

*PK PD Modelling and simulation in early
development*

When and how does it make sense

Eliane fuseau

17-18 March 2004,
Strasbourg

Club Phase I, AGAH

PK PD in early development

Law

Health authorities
Guidances ...

Drug development

Modelling

Formulation, PK, PD, ER
Bridging formulations,
populations

Ethics

Useless exposure
Risk/benefit ratio

Money

Development costs
Errors costs
Attrition

PK PD modelling in early development: scope

- Regulatory drive:
 - Need to improve efficiency of DD and of application review
 - ER, in discovery and development (pre-clinical to clinical pharmacology and to patients)
- Money/ time/ ethics
 - Bioavailability, PK, PD, bridging (formulations, populations, regions)
 - ↓ ↓ development of 2nd in class, of line extensions
- Label/ profile/money/ethics
 - Understanding the variability in response between subjects
 - Manage the individual risk/benefit ratio



Exposure-Response Relationships- Guidance for Industry

FDA Expectations:

Where we are, Where we'd like to be



Brian Booth

FDA/CDER/OCPB/DPE

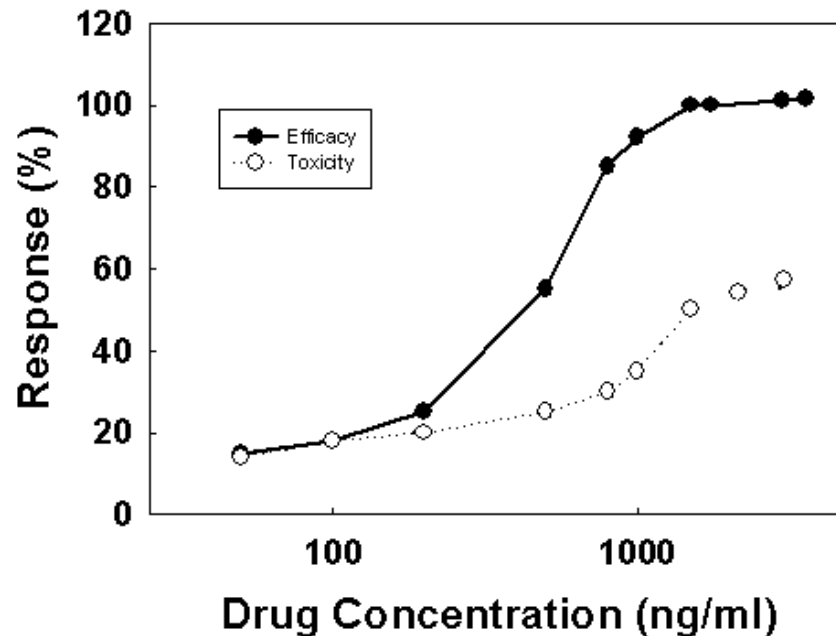
Boothb@cder.fda.gov

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

<http://www.fda.gov/cder/guidance/index.htm>

Purpose of the Guidance

To describe the role(s) of E-R relationships in drug development and the types of data and approaches that can be used to determine these relationships



Measuring Response

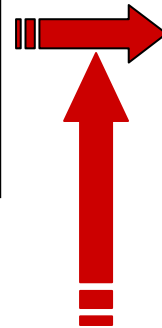
1. Clinical Endpoints
survival, cure, etc
2. Surrogate Endpoints
Blood Pressure, Progression Free Survival,
3. *Biomarkers*
prostate specific antigen,

Clinical Drug Development

Pre-IND → Phase 1 → Phase 2 → Phase 3 → NDA

1. Discovery & Development
- linking pre-clinical to human
 - proof of concept
 - guidance for future trials

Biomarkers?

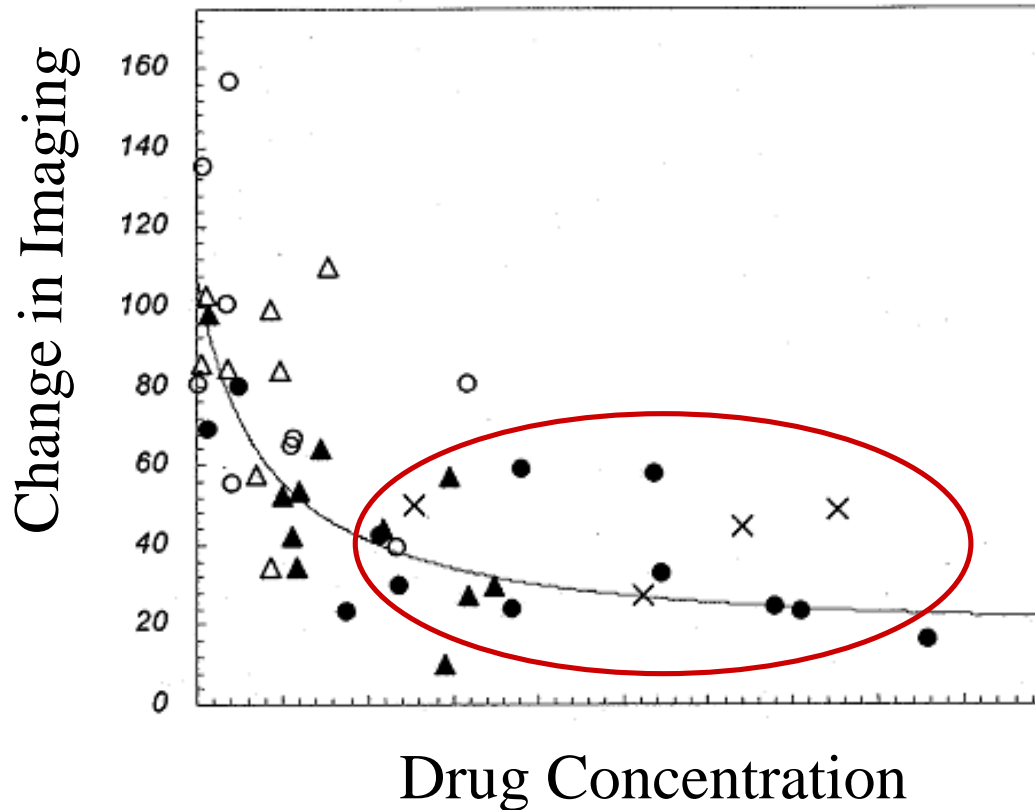


2. Safety and Effectiveness
- contribute 1° safety and effectiveness
 - support for 1° effectiveness
 - support for new populations, sub-populations, dosage forms, routes, regimens

End of Phase 2a
-PK/PD, M&S, CTS

1. Discovery & Development

(pre-clinical & phase 1) proof of concept, guidance for future trials



Line:
Biomarker
Response

Symbols:
Patient Response

Proposal for End-of-Phase 2A (EOP2A) Meetings

Advisory Committee for
Pharmaceutical Sciences
Clinical Pharmacology Subcommittee
November 17-18, 2003

