Best Practices in Physiologically based Pharmacokinetic modeling

Jan Schlender

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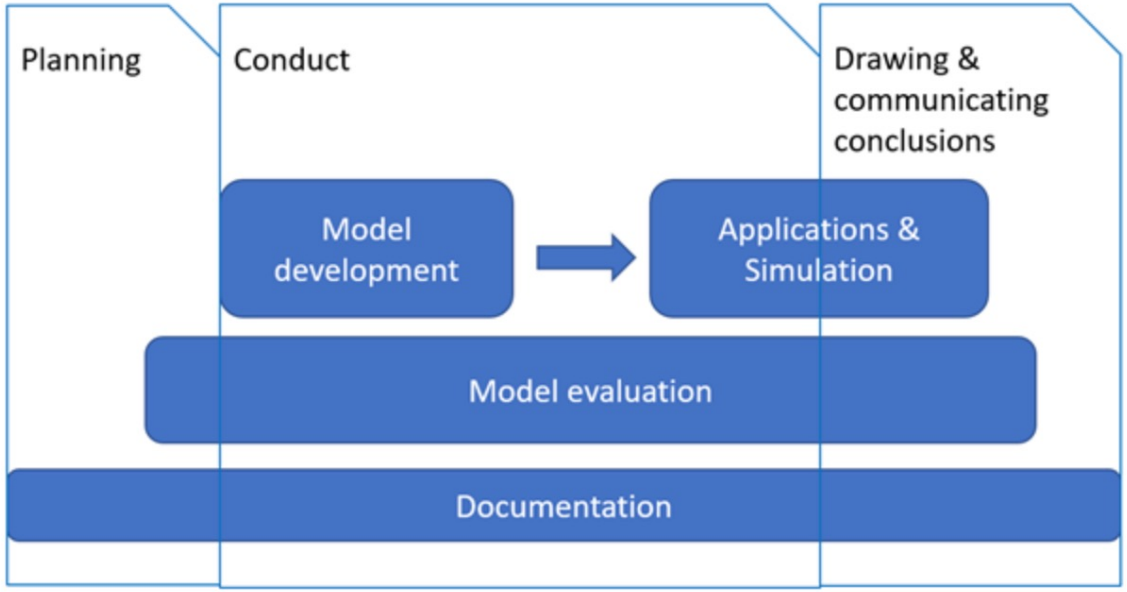
NOVARTIS | Reimagining Medicine

Motivation

The versatile nature of physiologically based pharmacokinetic (PBPK) modeling facilitates many opportunities of application but at the same time also for different approaches in terms of execution.

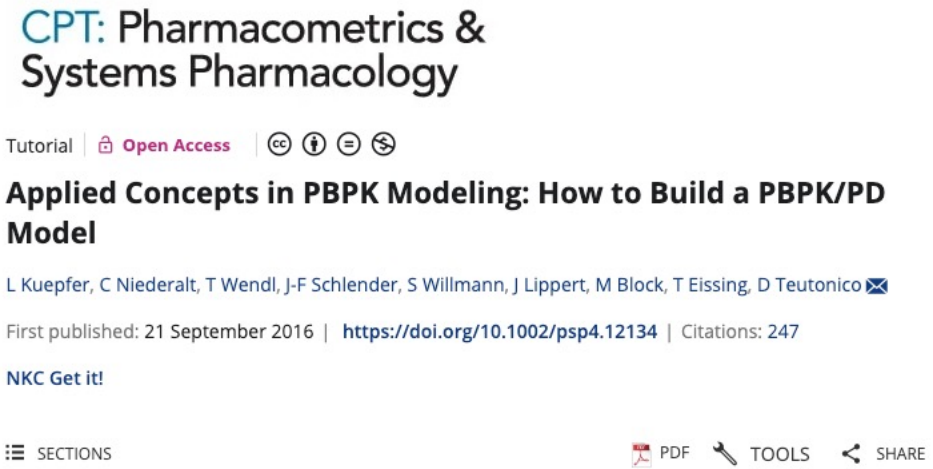
How should model development, including challenges addressed and assumptions made, be conducted and reported?

