Human Oral and IV PK Profile Prediction: PBPK Approaches

Part 5. Prediction of plasma concentration-time profiles in human by using the physiologically-based pharmacokinetic (PBPK) approach.

J Pharm Sci 2011,

P Poulin, RDO Jones, HM Jones, CR Gibson, M Rowland, JY Chien, B Ring, KK Adkison, MS Ku, H He, R Vuppugalla, P Marathe, V Fisher, S Dutta, VK Sinha, T Björnsson, T Lavé and JWT Yates

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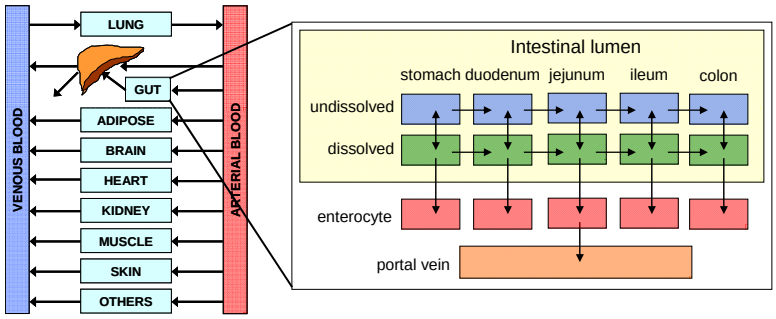
What is PBPK? – physiologically based pharmacokinetic model



SPECIES SPECIFIC INPUT
- tissue volumes
- tissue blood flows
- tissue composition
- intestinal pH, transit times
- models available for rat, dog, human

COMPOUND SPECIFIC INPUT
- CLint / CL
- plasma fu, bl:pl ratio, LogD, pKa
- Kp values (estimated from plasma fu, bl:pl ratio, LogD, pKa)
- solubility, permeability

used to predict plasma and tissue concentration time profiles after i.v. and oral administration…

Drug

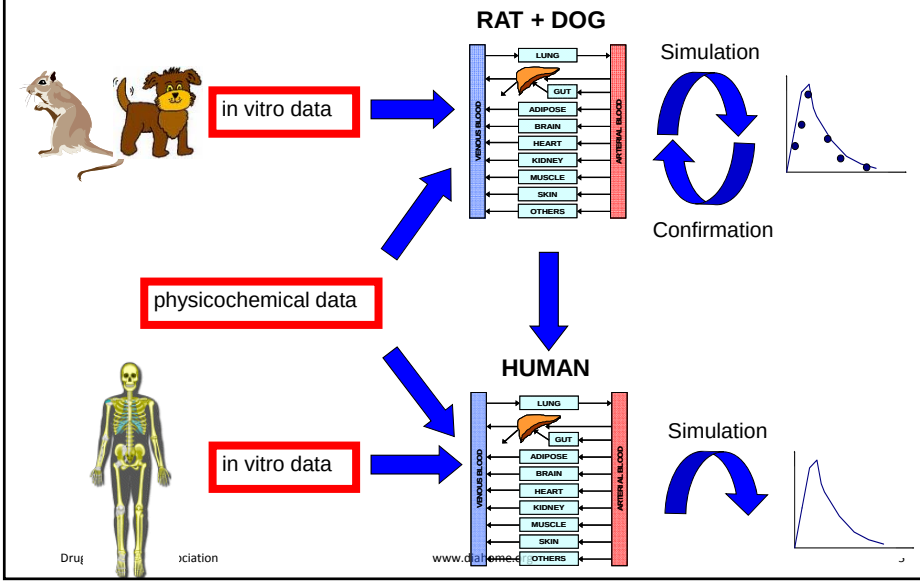
3

Main assumptions of the generic PBPK models

- Distribution of drug round the body is perfusion rate limited i.e. limited by the blood flow to each tissue
- Each tissue acts as a well stirred compartment
- Permeability across the tissue membrane is not a barrier to tissue distribution – valid for lipophilic small molecules
- Distribution is mainly governed by passive processes with no significant contribution of active transport
- Clearance is via the particular tissue or tissues selected i.e. liver / kidney etc

PBPK prediction strategy proposed in literature – pre-clinical validation prior to human prediction

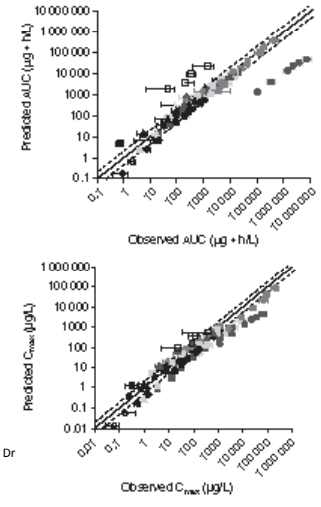
Jones et al 2006 CPK. Validated by DeBuck et al 2007 DMD and Jones et al 2011 CPK



