Quantifying and Communicating Uncertainty in Human PK and Dose Prediction

Douglas Ferguson

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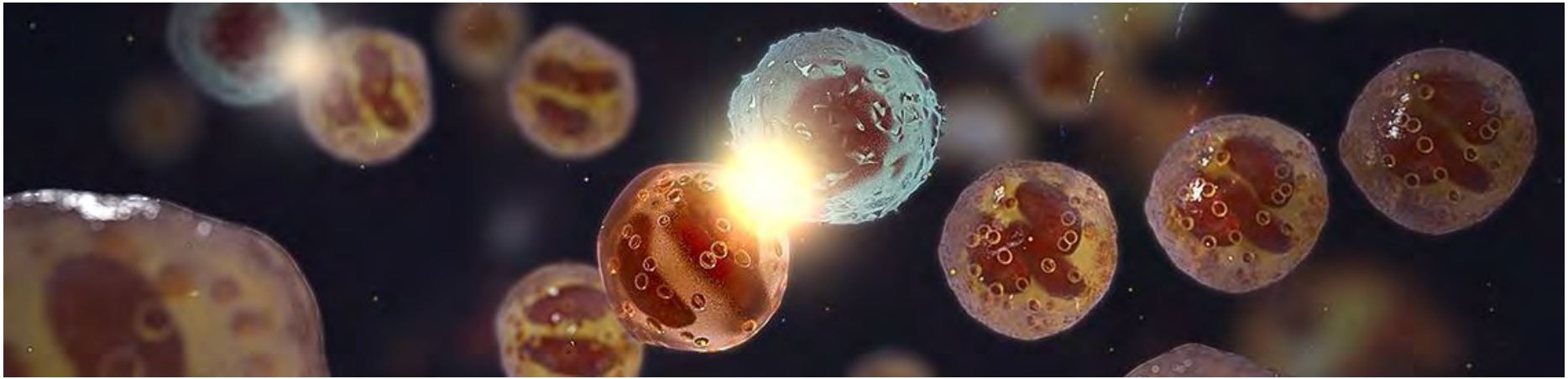


Introduction

- In drug discovery, prospective prediction of human pharmacokinetics facilitates the differentiation of possible clinical candidates and is a key step in the prediction of efficacious clinical dose, optimal dosing regimen and therapeutic index.

- Of similar importance to the prediction of point estimates for each human PK parameter, is the accurate quantitation and communication of the *uncertainty* in the point estimates.

- This presentation describes a ‘Monte-Carlo’ based approach to estimating prediction intervals for both primary PK parameters (such as Cl and V_{ss}) and key secondary parameters such as C_{max}, half-life & clinical dose.

Presentation Overview

- Introduction to sources of uncertainty (as applied to prediction of human PK and ‘efficacious’ clinical dose)
- Overview of reference datasets and process used to characterize the uncertainty associated with our standard PK parameter prediction tools/approaches
- ‘Monte-Carlo’ process used to combine the uncertainty in the individual predicted PK parameters to compute uncertainty in dose
- Example: drug discovery project used to illustrate the process of quantifying and communicating the uncertainty in PK and dose prediction


..I hate all this uncertainty!

Key sources of uncertainty in PK & dose prediction.

Model

- ***Model uncertainty*** reflects the predictive accuracy of a particular model.

Parameter

- ***Parameter uncertainty*** reflects uncertainty in the 'true' values of the mathematical model input parameters.

Translation

- ***Translation uncertainty*** reflects uncertainty in the translation from animal to man, or from one patient group to another.

Scenario

- ***Scenario uncertainty*** may reflects uncertainty in how the compound is to be administered or the efficacious target exposure.

Population

- **Population uncertainty** reflects uncertainty around the target population or the prevalence of a particular mutation.

The challenge is to recognise, quantify and communicate the implications of these sources of uncertainty in predictions

Examples of PK parameter prediction models - Clearance

Hepatocyte Cl_{int} based IVIVe

Cl_{int} estimates from human hepatocyte incubations are scaled to a liver (metabolic) Cl_{int} according to:

Scaled liver Cl_{int} = $Cl_{int,hep}$ *SF*fu_{blood}/fu_{inc}

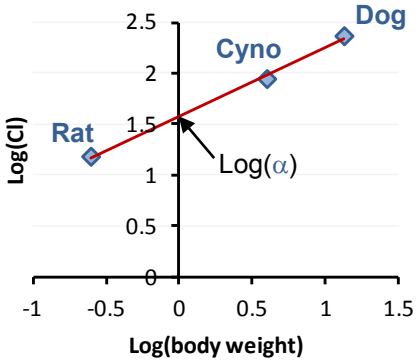
Where SF represents the product of hepatocellularity (10^6 cells/g_{liver}) and liver weight (g_{liver}/$kg_{body\ weight}$).

Scaled liver Cl_{int} is then converted to a 'Predicted hepatic metabolic $Cl_{int,\ in\ vivo}$' using established regression line *(to correct for the general systematic under-prediction of direct IVIVe).*

Input parameters are therefore human hepatocyte Cl_{int}, fu_p, blood:plasma ratio & fu_{inc}

Sohlenius-Sternbeck, A; Jones, C; Ferguson, D; Middleton, BJ; Projean, D; Floby, E; Bylund, J; Afzelius, A. Practical use of the regression offset approach for the prediction of in-vivo intrinsic clearance from hepatocytes. Xenobiotica 42(9): 841-843 (2012)

fu_p Corrected intercept method (FCIM)



Starts with a simple allometric plot….

$Cl = \alpha * BodyWeight^b$

This method predicts clearance from the equation below:

$$Human\ Cl = 33.35*(\alpha / Rfu_p)^{0.77}$$

(Where Rfu_p is the ratio of fu_p in rat to fu_p in man.)