Lawrence J. Lesko, Ph.D., FCP
Office of Clinical Pharmacology and
Biopharmaceutics, CDER, FDA

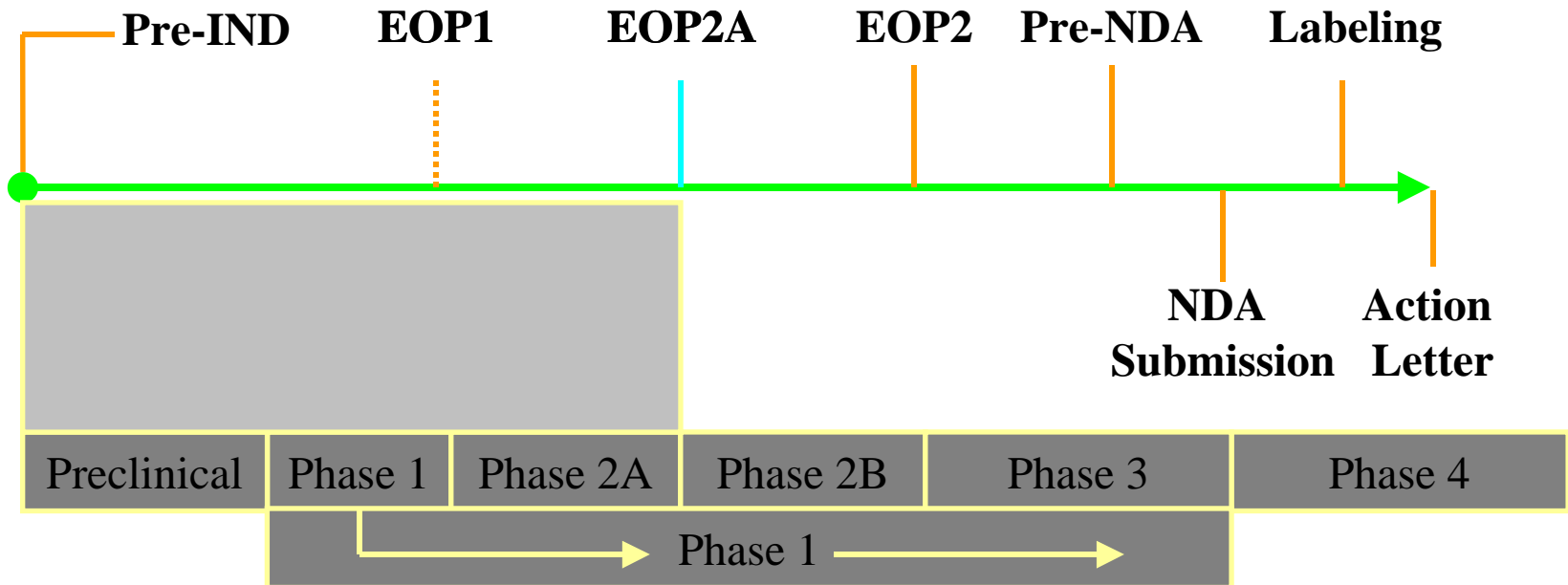
Guidances Driving Hypothesis

Exposure-Response Relationships: Study Design, Data Analysis and Regulatory Applications (2003)

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998)

Dose-Response Information to Support Drug Registration (1995)

Timing of Meeting



Rationale for Meeting Time

- Complete information on preclinical pharmacology and E-R
- Complete dose-tolerance (safety) data in healthy volunteers
- Initial efficacy (proof-of-concept) and safety data in patients
- Prior to so-called “registration or label studies” on special populations, drug interactions and food studies
- Discuss study designs using emerging technologies such as pharmacogenetics

Opportunity to Apply Mechanistic and Quantitative Methods

- Modeling and simulation to analyze all E-R data and explore dose choices
- Design of studies using computer-assisted clinical trial simulation
- Design of PPK studies to efficiently identify covariates affecting E-R
- Discuss therapeutic equivalence boundaries based on E-R to interpret special population studies

Which Drug Development Programs Would Benefit the Most?

Limited resources

- first-in-class or significant therapeutic advancement
- well-understood pathophysiology and pharmacology
- completeness of EOP2A background package
- experience of sponsor in drug development

Summary: Goals of EOP2A Meeting

- Decrease uncertainty in further drug development, e.g., phase 3
- Quantitative analysis of E-R data to suggest dose ranges for clinical study
- Identify missing or discuss necessary information prior to submission
- Improve informational quality and minimize delays in NDA review

PK and PD modelling & simulation Phase 1

■ PK

- Animal to man, FTIM, single dose PK, metabolic, PD (markers, surrogates).
- Formulation, absorption, absolute bioavailability, repeat-dose PK, dose-proportionality, time effect, dose effect.
- Demography, drug, food or disease interactions

■ PD

- Maximum tolerated dose in healthy, exposure
- Demography, drug, disease interactions
- Biomarkers, clinical endpoints
- ER estimation in healthy, in patients target population

PD evaluations: determination of ER

- Pre-clinical or human
- Needed: dose, time, repeated administration, disease on PK & PD
 - 3 or more dose levels (PK), large conc range (PD), optimise measures for PK and PD separately
 - SD vs. MD, wash-out followed by new SD
 - Complete profile for shape of model, sparse for pop estimates
 - PD should be all effects observed: wanted or adverse
 - Look for tolerance or sensitization
 - Look for PK and PD Drug-drug interactions
 - Consider variability: BSV, BOV, residual
- Estimate onset, duration and offset of effect
- Evaluate time effect on the disease: positive and/or negative control