How should analyses be performed at different stages in drug development to ensure robust results with confidence, reproducibility and traceability?



Best practices for OSP Suite

Where it started …



CPT: Pharmacometrics & Systems Pharmacology

Tutorial | Open Access

Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model

L Kuepfer, C Niederalt, T Wendl, J-F Schlender, S Willmann, J Lippert, M Block, T Eissing, D Teutonico

First published: 21 September 2016 | https://doi.org/10.1002/psp4.12134 | Citations: 247

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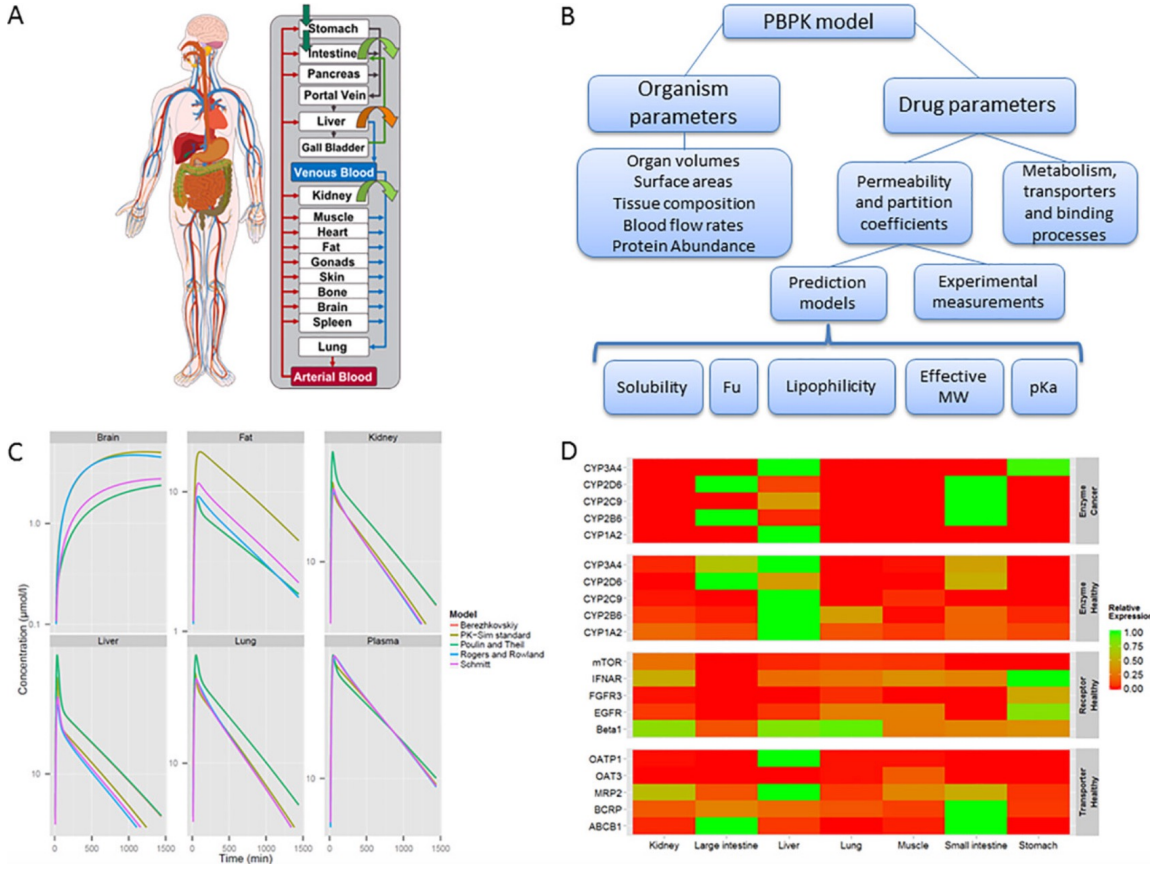
SECTIONS PDF TOOLS SHARE

- General introduction to PBPK modeling
- Building blocks in PBPK modeling
- Passive and active processes
- Best practices for PBPK modeling
- Case study: Developing a PBPK/PD model for Ciprofloxacin

