The use of PBPK and PK/PD strategies to aid candidate selection in drug discovery and early development

Dr. Andrés Olivares
DMPK/PD project Leader and Principal translational M&S Scientist
Roche Pharma and Early Developments (pRED), Roche Innovation Center Basel, Switzerland

andres.olivares@roche.com

Roche pRED

Introduction

PBPK in drug discovery and Development

PBPK in Roche's pRED

Case studies

Conclusions

What are PBPK models

Physiological parameters (drug-independent)

Tissue volumes and blood flows

Tissue composition

Intestinal pH, transit times

Enzyme and transporter abundance

Population and external factors to consider

Age, gender, race

Disease status

Genetic status

Smoking/diet

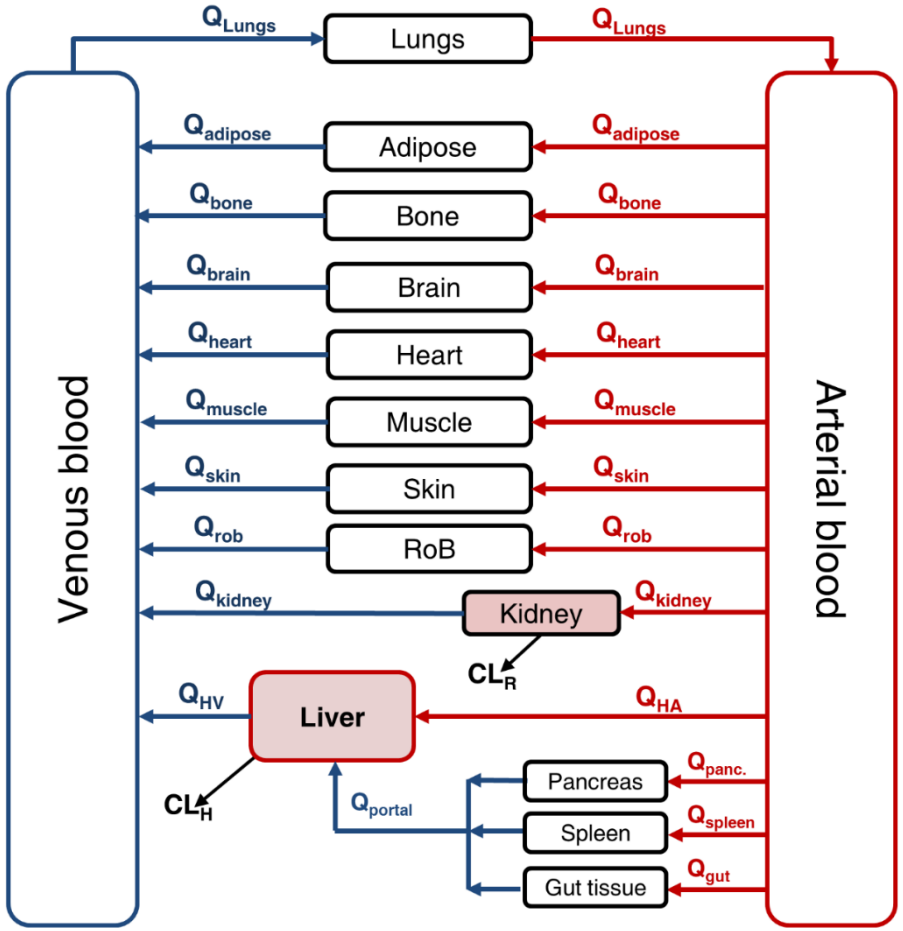
Drug-dependent parameters

LogP, pK_a, B/P, molecular weight

Permeability

Solubility, particle size

CLu_{int}



Introduction

PBPK in drug discovery and Development

PBPK in Roche's pRED

Case studies

Conclusions

Slide courtesy of Yumi Cleary (Clinical Pharmacometrics)

PBPK model applications in drug development

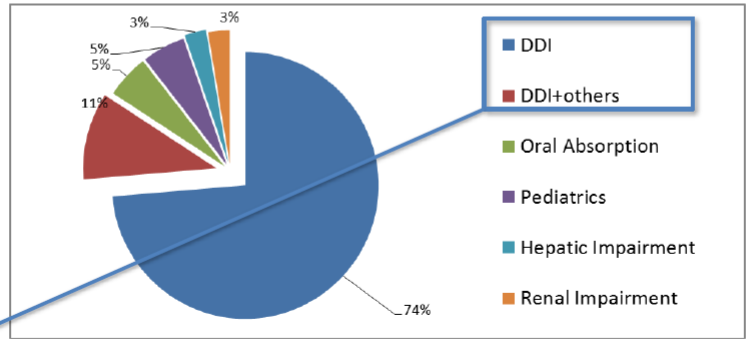
Increased regulatory acceptance over the years

PBPK submissions to the FDA since 2004

As of June, 2014	As of Aug, 2016
n = 96 (60% DDI)	n = 217 (60% DDI)
Sinha, MHRA Workshop, 2014	*Zhao, EMA Workshop, 2016*

DDIs: Drug-drug Interactions

PBPK supporting dosing recommendations in US prescribing information (38 cases 2009-2016)



Greater confidence in predicting DDIs

Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1601, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Office of Clinical Pharmacology, at 301-796-5008 or OCP@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2016
Clinical Pharmacology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 21 July 2016
2 EMA/CHMP/458101/2016
3 Committee for Medicinal Products for Human Use (CHMP)

4 Guideline on the qualification and reporting of
5 physiologically based pharmacokinetic (PBPK) modelling
6 and simulation
7

Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

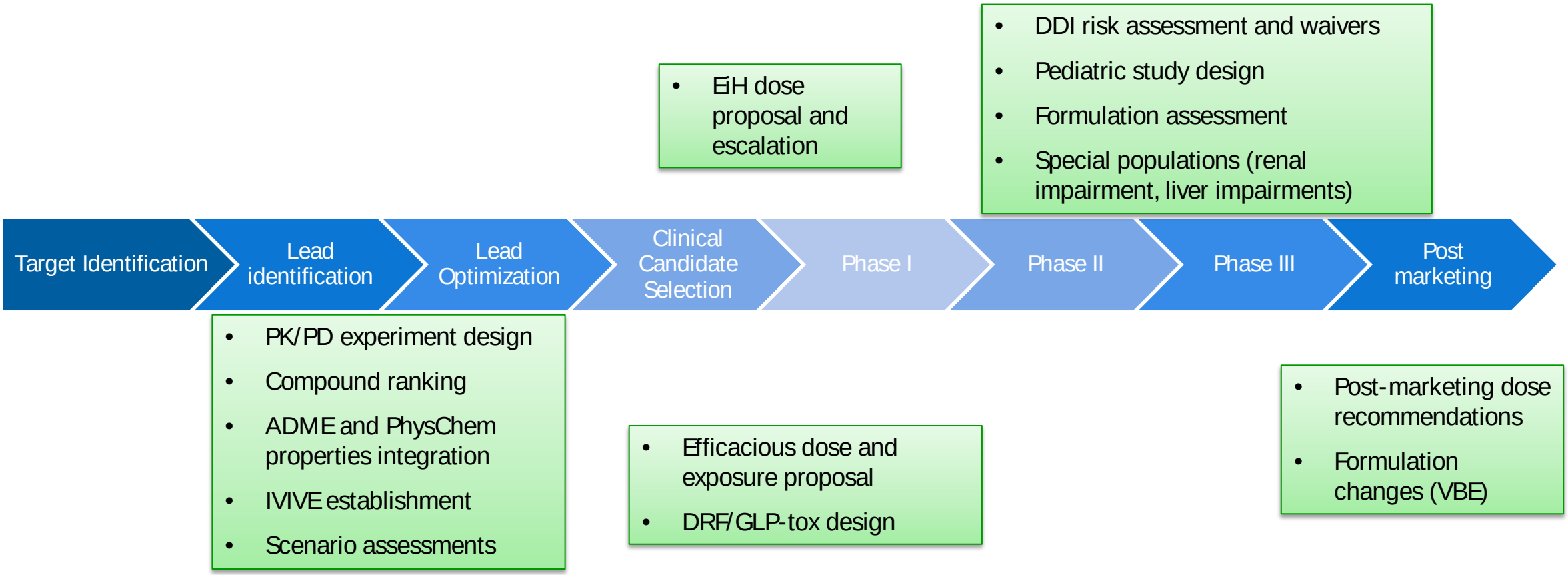
For questions regarding this draft document, contact (CDER) Office of Clinical Pharmacology Guidance and Policy Team at CDER_OCP_GPT@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2017
Clinical Pharmacology

PBPK/PD in drug development

The applications span from early discovery to late development



Introduction

PBPK in drug discovery and Development

PBPK in Roche's pRED

Case studies

Conclusions

Roche has a long history of applying PBPK modelling

Early adaptation and validation in projects

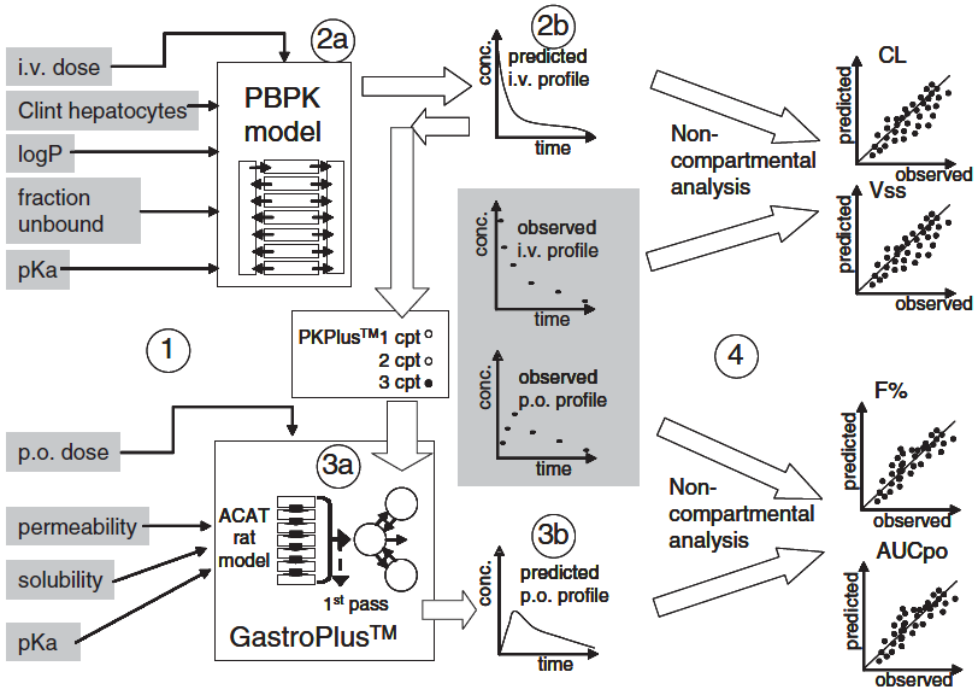


Figure 1. Steps taken in this evaluation.

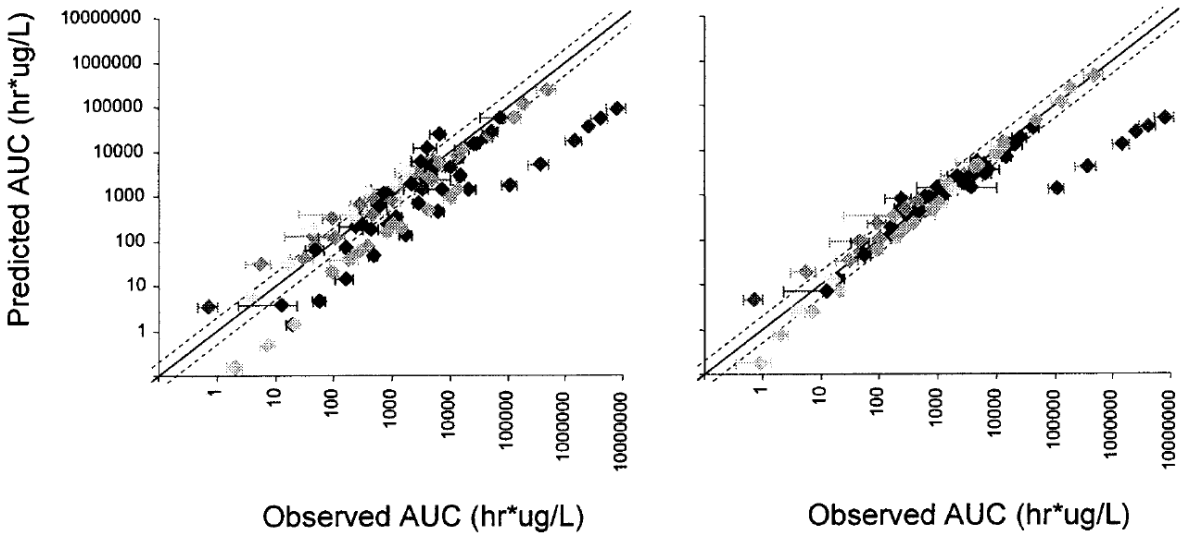


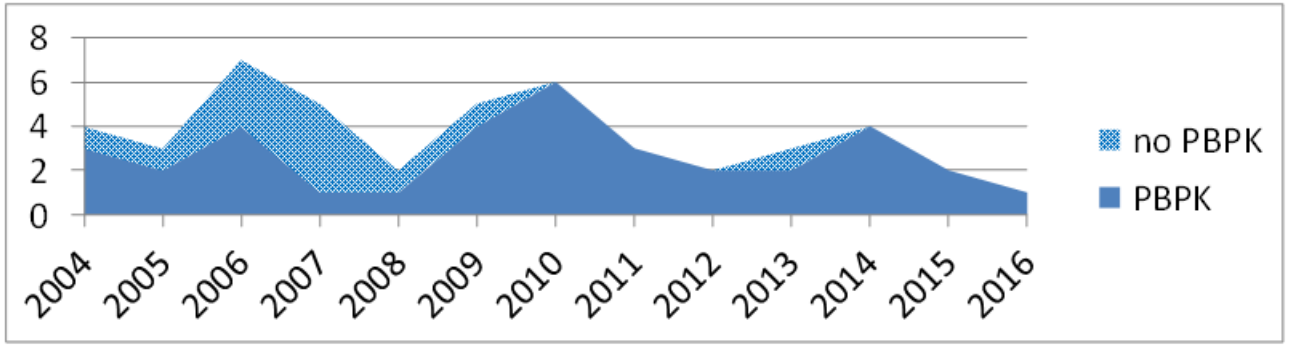
Fig. 3. Predicted versus observed AUC for 19 Roche compounds using the elementary Dedrick approach (left with 42% predictions within 2-fold of observed) and the physiologically based approach (right with 76% predictions within 2-fold of observed). Symbols with the same shade indicate different doses of the same compound.

Parrott et al. J Pharm Sci (2005); Parrot et al. Basic & Clinical Pharmacology and Toxicology (2005)

Slide courtesy of Neil Parrott (M&S)

Roche has a long history of applying PBPK modelling

Successful prediction of EiH doses and exposures



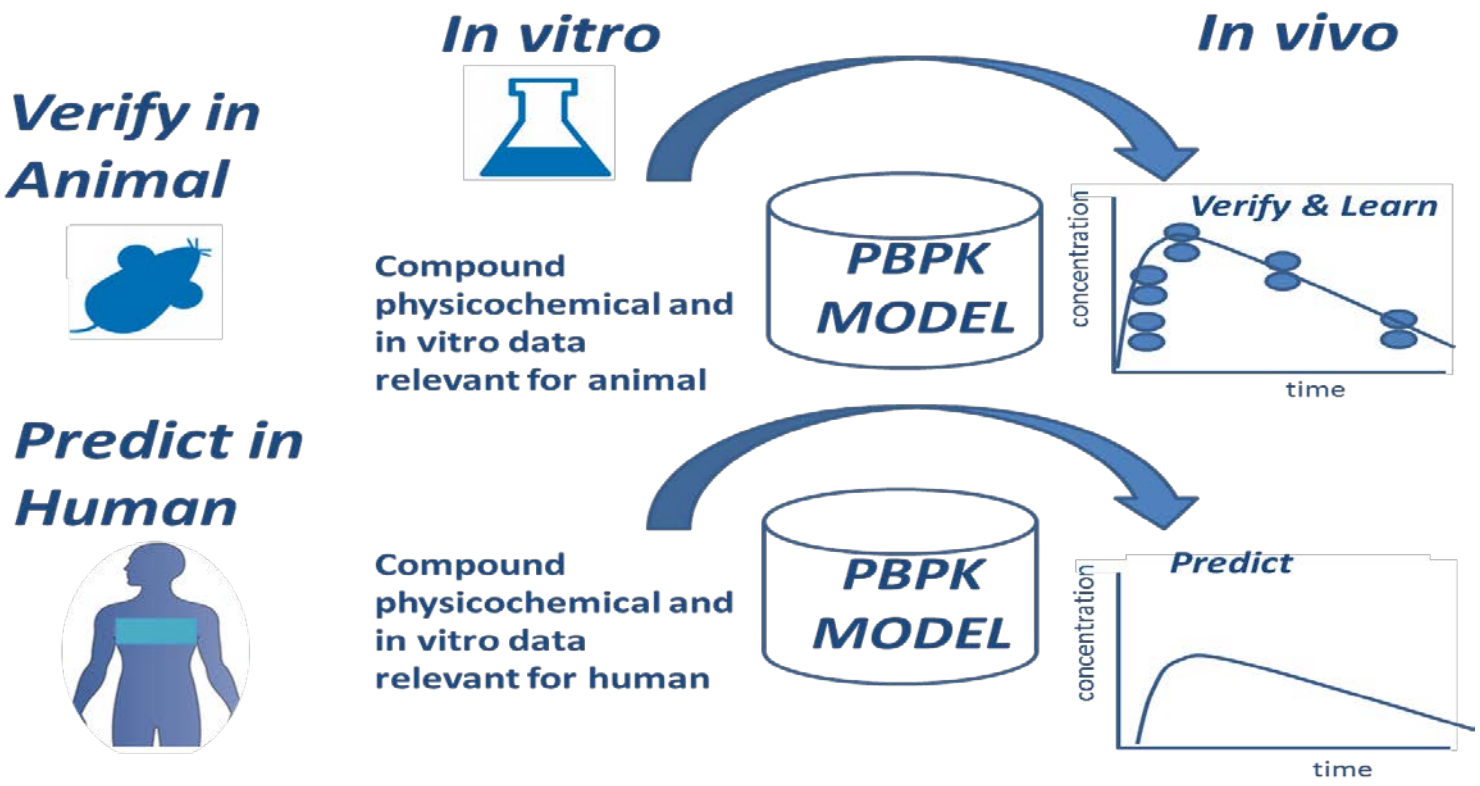
Since 2010, systematic use of PBPK predictions at EiH

N=33
Ave. fold error 2.1
69% within 2-fold

Parrott N, Delporte M, Lave T, Peck R and Ricci B. CPT (2017) (Abstract PII-109)

Roche's pRED PBPK strategy

A continuous learn and confirm approach



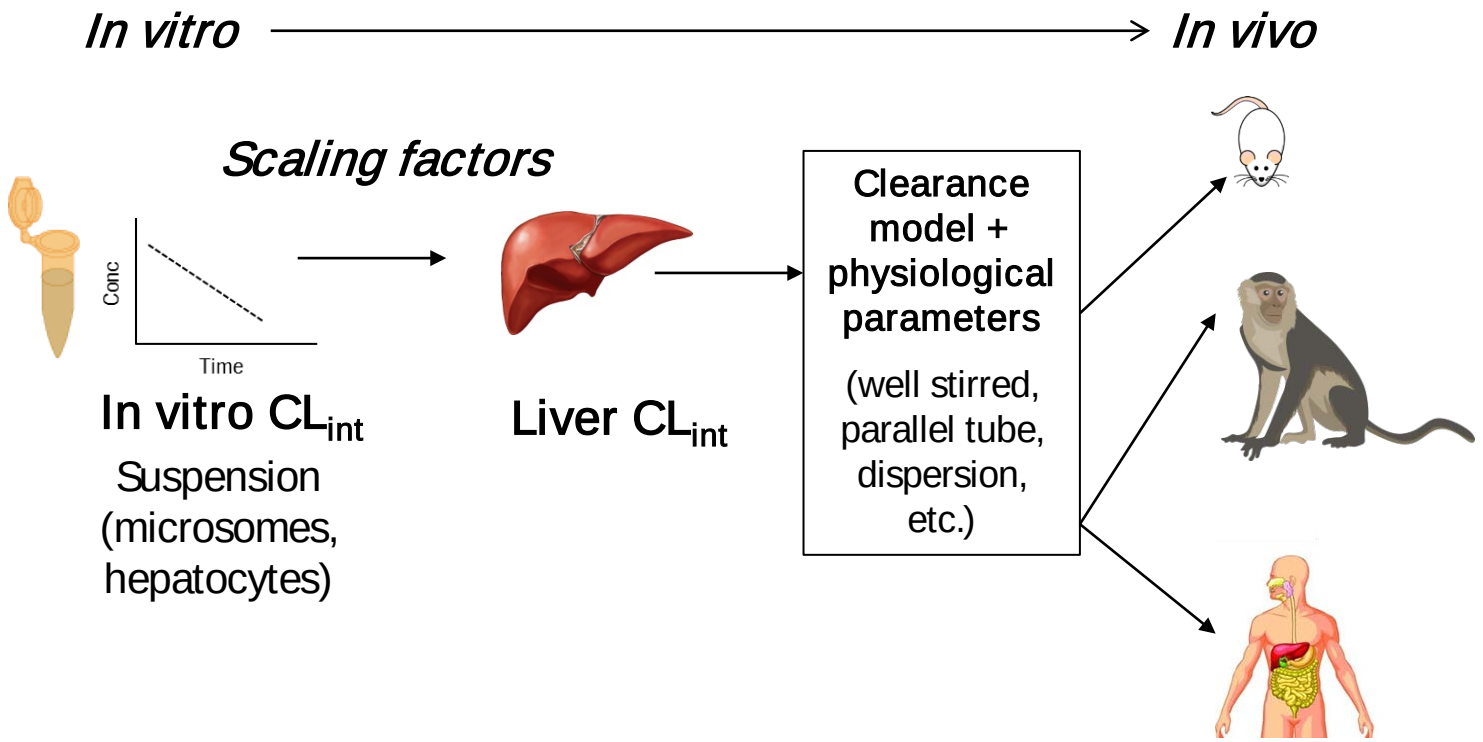
Overarching goal is to predict therapeutic window in humans as a function of dose using a PBPK/PD approach