Examples

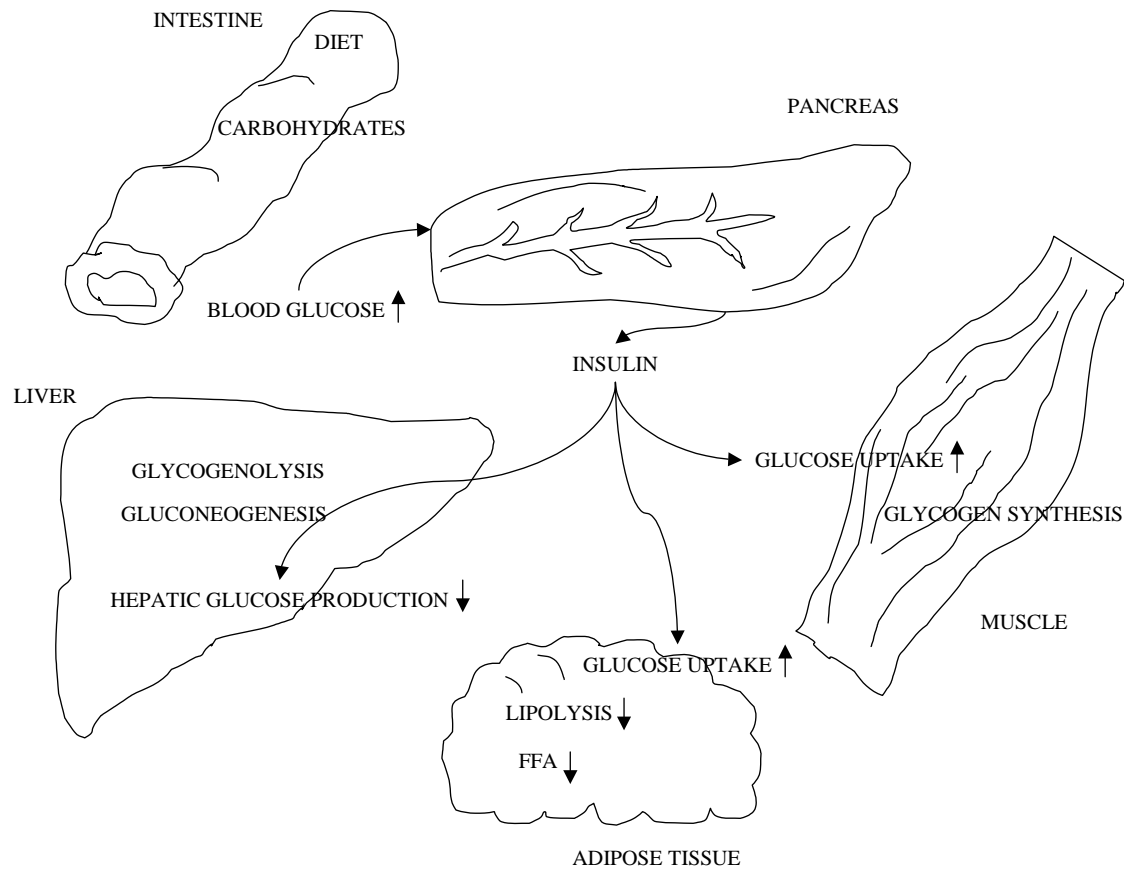
- PhD thesis, Dr Vibeke Hatorpe, DTC (Denmark)
 - M&S across a “complete” development program in diabetes, partially *a posteriori*
- Absorption/formulation example (EMF)
 - High permeability, low solubility drug
 - Particle size problem

Diabetes and role of PPAR α & γ

Key regulators of intra- and extra cellular lipid and lipoprotein metabolism.

- Triglyceride production and metabolism
- HDL cholesterol production and the reverse cholesterol transport pathway
- FFA metabolism
- Adipocyte differentiation
- Glucose metabolism: PPAR γ in glucose homeostasis is still debating

Blood Glucose Homeostasis



Complex mechanism, limited information ...

- PKPD modelling & simulation in the early phases of the development, from non-clinical to phase I and from phase I to phase II, development of
 - Allometric interspecies model from non-clinical PK to predict human PK.
 - PK model for healthy subjects and patients with type 2 diabetes.
 - PD model for the effects on glucose and lipid homeostasis in early clinical development (phase I) and in later phase clinical development (phase II).
 - Influence of demographics, baseline characteristics and disease state.
 - PD model for unwanted clinical outcomes and compare to the PD models for desirable clinical effects to assess the risk/benefit ratio.
 - Evaluate the predictive value of the models

NNC 61-0029 *In vitro* & *in vivo* data

- Transactivation assays
 - PPAR γ : NNC 61-0029 ~ Rosiglitazone
 - PPAR α : NNC 61-0029 ~ WY 14643
- In type 2 diabetic db/db male mice
 - ↓ fasting blood glucose, ↓ insulin, ↓ triglycerides
- Pre-clinical PK
 - Up to 4-week in rat (0, 0.1, 1, 5, 10, 25, 50 mg/kg),
 - 4-week toxicity in dog (0, 0.2, 1, and 5 mg/kg)
 - PK in mini-pig (SD 0.5 mg/kg)
 - PK in monkey (SD 14 mg/kg)
- Plasma protein binding; intrinsic clearance Cl_{int} (incubation with hepatocytes).

NNC 61-0029 human data

■ Phase 1 HS:

- DB, placebo-controlled, dose escalation (6 dose levels: 1mg to 90 mg), oral SD for safety, tolerability and the PK in 48 healthy males

■ Phase 1b HS + Patients:

- DB, placebo-controlled, //, MD (3 dose levels), 7 days in 24 HS, 21 days in 15 males with type 2 diabetes
- Fasting lipids and blood glucose at baseline and end of study
- Fasting lipids, fructosamine, insulin, C-peptide and FPG weekly prior to dose

NNC 61-0029 human data

■ Phase 2a

- DB, 3-months, randomised, //, placebo-controlled, 200 patients with type 2 diabetes, 4-week WO, treated for at least 3 months, six groups: maintenance dose, 0.1 mg to 7mg.
- Trough levels at all visits
- Efficacy: HbA_{1c}, lipids, apolipoprotein A-I, and total apolipoprotein B, FPG, insulin, C-peptide, fructosamine, 6 hour lipid and glucose profile after a standard meal.

Animal to man

■ Interspecies allometric Scaling

● Since low clearance (CYP450 mediated), use Boxenbaum two-terms power function:

$$● P = a \cdot WGT^b \cdot BW^y \quad \text{or} \quad P = a \cdot WGT^b / MLP$$

$$\text{with } MLP = 10.839 \cdot BW^{0.636} \cdot WGT^{-0.225}$$

● Intrinsic clearance correction

$$P = a \cdot WGT^b \cdot \left(CL_{an(\text{hepatocytes})} / CL_{h(\text{hepatocytes})} \right)$$

● Estimation of allometric coefficients by NONMEM

● PK estimation by species, with NONMEM

Results PK

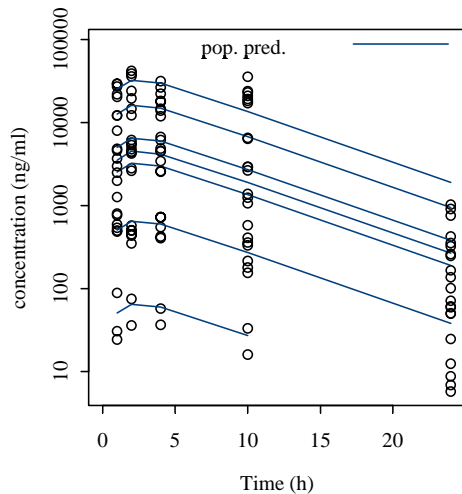
PK parameters in different animals after oral dose