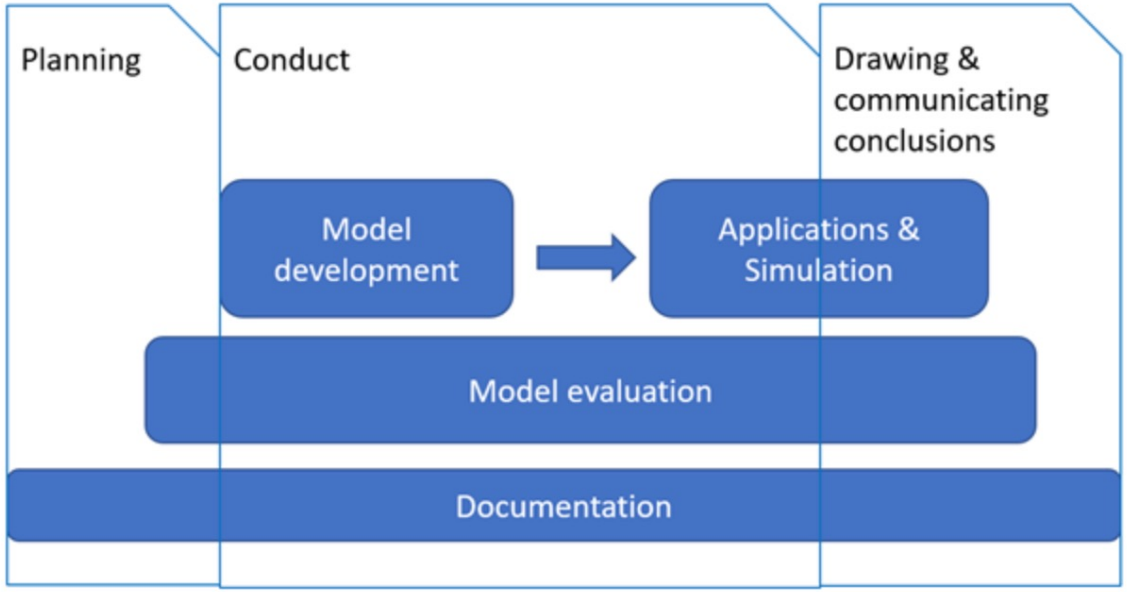


Best practices for OSP Suite

How it continued …

Working group after the open source launch with:

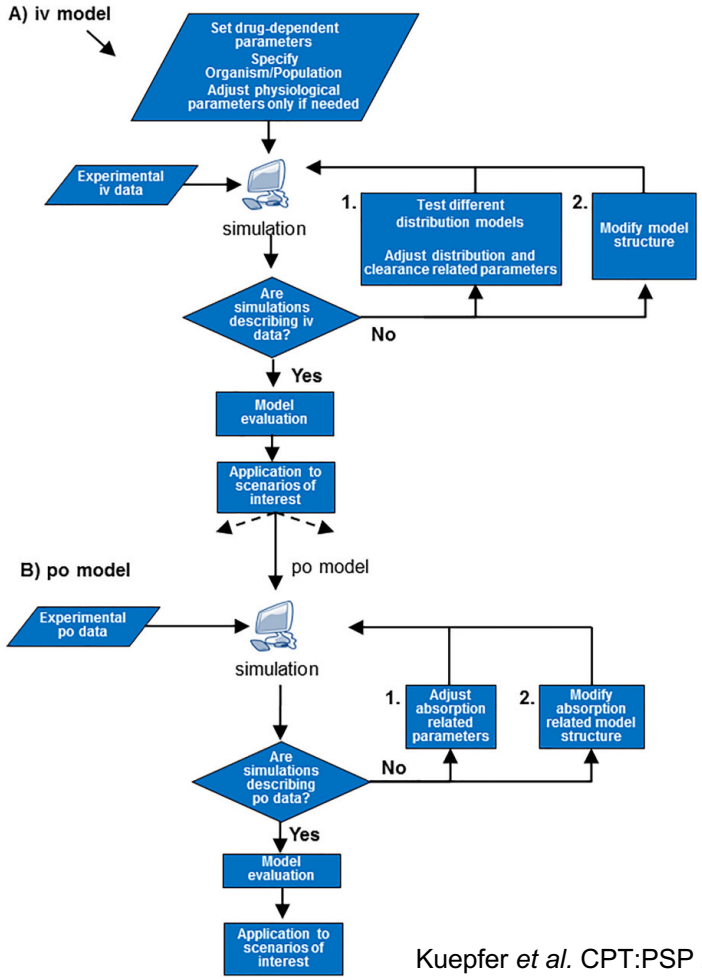
- Valerie Nock (BI)
- Erik Sjögren (Pharmetheus / Uppsala)
- Matthew Riggs (Metrum)
- Stephan Schaller (Esqlabs)
- Jan Schlender (Bayer / Novartis)



