ACCELERATING CANDIDATE SELECTION & GETTING TO THE RIGHT DOSE: THE MICRODOSING APPROACH

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OUTLINE OF PRESENTATION

- Describe reasons why a microdose approach might add value
- Describe what is meant by a microdose
- Describe what type of preclinical data may be needed for microdosing
- Give detailed examples of microdosing
- Indicate the advantages and limitations of microdosing

WHERE DO TRADITIONAL APPROACHES OFTEN FAIL?

- Prediction of clinical dose from preclinical pharmacology studies

- Prediction of human pharmacokinetics from preclinical data
  - allometric scaling
  - Dedrick plots
  - PBPK
  - *in vitro* with Cl_{int}, f_u & well-stirred model
  - combination

- Setting starting dose for dose escalation

SAVINGS IN TIME AND PATIENTS FROM THE USE OF ACCELERATED ENTRY DOSES

	Merbarone	DSG	HMBA
Maximum tolerated dose (mg/m^2 per day)	1,500	2,100	30,000
Entry dose (mg/m^2 per day)			
Conventional	12	3.2	900
Accelerated	96	80	4,500
No. of dose-escalation steps			
Conventional	15	21	10
Accelerated	7	9	4
No. of patients required			
Conventional	90	126	60
Accelerated	42	54	24
Time required (mo)			
Conventional	30	42	20
Accelerated	14	18	8
Savings (patients and time)	53%	57%	60%

DSG= deoxyspergualin; HMBA= hexamethylene bisacetamide

from Collins et al. (1990). J. Nat. Can. Inst.

HIGH LEVEL STRATEGY

- Alternative early clinical paradigm
  - Introduce human studies early
    - Using low single-doses
    - Supported by a rational but abbreviated regulatory package
- Make internal decisions better
  - Selection of compounds for traditional clinical development based on human data
  - Determine the potential of compounds prior to normal development
- Provide clearance & absolute bioavailability data using i.v. microdosing
- Not appropriate for every compound

DEFINITIONS OF MICRODOSE

- **The CHMP position paper (23 June 2004)**

"…less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained *in vitro* and *in vivo* (typically doses in, or below, the low microgram range) and at a maximum dose of ≤ 100 microgram."

- **FDA Guidance for Industry, Investigators, and Reviewers Exploratory IND studies (January 2006)**

"…less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic of the test substance with a maximum dose of ≤ 100 micrograms (for imaging agents, the latter criterion applies)."

WHAT TENDS TO BE THE RATE DETERMINING STEP IN TRADITIONAL EARLY DEVELOPMENT?

Is it?

- Normally the minimum of 14-day toxicology in 2 species
- Full safety pharmacology studies
- Pharmaceutical development and stability needs
- Kilos of API requested with full GMP to meet the above & future clinical needs

All the above but mainly the supply of sufficient API to meet the needs of a traditional FIH package

WHAT A.P.I. WOULD BE ACCEPTABLE FOR HUMAN MICRODOSING?

- Produced in a medicinal or process laboratory
- No analytical release data for starting materials
- Good laboratory notebook documentation to support CMC
- Adequate structural & purity characterization of final material
- Qualified by using the same batch as the toxicology study
- Use simplest formulation – e.g. extemporary preparation of drug in bottle
- Limited stability testing
- Some QA involvement of release process

SOME SAFETY CONSIDERATIONS

Study	Acute dose/ICH M3 Guidelines	CHMP/FDA microdose position	Recommendation
Toxicology	Single dose/extended observations in 2 species - GLP	Single dose/extended observations in 1 species - GLP	1 species should be adequate
	Identify no effect dose & dose limiting toxicity	Limit dose to 1000x clinical dose based on allometric scaling (CHMP)	1000x clinical based on surface area should be sufficient
	2 routes of administration, including clinical	2 routes of administration including IV (CHMP)	Single route sufficient if TK performed
	Both genders	Both genders	Single gender if only one to be used for microdose
Genotoxicity	Mutation & chromosome damage - GLP	Mutation & chromosome damage – abridged GLP	Abridged GLP should be adequate
Safety pharmacology	Standard battery CNS, CV, Respiratory	All available information including hERG	hERG & broad based receptor screen recommended

