Reporting and evaluation of predictive performance - what is missing in submissions today?

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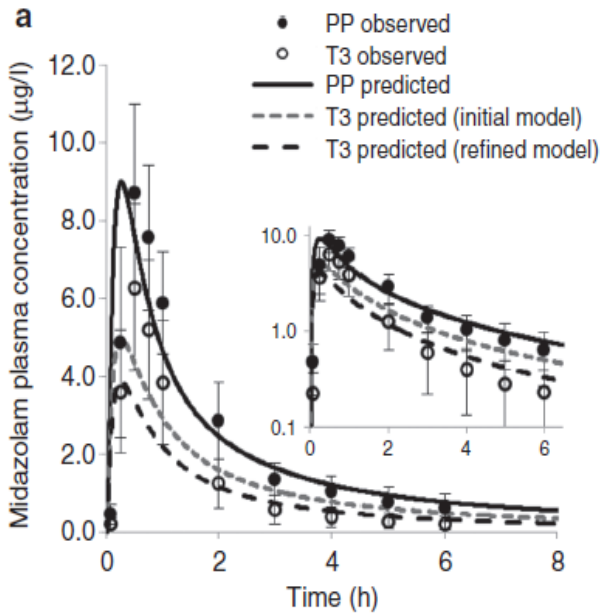
Comments on PBPK reports

- Standard of reporting of models is highly variable.
- Have discussed lack of qualification.
- Need to show drug model is predictive
- What is adequate precision? Often visual, or 2- fold?
- Parameters depend on the scenario- tend to focus on AUC, Cmax and T1/2.

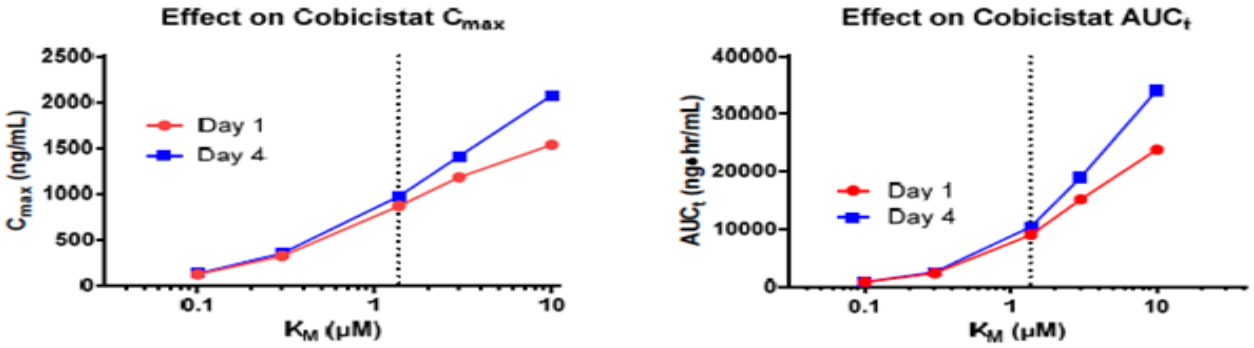


- Generally see a lack of investigation of uncertainty in the model parameters and discussion of their impact.
- Identifiability issues are ignored, or not addressed.
- Expected variability is not always well captured.

Characterising the level of confidence- the guideline

- The reliability of the model predictions should be addressed.
- Uncertainty reflects a lack of knowledge about the true value of a parameter or the validity of important assumptions.
- The uncertainty could be investigated by sensitivity analyses for specific input parameters.
- Often need to assess multiple parameters- methodology.
- Consider the impact of degree of uncertainty. Context of concentration-effect and concentration- safety.

Figure 11. **Effect of Varying the Michaelis Constant for the Metabolism of Cobicistat by CYP3A4 on Simulated Cobicistat Exposure**



Capturing variability in the prediction

- Uncertainty in parameters is not usually presented as a prediction with confidence intervals.
- Often have populations modelled and presented.
- Often 10 trials of 10 subjects. Enough?
- Total variability is not captured- arbitrary additional term sometimes used.