The full details of the published version of the article are as follows:

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JOURNAL: JOURNAL OF VETERINARY PHARMACOLOGY AND THERAPEUTICS

PUBLISHER: Wiley

PUBLICATION DATE: 28 May 2018 (online)

DOI: https://doi.org/10.1111/jvp.12666

Population Variability in Animal Health: Influence on Dose-Exposure-Response
Relationships: Part II: Modeling and Simulation

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Abstract:

During the 2017 Biennial meeting, the American Academy of Veterinary Pharmacology and
Therapeutics hosted a one-day session on the influence of population variability on dose-
exposure-response relationships. In Part I, we highlighted some of the sources of population
variability. Part II provides a summary of discussions on modeling and simulation tools that
utilize existing pharmacokinetic data, can integrate drug physicochemical characteristics with
species physiological characteristics and dosing information, or that combine observed with
predicted and in vitro information to explore and describe sources of variability that may
influence the safe and effective use of veterinary pharmaceuticals.

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    FDA's views or policies

Modeling and Simulation to Accelerate Understanding Sources of Variability in Animal and Translational Health.

Introduction

Computational modeling and simulation (M&S) is rapidly increasing in its acceptance as an important tool for describing, predicting and understanding how chemicals interact with biological systems (Lin et al., 2016). It can facilitate our appreciation of the sources of pharmacokinetic (PK) variability in a population, be it due to endogenous (e.g., enzyme polymorphisms, gender, age) or exogenous (drug-drug interactions, nutrients, disease, stress) factors. When applied correctly, M&S can decrease the financial and societal costs of drug development by optimizing study designs and by reducing the size and numbers of *in vivo* studies, thus satisfying the principles of Replacement, Reduction and Refinement (the "3R's). The availability of powerful desktop computers and user-friendly software have eliminated barriers to applying computational modeling in veterinary pharmacology and has shifted the challenge from one of software accessibility to that of its appropriate use.

Within the framework of the M&S arsenal, Monte Carlo simulations can be used to address uncertainties associated with interacting variables within real-life scenarios. Using repetitive random sampling from known distributions of model parameters, population dose-exposure characteristics can be generated. A well-known example of this application is the estimation of pharmacokinetic-pharmacodynamic (PK-PD) cutoff values when establishing antimicrobial clinical breakpoints. For example, using the distribution of PK parameter values derived from population PK studies, a specified dosing regimen, and a PK-PD target, we can define the minimum inhibitory concentration (MIC) at which 90% of the treated patients will achieve that PK-PD target (Maaland et al, 2013). Alternatively, it can be used to estimate the doses needed to achieve some targeted therapeutic effect (Dorey et al., 2017; Rey et al., 2014).

In keeping with our appreciation of the importance of these tools to support veterinary drug product development and use, an international group of modeling scientists were convened to promote and optimize the practice of M&S in animal health [the Animal Health Modeling and Simulation Society (AHM&S)] (Mochel et al., 2013b).

Approaches to the development of models describing and predicting blood level profiles can be described as top-down, bottom-up, or middle-out (Jamei et al., 2009; Tsamandouras et al., 2015).

Top-down: The fitting of blood level profiles to mathematical equations that define pertinent PK parameters and describe the location (e.g., means and medians) and variability associated with these parameters. The variability is further modeled in an effort to explain the sources of this variability (population subgroupings). The explained sources of variability can then be separated from the unexplained (random) error. The top-down approach can be used to support individualized dosage adjustments or to predict the dose-exposure relationships that may be observed in individuals that are within the modeled subgroup. These models are often empirical in nature and lack interpretability in terms of specific mechanisms (Duwal and von Kleist, 2016). However, they satisfy the principles of parsimony (also known as 'Ockham's Razor') whereby the descriptive model is optimized with the fewest parameters.

