pharmacogenomics and Metabolomics*** If participants in microdosing studies are genotyped for key factors that influence PK/PD parameters, it should be possible to quickly extrapolate the dose range variation for efficacy at pharmacological concentrations in various populations, leading to better-designed advanced clinical trials. If analytical problems can be resolved, it should also be possible to determine early how the metabolism of the candidate is influenced in stages of health and disease.

- ***Broader Choice of Volunteers*** Because of the trace amounts that are administered, it should also be possible to extend the scope of microdosing studies beyond that of first-time-in-human studies at pharmacological doses, which are limited to young persons who must meet a set of strict inclusion criteria. This would make more realistic settings possible, but it would require explicit guidelines that are presently lacking.

Results of CREAM trial testing a microdose of Midazolam



compared with the therapeutic dose

Source: Xceleron

Analytical Constraints and Perspectives

At present, most microdosing studies are tuned to analytics based on accelerator mass spectrometry (AMS), which is a slow and hardware-intense technology commercially available only at a few selected centers. Developments that combine AMS with liquid chromatography are ongoing, and soon should help to extend the applicability of microdosing to the ranges described above. By 2015, microdosing can be expected to be a firm element in early-stage drug development, and at some point it might even be mandated by regulatory authorities. The argument is already being made that it might be considered unethical to expose humans to pharmacological doses of investigational compounds that have not passed the "litmus test" of microdosing. The stage is set for an exciting new approach in drug development.