Parameter	Rat* (n=196; male=90 female=106)		Dog (n=24; male=12 female=12)		Minipig (n=4; female)	Monkey (n=2; female)	
	Estimate (%SE)	IIV (%)	Estimate (%SE)	IIV (%)	Estimate (%SE)	Estimate (%SE)	IIV (%)
<i>CL/F (ml/hr/kg)</i>							
Male	180 (7.4)	21.1	71.9 (12.9)	32.4			
Female	108 (6.9)	21.1	54.7 (9.7)	32.4	290 (43.4)	20.0 (5.8)	
Effect of Day	0.19 (48.7)						
<i>V/F (ml/kg)</i>	1080 (6.9)		401 (9.7)	26.2	1370 (13.1)	69.2 (20.4)	
<i>V_{ss}/F (ml/kg)</i>	-		927 (13.1)	46.8	5580 (17.5)	1810 (11.1)	
<i>Q (ml/hr/kg)</i>	-		135 (25.5)	95.9	2280 (17.0)	29.8 (20.5)	24.3
<i>ka (hr⁻¹)</i>	0.893 (23.6)	68.4	4.52 (15.0)		2.38 (15.8)	0.404 (13.9)	
<i>Random residual variability</i>	0.20 (11.9) 44.7%CV		0.142 (16.5) 37.7%CV		0.145 (18.2) 38.1%CV	0.0394 (51.8) 19.8%CV	

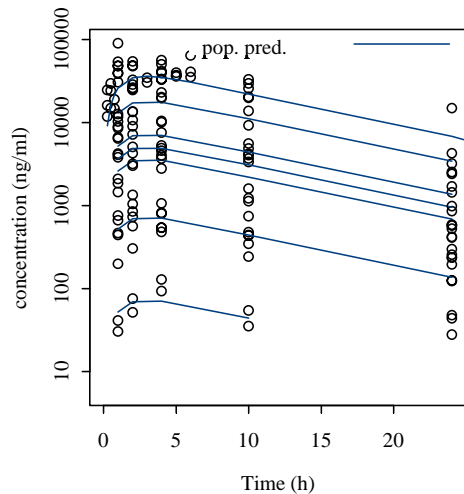
*CL/F, male=180*Day/(0.19+Day) and CL/F, female=108*Day/(0.19+Day)

PK Results

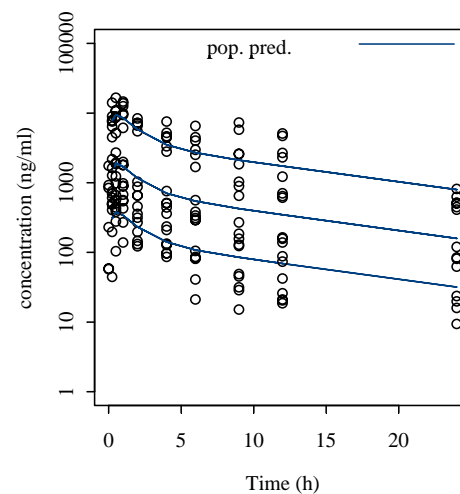
Rat, Male



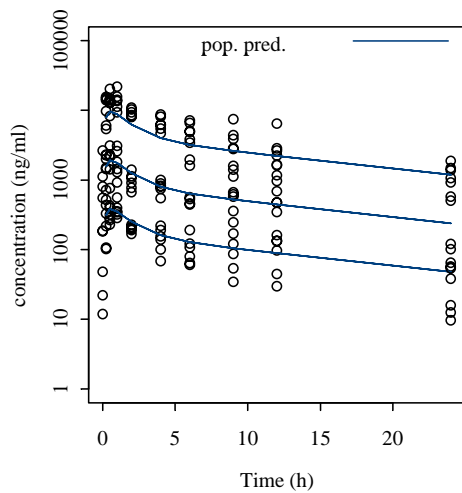
Rat, Female



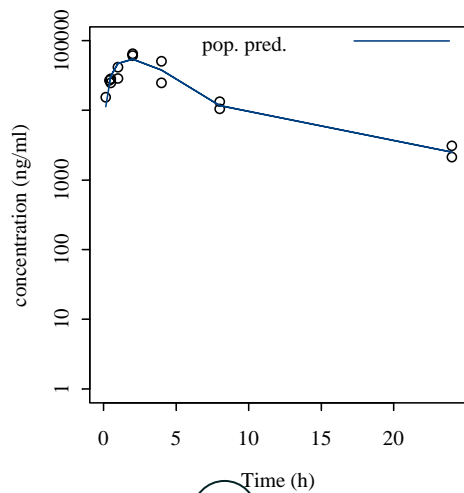
Dog, Male



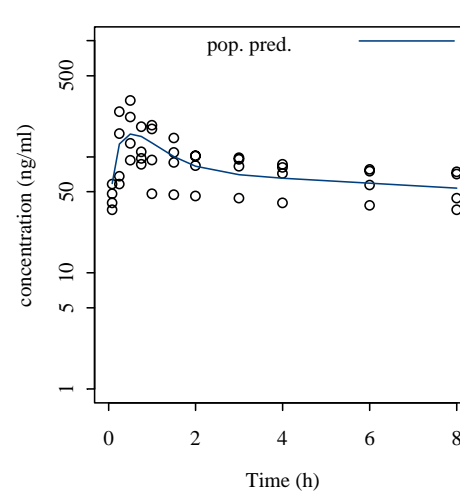
Dog, Female



Monkey



Minipig

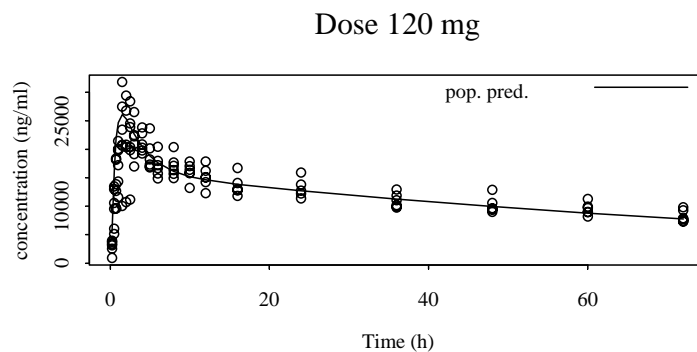
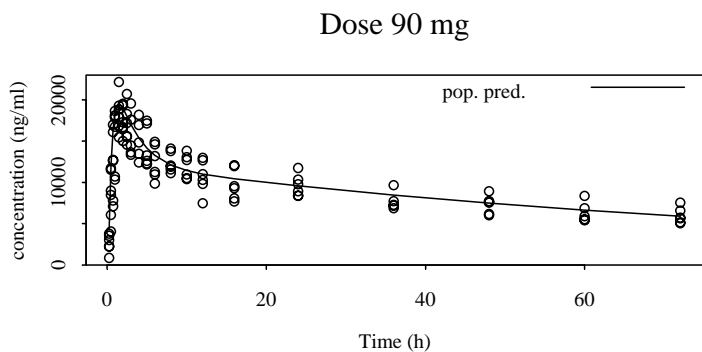
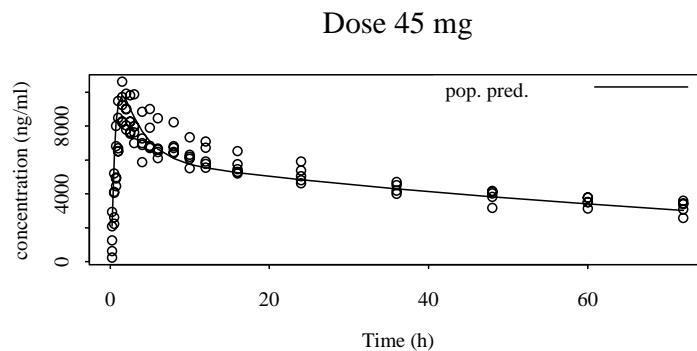
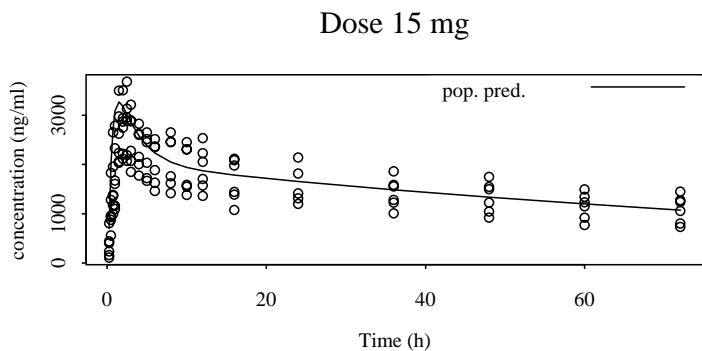
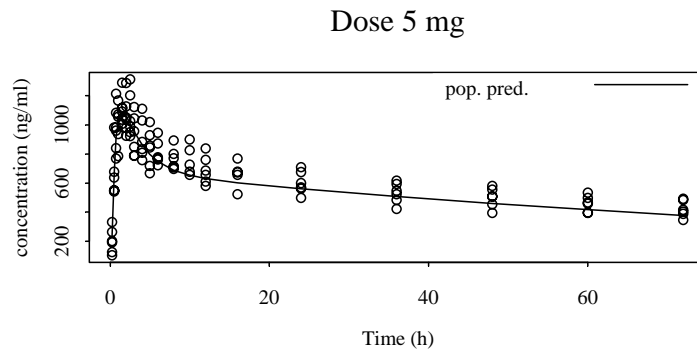
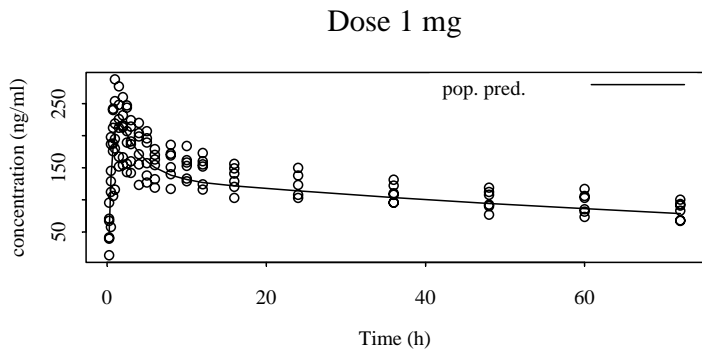


Allometric prediction in human

■ ~ complete failure

<i>Model notation</i>	<i>Human parameters in a 70 kg person</i>		
	<i>CL/F (L/hr)</i>	<i>V/F (L)</i>	<i>Vss/F (L)</i>
CL = $f(\text{WGT}, \text{SEX})$ V and Vss = $f(\text{WGT})$	3.9	0.60	49.97
CL = $f(\text{WGT}, \text{SEX}, \text{BW})$ V and Vss = $f(\text{WGT})$	-	-	-
CL · MLP = $f(\text{WGT}, \text{SEX})$ V and Vss = $f(\text{WGT})$	1.9	0.88	50.35
CL · (CL _{int,h} /CL _{int,an}) = $f(\text{WGT}, \text{SEX})$ V and Vss = $f(\text{WGT})$	0.49	0.90	72.60
Observed in a single dose study (clinical study I)	0.077	3.69	7.03