Jones, H., N. Parrott, et al. Clinical Pharmacokinetics, 2006. 45(5): p. 511-542.; Jones, H. M., I. B. Gardner, et al. (2011). Clinical Pharmacokinetics 50(5): 331-347

Focus on in vitro systems: Metabolic clearance

Monitoring IVIVE is key for SM optimization and human dose predictions

What is IVIVE?



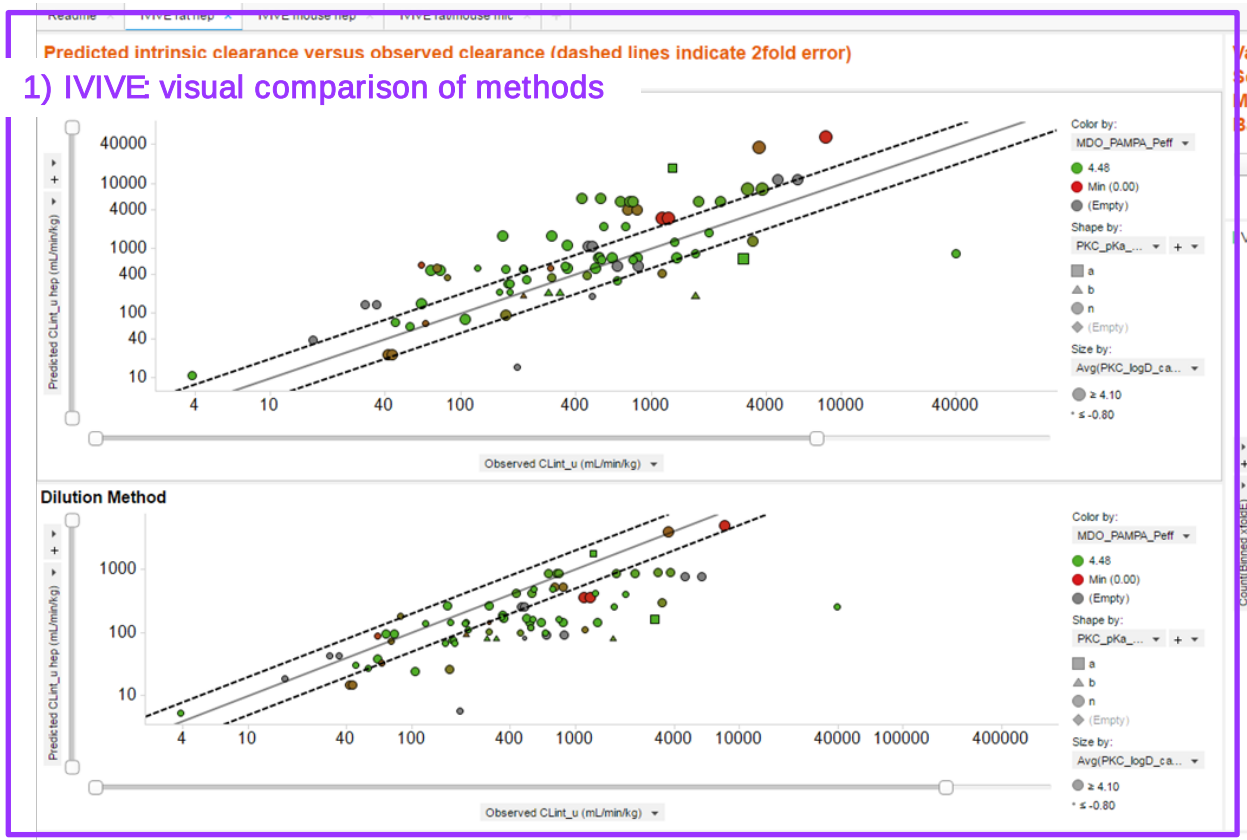
Why monitoring the IVIVE is important for project teams?

- ✓ Help project teams optimize series with regards to ADME properties
- ✓ Increase confidence on in vitro predictions, reduce SDPK measurements. 3Rs
- ✓ Help to understand the factors that are relevant for clearance predictions (logD, fup)
- ✓ Understanding the hepatic contribution to clearance
- ✓ Human dose predictions, understand limitations and methods that give better results in vitro

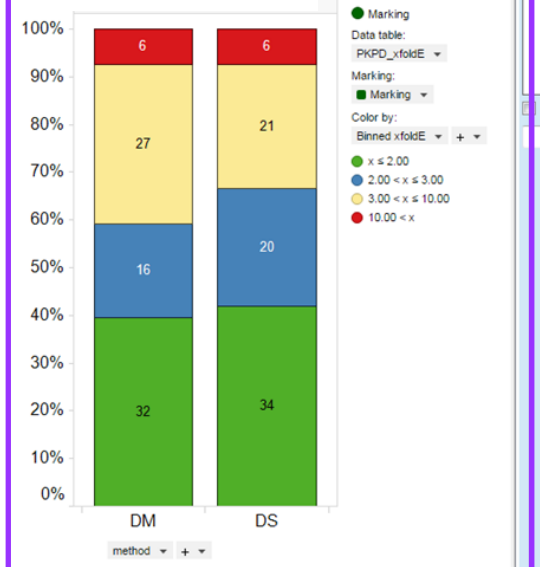
Focus on in vitro systems: Metabolic clearance

Automatic data integration and analysis of in vitro predictions

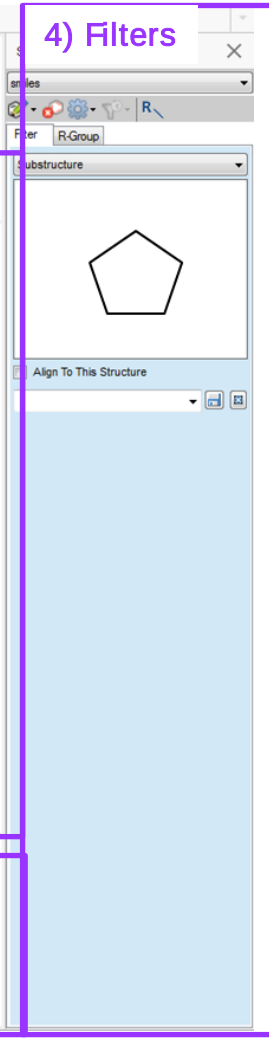
1) IVIVE: visual comparison of methods



3) Error metrics (% within x-fold)



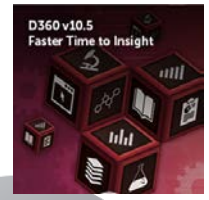
4) Filters



2) Quantitative predictions, data used for predictions

DM rat mL/min/kg	CLp hep scaled DS hum mL/min/kg	CLp hep scaled DS rat mL/min/kg	fup rat (measured)	BPratio rat (meas and calc)
22.98	7.13	56.93	29.00	10.81
22.98	7.13	56.93	29.00	10.81
12.60	4.04	0.87	3.85	5.37	30.12	1.00	1.00
12.60	4.94	0.87	3.85	5.37	30.12	1.00	1.00
41.00	14.82		15.35		45.98	0.53	1.00
23.28	59.34	0.49	22.14	5.15	39.04	13.60	1.00
23.28	47.70	0.49	22.14	5.15	39.04	13.60	1.00
23.00	26.44	0.74	20.52	3.94	38.87	22.23	1.00

TIBCO Spotfire



Introduction

PBPK in drug discovery and Development

PBPK in Roche's pRED

Case studies

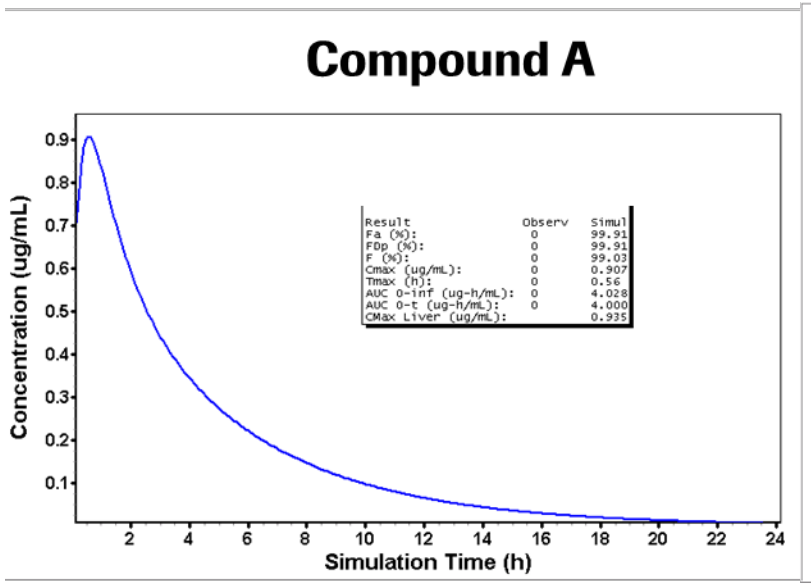
Conclusions

Case study 1
Compound prioritization using PBPK
PBPK modelling allows ADME data integration

Can we propose doses based on in vitro data only?

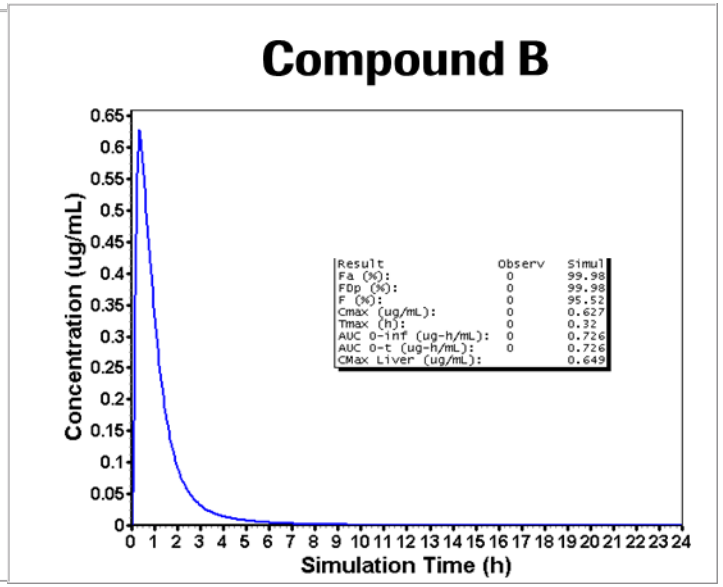
Data availability

Compound A



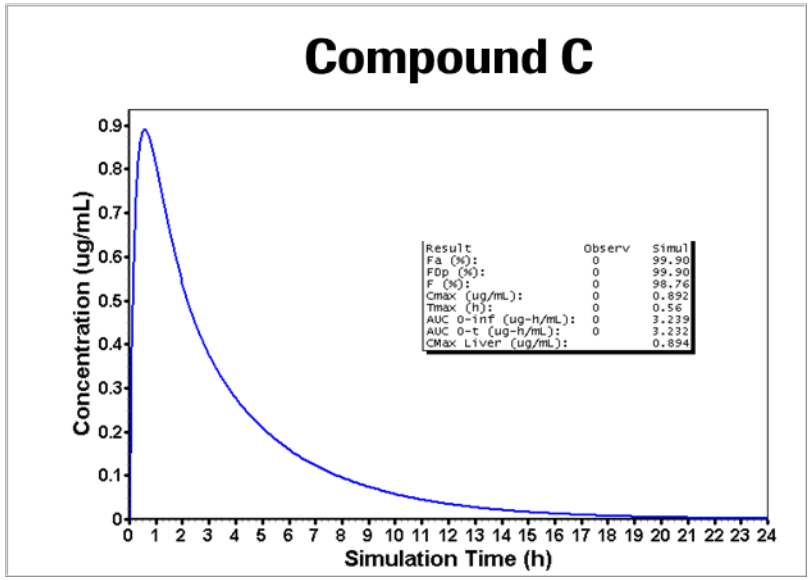
Only preliminary in vitro data

Compound B



All in vitro data, no SDPK

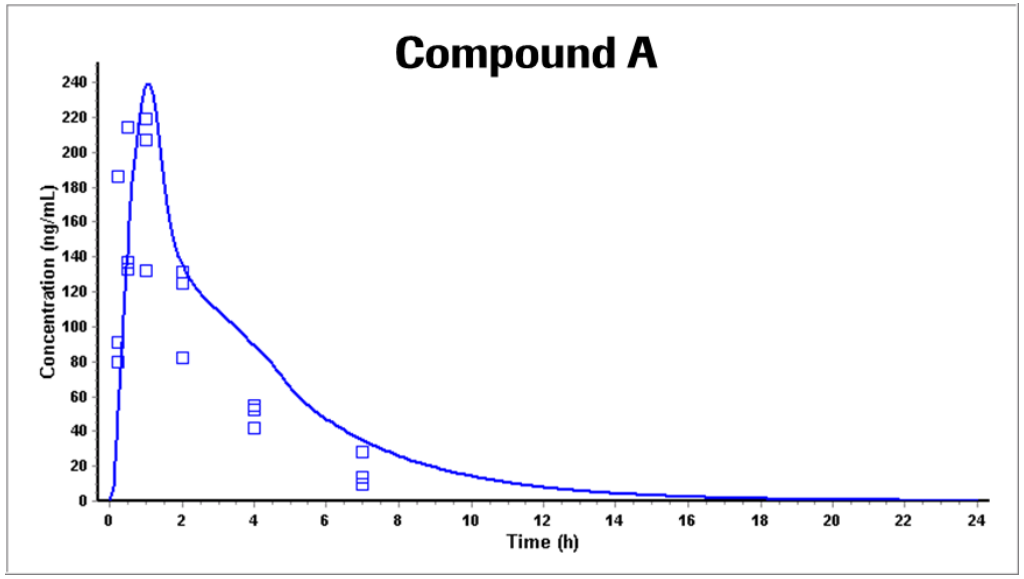
Compound C

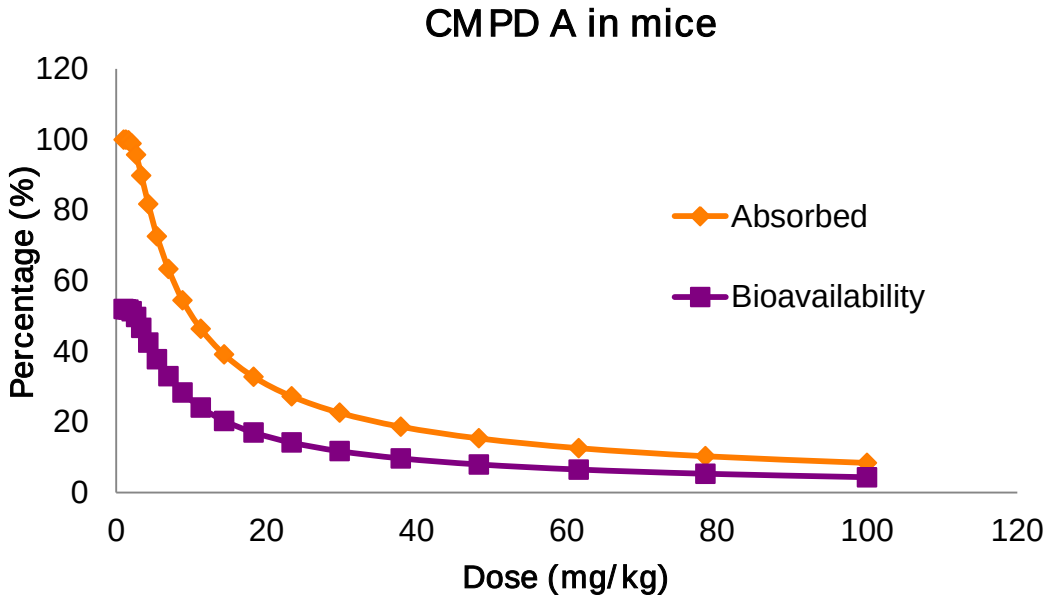


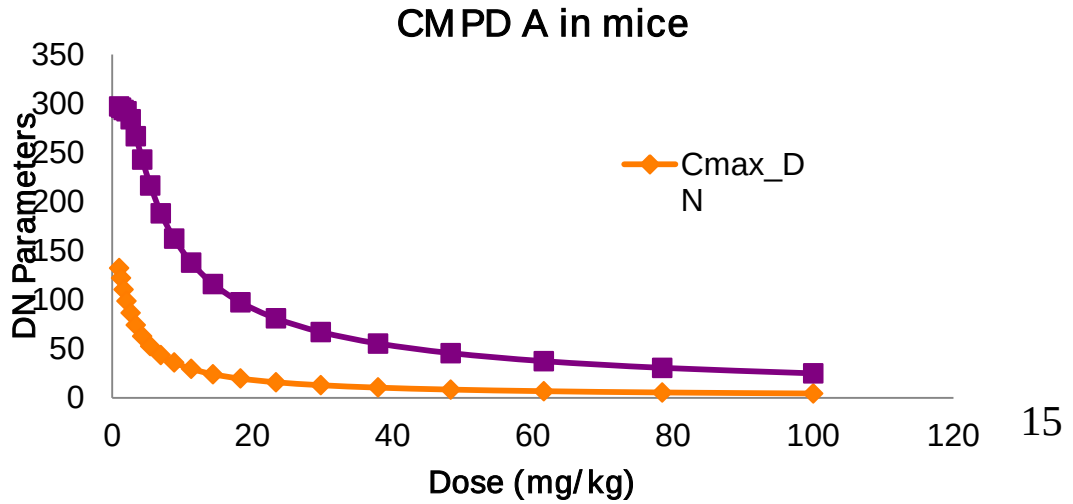
All data available, simulations are within 2 fold of expected

Case study 1
Dose optimization for PK/PD experiments
PBPK helps to illustrate possible non-linearities and select maximal doses

- Model developed with GastroPlus
- PK in mouse is well predicted by the model (Mechanistic)
- The compound is solubility limited
- Maximum doses established for PK/PD experiments