Best Practices | Open Systems Pharmacology (open-systems-pharmacology.org)

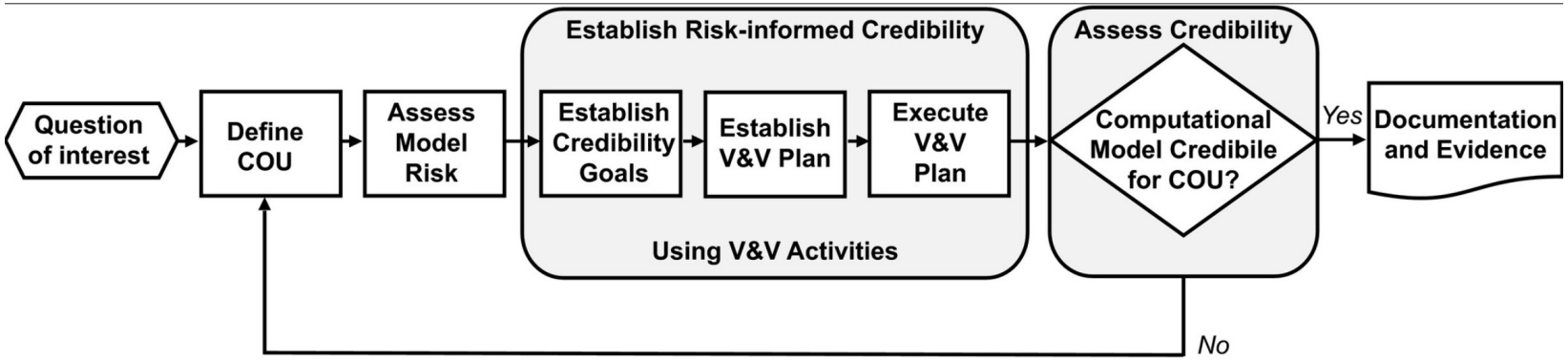
PBPK model development

- Conduct a requirements analysis before model development:
  - Define model purpose and context of use
  - Identify available observed data (*in silico*, QSA/PR, *in-vitro*, *in-vivo*).
  - Consider non-clinical and clinical data (e.g., animal PBPK model for human PBPK model development).
  - Evaluate impact of individual vs population mean data on model evaluation and qualification (variability and uncertainty assessments).
  - Outline model evaluation and qualification strategy.



Kuepfer *et al.* CPT:PSP 2016

PBPK model evaluation

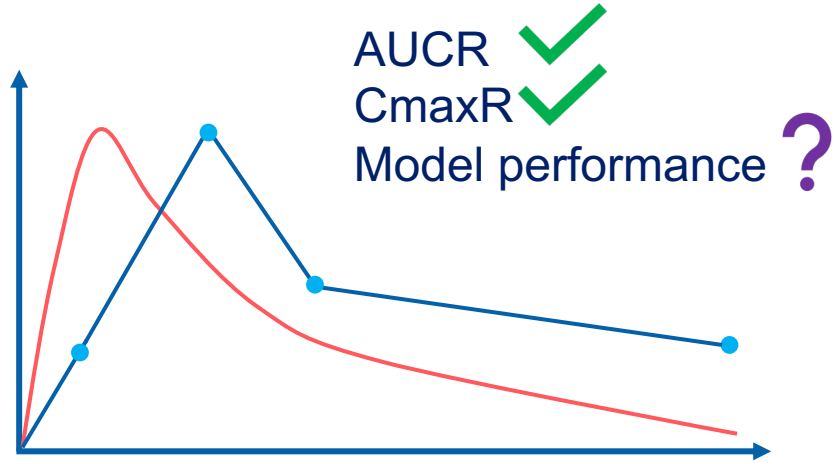


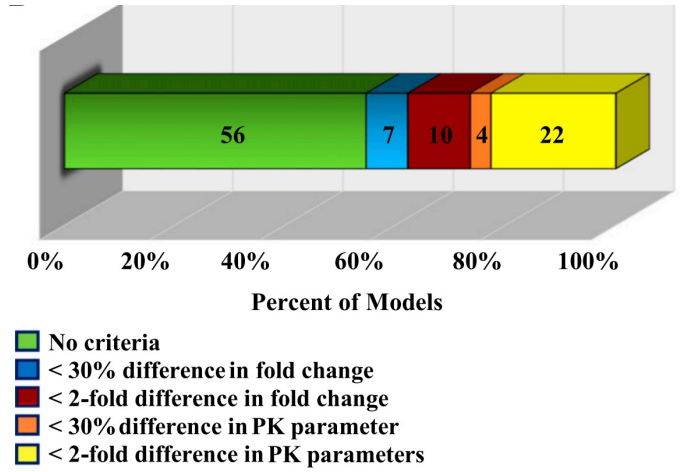
- Define the questions to address with the model in your analysis plan (context of use - COU).
- Consider the risk of biased or imprecise results from the chosen model.
- Define performance requirements for model success (model credibility).
- Define evaluation standards to determine if the model meets performance requirements.
- Assess model credibility during development and refine if necessary.
- Document evidence of model credibility.
- Develop a Credibility Assessment Framework to guide performance requirements.

Kuemmel *et al.* CPT:PSP 2020

PBPK model evaluation
Goodness-of-fit diagnostics

- Quantitative metrics of predictive performance for exposure endpoints of interest,
  - Cmax, Ctrough, AUC
  - Precision and bias calculations: root mean square error (RMSE), mean absolute error (MAE), mean relative deviation (MRD) geometric mean fold errors (GMFEs)
- Graphics
  - Overlay of observed and predicted concentration-time profiles. Depending on your focus (linear scale (e.g. focus on absorption) and / or logarithmic scale (e.g. focus on Distribution and elimination)).
  - Observed vs predicted of derived metrics, e.g., Cmax and AUC
- Standards for Model Evaluation Metrics
- Strategies for model development and evaluation
  - Case-based strategies for different application scenarios





Sager *et al.* Drug Metab Dispos. 2015

PBPK model evaluation
Parameter value sources and expectations of reliability

Use sensitivity analyses (SA) to evaluate the impact that variability or uncertainty in those values might have on model performance (e.g. Pedigree table)

PBPK and QSP modeling requires an understanding and acknowledgement of a **priori (structural)** and a **posteriori (practical) identifiability**, as well as characterization of uncertainty in the model parameters. **Local** and **global SA** can be used to quantify the influence of parameter variation on predictive performance.

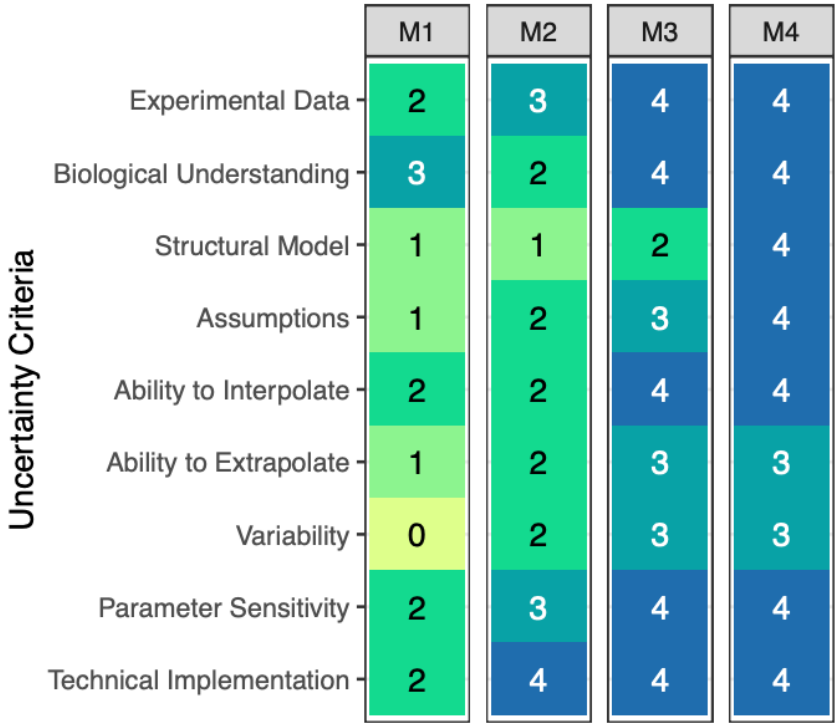


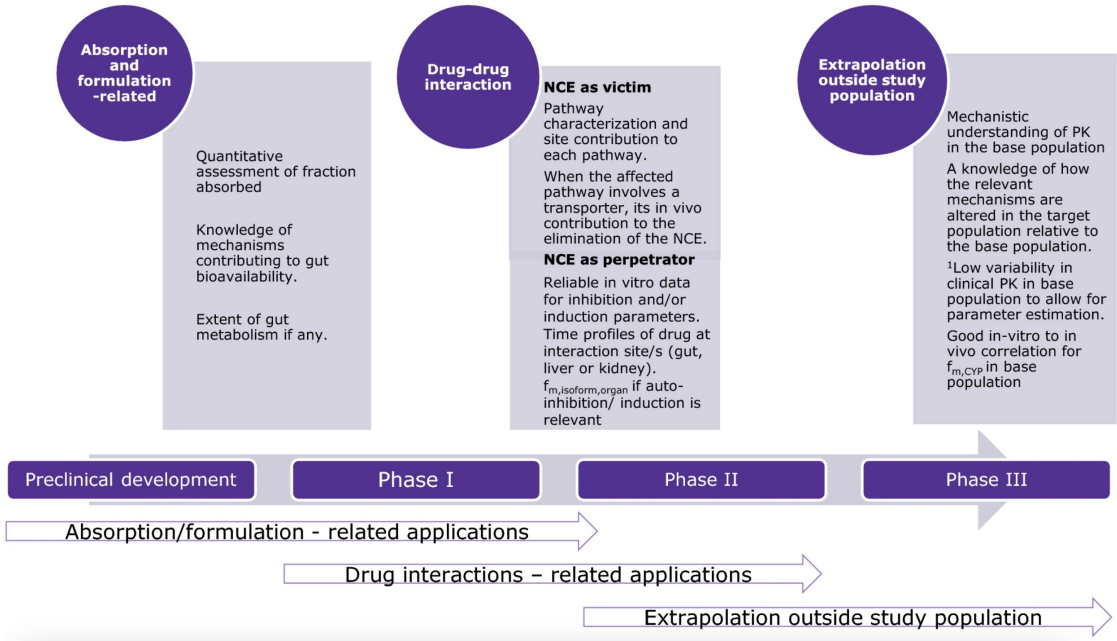
Figure 1 Example pedigree table for four hypothetical models that were used to: explore hypotheses about a particular disease pathway (M1), predict the first in human dose (M2), select a phase 3 dose (M3), and support a change in label (M4).

https://opensource.nibr.com/xgx/Resources/Uncertainty_Assessment_Pedigree_Table.pdf

PBPK model application and simulation
Simulation design / strategy considerations

A validated model can be applied to make prospective predictions for an unstudied population, or used to simulate an unstudied scenario

1. Consider physiological variability by applying population simulations
2. Sensitivity analysis on relevant parameters:
   i. Assess uncertainties in model results to identify the most sensitive ones for a specified model output.
   ii. This can include uncertain parameters for active processes or all parameters in the model.
3. Simulate best- and worst-case scenarios:
   i. Evaluate the effect of changing uncertain parameters to extreme values
   ii. Assess uncertainties regarding underlying mechanisms by simulating model alternatives.
   iii. Use the results to determine if the conclusions of the modelling work are robust.



