



**PIPMG - Pharmaceutical Industry Project Management Group**

Autumn Meeting - 7<sup>th</sup>/8<sup>th</sup> November 2006 – Missenden Abbey

**PHASE 0 - KEYHOLE TO THE FUTURE**

Chaired by Ralph White (PPMLD)

**Introduction**

One of the keys to successful drug development is early reduction of risk to improve the chance of a return on the enormous, escalating investment.

Traditionally, de-risking in early development has focussed heavily on identifying toxicological, manufacturing and formulation issues; relying solely on animal models to predict the candidate's efficacy and pharmacokinetic profile.

Phase 0 is sometimes used to describe the whole programme from candidate selection to start of Phase I, but at this meeting it was defined as administration of sub-therapeutic doses to provide pharmacokinetic and pharmacodynamic information.

Might there be an advantage for your leads and candidates in peeping through the keyhole to catch a glimpse of their human distribution, anatomical location or binding - otherwise only obtainable by exposing subjects to near-therapeutic doses in Phase I ?

How will Regulators develop guidelines for these microdosing studies – that appear to fall below the 'Regulatory Radar' - and will investors & stakeholders be guided by the outcomes ?

"The clues are there.. Let's look at the evidence" (Frost,D & Grossman,L ☺).

**The Challenges of Modern Product Development**

Graham Lappin (Xceleron)

The concept of microdosing dates back to a study in 1990 conducted at the Livermore lab by Turteltaub *et al.* They administered a <sup>14</sup>C-labelled Class 2B carcinogen (MelQx) to human volunteers - to examine DNA-adduct-formation - but the dose (300ng/kg) was only what could be expected from consuming a well-cooked burger. The experiment showed that, in man, unlike animals, adduct-formation was linearly related to dose.

The Liquid Scintillation Counting (LSC) detection used at the time was very insensitive by comparison with Accelerator Mass Spectrometry (AMS) - which reduces the required number of <sup>14</sup>C-atoms by about a million-fold. Where visualisation of distribution is required, Positron Emission Tomography (PET) is the preferred detection-method. Liquid Chromatography coupled with Mass Spectrometry (LC-MS) is also possible but less sensitive than AMS.

Data for the mid-eighties show about 60 NCEs launched per year for an annual R&D expenditure of ~\$10bn. Early noughties data show ~10 NCEs have cost ~\$60bn each. While there are multiple and inter-related reasons for development failure, pharmacokinetic profile (PK) is a significant source of attrition. PK *per se* is cited as the cause of only about 1 in 10 project-



terminations but it lies at the interface of safety, efficacy, dose and cost-of-goods. An early readout can be invaluable if PK is believed to be a major indicator of future success.

The key features and questions of the microdosing concept are :

- Microdosing should require a reduced toxicology package
- Human PK data could be obtained earlier in development
- *In vitro* and animal predictors may not be reliable \*
- Human PK data, albeit at a low dose, may be more predictive \*
  - \* “Right Species, Wrong Dose” vs. “Wrong Species, Right Dose”

The concept could be particularly powerful at lead-optimisation if there is reason to believe that PK is a discriminating factor and if microdosing is expected to be predictive. A case-study showed selection of a candidate with 80% oral bioavailability while other leads had 60% and 10%. Precision is not essential at this stage - just reduction of risk.

Using a conventional early development programme (and if chemical scale-up goes well), a Phase I readout on PK could be obtained in 18 months at a cost of ~\$4m. Such an investment could rarely be justified for more than one candidate in parallel. By contrast, a programme to obtain Phase 0 microdosing data might be achieved in a third of the time and at a tenth of the cost. In another case-study, a retrospective microdosing study showed that the 1% bioavailability eventually seen in Phase I might have been predicted earlier.

The full potential of microdosing is best realised when it is used alongside other tools including PK/PD modelling, allometric scaling and preliminary *in vitro* & *in vivo* data. In a third case-study, allometric scaling showed high clearance in only 1 of 4 experimental species, but microdosing showed that it was this outlier that was predictive for man.

Further case studies with anti-infectives showed that microdosing could help selection of an appropriate route by demonstrating penetration to the sites of infection (skin-blister or bronchial biopsy). There could be similar potential in showing that a CNS drug could reach the cerebrospinal fluid or that PK in otherwise healthy adults were a predictor for paediatrics or in renal/hepatic impairment.