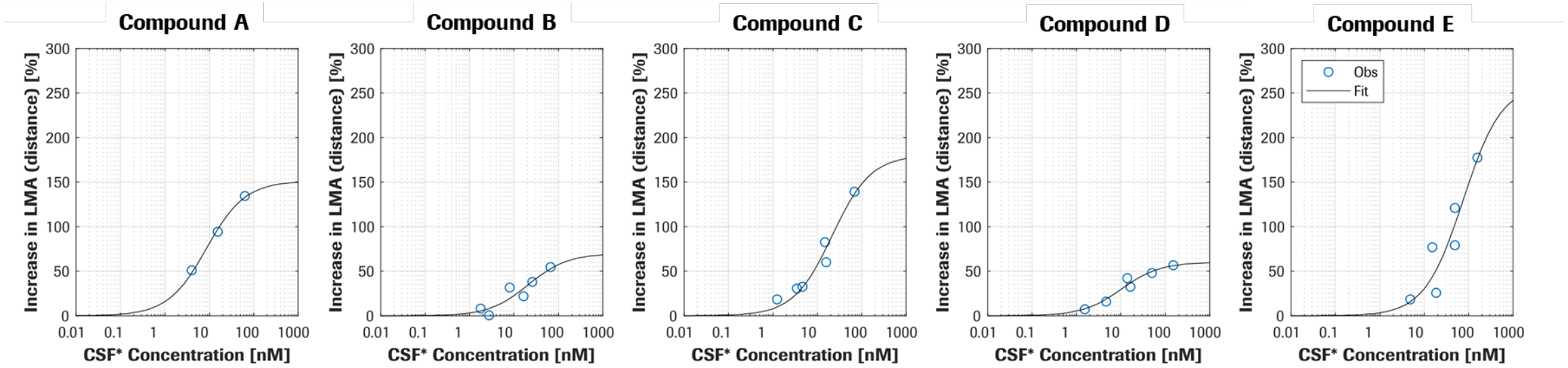




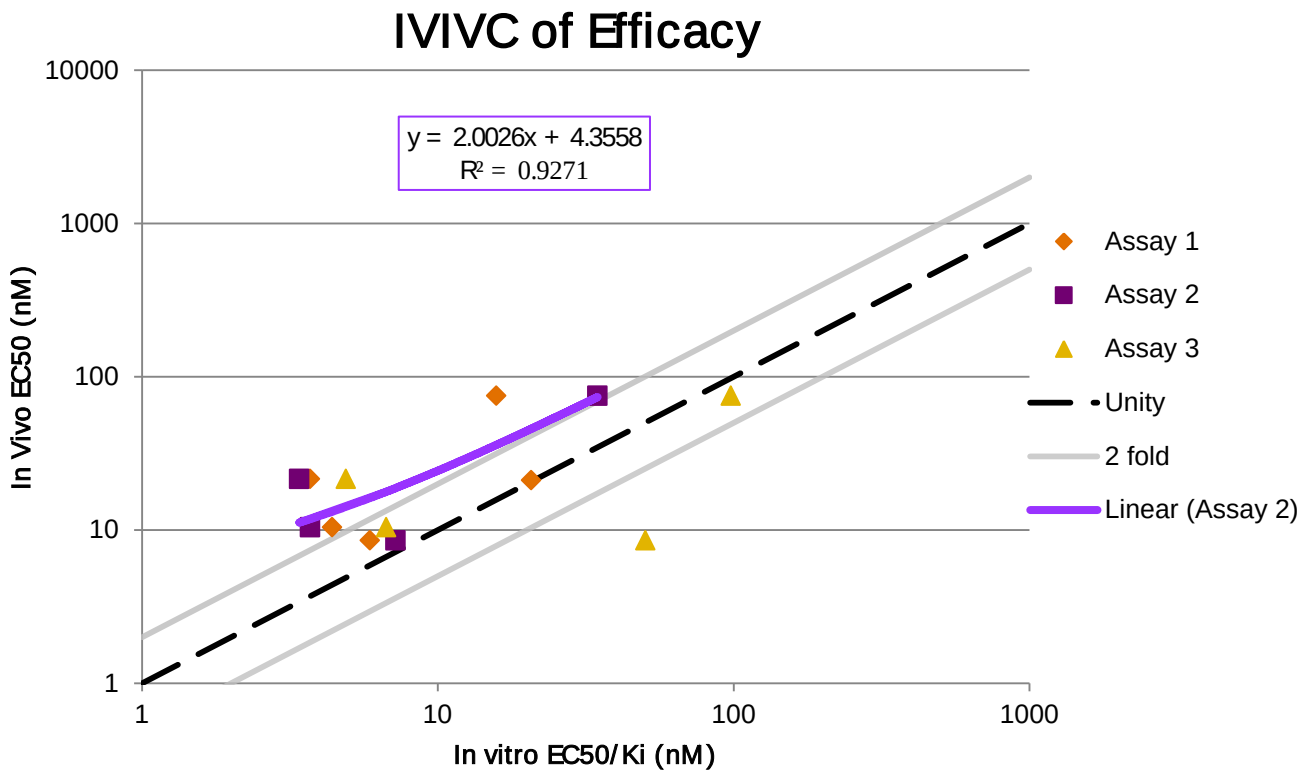


Case study 2
Systematic PK/PD to increase confidence in target and assays
Guide compound selection using early PK/PD approaches

- Neuroscience project
  Question:
- What is the in vitro assay (binding) that can be linked to the in vivo observed effects?
- Can we stablish an IVIVC for potency to minimize the animal experimentation (3Rs)?



Case study 2
Systematic PK/PD to increase confidence in target and assays
An IVIVC for potency was established



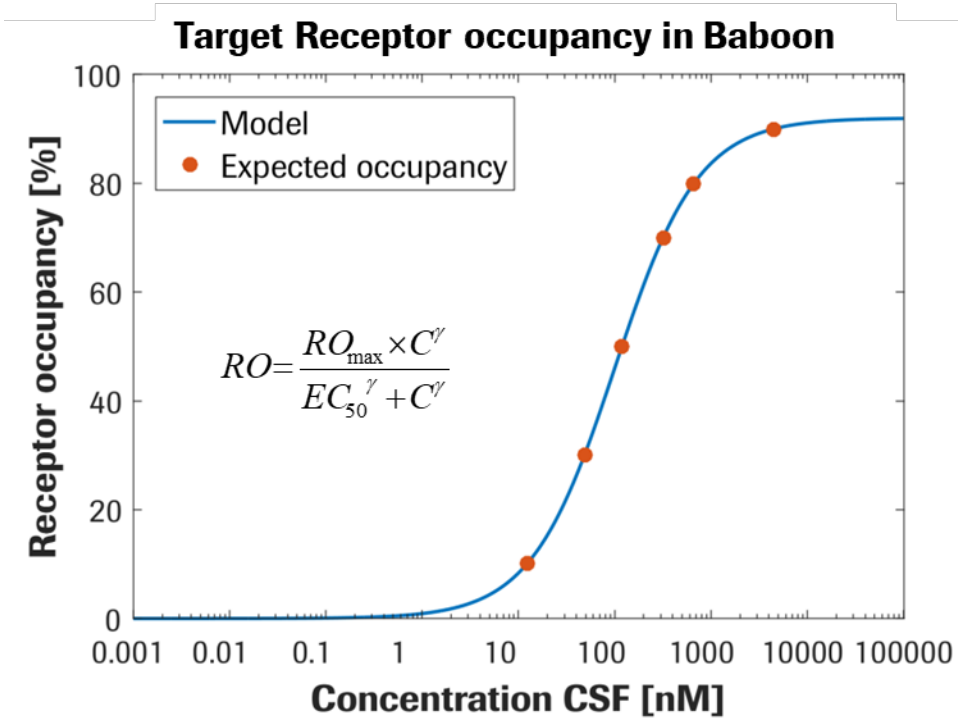
Outcome:

- Potency measured in **Assay 2** was correlated with in vivo potency
- Stopped in vivo activities and only profile and select compounds based on **Assay 2**
- **Reduced number of in vivo studies (3Rs)**

Despite limited number of compounds, Assay 2 is a better predictor of the in vivo efficacy

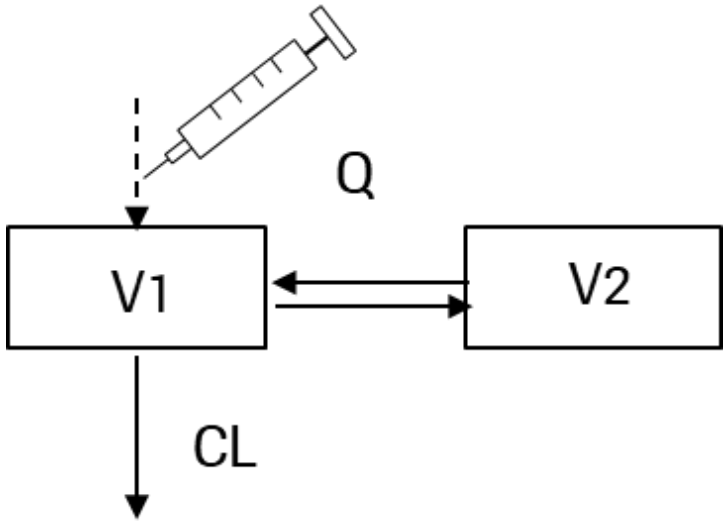
Case study 3
Designing informative PK/PD experiments
Receptor occupancy study in large primate species

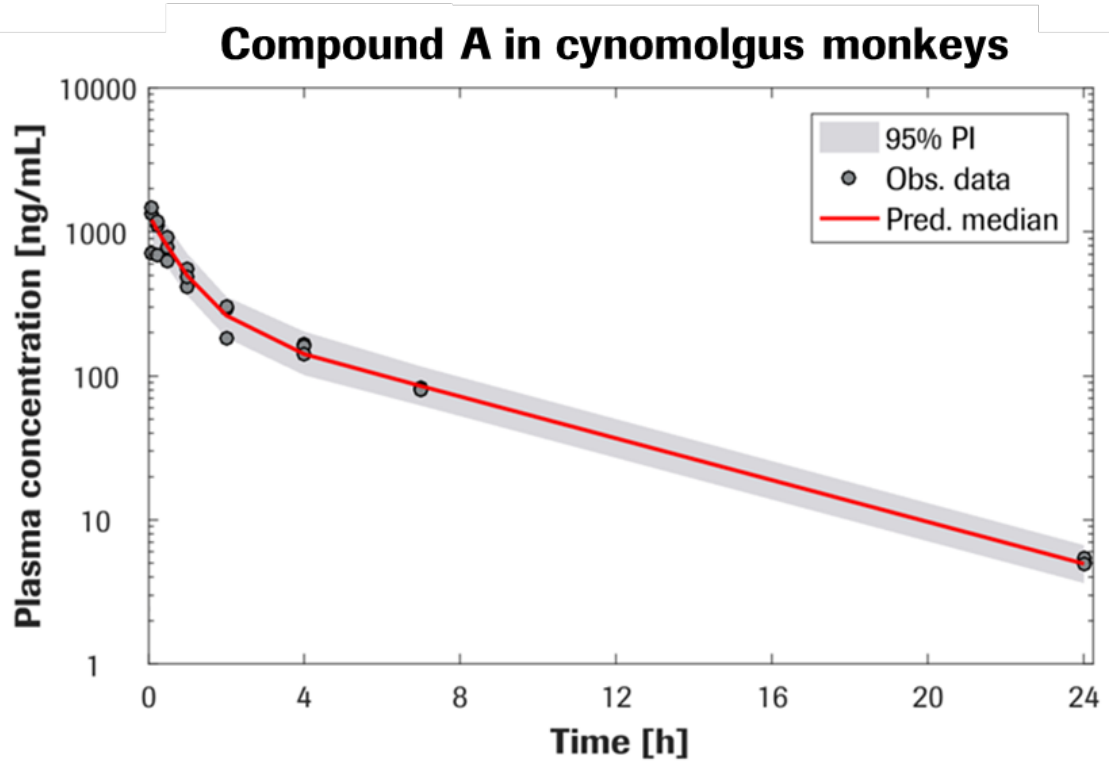
- In **project B** there was a disconnection between in vitro and in vivo target engagement measurements (receptor occupancy) in rodents
- Baboon PET occupancy studies have shown to be predictive of human receptor occupancy
- Project timelines were very stretch
- How can we design an informative, quick and lean receptor occupancy study in Baboons
  - ✓ **Requirements:**
    - ✓ IV infusion
    - ✓ Concentration had to be maintained at steady state for 1.5 h (PET Scan)
    - ✓ Infusion volume is restricted, and the compound has solubility limitations



Case study 3
Designing informative PK/PD experiments
Step 1: Use existing data to generate a PK model

In-house SDPK data in Cyno after IV data can be described by a two-compartment model.

