MANCHESTER 1824

The University of Manchester

# The Role of Modelling and Simulation in Drug Development

*Leon Aarons*

*Manchester Pharmacy School*

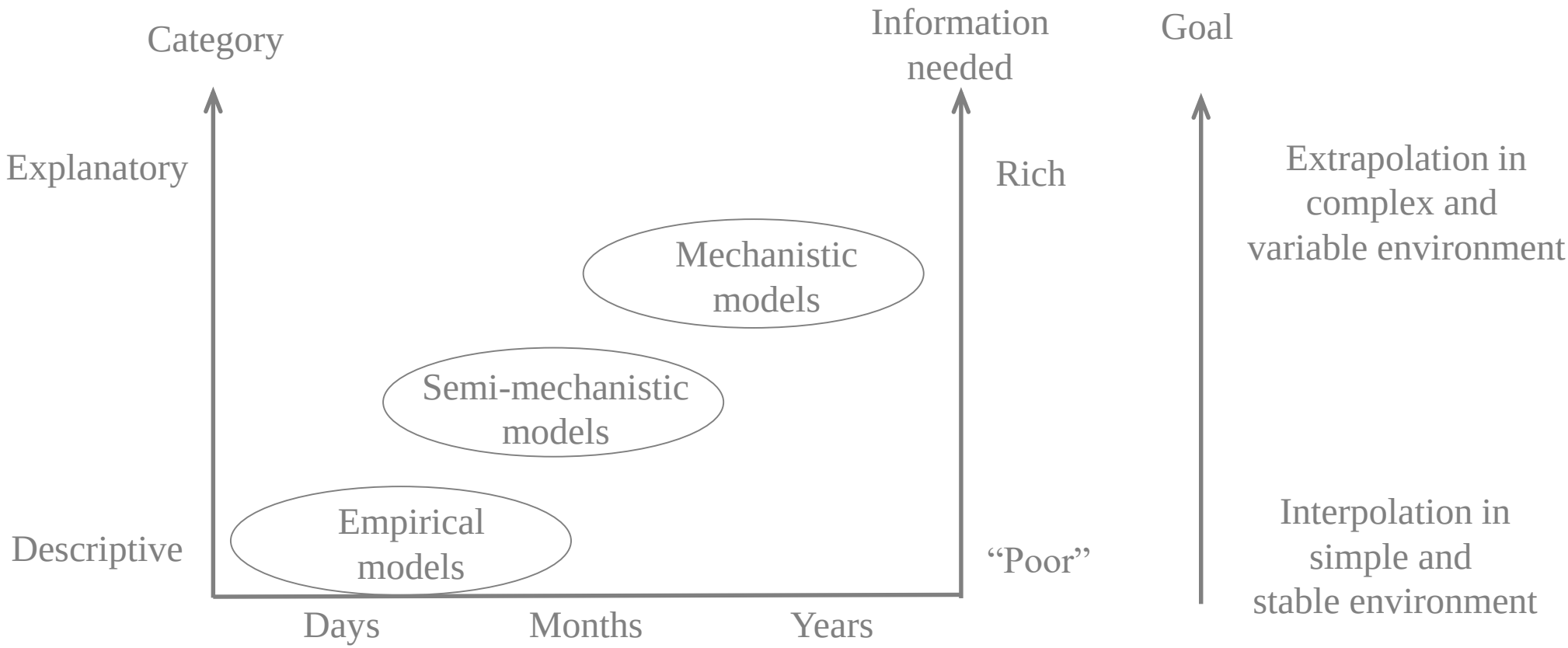
*The University of Manchester*