IF ABRIDGED PACKAGE ADOPTED

API NEEDS GO FROM KG TO <<100G

ADME REQUIREMENTS

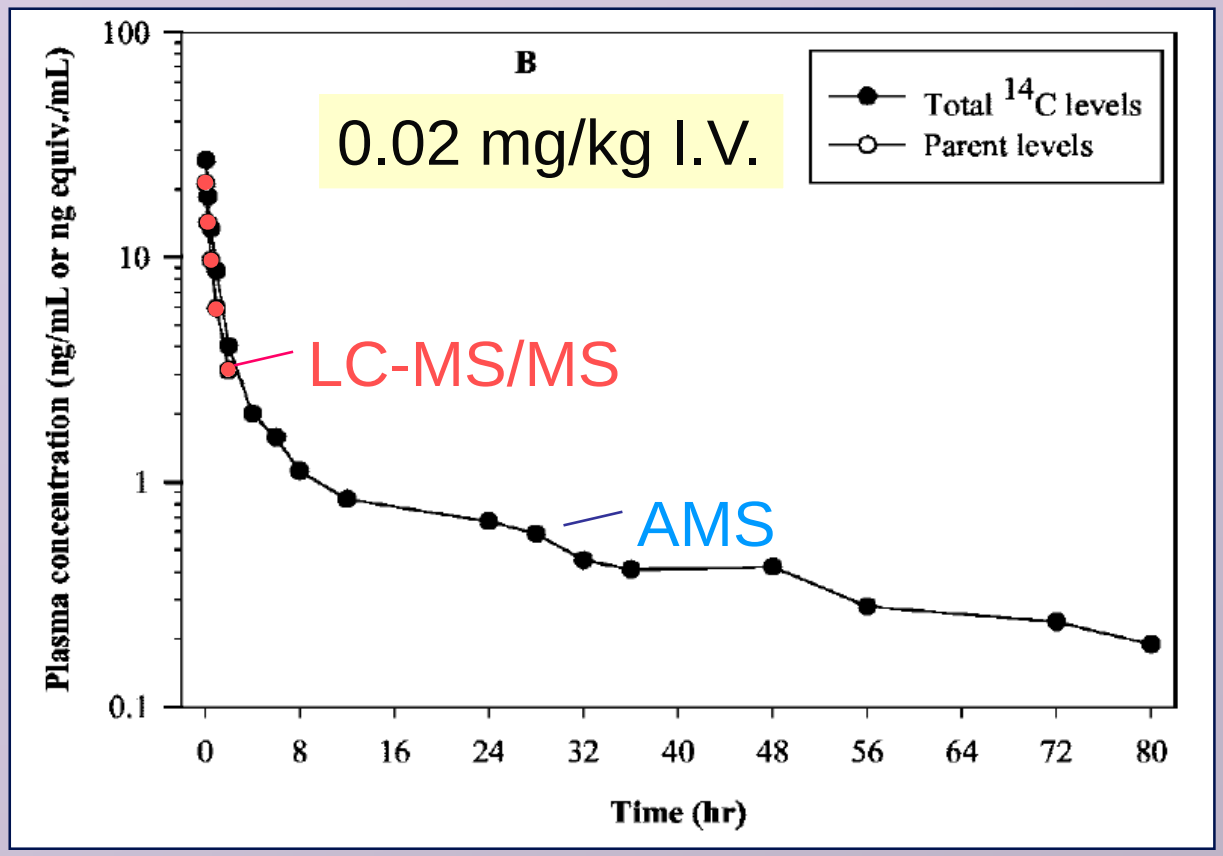
- Standard *in vitro* assays
  - solubility
  - permeability
  - metabolic stability
  - protein binding
- *In vivo* oral & iv PK (1 or 2 species)
- Comparable metabolism between toxicological species & man *in vitro*
- TK support for toxicological study
- Preclinical proof of linearity as appropriate (microdose PK ‘v’ pharmacological dose PK in non-rodent species)
- Suitably sensitive analytical method for microdose study

ANALYTICAL METHODS

- **AMS**
  - Very sensitive
  - Requires long lived radioisotope (^{14}C)
  - Measures total radioactivity with additional separation step for specificity
  - Specialized equipment
- **LC-MS-MS**
  - Less sensitive (low pg to high fg/ml)
  - Uses normal compound
  - Specific for compound of interest
  - Fast turnaround using standard equipment possible

