Multi-species translational PK/PD modelling in type 2 diabetes
Nathalie Perdaems, Sylvain Fouliard and Marylore Chenel
Clinical Pharmacokinetics and Pharmacometrics division, Servier, France

Context
In type 2 diabetes (T2D), several animal models are routinely used by the pharmacologists. Being able to describe the outcome of pharmacology studies (e.g. glucose tolerance tests, basal glucose and insulin), a single mechanistic PK/PD framework is of high value for compounds screening, support to dose selection in animals, and translation of the outcomes in patients. In this context, a PK/PD model was developed in ob/ob mice for a S Drug and a reference compound (Rosiglitazone). However, the disease features are different in each species and have to be well characterised using data without treatment before any compound effect transposition.

1) Building the PK/PD model in mice:
- PK models for S Drug and Rosiglitazone
- PK/PD model w/wo treatment

NONMEM version 7.3.0.

Results
1) PK/PD model in mice:
   • Good description of the 3 biomarkers
   • Population PK/PD parameters in mice
   • VPC after S Drug (Dose 4)

2) Prediction of an active dose in diabetic monkeys:
   • Inter-species translation
   • Scaling of system parameters
   \[ \theta_{\text{-scaling}} = \theta_{\text{mouse}} \left( \frac{\text{mouse weight}}{\text{monkey weight}} \right)^{\alpha} \]
   \[ \alpha = 1 \] for volumes
   \[ \alpha = -0.25 \] for rate constants

3) Refinement of the disease model in patients:
   • To scale S drug PK/PD model in monkeys to support dose-efficacy assessment
   • To refine the T2D disease model through PK/PD scaling in patients using literature data

Conclusion
In order to propose a relevant translational modelling strategy for drug development, the disease should be well understood and its specificities modelled in each species, as well as in patients. This scaling operations are far from being trivial and reference compounds are very useful in characterising the disease in each population.

References: