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## *Monday, May 19, 2025*

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# *Session 1 – Student and Resident Presentations*

## **Pharmacokinetic and Pharmacodynamic Determination of IV Butorphanol and Morphine in Cattle**

**Earl Ford IV, BS, MS**<sup>1,2</sup>, Kelley Varner DVM DACVAA<sup>3</sup>, Ronald Baynes DVM, PhD<sup>1,2</sup>

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The use of analgesics in cattle has increased in recent years, driven by heightened societal concern for animal welfare. The lack of pharmacokinetic and pharmacodynamic (PK-PD) data on analgesics in cattle has hindered the establishment of known dosing strategies and withdrawal intervals (WDI) limiting their use due to food safety concerns. Currently there is little known about the dosing strategy, efficacy, or food safety of two commonly used opioid drugs, morphine and butorphanol. We aim to investigate the PK-PD profiles of morphine and butorphanol in healthy cattle to begin to understand the usefulness of these drugs. We hypothesize that morphine will produce greater sedation with a longer duration of action than butorphanol and that morphine will reach plasma concentrations consistent with those producing analgesic effects in other species. Eight Holstein-cross steers and six Holstein-cross heifers will be used in a blinded, randomized trial consisting of two treatments (0.2 mg/kg morphine & 0.02 mg/kg butorphanol) with a minimum 72-hour washout period between treatments. PD parameters, including heart and respiratory rate, temperature, sedation scores, excitation scores, and thermal threshold nociception will be collected before, during and after treatment. PK samples will be obtained at baseline and predetermined time points for 24 hours following administration. Preliminary data shows that both butorphanol and morphine are rapidly excreted and tolerated well at all doses in healthy cattle. This study, in conjunction with future tissue analysis, will provide valuable insights, potentially leading to more effective and safe pain management strategies in cattle.

## **Tissue residue depletion of cannabinoids in cattle fed industrial hemp**

**Bailey R. Fritz, DVM**, Michael D. Kleinhenz, DVM, PhD, DACVCP, Geraldine Magnin, PhD, Jason J. Griffin, PhD, Mikaela M. Weeder, BSc, Andrew K. Curtis, MS, PhD, Miriam S. Martin, MS, PhD, Alyssa A. Leslie, BSc, Katie E. Kleinhenz, DVM, MS, Blaine T. Johnson, Scott A. Fritz, DVM, DABVT, Johann F. Coetzee, BVSc, Cert CHP, PhD, DACVCP, DACAW, DECAWBM, MRCVS,

**Keywords:** industrial hemp; cannabinoids; tissue residue; cattle; withdrawal

### **Abstract**

Despite interest in the use of industrial hemp (IH) in cattle feed, there is no safety data on tissues from exposed cattle. The objectives of this study were to describe the cannabinoid tissue residue profile and estimate withdrawal times in cattle fed IH. Twenty male Holsteins received oral IH at a dose of 5.5 mg/kg/d cannabidiol (CBD) for 14 d. Liver, kidney, muscle, and adipose tissue were collected at euthanasia on days 15, 16, 17, 19, and 22. Cannabinoid content was quantified with liquid chromatography mass spectrometry. Withdrawal periods were estimated using the FDA WithdrawalApp in R with a 10 ng/g tolerance. Adipose samples are still being analyzed. The psychoactive cannabinoid  $\Delta$ -9-tetrahydrocannabinol was detected in liver and kidney tissues. Cannabidiol was detected in liver, kidney, and muscle tissues. The withdrawal times for liver, kidney, and muscle were 68, 21, and 39 d, respectively. Our current data suggest that CBD residues deplete the slowest. While our results will inform decisions regarding the inclusion of IH in cattle feed, further discussions with the FDA are needed to confirm the marker residue of interest and set a tolerance limit for edible tissues from cattle exposed to IH.

## **The Effect of Extra-Label Dosing Regimens on Drug Residues and Pharmacokinetics in Non-Lactating and Dry Dairy Cattle**

**Ranee A. Miller, PhD**, Geof W. Smith, DVM, PhD, DACVIM, Jennifer L. Halleran, DVM, PhD, DACVIM-LAIM, Derek M. Foster, DVM, PhD, DACVIM, Ronald E. Baynes, DVM, PhD

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**Keywords:** eprinomectin, ceftiofur, pharmacokinetics, milk residues, dairy cattle

Dairy cattle veterinarians are responsible for selecting effective treatments while being mindful of costs and potential violative residues. They must also consider the practicality of administering treatments in various production settings. These limitations, coupled with the lack of labeled pharmaceutical products, compel veterinarians to develop innovative solutions using extralabel dosing regimens. The primary aim of these studies was to examine the effects of prophylactic extralabel dosing regimens on the pharmacokinetics and resulting residues of two different drug classes in prepartum heifers and dry dairy cattle. The compounds analyzed in these experiments were eprinomectin, a long-acting parasiticide, and ceftiofur, a third-generation cephalosporin. We hypothesized that residues resulting from these extralabel practices would remain below the FDA tolerance levels in milk, posing minimal to no food safety risks for consumers. This research utilized controlled experimental trials to investigate how deviations from approved label instructions affect drug distribution, elimination, and potential residue persistence in milk. Once lactation began, milk samples were collected, measured using analytical chemistry techniques, and modeled to generate pharmacokinetic parameters. Neither of the extralabel regimens produced violative milk residues. These innovative extralabel dosing regimens may offer effective solutions to address diseases affecting the dairy cattle industry while minimizing the risk of violative residues in milk collected from treated cattle. The findings from these studies emphasize the need for evidence-based withdrawal intervals tailored to various animal categories to ensure consumer safety.

## **Avoiding Drug Residues: A Multivariate Approach to Estimating Withdrawal Interval in Goat Edible Tissues Following Extralabel Administration of Flunixin Meglumine**

**Farha Ferdous Sheela**<sup>1</sup>, PhD, Ronald E Baynes<sup>1</sup>, Jacqueline Hughes- Oliver<sup>2</sup>, Jim Riviere<sup>1</sup>, Majid Jaber<sup>3</sup>

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Flunixin meglumine is a nonsteroidal anti-inflammatory drug (NSAID) commonly used as an extra-label in goats to treat various conditions. Therefore, determining an extended withdrawal time (WDT) is necessary to lower the possibility of violative residues during slaughter. The United States Food and Drug Administration fits the univariate linear regression model using the ordinary least squares method (OLS) by considering the concentrations at or above the limit of detection (LOD). This method defines the WDT as the time point at which the upper limit of 95% confidence interval of 99% quantile falls at or below a specified safe concentration level or tolerance. Since the tissues collected from an animal—namely the liver, kidney, muscle, and fat—may exhibit potential correlations, a multivariate linear regression model (MvLR) is suitable for capturing these inter-tissue dependencies.

Additionally, excluding concentrations below the LOD could remove observations from the terminal phase of the depletion curve, which would significantly influence the slope of the regression line and, consequently, the estimates of WDT. Instead of exclusion, treating these concentrations as censored observations may yield more reliable parameter estimates. Therefore, this study aims to incorporate the dependency structure among tissues and recognize the censoring pattern in the dataset. It included twenty Boer goats, with five goats randomly euthanized at four different time points for tissue collection. The ordinary least squares (OLS) and generalized least squares (GLS) methods estimate regression parameters within the MvLR framework. The expectation conditional-maximization (ECM) algorithm also estimates parameters within the censored MvLR framework. To estimate the extended WDT, namely withdrawal interval (WDI), we apply the multivariate t-distribution to calculate the upper limit of the 95% confidence interval for the 99% quantile. A simulation study was also conducted to evaluate the performance of the models.

## Pharmacokinetics and pharmacodynamics of vonoprazan in horses

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**Keywords:** acid-blocker, equine, gastric ulcer, novel treatment.

Current treatment options for equine gastric ulcer syndrome (EGUS) have several limitations e.g. omeprazole, a proton pump inhibitor (PPI), and common treatment for EGUS treatment needs be administered on an empty stomach. Potassium-competitive acid blockers, like vonoprazan, are another class of drugs used to treat gastric ulcers that appear to offer benefits over PPIs in humans and might offer advantages to omeprazole in horses. This study describes the pharmacokinetics, and effects on intra-gastric pH of a single administration of vonoprazan. Six horses received 0.5 and 1 mg/kg vonoprazan, 4 mg/kg omeprazole and 60 ml water in a randomized four-way balanced crossover design. Blood samples were collected prior to and for 72 hours post-administration. Drug concentrations were determined using liquid-chromatography-mass spectrometry and non-compartmental analysis performed. Intra-gastric pH was measured continuously 12 hours pre- and 24 hours post-drug administration. The percentage of time that intra-gastric pH remained above 4 was compared across treatments. For vonoprazan at 0.5 and 1 mg/kg, respectively,  $C_{max}$  was  $23.7 \pm 14.0$  and  $55.8 \pm 18.1$  ng/mL,  $T_{max}$  0.875 (0.25-3.0) and 0.625 (0.08-1.0) h and  $HL-\lambda_z$   $5.74 \pm 1.65$  and  $5.9 \pm 1.86$  h. There was a difference in the percentage of time intra-gastric pH remained above 4 before [85.5% (45-90.5)] and after vonoprazan administration [91.85% (80-90)] ( $p=0.007$ ) at 1 mg/kg. The percentage of time above pH 4 after vonoprazan at 1mg/kg was higher ( $90.28 \pm 5.6$ ) when compared with placebo ( $5.68\% \pm 39$ ) ( $p=0.021$ ). Vonoprazan was well tolerated and effectively maintained pH above 4 at the 1 mg/kg dose in the studied horses.

## Pharmacokinetics and Anti-inflammatory Effects of Intramuscular Betamethasone in Horses

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**Keywords:** betamethasone, horse, anti-inflammatory, pharmacokinetics

The use of corticosteroid esters, such as betamethasone sodium phosphate/betamethasone acetate in performance and racehorses is commonplace. While the pharmacokinetics and pharmacodynamics of betamethasone following intra-articular administration to horses has been well described, studies characterizing intramuscular administration are lacking. This study was conducted to describe the pharmacokinetics, effects on cortisol suppression, and anti-inflammatory effects of betamethasone following intramuscular administration to horses. Twelve horses received a single intramuscular dose of 12 mg betamethasone (BetaVet®). Blood and urine samples were collected at various times post administration for up to 408 hours. Concentrations of betamethasone were determined using liquid chromatography-tandem mass spectrometry and pharmacokinetic parameters determined using NLME compartmental modeling. The possible effects of covariates (age, weight, and gender) on between subject variability for the structural pharmacokinetic parameters was assessed. The duration of pharmacodynamic effects was assessed by measuring changes in cortisol, and inflammatory biomarkers utilizing an ex vivo model of inflammation. The covariates were not found to have significant effects on the variability of pharmacokinetic parameters. Intramuscular betamethasone administration resulted in low but sustained plasma concentrations. The  $C_{max}$ ,  $T_{max}$ , and terminal half-life (mean  $\pm$  SD) of betamethasone were  $5.86 \pm 0.83$  ng/mL, 0.68 (0.5-2.0) hours, and  $34.2 \pm 24.1$  hours, respectively. Significant suppression of endogenous cortisol was observed for 360 hours. The prolonged residence time of drug in the body is likely due to slow release resulting in a slower rate of absorption, relative to elimination (flip-flop effect). The prolonged detection time warrants an extended withdrawal time prior to competition in performance horses.