Input parameters are therefore plasma Cl in preclinical species & fu_p in rat and man.

Tang H, Mayersohn M. A novel model for prediction of human drug clearance by allometric scaling. Drug Metab Dispos 2005:33: 1297-1303

Example of PK parameter prediction models - V_{ss}

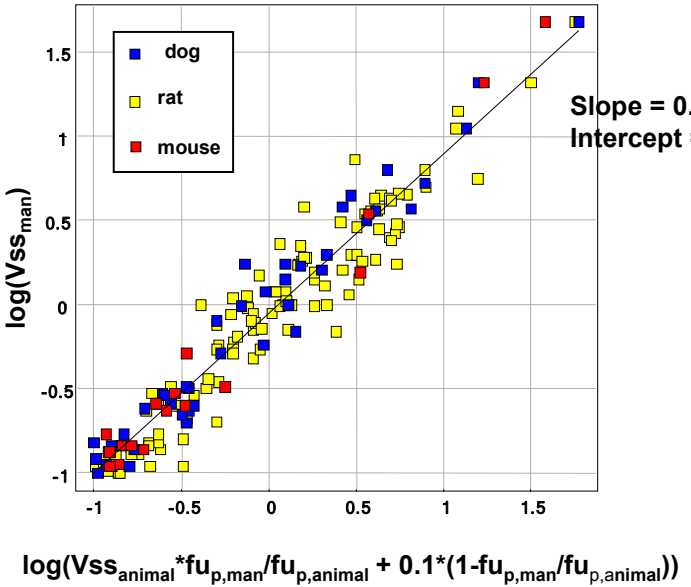
'McGinnity 2007' V_{ss} prediction

Assumes tissue binding (fu_t) is equivalent in animals and humans and that the lower limit of V_{ss} = distribution volume of albumin = 0.1 l/kg

$$V_{ss,man} = \frac{fu_{p,man}}{fu_{p,animal}} V_{ss,animal} + 0.1\left(1 - \frac{fu_{p,man}}{fu_{p,animal}}\right)$$

Small regression correction is applied to the prediction from each species and the geometric mean of the prediction from each species in obtained.

Input parameters are therefore plasma V_{ss} in preclinical species & fu_p in preclinical species and man.



McGinnity, DF; Collington, J; Austin, RP; Riley, RJ. Evaluation of Human Pharmacokinetics, Therapeutic Dose and Exposure Predictions Using Marketed Oral Drugs. Current Drug Metabolism 8(5): 463-479 (2007)

Typical ‘Dose Nomogram’….

Target exposure uncertainty: low, average and high *(in this example numbers refer to AUCu/potency)*

Range of human Clearance predictions reflecting estimated uncertainty

Cl (ml/min/kg)	PD target		
	Low (83)	Mean (139)	High (245)
1.4	**500**	**900**	**1600**
2.0	**700**	**1250**	**2250**
2.6	**950**	**1600**	**2900**

Color coded to reflect a specific risk. *(In this case the risk shown is formulation feasibility and risk of exceeding MAD)*

Doses necessary to achieve the target AUC based on the variability of CL and PD targets.

- Main weakness of this approach is that it doesn’t *usually* express the likelihood of the various scenarios described.
- Only deals with 2 dimensions of uncertainty…which may not be sufficient.

Datasets used to assess the uncertainty associated with individual PK parameter estimation methods

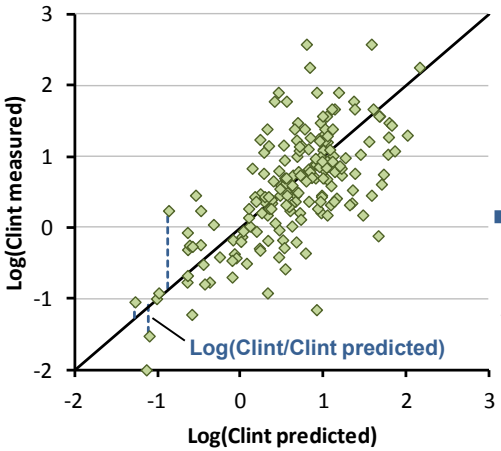
- Lombardo et al. 2013 dataset[1] (~400 compounds; human, rat, dog and monkey PK; Cl, V_{ss}, fu_p)
  - Øie-tozer V_{ss} *(rat only, dog only, rat & dog average fu_t)*
  - McGinnity V_{ss} *(rat only, dog only, rat & dog geomean V_{ss} prediction)*
  - FCIM Cl* *(rat only fixed exponent; rat and dog)*
- Astrazeneca internal V_{ss} dataset (~110 compounds; human, rat & dog V_{ss} & fu_p)
  - McGinnity V_{ss} *(rat only, dog only, rat & dog geomean V_{ss} prediction)*
- Paine 2011 renal clearance database[2] (35 compounds)
  - Renal Cl* correlation method *(rat correlation, dog correlation)*
- Astrazeneca internal Human heps & human Mics test set compounds
  - IVIVe derived hepatic Cl* from human heps and human Mics

1. Lombardo F. et al. Comprehensive assessment of human pharmacokinetic prediction based on in vivo animal pharmacokinetic data, part 2: clearance. J. Clin. Pharmacol. 53(2):178-191 (2013)

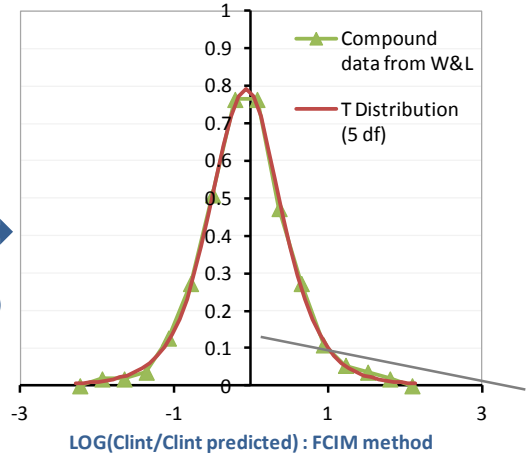
2. Paine, SW et al. Prediction of human renal clearance from preclinical species for a diverse set of drugs that exhibit both active secretion and net reabsorption. Drug Metab. Dispos. 39(6):1008-13 (2011)

Assessing uncertainty distributions...