If used intelligently, and probably not routinely, microdosing has the potential to “change the rules” of established early development strategy.

## Reference

Lappin G & Garner RC (2003) Big physics, small doses - the use of AMS and PET in human microdosing of development drugs. *Nature Reviews (Drug Discovery)* **2**, 233-240



## Microdosing & Imaging – Focus on the Brain

Ilan Rabiner (GSK)

In this presentation, the emphasis switched from detection and measurement to biodistribution PET studies and their potential to show quantitatively & graphically that novel drugs will reach their targets. Imaging is especially valuable where sampling or biopsy are impossible.

Satisfactory imaging requires that the radiotracer (labelled entity) has additional properties (target-specificity, affinity, rapid kinetics) that further define it as a radioligand. The majority of drugs do not have these properties – which are needed to quantify physiologically meaningful parameters that relate to drug-target interactions.

Specificity for the target can either be absolute in the sense of binding to an enzyme or receptor, or anatomical – penetration into a particular tissue or compartment. The kinetics need to be fast enough to provide accurate quantification.

Microdosing studies may answer some of the key questions in drug development, but it is important to understand their limitations. They cannot, for instance, provide a definitive proof of concept in terms of predicted pharmacodynamic effect. They may give some information on target-binding and the expected time-course of the PK/PD relationship. Their main value is in understanding biodistribution.

Further limitations include the novel chemistry to synthesise the radioligand - which may be technically challenging, expensive & difficult to source. Radiochemical purity needs to be >95% and not all molecules can be labelled. Corrections need to be applied for purity, scatter from unrelated areas and the volume of blood in the target-organs.

When interpreting the results, it is important to consider that :

- Low levels of penetration do not rule out pharmacological activity
- Fraction specifically bound, not total concentration, is the key parameter
- An *in vivo* estimate of  $K_d$  is needed to estimate target-occupancy
- PK may be non-linear with increased dose (clearance may saturate)
- Observations are limited to a short timescale  
(e.g. up to 2hrs for  $^{11}\text{C}$ -, or 4hrs for  $^{18}\text{F}$ -labelled compounds)

It follows that the use of microdose-imaging requires careful planning and evaluation of pros & cons before making it part of a project strategy. The Project Team needs to understand the limitations and, if possible, decide on decision-criteria in advance.

## Tracer Microdosing - The Rôle of Molecular Imaging in Drug Development

Bengt Långström (Uppsala Imanet & GE Healthcare)

The strategic significance of tracer microdosing was prominent in Professor Långström's introduction, showing it as an integrating factor for pharmacology, medicine, genomics, proteonomics & technology - and suggesting that it may be a "game-changer."

Selection and manufacture of the tracer requires a decision on a suitable radionuclide...

- high specific radioactivity to maximise sensitivity
- relatively short half-life (~1hr) to limit exposure
- reasonably straightforward incorporation into the ligand

Commonly used radionuclides include  $^{11}\text{C}$  and  $^{18}\text{F}$ , but  $^{68}\text{Ga}$  (gallium) has great potential because it can be generated without using a cyclotron.

The range of reactions for  $^{18}\text{F}$  is limited but some those that are possible are extremely valuable. However,  $^{11}\text{CO}_2$  is at the head of a cascade of possible reactions to produce many reactive groups and substituents.  $^{11}\text{CH}_3\text{I}$  (methyl iodide) is a new route to further substituents while  $^{11}\text{CO}$  (carbon monoxide) is a new branch of labelling chemistry with many possible products including amides.

Use of  $^{11}\text{CO}$  in conjunction with aryl halides has made it possible to produce a "library" of aryl amides for screening in binding studies. With sufficient specific radioactivity it is possible to carry out real-time autoradiography of living tissue-slices on a phosphor imaging plate giving spectacular visualisation of localised receptor binding that can be verified with antagonists etc.

A range of techniques have been developed to aid interpretation of Phase 0 molecular imaging studies :

- Linearity can be investigated in parallel using a primate species
- Haemoglobin labelled with  $^{11}\text{CO}$  can be used to subtract the vascular contribution
- Magnetic Resonance Images (MRI) allow superimposition of more detailed anatomy
- The metabolic marker  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) can be used to highlight cancerous cells.
- Pittsburgh-Compound-B (PIB) is a tracer specific for amyloid in Alzheimers

The safety & regulatory considerations include an appraisal of the risks from exposure both to chemicals and to radioactivity in relation to the acceptable lifetime risk and thresholds of toxicological concern. Despite the high levels of specific radioactivity required, it is usually straightforward to keep the exposures within acceptable limits.