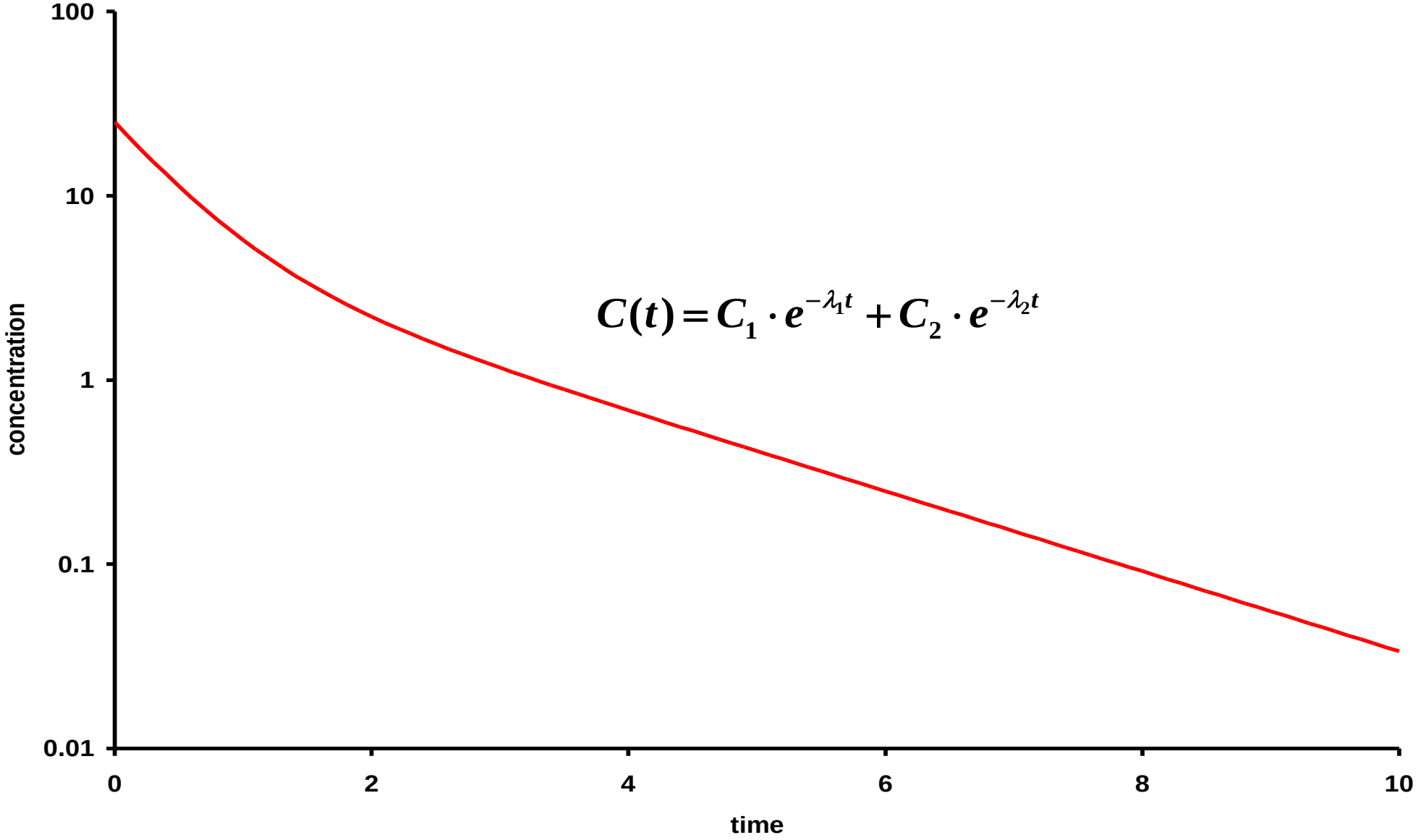
# Plan

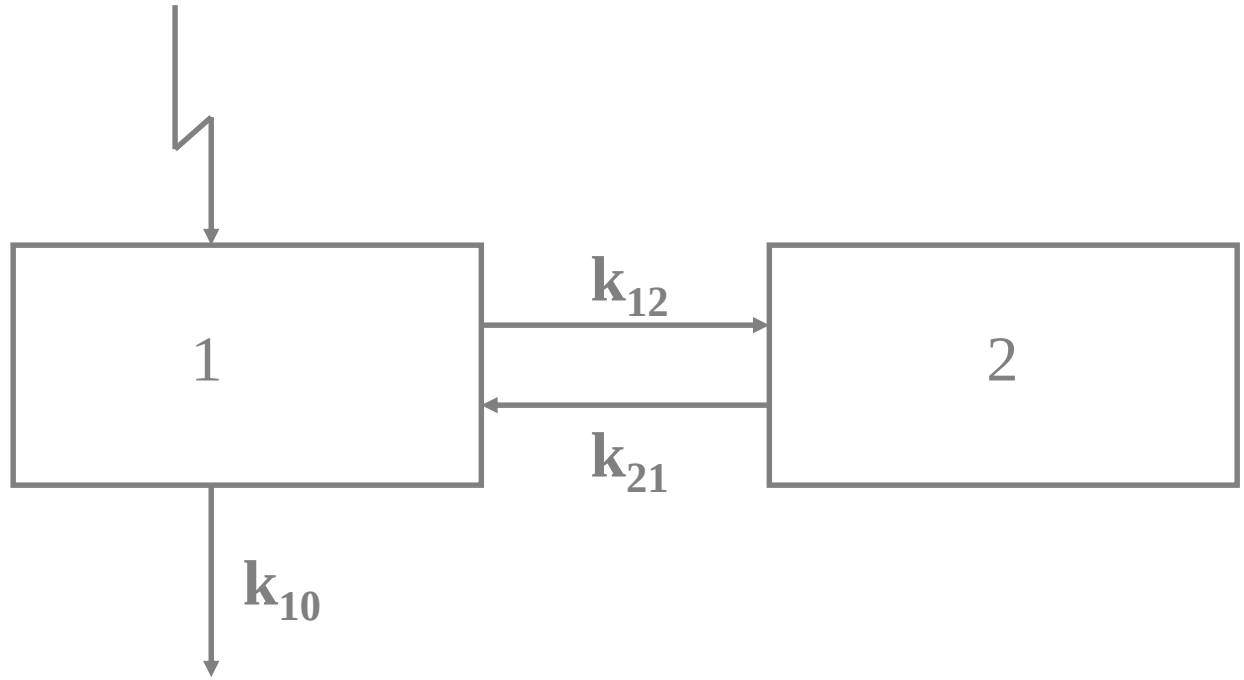
- Overview
- Role of modelling in Phase I drug development
- Role of modelling in the development of anti-cancer agents
- Summary