Choose the method that best suits the study objectives and your needs

ULTRA-SENSITIVE PK-ADME



Sandhu et al. Drug Metabolism and Disposition 32:1254–1259, 2004

THE UNDERLYING RATIONALE FOR AN ABRIDGED SAFETY PACKAGE

- No pharmacological activity - primary
  - secondary
- Metabolism in toxicology species comparable to man (*in vitro*)
- Any known species sensitivity taken into consideration
- No genotoxicity
- Toxicokinetics to prove adequate exposure
- Combination of GLP and robust non-GLP studies

THE 'CREAM' TRIAL

- **Objective:**

  Evaluation of the potential and limitations of the microdosing approach as an aid in early drug candidate selection

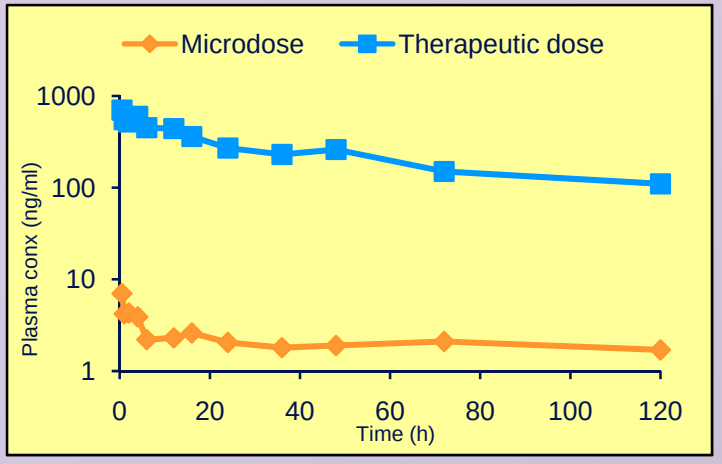
- **Approach:**

  Retrospectively test the ability of a microdose to predict the pharmacokinetics of compounds at therapeutic doses using compounds previously and safely dosed to man

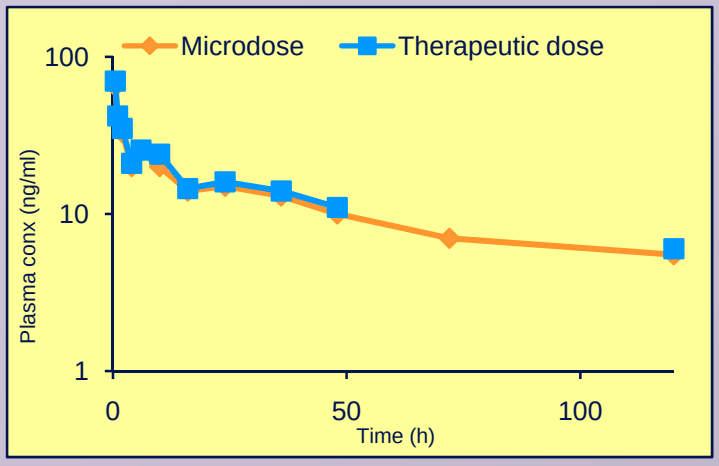
REPRESENTATIVE EXAMPLES FROM THE 'CREAM' TRIAL