Molecular imaging using PET can contribute to drug development by :

- Demonstrating action on the target system at an anatomical or receptor level – either locally (e.g. receptor kinetics) or on downstream processes (e.g. using a labelled enzyme-substrate).
- Estimating PK parameters to predict absorption, distribution, metabolism & excretion. Investigating ADME mechanisms such as efflux pumps. Comparing routes of administration.
- Translation from *in vitro* to *in vivo* – visualising receptor interactions (e.g. localisation, intensity & persistence in specific brain-regions) and predicting dose by reference to animal models.

All or any of these benefits can be used to assist a proof of concept - to investigate, learn and eventually confirm mechanisms of drug action.

### **The Regulatory Climate**

Carolyn Belcher (Constella Group)

Regulatory Authorities need to plot a difficult course between encouraging medical innovation on the one hand and ensuring human safety on the other.

The European Agency for the Evaluation of Medicinal Products (EMA) first issued its “Position Paper on non-clinical safety studies to support clinical trials with a single microdose,” in July 2003. The US Food & Drug Administration (FDA) issued exploratory IND guidance in January 2006 which treats microdosing studies as part of Phase I.

The usual testing requirements before administration to human subjects include toxicology studies in two species - using doses that demonstrate both a no-effect level and the nature of effects that would be expected at higher doses. Drug substance and product for Phase I must comply with Good Manufacturing Practice (GMP). It is in these areas that the special regulations for Phase 0 microdosing have the greatest impact on cost, duration and animal-use.

A microdose is defined as either 1/100 of the expected pharmacological dose or a dose in the low microgram range and not exceeding 100 micrograms (e.g. 10µg or less if the pharmacological dose is 1mg). The EMA requires, & FDA prefers, a 1000-fold toxicological safety-factor (e.g. 10mg to cover a 10µg microdose).

Though not identical in their guidance, both authorities view microdosing favourably and seem to agree that :

- Since microdosing studies are designed not to induce pharmacological effects, the potential risk to human subjects is very limited
- Microdosing studies can be initiated with fewer preclinical safety data
- Phase 0 may help to reduce the number of subjects in later trials and the number of unnecessary trials
- Though not the primary objective of the regulations, strategies including microdosing may require less use of experimental animals



## Table Workshops

### Why Phase 0 ? - Strategic Project Management Issues

#### *Business Drivers*

- Potential reduction of risk (but beware Phase 0 risks, non-linearity etc.)
- Differentiation between candidates in the lead-optimisation phase
- Potential downstream cost-savings (but early additional cost & delay)
- More confident commitment to scale-up of manufacture & toxicology

#### *Attractiveness to Investors and Licensees*

- Risk-reduction may create milestones for further investment
- Phase 0 outcomes may be seen as “clinical data”
- Avoid using Phase 0 inappropriately, under pressure from investors

#### *Which types of project would benefit ?*

- Cases where pharmacokinetics are a key issue (e.g. antibiotics)
- Where presence (or absence) in a particular location would indicate success
- Investigation of specific human metabolism (e.g. pro-drugs)
- Selection of back-ups or follow-ups where the differentiating issue is clear
- Use cautiously with unprecedented mechanisms \*
- Less likely to be predictive for chronic treatments

#### *Strategic Considerations*

- (\*) Outcomes may help to distinguish between potential indications
- Genuine Proof of Concept unlikely except in special cases

#### *Implications for the Project Team*

- Manage expectations of stakeholders (senior management & investors)
- Agree in advance the criteria for different potential courses of action

**Next Meeting** - “Turbocharging Project Management” – 22<sup>nd</sup>/23<sup>rd</sup> May 2007 – Holiday Inn - Oxford UK

A series of talks and workshops aimed at improving Project Team culture and performance. Proposed content includes :

- Case-Study - How a training programme has contributed to a stronger Project Team culture at GE
- Secrets of Success in Risk Management
- The role of Six-Sigma in improving pharmaceutical development
- Different ways in which a Project Office can improve team & project performance
- Core Competencies for Project Team members
- Key points in the Project Team life-cycle – Startup, Boost & Closure

**Phil Dolamore**