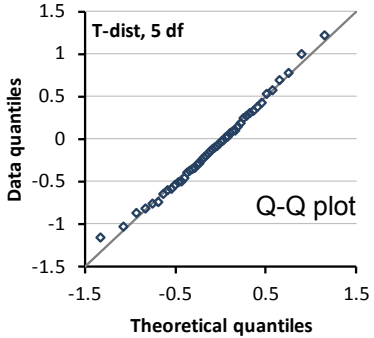
- The distribution of LOG(measured parameter/predicted parameter) was used to assess the predictive accuracy for each method when applied to the relevant test set(s)



Histogram of $Log(Cl_{int}/Cl_{int}$ pred.) values



Y-axis shows 'frequency'
AUC = 1



- Example shown is the result of applying the FCIM to the W&L dataset. Green triangles derived from a histogram of the data (using 0.5σ bin width). Red line is the equation for T-distribution (5 df; Std dev = 0.48)

- The uncertainty distributions for each PK prediction method are generally best described by either a Normal or T-distribution *(example QQ plot shown)*

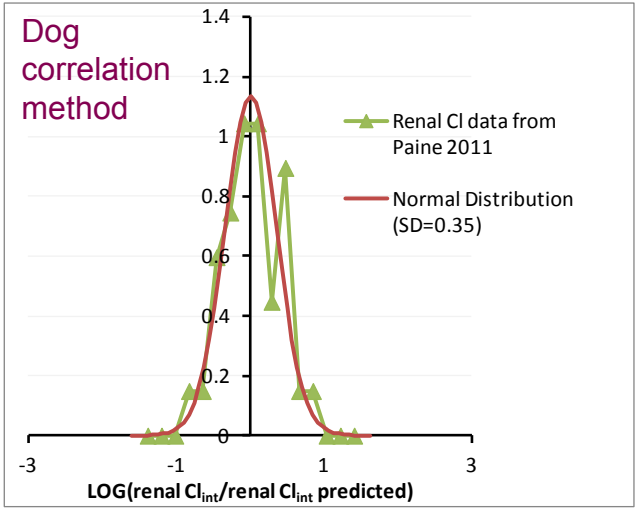
- Each distribution is characterized by type (Normal or T), number of df (if required), bias & standard deviation and used as an estimate of the prediction error distribution associated with that method.

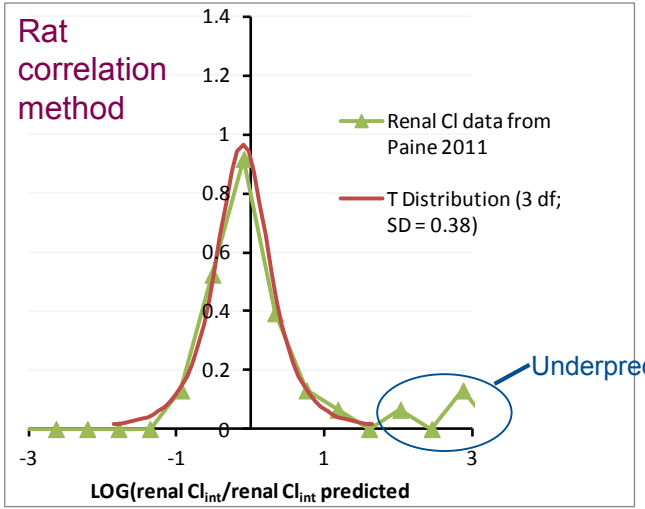
Renal Cl correlation method – use of Renal 'Cl_{int}'

Normally this method is based upon the assumption that renal Cl in man can be predicted from renal Cl in animals by correcting for interspecies differences in fu_p and KBF.

$$\text{Renal Cl}_{human} = \text{Renal Cl}_{dog} * (fu_{p,human}/fu_{p,dog}) * (KBF_{human}/KBF_{dog})$$

However, for the purposes of uncertainty assessment, it is simpler to convert to a 'renal Cl_{int}' *[$KBF*Cl_{renal}/(KBF-Cl_{renal})$].*



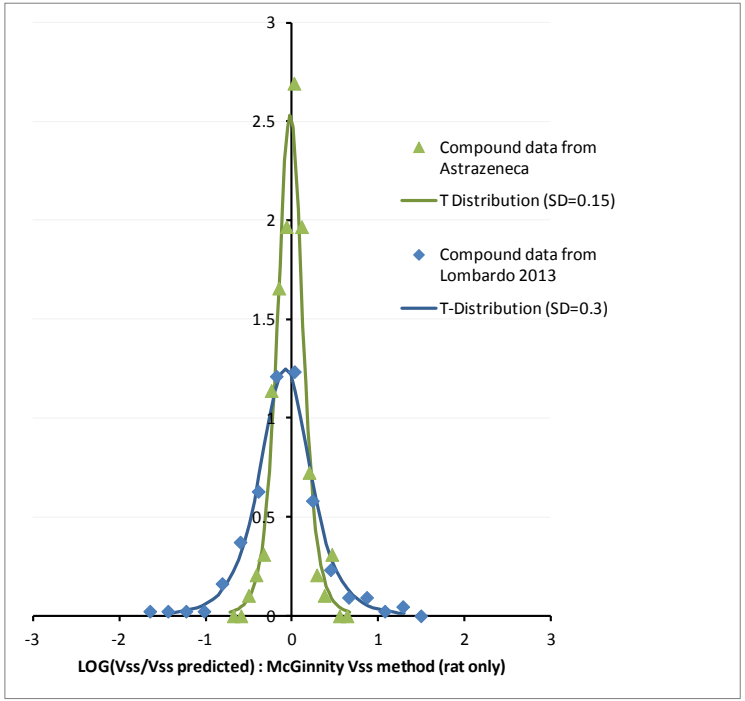


Assessing predictive accuracy in terms of Cl_{int} prevents the prediction of possible 'true' values of Cl_{renal} that exceed KBF.