RMI Pharmacokinetics

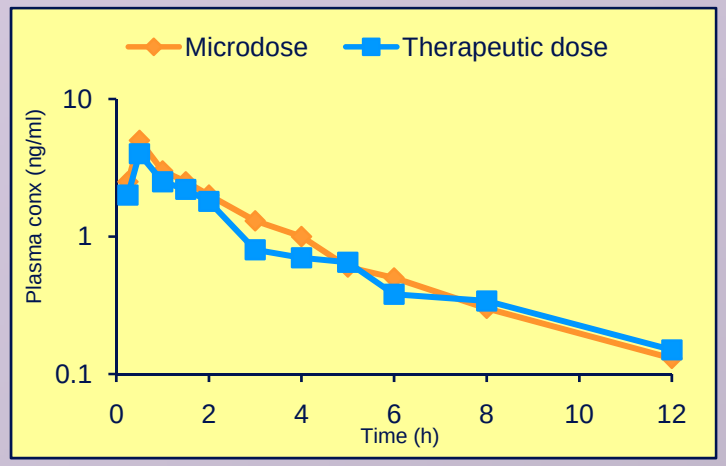
Warfarin



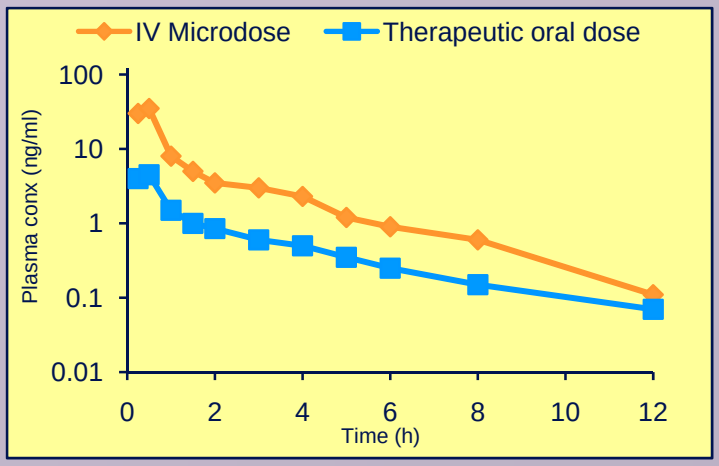
Diazepam



Midazolam



Erythromycin



Redrawn from Lappin et al Clin. Pharmacol. Ther., 2006

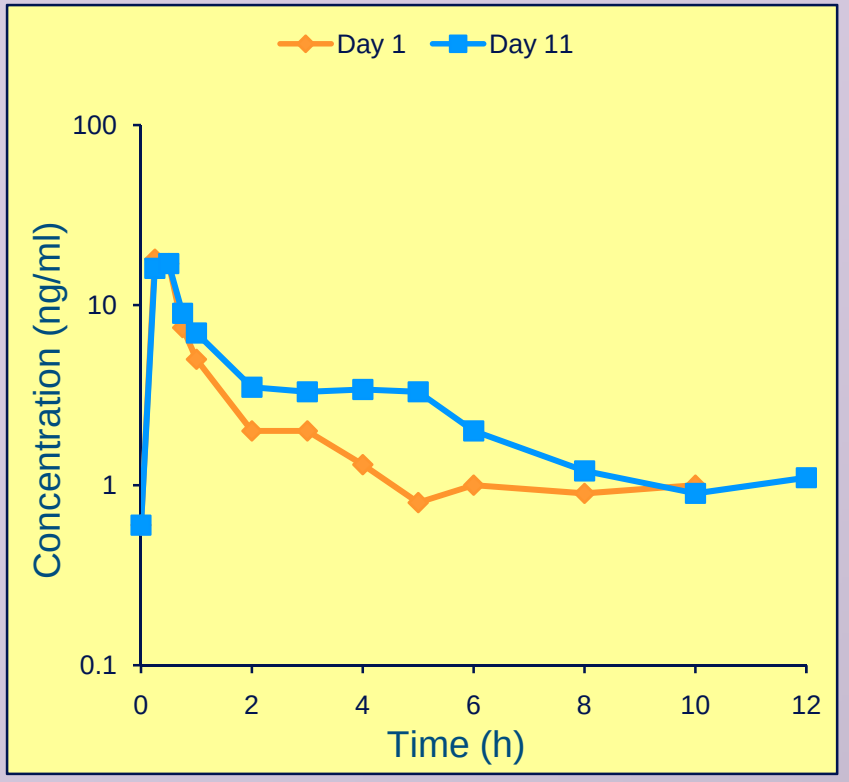
GENERAL CONCLUSIONS FROM 'CREAM' TRIAL

- Microdose iv tends to predict the iv kinetics of a drug following a therapeutic dose reasonably well.
- Simultaneous administration of microdose iv and oral therapeutic dose allows accurate estimation of the oral bioavailability of therapeutic dose.
- Microdose predicts the behaviour of the drug in solution and does not address dissolution aspects of solid dosage forms.
- Microdosing orally tends to predict the events following a therapeutic oral dose, even when there is first pass loss (eg midazolam)