# Models

# The type of model to be developed should be driven by the available information and the goal of the simulations



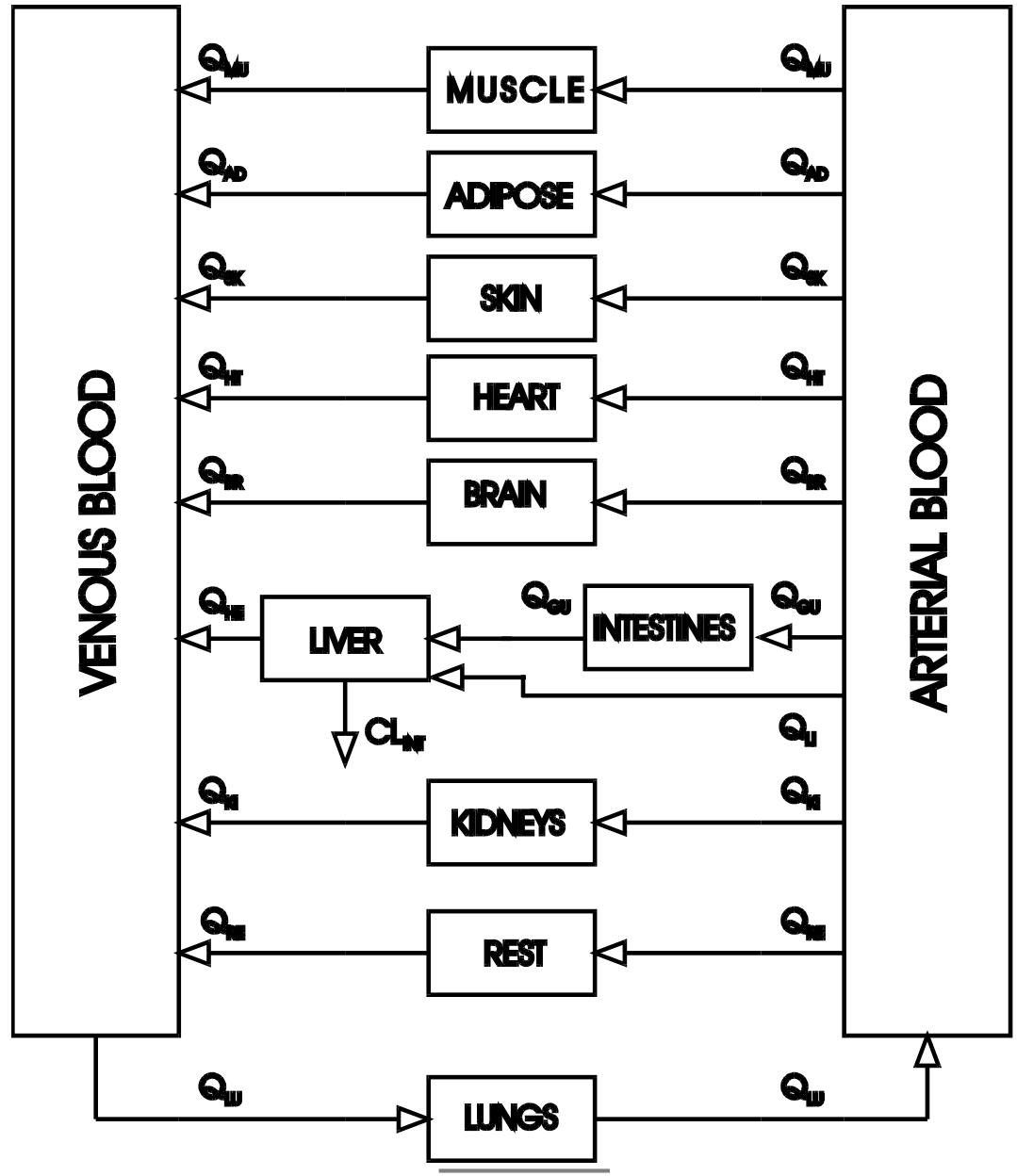

100
10
1
0.1
0.01
concentration
0
2
4
6
8
10
time
$C(t) = C_1 \cdot e^{-\lambda_1 t} + C_2 \cdot e^{-\lambda_2 t}$




$$V_1 \cdot \frac{dC_1(t)}{dt} = -k_{12}V_1C_1(t) - k_{10}V_1C_1(t) + k_{21}V_2C_2(t)$$

$$V_2 \cdot \frac{dC_2(t)}{dt} = k_{12}V_1C_1(t) - k_{21}V_2C_2(t)$$

# PBPK MODEL


VENOUS BLOOD
ARTERIAL BLOOD
MUSCLE
ADIPOSE
SKIN
HEART
BRAIN
LIVER
INTESTINES
KIDNEYS
REST
LUNGS
$Q_{MU}$
$Q_{AD}$
$Q_{SK}$
$Q_{HT}$
$Q_{BR}$
$Q_{HE}$
$Q_{GU}$
$Q_{LI}$
$Q_{KI}$
$Q_{RE}$
$Q_{LU}$
$CL_{INT}$

$$Kp_H \cdot V_H \cdot \frac{dC_{out,H}(t)}{dt} = Q_H \cdot C_A(t) - Q_H \cdot C_{out,H}(t) - CL_{\text{int}} . Kp_H \cdot C_{out,H}(t)$$

# Role of Modelling and Simulation in Phase I Drug Development

L. Aarons, M. Karlsson, F. Mentré,
F. Rombout, J.-L. Steimer, A. van Peer
COST B15

**Brussels January 10-11, 2000**

**Eur.J.Pharm.Sci. 13, 115-122 (2001)**


# COST

European **CO**operation in the Field of **S**cientific and **T**echnical Research

# Definition of Phase I

- **Phase I is the transition Phase from preclinical to clinical evaluation**

**•Learning process primarily focused on:**

**- Safety (Tolerability)**

**- PK/PD**

**- Metabolism**

**- Potential interactions (drugs/food)**

**- Dosage form development (equivalence)**

# Phase I Safety ¥ Tolerability Data

- FIM and S/MD study wide dose range
- Escalation  design
- Healthy subjects
- Small numbers
- High quality data

# Traditional Approach

- Plot and summarise the data
- Guess doses to progress based on incidence of unacceptable safety
- Do another study

# Integrated PK/PD Approach

- Plot and examine data
- Model pk/pd data in ongoing fashion
- Simulate scenarios
- Plot regimen-response-responder surface
- Design next study

# Combining *In Vitro* PD Parameters with Phase I PK: Concept


- Estimate pharmacokinetics in healthy volunteers
- Use in vitro PD parameter to predict PD effect in humans

# PK/PD model

Allows:

- Simulation of pharmacological actions:
  - different drug regimens
  - alternative drug formulations
  - drug interactions/genetic polymorphism
  - patient populations
  - other

# PK/PD model

Allows:

- Scaling between different compounds of same class
- Optimization of Phase II trial design (CATD)
- Evaluation of assumptions

# Role of M&S in Phase I today

- Used for a long time
- Used for many purposes
- Stringency and strategy in implementation often lacking

# Changes Affecting M&S in Phase I

- **Phase I**
  - Earlier/faster into patients
  - Increased learning features
  - Biomarkers
  - Adaptive designs
  - Earlier Proof-of-Concept
- **M&S**
  - Population approach
  - PK/PD
  - Clinical Trial Simulation