Overall uncertainty in PK parameter prediction results from combination of input parameter and model uncertainty

Example McGinnity V_{ss} Method

- The distribution of LOG($V_{ss}/V_{ss\ predicted}$) appears to vary depending upon which reference set is used. The apparent larger uncertainty with the W&L dataset probably arises from incorporation of poorly defined PK datasets and inter-lab differences in determination of fu_p for different species.
- Realistic assessment of the overall uncertainty associated with a particular method requires that the reference data set, used to probe the accuracy of method, is of similar 'quality' to that available for the test compound.

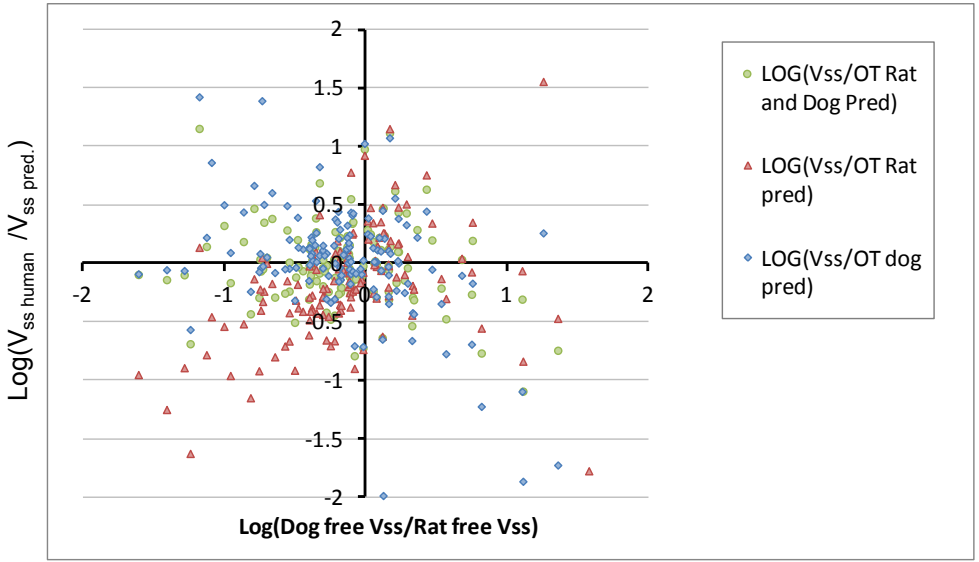


Human PK parameter prediction methods: Distributions

			Log(measured/predicted)			
	Method	**Parameter assessed**	**Distribution shape**	**Std Dev (σ)**	**Bias**	**Dataset**
Hepatic CL	Hep Cl_{int} IVIVe	*in-vivo* Cl_{int}	Normal	0.4	0	AZ
	Mic Cl_{int} IVIVe	*in-vivo* Cl_{int}	Normal	0.46	0	AZ
	FCIM *(based on rat PK only)*	*in-vivo* Cl_{int}	T-Dist. (5 df)	0.48	-0.066	Lombardo 2013
	FCIM *(based on rat and dog PK)*	*in-vivo* Cl_{int}	T-Dist. (5 df)	0.38	-0.085	Lombardo 2013
Renal CL	Renal Cl correlation method - *dog*	Renal 'Cl_{int}'	Normal	0.35	0.0133	Paine 2011
	Renal Cl correlation method - *rat*	Renal 'Cl_{int}'	T-Dist. (3 df)	0.38	-0.092	Paine 2011
V_{ss}	Øie-tozer V_{ss} *(rat only)*	V_{ss}	T-Dist. (4 df)	0.3	-0.14	Lombardo 2013
	Øie-tozer V_{ss} *(dog only)*	V_{ss}	T-Dist. (4 df)	0.3	0.05	Lombardo 2013
	Øie-tozer V_{ss} *(rat and dog)*	V_{ss}	T-Dist. (4 df)	0.25	-0.032	Lombardo 2013
	McGinnity V_{ss} (*rat only*)	V_{ss}	T-Dist. (5 df)	0.15	-0.02	AZ
	McGinnity V_{ss} (*dog only*)	V_{ss}	T-Dist. (5 df)	0.11	0.042	AZ
	McGinnity V_{ss} (*rat and dog*)	V_{ss}	T-Dist. (5 df)	0.075	0.016	AZ

Correlation of residual distribution with compound properties..

Example:



- Standard deviation of residual distribution appears to be correlated to fold-difference in free Vss between dog and rat (i.e. greater uncertainty in human Vss prediction when rat and dog free Vss don't 'agree')
- May be appropriate to take these sort of observations into account when estimating the uncertainty distribution for a new compound.