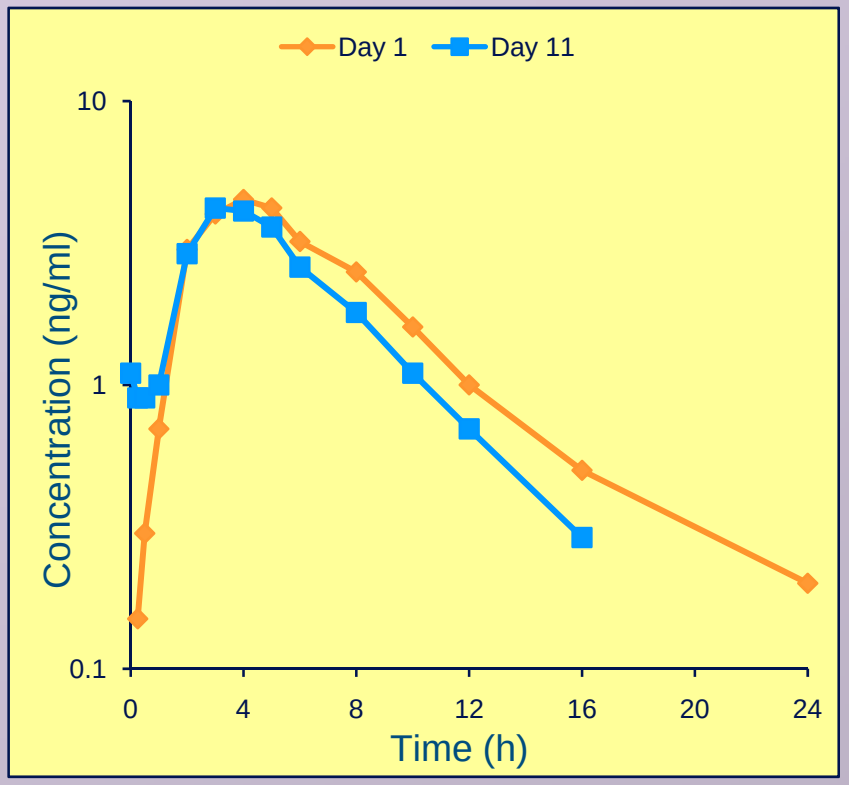
ABSOLUTE BIOAVAILABILITY OF NELFINAVIR

RMI Pharmacokinetics

Intravenous



Oral



Conclusions

- The absolute oral bioavailability of nelfinavir decreased from 88 to 47% over an 11 day dosing period
- This was due to increased 1st pass metabolism which reformulation would not resolve
- Intravenous microdosing with AMS identified the issue allowing effetive cost-benefit decisions

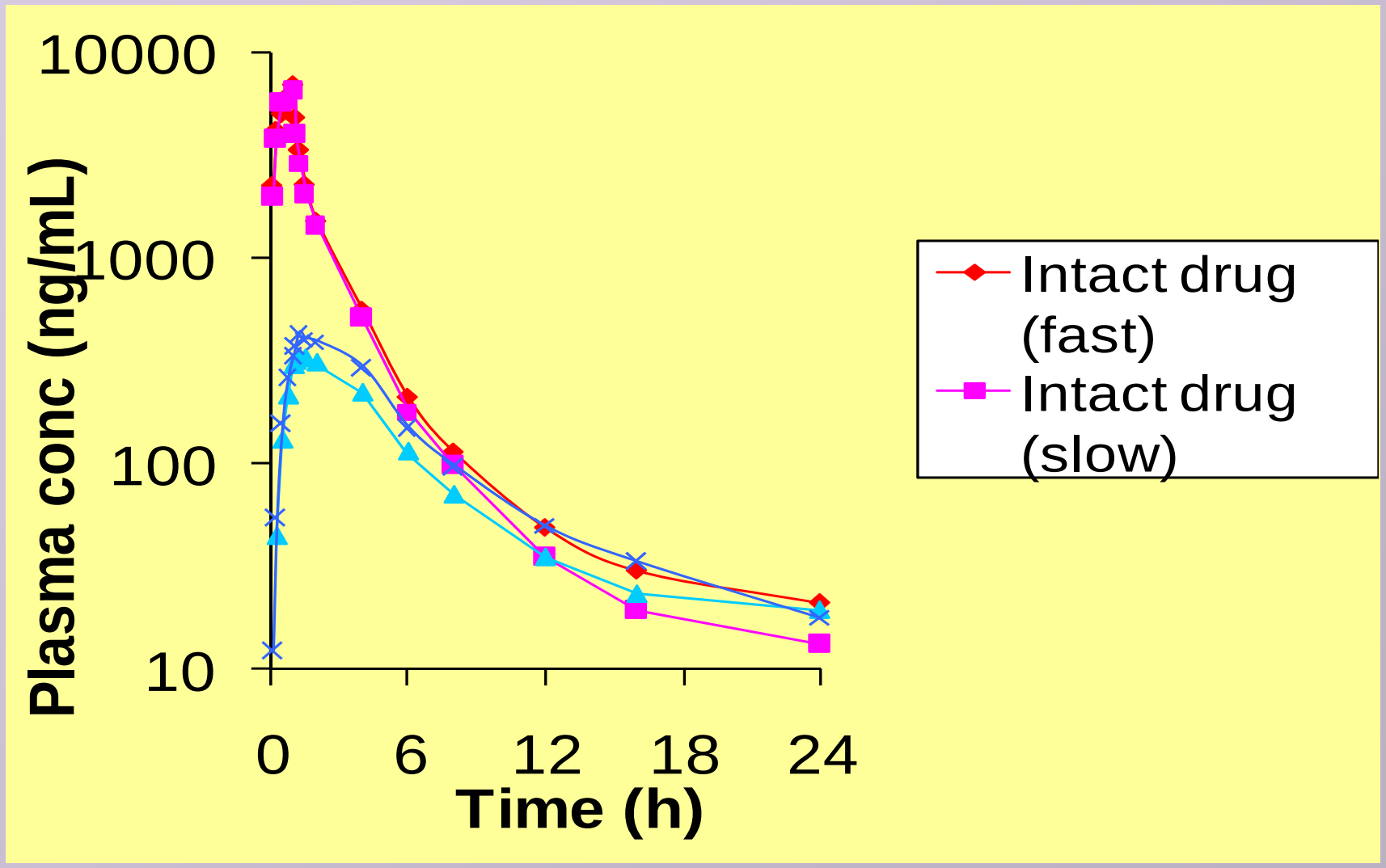
Data from Sarapa et al J. Clin. Pharmacol. 2005

