Animal Health M&S Society: A new society promoting model-based approaches for a better integration of quantitative pharmacology in veterinary sciences

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Background

- **Situation:** Modeling & Simulation techniques have been sparsely applied to projects in veterinary sciences. The challenges in this area comprise of all apparent from the human field but include some additional specific to Animal Health.
- **Opportunity:** The foundation of this society provides the prospect to elaborate more systematically on the animal health specific challenges and to have a more organized exchange of ideas and experiences.

AHM&S Organization

- The Animal Health Modeling & Simulation Society (AHM&S) is a newly founded association (2012) that aims at promoting the development, application, and dissemination of modeling and simulation techniques in the field of Veterinary Pharmacology and Toxicology.
- The association is co-chaired by Pr. Johan Gabrielsson (Europe) and Pr. Jim Riviere (USA), and currently consists of core members from both academia and industry

Highlights

- Satellite workshop of AHM&S at PAGE 2013
- Session at PAGE 2013 dedicated to modeling within the Animal Health field
- Regular meetings of AHM&S members presenting and discussing latest results
- The AHM&S offers a new scientific platform promoting cross-fertilization among basic, translational, and clinical research between species, using model-based approaches.

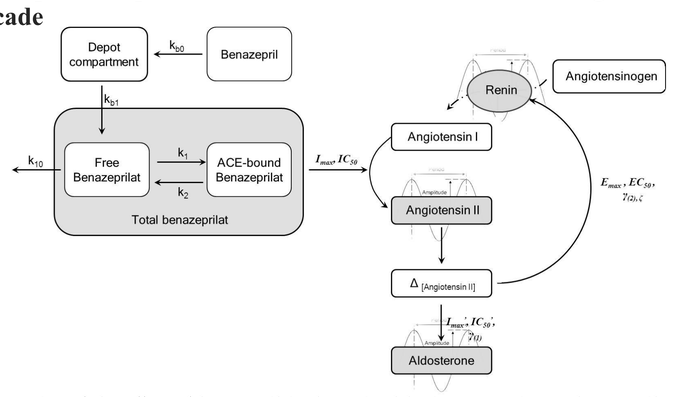
Objectives

- **The primary objective** of the society is to support the community to maximize the value of pharmacokinetic/pharmacodynamic data to identify factors (behavioral, physiological, pathological, managerial) accounting for differences in drug safety and efficacy in animals and addressing human health issues (residues in edible tissues, dissemination of antimicrobial resistances) .

Quantitative pharmacology

- Pharmacokinetics and pharmacodynamics comprise traditionally distinct disciplines within pharmacology. It is our intention to show that by deliberately, closely and systematically integrating these disciplines, our understanding of drugs and the efficiency and effectiveness of drug discovery and development may be greatly enhanced.

Figure 1. Integrated pharmacokinetic/pharmacodynamic model of benazeprilat disposition and effect on the canine renin-angiotensin cascade



The dynamics of the effect of benazepril is determined by its conversion to benazeprilat, the binding to ACE (angiotensin converting enzime), the following influence on aldosterone but also the feedback loop back to renin, influencing the whole cascade.
The population modeling included circadian rhythms for renin, angiotensin II and aldosterone[1] *and the effects of various compounds interacting with the renin-angiotensin cascade.*

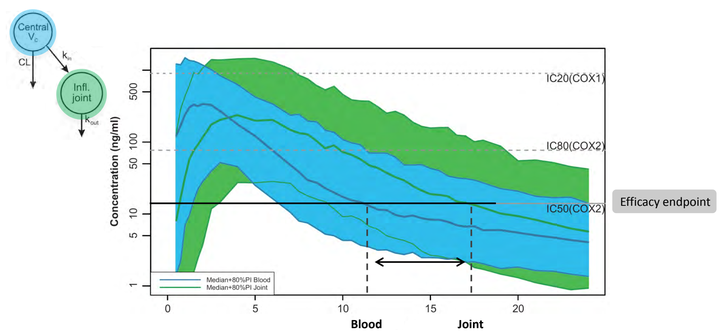
Trial design and analysis

- Optimization of trial design through simulation of scenarios; provide support to trial analysis, interpretation, and decision making. This goal includes but is not limited to: adaptive designs, dose finding, compliance modeling, and evaluation of endpoints.

Dosing regimen determination

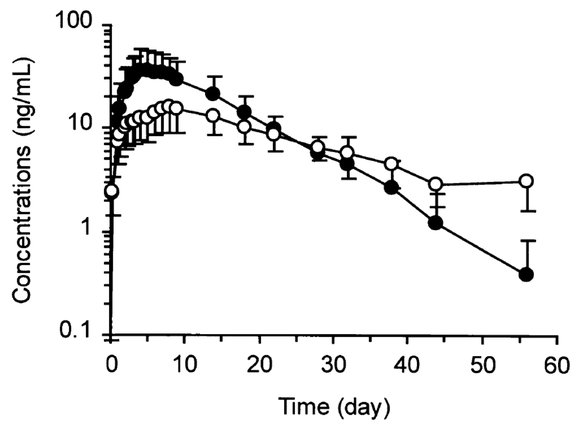
- Conduct of dose/exposure/response modeling to estimate an efficacious and safe dose for a new or already existing molecule to be used in companion animals (individual treatment), and food producing animals (collective treatment).

Figure 2. ***Distribution of robenacoxib in blood versus inflamed joints***



Prediction intervals for the distribution of robenacoxib in blood (blue) versus inflamed joints (green). The population modeling showed that the compound stayed longer in the inflamed joint supporting the once daily administration in dogs with osteoarthritis.[2]

Figure 3. Collective treatment: Licking or not – PK profiles change



Pharmacokinetic profiles of the ivermectin pour-on formulation when cattle was either tethered with a loose chain so that they could lick themselves and their immediate neighbors (black dots) or when they were isolated and fitted with a neck collar to prevent licking (open circles). Higher systemic availability of the compound was observed in "the lickers"(reproduced from [3]*).*

Disease modeling

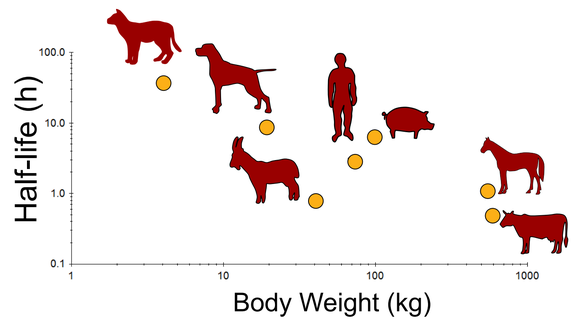
- Quantitative characterization of the disease process as a function of time and other predictors; to determine relationships among prognostic factors, biomarkers, and clinical outcomes in available data.

Inter-species comparison and scaling

Table 1. Diversity of species to cover for Animal Health[4]

Species	Animals (Mio)	Order
Dog	170	Carnivora
Cat	200	Carnivora
Rabbit	800	Lagomorpha
Sheep, Goat, Cattle	3332	Cetartiodactyla
Pig	956	Suidae
Horse, Donkey & Mules	105	Perissodactyla
Goose & Duck	1395	Anseriformes
Guinea fowl, Chicken,...	16877	Galiformes
Salmon & Trout		Salmoniformes
Others...		

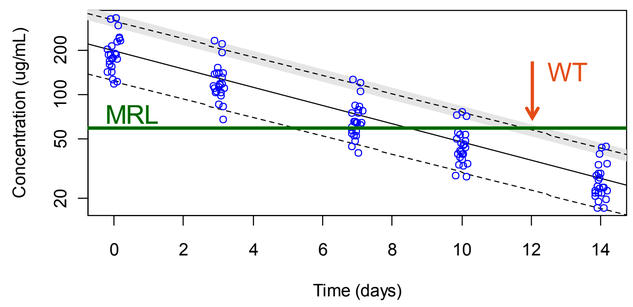
Figure 4. Inter-species scaling is not always simple – an example for salicylate half-life (from P-L Toutain following [5]). In addition interspecific extrapolations is also an issue for fish, birds and exotic species



Withdrawal time determination

- In food animal medicine the veterinarian must ensure that an effective dose of drug is given but also that the edible products from the treated animals do not contain residues of the drug at or above the permitted concentrations when processed for marketing.

Figure 5. Withdrawal time (WT) - determined by the population



EMA: "It is recommended in this paper to determine withdrawal periods at the time when the upper one-sided 95% tolerance limit for the residue is below the maximal residual level (MRL) with 95% confidence."

References:

[1] Mochel et al. Journal of Veterinary Pharmacology and Therapeutics 36(2):174-80, 2013.
[2] Silber et al. Pharmaceutical Research 27(12), 2633-45, 2010.
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[4] Toutain et al., in F. Cunningham et al. (eds.), Comparative and Veterinary Pharmacology, Handbook of Experimental Pharmacology 199, Springer-Verlag Berlin Heidelberg 2010.
[5] Lees, in Riviere JE, Papich MG (eds), Veterinary Pharmacology and Therapeutics, 9th edn. Wiley-Blackwell, Ames, IA 2009.

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