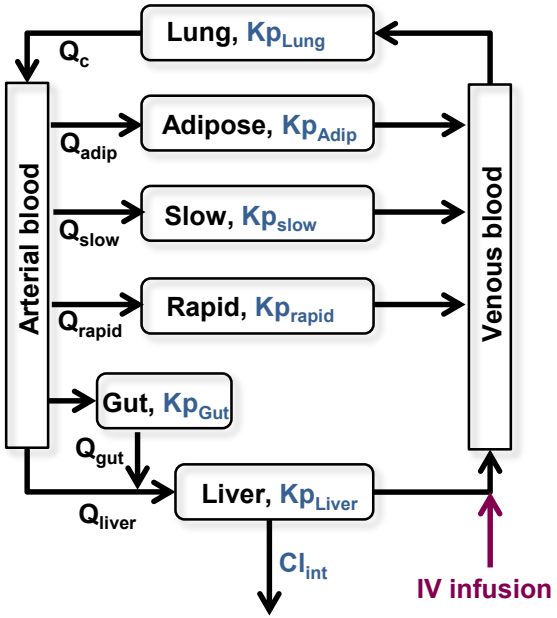
Dealing with PBPK models?

- More challenging to establish uncertainty distributions for PBPK models as there are multiple tissue Kp values that contribute to V_{ss} and the overall 'shape' of the concentration time profile
  - *Requires analysis of full concentration vs time profiles in each test sets…….and how to quantify accuracy of 'shape' prediction?*

- However, because PBPK models are based on similar assumptions (equivalent tissue binding across species) and input data as other V_{ss} prediction methods *(e.g. McGinnity & Øie-Tozer)* the distribution of Log(V_{ss}/V_{ss} pred) should be similar
  - *This is supported by a PhRMA assessment that demonstrated similar predictive accuracy when comparing Arundel PBPK with other V_{ss} prediction methods**

- Application of PBPK models requires point estimates of human tissue:blood partition coefficients. Simplest approach is to assume equal predictive error (log($Kp/Kp_{predicted}$) for all tissues when dealing with V_{ss} prediction.

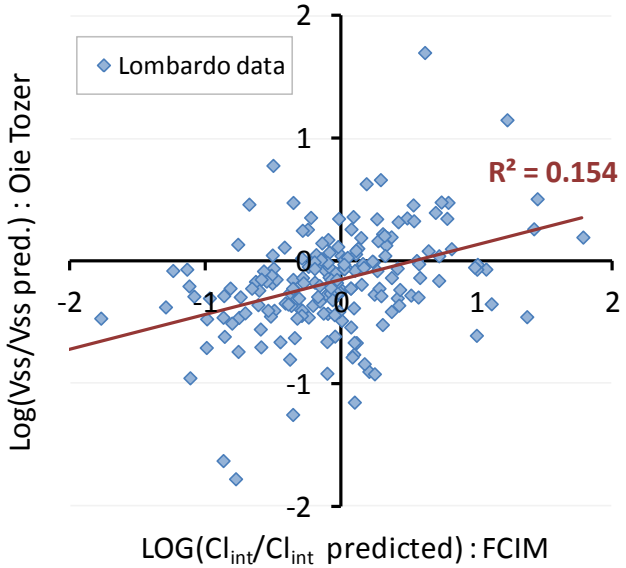
- Dealing with uncertainty at the Kp level (rather than V_{ss}) prevents the generation of non-physiologically possible 'true' values of V_{ss} for low V_{ss} compounds.



*Jones, RD et al. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 2: Comparative assessment of prediction methods of human volume of distribution. J. Pharm. Sci. 100(10): 4074-89 (2011)

Correlation

- The correlation between 'residuals' [i.e. Log(measured/predicted)] for different methods was also assessed (for the range of PK parameter prediction models)



- In the example shown both FCIM Cl_{int} and McGinnity V_{ss} rely upon the ratio of $fu_{p,\ human}$ / $fu_{p,\ rat}$. Results is a slight correlation between method residuals.

Generally there was low correlation between the residuals for V_{ss} and Cl prediction methods

Combining uncertainty distributions in a Monte-carlo approach...

- **Key assumption**: for a new test compound, the distribution of *possible* 'true' values (for a given human parameter) relative to the point estimate prediction, will be equivalent to the corresponding distribution of (*known*) true values relative to the single point 'predictions' for the established set of reference compounds. *[Note: there will be only one actual true population mean value..]*

