'…step out of the failing 'regulatory driven' approach and use a more 'scientifically driven' paradigm…'

editorial

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Less is more: the human microdosing concept

Drug development is a long, complex and expensive activity. Typical development times are between 10 and 15 years, with costs in the region of UK£1 billion for newly marketed drugs [1]. Over the past ten years, R&D expenditure has increased almost exponentially year-on-year, but the number of new molecular entities (NCEs) being registered for marketing is either static or declining [2]. This is an unsustainable situation in need of a fast effective solution; an opinion echoed by the FDA, which has voiced concerns that excessive development costs are preventing new life-saving medicines reaching the patient at an affordable price (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html). In the 'Critical Path' document, the FDA has asked why the tools of the past century are being used to develop drugs of the 21st century, stating that: 'A new product development tool kit…is urgently needed to improve predictability and efficiency along the critical path'. At Xceleron, we believe that human microdosing, enabled by the ultrasensitive analytical capability of accelerator mass spectrometry (AMS), is one such 21st century tool.

Do we have the right models to predict human pharmacokinetics?

Understanding the metabolism of a development drug is key to determining whether an NCE is 'drugable'. Current methods of investigating drug metabolism pathways before entering human studies rely on animal, *in vitro* and *in silico* models. When taking drugs into humans for the first time, there is always a concern that drug metabolism pathways and pharmacokinetics (PK) might differ substantially from those predicted from the model studies. Our pharmaceutical industry contacts indicate that allometric scaling in which animal model PK is used to predict human PK is incorrect in ~1 in 3 occasions. Whereas some of these metabolic differences could be of no practical consequence, others are so serious that the development programme can be taken no further. Statistically, a third of compounds fail at the Phase I stage – a figure that is too high and too expensive to be sustainable, particularly for small- to medium-sized biotechnology companies.

Early human ADME information with microdosing

The pharmaceutical industry should be getting their drug candidates into humans faster – to assess more precisely their value in the target species. A new experimental approach developed to address the issue of obtaining human drug metabolism PK is human microdosing, or human Phase 0 studies. We

1359-6446/04/$ – see front matter PII: S1359-6446(04)03418-5

believe in the principle that 'the best models for humans are humans', hence sub-pharmacological doses of drug are administered to human subjects to provide early human data on basic PK parameters, such as clearance, volume of distribution and half-life.

Microdosing is dependent on the availability of ultra-sensitive analytical methods that are capable of measuring drug and metabolite concentrations in the low picogram to femtogram range. AMS [3,4], the most sensitive measuring device invented to date, enables the microdosing concept. Minute amounts of a radio-tracer, usually [^{14}C], are used and body samples are taken over a period of time. Samples are then processed in the laboratory and the drug content analysed using this highly sensitive atom counter.

Key features of an AMS microdosing study are:

- only gram quantities of drug are required for safety testing: either 100 μg or one hundredth of the pharmacological dose of a drug is administered to the subject, depending which is the lesser amount;
- a minimal toxicology package is required;
- microlitre quantities of sample can be analysed;
- data can be generated in 4–6 months from commencement of the toxicology to obtaining human PK data (in contrast to Phase I study timelines of 12–18 months);
- the costs of conducting a microdose study programme are a fraction of those of a full Phase I study programme.

Uses of microdosing

The ability to conduct a truncated toxicology programme, such as outlined in the European Medicines Agency's Safety Working Party Position paper (http://www.emea.eu.int/pdfs/human/swp/259902en.pdf), ensures that microdosing studies can be used in several ways.

If, during the drug discovery process, several molecules are identified that have good pharmacological activity but similar or differing animal PK, comparative human microdose studies can be conducted to establish human PK. Armed with this information, the human PK data can then be used to:

- assist in the candidate selection process;
- help to establish the probable pharmacological dose and thereby determine the first dose for the subsequent Phase I study on the selected candidate;
- calculate the potential cost of goods – for a drug that is expensive to manufacture, the pharmacological dose could be so great that the drug becomes uneconomical to produce;
- select the best species for long-term toxicological studies from microdose metabolite profiling data.

This parallel way of conducting microdose studies is most appropriate when several drug candidates are available – with between two and five molecules using parallel human subject groups. Each molecule might be administered in a crossover design, such as an intravenous dose followed, after a suitable washout period, with an oral dose. Thus, volume of distribution (V_d) and clearance (C_l) can be obtained, as well as other standard PK parameters. Information on parent drug and metabolite(s) can be obtained through chromatographic separation of an appropriate extract (e.g. plasma), followed by AMS analysis of collected chromatography fractions.

In some cases, the drug discovery process might only yield a single molecule. In our view, microdosing can be still be useful in such circumstances, because it can quickly establish if it is worth taking the molecule forward before committing large-scale resources to a full Phase I study. On occasion, a metabolic pathway is identified in human hepatocytes or liver microsomes that is not seen in animals. Microdosing can be used to establish if the pathway occurs *in vivo*.

The database for microdosing studies is extremely limited. Interestingly, adoption of this technique is accelerating as the regulatory climate in Europe has changed, permitting microdose studies to be conducted with a minimal toxicology package (the FDA is currently reviewing its position on microdosing and new guidelines are expected shortly).

The CREAM trial: a tough test of the microdosing concept

A 'microdose' might not predict the behaviour of clinical doses, although we do have a body of evidence that, for many drugs, linearity or near-linearity is approached. Non-linearities could be induced when binding, metabolising or eliminating systems become saturated.

To address the issue of non-linearity, a collaborative industry sponsored trial [Consortium for Resourcing and Evaluating AMS Microdosing (CREAM)] was undertaken, which included several drugs for which it was difficult to predict human PK because of, for example, high first-pass effects. Each of the compounds was administered to subjects at a microdose level and at a therapeutic dose level in an appropriate randomized crossover design. The trial was set up to be a rigorous test using compounds that were expected to pose a considerable challenge to the microdosing concept. Of the five drugs investigated (Table 1), microdose PK data reflected pharmacological dose PK for three compounds, and gave important metabolism data for one drug (unfortunately one compound was a no-test).

Although this study was not exhaustive, it demonstrated ~70% correspondence between microdose and pharmacological dose PK. For example, the microdosing study performed with midazolam gave excellent correlation with the pharmacological dose, which was seen as highly significant because this is a well-known substrate for cytochrome P450 3A4. Many sceptics of the microdosing concept suggested that drugs with high first-pass metabolism would not be predictive at microdose levels.

Warfarin did not show perfectly predictive PK between the microdose and the pharmacological dose because the microdose over-predicted the half-life of warfarin. However, the microdose did demonstrate *in vivo* metabolism and

TABLE 1

CREAM trial drugs

CREAM trial drug	Selection rationale	Microdose result
Warfarin	Stable *in vitro* but exhibits extensive, albeit slow, metabolism *in vivo* Substrate for CYP2C9	Not predictive: although slow metabolism and long half-life identified
Midazolam	A selective substrate for CYP3A4 High first-pass metabolism	Predictive: excellent correlation of key PK parameters
Diazepam	Low clearance, basic compound eliminated via CYP2C19 Linear kinetics over a range of doses (possibly not at microdose)	Predictive: excellent correlation of key PK parameters
Erythromycin	Substrate for CYP3A4 and the intestinal efflux transporter P-glycoprotein	Issue in administration: no test
ZK253 (drug candidate dropped after Phase I)	Bioavailability difficult to predict from animal models Low bioavailability in humans	Predictive: extremely low bioavailability was identified

Abbreviation: CYP, cytochrome P450.

would have been indicative of some sort of receptor-binding activity.

With diazepam, not only were the PK parameters highly predictive but, again, there was a strong correlation when a metabolite profile was determined at microdose and pharmacological dose.

Other unpublished studies that we are aware of support this high percentage predictivity. Considering that the compounds used in the CREAM trial were selected because of their challenging PK properties, we consider the CREAM trial to be a considerable success.

Although we at Xceleron believe the CREAM trial data to be compelling, we recognize that many will need to see the concept tested on a much wider scale to assess the circumstances where it might not be applicable. Therefore, centralized- and industry-funding should be made available to develop a published database of information on human microdosing.

Microdosing: a tool for 21st century drug development

There is little doubt that the current approach to drug development requires an overhaul. To step out of the failing 'regulatory driven' approach and use a more 'scientifically driven' paradigm, the pharmaceutical industry needs to make faster, more decisive decisions based on better quality information.

CREAM gives a strong indication of the value of microdosing, and it is my view that microdosing will become an accepted approach in drug development and that eventually all first in-human studies will commence with a microdose analysis.

Is it ethical to expose human subjects to a pharmacological dose of a potential drug that has poor PK properties, and the development of which is terminated based on the data generated, when the same information could have been obtained in a microdose study? How many drug candidates have been rejected from the development process because current models did not predict their PK properties in humans? Has there not been an unnecessary use of animals, including dogs and primates, investigating the abandoned compound?

Microdosing will make a contribution to smarter drug development by enabling early human data to be obtained. As a result, drug selection will become more human-based and, therefore, more predictive.

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