Use of Physiologically Based Pharmacokinetic (PBPK) Models to Support Canine Drug Product Development

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Introduction: Using Danazol (DNZ), a high permeability-low solubility BCS II drug, the following work demonstrates the use of PBPK models to support canine therapeutic drug product development. Simcyp Dog Version 14 is an in silico PBPK simulator which combines mechanistic modelling and simulation with *in vitro- in vivo* extrapolation (IVIVE) to predict drug pharmacokinetics in the beagle dog. The simulator combines the various aspects of **'Systems Data'** and **'Drug Data'** along with specifics of the **'Trial Design'** to predict **'WHAT IF'** scenarios using a mechanistic **'Bottom Up'** approach (**Figure 1.**)

Methods: Simcyp Dog Version 14 was used to predict the plasma concentration-time (Cp-t) of Danazol after intravenous (IV, 3 mg/kg) and oral dosing. The parameter estimation module was used to estimate the systemic clearance of DNZ after IV administration using the Cp-t profiles published by Liversidge et al[1]. The volume of distribution (Vss) was predicted using the Berezhkovskiy corrected Poulin & Theil method in combination with DNZ physico-chemical parameters. The passive intestinal regional permeability (P_{eff} x 10^{-4} cm/s) was predicted using the inbuilt mechanistic permeability 'MechPeff' model. Input parameters to the model are shown in **Table 1.** Keeping the disposition parameters constant, simulations were performed for oral dosing of (A) 20 mg/kg DNZ-β Cyclodextrin (β-CD) Solution[1]; (B) 20 mg/kg Aqueous DNZ Suspension[1]; (C) 2 mg/kg Solution/Suspension (API dissolved = 100%) with solubilizers[2]; (D) 2 mg/kg Solid API in Capsule[2]. A sensitivity analysis was also performed to analyze the effect of dose, particle size and intrinsic solubility on the fraction absorbed (fa) of DNZ.

Table 1.

Input Parameter	Value
Mol. Wt.	337.5
LogPo:w	4.53
fu	0.0272
B/P	1.306
Ionization type	Neutral
Predicted Dog P_{eff} ($x10^{-4}$ cm/sec)	0.663 (Jejunum)
Intrinsic solubility (mg/mL)	0.00084
V_{ss} (L/kg)	3.54
CL_{IV} (mL/min)	158
Gastric Emptying (h)	0.135 (Fasted)

Figure 1.

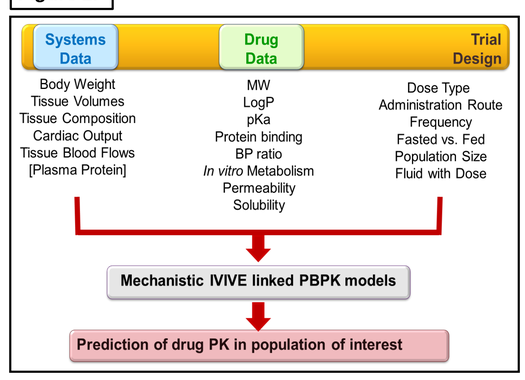


Figure 2.

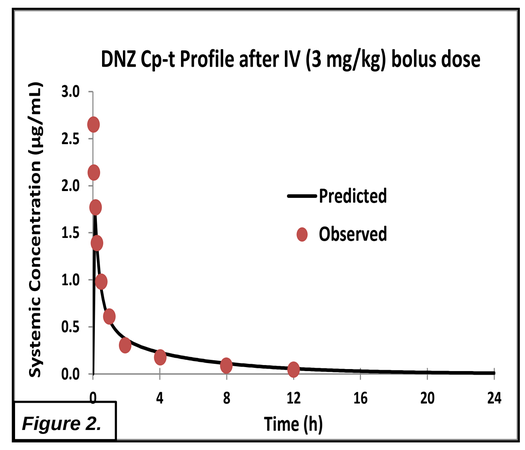


Figure 3.

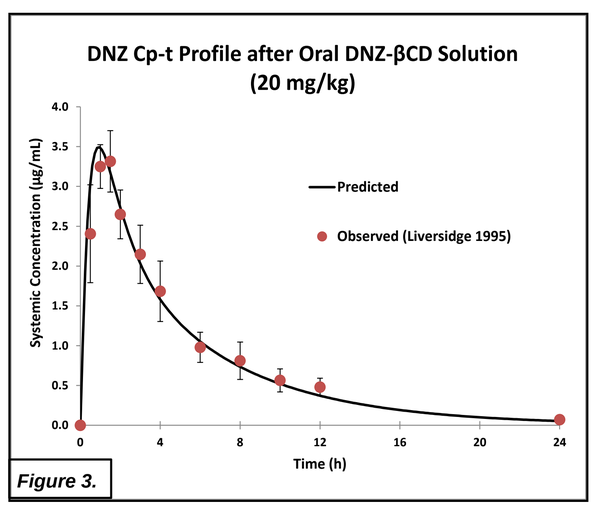


Figure 4.

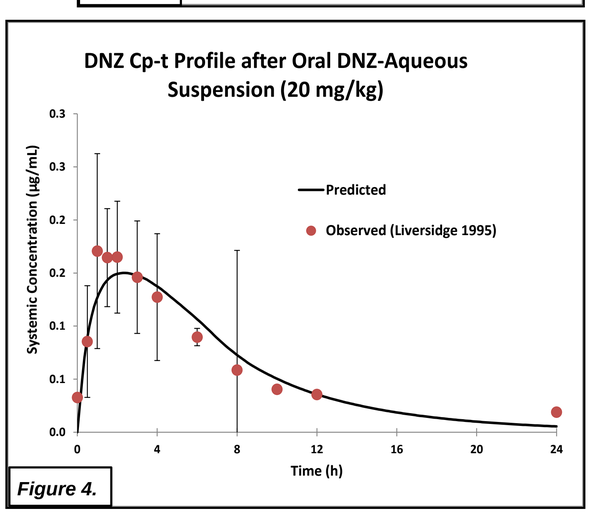


Figure 5.

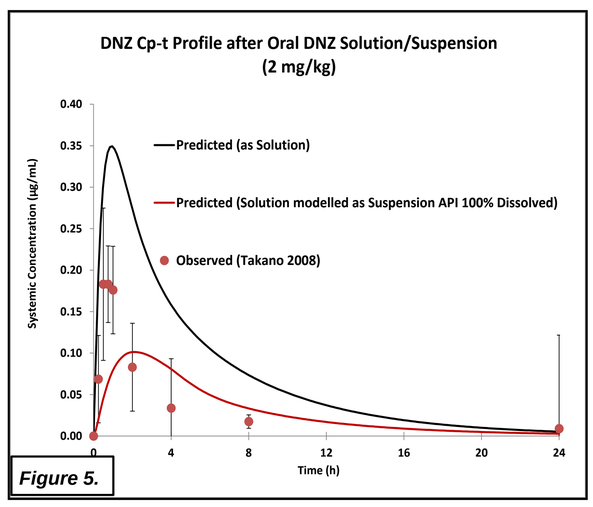


Figure 6.

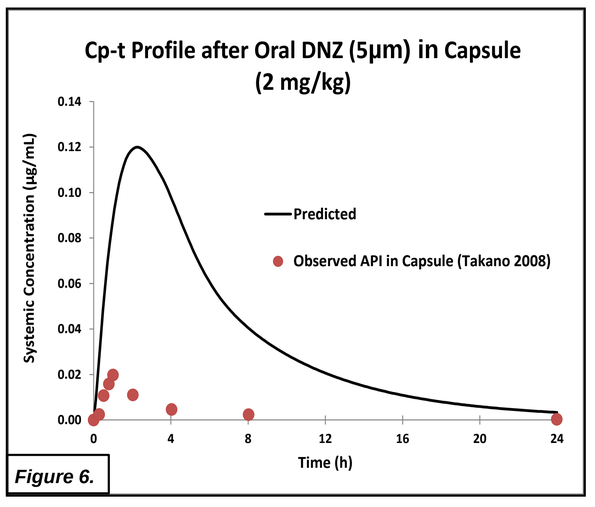


Figure 7.