# How Can PK M&S in Phase I Increase the Productivity?

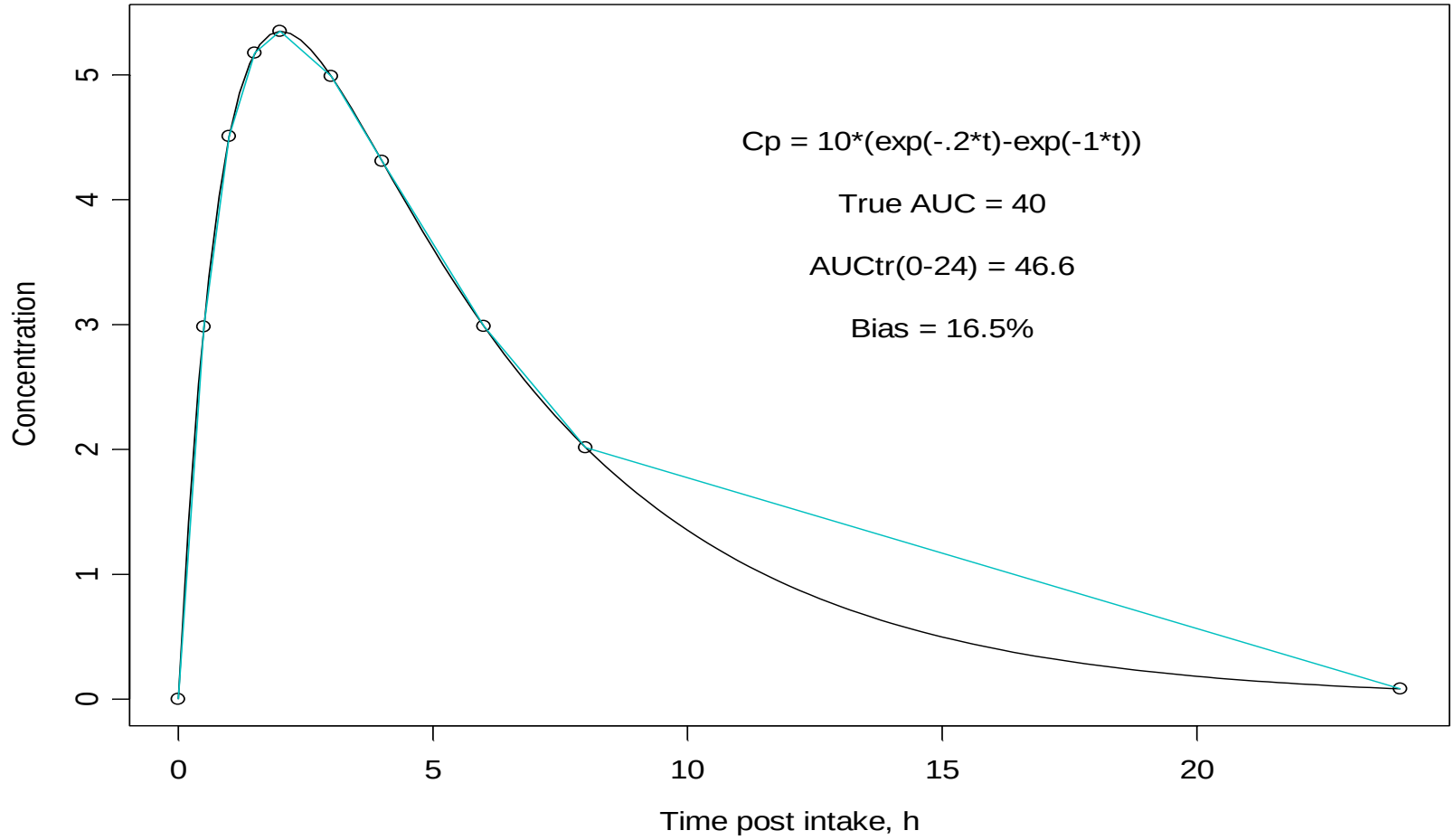
- Reduction in the number of clinical trials to be performed
- Provide information leading to better designed studies
- Influencing the future label
- State-of-the-Art analyses of study results

# Modelling versus Non-Modelling

- Non-modelling advantages
  - Easy to implement and standardize
  - No lack of competent personnel
  - Studies designed for non-modelling analysis
- Conclusion: ”Modelling is not required routinely for these types of studies and should only be considered if it can provide added value with a valid rational”

Quote from Azhar Khan, Medeval, UK

# Noncompartmental analysis vs modelling



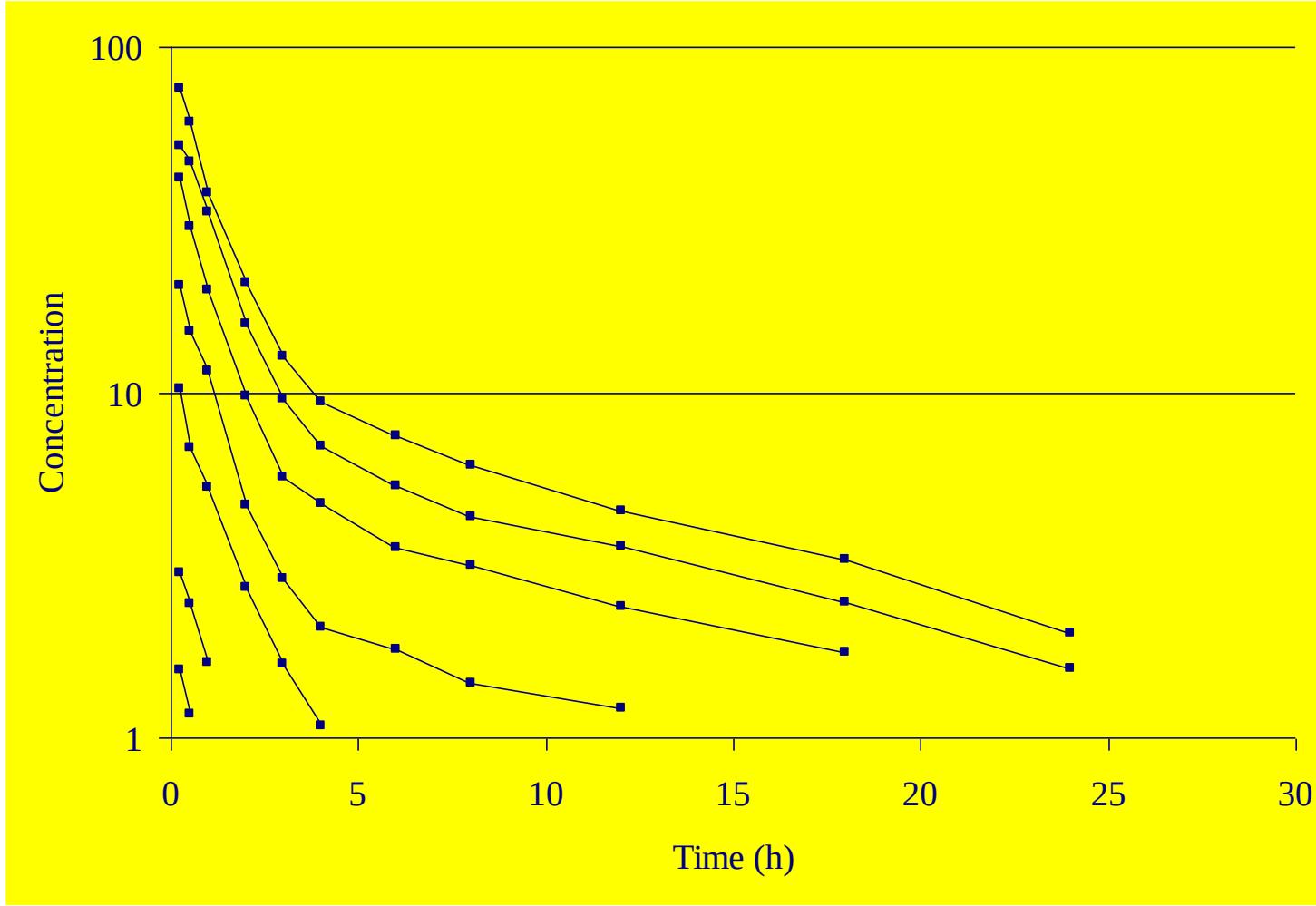
# Situations where modelling is invaluable