## Comparative pharmacokinetics and efficacy of intranasal or intramuscular atipamezole in dogs with and without xylazine sedation

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**Keywords:** atipamezole, pharmacokinetics, xylazine, reversal agents, sedation

**Background:** The  $\alpha$ 2-antagonist atipamezole (ATIP) is only approved for intramuscular (IM) use in dogs, which may be less accessible than intranasal (IN) dosing.

**Objectives:** To characterize the pharmacokinetics (PK) of ATIP in healthy Beagle dogs after IM and IN dosing, and to compare the efficacy of IM versus IN ATIP for reversing xylazine sedation.

**Methods:** Two study phases were performed, both as two-sequence, two-period randomized crossover experiments with one week washout between periods. In the phase 1 PK study, ATIP was administered at 0.2 mg/kg bw via IN and IM injections, but without xylazine. In phase 2, each dog was sedated with xylazine (1.1 mg/kg bw IV) prior to ATIP reversal and blood collection, while monitored for sedation level. ATIP was quantified in plasma using a validated HPLC-MS/MS method.

**Results:** ATIP was rapidly absorbed and excreted after both routes, but  $C_{max}$  and AUC were higher after IM dosing ( $p < 0.001$ ). Relative IN bioavailability was 33–50% of the IM dose. Xylazine reversal was more rapid after IM versus IN ATIP ( $p < 0.01$ ), but both routes led to complete reversal to baseline sedation scores within 40 minutes.

**Conclusion:** IN ATIP was slower for reversing  $\alpha$ 2-agonist sedation in dogs but is a viable dosing strategy if parenteral administration is not an option. Doubling the label IM dose of ATIP may be warranted if administered IN to account for decreased bioavailability.

## *Poster Presentations Abstracts*

### **Effects of isoflupredone on plasma electrolyte levels and fractional excretion following a single intramuscular administration to horses.**

Camilo J. Morales DVM, MS, DACVIM<sup>1</sup>; Juliana M. Sullivan BS<sup>1</sup>; Heather K. Knych MS, DVM, PhD, DACVCP<sup>1,2</sup>

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**Keywords:** corticosteroids, hypokalemia, hyponatremia, horse, inflammation.

Isoflupredone acetate (IA) is a synthetic glucocorticoid used in veterinary medicine for its potent anti-inflammatory effects. Hypokalemia has been documented in horses after long-term IA use. However, the effect of a single IA administration on electrolytes has not been studied. The goal of this study was to describe the effects of a single IM dose administration of IA on plasma electrolytes and fractional excretion (FE). We hypothesized that a single IA dose would affect plasma potassium concentrations and FE. Twelve (8 geldings and 4 mares) healthy Thoroughbred horses received a 20 mg IM dose of IA. Blood and urine samples were collected before administration. Blood was collected for 72 hours, and urine was collected again at 72 hours. Drug concentrations were determined using liquid chromatography-mass spectrometry. Electrolytes in plasma and urine were measured by ion-selective electrodes. Comparisons before and after IA administration were performed. Concentration of IA after 72 hours of administration was 0.23 (0.03 – 0.39) ng/mL. Serum potassium significantly decreased after ( $2.7 \pm 0.71$  mmol/L) compared to before ( $3.8 \pm 0.67$  mmol/L) IA administration ( $P=0.0006$ ). Serum sodium significantly increased after [140 (138–142 mmol/L)] compared to before [137 (135–139 mmol/L)] IA administration ( $P<0.0001$ ). Potassium FE increased from [39 (20–61) %] to [68.92 (27–73) %] ( $P=0.03$ ) and sodium FE decreased from [2.3 (1.47–3.72) %] to [1.61 (0.51–3.03) %] ( $P=0.03$ ) after IA administration. A single intramuscular administration of IA significantly decreased serum potassium and increased serum sodium in accordance with the FEs after 72 hours administration to horses.

## Pharmacokinetics and Anti-inflammatory Effects of Intramuscular Isoflupredone in Horses

Juliana Sullivan, BS<sup>1,2</sup>, Daniel S. McKemie, BS<sup>1</sup>, Philip Kass, DVM, PhD<sup>3</sup>, and Heather K. Knych, DVM, PhD, DACVCP<sup>1,2</sup>

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**Keywords:** isoflupredone, horse, anti-inflammatory, pharmacokinetic

Corticosteroids, such as isoflupredone, are effective anti-inflammatory medications and as such are commonly used to treat inflammation associated with training and injuries in performance horses. While the pharmacokinetics and pharmacodynamics of isoflupredone following intra-articular administration to horses has been well described, studies characterizing intramuscular administration are lacking. This study was conducted to describe the pharmacokinetic and anti-inflammatory effects of isoflupredone following intramuscular administration to horses. Twelve horses received a single intramuscular dose of 20 mg isoflupredone, and blood and urine samples were collected at various time points until 312 hours post-administration. Isoflupredone and hydrocortisone concentrations were measured using liquid chromatography-tandem mass spectrometry, followed by pharmacokinetic analysis. An ex vivo model of inflammation was used to assess the effect of isoflupredone on inflammatory biomarkers as a measure of the duration of pharmacodynamic effect. The  $C_{max}$ ,  $T_{max}$ , and terminal half-life (mean  $\pm$  SD) of isoflupredone were  $1.55 \pm 0.43$  ng/mL, 2.8 (1-4.5) hours, and  $39.6 \pm 22.08$  hours, respectively. The prolonged residence time of drug in the body warrants an extended withdrawal time prior to competition in performance horses.

## **Pharmaceutical exposure and toxicosis in dogs: a retrospective study of 223 cases from a Canadian veterinary teaching hospital (2018-2023)**

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**Keywords:** pharmaceutical toxicity, veterinary toxicology, drug overdose, ibuprofen toxicity, OTC drug toxicity

**Background:** Ingestion of pharmaceuticals is a common cause of poisoning and hospitalization in companion animals. Pets may be exposed through accidental over-administration of prescribed veterinary drugs, intentional administration of human drugs that the owner does not realize is unsuitable for animals, or access to unattended medications.

**Objective:** To document cases of exposure and toxicosis in dogs due to suspected and confirmed pharmaceutical ingestion admitted to a veterinary teaching hospital over a 6-year period (2018-2023).

**Methods:** Medical records were retrieved from the veterinary hospital database using keywords related to general poisoning. Results were then filtered using keywords related specifically to pharmaceutical ingestion. Information pertaining to hospitalization, patient signalment, treatment, and case progression were collected and analyzed to characterize common factors in canine pharmaceutical poisoning cases.

**Results:** Pharmaceutical ingestion was reported in 223 canine poisoning cases (confirmed in 102 cases) over six years involving 32 different categories of pharmaceuticals. The most common pharmaceutical categories ingested by dogs were non-steroidal anti-inflammatory drugs (NSAIDs; n=86) and acetaminophen (n=29). Normal clinical exams on presentation were noted in 164 cases. Accidental drug exposures (n=211) were more common than intentional pharmaceutical administration (n= 12). Patients were exposed to human pharmaceuticals 5x more frequently than veterinary. Survival-to-discharge rate was 99.6%. The most common therapies administered were emesis induction, activated charcoal, fluid support, and gastroprotectants.

**Clinical significance:** Pharmaceutical exposure, especially from over-the-counter human medications, was a common occurrence for hospital admission in dogs described in this study. Improved client education is needed to avoid preventable pharmaceutical exposures.

## **Effect of Transdermal Non-Steroidal Anti-Inflammatory on Mammary Gland Integrity of Holstein Cows Challenged with *E. coli***

Ana B. Montevecchio, Kristi L. Jones, Modesto Hernandez, Ahmadrza Mirzaei, Luana Factor, Pamela L. Ruegg, Fiona Maunsell, Pedro Rodriguez, Jantijn Swinkels, Todd R. Bilby, R. Bruckmaier, Ricardo C. Chebel

The aim of this experiment was to evaluate the effects of a novel transdermal non-steroidal anti-inflammatory drug (NSAIDs; e.g., flunixin meglumine) on the local inflammatory response markers and productive responses of Holstein cows following an *E. coli* challenge. A total of 88 clinically healthy cows ( $272 \pm 89.2$  DIM) with no signs of mastitis and negative for gram-negative bacterial growth in milk samples from individual quarters were included in the study. On the day of enrollment (d -11; d 0 = challenge day), cows were randomly assigned to one of three treatment groups: positive control (PCON) – one quarter infused with sterile phosphate buffered saline (PBS; n = 30), negative control (NCON) – one quarter challenged with *E. coli* (strain P4, USDA, known to induce moderate to severe mastitis) and another infused with sterile PBS (n = 29), and transdermal flunixin (TFM) – one quarter challenged with *E. coli*, another infused with sterile PBS, and administered transdermal flunixin 12 hours post-challenge (n = 29). Cows were not milked for 12 h after the challenge but resumed milking twice a day thereafter. Milk samples were collected before each milking from 0 to 168 h post-challenge. Quarter milk samples were analyzed for somatic cell count, bacterial growth, and concentrations of bovine serum albumin (BSA), lactate dehydrogenase (LDH), and electrolytes. Daily milk yield was recorded using the farm's milking monitoring system. For the statistical analysis we used a completely randomized split plot design with repeated measures. Treatments did not ( $P \geq 0.14$ ) differ regarding lactation number, days in milk, milk production, and BCS pre-challenge. Challenge quarters of cows in the TFM treatment had ( $P < 0.01$ ) lower CFU and somatic cell linear score than challenged quarters of cows in the NCON treatment. Although treatment did not ( $P = 0.38$ ) affect BSA concentration in challenged quarters, it affected ( $P \leq 0.04$ ) LDH and electrolytes concentration, and milk yield. The controlled infection model successfully induced mastitis. Treatment with transdermal flunixin mitigated potential damage to the milk-blood barrier, while also promoting faster recovery of milk production.

## **Efficacy of a 20:1 CBD:THC Cannabis Herbal Extract for Pain and Inflammation in Dogs Following Tibial Plateau Levelling Osteotomy**

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**Keywords:** cannabidiol, CBD, cannabinoids, analgesia, orthopedic surgery

**Background:** Cannabidiol has shown potential for managing pain and inflammation in dogs, but evidence for use as a post-operative analgesic is limited.

**Objective:** To evaluate the analgesic efficacy of two oral dose regimens of a cannabinoid herbal extract (CHE) in client-owned dogs undergoing tibial plateau leveling osteotomy (TPLO) for cranial cruciate ligament rupture (CCLr), and to correlate observed effects with plasma cannabinoid concentrations.

**Methods:** Forty-seven dogs were enrolled in a randomized, double-blinded, placebo-controlled clinical trial over 22 months. Dogs received 0, 2, or 5 mg CBD/kg (via a commercially available 20:1 CBD:THC CHE) in addition to a standard analgesic protocol. Veterinary assessments were performed on days +1 and +14 post-operatively (Glasgow Composite Pain Scores, stifle range of motion, thigh and stifle circumference, and gait symmetry ratios). Owners completed a modified Canine Brief Pain Inventory (CBPI) on days +3, +7, and +14. Plasma cannabinoid concentrations were analyzed using LC-MS/MS. Data were analyzed using linear mixed models and generalized estimating equations.

**Results:** All dogs improved from day +1 to day +14 and there were no significant differences between treatment groups, though a potential treatment x day interaction for symmetry was noted. No serious adverse events were reported; mild gastrointestinal effects were noted in a few cases. Plasma cannabinoid concentrations were inconsistent between dogs and did not correlate with clinical outcomes.