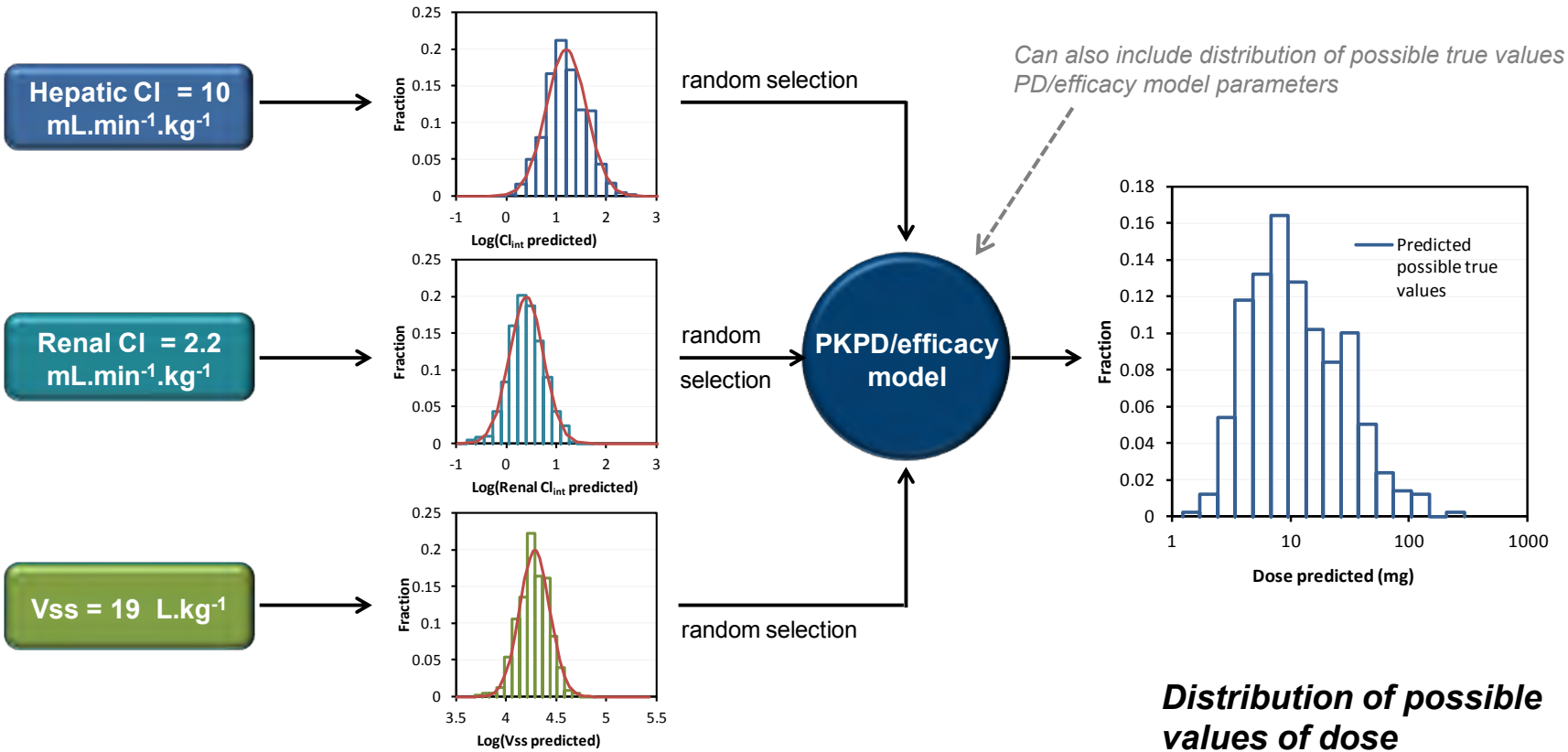
- **Step 1:** Derive the point estimate prediction for each relevant PK parameter

- **Step 2:** Generating lists of *possible* 'true' values distrubuted around the point estimate predictions.

- **Step 3:** Randomly sample a single *possible* true value for each primary parameter (e.g. hepatic Cl, V_{ss}, renal Cl..) from the respective distributions and then calculate/estimate a single value for each secondary parameter (such as $T_{1/2}$, C_{max}, Dose..) .

- Step 3 is repeated a large number of times (say 1000…) to give a distribution of possible true values for each secondary parameter of interest.

Schematic of process used to estimate prediction intervals



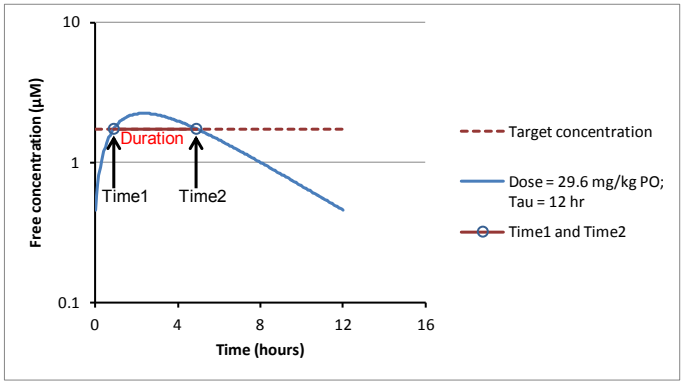
Point estimate predictions

Distributions of possible 'true' values of primary parameters

Distribution of possible values of dose

Monte-carlo dose prediction – process for 'closed form' dose equations

Example: one compartment PK; first order absorption; aiming to maintain free concentration above target for specified time at steady state



$$Time1 = \frac{Ln\left[\frac{(1 - e^{-Ka*Dur})}{(1 - e^{-Ka*tau})} * \frac{(1 - e^{-Ke*tau})}{(1 - e^{-Ke*Dur})}\right]}{K_a - K_e}$$

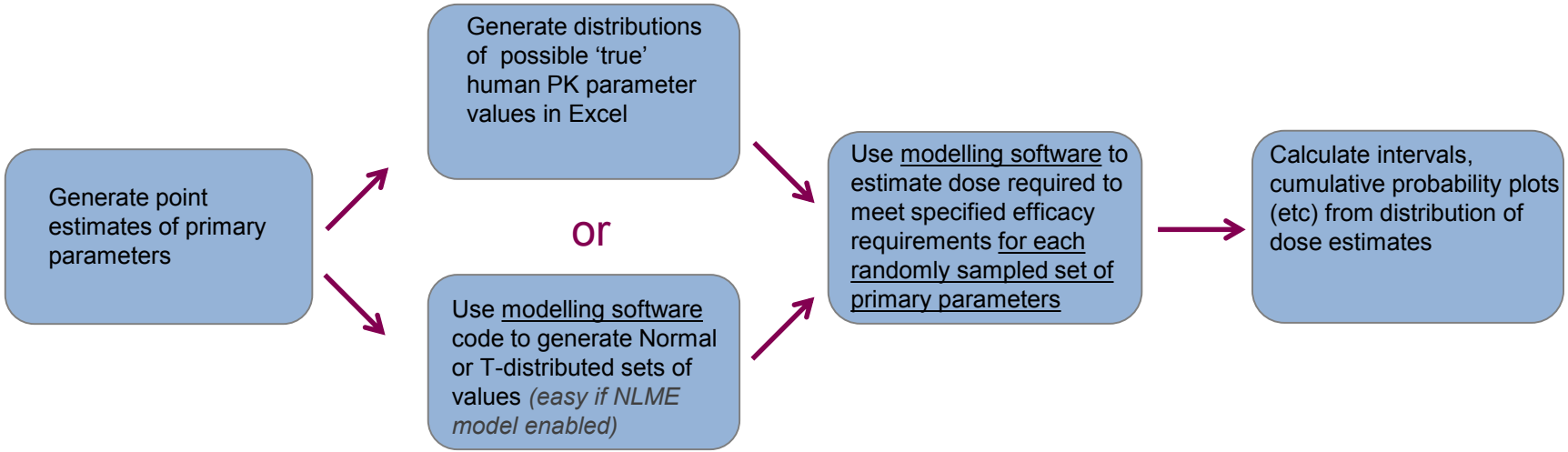
$$Dose = \frac{Target\ free\ conc * V_{ss} * (K_e - K_a)}{fu_{blood} * K_a * F * \left[\frac{e^{-Ka*Time1}}{(1 - e^{-Ka*tau})} - \frac{e^{-Ke*Time1}}{(1 - e^{-Ke*tau})}\right]}$$

Entire process readily accomplished in Excel

Generate point estimates of primary parameters → Generate distributions of possible 'true' values *(using Excel RAND, NORMINV & TINV functions)* → Calculate dose using randomly sampled sets of parameters values in closed form dose equation → Calculate intervals, cumulative probability plots (etc) from distribution of dose estimates

Monte-carlo dose prediction – process for differential equation based dose prediction

Requires the use of model fitting software….but is the same as point estimate dose prediction (just repeated ~1000 times)



The 'difficult' part of the process is making qualified prior estimates of uncertainty distributions

Example: AZ Drug discovery project

- Oral delivery (once a day)
- Multi-exponential plasma kinetics with both hepatic and renal Cl.
- Aiming to achieve free plasma concentration that equals the free 'IC_{50}' at 12 hours.

Note: this is simple example to illustrate concepts

PK parameter prediction methods employed

- Hepatic Clearance – estimated from Cl_{int} in hepatocytes using standard IVIVe approach. Predicted *in-vivo* hepatic clearance (10 ml/min/kg) was converted to *in-vivo* hepatic Cl_{int} by application of reverse WSM

- Renal Clearance – estimated from dog renal clearance using the 'Dog renal Cl_{int} correlation method'. Predicted renal Cl = 2.2 ml/min/kg.

- Distribution - Arundel PBPK* approach applied using rat as primary species to derive tissue Kp values. Predicted V_{ss} = 19.3 l/kg.

- f_{abs} assumed to be 1 (based on high permeability and high f_{abs} in all pre-clinical species)

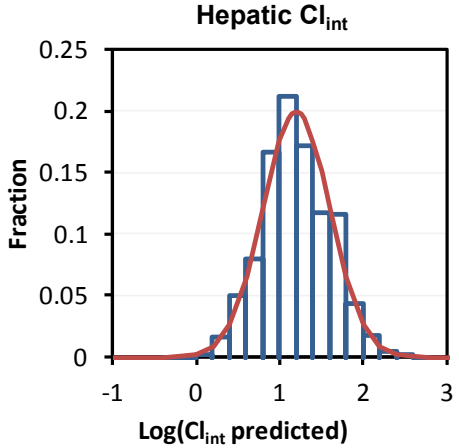
- K_a assumed to be 3.5 hr^{-1} (GI prediction software)

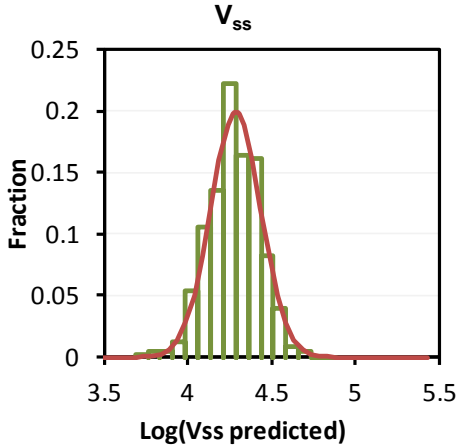
*Arundel, PA (AstraZeneca UK). A multi-compartment model generally applicable to physiologically-based pharmacokinetics. Poster session presented at: 3rd IFAC Symposium on Modeling and Control in Biomedical Systems; 1997 March 23-26; University of Warwick

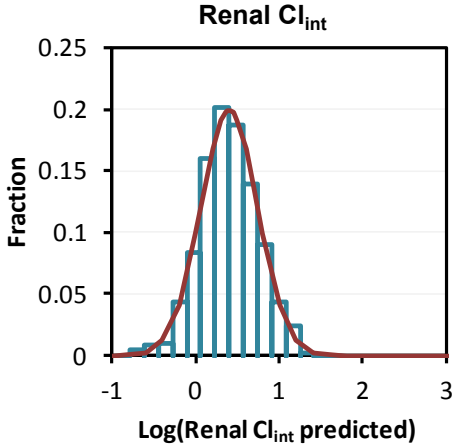
Distributions of possible ‘true’ values for primary PK parameters..

- Model was written in Phoenix WinNonlin® to generate 500 sets of values for hepatic Cl_{int}, renal Cl_{int} & tissue Kps distributed around the point estimates. *(Note: V_{ss} values were then derived as a function of Kp values)*

- For each parameter the generated distribution of possible ‘true’ values was assessed to ensure that it was consistent with the expected shape (based on the assumed distribution of prediction errors).