Bottom-up: A systems approach integrating drug physicochemical characteristics, patient characteristics, drug PK (where volume of distribution and clearance can be specifically modeled in accordance with observed PK profile information), transporter function, and enzyme abundance and kinetics. The models are used to predict the distribution of blood level profiles likely to be observed across a patient population. These models are also invaluable for exploring "what if" scenarios, for identifying the rate limiting factors in drug absorption and clearance, predicting drug-drug interactions, for dosage regimen selection, and for predicting dose-exposure relationships in the presence of polymorphisms in enzyme or transporter functions (Darwich et al., 2017; Margolskee et al., 2017):

Depending upon the available information and the objective for employing this method, the bottom-up approach may be executed using either fully mechanistic or semi-mechanistic models:

- Fully mechanistic model: PK predictions are generated by integrating the full PBPK model (host physiology, drug physicochemical characteristics, formulation effects, and trial design) with the underlying processes driving drug absorption, distribution, metabolism and elimination. These models can segregate processes of absorption, distribution and elimination. Drug clearance is typically estimated through the use of

in vitro metabolism data. Since the resulting models do not rely on any in vivo data to arrive at the model input parameters, these are considered fully mechanistic models. However, purely mechanistic models are often difficult to establish due to information gaps present in the necessary in vitro metabolic data. For this reason, in vivo clearance estimates (e.g., from published sources, potentially from a different population than that being modeled) are input into the model and a retrograde calculation used to derive an "in vitro intrinsic clearance". That estimated value is used to generate the species-specific systemic clearance value using physiological scaling parameters to harness the inter-individual variability of that species (T'jollyn et al., 2015). Such models still qualify as being fully mechanistic because predictions reflect all identified sources of population variability.

- Semi-mechanistic model: existing PK data such as volume of distribution and clearance are set as the specified model parameter values. In this case, the opportunity to estimate the inter-individual variability is lost. However, a fully mechanistic approach can still be used to explore the process of oral drug absorption. Semi-mechanistic methods are often used when establishing in vivo/ in vitro correlations, predicting formulation effects on drug bioavailability, or for formulation optimization.

Middle-out: This is a hybrid of bottom-up and top-down approaches where observed clinical data ('top down') are examined from the perspective of predictions derived through the use of mechanistic models (bottom-up). The resulting fitted output values are used to refine the PBPK model in accordance to the changes necessary to minimize the difference between observed and fitted values (Tsamandouras et al., 2015; Zhuang and Lu, 2016). While this approach to M&S can potentially be a powerful alternative to traditional compartmental or population-based modeling methods, it is important to recognize it also has a substantial risk of generating model parameter values that while providing a good fit to the observed data, may lack biological relevance (or may lack logical rationalization as to the fitting of that parameter). Therefore, investigators should use the middle-out approach with great caution, acknowledging the potential limitations in their data interpretation and in predictions generated via model extrapolation.

The relationship between these three approaches is illustrated in Figure 1.

Nonlinear mixed-effects (NLME) models

NLME modeling is typically a top-down approach that is used to describe the disposition kinetics of therapeutic drugs and to identify sources of population PK variability.

Prior to the 1970's, population parameters were estimated by pooling the individual subject data into a single concentration-time profile, ignoring between-subject differences (referred to as 'naïve pooling'). In subsequent years, the individual subject data were fitted separately and the average parameter values were determined. This method of data analysis is often referred to as a 'two-stage approach'. Both naïve pooling and two stage approaches are subject to potential bias due to problems with dosing compliance or to missing data (Mould and Upton, 2012).

A major shift in population PK characterization occurred when NLME models integrated into the therapeutic drug monitoring of heart disease patients to optimize their digoxin dosing regimens (Sheiner et al., 1972). The authors proposed a quantitative approach for analyzing clinical sparse data, recognizing that the relationship between observed data and model parameters was non-linear.

When using naïve pooling or two stage methods, between-subject variability is perceived as 'noise' that should be overcome. Consequently, these approaches often lead to the use of complex study designs and restrictive inclusion criteria (Ette and Williams, 2004). In contrast, the core attribute of NLME models is its ability to separate the (between- and within-subject) variability from the measurement error (noise). In so doing, much of the between-subject variability can be explained by identifying influential population characteristics (e.g. age, bodyweight, gender or breed). These characteristics can then be incorporated into the model structure to further expand its exploratory value. The residual (unexplained) variations in drug concentrations or responses consists of within-subject variability, inter-occasion variability (e.g. change in oral bioavailability between dosing sequences), bioanalytical measurement error, and model misspecification (i.e., approximation errors associated with the mathematical description of the true underlying biology).