Peter *et al.* ClinPK. 2019

PBPK model documentation

- **Essential documentation** attributes include:
  - clear analysis objectives
  - transparency on assumptions and their impacts
  - communication of key findings
  - materials for complete reproduction of the analysis
- For internal decision-making, a minimum level of documentation includes a short analysis/simulation plan or memo and a memo/**abbreviated report** or **slide presentation** documenting results
- For regulatory interaction or registration, a more **structured documentation** is require: analysis plan, simulation plan, and report, with sufficient detail for independent review including an electronic package
- **Analysis outputs** should be included in regulatory documentation, supporting dosing recommendations, claims, and addressing strategic questions
- **Quality assurance**, control, and verification ensure the integrity of data, processes, and technical solutions. Independent peer review and QC/verification measures are recommended
- **Assumptions** should be set, evaluated, and documented transparently. Important assumptions should be identified and pre-specified in the analysis or simulation plan.

Marshall *et al.* CPT:PSP. 2016

PBPK model documentation
Assumption setting, evaluation, impact assessment

Important assumptions	Justification	New/ established	Testable/ not-testable	Test/approach to assess impact	Evaluation
Pharmacological assumption Emax model fixed to 100% is a more physiological description of the data compared to a linear model.	Emax model is not better than linear model; however, for this drug class, Emax of 100% is more realistic	New	Testable with a wider range of concentrations (external/ future study).	Comparison of simulated metrics of interest between the two competing models.	To achieve a 90% response (assumed to be clinically meaningful) requires a twofold higher dose using the Emax model compared to the linear model. ➔ Test doses suggested by Emax model in Phase 2.
Physiological assumption No difference in clearance between healthy subjects and patients.	Patients with major depression disorders are considered as healthy subjects (in regard of ADME/PK features) once age and weight are taken into account.	Established	Testable by pooling healthy subjects and patient data, assuming that all other qualities across the pooled trials are exchangeable.	Combined analysis with healthy subjects and patients.	Combined analysis found only a 10% lower clearance in patients. ➔ No dose adjustment necessary for PK reasons
Disease assumption: Linear progression of disease with a slope of X/year	Cannot be estimated directly from the dataset, but supported by literature review	Established	Not testable with the present dataset	Sensitivity analysis changing the value of the slope for disease progression from X to Y	Varying the slope by X and Y will not change the selected dose for P3 ➔ Selected dose for P3 can be implemented Varying the slope by X and Y will change the selected dose for P3 drastically ➔ Three different doses should be tested
Data assumption: Data below limit of quantification (BLQ) have no impact on analysis results	There are <20% BLQ concentrations after treatment	New	Testable	Run final model with BLQ using M3 method (Beal 2001[82]) and compare to model without BLQ	Negligible changes in parameter estimates ➔ Final model excluding BLQ observations selected
Mathematical and/or statistical assumption Similar variability in clearance between adults and children	Physiological and PK knowledge	New	Not testable at the stage of predictions but can be evaluated with data from children	Sensitivity analysis on the variance value of clearance	If variance is 2-fold, children would be still with the highest dose in the safety range established for adults? ➔ Suggested dosing can be used in Children

Marshall *et al.* CPT:PSP. 2016

Summary

- Defined question of interest, context of use and specific intended purpose
- Assess the impact & risk of applying PBPK
- Define the outline of the strategy for PBPK
- Gather evidence for suitability of a PBPK platform
- Perform PBPK model development
- Assess and justify the applicability of PBPK for the intended use considering impact and risk
- Apply PBPK for intended use prudently under the umbrella of qualification
- Provide an appropriate level of documentation of planning, conduct and reporting

modified from Frechen and Rostami. Pharm Res. 2022
Best Practices | Open Systems Pharmacology (open-systems-pharmacology.org)

Thanks you!

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