**Conclusions:** Inclusion of a 20:1 CBD:THC CHE to standard analgesic protocols did not reduce pain and inflammation in dogs following TPLO surgery.

## Assessing the acceptance and effectiveness of individualized antimicrobial use scorecards distributed to veterinary providers

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**Keywords:** antimicrobial use; benchmarking; antimicrobial stewardship; One Health; companion animals

Reporting antimicrobial use is a core principle of veterinary antimicrobial stewardship. Benchmarking, the process of comparing antimicrobial use across groups, can help clarify differences in prescribing at an individual, service, and hospital level. The goals of this study were to evaluate the feasibility of implementing internal benchmarking via individualized antimicrobial use scorecards within a small animal veterinary teaching hospital. Scorecards were provided to rotating interns (n=15) and residents of the emergency and critical care (ECC; n=13) and internal medicine (IM; n=8) services. Prescribing metrics were calculated from prescriptions of systemic antimicrobials over three months and included total antimicrobial, beta-lactam, and fluoroquinolone prescriptions measured for outpatients per 100 outpatient visits and normalized for inpatients to per week on the IM or ECC services. A qualitative survey, consisting of a mix of closed and open-ended questions, was distributed to obtain scorecard feedback. Total outpatient antimicrobial prescription median(range) per 100 outpatient visits by group were: IM 10.0(3.7-18.8), ECC 14.3(6.7-31), Intern 19.8(7.7-27.8). For all groups combined, ampicillin-sulbactam had median(range) 1.6(0.3-6.43) prescriptions per week and enrofloxacin had 0.25(0-1.44) prescriptions per week. 11/15 interns (73%) and 14/21 residents (67%) responded to the survey. Initial impressions of the scorecard were positive in 17/25 (68%), neutral in 6/25 (24%), and negative in 2/25 (8%) recipients. 6/11 (55%) interns and 3/14 (21%) residents expressed that the scorecards will probably affect their future antimicrobial prescribing. These findings suggest individualized antimicrobial use scorecards are a feasible and well-received stewardship intervention. Further studies are needed to confirm an effect on prescribing behavior.

## Stability of cefovecin strength with frozen, refrigerated, and room temperature storage

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**Keywords:** Third-generation, cephalosporin, stability, veterinary practice, small animal

Some veterinary clinics freeze reconstituted cefovecin beyond its 56-day shelf-life in glass vials, plastic syringes, or the manufacturer's multidose vial (MDV). Per CVM Drug Stability Guidelines, 90% potency/strength is required for an efficacious product.<sup>1</sup> Reconstituted cefovecin was hypothesized to remain above 90% strength beyond 56 days with frozen storage. Cefovecin aliquots from 3 lots, reconstituted per manufacturer's instructions, were frozen in sterile plastic syringes, plastic blood tubes without additive (red top), or MDVs. Reconstituted cefovecin from each lot was also stored at room temperature (Troom) or refrigerated (manufacturer's condition) in MDVs. Cefovecin strength was regularly measured using HPLC-UV (2.1 mm x 50 mm (2.7 μm) Poroshell 120 EC-C18 column and at incremental concentrations (0.3125 to 20 mg/ml). Rates of change were determined by linear regression with robust errors. Cefovecin strength of each sample was compared to strength at reconstitution. Over 400 days, 13 freeze-thaw cycles for MDVs, strength was unchanged for frozen samples (P=0.987, 0.088 and 0.373 for syringes, blood tubes, and MDVs, respectively). Refrigerated cefovecin strength decreased 0.15%/day (95% CI -0.20 to -0.10) for 40 days, P<0.0001. At Troom, strength decreased 0.66%/day (95% CI -0.84 to -0.48), P<0.0001. Lower bounds of 95% CIs for refrigerated and Troom samples were predicted to cross -10% at 56 and 14 days, respectively. For these samples, the hypothesis of cefovecin strength above 90% for greater than 56 days with frozen storage was accepted.

<sup>1</sup> Center for Veterinary Medicine. 2008; <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-5-drug-stability-guidelines>

## Survey and analytical bias of therapeutic drug monitoring of gentamicin in horses

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**Keywords:** Aminoglycosides, equine, assay, HPLC, Bland-Altman

The purpose of this study was twofold: 1) to assess the status of therapeutic drug monitoring (TDM) of gentamicin and 2) to compare the values determined by immunoassay to those from an instrumental method. In 2015, an email-based survey was disseminated to 33 veterinary teaching hospitals (VTH) in the United States and Canada to assess TDM practices. Commercially available immunoassays used for routine TDM of aminoglycosides measure total gentamicin concentrations in serum or plasma, rather than the individual components within the gentamicin complex. Consequently, immunoassays and instrumental methods may yield different results. Gentamicin was administered to horses and estimated concentrations in heparinized plasma were determined for three different gentamicin components (C1a, C2, C1) using high performance liquid chromatography (HPLC) and compared with gentamicin concentrations determined by an immunoassay (Siemens Xpand). Thirty-one (94%) of the institutions contacted responded to the questionnaire. This survey revealed that 39% of respondents performed TDM of aminoglycosides, while a smaller minority (16%) of the respondents indicated that TDM was determined in house at their hospital. A median of 2.8 samples per VTH were performed annually. When values for plasma gentamicin concentrations determined by HPLC were compared with those obtained using the immunoassay, the bias (mean difference) was 35%, by a Bland-Altman analysis. Higher gentamicin concentrations were consistently determined by HPLC as compared with the immunoassay, indicating a systemic bias. A follow-up TDM survey should be obtained to identify trends and current practice in the use of aminoglycoside TDM in the United States and Canada.

## **Ex-vivo carprofen removal from horse whole blood via two hemoperfusion devices: a pilot study**

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**Introduction:** Hemoperfusion and intralipid have been used to treat severe non-steroidal anti-inflammatory drug intoxication. This study aimed to evaluate plasma carprofen concentrations during ex vivo hemoperfusion. We hypothesized that hemoperfusion columns would significantly reduce plasma carprofen concentrations and that intralipid would not interfere with hemoperfusion.

**Methods:** Four 500 mL units of whole equine blood were collected. All four units received 240 mg of injectable carprofen. Two of the units received 99 mL of 20% intralipid emulsion. All units were filtered through an activated carbon (Aimalogic Dublin 100) and a polymer bead (VetResQ 50) for two hours. Plasma samples were collected at 11 time points for analysis using a high-pressure liquid chromatography analysis. Extraction and reduction ratios were calculated.

**Results:** Dublin 100 column decreased carprofen levels from 274 to 41 mcg/mL (85%) in non-lipemic blood and from 268 to 58 mcg/mL (78%) in lipemic blood. VetResQ 50 column reduced concentrations from 276 to 78 mcg/mL (72%) in non-lipemic blood and from 222 to 105 mcg/mL (53%) in lipemic blood. The median extraction ratio of carprofen on Dublin 100 was 10% (IQR 7–18%) in lipemic blood and 8.5% (IQR 0–14%) in non-lipemic blood. For VetResQ 50, the median extraction ratio was 29% (IQR 27–32%) in lipemic blood and 30% (IQR 28–32%) in non-lipemic blood.

**Conclusions:** Hemoperfusion columns significantly reduced plasma carprofen concentrations. Although the VetResQ 50 had higher overall extraction ratios, the Dublin 100 achieved a greater reduction ratio. Intralipid emulsion slightly decreased the reduction ratio in both columns.

## Session 2 – P-glycoprotein Substrate Status in Veterinary Drugs

### How Knowing a Drug’s P-glycoprotein Substrate Status Can Improve Drug Safety for Canine and Feline Patients

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#### P-gp and drug disposition

P-glycoprotein’s (P-gp) role in drug disposition in dogs and cats has been described elsewhere<sup>1-3</sup> so will be reviewed only briefly here. For drugs that are P-gp substrates (Table 1), P-gp functions as a highly efficient drug efflux pump, actively pumping the substrate drug out of cells or tissues that express P-gp. Although a variety of cells and tissues have been shown to express P-gp, only three sites appear to impact the disposition of substrate drugs in a clinically relevant manner. From the perspective of a practicing companion animal veterinarian, the three sites to worry about in a patient with P-gp deficiency are (i) the blood brain barrier (enhanced CNS penetration of P-gp substrate drugs); (ii) biliary canaliculi (decreased biliary excretion of P-gp substrate drugs); and (iii) lymphocytes (increased intracellular concentration of P-gp substrate immunosuppressants). Additional details regarding the clinical consequences of P-gp deficiency at each of these sites is provided several paragraphs below.

Table 1. Some P-gp substrate drugs/drug classes that are prescribed to canine and/or feline patients.

Acepromazine	Emodepside	Macrocyclic Lactones
Butorphanol	Grapiprant	Maropitant
Cyclosporine A	Ketoconazole	Methylprednisolone
Doxorubicin	Loperamide	Vinca alkaloids

#### P-gp deficiency

“Intrinsic” P-gp deficiency in dogs is caused by a 4 base-pair deletion mutation in the canine ABCB1 (formerly MDR1) gene<sup>4</sup> and, in cats, by a 2 base-pair deletion mutation in the feline ABCB1 (MDR1) gene<sup>5</sup>. Because each of these deletion mutations generates multiple premature stop codons, animals that inherit 2 mutant alleles have no functional P-gp and are extremely susceptible to adverse reactions caused by P-gp substrates while heterozygotes (animals that inherit 1 mutant and 1 normal allele) have partial P-gp function and are more susceptible to P-gp-mediated adverse reactions than animals with normal P-gp function (2 copies of the wildtype MDR1 allele) but generally less sensitive than animals with 2 mutant alleles. To put it more succinctly, in terms of sensitivity to P-gp substrate drugs MDR1 mutant/mutant > MDR1 mutant/normal >> MDR1 normal/normal. The canine MDR1 mutation is more common in herding breeds (reviewed elsewhere<sup>3</sup>) but occurs in mixed breed dogs and the author has even been identified purebred Siberian Huskies and Boxers with the MDR1 mutation. The feline

MDR1 mutation appears to affect Maine Coons more than any other breed (frequency of ~ 5%) and occurs at a frequency of ~1% in nonpurebred cats (i.e., domestic short-, medium-, and longhairs)<sup>6</sup>.

Phenoconversion is a term used in human pharmacogenetics to explain when an individual's genotype with respect to a particular drug metabolizing enzyme mismatches the observed phenotype of that individual. Phenoconversion is due to non-genetic factors (often a drug-drug interaction). While this phenomenon does occur in dogs and cats with MDR1 normal/normal genotypes, the word phenoconversion is neither user-friendly nor intuitive. The author prefers "extrinsic" or "acquired" P-gp deficiency. Acquired P-gp deficiency occurs when an MDR1 normal/normal animal is concurrently treated with two P-gp substrate drugs that then compete for binding sites within the P-gp binding pocket. Competition for P-gp-mediated efflux can increase CNS penetration, decrease biliary clearance and/or enhance intracellular lymphocyte concentrations of one or both drugs. Importantly, acquired P-gp deficiency has the potential to affect all dogs and cats and has caused fatal adverse drug reactions in both species.

### **Clinical Consequences of P-gp Deficiency**

The clinical consequences of P-gp deficiency for a particular patient depend on the severity of P-gp deficiency (i.e., MDR1 mutant/mutant vs MDR1 mutant/normal genotype vs acquired), the patient's health status, and the P-gp substrate(s) involved. Depending on the P-gp substrate, the adverse effect may involve increased CNS penetration causing neurological toxicosis, impaired biliary excretion resulting in delayed clearance and greater exposure to the drug increasing the risk for adverse drug reactions, or increased drug concentrations within lymphocytes.