Retrospective validation of PBPK approach at Roche and J&J

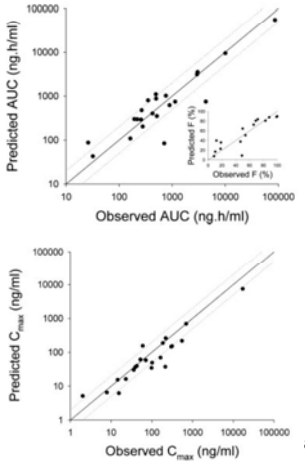
Clinical Pharmacokinetics, 2006, Jones et al

Retrospective evaluation of human PK prediction using PBPK with 19 Roche compounds (1998-2002)



Drug Metabolism and Disposition, 2007, DeBuck et al

Retrospective evaluation of the prediction of human PK using PBPK methodology with 26 J&J compounds



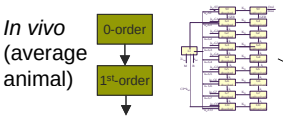
PhRMA retrospective PBPK study

- Simulation of human iv and oral profiles using inhouse PBPK model (Fenneteau et al., 2009)
- Simulations performed for 95 oral compounds and 18 iv compounds from 12 member companies
- Simulations performed using a wide range of in vitro and in vivo based input data (see next slide)
- No validation in pre-clinical species. Simulation performed directly in human
- Prediction accuracy determined via:
  - plasma concentration–time profiles at the lowest dose tested in the single ascending doses studies in fasted healthy volunteers.
  - PK parameters: AUC, MRT, terminal T1/2, plasma Cmax Clast, Tmax, and Vz or Vz/F.
- Statistical parameters calculated: average fold error (AFE), absolute average fold error (AAFE), root mean squared error (RMSE), correlation of coefficient (r), and concordance correlation coefficient (CCC), specific fold errors of deviation between the predicted and observed values (% fold error < 2, < 3, and < 10)

PhRMA PBPK model methodology

Absorption

In vivo (average animal)

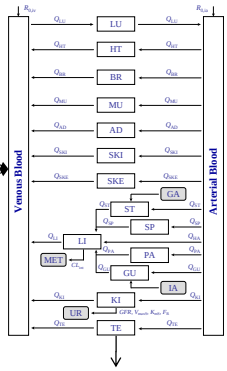


In vitro (ACAT)

Distribution

In vitro: (Tissue composition)

In vivo: (Arundel/Jansson algorithm)

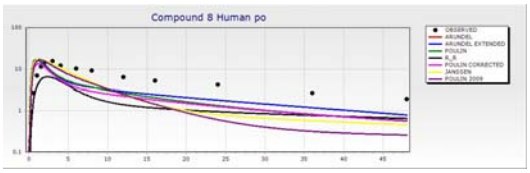


Metabolism/Elimination (Clearance)

In vitro: hep, HLM data

In vivo: allometry

- **Combining different methods for the prediction of absorption and CL into the range of systemic PBPK variations results in a significant number of simulations**



Comparison of i.v. predictions

		Human i.v. PK Prediction								
PK[a]	Simulation Scenarios	n^b	% < 2-Fold	% < 3-Fold	% < 10-Fold	AFE	AAFE	RMSE	r	CCC
$AUC_{0\text{-}t,i.v.}$ [(ng h)/mL]	PBPK (V_{ss}, JA; CL, FCIM)	15	67	87	93	0.72	1.9	0.39	0.99	0.93
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	14	71	93	100	0.92	1.8	0.30	0.52	0.92
$C_{first,i.v.}$[c] (ng/mL)	PBPK (V_{ss}, JA; CL, FCIM)	15	60	73	93	0.62	2.3	0.46	0.99	0.87
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	14	57	64	86	0.60	3.1	0.73	0.61	0.57
$T_{1/2,i.v.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM)	14	50	57	93	1.2	2.3	0.47	0.90	0.65
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	13	54	85	100	1.1	2.1	0.40	0.99	0.72
$MRT_{i.v.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM)	15	53	73	93	0.71	2.1	0.44	0.83	0.67
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	14	64	93	100	0.92	1.8	0.30	0.52	0.92
$C_{first,i.v.}$[c] (ng/mL)	PBPK (V_{ss}, JA; CL, FCIM)	15	60	73	93	0.62	2.3	0.46	0.99	0.87
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	14	57	64	86	0.60	3.1	0.73	0.61	0.57
$T_{1/2,i.v.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM)	14	50	57	93	1.2	2.3	0.47	0.90	0.65
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	13	54	85	100	1.1	2.1	0.40	0.99	0.72
$MRT_{i.v.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM)	15	53	73	93	0.71	2.1	0.44	0.83	0.67
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE)	14	64	93	100	0.90	1.8	0.30	0.98	0.78

Prediction accuracy of i.v. profiles is lower than published datasets

But for many parameters reasonable prediction accuracy is still achieved (% < 2 fold = 70%)

In vitro approaches are slightly better than in vivo approaches

Comparison of oral predictions

		Human p.o. PK Prediction								
PK[a]	Simulation Scenarios	n^b	% < 2-Fold	% < 3-Fold	% < 10-Fold	AFE	AAFE	RMSE	r	CCC
$AUC_{0\text{-}t,p.o.}$ [(ng h)/mL]	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_1})	84	25	44	74	0.17	11	1.7	0.88	0.45
	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_2})	82	28	45	84	0.41	4.2	0.78	0.87	0.75
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE, estimated $Sol_{fasesif}$)	33	21	30	64	0.37	7.8	1.2	0.47	0.58
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE, measured $Sol_{fasesif}$)	18	11	28	61	0.14	11.1	1.3	0.96	0.38
$C_{max,p.o.}$ (ng/mL)	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_1})	84	14	31	71	0.16	12	1.6	0.67	0.45
	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_2})	82	20	35	79	0.38	4.9	0.81	0.65	0.72
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; estimated $Sol_{fasesif}$)	33	24	33	70	0.39	7.3	1.1	0.94	0.59
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; measured $Sol_{fasesif}$)	18	17	22	56	0.15	11.9	1.3	0.78	0.25
$T_{1/2,p.o.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_1})	83	48	71	93	1.3	2.4	0.46	0.36	0.51
	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_2})	82	48	71	93	1.3	2.4	0.46	0.36	0.51
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; estimated $Sol_{fasesif}$)	32	44	75	97	1.3	2.5	0.52	0.55	0.42
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; meas. $Sol_{fasesif}$)	17	35	65	94	1.1	3.0	0.62	0.44	0.29
$MRT_{p.o.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_1})	84	69	85	95	0.68	1.8	0.36	0.52	0.60
	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_2})	82	70	85	95	0.67	1.8	0.36	0.53	0.60
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; estim. $Sol_{fasesif}$)	33	85	94	97	0.81	1.7	0.32	0.62	0.63
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; meas. $Sol_{fasesif}$)	18	78	89	94	0.70	1.8	0.39	0.62	0.53
$T_{max,p.o.}$ (h)	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_1})	84	57	80	99	0.94	2.0	0.37	0.18	0.37
	PBPK (V_{ss}, JA; CL, FCIM; k_a, F_{abs_2})	82	57	81	100	0.91	1.9	0.35	0.34	0.39
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; estimated $Sol_{fasesif}$)	33	49	64	100	1.1	2.4	0.45	0.39	0.33
	PBPK (V_{ss}, $TC_{K_{pu}}$; CL, IVIVE; measured $Sol_{fasesif}$)	18	50	67	100	1.5	2.4	0.43	0.54	0.39

Prediction accuracy of oral profiles is extremely low (much lower than published datasets)

Poor prediction of bioavailability – FPE and fa

Summary of main findings from PhRMA analysis

- Results from these analyses were somewhat disappointing particularly in terms of oral profile prediction
- Rationalised by:
  - data is generated using a range of methodologies from each of the companies
  - no detailed knowledge of the compound properties wrt model assumptions
  - the strategy proposed in the literature of validation in animals before human simulation was not followed due to time constraints
  - commercial software incorporating full dissolution / refined absorption models not validated
- these combine to explain some of the poorer predictions

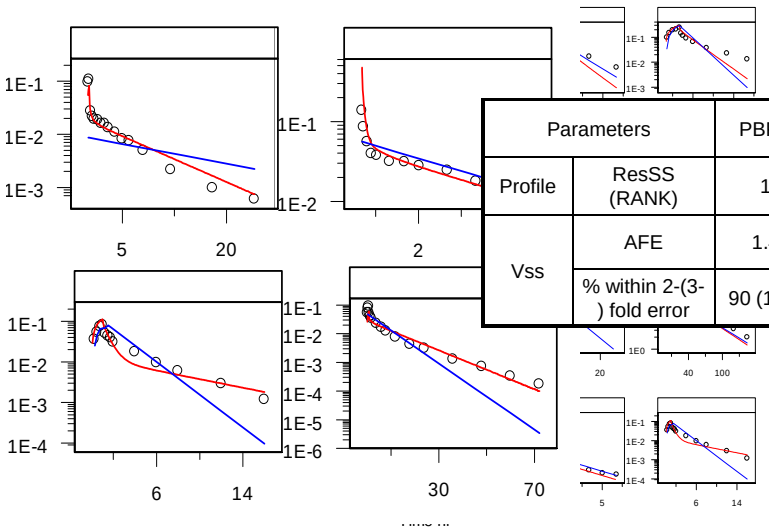
Similar evaluation at Pfizer – comparison of PBPK with empirical methods