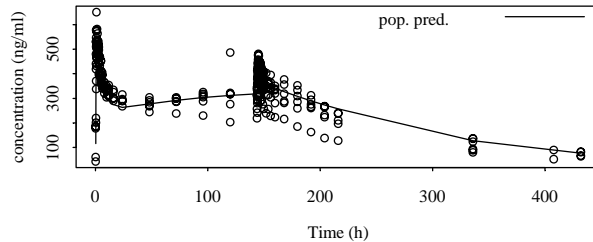
Human PK SD Healthy subjects



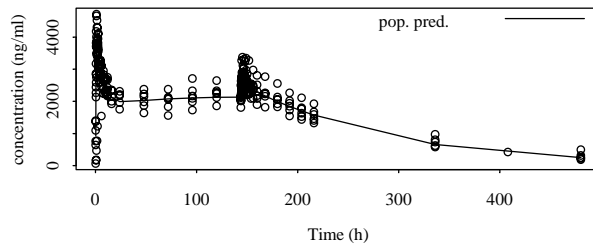
Human PK, MD HS & patients

HS

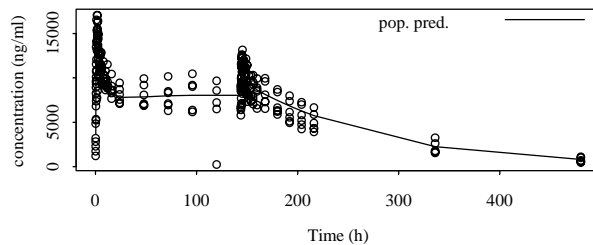
Dose 0.5 mg



Dose 4 mg

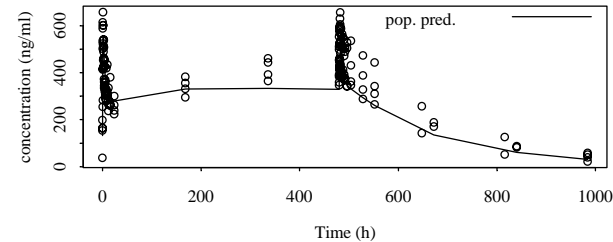


Dose 16 mg

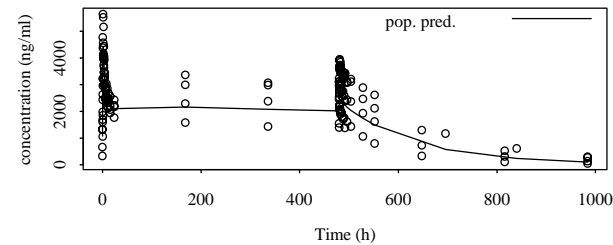


Type 2 diabetes

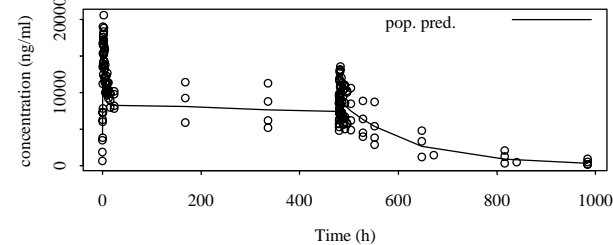
Dose 0.5 mg



Dose 4 mg

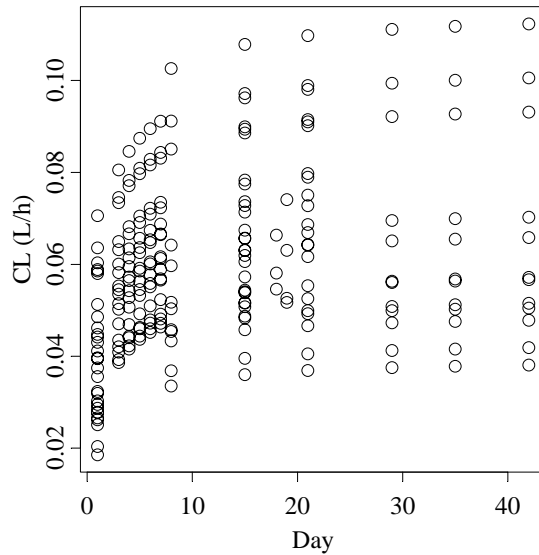


Dose 16 mg

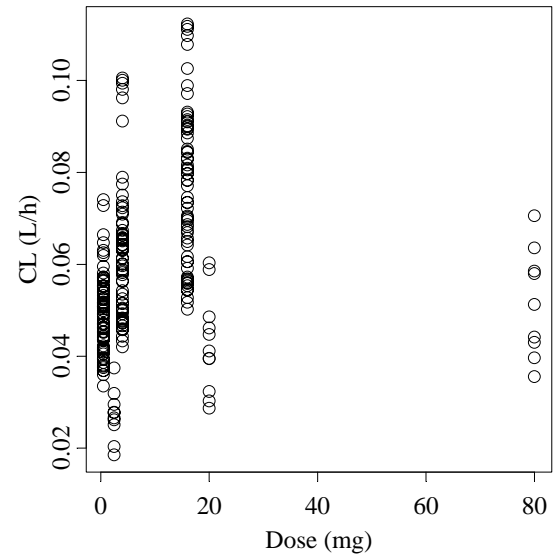


Human PK, effect of time, of dose

Clearance vs Day



Clearance vs Dose



Pharmacodynamic Analyses

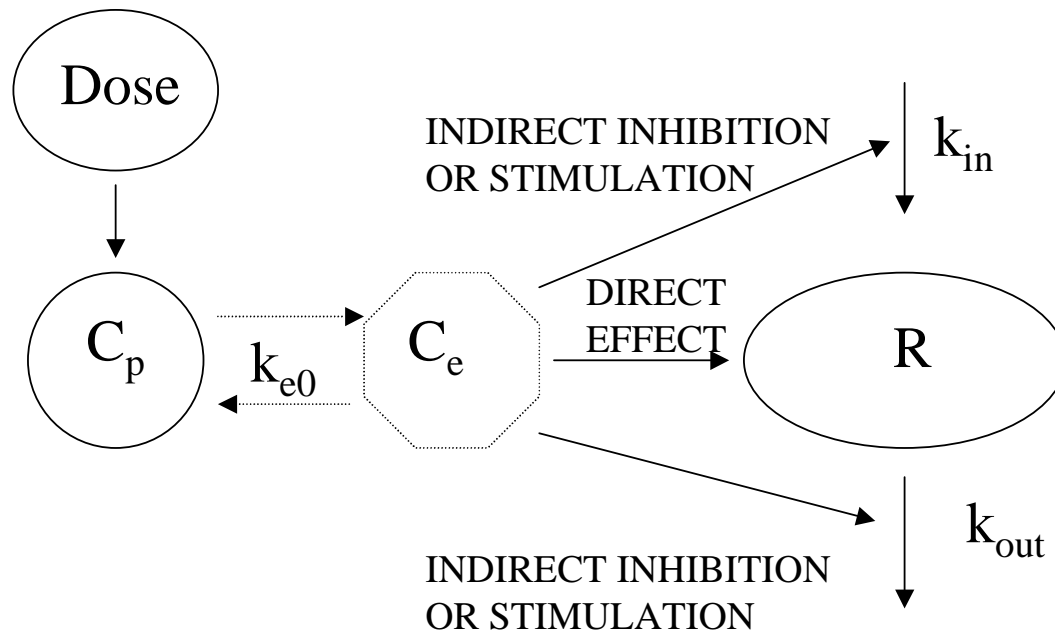
■ PD variables:

- biological markers of the glucose lowering effect: FPG, fructosamine
- biological markers for the effect on the lipid profile triglycerides, free fatty acids (FFA), high-density lipoprotein (HDL) and low-density lipoprotein (LDL)
- safety variable: haemoglobin

■ Analysis methods

- Univariate analysis of each PD variable with PK marker: dose,
- Graphical exploration of relationships between PD variables AUC or C_{min-ss}
- Selected PD variables analysed with other PD variables as covariates, to evaluate if these variables were a better predictor

General PKPD models



Endpoints and models

- FPG, triglycerides
 - Indirect response model with loss of stimulatory response
 - Effect compartment, to allow for the difference in time to reach PK and PD steady-state
- FPG, fructosamine, triglycerides, free fatty acids, HDL and LDL
 - Inhibitory or stimulatory sigmoid E_{max} , with or without effect of time and with dose, plasma concentration or AUC as independent variable

Phase 1 data, HS and patients

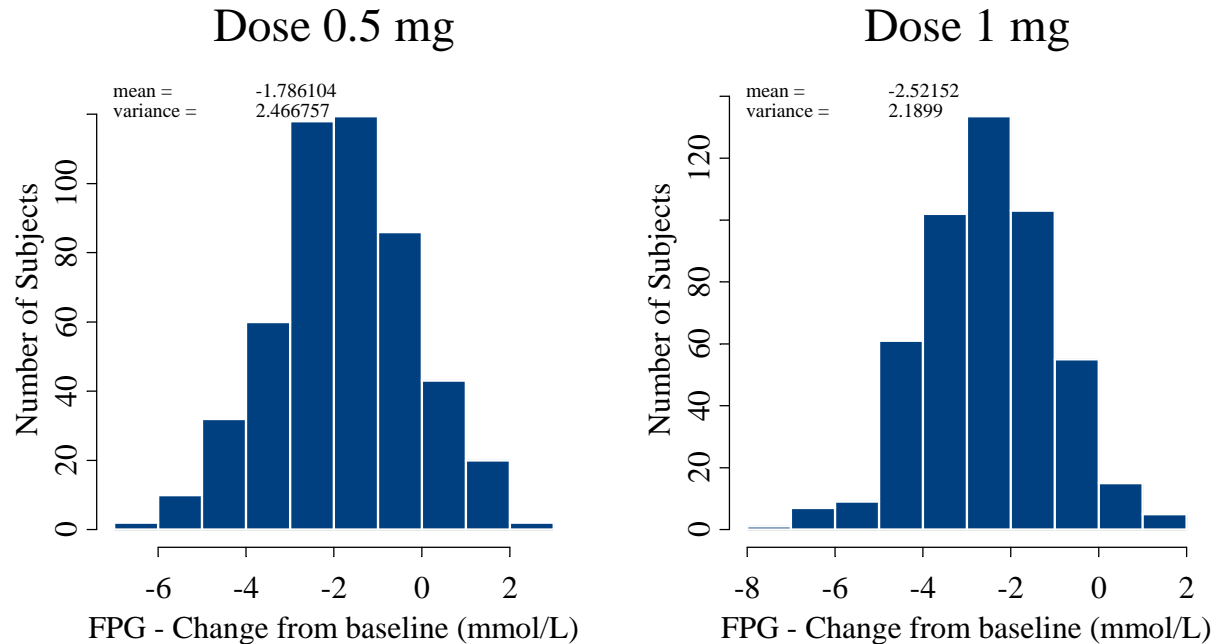
Variable	Model parameters	Population Estimate	95% CI	Intersubject variability (\pm SD or %CV)	Residual variability (\pm SD or %CV)
TRIG	$E = E_0 - \frac{E_{max} \cdot AUC^\gamma}{EAUC_{50}^\gamma + AUC^\gamma}$				
	E_0 (mmol/L)	1.8	[1.5 ; 2.1]	± 0.6	
	E_{max} (mmol/L)	1.4	[0.8 ; 1.9]		
	$EAUC_{50}$ (ng/ml*h)	182	[0 ; 397.6]	222	
	γ	0.65	[0.06 ; 1.24]		
HDL	$E = \alpha \cdot TRIG^\beta$				± 0.2
	α (mmol/L)	1.29	[1.17 ; 1.41]	20.3	
	β	-0.206	[-0.31 ; -0.1]		
LDL	$E = \alpha \cdot TRIG^\beta$				± 0.1
	α (mmol/L)	3.07	[2.62 ; 3.52]	27.7	
	β	0.27	[0.2 ; 0.34]		
					± 0.3

Phase 1 data, in HS and patients

Variable	Model parameters	Population Estimate	95% CI	Intersubject variability (\pm SD or %CV)	Residual variability (\pm SD or %CV)
FFA	$E = E_0 - \frac{E_{\max} \cdot Dose}{ED_{50} + Dose}$				
	E_0 (mmol/L)	0.49	[0.41 ; 0.56]	17.7	
	E_{\max} (mmol/L)	0.34	[0.27 ; 0.41]		
	ED_{50} (mg)	1.33	[0 ; 3.05]		29.9
FPG	$E = E_0 - \frac{E_{\max} \cdot Dose^{\lambda}}{ED_{50}^{\lambda} + Dose^{\lambda}}$				
	E_0 (mmol/L)	10.9	[9.5 ; 12.2]	\pm 2.0	
	E_{\max} (mmol/L)	1.44	[0.4 ; 2.5]		
	ED_{50} (mg)	0.47	[0.3 ; 0.7]		
	γ	5.4	[1.9 ; 8.8]		\pm 1.0
FRUC	$E = \alpha + \beta \cdot FPG$				
	α (mmol/L)	274	[219 ; 329]	15.8	
	β	5.9	[1.4 ; 10.4]		

Dose selection for phase IIa

- Monte Carlo simulations of 1000 patients, 24 weeks



Population distribution of reduction in FPG
after 24 weeks of treatment

Overall conclusion

... the work provides considerable information on the pharmacokinetics and pharmacodynamics ... summarised as:

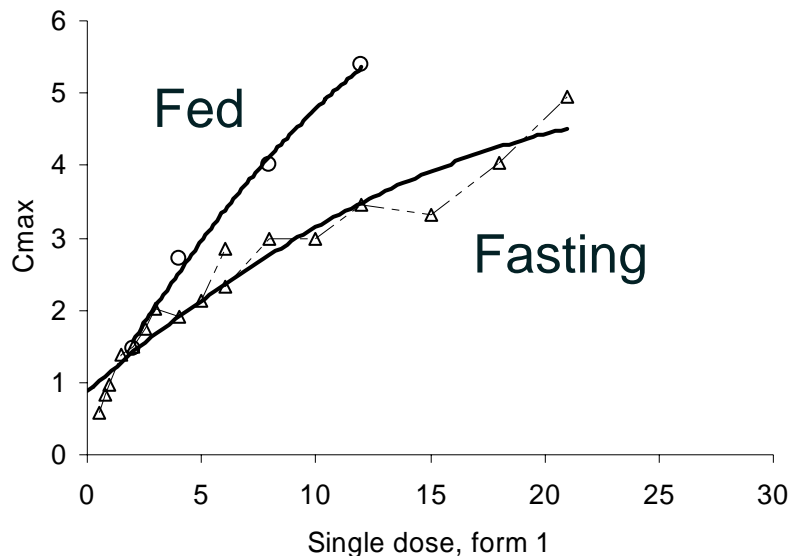
- IIV in the PK and PD of a PPAR α and γ activator and identification of covariates added valuable information in the characterisation of the compound.
- proved to be a useful tool in dose and dose range selection by population simulations.
- small population sample was predictive in a larger population sample.
- Mixed effects PK modelling during non-clinical phase and subsequent interspecies allometric scaling did not adequately predict human pharmacokinetic parameters. The value of using ... prospectively is questionable and should be considered on a case-by-case basis.
- Predictions of IIa were accurate
- A dead mouse killed NNC 61-0029