Adverse effects resulting from increased CNS penetration of P-gp substrate. The importance of P-gp as a component of the blood-brain-barrier was first demonstrated in *mdr1a* knockout mice in which brain concentrations of the P-gp substrates ivermectin, loperamide and ondansetron were 88-fold, 13-fold and 4-fold greater than those in wildtype mice<sup>7,8</sup>. Roughly 5 years later, the canine MDR1 mutation was determined to be the cause of "ivermectin sensitivity" in collies and other herding breed dogs<sup>5</sup>. Subsequent reports confirmed that canine and feline P-gp prevents or greatly decreases brain penetration of not just ivermectin, but many other P-gp substrate drugs including other macrocyclic lactones (eprinomectin is especially problematic for cats)<sup>9</sup>, loperamide, acepromazine, butorphanol, maropitant and others<sup>3</sup>. Enhanced brain penetration of these P-gp substrates in a dog or cat with P-gp deficiency results in CNS depression which can be mild to moderate (maropitant, butorphanol, acepromazine) or severe and potentially fatal (loperamide, macrocyclic lactones). The author is aware of several MDR1 normal/normal dogs experiencing neurological toxicity after concurrent treatment with the P-gp substrates ketoconazole and ivermectin (300  $\mu$ g/kg). Similarly, administration of the label dose of eprinomectin concurrently with the P-gp substrates cyclosporine A or methylprednisolone in MDR1 normal/normal cats resulted in severe neurological toxicity. These are examples of phenoconversion or acquired P-gp deficiency demonstrating that co-administration of two P-gp substrates can cause serious, even fatal, neurological toxicity in any dog or cat.

Adverse effects resulting from blunted biliary excretion. A complete lack of biliary excretion of a radiolabeled P-gp substrate in MDR1 mutant/mutant dogs<sup>10</sup> has been demonstrated experimentally<sup>10</sup>. One would expect the same for cats homozygous for ABCB1/1930\_1931del TC. Clearance of P-gp substrates in P-gp deficient dogs and cats, therefore, should be expected

to be prolonged, potentially resulting in increased overall drug exposure. Grapiprant clearance from the central compartment of P-gp deficient dogs (MDR1 mutant/mutant) is 71% lower than that of dogs with normal P-gp function<sup>11</sup> P-gp deficient dogs were more likely to experience gastrointestinal adverse effects from grapiprant than dogs with normal P-gp function<sup>11</sup>. The P-gp substrate vincristine is significantly more likely to cause neutropenia and thrombocytopenia in P-gp deficient dogs (heterozygous or homozygous for ABCB1-1 ) than in dogs with normal P-gp function<sup>12</sup>. The primary route of excretion for vincristine is P-gp-mediated biliary excretion of the parent compound. P-gp deficiency results in delayed clearance and greater overall exposure to vincristine. Acquired P-gp deficiency results in similar defects in biliary clearance. A Boston Terrier cross (MDR1 normal/normal genotype) experienced grade 4 gastrointestinal toxicity and myelosuppression, leading to sepsis, cardiac arrest and death after concurrent treatment with the P-gp substrates vinblastine and ketoconazole<sup>13</sup>.

Adverse effects resulting from increased intracellular lymphocyte concentrations. The immunosuppressants cyclosporine and tacrolimus function by inhibiting intracellular T-cell receptors resulting in decreased expression of cytokines such as interleukins and interferon- $\gamma$ .

Because T-cell plasma membranes normally express P-gp, dogs and cats with P-gp deficiency will accumulate higher concentrations of P-gp substrates (i.e., cyclosporine or tacrolimus) within their T-cells relative to dogs and cats with normal P-gp function. This has been documented in a Border Collie (MDR1 mutant/normal) treated with a relatively low dose of cyclosporine. The dog developed secondary infections presumed to be the results of excessive immunosuppression despite cyclosporine plasma concentrations at the low end of the therapeutic range.

Pharmacodynamic monitoring, however, demonstrated nearly complete suppression of interleukin-2 mRNA synthesis (<5% of control). Typically, cyclosporine concentrations within the therapeutic range suppress interleukin-2 synthesis in the range of 25-50% of control.<sup>14</sup>

### **Preventing P-gp-Mediated Adverse Drug Reactions**

The requisite pieces of information for preventing P-gp-mediated adverse drug reactions are (i) the P-gp status of the canine or feline patient and (ii) the P-gp substrate status of the drug(s) being administered. If a P-gp substrate drug is being administered to a patient with P-gp deficiency or if two or more P-gp substrate drugs are being administered to any dog or cat, then either selection of alternative drugs or dose modifications may need to be instituted. While determining the P-gp status of dogs and cats is a straightforward and inexpensive process for pet owners and veterinarians, determining the P-gp substrate status of a drug may not be. While the P-gp substrate status of human drugs is often included in the label information, the corresponding information is not available for canine or feline drug products. Inclusion of P-gp substrate information on the label of drugs intended for canine and feline patients could prevent serious and potentially fatal adverse drug reactions in dogs and cats.

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## **Industry / Academia/ FDA-CVM Collaboration to Qualify a Transgenic Mouse Model as an Alternative to Collie Safety Studies**

### **Scientific Background**

Currently, all animal health macrocyclic lactones are assessed for neurotoxicity in MDR1-mutant dogs during the drug development process. Specifically, as macrocyclic lactones are known to cause Central Nervous System (CNS) toxicities in herding-type dogs as well as other breeds, all new drug products containing a macrocyclic lactone are examined in an “Ivermectin-Sensitive Collie Safety Study” to determine whether they will cause CNS toxicities in MDR1-mutant dogs.

The increased sensitivity to drugs with CNS toxicities in MDR1-mutant dogs is due to a genetic defect in their ATP- binding cassette, sub-family B member 1 (ABCB1) gene. The ABCB1 gene encodes for P-glycoprotein (P-gp), a transmembrane efflux protein that affects the absorption, distribution and elimination of certain drugs. Without this functional protein pump, substrates can more readily reach higher concentrations to cause CNS neurotoxicity.

Noted academic experts, regulatory bodies and major animal health companies have expressed concerns about the Ivermectin-Sensitive Collie Safety Study including lack of robust validation, false positive results, inter and intra animal variation, the need for repeated exposure to ivermectin to demonstrate sensitivity, availability of research animals and animal welfare concerns. Two novel transgenic mouse strains (Yancy 1 and Yancy 2) have been created to contain the mutant and wild type canine P-gp protein, respectively. Studies using this transgenic mouse model to assess neurotoxicity have been published by FDA-CVM. This transgenic mouse model has the potential to reduce the need for Collie safety assessment of macrocyclic lactones, and to provide safety information of other P-gp substrates.

### **Research Goal**

The overarching goal of this collaboration is to generate sufficient data utilizing the transgenic mouse model to be confident that it could predict the toxic potential of P-gp substrates in dogs with the ABCB1 mutation. By qualifying the transgenic mouse model with a number of P-gp substrates, it could become an alternative to the ivermectin-sensitive Collies needed to address concerns for canine drug safety.

### **Innovation and Collaboration**

As an innovative collaboration between several major Animal Health companies, the Food and Drug Administration and Academia (Washington State University), this work is a novel approach to develop alternative test methods to assess clinical safety in dogs carrying the ABCB1 genetic defect.

### **Benefits**

Importantly, this work is in line with commitments to reduce, refine and replace animal use in research. Successful validation would have significant animal welfare advantages over the current

practice of using Collies to assess the CNS effects of macrocyclic lactones. Further, a laboratory model in rodents would provide an opportunity to refine the methods to assess CNS toxicity to be more reliable, repeatable, and objective.

### **Work to date**

In 2018, the Animal Health Institute (AHI) joined with the American Academy of Veterinary Pharmacology and Therapeutics (AAVPT) to host a 2-day workshop on ‘Issues and Alternatives for Safety Assessment of Macrocyclic Lactones in P-gp Deficient Dogs.’ AHI served as the convening organization. Approximately 50 attendees participated in the workshop which was supported by donations from animal health pharmaceutical companies. FDA-CVM actively participated in the planning of the session and in the workshop discussions. Workshop participants strongly supported the concept of FDA-CVM, academia and industry working together to validate/qualify a transgenic mouse model.

AHI served as the facilitator to continue the work proposed by the workshop participants. An AHI subcommittee was formed in 2020, comprised of representatives from industry, FDA-CVM, and academia, to develop a formal collaboration to validate/qualify the FDA-CVM transgenic mouse model to assess neurotoxicity in MDR-1 mutant dogs. The subcommittee has accomplished several important goals to date including:

- Established a collaborative agreement to work between FDA-CVM/Industry/Academia.
- Defined the data needed for industry and FDA-CVM to robustly assess the model
- Agreed on test compounds and study design to validate/qualify the transgenic mouse model.
- Ensured the proposed study design addresses FDA-CVM expectations.
- Successfully re-established a breeding colony of Yancy 1 and 2 transgenic mice.
- Designed a series of *in vivo* studies to validate/qualify the transgenic mouse model.
- Completed an initial pilot *in vivo* study to assess research methodologies.
- Refined research methodologies to validate/qualify the transgenic mouse model.

The subcommittee has implemented a Research Collaboration Agreement (RCA) between individual Animal Health companies, Washington State University and FDA-CVM to conduct a series of experiments to qualify the transgenic mouse model. The studies will utilize 3 positive controls known to be substrates for canine P-gp that cause CNS clinical signs in MDR-1 mutants (ivermectin, moxidectin and loperamide) and a negative control (cyclosporin) that is a canine P-gp substrate but does not result in observable CNS signs to validate/qualify this model as an alternative for studies in MDR-1 mutant Collies.

In early 2023, the team completed a pilot study to assess research methodologies and evaluate signs of CNS toxicity of ivermectin in Yancy1 and Yancy 2 mice versus wild type mice at FDA research facilities. Results showed that neurotoxicity could be induced in the current transgenic mouse lines following ivermectin dosing by oral and subcutaneous routes. Currently, mice are being bred for a second round of pilot studies with all 4 drugs (positive controls: ivermectin,

moxidectin and loperamide; negative control: cyclosporin) to refine doses for future studies. The team has also initiated a new breeding program for Yancy 1 and Yancy 2 mice to ensure that the transgenic lines are genetically pure. The team believes this is an important activity to ensure we have a stable line of transgenic mice for future use. Following completion of the breeding program and the pilot work, the team will conduct bridging studies to ensure that the new mouse lines are similar to previous lines. The formal work to validate/qualify the transgenic model with the 3 positive controls and the negative control will follow along with a toxicokinetic study of selected compounds in transgenic mice. All studies will be conducted at FDA research facilities except for the toxicokinetic study which will be sponsored by the industry partners at a global contract research organization.

In a supporting *in vitro* study, Dr Mealey’s laboratory confirmed that loperamide, cyclosporine, ivermectin and moxidectin are strong substrates for canine PGP using a canine cell line.

Importantly, the subcommittee has outlined a series of potential publications to ensure that the results from this work are publicly available.

<b>AHI MDR1 Subcommittee Members</b>			
Raker	Carl	Animal Health Institute	
Desevaux	Cyril	Boehringer Ingelheim Animal Health	
Qureshi	Tariq	Ceva Animal Health	
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## **Development and Validation of an Ivermectin Sensitive Collie Colony**

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P-glycoprotein, encoded by the MDR1 or ABCB1 gene, is an integral component of the blood-brain barrier as an efflux pump for xenobiotics crucial in limiting drug uptake into the central nervous system.