- 21 compounds (across therapeutic areas, CL mechanisms, Pfizer sites and for which IV and oral clinical data is available)
- PBPK simulations implemented in GastroPlus
  - CL estimated from HLM (for P450 cleared substrates) or allometric scaling from single species (for all other compounds) / observed CL also used for comparison
  - Distribution characteristics estimated using published tissue composition equations
  - Absorption characteristics estimated from LogD, LogP, pKa, solubility and permeability data
  - Approach to validate distribution and absorption prediction pre-clinically before human simulation
- One compartmental approach in WinNonlin
  - CL as GastroPlus; Fh calculated from predicted CL
  - Vss estimated assuming unbound volume is same as in rat
  - Fa and Ka calculated from rat
- Assess prediction of plasma concentration profiles together with CL, Vss, AUC, Cmax, terminal half life – detailed stats analysis (ResSS)

How well is distribution and profile shape predicted?

PBPK v Empirical method

Observed CL / Predicted distribution

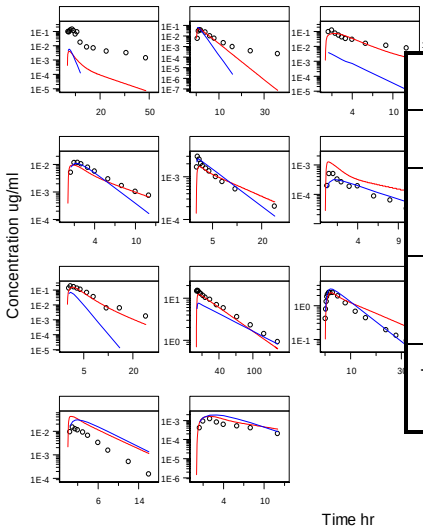


Parameters		PBPK	Empirical Approach
Profile	ResSS (RANK)	1	2
Vss	AFE	1.4	1.6
	% within 2-(3-) fold error	90 (100)	75 (85)

How well is absorption predicted?

PBPK v Empirical method

Observed CL / Predicted distribution / Predicted absorption

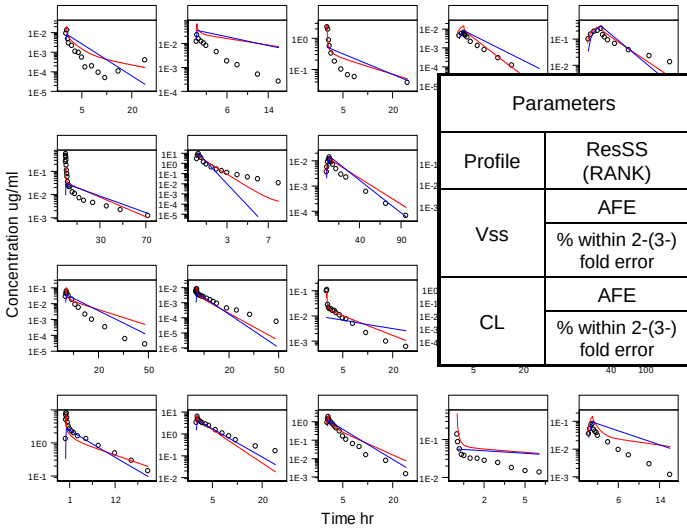


Parameters		PBPK	Empirical Approach
Profile	ResSS (RANK)	2	3
AUC	AFE	1.9	2.5
	% within 2-(3-) fold error	76 (82)	65 (71)
Cmax	AFE	1.9	2.1
	% within 2-(3-) fold error	76 (88)	71 (88)
Terminal Half Life	AFE	2.0	2.7
	% within 2-(3-) fold error	65 (76)	65 (76)

How well is an iv profile predicted?

