PBPK model unknows vs. amount of data

- May not be possible to uniquely identify the parameter values θ
- Drop out non-sensitive parameters based on matrix of sensitivity functions

$$\frac{\partial y_i}{\partial \theta_j} \cdot \frac{\Delta \theta_j}{\Delta y_i}$$

- Which parameters Θ_j cause large/small changes to output y_i when changed?
  - Fix parameters that are non-sensitive
    - Part of “Preliminary model calibration”

Preliminary model calibration

- 1st goal : fix non-sensitive parameters
- 2nd goal : estimate prior distribution for the parameters
  - Fit ODE model for sensitive parameters to a “calibration” data sets via optimisation

Table 1
Pharmacokinetic studies in rats, mice, monkeys, and humans used for model development and evaluation.

Reference	Dose regimen	Matrix	Cal	Opt	Eva
Sprague Dawley rat					
3M unpublished data	Single oral dose at 2 mg/kg	Plasma	X		
Chang et al. (2012)	Single oral dose at 4.2 mg/kg	Plasma	X		
Johnson et al. (1979)	Single IV dose at 4.2 mg/kg	Urine	X		
Kim et al. (2016)	Single oral dose at 2 mg/kg	Plasma	X		
Kim et al. (2016)	Single IV dose at 2 mg/kg	Plasma		X	
3M unpublished data	Daily oral dose at 1 mg/kg for 4 weeks	Plasma		X	
3M unpublished data	Single oral dose at 15 mg/kg	Plasma		X	
Chang et al. (2012)	Single oral dose at 15 mg/kg	Urine		X	
Seacat et al. (2003)	Daily oral dose at 0.03, 0.13, 0.34, 1.33 mg/kg for 14 weeks	Plasma; liver			X
CD-1 mouse					
Chang et al. (2012)	Single oral dose at 20 mg/kg	Plasma; liver, kidney, urine	X		
Chang et al. (2012)	Single oral dose at 1 mg/kg	Plasma; liver, kidney, urine		X	
Cynomolgus monkey					
Chang et al. (2012)	Single IV dose at 2 mg/kg	Urine, plasma	X		
Seacat et al. (2002)	Daily oral dose at 0.03, 0.15 and 0.75 mg/kg for 26 weeks	Plasma		X	
Seacat et al. (2002)	Daily oral dose at 0.03, 0.15 and 0.75 mg/kg for 26 weeks	Liver			X
Human: general population					
Haug et al. (2009)	Unknown	Plasma	X	X	
Fabrega et al. (2014)	Unknown	Plasma; liver, kidney			X
Olsen et al. (2003a)	Unknown	Plasma			X
Olsen et al. (2003b)	Unknown	Liver			X
Olsen et al. (2008)	Unknown	Plasma			X

Note: All graphic pharmacokinetic data were extracted from selected studies using WebPlotDigitizer (version 4.10, https://automeris.io/WebPlotDigitizer/; last accessed December 28, 2018.). The 3M unpublished data were extracted from the Loccisano et al. (2012). Cal: Calibration; Opt: Optimized by MCMC algorithm; Eva: Evaluation.