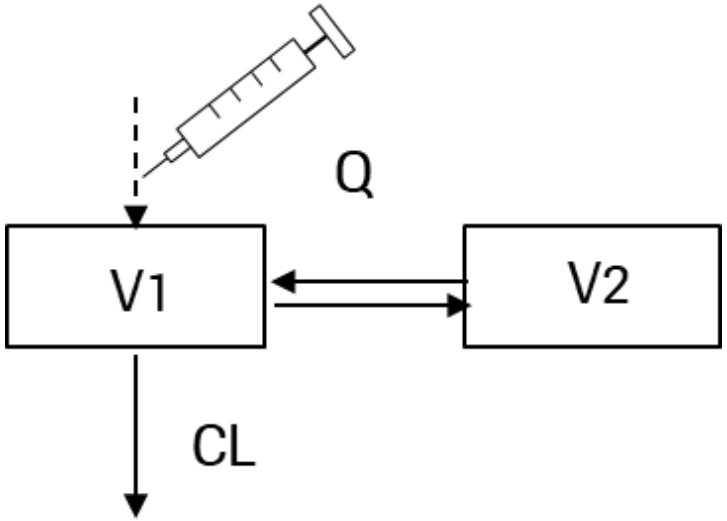


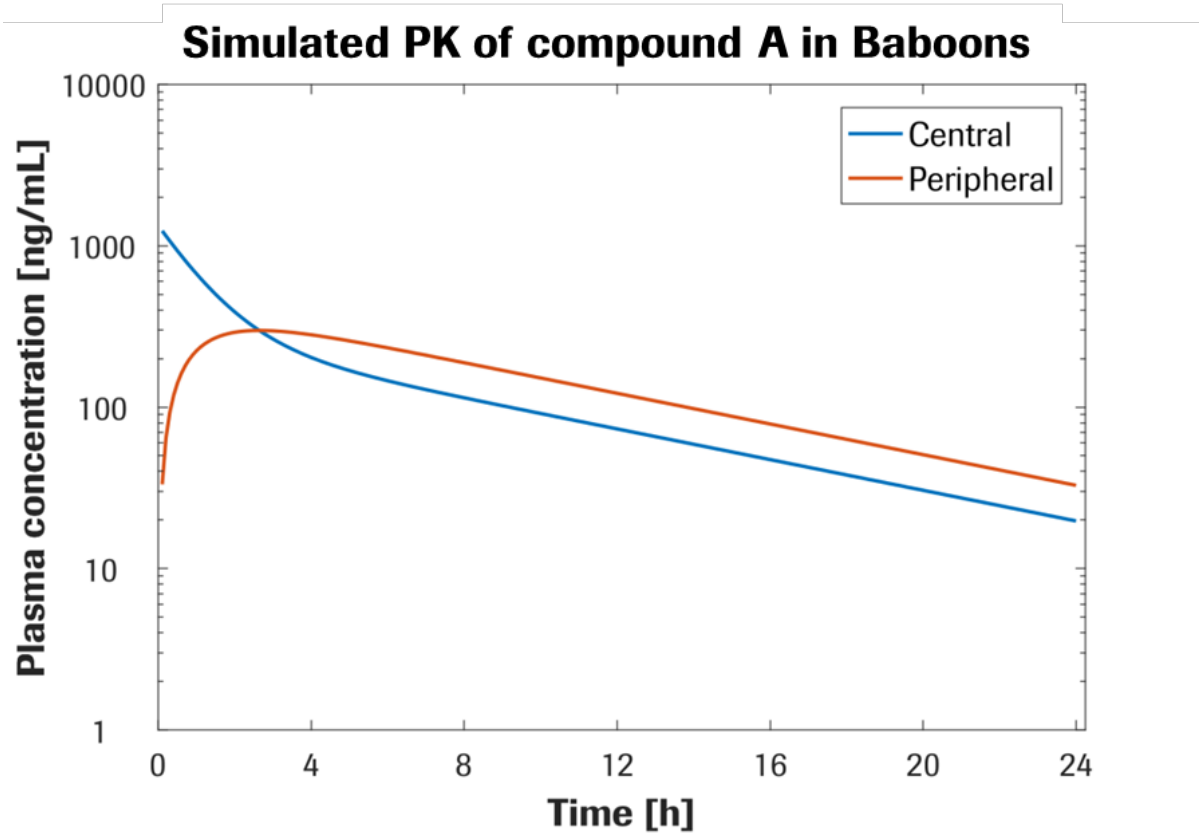


*For a standard 5 kg Cynomolgus monkey.

Case study 3
Designing informative PK/PD experiments
Step 2: Adapt the model to a Baboon using allometric scaling

In-house SDPK data in Cyno after IV data can be described by a two-compartment model.





For a standard 27 kg Baboon.

Case study 3
Designing informative PK/PD experiments
Step 3: Model based experimental design

Required study design:

Two infusions, loading and maintenance:

1. Loading infusion lasting around **45 min**
2. Maintenance infusion of **90 min** (PET scan)

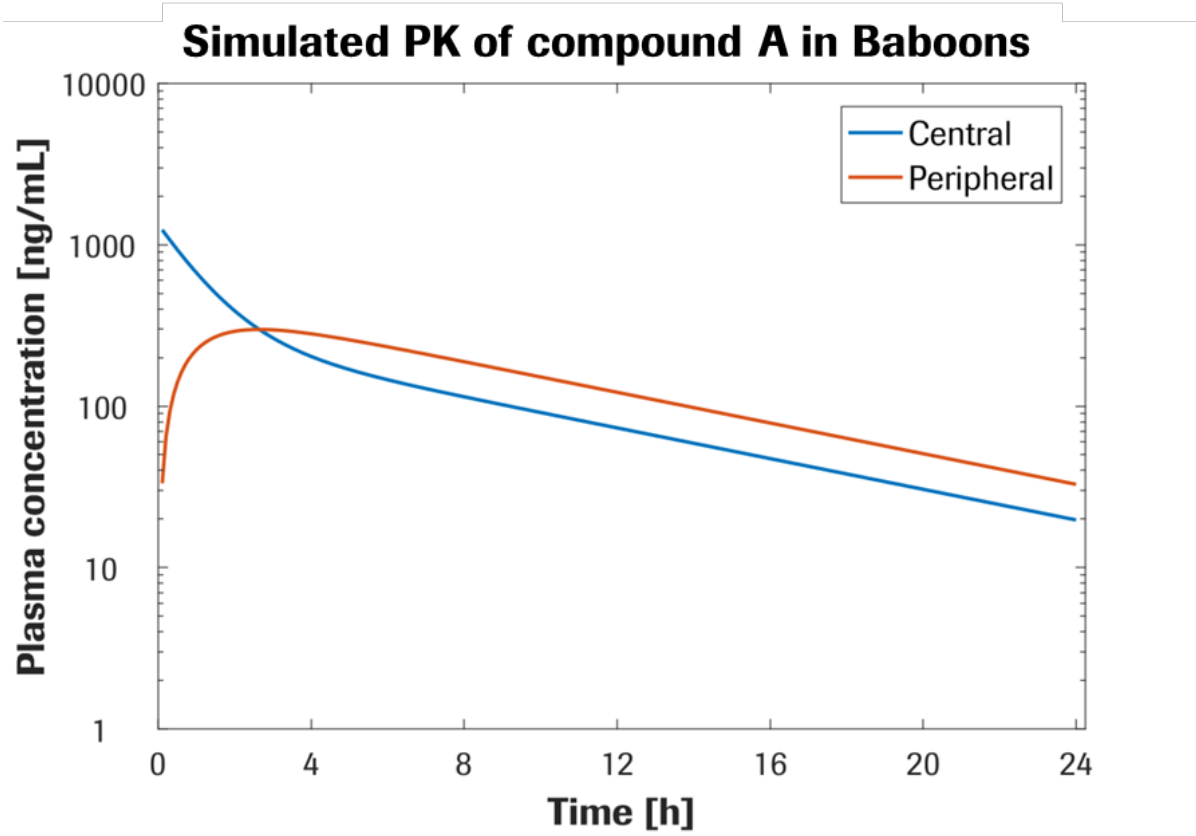
Total experiment time ca. **2.5 hours**

Design for a one compartment model:

Loading dose (mg) = Target concentration*Vss

Rate of infusion (mg/h) = Target concentration*CL

This applies for a two compartment model as long as the equilibration between compartments is relatively fast (i.e., Q >> CL)



Case study 3
Designing informative PK/PD experiments
Step 3: Model based experimental design

Required study design:

Two infusions, loading and maintenance:

1. Loading infusion lasting around **45 min**
2. Maintenance infusion of **90 min** (PET scan)

Total experiment time ca. **2.5 hours**

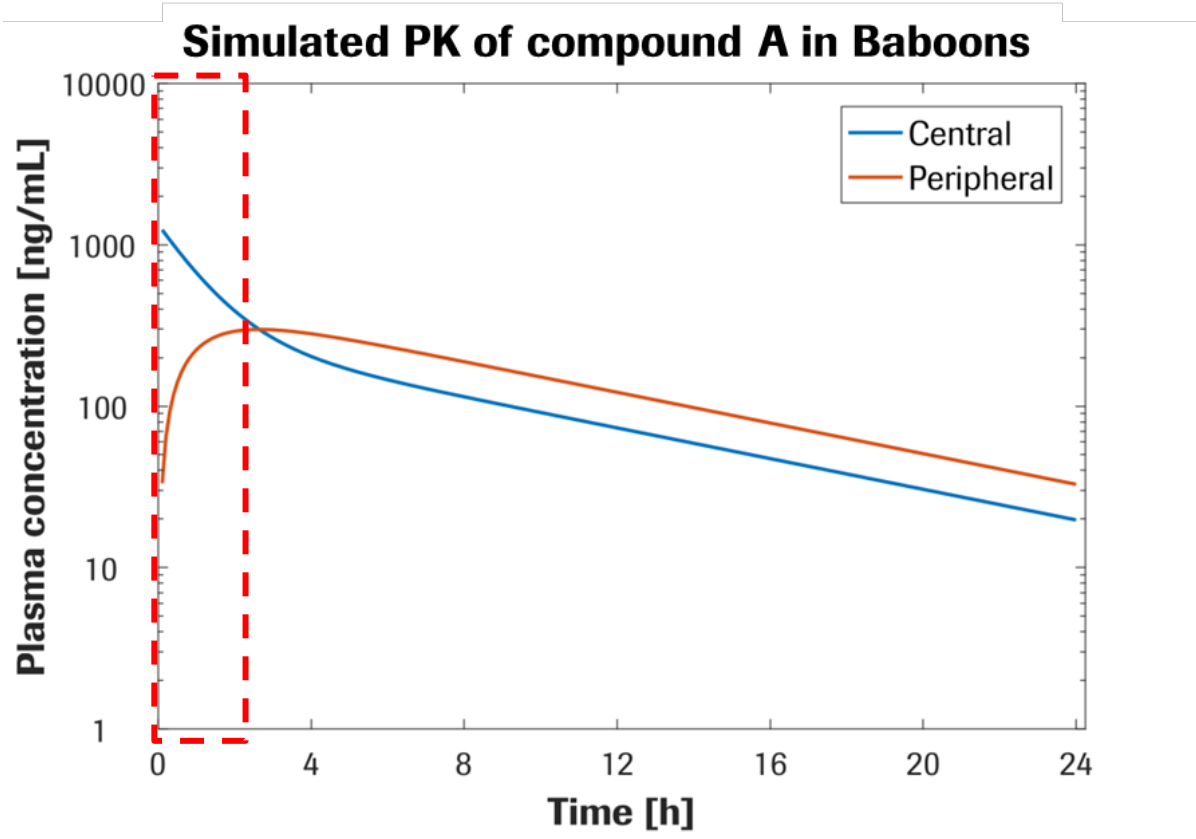
Design for a one compartment model:

Loading dose (mg) = Target concentration*Vss

Rate of infusion (mg/h) = Target concentration*CL

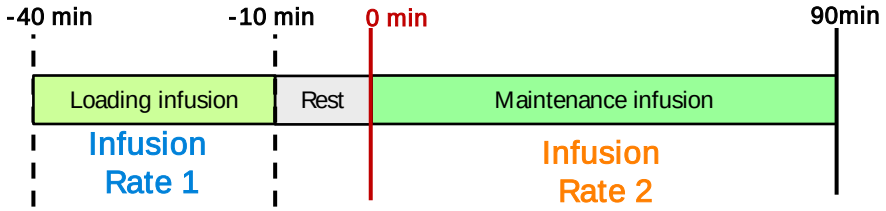
This applies for a two compartment model as long as the equilibration between compartments is relatively fast (i.e., Q >> CL)

However this is not our case as the equilibration time is similar to the time required for the experiment (ca. 2.5 h).



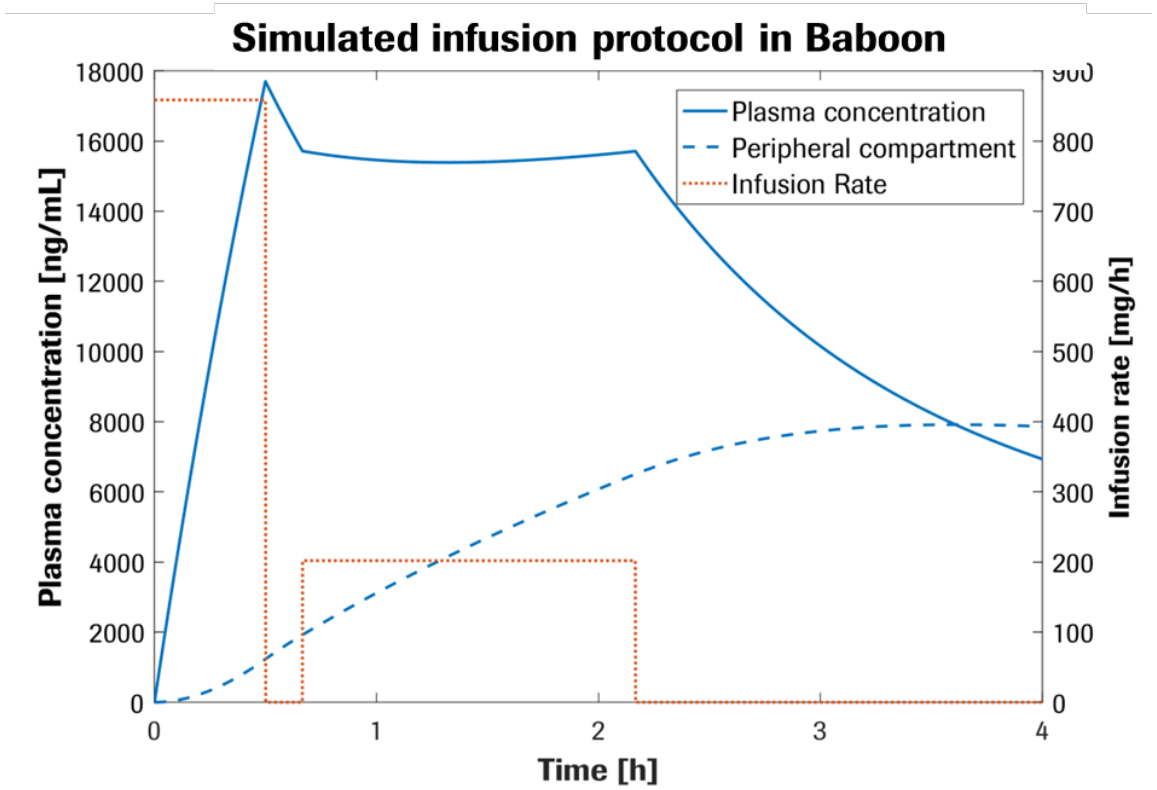
Case study 3
Designing informative PK/PD experiments
Step 4: Experimental design proposal based on optimization

Proposed study design



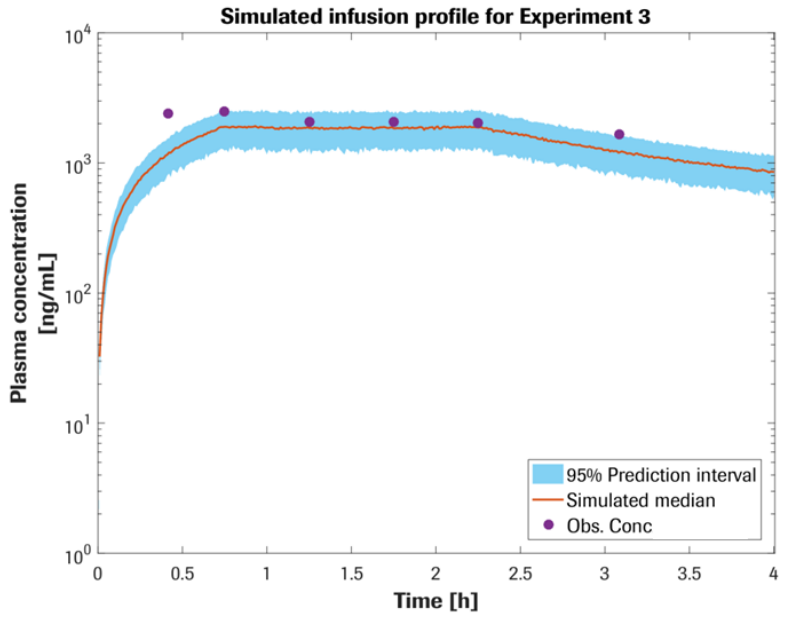
RO [%]	Target plasma conc. [ng/mL]
10	Conc. A
30	Conc .B
50	Conc. C
70	Conc. D
80	Conc. E
90	16,000

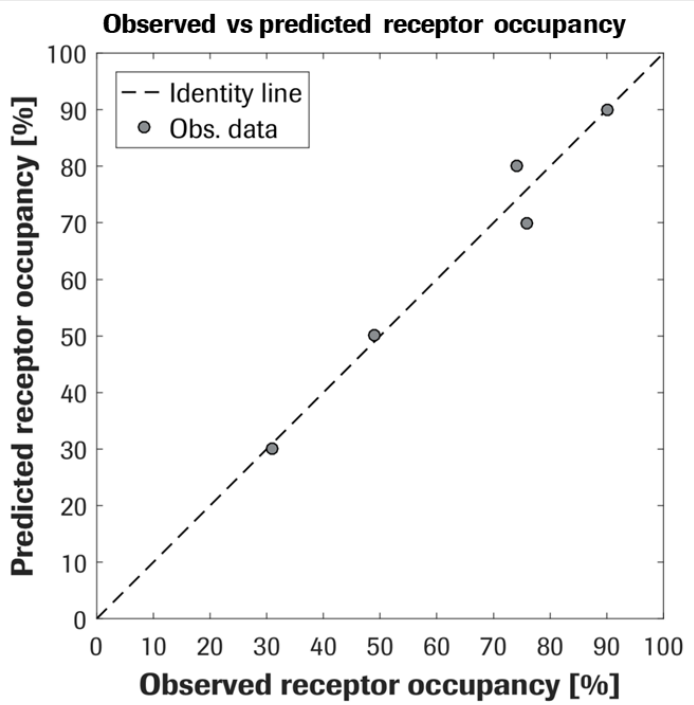
Optimization of the design was done in Matlab using a minimization algorithm to the required target concentration levels



Case study 3
Designing informative PK/PD experiments
Model evaluation and outcomes

- Model predictions were in line with observations (concentration and occupancy)
- Optimized design was highly informative: no need for additional dose levels or repeating dose levels (3Rs)
- Emax and EC50 precisely estimated with only 5 doses levels.
- Time savings of 3-4 weeks
- Higher confidence in project team due to refined potency for the compound in Baboons (higher than in rodents)
- Increase confidence in project team towards the use of M&S approaches





Case study 4
Designing informative GLP-tox experiments with PBPK
Optimizing doses to achieve expected exposure multiples

- In **project C** minipigs were used as relevant tox species
- DRF studies tested doses up to 450 mg/kg obtaining good exposure multiples
- For the GLP-tox study the API supply was limited and in critical path, potentially delaying Ei-GLP tox if high dose in the DRF was maintained
- From DFR (chronic) and MTD (single dose) studies it was observed that the PK in minipigs likely non-linear due to absorption limitations at higher doses levels
- **Use PBPK modelling to evaluate the impact of dose in the expected exposure multiples**

Case study 4
Designing informative GLP-tox experiments
PBPK modelling approach in minipigs

Two step model development:

Step1

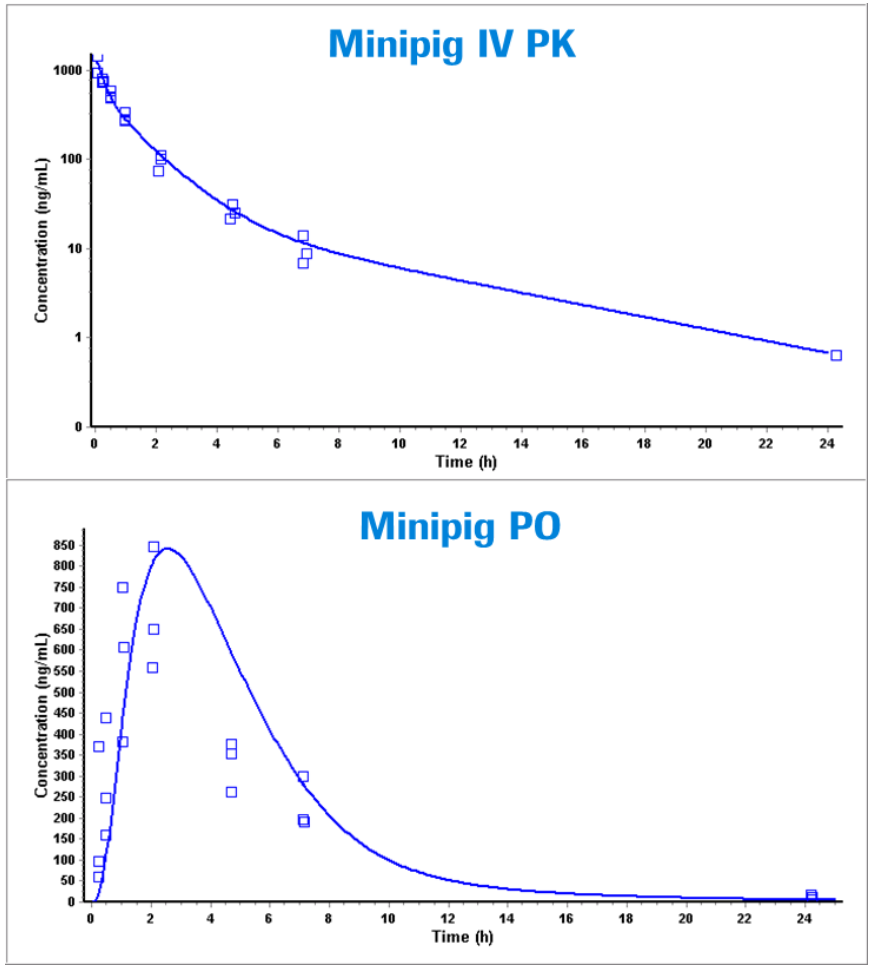
- IV data was used to define drug disposition (compartmental)

Step 2

- Absorption model predicted with GastroPlus (ACAT) mechanistically
- Certain parameters were optimized to match observations (precipitation time)

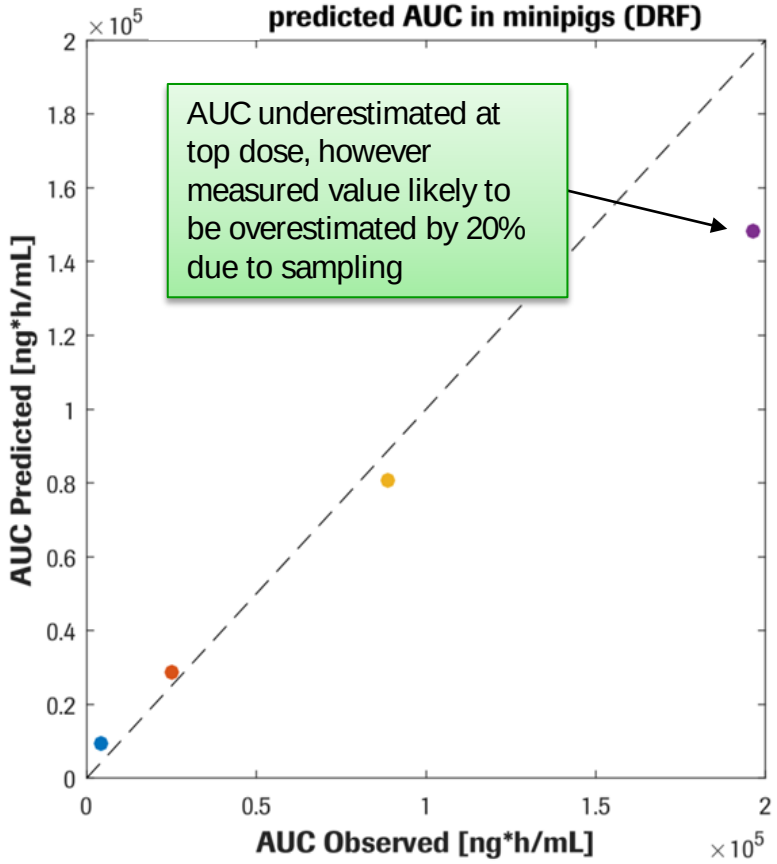
Step 3

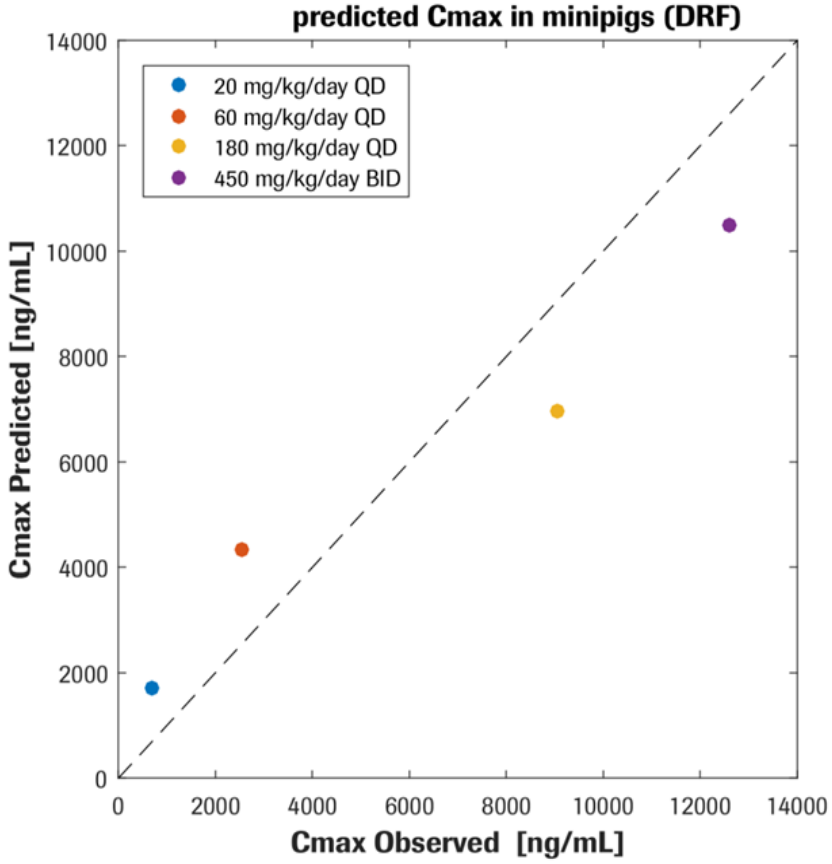
- Model prediction were contrasted with observations of DRF and MTD studies



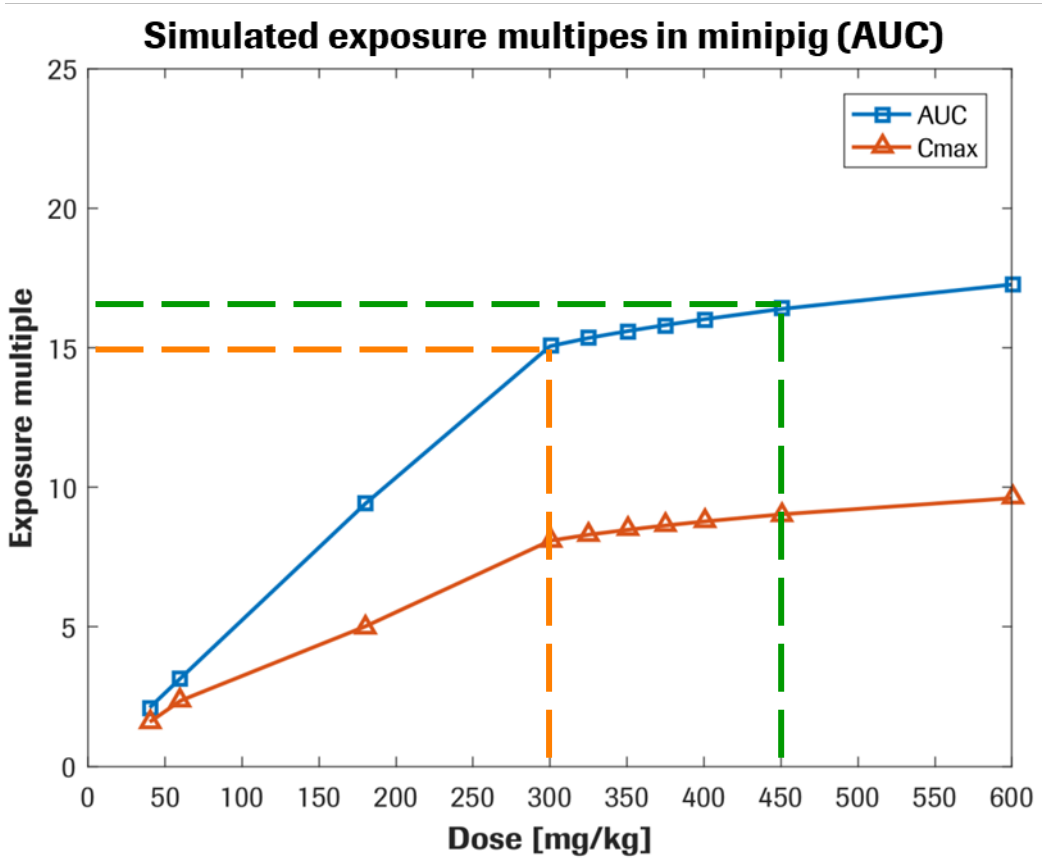
Case study 4
Designing informative GLP-tox experiments
Model validation with DRF data

The model captures the non-linearities in exposure very well and can be use to prospectively predict exposures and different dose levels





Case study 4
Designing informative GLP-tox experiments
GLP-tox dose proposal based on PBPK model sensitivity analysis



Outcome

- Model-based sensitivity analysis suggested a lower dose (300 mg/kg) could be used for the GLP-tox achieving similar exposure multiples as the 450 mg/kg dose
- API requirements were reduced by **ca. 25%** and API supply was sufficient for start of the GLP-tox study in time.
- Timely Ei-GLP tox with proposed doses and no delays in project timelines (in fact, the project progressed 2 months ahead of time)
- The exposure multiples obtained during the GLP-tox were in line with expectations

Introduction

PBPK in drug discovery and Development

PBPK in Roche's pRED

Case studies

Conclusions

Conclusions

- The use PK/PD approaches in discovery and early development adds value to the project teams and help to answer key questions
- Systematic PK/PD strategies help to gain target and assay confidence and guide compound selection by stablishing early IVIVCs
- PBPK modelling is a powerful tool in drug development and discovery, it allows data integration and scenario exploration.
- Modeling needs to be applied to answer the right questions, there is a significant risk of modelling "just because". This can be time consuming and might not be as informative as simple solutions (*"Horses for courses")*

Acknowledgements

Neil Parrott
Michael Gertz
Rodolfo Gasser
Robert van Waterschoot
Axel Pähler
Yumi Cleary
Stefanie Bendels
Michael Honer
Alessandro Brigo
Stephen Fowler
Michael Otteneder
Sherri Dudal
Thierry Lavé
and all the project team members

Doing now what patients need next