PBPK v Empirical method

Predicted CL / Predicted distribution

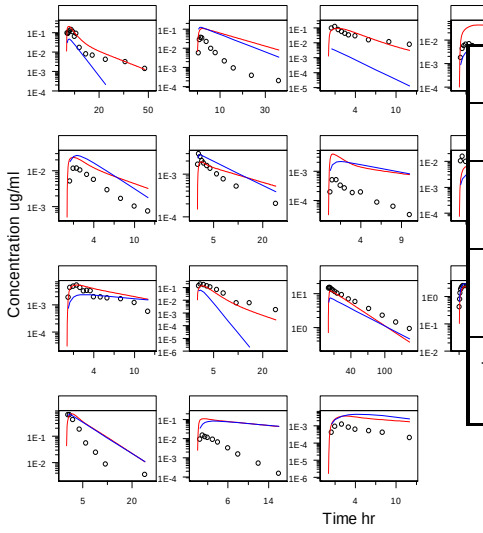


Parameters		PBPK	Empirical Approach
Profile	ResSS (RANK)	1	2
Vss	AFE	1.4	1.6
	% within 2-(3-) fold error	90 (100)	75 (85)
CL	AFE	1.6	1.6
	% within 2-(3-) fold error	80 (85)	80 (85)

How well is an oral profile predicted?

PBPK v Empirical method

Predicted CL / Predicted distribution / Predicted absorption

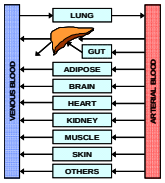


Parameters		PBPK	Empirical Approach
Profile	ResSS (RANK)	1	2
AUC	AFE	2.7	3.9
	% within 2-(3-) fold error	50 (72)	33 (56)
Cmax	AFE	2.0	2.5
	% within 2-(3-) fold error	67 (72)	44 (61)
Terminal Half Life	AFE	2.1	2.5
	% within 2-(3-) fold error	61 (83)	50 (61)

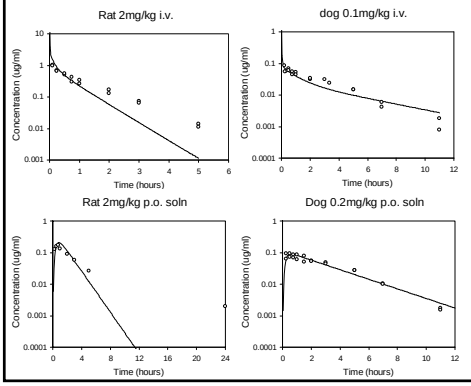
Pfizer FIH prospective prediction example

Input data and model

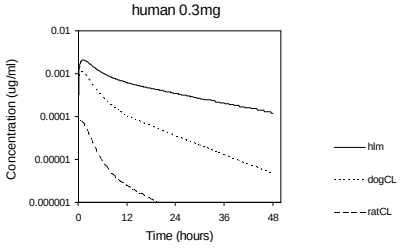
solubility, permeability, PPB, bl:pl ratio, pKa, MW, RLM / DLM / HLM, LogD



Initial validation in animals – i.v. and oral



Human simulation



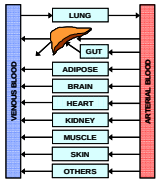
Based on knowledge of metabolism dog CL and HLM data were expected to give the most accurate prediction.

Rat included for completeness

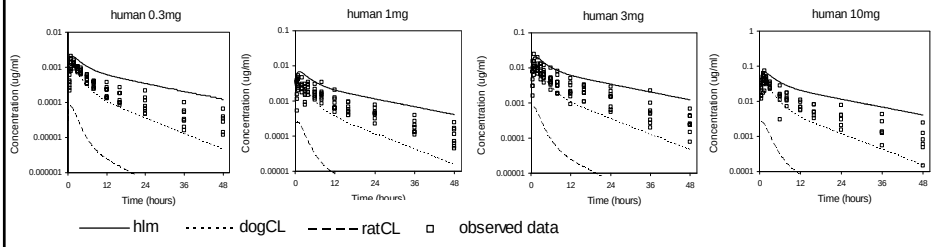
Pfizer FIH prospective prediction example contd.

Input data and model

solubility, permeability, PPB, bl:pl ratio, pKa, MW, RLM / DLM / HLM, LogD



Human simulated and observed data



N.B. PBPK approach gave a better prediction of profile and shape than standard one compartmental model (data not shown)

Thoughts and recommendations moving forward

- PBPK methodology is more accurate at prediction i.v. rather than oral profiles (literature data, PhRMA evaluation and Pfizer data)
- Reasons for poor predictions tend to include misprediction of absorption, gut metabolism and first-pass hepatic CL
- Results highlight the importance of thorough understanding of the assumptions and limitations of these models
- Predictions should not be performed blindly – a limited amount of in vivo data is required to perform some validation of the assumptions
- In this context, PBPK modelling offers promise for performing PK predictions in the absence of extensive in vivo data