Microdosing: a new approach to clinical drug development

Human microdosing – or Phase 0 trials – offers a way of developing drugs in a faster, more cost-effective and ethical way than ever before.

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“the difficulty lies not in the new ideas, but escaping from the old ones”
– John Maynard Keynes, Economist

Re-engineering the drug development process is no longer just a desirable thing to do – it has become an imperative. New drug approvals are in decline whilst the cost of drug development is rocketing (Figure 1). Combinatorial chemistry, high throughput screening and the -omics revolution all present tremendous opportunities for new drug development. However, we need to abandon the ‘old ideas’ of drug development in order to make the most of the abundant new drug targets that the -omics technologies have provided.

Figure 1.

R&D Costs for Pharmaceutical Manufacturers are Rising But Research Productivity is Not

Source: PhRMA Annual Survey, 1996 and FDA
R&D costs represent aggregate R&D spending by the members of the PhRMA. NDA submitted are fiscal year numbers 1993-1998 and do not include refusal to file or withdraw before filing NDA.
One ‘new approach’ – human microdosing or human Phase 0 trials – offers a way of developing drugs in a faster, more cost-effective and ethical way than ever before (Figure 2).

The principle of human microdosing is that of safely administering sub-pharmacological amounts (microdoses) of NCEs and NMEs to humans to gain valuable information on human pharmacokinetics (PK), pharmacodynamics (PD) and metabolism at a much earlier stage than is currently the case. Central to this approach is the concept that “the best model for man is man”.

It is estimated that one-third of drug candidates fail at Phase I, many due to PK/PD, safety or efficacy issues. The latest estimate from the Tufts Center for the Study of Drug Development is that it costs up to $15 million and takes 18 months to get a molecule through Phase I. If the development programme were to be terminated at this stage, then human volunteers would have been unnecessarily exposed to a failed drug and large numbers of animals would have been used – possibly including primates. The aim of microdosing studies is to ‘kill’ compounds early, as well as selecting drug candidates with optimal PK to take through to Phase I.

This pre-selection of drug candidates on the basis of early human data allows precious resources to be spent on those drug candidates most likely to be ‘winners’.

Enabling technologies
Two ultrasensitive analytical ‘big physics’ technologies – Accelerator Mass Spectrometry (AMS) and Positron Emission Tomography (PET) – are central to the establishment of the human microdosing concept.

AMS is the most sensitive measuring device ever invented in that it can count individual atoms (Figure 3). After administering microdose quantities (100 micrograms or less) of NCEs/NMEs which have been lightly labelled with a suitable tracer (for example $^{14}$C), samples of blood, urine, faeces, sweat, tissue or exhaled air can be taken, processed and analysed by the AMS instrument. Valuable PK information is then derived from the resulting information such as $\text{AUC}$, $\text{C}_{\text{max}}$, $\text{t}_{1/2}$, $\text{CL}$ and so on.

As AMS measures individual atoms of the isotope and not radioactive decay events, the technique requires the molecule to be labelled with an isotope with a low natural abundance. In the case of $^{14}$C, a statistically significant measurement can be made on just 1,000 atoms. This makes AMS approximately one million times more sensitive than conventional Liquid Scintillation Counting and up to 100,000 times more sensitive than LC-MS. In HPLC-AMS studies, Limits of Detection of as little as 0.0008 dpm/fraction have been obtained. For a highly radiolabelled drug, this would be equivalent to approximately 2 femtograms.

After the appropriate calculations are made, typical outputs from an AMS analysis are the basic PK characteristics for a drug – namely, $\text{C}_{\text{max}}$, $\text{AUC}$, $\text{V}_d$, $\text{CL}$ and $\text{t}_{1/2}$. The key to this powerful technique lies in its ultrasensitivity; only microlitre or milligram quantities of sample and minute levels of the $^{14}$C tracer (producing virtually undetectable, nanocurie levels of radioactivity) are required to provide this invaluable data. The most important application of AMS human microdosing is in ranking a number of drug candidates according to their human PK characteristics, so that the most favourable one can be progressed into Phase I.

PET, a three-dimensional imaging technique, also uses a radioactive tracer to label drugs. Owing to the short half-life of these positron emitters, the radiation exposure that results is acceptable –
although higher than for AMS studies. PET can be used to provide pharmacodynamic (PD) information, for example receptor selectivity or occupancy profile, through the use of short half-life isotopes. The radiolabels which are commonly used for PET studies, such as $^{11}$C or $^{18}$F, will generate images using gamma cameras to provide an understanding of the distribution of the labelled drug candidate in the body in real time. An example of this is observing whether CNS drugs actually penetrate the blood/ brain barrier.