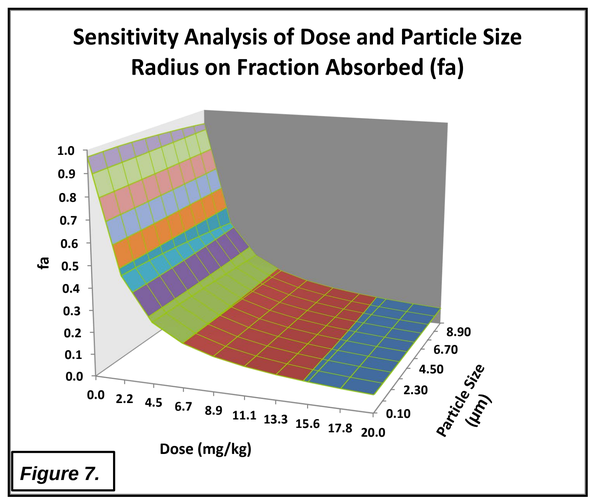
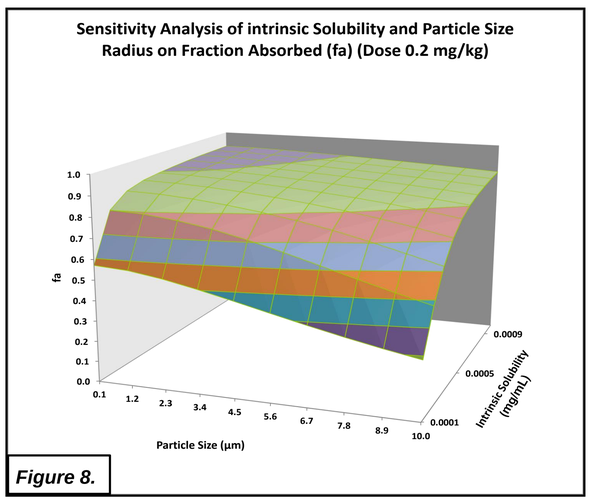


Figure 8.



Results: Figure 2 shows Simcyp Dog predicted vs. observed Cp-t profiles after IV administration of DNZ. The estimated systemic clearance was 158 mL/min and the predicted Vss was 3.54 L/kg for the simulated 10 kg beagle. Table 2 shows the predicted vs. observed PK parameters for the various orally dosed formulations of DNZ.

Table 2.

Figure	Formulation (Dose mg/kg)	Tmax, h (±SD)		Cmax, µg/mL (±SD)		AUC_{0-t}, µg.hr/mL (±SD)		F (±SD)	
		Obs.	Simcyp	Obs.	Simcyp	Obs.	Simcyp	Obs.	Simcyp
3	DNZ-βCD (20)	1.2 (0.2)	0.94 (0.3)	3.94 (0.14)	3.8 (0.9)	20.4 (1.9)	18.30 (5.5)	1.06 (0.12)	0.8
4	DNZ-Aqueous Susp (20)	1.7 (0.4)	2.88 (1.2)	0.20 (0.06)	0.16 (0.06)	1.0 (0.04)	1.33 (0.8)	0.05 (0.02)	0.06 (0.03)
5	DNZ Solution in Vit.E+DMSO (2)	0.5 (NA)	0.94 (0.3)	0.183 (0.04)	0.38 (0.1)	0.61 (0.14)	1.83 (0.6)	NA	0.8
5	DNZ Soln. Modelled as Susp (2)	0.5 (NA)	2.2 (0.8)	0.18 (0.04)	0.11 (0.04)	0.61 (0.14)	0.72 (0.4)	NA	0.3
6	DNZ 5µm IR Capsule (2)	1 (NA)	2.5 (0.9)	0.02 (NA)	0.13 (0.04)	0.074 (0.03)	0.9 (0.4)	NA	0.4

Figure 5 shows DNZ modelled as solution and suspension with 100% API dissolved (thus enabling interplay of precipitation & super-saturation on Cp-t). As solution, the simulations over-predict, but as suspension, the prediction are within 2-fold of observed indicating precipitation of drug in lumen.

Predicted Cp-t profiles of DNZ after oral administration of 5µm API in capsule showed significant over-prediction (Figure 6).

Figure 7 & 8 show the sensitivity of Dose, Particle Size (PSD) and Solubility (IS) on fa. The fa is sensitive to PSD only at lower doses up to 4.5 mg/kg.

This work is a result of the Co-operative Research & Development Agreement Between the FDA and Simcyp Limited

Conclusions: Simcyp Dog was reasonably successful in predicting the Cp-t profiles for a BCS II drug (DNZ) after administration of different formulations. This encouraging outcome supports the utility of these models as a tool for exploring 'What-If' scenario predictions to optimize canine drug product development, regulation and to help explain sources of population variability encountered in clinical practice. This work is 'In Progress' as we continue to explore reasons for over-predicting fa for low dose API in capsule.

References:

1. Liversidge G. Int. J. Pharm. 125:91-97, 1995. **2.** Takano R. Pharm. Res. 25 (10); 2334-44, 2008