EMF example 1: chronic disease, CNS

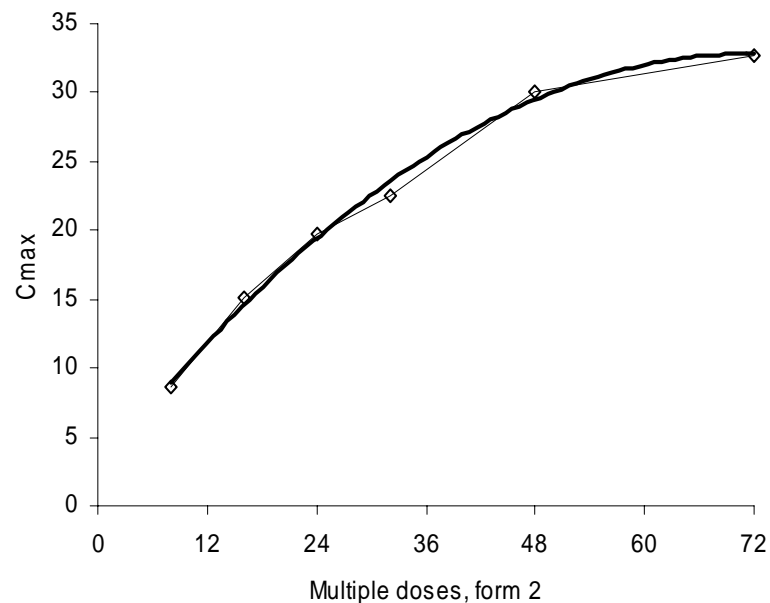
- Healthy subjects

Form 1: SD	0.05 - 21, MD	1 - 12
Form 2: SD	4,	MD 4 - 72

Effect of dose on Cmax & AUC



Effect of dose on Cmaxss



- Phase 2/3

Form 1: MD	1 - 16
Form 2: MD	4 - 32

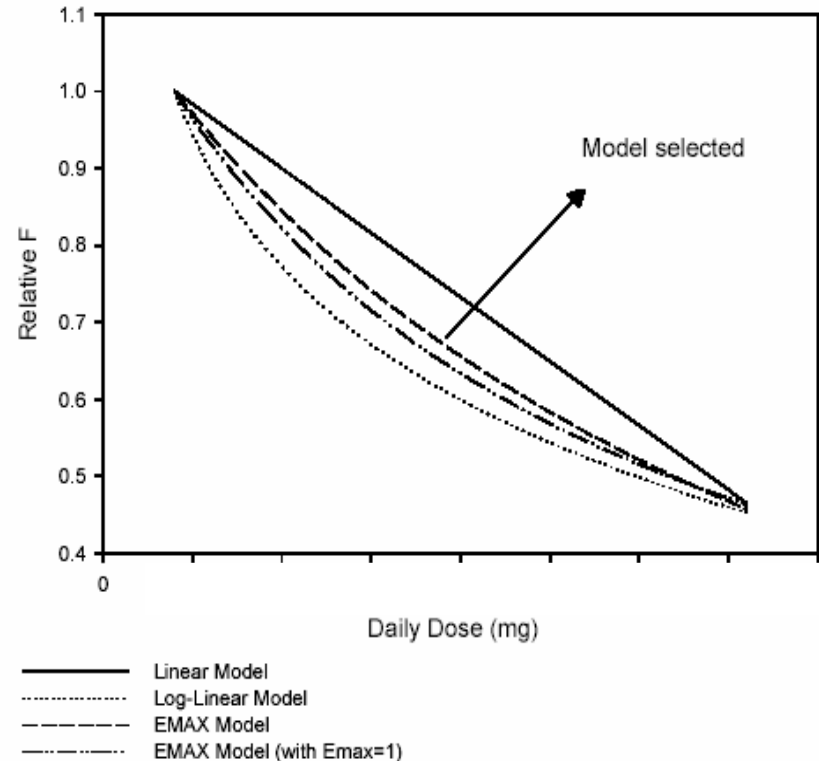
Example 1

- High permeability; very low solubility, depends on particle size
- Bioavailability at SD:
 - ↑ with food,
 - ↑ when particle size ↓,
 - ↑ when body size ↑ (for same dose)
 - ↓ when dose ↑ (for same subject)
- Form 1 & 2 ~ BE at SD 4
- C_{avss} in phase 2a&b, 3:
 - ↑ exposure with form 2 vs. 1, ↓ apparent Cl

PK and ER modelling program

- Model for F_{rel} developed in healthy and patients
- Pooled all patient studies, all forms, all doses, all populations (age 2-80)
- Estimate PK in target population
- Derived exposure at each visit
- Estimate ER relationship for efficacy clinical endpoints
- Safety: exposure in subjects with typical AE vs. subjects without

Effect of total daily dose on relative bioavailability



Results of modelling and net profit

- Differences between HS studies explained by formulations, substance batches (particle size), dose per kg
- Complete bridging between formulations/doses: gap closed
- Complete bridging between populations: adults and children
- Very limited BSV on PK
- Food effect irrelevant during chronic treatment: no dosing recommendation
- Precise estimation of DDIs in target population:
 - effects of each concmed on drug X PK
 - effects of X, demography and other concmeds on usual medications

Results of modelling and net profit(cont)

- Efficacy ER not affected by formulation, study design (for identical endpoint), by concomitant medications
- Differences in response between studies explained by:
 - Relative bio between formulations
 - Baseline disease severity
 - Differences in placebo response between population: children, adolescent and adults
 - Different concomitant medications with period of development, leading to diff drug-drug interactions
- No need for other bridging data between form 1 & 2 (money, exposure of healthy subjects, time)
- ER Model available for line extensions (paediatric formulation)
- ER requirements satisfied (maybe...)

PKPD tools/skills to acquire

- Predictions of absorption, metabolism, disposition from structure and physico-chemical properties: SIMCYP, Gastroplus...
- PK analysis, PKPD, parameter estimation, design ...WinNonlin, Kinetica
- Population PK, PKPD: NONMEM
- Simulations: WinNonlin, WinNonmix, Nonmem, SAS, TS2..
- Databases: clinical data, PK data...

Building the knowledge database with M&S

- Predict human PK:
 - from animal, from drug properties, IVIVC,
 - Microdosing and AMS/PET
- Build model for ER from pre-clinical, animal studies
- Select human dose based on pre-clinical ER and predicted PK
 - Optimise design of FTIM study
- Build PK and ER model with biomarkers from FTIM
 - To design best phase I and phase 2a package using/for modelling and simulation.
- Evaluate ER in target (EOP2a meeting):
 - revise phase II and III program/ label/ product profile