The regulatory position

The concept of human microdosing has been recognised and indeed provided for on both sides of the Atlantic.

In Europe, the EMEA position paper (adopted in July 2003) sets out the non-clinical studies required to support clinical studies involving human microdosing. Significantly, the paper provides for a much abbreviated pre-clinical testing programme compared with that required for the traditional Phase I study. At the moment, human microdose studies do not require regulatory approval in Europe; however, the Clinical Trials Directive (which is due to come into force across Europe on 1st May 2004) will then require regulatory approval for such studies.

The EMEA sets out its definition of a microdose as follows:

- 1/100th of pharmacological dose based on animal data / in vitro systems,

OR

- a dose in or below the low microgram range but not to exceed 100 micrograms.

In the US, microdosing studies can be undertaken in an academic institution under the Radioactive Drug Research Committee (RDRC) – 21 CFR 361.1 procedure. Microdose studies are not intended for immediate therapeutic or diagnostic purposes to determine the safety or efficacy of the drug in humans, and therefore under this Regulation they are not subject to an IND.

The ethical dimension

No less powerful and central to the whole debate about human microdosing is the question of ethics.

- Is it right to expose healthy volunteers to an NCE at the Phase I stage with only animal and in vitro data to support the dose administered?
- If we have the ability to reduce the failure rate of drug candidates at Phase I for PK / PD reasons, shouldn’t we be doing it?
- Conversely, how many perfectly good ‘druggable’ candidates have been thrown out due to inappropriate animal results which may have been ‘saved’ by human microdosing?

Compelling evidence

The key concern within the pharmaceutical community with regard to the microdosing concept is whether the sub-pharmacological levels used in such studies are predictive of PK / PD at pharmacological levels. There is considerable discussion about ‘linearity’ – which in the author’s view is...
something of a ‘red herring’. The key is whether the information provided is ‘scalable’ rather than ‘linear’ and so useful in ranking multiple drug candidates.

Of the ten human microdosing studies performed to date at Xceleron (York, UK) and Quintiles (Uppsala, Sweden) using either AMS or PET technologies, all have shown linearity. All have been client-sponsored activities and so have involved drug candidates chosen by the client. Is this a trend or just good fortune? This question is to be addressed by the ‘CREAM’ trial (the Consortium for Resourcing and Evaluating AMS Microdosing) which is currently well underway. Xceleron, in conjunction with the clinical CRO Pharma BioResearch in the Netherlands, has devised a study programme which addresses the key question of whether microdose PK is predictive of pharmacological dose PK. The CREAM trial is being co-sponsored by Eli Lilly, F-Hoffman La Roche, Schering AG and Servier Laboratories, and is under the Chairmanship of Professor Malcolm Rowland, the internationally-known pharmacokineticist.

Whether pharmacokinetic data obtained after a microdose allows prediction of pharmacokinetics at pharmacological dose levels is likely to depend on the bioavailability, pharmacokinetic and/or ADME characteristics of a given drug. For the CREAM trial, five drug compounds have been selected with known and different pharmacokinetic characteristics which are representative of a larger group of therapeutics. Each of these compounds has been administered at a microdose level and at a therapeutic dose level to human volunteers using a cross-over design. The drug compounds selected are all cases where it is known that animal and/or in vitro data fails to predict human PK – for example, drugs with a long half-life, low bio-availability or transporter substrates. Hence the CREAM trial should provide a clear understanding of the potential for human microdosing. Initial results are expected in the second quarter of 2004.

Harnessing the benefits of human microdosing

The concept of microdosing is a compelling one – using the ultimate target species to gain relevant predictive information so as to speed the development of new drugs. The ultrasensitive measurement techniques required to enable the concept are now available. The key regulatory bodies have recognised its value and have made provision for its use. Ethically, it can be argued that there would be a number of advantages to using the technology. Finally, it is a concept that has been shown to work and, through the CREAM trial, will gain wider acceptance in the very near future. Pharmaceutical and biotechnology companies should be building the microdosing approach into their late stage discovery programmes now if they are to avoid expensive drug failures later in clinical development as a result of PK issues.

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