The use and development of NLME PK-PD models in human medicine continues to expand due to efforts to identify covariates describing physiological factors known to affect drug

disposition and/or responses. They can also be used as a framework to conduct meta-analysis studies across various published literature (Li et al., 2014, 2015; Ogungbenro and Aarons, 2014), an application that could have widespread applications in veterinary pharmacology. Within animal health, published examples of NLME modeling are also available (e.g., Silber et al., 2010; Cox et al., 2011; Fink et al., 2013; Pelligand et al., 2016, Mochel et al., 2013a, 2014, 2015) and have been described in a recent review article by Bon et al. (2017). Interested readers can refer to these publications for further details.

Physiologically-Based Mechanistic Oral Absorption Modeling in Dogs:

Physiologically based pharmacokinetic (PBPK) models linked with in vitro – in vivo extrapolation (IVIVE) techniques form a bottom-up platform integrating diverse information related to species (physiology & anatomy) and drug parameters. The models then translate these diverse sources of information into a description of drug PK properties, enabling investigators and clinicians to prospectively predict PK profiles. These predictions can be used to reduce the need for in vivo data and is particularly useful during initial stages of drug product development (predicting the impact of formulation and/or patient characteristics on dose-concentration-exposure relationships). However, model qualification and verification ultimately necessitates an evaluation of how well the in silico predictions compare to that of the actual in vivo data.

The Simcyp PBPK platform (human and animals) is based on an original and unique concept of an 'inter-linked component' structure that enables a separation of trial design parameters (dose, route, frequency of administration etc.), animal (species) parameters (system-anatomy, physiology etc.) and drug parameters (drug physicochemical characteristics). When interacting with each other via mechanistic – IVIVE models, these parameters determine predicted values for drug absorption, distribution, metabolism, transport and elimination (Jamei 2016) (Figure 2).

Using this framework, other complex modular components can be added such as:
   a. The Advanced Dissolution, Absorption and Metabolism (ADAM) model to mechanistically predict absorption of orally administered drugs
   b. Permeability limited liver, gut, kidney and brain models to study the effect of efflux and uptake transporters in the tissue organ of interest

Although this discussion has focused on the Simcyp PBPK platform, numerous other programs are also available. Each one presents its own unique set of attributes and assumptions and the selection of one over the other often reflects personal preference (e.g., see Margolskee et al., 2017b). Examples of available software tools include GastroPlus^{TM} (http://www.simulations-plus.com/assets/GastroPlus_1-24-17.pdf), GI-Sim (Sjögren et al, 2013), and PK-Sim^R (http://www.systems-biology.com/products/PK-Sim.html).

Regardless of the platform selected, when a well-informed PBPK model is coupled with reliable estimates of intrinsic drug parameter values (internal validation) and its performance has been confirmed using external datasets (external validation), the prediction model becomes more robust. This approach is commonly referred to as an 'in vitro-in vivo extrapolation linked PBPK approach' (PPBK-IVIVE) (Rostami, 2012). Furthermore, the separation of systems (species) parameters from the drug parameters also enables the investigation of 'what-if' scenarios and model extrapolation. This extrapolation may take the form of translating data generated in a normal healthy beagle population to predict profiles that may occur in a population of dogs from another breed, to dogs expressing an enzyme or transporter polymorphism with a given polymorphism (enzyme or transporter), or in dogs associated with a difference in a particular physiological attribute such as altered renal function, faster gastrointestinal transit time, or a difference in the percentage of body fat.

There are numerous published examples where PBPK software has utilized canine-specific population models to explore the critical factors influencing in vivo drug absorption. For example:

- The importance of particle size on the oral absorption of a low solubility compound, cilostazole, was studied using PK-Sim^R in beagle dogs (Willmann et al., 2012).
- A comparison of human and canine oral absorption of various experimental formulations of ciprofloxacin was generated using GastroPlus^R (using both the human population module and the beagle population module), showing differences in the primary location of drug absorption in dogs versus humans and underscoring the role of absorption (as opposed to dissolution) constraints on the observed bioavailability limitations in dogs versus humans. These results were consistent with the PK

observation that sustained release ciprofloxacin formulations are inappropriate for use in dogs (Martinez et al., 2016, 2017).