Dogs homozygous for a 4-base pair deletion of the canine MDR1 gene show altered expression or function of P-glycoprotein, resulting in neurotoxicosis after administration of drugs such as avermectins

MDR1 gene mutations have been shown to occur in varying prevalence in dog breeds. A higher prevalence is seen in herding breeds such as Collies.

Regulatory authorities have been aware of this special safety consideration for decades and the pathway for approval of drugs containing avermectins (e.g. ivermectin, moxidectin, and milbemycin) includes a study to evaluate the drug's safety at several multiples of the label dose in dogs demonstrated to be sensitive to previous ivermectin exposure.

Clinglobal is the world's only truly multinational veterinary contract research organization with laboratories in South Africa, Morocco, France, and the United States. Built on a foundation of antiparasitic expertise, we are evolving to offer a complete development solution to our sponsor companies. As part of that offering, the establishment of a stand-alone ivermectin sensitive collie model was seen to be of strategic importance.

This presentation will review some of the challenges faced with setting up a suitable colony:

- Heterozygotes vs homozygotes
- A Collie is not a Beagle!
- Housing and husbandry requirements for a long-term model
- Animal welfare
- Validating the testing protocol
- Assessment of clinical signs
- The importance of trained, experienced technicians

# MDR-1 Mutation in Collies: Exploring its impact on Loperamide PK using mechanistic Physiologically-Based PK Modelling

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## Background

Physiologically based pharmacokinetic modelling (PBPK) uses mathematical equations to describe the absorption, distribution, metabolism, and excretion of a drug in the body. This is achieved by considering blood flow and organ composition and density for the major organs in the body. While mechanistic PBPK modelling is an approach routinely used in human drug development, its use in veterinary medicine is currently limited. Other than its application in predicting tissue residue levels after extra-label use in food-producing animals (1), it is rarely used to support veterinary drug product development. Rather, simplified animal PBPK models are typically limited to its use for preclinical research, employing measured clearance and volume of distribution ( $V_{ss}$ ) data as inputs, and do not aim to scale from *in vitro* data or quantitative-structure-activity-relationship (QSAR) models to *in vivo*. Additionally, for the dog, PBPK models typically employ physiological attributes associated with the research colony Beagles, even though we now recognize that these dogs do not account for the breed-specific differences in drug pharmacokinetics that can occur (2, 3).

In this work (4), we not only developed a PBPK model that utilizes the physiological attributes of a breed other than the research Beagle, but we also explored the utility of this model to predict the effects of genetic polymorphisms on the drug PK characteristics of that breed. Collies are used as an example of a breed that has a high frequency of the mutation in the P-glycoprotein (P-gp) transporter, caused by a frame-shift deletion of four base pairs at the 59-end of the canine *Mdr1* open reading frame (2, 5). This mutation leads to premature termination of P-gp synthesis and expression of a non-functional protein. The drug loperamide was chosen to explore the effect of the P-gp mutation as it is a P-gp substrate with only 2 main routes of elimination: biliary clearance and metabolism via the Cyp3a12 enzyme. A difference in the pharmacokinetics was expected to occur when a mutant (Mu) Collie population was simulated due to the lack of P-gp associated biliary clearance when compared to the wild type (WT) Collies. The aim was to perform *in vitro*-to-*in vivo* extrapolation (IVIVE) that could be linked within a PBPK model, using data from the literature.

## Development of the IVIVE-PBPK model

The model consists of 3 components: a structural model, population-specific properties, and drug-related input parameters. PBPK modelling and simulations were performed using the Simcyp Animal Simulator for the Dog (Version 23; Certara UK Ltd, Sheffield, UK). Inputs for the Collie model were derived from published literature. Where breed-specific Collie data was not available, inputs from the Beagle were used. Population variability was accounted for by using coefficients of variation based on those previously derived from Beagle and human data for Cyp3a12 and P-gp, respectively.

A whole-body full PBPK structural model was selected, which includes a compartment for each of the major organs (adipose, bone, brain, gut, heart, kidney, liver, lung, muscle, skin, spleen and pancreas). In addition, the Advanced Dissolution, Absorption and Metabolism (ADAM) model (6) was included to simulate the absorption and efflux of the drug in the intestine, across eight intestinal compartments (Duodenum, Jejunum segments I-V, Ileum and Colon). Finally, the permeability-limited liver model (PerL) (7) was included in the model to simulate perfusion-limited behaviour of the drug on the sinusoidal membrane.

The inputs for loperamide were derived from *in vitro* and physicochemical data from the literature, and tools within the Simcyp Simulator were used for the calculation of the blood-to-plasma ratio and effective intestinal permeability. The Michaelis-Menten kinetics for the active P-gp transporter were derived using the Simcyp In Vitro (data) Analysis (SIVA) toolkit (Version 5; Certara UK Ltd, Sheffield, UK) from *in vitro* measurements. Due to the lack of canine-specific data for P-gp, and the close (93%) (8) homology to the human P-gp, the data from human P-gp was used with a relative expression factor (REF) of 1.86 applied to the hepatic P-gp to account for the differences in expression between the intestine and the liver. In addition, a relative activity factor (RAF) of 10 was applied to both the intestinal and hepatic P-gp following a sensitivity analysis to examine the effects of enterohepatic recirculation (EHR).

During the development of the PBPK model, we used the observed data from Mealey *et al.* (9) to verify that the model could recover intravenous (IV) and oral doses of loperamide for both the Mu and WT Collies. With the exception of the 0.01 mg/kg WT dose, which was used during a sensitivity analysis to derive the RAF for P-gp, the observed data from Myers *et al.* (10) were not used during the development of the model but were retained as an independent verification data set. Since the 0.01 mg/kg dose was not included in the verification set and, thus, no clinical data was used for building the model for Mu Collies, the spirit of a bottom-up model was maintained.

## Model Performance

The simulated concentration-time profiles for both the WT and Mu Collies recovered the observed oral doses of 0.01 – 0.2 mg/kg, and 0.05 – 0.2 mg/kg, for the Mu and WT Collies respectively. The simulations were within two-fold of the observed mean area under the curve (AUC) and maximum concentration ( $C_{max}$ ) for all doses. The absolute average fold error was 1.40 and 1.24 for the  $AUC_{0-24h}$  and  $C_{max}$ , respectively for the WT ( $n = 7$ ) and 1.18 and 1.51 for the  $AUC_{0-24h}$  and  $C_{max}$ , respectively for the Mu ( $n = 10$ ) dogs. Overall, dose-proportionality was observed across all doses for both Mu and WT dogs, which suggested that saturation of the P-gp and of Cyp3a12 did not occur at any of the doses. The absence of transporter saturation was supported by comparing the  $K_m$

with the markedly lower simulated enterocyte and hepatocyte unbound concentrations. Although Michaelis Menten kinetics were not used to simulate the Cyp3a12 kinetics, thereby precluding enzyme saturation within the model, the high abundance of Cyp3a12 in the liver and upper gastrointestinal tract supported this assumption.

#### *Loperamide Pharmacodynamic Effects*

Since loperamide has been known to affect its own absorption through changing the transit time in humans (11, 12), a sensitivity analysis was run to examine the effects of extending the small intestinal transit time (SITT) and the colonic transit time (CTT) by 20% (a value selected on the basis of the published human data (12)). The fraction of loperamide absorbed into the enterocyte ( $f_a$ ) was predicted to change by approximately 1% when either the SITT or CTT was increased in WT or Mu dogs, which suggested that the model did not need to account for this pharmacodynamic effect.

#### *The effect of P-gp in Collies*

As the P-gp transporter is completely inactive in the Mu Collies, the model provided an opportunity to explore the ways in which the absence or presence of functional P-gp could be influencing loperamide oral bioavailability. This is an important step in that the decreased  $f_a$  could alter the fraction not metabolized within the enterocyte ( $F_G$ ). Recognizing these contrasting effects could be particularly important in cases where there is an active (toxic or effective) metabolite formed during the oral absorption process. Moreover, although the presence of active P-gp provides for an additional route of elimination not seen in the Mu dogs (i.e., biliary secretion), P-gp is also responsible for the EHR that can occur.

The possibility of the contrasting effects of EHR and biliary secretion on half life ( $T_{1/2}$ ) was consistent with the predicted and observed loperamide data where the effect of the P-gp mutation on  $T_{1/2}$  was much less than expected. To examine this more closely, simulations were run using a single dog (population representative) to measure loperamide distribution in WT, Mu, and WT dogs with inactive EHR. The WT with inactive EHR had a significantly lower  $T_{1/2}$  when compared to the WT and Mu dogs, which suggested that EHR causes the comparable  $T_{1/2}$  simulated in the populations. This was particularly noticeable when the simulations were extended beyond the 24-hour simulation time used for the population simulations to match the study design in Myers *et al.* (10), i.e., to 72 hours. The longer trial design allowed the model to fully account for the biphasic plasma concentration-time profile. Sensitivity analysis on the intestinal and hepatic P-gp activity individually showed that  $f_a$  and  $F_G$  were sensitive only to intestinal P-gp.

The Mu Collie population also had a higher simulated mean  $AUC_{0-24h}$  and a lower total clearance as compared to the WT dogs administered the same dose of loperamide. This was likely due to the lack of biliary clearance in the Mu dogs. This assumption was supported by simulations, where a nearly 2-fold increase in unbound  $C_{max}$  in the intracellular water of hepatocytes was simulation for the Mu Collie, compared to WT with and without EHR. Sensitivity analysis showed that  $AUC_{0-24h}$  was sensitive to hepatic P-gp activity, whereas intestinal P-gp activity only had a minor impact. This analysis also supported the assumption of the role of biliary clearance in the difference in AUC observed between the Mu and WT dog populations (10).

### *Sources of Inter-individual Variability*

Despite the successful predictions, high variability was noticed between individuals both from the Mu and WT populations, with certain individuals from the observed data presented outside the prediction limits. Loperamide appears to be primarily a P-gp substrate, so for the WT this could be accounted for by disparities in transporter function. However, in the Mu dogs the key elimination pathway is Cyp3a12 metabolism. One possible source of variability could be Cyp3a12 polymorphism which has been measured in dogs (13), but to date published information on its effect on drug metabolism is limited. In humans, loperamide is also a substrate of CYP2C8 (14), but the canine ortholog (Cyp2c21/41) was not included in the model due to absence of information about this elimination route of loperamide in dogs. Variability in the Mu population due to these enzymes is considered unlikely as no Cyp2c21/41 polymorphisms have been reported to date, and the gene encoding for Cyp2c41 is absent in many dogs (15).

### *Conclusions*

Our model is the first example of an IVIVE-PBPK model simulating the P-gp substrate, loperamide, in Collies. The model was able to capture observed data over a range of oral and IV doses in both Mu and WT Collie populations. The main challenge with a bottom-up approach was the availability of data, particularly to describe the canine-specific metabolism and transporter kinetics of loperamide.

### *Future Directions*

The overall aim is to use this model and bottom-up approach with other drugs for the Collie, but also the loperamide model in combination with appropriate breed-specific canine *in vitro* data for other breeds. However, prior to that there is the need to fill the gaps we have identified in published breed-specific physiology (16). In addition, other compounds with comparable but also different elimination pathways must be simulated in the Collie model to further verify the model.