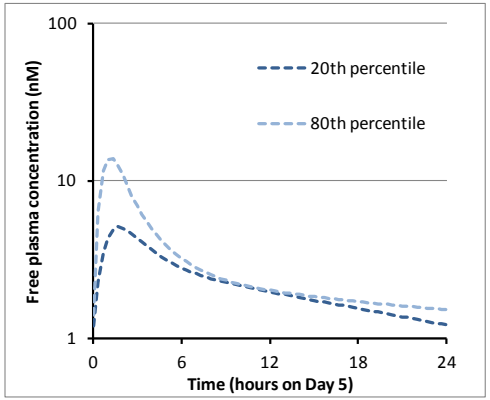


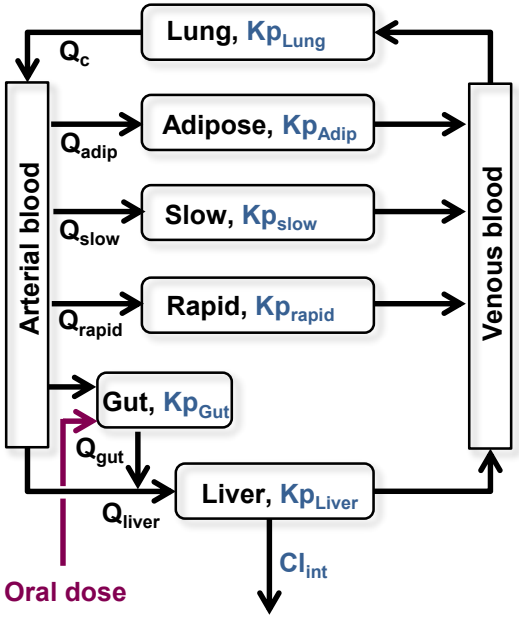


- Monte Carlo approach was used to randomly sample possible ‘true’ values from each parameter distribution - to create sets of possible primary parameter values….

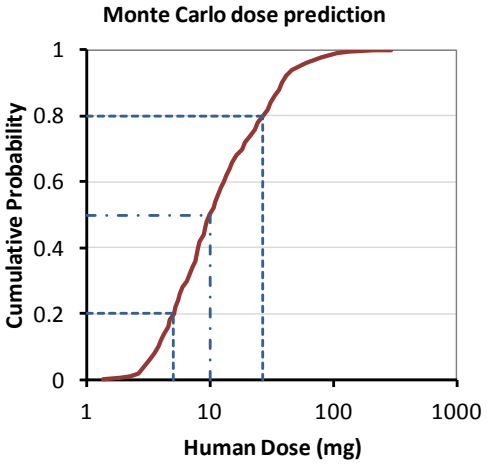
Monte Carlo analysis –using Arundel PBPK model

- PBPK model was written in Phoenix WinNonlin®
- Target (free) plasma concentration was set at 2 nM at 12 hours post dose on Day5. *(Note: uncertainty in target concentration was not considered)*
- 500 sets of *possible* 'true' PK parameter values were randomly sampled from the assumed distributions
- For each randomly sampled set of possible 'true' PK parameter values the oral dose was optimized such that the target free plasma concentration was attained

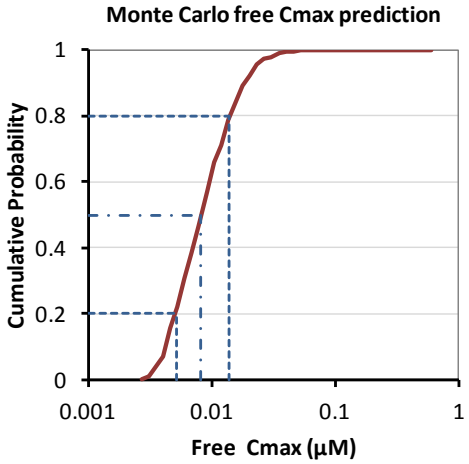




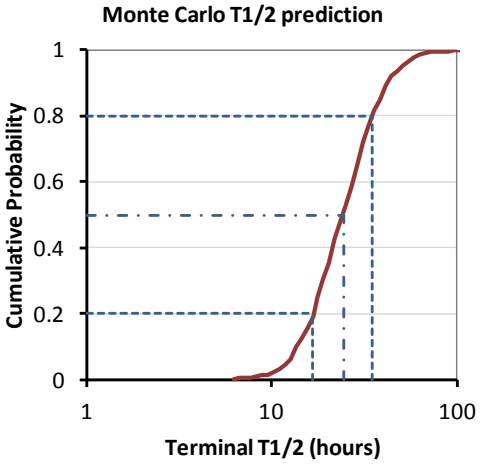
Monte Carlo – Cumulative probability curves



20% probability ≤ 5 mg
50% probability ≤ 10 mg
80% probability ≤ 27 mg



20% probability ≤ 5.1 nM
50% probability ≤ 8.2 nM
80% probability ≤ 13.9 nM



20% probability ≤ 17 hour
50% probability ≤ 25 hours
80% probability ≤ 35 hours

- These plots allow the impact of uncertainty in predicted PK to be quantified in terms of 'risk' to the project…..
- Example – quantify the probability that the required dose will exceed the estimated maximum absorbable dose
- Example – quantify the probability that the free C_{max} will exceed a threshold associated with secondary pharmacology or safety signals.

Conclusions/Comments

- Process described is a relatively simple approach for combining uncertainty in multiple predicted primary parameters to estimate uncertainty in key secondary parameters.
- Assessing the impact of uncertainty in PK prediction on key project 'risks' provides clarity for decision making.
- Work remains to be done to further refine our understanding of how certain observations impact the likely 'uncertainty' in PK prediction'. E.g.
  - *If rat & dog have the same unbound V_{ss} how much does that reduce the uncertainty in human V_{ss} prediction?*
  - *To what extent does the accuracy of rat and dog Cl prediction by hepatocyte Cl_{int} IVIVe impact the uncertainty in human Cl predictions by hepatocyte Cl_{int} IVIVe?*
- Need to continually track the accuracy of human PK prediction as clinical data on new candidate drugs becomes available. Ensure the predictive performance is in line with expectations.

Acknowledgements

- Robin McDougall
- James Yates
- Middleton, Brian J
- Peter Webborn
- Peter Gennemark

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