- Censoring because of assay limitation (in PK and/or PD)
- Characterisation of non-linearity
- Estimating exposure-response relationship
- Combined analysis
- Sparse sampling studies
- Special populations
- Integrating PK/PD knowledge for decision making
- Simulation of phase II trials

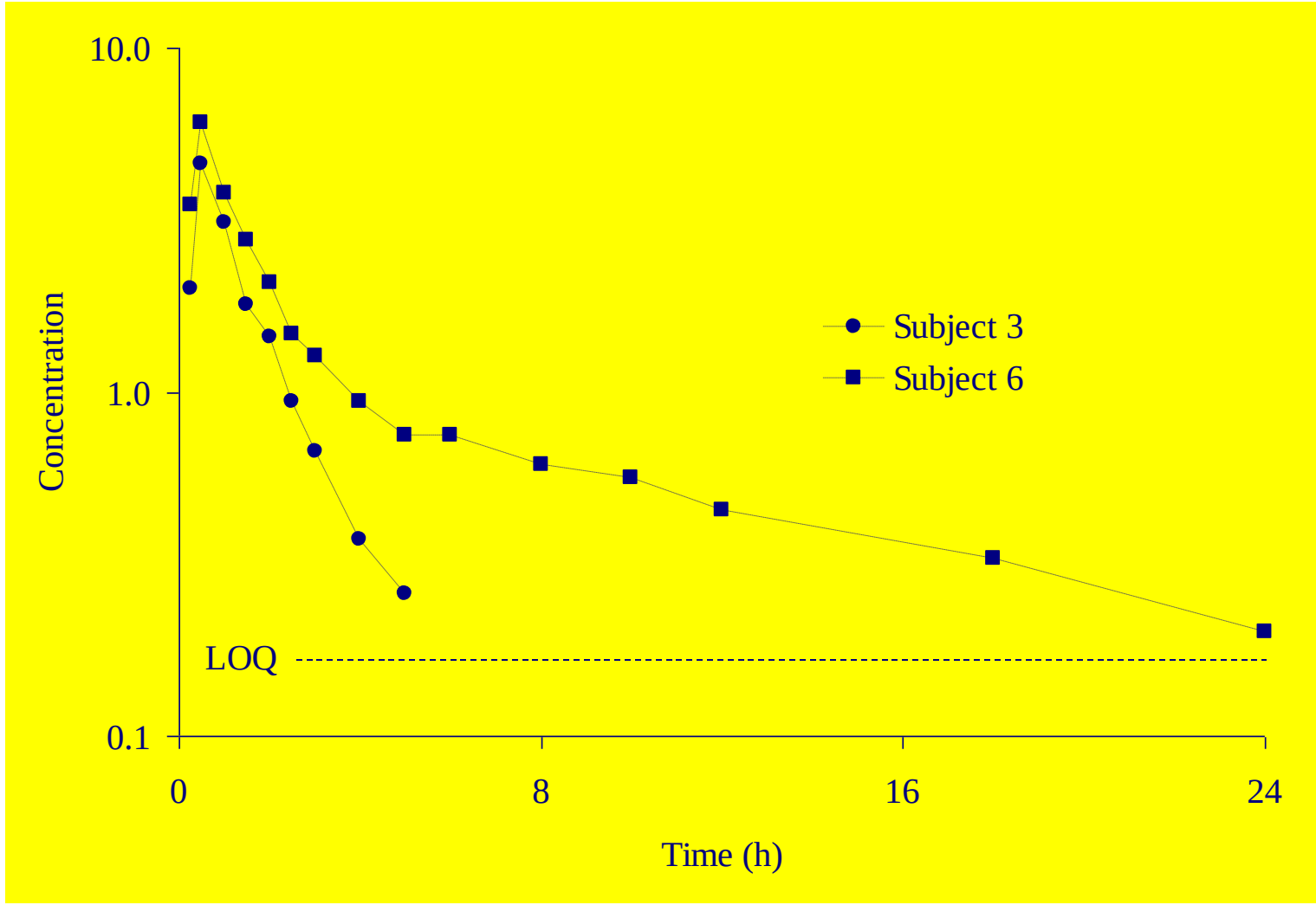
# Individual vs population modelling

- Individual modelling
  - Nonlinear regression of data from individual subjects
  - Standard two-stage (STS) method to obtain mean and variance of parameters
- Population modelling
  - Non-linear mixed effects modelling of data from all subjects data simultaneously