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## *Session 3: How AI and Machine Learning May Change Veterinary Medicine*

### Artificial Intelligence in Pharmacovigilance

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### Overview of Pharmacovigilance Processes

The World Health Organization defines pharmacovigilance (PV) as, "...the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem" [1]. An animal health (AH) version can be found in VICH GL 24: "...the detection and investigation of the effects of the use of [veterinary medicinal products (VMPs)], mainly aimed at safety and efficacy in animals and safety in people exposed to the products" [2]. This guideline also provides definitions of other terms in common use in AH PV including "adverse event" (AE), "adverse reaction" (AR), "serious adverse event", "unexpected adverse event", and an "adverse event report" (AER). An AER is "a direct communication from an identifiable first-hand reporter that includes at least the following information: an identifiable reporter, an identifiable animal(s) or human(s), an identifiable VMP, and one or more adverse events". Another VICH GL (42) provides the long list of data elements, some mandatory and others optional, that marketing authorization holders (MAHs, i.e., sponsors) are expected to attempt to collect when MAHs receive AE reports [3]. When AE reports or cases are recorded in a MAH's PV database, the verbatim clinical signs are coded to terms in the Veterinary Dictionary for Drug Related Affairs (VeDDRA) [4], cases are assessed for seriousness (defined in guidance or regulations, e.g., VICH GL 24, 21 CFR § 514.3 [5]), expectedness, and causality, and quality checks are performed. The reports are then submitted, as required, to health authorities (HAs). The quality and completeness of reports can vary widely and are often confounded by concomitant product administration or comorbid medical conditions.

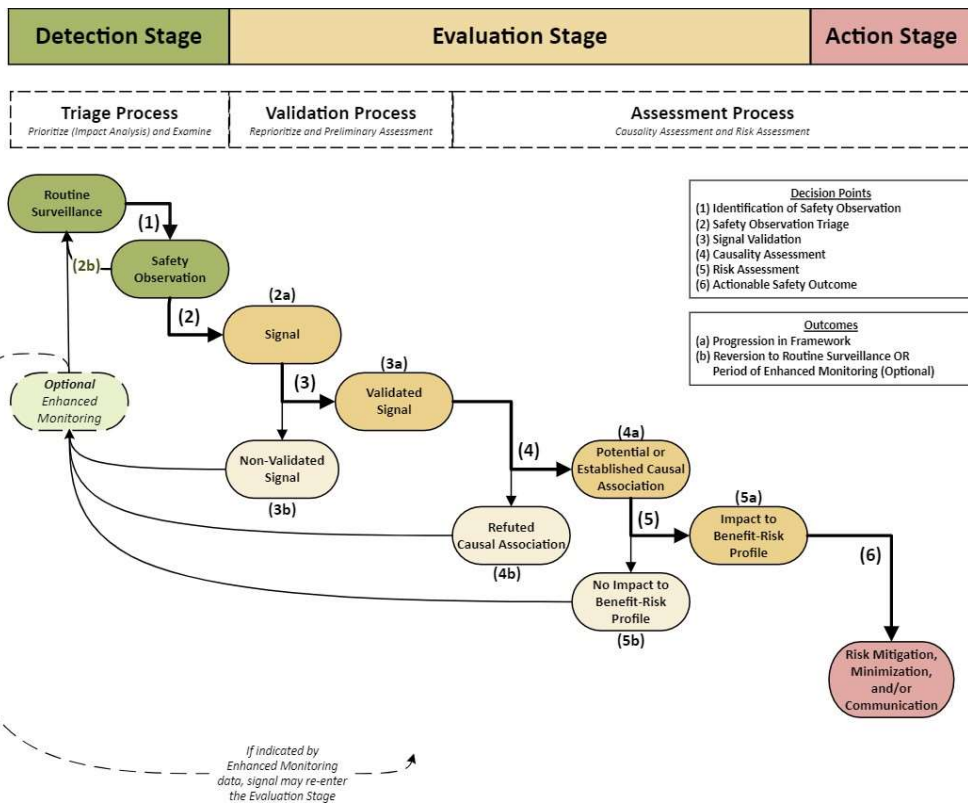
Individual case or aggregate reporting requirements vary by HA and, depending on the jurisdiction, MAHs may be required to analyze AE data for safety observations or signals, validate and assess these findings, draw conclusions on changes to a product's benefit-risk profile, if any, and communicate these to HAs. Starting with the European Medicines Agency (EMA), this signal management (SM) approach has become required by regulations in some

jurisdictions and the concepts of SM are being leveraged in others. Seven models or frameworks for performing SM activities exist [6-12] with similar stages or steps: detection, evaluation, and actions (Figure 1). Signals that are validated based on data from the signal source are assessed through cumulative review of all available evidence to reach a high-quality decision and outcome on the impact on the benefit-risk profile.

AEs can originate from several sources including, but are not limited to, the following: biomedical literature, clinical trials, epidemiological studies, laboratory safety studies, longitudinal data, social media, or spontaneous reports following product approval. Each has advantages and disadvantages [7,10,13]. As post-approval reports to spontaneous reporting system (SRS) databases continue to be the primary source of most safety observations in AH, this discussion on the potential applications of artificial intelligence (AI) to PV will be limited to applications to SRS databases. Out of scope are potential applications to “big data” or real-world data to generate real world evidence.

Both qualitative and quantitative approaches are used to identify safety observations with the latter generally employed when the volume and complexity of data held in the database exceeds the capacity to perform qualitative, manual reviews and analyses. Several quantitative approaches are used, including frequency and disproportionality statistical measures.

Figure 1. Signal Management Stages, Processes, and Decision Points



From: *A Flexible Signal Management Framework for Animal Health Pharmacovigilance*. Animal Health Institute ADS WG7, 2024, with permission [10].

## AI in Pharmacovigilance: Opportunities and Challenges

The Organization for Economic Co-operation and Development (OECD) defined an AI system as “a machine-based system that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments” [14]. AI-related terms include, but are not limited to, the following: algorithm, classification, deep learning (DL), generative AI (gen AI), hallucination, human in the loop, large language model (LLM), machine learning (ML), natural language processing (NLP), neural network, ontology, prediction, predictive analytics, regression, supervised ML, training data, and unsupervised ML. Definitions and descriptions of these terms and concepts can be found in the references [15-18].

Duggirala et al. [19] recently suggested Bayesian methods employed in disproportionality analyses of PV data represent an early form of AI in a ML domain, demonstrating AI-like analytics. Others would disagree [17]. Examples of AI applications to PV from biomedical literature were largely based on “old school” AI and ML models predating gen AI. Pham et al. [20] evaluated the performance of ML algorithms (association rules, random forests, and Monte Carlo logic regression), Bayesian and frequentist disproportionality analyses (DPA), and multivariate methods in detecting drug-AE associations applied to the FDA Adverse Event Reporting System (FAERS) [21] database against a test set of positive and negative controls [22]. Interestingly, the Bayesian DPA approaches outperformed frequentist DPA and ML approaches. Xu et al. [23] reported on a comparison of “statistical distance” AI algorithms using the FDA CVM openFDA database [24] and adverse events reported to that database for selamectin and spinosad following administration to dogs and cats. In a proof-of-concept study using the DataRobot platform [25], Whittle et al. [26] demonstrated the potential use of ML applied to a line listing exported from a PV database for identifying cases of highest quality and completeness. Based on a systematic literature review Salas et al. in 2022 [27] identified the following top four uses of AI in PV: identification of AEs and ARs, processing safety reports, extraction of drug-drug interactions, and identification of populations at high risk or guidance for personalized care.

The ever-increasing volume of cases reported to SRS databases year-over-year is exceeding the ability to manually collect, process, and analyze cases, thus driving the need for innovative tools such as automation (AU) and AI/ML. Other drivers include multiple layers of data from multiple sources, reporting calls getting longer and more complex, and the need for voice to text processing. Hauben & Hartford [17] reviewed the potential applications of AI in PV, including the use of ML to extract case information and AI to support post-approval signal evaluation. The authors emphasized the importance of a well-defined scope particularly for novices in this field. In addition, it is important that the absolute performance of ML models be evaluated for the intended application on PV datasets from the target SRS database. As a result, ML platforms do not replace the need for domain expertise in framing the problem to be investigated, customizing the platform tools, and interpreting the output.

Gen AI represented an “aha moment” in the development of AI. In the year following initial release of ChatGPT, the enthusiasm for the potential of gen AI in human health PV was evident

at the World Drug Safety Congress Americas (WDSCA) 2023 [28] where AI & Machine Learning and Next Gen Tech & Data were two of the 10 conference themes with multiple presentations on AU, AI, and ML. Approximately 40% of vendors were offering some capability in providing tools or advice in AU, AI, or ML. When pressed for examples of deployment in PV databases, most of these vendors could not provide an answer. An informal poll of attendees of one session revealed very few had implemented AI in their PV systems. Some of the challenges presented during the Congress included limited acceptance by HAs, lack of performance and quality assessment standards, the need for use of true sources of data, lack of standardization at data collection, variability and size of model training data sets, demonstrating return on investment, and availability and cost of training dictionaries.

Some examples of what was working with high accuracy, but still needing medical/human review, included rules-based case processing (AU), follow up query generation, and structured narrative generation. Less accurate were character recognition for case intake, medical coding using ML, and language translation. Accuracy for assessing expectedness, causality, or seriousness was demonstrated in limited, controlled PV databases. One large pharma company used chatbot and copilot technology for case triage, quality control, and querying. Other potential applications included human-assisted ML to decrease risk of missing AEs due to human error, identification of extra-label use, and identification of duplicate reports. Aggregate report preparation was also noted as a potential application with human oversight particularly for discussion and conclusion sections. The extraction of PV data from the biomedical literature had become an established application of AI in human health PV. ML may facilitate signal detection through linking of data sources. Gen AI has potential for signal detection when applied to RWD. At that time (October 2023), while AU seemed to be more advanced, AI/ML for PV was still in a hype phase.

The tone for AI applications to PV during the WDSCA a year later [29] was more pragmatic and focused on patient safety and risk management and how AI/ML could be leveraged. AI was framed more as a tool and less as a “silver bullet” with several barriers that needed to be overcome. AU at case intake and AI-assisted literature searches had been established practices for many MAHs. Focused applications were emphasized with fit for purpose use cases within a specified domain. Reference was made to customized enterprise gen AI, LLM models, or multiple small language models that were focused and trained on domain specific knowledge. Examples were provided for application of copilot ML in controlled, safe environments. While examples of narrative generation and aggregate report writing were noted, emphasis was also placed on the need for humans in the loop. Concerns were raised over hallucinations and fake data, which cannot be tolerated in PV. It was suggested by one speaker from a major PV vendor that inaccuracies may lead to gen AI becoming obsolete.

One speaker [30] described six levels of AI automaticity ranging from not autonomous (all tasks performed by humans) to fully autonomous (humans not in the loop) and provided PV relevant examples. An example of all tasks performed by a human was causality assessment by a medical reviewer based on a case series with synthesis of causality based on medical and scientific expertise. For signal detection to be other than not autonomous, the ML model will need to be

trained on domain specific knowledge. A conditionally autonomous example was causality assessment based on a domain-specific framework such as that described by Wang [31] for idiopathic drug-induced liver injury. An example of a potentially highly autonomous application in risk minimization, depending on the level of risk involved, was generation of tailored education programs customized to the individual patient.

