Translation of Pre-Clinical Pharmacokinetic Parameters in the Determination of Dosing in First Time in Human Studies

Alun Bedding, Director, Statistical Consulting, GlaxoSmithKline

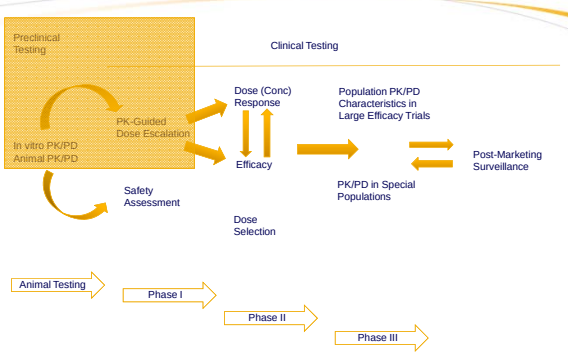
Biannual non-clinical statistics conference
September 2012, Potsdam

What am I going to talk about

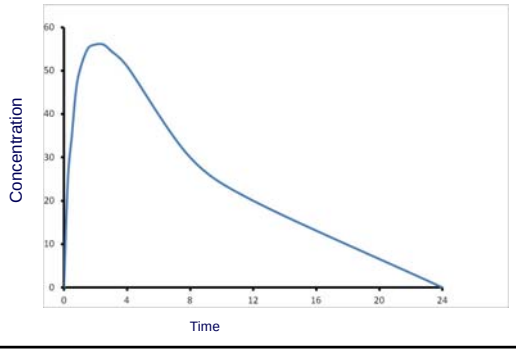
- The role of pharmacokinetics in drug development
  - From pre-clinical through the clinical development spectrum
  - A typical PK profile for an orally administered drug
- How PK is used to choose dose
  - FDA Guidance on Minimum Recommended Starting Dose
  - Use of PK data and simple allometric scaling
- Methods for prediction of FTIH dose from pre-clinical PK
  - PhRMA Clinical and Preclinical Development Committee (CPCDC)
- On-going GSK work
  - Methods of prediction, data set collection, statistical comparisons

The Role of Pharmacokinetics in Drug Development

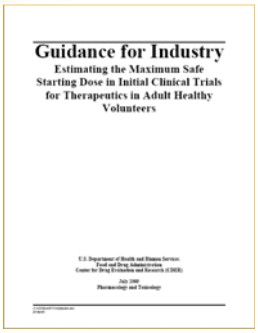
(Reproduced from Rowland and Tozer)



Typical Concentration-Time Profile for an Oral Drug

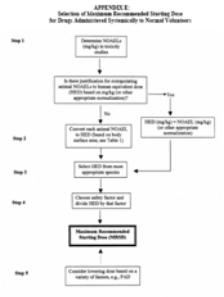


How is PK Used to Select a Starting Dose



Guidance for Industry

Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers



Method by Reigner and Blesch (2002)

- Instead of using dose Reigner and Blesch use systemic exposure – e.g. AUC
- The desired systemic exposure = that which corresponds to the NOAEL
- If available from more than one species – the species with the lowest AUC is used
- Uses clearance of the drug in humans predicted by allometric scaling

$$SD = AUC_p \times CL_h$$

- Where
  - SD = Starting Dose
  - AUC_p = Pre-clinical AUC
  - CL_h = Human clearance estimated using allometric scaling

Allometric Scaling

- The theory of allometric scaling assumes you treat a species as a large animal
- $Y = aTBW^b$ or $Ln(a) + b * Ln(TBW)$
- One common slope and one common intercept
- Slope is dictated by biological processes thus has an exponent with median a value of 0.75 or 0.67
- Intercept is a function of drug properties, thus can approximate to clearance
- If true can scale from one species

$$CL_{Human} = CL_{Animal} \times \left[\frac{Weight_{Human}}{Weight_{Animal}}\right]^b$$