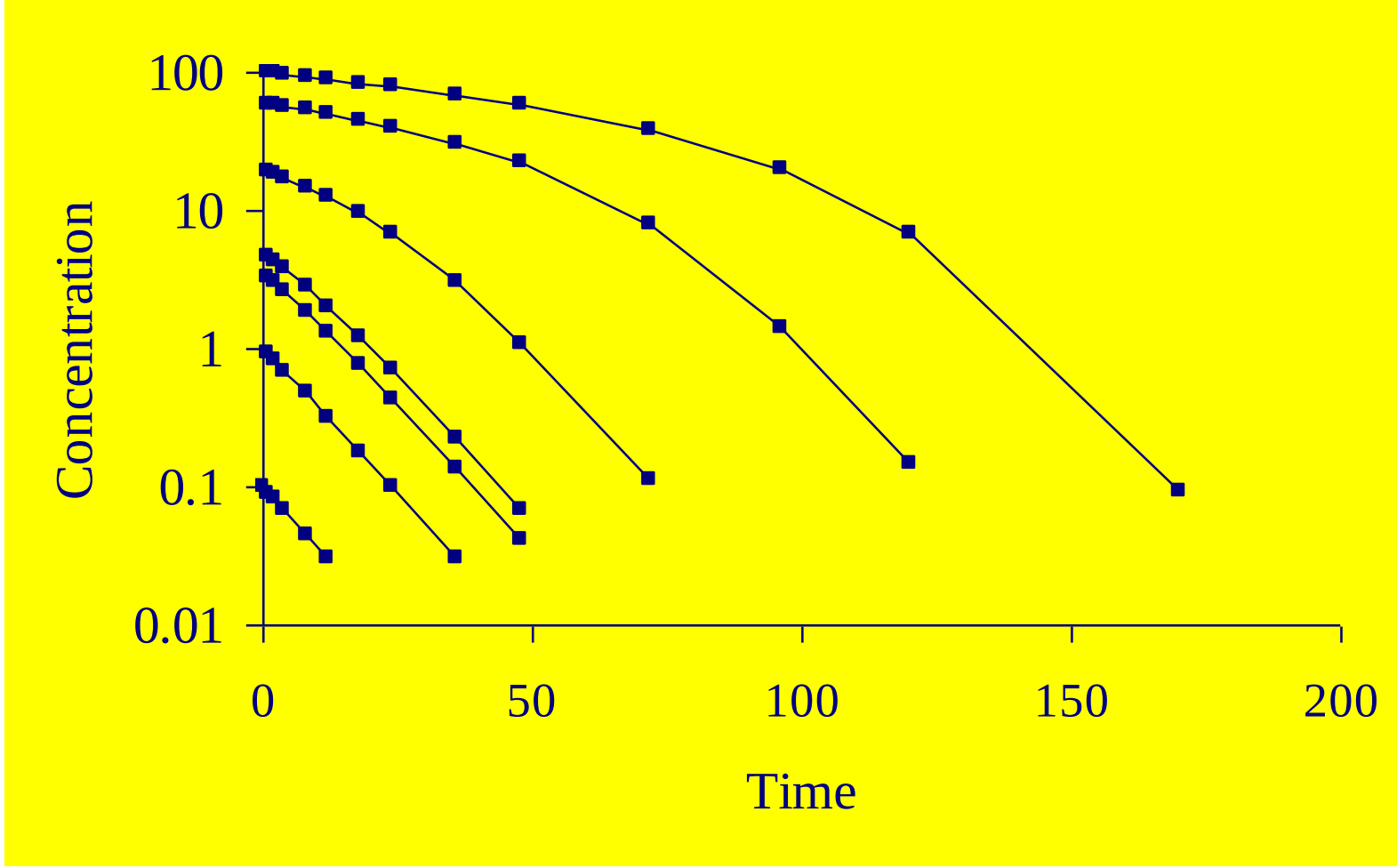
# Tolerability studies



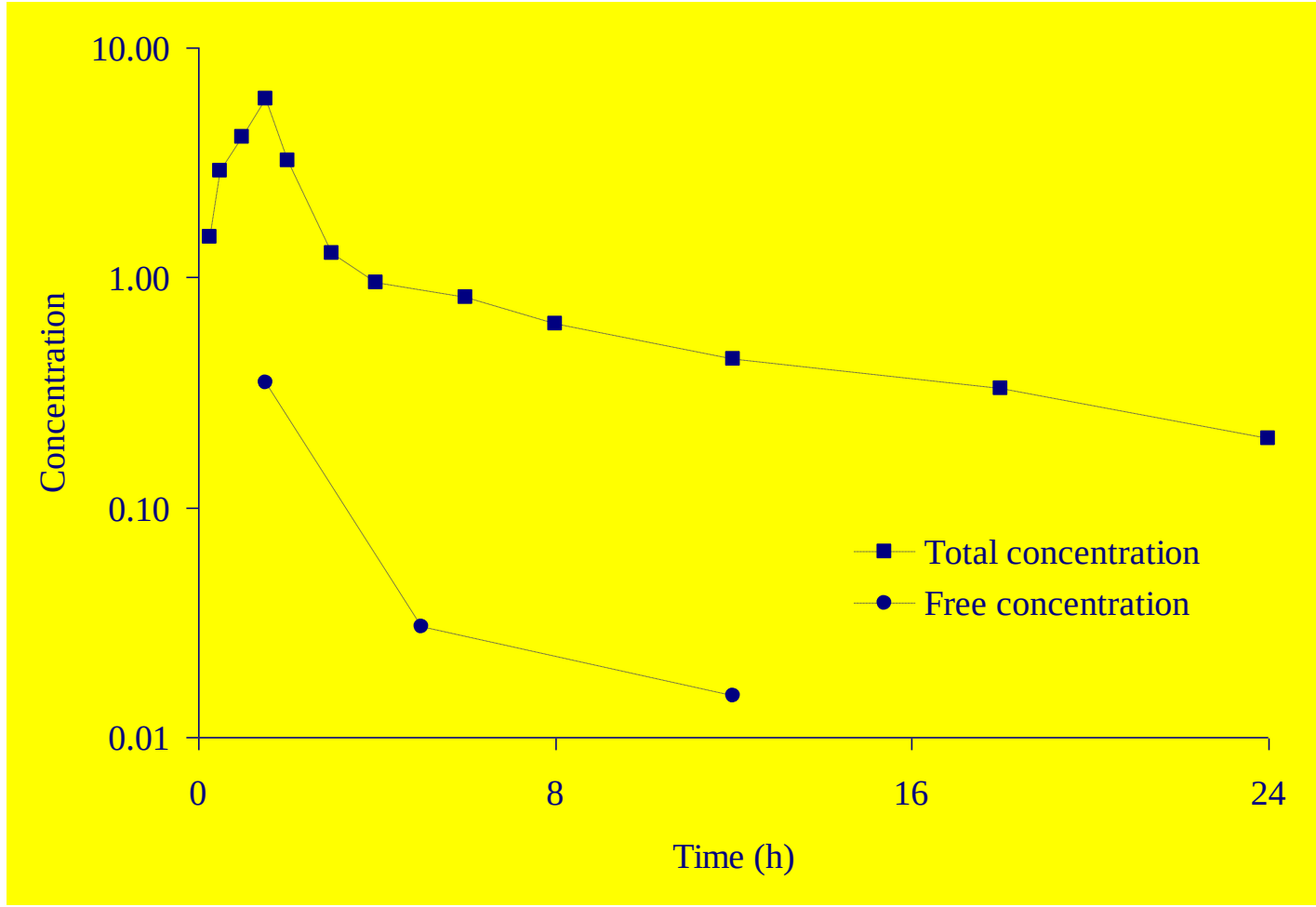
# Imbalance and confounding



# Non-linear PK



# Rich + sparse data



# (Human) resource needs and expertise

- "New" role: "pharmacometrician" **- pharmacomagician**
  - Hybrid of statistician, systems scientist, clinical pharmacologist, software specialist
  - A "facilitator", "translator", "integrator" within the clinical team
- Issues:
  - Not many such scientists "on the marketplace"
  - Training?
    - Past: on the job; specialized workshops;...
    - Future: University degrees?