- The ability to model the effect of food on oral bioavailability was explored for weak acids (mavacoxib and celecoxib) in dogs using the beagle population module of Simcyp (Martinez et al., 2013). Food effects in dogs were also accurately modeled for cilastazole using PK-Sim^R in beagle dogs (Willmann et al., 2012).

- Most recently, a mechanistic approach was applied for predicting the oral bioavailability of danazol when administered across a range of formulations to beagle dogs. Predictions were subsequently verified using published *in vivo* data. Using the ADAM model that divides the dog gastrointestinal tract (GIT) into 9 segregated segments (stomach to the colon), the rate of drug dissolution, permeability, gut metabolism and fraction absorbed (fa) were mechanistically predicted. A unique aspect of the ADAM model is its ability to assess the dynamic behavior of GIT fluid volumes based on GI transit times (GITT), GIT secretion rates and absorption rates. The impact of formulation both on in vivo dissolution and absorption were explored. Preliminary results from this work were presented at the European Association of Veterinary Pharmacology and Toxicology meeting in 2015 (Pade et al., 2015), and the full study is currently submitted for publication (Pade et al., 2018).

Unfortunately to date, there is a gap in the publication of studies using in silico models to support drug development in dogs even though software programs such as GastoPlus^R, PK-Sim^R, and Simcyp^R have physiology modules specifically tailored to the beagle dog. Hopefully, these examples of the insights and of the efficiency that can be gained by using PBPK approaches will stimulate the application of this tool to support formulation development, for understanding the factors that can influence the absorption and in vivo dissolution of oral drug formulations, and sources of variability that can exist across a population of dogs.

Practical Implications of Population Variability in the Animal Health Industry

The session concluded with a presentation and discussion of the use and concern of M&S in animal health. The key points addressed are provided below:

- *Uncertainty regarding the current regulatory framework concerning population variability in the drug development business?*

From the perspective of human therapeutics, the importance of considering both genotypic and phenotypic variability is recognized and therefore has been incorporated into the regulatory guidances both of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) and of the European Medicines Agency (EMA). In addition to general guidelines on population PK (CHMP/EWP/185990/06 and FDA GFI 1999) and on the use of PBPK models (CHMP/211243/2014 and FDA draft GFI 2016), specific guidelines are now available for a variety of factors that can alter drug dose-exposure-response relationships. Furthermore, the CHMP/37646/2009 and FDA GFI 2013 encourage early implementation of pharmacogenomics testing during the clinical phases of product development to promote a more complete understanding of the kinds of PK and PD variability that should be considered within the target patient population.

The potential impact of genotypic and phenotypic variability has not been comparably appreciated or addressed by either the US or by the European regulators of veterinary drug product applications. Currently, due to the absence a legal framework supporting a requirement for the submission of PK data, the FDA Center for Veterinary Medicine (CVM) cannot routinely require such information to be generated as part of a new animal drug application. In contrast, PK data generated at the clinical dose are required within Europe for veterinary drug registration and the EMA's Committee for Medicinal Products for Veterinary Use (CVMP) has published a draft guideline on the conduct of PK studies in the target animal species
(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/11/WC500238890.pdf).

It is interesting to note that the 2017 CVMP draft guidance includes concepts of population PK as was originally addressed in the January 2016 EMA/CVMP concept paper titled "Concept paper for the revision on the guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-Final)". This concept paper briefly pointed to the need to consider sources of veterinary PK variability as potentially captured via population PK studies, the use of in silico PBPK models, by assessing the difference in PK in healthy versus diseased animals, and by developing an understanding of the impact of

pharmacogenetic variation on population dose-exposure-response relationships. In that regard, should be noted that this approach has already been used to support pre- and post-marketing adjustments in dosage regimen for the veterinary drug, mavacoxib (Cox et al., 2011).

The other mention of population variability within the veterinary regulatory framework is embedded in the latest revision of the Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1). For the selection of clinical breakpoints for veterinary antimicrobial drugs, the guideline encourages the use of Monte Carlo simulations (see supra), using PK data for stochastic estimation of antimicrobial exposure in the target population at the licensed dose.

- *Pinpointing the origin of the variability in veterinary species:*

Although not originally conducted to support veterinary drug development, the study by Paulson et al. (1999) was a landmark paper within veterinary community because it revealed a genetic origin for the large differences in celecoxib metabolism observed across a group of 242 laboratory beagles. Since then, similar within-breed variability in PK (driving the observed variability in the duration of clinical efficacy) was reported with the veterinary drug cimicoxib (Jeunesse, et al., 2013). Although clinically relevant variability in population PK was not observed among studied client-owned dogs (representative of 4 different breeds), Part I of this AAVPT meeting report provides numerous examples of clinically relevant polymorphisms now recognized across veterinary species (Martinez et al., submitted for publication)

Understanding some of the potential reasons for sub-optimal responses is grounded in the link between PK and PD (Toutain and Lees, 2004), population variability (sources of inter-animal variability identified through the inclusion of explanatory covariates), and inter-occasion variability (where the kinetics may vary within the same subject dosed one several occasions). Sources of PD variability include the variability associated with disease expression, the time course of its clinical manifestation, and the relationship between drug exposure and clinical effect. Experienced clinicians can address the issue of PD variability by: (i) monitoring the clinical response (e.g., the blood pressure in response to antihypertensive therapy); (ii) monitoring biomarkers of a clinical response (e.g., glucose

curve, international normalized ratios for anticoagulation); (iii) the use physiologically relevant information to adjust dosage (e.g., carboplatin dose informed by GFR in cats, see Bailey et al. 2009); and (iv) relying on therapeutic drug monitoring. Nevertheless, adverse drug reactions (including lack of efficacy) still occur due to variability in dose-exposure-response relationships.

- *What could the future look like?*

The "hot button question" was whether (when) it is appropriate to document variability in the target population within the drug development process? A SWOT (Strength/Weakness/Opportunity/Threat) analysis was proposed based upon results obtained when interviewing a sample of representative members of the veterinary industry, regulatory bodies and academia (Figure 3):

The results of this analysis can be summarized as follows:

Perceived Strengths:
Internal resources can contribute to the usefulness of documenting population variability in animal species through: (i) identification of relevant covariates; (ii) dose optimization; (iii) providing an opportunity to use sparse PK data to document clinical population behavior; (iv) the identification of factors that can alter drug kinetics in edible tissues; and (v) provision of an approach for handling situations where dose is uncertain (for example when the drug is given to a group in food or water). With the availability of PK competency within a drug company, a small increase in effort (e.g., training) could yield highly rewarding results.

Perceived Weaknesses:
There continues to be numerous factors that lead to a resistance to the documentation of sources of population variability. These include: (i) a perceived lack of incentive, as this information is not currently encouraged or recommended by regulatory agencies, particularly the USFDA CVM; (ii) a limited awareness of altered therapeutic (safety and effectiveness) profiles or drug residue levels that have been documented in animal health due to drug-drug interactions, polymorphisms in influx or efflux transporters or in drug metabolizing enzymes; iii) a lack of published studies showcasing the impact of physiological and environmental factors on drug PK and therefore PD and residues; iv) a lack of awareness of and training in

veterinary population PK; and (iv) concerns associated with potential additional cost, time delays, regulatory oversight, and the need to outsource these analyses.

Perceived Opportunities:

M&S approaches serve as highly effective tools for combining preclinical and clinical data to: (i) de-risk dose-determination studies; (ii) enrich clinical trial design (allows for the recruitment of an animal population that is more likely to respond to the drug); (iii) inform the drug sponsor of conditions that may necessitate therapeutic drug adjustments; and iv) provides a strong basis for the understanding of adverse drug reaction by clinicians and during post-marketing surveillance. Moreover, M&S provides an important mechanism by which once can reduce animal use (3Rs), especially though model and data sharing, thereby promoting a OneHealth solution to the problem of antimicrobial resistance.

Perceived Threats:

Expressed concerns resisting the documentation of variability in target population include: (i) the fear that variability documentation may become an additional compulsory requirement imposed by regulators; (ii) a perceived lack of relevance and motivation for this information in veterinary medicine; (iii) concerns that regulators will punish innovation (lack of reward and more constraints imposed); and iv) this could lead to a re-opening of flexible labelling concepts to address potential needs to adjust dose or withdrawal times as a function of drug-drug interactions or population subgroups.

Future recommendations:

Based upon recommendations and expressed comments received during this one-day session, it is concluded that the following initiatives should be explored to encourage and facilitate the adoption of population variability characterization by the veterinary drug industry:

- Regulators and industry should showcase proof of concept cases where population variability characterization led to successful registration outcomes. There needs to be greater attention given to the sharing of evidence that this business model is cost effective for companies that wish to make the best possible use of PK and PD data accumulated during all stages of drug product development. Regulators should consider incentivizing the use of PK and M&S approaches through (for example) the possibility of omitting

certain studies (e.g., dose-determination studies) and/or the acceptability of confirming efficacy in one or (or limited) dosage regimens in clinical trials. Industry-government discussions should occur early during the drug application process to facilitate implementation of population PK-PD as part of the application dossier.

- Academia and industry should be encouraged to increase their level of interaction through the development of collaborative research projects, the sharing of expertise, and through the development of model banks such as those provided by the Drug Disease Model Resources (DDMoRe) consortium (http://www.ddmore.eu/). In veterinary drug development, innovation in population PK and pharmacometrics is often driven by academic centers rather than by government due to the limited resources of regulatory agencies. Scientific associations such as the AAVPT, the European Association of Veterinary Pharmacology and Toxicology (EAVPT), the AHMSS, and specialist colleges such as the European College of Veterinary Pharmacology and Toxicology (ECVPT) should rejuvenate and develop comprehensive training programs in pharmacometrics and computational pharmacology to meet the evolving needs of the industry and of the animal health community
(http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2009/11/WC5000099 23.pdf).

- Training should be offered to promote progression to different competency tiers, including: (i) basic "essential awareness"; (ii) intermediate knowledge and skillset development for assessors at regulatory agencies; and (iii) expert scientist through the development of tailor-made courses. Importantly, joint training for assessors and pharmaceutical industry could help stakeholders and regulators to "speak the same language".

- Software developers can play a pivotal role in ensuring the acceptance and use of PK/PD and population PK modelling and PBPK software by outreach to non-specialist scientists within industries. This outreach could take the form of webinars and workshops.

Concluding Thoughts

When studying the pharmacology of a drug, the modeling approach (top-down versus bottom-up or a hybrid of the two) should be chosen based on research objectives and by what is already known about a compound. If very little is known, empirical and descriptive models

can be invaluable for providing an initial understanding of the interactions that can occur between the drug and a biological system. Empirical (model fitting) approaches are also appropriate if the research goal is very specific (e.g., to compare the bioavailability between two formulations of a given drug). As our knowledge about a drug increases, the development of mechanistic models become possible, and these can then be used to extrapolate and predict the outcomes of different 'what-if 'scenarios to gain insights into formulation effects and population differences in drug exposure.

While therapeutic drug monitoring has contributed to an appreciation of the population variability in human medicine, it has been rarely used within the framework of veterinary medicine. Considering that, for example, 105 genotypes have been identified for human CYP2D6 (with 29 of these associated with little to no activity) [http://www.cypalleles.ki.se/l], it is easy to see the challenges that would accompany efforts to predict population variability solely based on genetics. To address this gap and in addition to therapeutic drug monitoring, several in silico tools are available to help unravel these and other complex situations. Whether it involve the use of mechanistic models to understand the PK implications of polymorphic forms of drug metabolizing enzymes and transporters or the use of computational models to identify critical covariates within a population, the availability of mechanistic models enables experimental data (both in vivo and in vitro) to be far more information-rich than it has been in the past. We can continually adjust our expectations as more data are collected across a range of samples from the population of animal patients.

The necessary tools and knowledge are available. The importance of understanding the various sources of population variability and the corresponding utility of data assessments using M&S computational tools has been showcased in Parts I and II of this 2017 AAVPT meeting report. Whether using the top-down, bottom-up, or middle-out approach, integrating M&S into efforts to understand the relationship between a drug or formulation and the behavior of the drug within the targeted animal population will be invaluable for meeting the ever-changing therapeutic needs associated with animal health. As a community, we need to encourage the generation and evaluation of drug and drug product PK as a critical component of efforts to obtain drug/drug product understanding. There needs to be more widespread use of in silico tools for population predictions, data interpretation, and formulation development. Importantly, we need to train our young scientists to understand the importance of PK and

sources of population variability and how to appropriately apply in silico modeling procedures, appreciating its pharmaco-statistical underpinnings and recognizing the importance of identifying/challenging their model's underlying assumptions.

It is the hope of the authors of this report that the information conveyed in Part II illustrate the strengths and opportunities for the described M&S approaches to improve the efficiency of the drug product development process (formulation optimization, clinical trial design, and safety and effectiveness trial analysis), to provide information to veterinary practitioners that will support prescribing practices that are in accordance with factors that may influence product safe and effective use, and to serve as an evaluation tool for regulators during pre-market product assessment, protocol development, and during the evaluation of potential causes for adverse post marketing experience reports. It is now up to the community of veterinary pharmacologists and those of us involved in the development and/or regulation of veterinary pharmaceutical to generate and use this information appropriately.

Conflict of interest statement

The authors report no conflicts of interest.

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Author Contribution Statement:
Although this was a collaborative effort, the following were primary areas of contributions for the individual authors:

MNM: Abstract, Introduction, Conclusions, Decision on manuscript contents
RG: NLME models
JM: NLME models
DP: PBPK models
LP: Practical implications of population variability in the animal health industry

All authors have read and approved of the contents in this final manuscript.

Figure 1. An illustration of the interrelationship and unique attributes associated with the top-down, bottom-up and middle out approaches to M&S
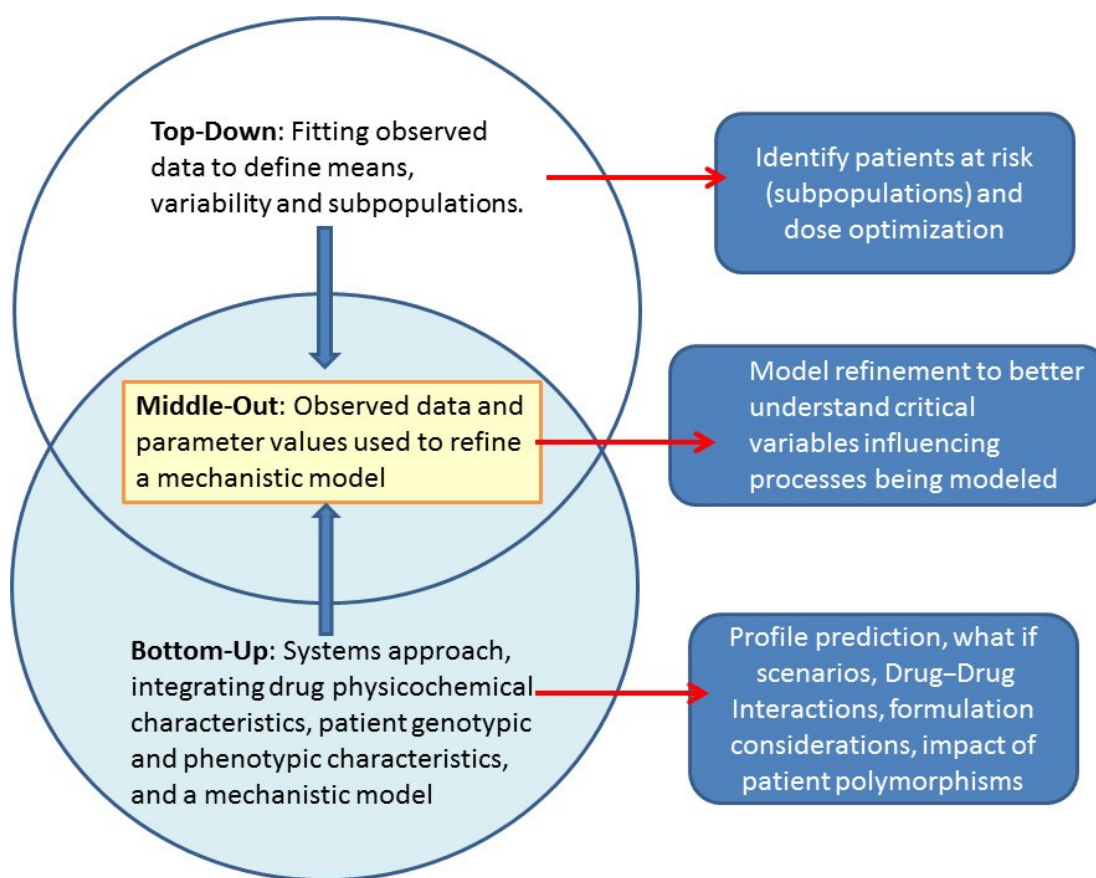