The FDA published a discussion paper on AI/ML in May 2023 [32] that focused primarily on product development but included a section on post marketing safety surveillance. Potential applications included identification of AEs across data sources, case processing such as validity and duplicate checks, coding, quality control, and prioritization based on expectedness. Other applications may include case assessment for causality and seriousness. Case submission may also be facilitated with rules for individual and aggregate case reporting to the HAs.

In September 2024 the EMA/CHMP/CVMP issued a reflection paper on the use of AI in the medicinal product lifecycle [18]. The document stated the need for active efforts to minimize introduction of bias into AI/ML applications and promotion of reliable and trustworthy AI. Differences between human and veterinary domains were noted; specific veterinary guidance was likely needed. Unique to PV was a statement that a more flexible approach to AI/MI modelling and deployment may be appropriate for tasks such as classification, severity scoring, and signal detection.

In January 2025, the FDA issued for comments a draft guidance for industry focusing mostly on AE models used in drug development and providing a seven-step approach to demonstrate AI-enabled evidence generation that is sound for use in a regulatory setting [33]. Establishing model credibility within the context of use was central to this approach. While the document touches on the potential AI may have in a MAH's PV practices, insights into how FDA CVM views the potential for AI/ML in safety surveillance is contained a recent publication [19] that includes automation of tasks, case processing, case validity assessment, VeDDRA coding, and case prioritization. Other potential applications include screening of literature, social media, clinical trial reports, and veterinary electronic health records (VEHRs) for AEs. The authors also noted challenges for applying AI/ML including securing funding, availability and quality of data, limited standardization of VEHR data, and integration challenges.

In parallel with the release of reflection and draft guidance documents from HAs, the Council for International Organizations of Medical Sciences (CIOMS) Working Group XIV [34] is developing a report on AI in PV. An update on the Working Group's progress is expected in April or May 2025.

## Discussion

The opportunities for plugging in AU/AI/ML into PV processes are many, as are the challenges. Many of these opportunities and challenges are summarized in this report.

The need for innovative PV solutions is based on the increased volume and complexity of SRS cases, including multiple layers of data from multiple sources. Additional demands placed on MAHs are evolving with divergent processes for SM and reporting requirements [8,12]. The further along in the SM process observations/signals advance, the greater the need for oversight from medical, scientific, and subject matter experts. That said, simply adding more human resources is not the answer.

The science and activities of AH PV encompass detection, assessment, understanding, and prevention of AEs that impact the benefit/risk profiles of products intended to treat or prevent diseases in animal patients. AH PV operates in a regulated GxP environment with growing challenges and complexity. It remains to be seen what the regulatory guardrails will be for AH PV in applying AU/AI/ML to address these challenges. At one end of the spectrum is an expectation for credibility and trustworthiness of ML models based on some set of performance standards. These could be defined and specified in an organization's procedures, work instructions, or guidance documents and subject to regulatory inspection. This is like the current use of DPA in AH PV [8,35,36]. At the opposite end of the spectrum stringent credibility and performance standards, appropriate for GLP, GMP, or GCP can be envisioned that are counter to the position that PV may allow a more flexible approach to AI/ML modelling and deployment [18]. What is "good enough" has yet to be defined and perhaps it should not be until more experience is gained and shared among stakeholders.

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# Enhancing Pharmacokinetic Data Extraction with LLMs and Rule-Based Methods: A Hybrid Approach Using Machine Learning and Regex

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**Abstract:** Data curation has significant research implications across all application areas, including pharmacology. In the field of pharmacology there is a notable absence of comprehensive, centralized, and up-to-date repositories of pharmacokinetic (PK) data. This poses a significant challenge for research and development (R&D) as manual data collection can be a time-consuming and challenging task to collect all the required quantitative PK parameters from diverse scientific publications. This quantitative PK information is predominantly organized in tabular format, mostly available as XML, HTML, or PDF files within various online repositories and scientific publications, including supplementary materials. The objective of this paper is to address the knowledge gap by introducing a system that automates the extraction and formatting of data from tables found in published documents, while also taking reading order detection into account. The proposed system encompasses a comprehensive approach to table data extraction that systemically addresses a wide range of both simple and complex table layouts. The results from the table data extraction project show that the proposed system can effectively and efficiently collect PK data from tables in the XML format of scientific literature. **Keywords:** Text and data mining, pharmacokinetics, automated algorithm, table extraction, large-scale information mining.

**Introduction:** The primary objective of pharmacology and drug development is to discover and optimize therapeutic compounds that exhibit favorable PK and pharmacodynamic (PD) properties. Both in human and veterinary medicine, there is a compelling emphasis on comprehending the PK properties of chemical substances and pharmaceutical drugs. The PK properties of a drug play a critical role in the drug discovery process, as a poorly designed study with an incorrect dosing threshold can significantly jeopardize the overall safety profile as well as the efficacy of a new drug and may lead to its termination during the clinical development phase [1-2]. The druggability of a compound largely hinges on its metabolism and PK properties. These aspects pose significant challenges in the field of pharmaceutical research and development (R&D) [3]. Additionally, there is a notable lack of centralized, comprehensive, and up-to-date repositories for PK data within the drug development pipeline. This absence makes it time-consuming and difficult to gather the necessary quantitative PK parameters from various scientific publications.

To address this challenge, we started with the development of an automated web crawling paradigm to search for and extract drug PK profiles, which are critical for safety assessment and clinical applications [4]. This system, called Web-Crawler for PK (WCCK), supports the Food Animal Residue Avoidance and Depletion (FARAD) program by facilitating scientific article downloads from existing bibliographic databases (Figure 1). For over 40 years, the Food Animal Residue Avoidance Databank (FARAD) team has manually extracted tabular data and other information from literature and regulatory agencies. However, with the increasing volume of daily publications, there is an urgent need to automate this process. Improving PK predictions of novel chemical entities or drugs can be achieved by leveraging knowledge and understandings gathered from previous studies conducted on other compounds. However, the process of searching for, curating, and standardizing the relevant PK information from scientific literature still presents a constraint in the development of robust algorithms aimed at enhancing the preclinical and clinical phases of drug development. Collecting and compiling all the essential quantitative PK parameters from scientific publications for R&D purposes is a challenging task. Furthermore, the quantitative PK data in scientific publications is commonly presented within tables, including supplementary data, which can often exhibit complexity and can be challenging to interpret accurately. This complexity further complicates the task of detecting and converting the information into a scientifically meaningful order.

Various studies confirmed that by leveraging natural language processing (NLP) and large language models (LLMs), a robust repository of prior published data from scientific articles can be established [5-8]. However, the full capabilities of these LLMs in comprehending data from tables with diverse layouts, heterogeneous data, named entity recognition and classification, relationship identification and classification, and metric system identification and classification, still need further exploration [9-10]. Extracting information from tables remains a challenge due to the lack of a systematic approach to handle diverse structures of tables found in literature. This can lead to reduced performance efficiency and difficulty in collecting relevant table information tailored to specific requirements. As part of the layout

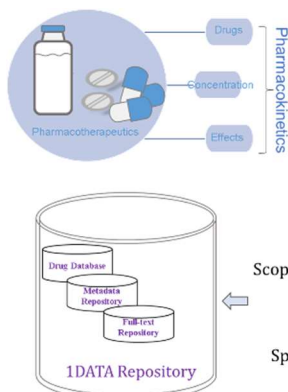


Figure 1: Automated web crawler for PK analysis [1] data analysis [1].

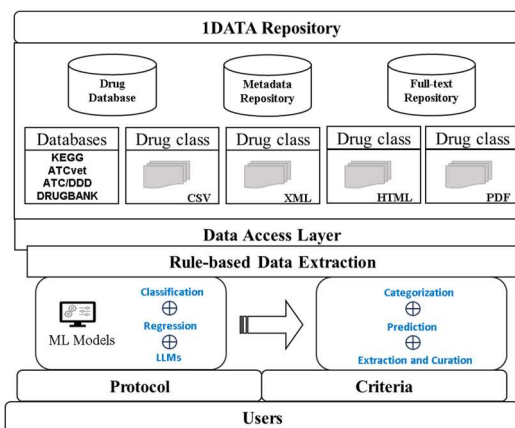


Figure 2: Data extraction, curation, and predictive models for PK

challenges, these workflows may also struggle to extract information from complex tables with spanning cells across rows, columns, or both. It is important to develop an algorithm capable of effectively managing merged rows and/or columns in data table, ensuring proper distribution, detecting the reading order, and accurately extracting information. However, creating such an algorithm is challenging due to the diverse array of table formats that exist. Automated systems encounter challenges when it comes to efficiently interpret this information [11-13]. Reading order detection is a crucial component of these techniques as it ensures that the data is interpreted in the same way as human readers comprehend it [14]. When it comes to extracting information from multi-dimensional tables, a step-by-step approach is necessary. This begins with identifying the table itself, followed by analyzing its function, structure, and meaning. Finally, the data can be extracted from each individual cell of the table using syntactic processing. This method showed to have a higher level of performance efficiency [15].

**Methodology:** The proposed rule-based table data extraction and curation system implemented on top of the WCPK is centered on PK data retrieval across species. This data is taken from the established drug-class-specific article repositories and made easily available through text and data mining (TDM) service. Considering the scenario where the quantitative PK data in scientific publications is commonly presented within tables, including supplementary data, we focused on the data extraction from tables of WCPK literature (Figure 2).

In this study we focused on combining a rule-based data retrieval pipeline with LLM approaches to extract PK data from tables from scientific articles of XML file formats (Figure 2). Each article is then analyzed to extract tables, identified the diverse and complex table layouts, converted them to desired formats to establish a comprehensive data extraction and accurate interpretation. Table diversities were handled by selecting appropriate xml tag elements within the table cell entry elements. After identifying and addressing the table layout diversities, Beautiful Soup [16] data parsing libraries (third-party packages) as well as LLM APIs. The initial part of table pipeline is implemented using rule-based algorithms and Beautiful Soup, a Python package for performing XML or HTML parsing [16, 17] and then used to train LLM models. Based on rule-based algorithms, collected data are saved as CSV with columns representing drug or active substances, and related physiological PK data including dose, clearance, species, volume of distribution, half-life. To enhance the scalability and accuracy of PK data extraction, the proposed system integrates LLMs to address the limitations of rule-based methods in handling irregular table formats and terminological inconsistencies. Tables are initially extracted from XML-format scientific articles and converted into CSV files. These tables often contain irrelevant content or inconsistently structured data, necessitating additional processing before they can be used for meta-analysis.

**Results and Discussion:** Thousands of full-text scientific articles in XML file formats were considered for table extraction in this study [4]. As discussed in the methodology section, XML parsing is performed using *Beautiful Soup* where it exclusively looks for available tables. Then for each table its layout is identified, and the desired table data extraction module is invoked. Every table within the XML file is processed in the same manner. It is transformed into a string format according to the specific table format and subsequently sent to the content retrieval module. Here all the information from the table is recorded in a .csv file with

details such as PK parameters, units, values, followed by the entire string which is row-wise or column-wise parsed table content.

As a result, one of the tables from, for example, '10.1016/j.smallrumres.2018.01.001' is identified as common table format with the possibility of row-wise parsing. Parsed results for the selected table are shown in Figure 3, having PK Parameter, unit, value, followed by header line and drug name present in the table title, for each row. An example of table identified using BeautifulSoup's findAll method for the XML file version is shown in Figure 3a. While extracting the table blank content was replaced with 'NaN' for easy handling. Content retrieved here is in the same structured format, however, for data curation text and data mining studies unstructured data will be more helpful (Figure 3b). Considering this fact, further data extraction is planned with focus given on extracting the PK parameters and its interventions matching the identifiers that are set in the defined procedure. It will generate an outcome in an unstructured manner, following a row-wise curation criterion (Figure 3c). For tables that have a transposed format, the curation path applied will be column-wise generating unstructured sentence case outcome. The result of table information extracted as a sentence which has drug name MEL for meloxicam from the table title is appended at the end of each row data. [Note: || indicates separation between table rows].