# Conclusions

- Potential of M&S not exploited enough
- Requires trained scientists
- Requires commitment
- Cost-benefit to be assessed
- Increased modelling of rich data
- Population modelling
  - Pros outweigh Cons
  - Requires investment in training

# The Role of Modelling and Simulation in the Clinical Development of Anti-Cancer Agents

L. Aarons, M. Karlsson, F. Mentré,

A.v. Peer, F. Rombout, H. Schaefer,

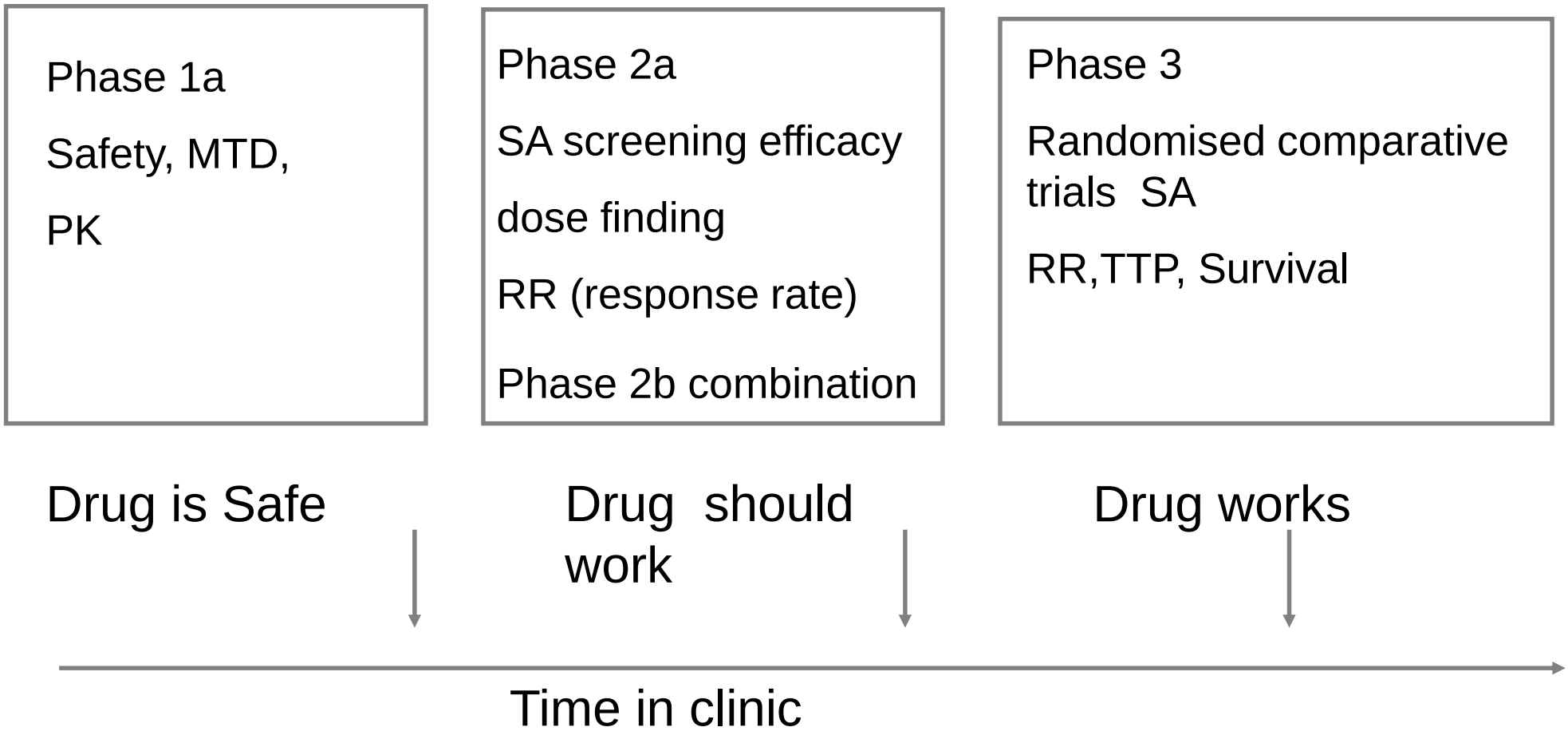
J.-L. Steimer, I. Trocóniz

COST B15

**Brussels March 7-8, 2001**

**J.Pharmacokin.Pharmacodyn. 31, 419-440 (2005)**

# Traditional Oncology Development



# Phase I Populations

- Typically pretreated cancer patients with solid tumors
- Untreated cancer patients
- Patient volunteers
- Human volunteers
- Non cancer patients

# Treat 3 patients at the lowest dose and then escalate according to the following scheme.

| Number of Patients with DLT | Next Dose Level |
|---|---|
| 0/3 | Escalate to next dose |
| 1/3 | Accrue 3 patients at same dose. |
| 1/3 + 0/3 = 1/6 | Escalate to next dose. |
| 1/3 + {1/3, 2/3, or 3/3} > 1/6 | Stop: recommend previous dose. |
| 2/3 | Stop: recommend previous dose. |
| 3/3 | Stop: recommend previous dose. |

# Modified Continual Reassessment Method

- Method for estimating the MTD within a Bayesian framework.
- Medical experts provide initial estimates of P{DLT} for each pre-defined dose level.
- Define a target P{DLT} that will define the MTD. (i.e. the dose with this P{DLT} is the MTD.)
- Choose a dose-toxicity curve
  - Flexible enough to represent a wide range of possibilities.
  - Usually defined by a single parameter.

# Dose assignment and escalation scheme

- Assign first cohort of 3 patients to lowest dose.
- Observe responses and update model of dose-toxicity relationship and with it the estimates of P{DLT} at each dose level.
- Assign next cohort to the dose whose updated estimate of P{DLT} is closest to the target.
- Repeat until a minimum of n(18) patients have been evaluated and the next cohort would be assigned to a dose that m(6) patients have already been assigned.

# Endpoints  issues in Cancer trials

- **Overall Survival** -”hard” endpoint
  - long follow up
  - confounded by sequential therapy and crossover
  - distinguish disease specific from other causes eg Aes
  - requires a control arm
- **Disease and Progression Free Survival -**
  - faster than overall survival
  - reflects primary intervention not salvage
  - reflects quality of life
  - can be appropriate for “ cytostatics” or some tumors ( eg gliomas)
  - may not be a reliable surrogate for overall survival if  improvement is small or if salvage effective
  - requires a control arm

# Potential Use of Surrogates

- Decrease Size, Cost and Duration of clinical trials
- Provide evidence to proceed to further development or early termination
- Assist dose & schedule selection in human trials
- Guide individual patient therapy
- Give insights into disease mechanisms
- Select Clinical subject characteristics for further study

# Surrogate Measures in Oncology

- Pharmacokinetic parameters in plasma or tissues
- Hematology and Biochemistry
- Disease specific markers (eg bone turnover)
- Tumour specific markers (PSA, CEA)
- Gene or protein expression
- Cytogenetics (Ph1 chromosome )
- Receptor activation status /circulating receptor, Cytokines
- Imaging - FACS, MRI & PET

# Integration of information and data

Potential candidates for use as PK parameter

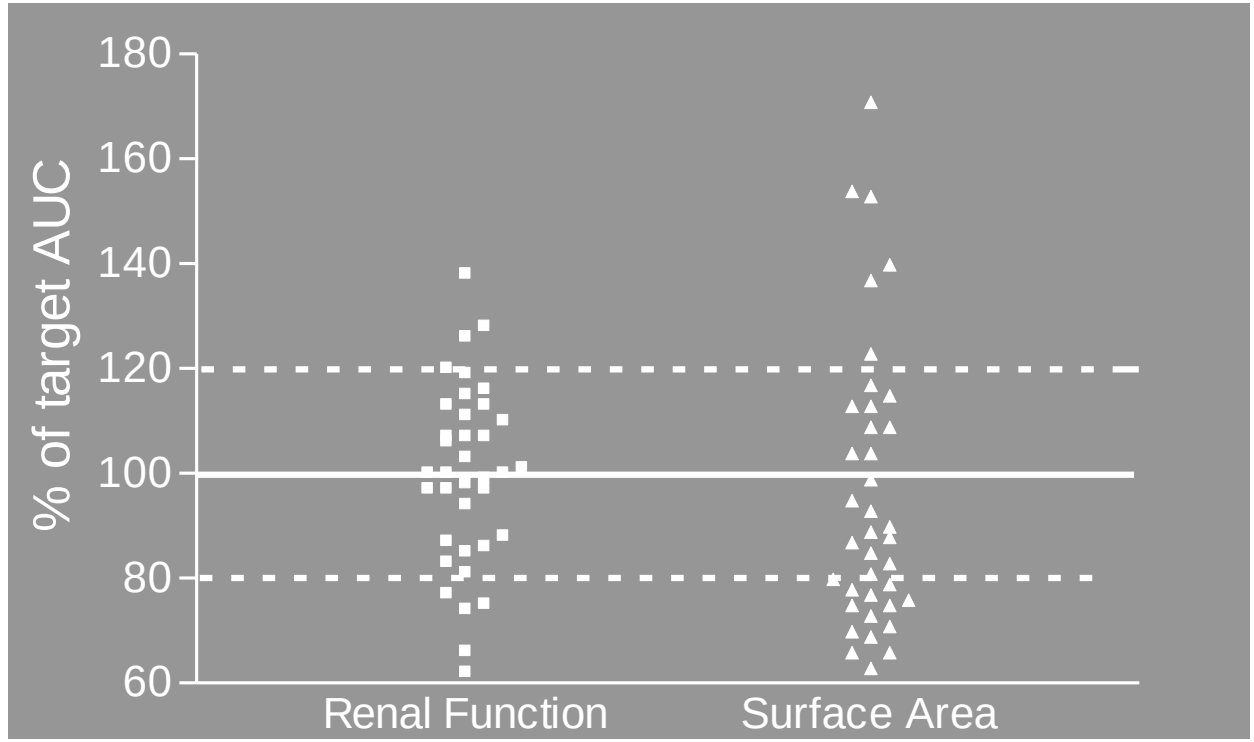
- AUC
- $C_{max}$
- $C_{ss}$
- Time over threshold
- Cumulative AUC
- AUC intensity

There is no universal PK parameter for use in PK/PD modelling

# Carboplatin

$$CL = \Theta_1 + \Theta_1 \bullet CLcr$$

# Observed carboplatin AUC as percentage of target following surface area or renal function based dosing




**Calvert and Boddy, Newcastle**

# Paediatric Carboplatin dosing formula

$$D = AUC \times (Cl_r + Cl_n)$$

$$D = AUC \times \left\{ \left( \left[ \frac{0.693}{t_{1/2}} \right] \times \left[ 0.52 \times \left( 843 \times BW^{0.891} \right) \right] \right) + (0.36 \times BW) \right\}$$

where

| | | |
|---|---|---|
| D | = | dose (mg) |
| AUC | = | area under plasma free Pt concentration time curve (mg/ml.min) |
| Cl | = | clearance |
| $Cl_r$ | = | renal clearance |
| $Cl_n$ | = | non-renal clearance |
| $t_{1/2}$ | = | $^{51}$Cr EDTA plasma half life (min) |
| BW | = | body weight (kg) |

# Results

**AUC as % of target (mean and 95% CI)**

| | |
|---|---|
| SA based dosing | 95 (86 - 103) % |
| RF based dosing | 98 (93 - 103) % |

**Courses within 20% of target**

| | |
|---|---|
| SA based dosing | 49 % |
| RF based dosing | 74 % |

# Summary

- PK/PD is model driven
- PK/PD models aid the interpretation of pharmacological data and can be used prospectively to design subsequent studies **learning/confirming**
- Nonlinear mixed effects modelling allows data from a variety of unbalanced, sparse designs to be analysed
- Software for nonlinear mixed effects modelling is now widely available -

  **even for amateurs!**