Figure 2. Separation of Systems (species) data versus Drug data and Trial Design
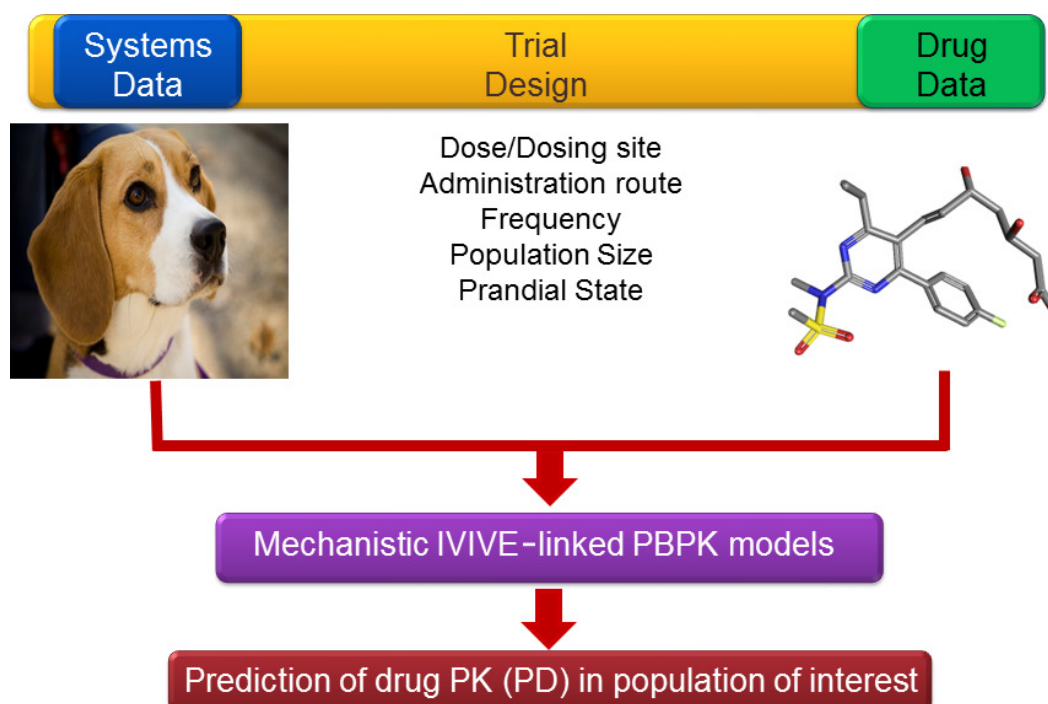
Figure 3. SWOT analysis for veterinary Pharma: documenting variability in the target population

STENGHTS:
Usefulness in animal species:
-Identify relevant covariates
-Optimise dose
-Sparse PK data
-Residue: identify factors that can alter drug kinetics in edible tissues
-Handles dose *uncertainty*
Little extra effort if PK culture

WEAKNESSES:
-No perceived incentive
-Less awareness of DDI and CYP450 polymorphisms
-Lack of awareness of and training in popPK
-No guidance yet
-COST
-Small businesses need to outsource

OPPORTUNITIES
Fantastic tool to combine preclinical and clinical data:
-Derisk dose determination
-Field trial enrichment
-Informs therapeutic adjustment
-Understanding of ADR
Reduce animal use (3Rs), model sharing
OneHealth contribution (AMR)

THREATS:
-Fear it becomes compulsory ("another requirement")
-Relevance and motivation for veterinary patients (futility of personalized medicine?)
-Risk of *punishing* innovation
-Complicates registration with flexible labelling due to residue

Helpful
to achieving the objective

Harmful
to achieving the objective

Internal origin
(attributes of the organization)

Strengths

Weaknesses

External origin
(attributes of the environment)

Opportunities

Threats

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