PhRMA Clinical and Preclinical Development Committee

PhRMA CPCDC Initiative on Predictive Models of Human Pharmacokinetics, Part 1: Goals, Properties of the PhRMA Dataset, and Comparison with Literature Datasets

- Limited Duration Key Issues Team - Predictive Models of Human PK
  - Assess prediction methods
  - Verify impact of protein binding
  - Compare monkey with Rat and Dog
  - Predict PK properties and full plasma profiles
  - Evaluate the prediction methods based on the degree of accuracy
  - Provide a mechanistic understanding of why one method provides better predictions than another

Methods to Compare Plasma Clearance

- Allometry
- Simple and multiexponential allometry
- Fu corrected intercept
- Rule of exponent
- Normalized allometry
- Single species scaling
- Two-species scaling
- Animal-human proportionality
- Calculation methods
- QSAR equation based on molecular descriptors and preclinical CL in vivo data
- Microsomes and hepatocytes

Eight Statistical Parameters

- Number of predictions/drugs
- % less than two-fold error of deviation
- %less than three-fold error of deviation
- % more than ten-fold error of deviation
- Absolute fold errors
- Root mean square error
- Concordance correlation coefficient

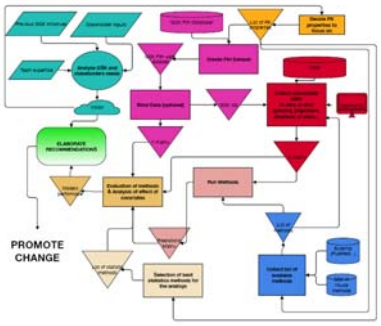
Conclusions from looking at Clearance

- Prediction of human CL based on nonclinical CL data (allometry) was slightly more accurate than predictions based on *in vitro* data
- The fu Intercept Correction Method (FCIM) and two-species-based allometry (rat–dog) were the best performing allometric methods.
- The best IVIVE methods for predicting human CL were the microsomal method corrected for both binding in plasma and incubation medium and hepatocyte method not corrected for any binding.
- Work is expanded to look at volume of distribution

GSK Human Pharmacokinetics (PK) and Dose Predictions Initiative

- Overall Goal
  - Evaluate the applicability of the recommendations of the PhRMA CPCDC Predictive Models of Human PK working group within the GSK drug domain.
- Comparing those methods found to be the best performing in the prediction of FTIH PK data with GSK current methods
- Stage I – GSK dataset collection
  - Collection of in-house human PK data from FIH and clinical trials studies (reference data)
  - Collection of associated discovery and pre-clinical data
  - Calculation of human PK according to the several predictive models used by PhRMA and/or internally in GSK
- Stage II – Analysis of dataset and production of recommendations
  - Selection of statistical analysis methods for the comparison of several predictions with the *reference data*
  - **Performance of statistical analysis and ranking of predictive methods, based not only on comparison of means but also on comparison of variability**
  - Produce recommendations and publish in a peer reviewed journal
- ***To be completed by end 2012, further work to be carried into 2013***

Flowchart of the GSK Human Pharmacokinetics (PK) and Dose Predictions Initiative



Statistical Methods to Be Used for Comparisons

- PhRMA ones
  - Number of predictions/drugs,% less than two-fold error of deviation, %less than three-fold error of deviation, % more than ten-fold error of deviation, Absolute fold errors, Root mean square error, Concordance correlation coefficient
  - Bayesian methods –
    - we are not just interested in point estimates, the distributions for the parameters is of more interest. Look at the posterior distribution from a Bayesian analysis of the data predicted using each of the methods. How does this compare to the distribution of the FIH data.
    - Posterior predictive distribution from the Bayesian analysis of the pre-clinical – how does it compare to the FIH data.
  - ?????

Conclusions

- PK data is used to predict FIH doses but the process uses different methods each of which have plusses and minuses.
- Much work done in this area resulting in the PhRMA report
- How much has been adopted in companies and what are the relative implications?