Examples of Human Microdosing using conventional LC-MS-MS

EXAMPLE 1: VARIABLE PREDICTION OF CLEARANCE FROM PRECLINICAL DATA

- Potential oncology drug administered to phenotyped healthy volunteers as a constant rate infusion
- Intact drug and major metabolite measured by LC-MS-MS
- No drug-related adverse effects
- Clearance close to highest value predicted
- Clearance available for calculation of infusion rate required to achieve efficacious target concentration – reduction of number of sub-efficacious dose escalations in cancer patients
- Possible need for reformulation identified due to higher dose required
- No clinically significant difference between fast and slow metabolizers for intact drug or metabolite
- Time taken from decision to microdose to obtaining clinical data, < 3 months

A CLINICAL MICRODOSE EXAMPLE OF A COMPOUND ADMINISTERED AS AN IV INFUSION



EXAMPLE 2: IS THE HALF-LIFE ADEQUATE FOR ONCE DAILY DOSING?

- Preclinical data predicted different half-lives depending on species – if the lowest value the compound was not developable
- Six healthy volunteers given the compound orally and the plasma concentrations of intact drug determined by LC-MS-MS (LLQ 1pg/ml)
- The plasma half-life was at the high end predicted and would not preclude the compound from moving forward
- Source of the variability in the preclinical data identified as protein binding in the *in vitro* microsomal assays for intrinsic clearance
- Time from decision to microdose and availability of clinical data 4 months

EXAMPLE 3: IS THE BACK-UP STRATEGY WORKING?

- Original lead compound had a long half-life in human precluding further development and a back-up was needed with a shorter half-life
- Microdose (10µg) given to healthy volunteers and plasma concentrations measured by GC-MS
- Half-life was significantly shorter and within the desired range confirming the strategy of the project team
- Linearity of clinical microdose pharmacokinetics confirmed in subsequent single dose escalation study

SUMMARY: THE DOWN SIDE OF MICRODOSING

- Only appropriate for resolving pharmacokinetic issues
- Not appropriate if dissolution rate limitation suspected at oral therapeutic doses and exposure is end point
- Not appropriate if saturable first pass metabolism expected at oral therapeutic doses
- Not appropriate when dose-dependent kinetics are suspected within the normal therapeutic range

SUMMARY: THE UP SIDE OF MICRODOSING

Early clinical pharmacokinetics can be obtained rapidly at minimal risk for:

- Selection of better compounds with less chance of failure in later clinical development
- Design of safer and more effective dosage regimens earlier
- Potential for reduced development times (e.g. fewer escalations)
- Fewer patients exposed to sub-efficacious doses (oncology)
- Help identify reason(s) for preclinical uncertainty
- Quicker access of patients to new more effective medicines