Recognizing the structure of a table is important for machines to comprehend and extract relevant data from it. While our algorithm provides a universal process to convert XML tables of varying complexity, there are uncertainties related to the table layout and potential issues with the data itself. The table header is particularly significant in comprehending the table's contents. When it comes to XML table headers, they consist of multiple row tags that can contain header or table data entry tags. The table body also includes both data and header tags. In a way, it increases the complexity of

**Table 1**  
Pharmacokinetic parameters of MEL after IV administration at 0.5 mg/kg in lactating goats (n = 6).

Parameter	Units	IV
		Mean SD
AUC	h*ng/mL	26499 ± 4233
K10	1/h	0.12 ± 0.03
K12	1/h	0.64 ± 0.38
K21	1/h	1.13 ± 0.71
K10_HL	h	6.07 ± 1.18
Alpha	1/h	1.82 ± 1.09
Beta	1/h	0.07 ± 0.02
Alpha_HL	h	0.53 ± 0.35
Beta_HL	h	9.96 ± 2.51
A	ng/mL	1223 ± 153.71
B	ng/mL	1840 ± 357.69
AUMC	h*h*ng/mL	374373 ± 120223
MRT	h	13.88 ± 3.36
CL	mL/h/kg	19.38 ± 3.86
Vss	mL/kg	262.37 ± 50.74
V1	mL/kg	165.76 ± 23.06
V2	mL/kg	96.61 ± 31.07

Area under the curve (AUC), elimination rate from compartment 1 (K10), rate of movement from compartment 1-2 (K12), the rate of movement from compartment 2-1 (K21), half-life of the elimination phase (K10\_HL), rate constant associated with distribution (α), rate constant associated with elimination (β), distribution half-life (Alpha\_HL), elimination half-life (Beta\_HL), intercept for the distribution phase (A), intercept for the elimination phase (B), area under the first moment curve (AUMC), mean residence time (MRT); total clearance (CL), volume of distribution at the steady state (Vss), volume of compartment 1 (V1), and volume of compartment 2 (V2).

Parameter	Units	IV	
	NaN	NaN	Mean SD
2	AUC	h*ng/mL	26499 ± 4233
3	K10	1/h	0.12 ± 0.03
4	K12	1/h	0.64 ± 0.38
5	K21	1/h	1.13 ± 0.71
6	K10_HL	h	6.07 ± 1.18
7	Alpha	1/h	1.82 ± 1.09
8	Beta	1/h	0.07 ± 0.02
9	Alpha_HL	h	0.53 ± 0.35
10	Beta_HL	h	9.96 ± 2.51
11	A	ng/mL	1223 ± 153.71
12	B	ng/mL	1840 ± 357.69
13	AUMC	h*h*ng/mL	374373 ± 120223
14	MRT	h	13.88 ± 3.36
15	CL	mL/h/kg	19.38 ± 3.86
16	Vss	mL/kg	262.37 ± 50.74
17	V1	mL/kg	165.76 ± 23.06
18	V2	mL/kg	96.61 ± 31.07

conversion of table objects for further processing in programming languages which may result in inconsistencies in the PK information due to authors choice. Similarly, other table features such as a) b)

c) AUC h\*ng/mL 26499 ± 4233 Parameter NaN Units NaN IV Mean SD. MEL || K10 1/h 0.12 ± 0.03 Parameter NaN Units NaN IV Mean SD. MEL || K12 1/h 0.64 ± 0.38 || K21 1/h 1.13 ± 0.71 Parameter NaN Units NaN IV Mean SD. MEL || K10\_HL h 6.07 ± 1.18 Parameter NaN Units NaN IV Mean SD. MEL || Alpha 1/h 1.82 ± 1.09 Parameter NaN Units NaN IV Mean SD. MEL || Beta 1/h 0.07 ± 0.02 Parameter NaN Units NaN IV Mean SD. MEL || Alpha\_HL h 0.53 ± 0.35 Parameter NaN Units NaN IV Mean SD. MEL || Beta\_HL h 9.96 ± 2.51 Parameter NaN Units NaN IV Mean SD. MEL || A ng/mL 1223 ± 153.71 Parameter NaN Units NaN IV Mean SD. MEL || B ng/mL 1840 ± 357.69 Parameter NaN Units NaN IV Mean SD. MEL || AUMC h\*h\*ng/mL 374373 ± 120223 Parameter NaN Units NaN IV Mean SD. MEL || MRT h 13.88 ± 3.36 Parameter NaN Units NaN IV Mean SD. MEL || CL mL/h/kg 19.38 ± 3.86 Parameter NaN Units NaN IV Mean SD. MEL || Vss mL/kg 262.37 ± 50.74 Parameter NaN Units NaN IV Mean SD. MEL || V1 mL/kg 165.76 ± 23.06 Parameter NaN Units NaN IV Mean SD. MEL || V2 mL/kg 96.61 ± 31.07 Parameter NaN Units NaN IV Mean SD. MEL merged-column,

**Figure 3:** a) Table extracted from the following XML document: <https://doi.org/10.1016/j.smallrumres.2018.01.001>, b) program extracted table, c) Result of table information extracted as a sentence which has drug name MEL from the table title, appended at the end of each row data. [Note: || indicates separation between table rows] Sentence format outcome with parameter, value, units.

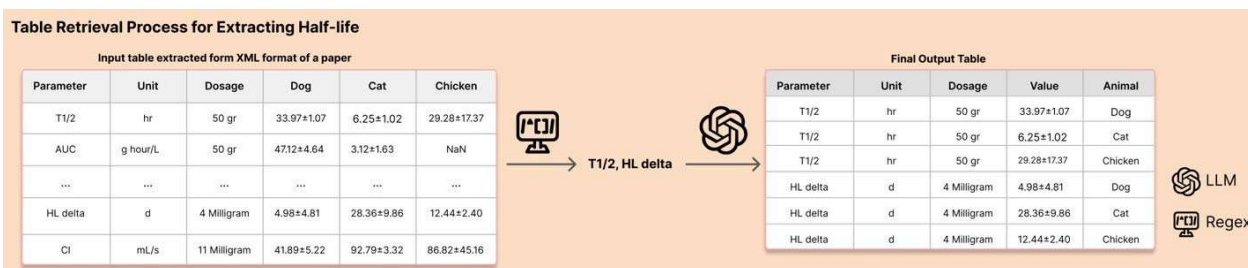
merged-row, and spanning cells, also increase the complexity of tables. Even though the proportion of span cells is usually low in a complicated table, they may contain more semantic information when table headers are present in them. Therefore, recognizing complicated table structures is an important part in the text and data mining of tables. The proposed algorithm has the ability to identify intricate table arrangements, recognize table headers through header titles or table data *entry* tags in merged-column, merged-row, or spanning cells, transform them into a data frame, and eventually produce the necessary parameters and values.

In the realm of R&D, literature mining scientific articles is an essential tool for ensuring the reproducibility of research information and facilitating comparison to other studies. While PDF has long been the favored format for electronic scientific articles, XML and HTML file types are growing in popularity due to their flexible information retrieval capabilities. This study aims to develop a system for detecting and extracting tables from XML versions of scientific literature, taking advantage of the structured organization and specific tags assigned to each file element, including images, tables, and text content. The information taken from a table is transformed into a sequence of words so that quantitative data, such as PK parameters, can be extracted and reported. The proposed system involves various steps, including analyzing the table's layout to detect the reading order, identifying, and extracting PK parameters, and storing the data with the appropriate units provided in the table cells.

This paper examines the automatic machine extraction of PK data from tables in XML versions of scientific articles. In this system, we learned about and solved important challenges in table detection and extraction from XML file formats focusing on the PK domain. The proposed system is an integration of five steps: table detection, table extraction, reading order detection, PK data recognition with parameter specifier identification, and PK data extraction. Moreover, our understanding of this information has enabled us to enhance the algorithms to obtain a deeper understanding of the inherent reading sequence of the data, where the cells and headers have a predetermined connection. In such situations, comprehending the order of the cell and header features is crucial to transforming tables into meaningful knowledge.

Figure 3 presents a representative example of our method system's table retrieval and standardization workflow for PK data, specifically focusing on half-life parameters. The input table, extracted from an XML-formatted scientific publication, contains multiple PK parameters with heterogeneous units, inconsistent naming conventions, and values distributed across different animal species (e.g., Dog, Cat, Chicken). To address these challenges, our method employs a hybrid extraction pipeline. Initially, a rule-based module using regular expressions (regex) identifies relevant half-life parameters such as "T1/2" and "HL delta," accommodating terminological variability. Once identified, the corresponding rows and columns are isolated from the input table. Subsequently, the filtered data is reformatted and processed through a LLM, which restructures the information into a standardized tabular format. Each row in the final output table clearly maps a PK parameter to its unit, dosage, observed value, and associated animal species. This two-stage process ensures that semantically similar but structurally diverse entries are normalized, facilitating downstream applications such as meta-analyses, regulatory evaluations, and machine learning-based PK modeling.

The evaluation of our information extraction from tables was conducted using two complementary datasets: a manually curated real-world collection and a large-scale synthetic dataset. The real-world dataset included 15,000 PK parameter samples sourced from the FARAD repository, representing over four decades of curated data focused on U.S. food animals (Figure 4). However, this dataset's limited scope in



species, drug diversity, and table variations prompted the generation of more than 10,000 synthetic tables. These were created to mirror a wide range of real-world table formats, terminologies, and structural

**Figure 4:** Example of our method’s Table Retrieval Process for Extracting Half-life Parameters. The input table, extracted from an XML-formatted scientific article, contains mixed PK parameters, units, dosages, and species-specific values. Our method applies a hybrid approach using regex for parameter identification and an LLM for table restructuring, converting the unstructured data into a clean, standardized output table

inconsistencies, ensuring robustness and adaptability across diverse use cases.

System performance was evaluated using two primary metrics: row-wise accuracy and cell-wise accuracy. Row-wise accuracy measures whether a generated row exactly matches a reference row in all values, indicating the system’s ability to reconstruct full records. Cell-wise accuracy, in contrast, assesses the correctness of individual cell values independent of their row context. Together, these metrics offer complementary views of system performance, with row-wise accuracy capturing comprehensive table reconstruction and cell-wise accuracy reflecting finer-grained extraction precision. Our method demonstrated strong performance, particularly on the synthetic dataset. In the parameter identification stage, the regex-based module achieved 98% exact match accuracy for extracting half-life values from synthetic tables. In the complete pipeline, which combines regex-based identification with LLM-based table reconstruction, the system achieved high accuracy for both generated and real datasets. For generated data, our method reached 93% cell-wise and 87% row-wise accuracy for half-life, and 96% cell-wise and 94% row-wise accuracy for Cmax (Table 1). On the real-world dataset with 50 samples, our method achieved 74% row-wise and 87% cell-wise accuracy for half-life extraction, outperforming both LLaMA 70B and DeepSeek-R1 671B. These results confirm our method’s capability to accurately extract and structure PK parameters from diverse and complex tables.

**Table 1: Comparison of Extracting PK Parameters Accuracy Across Different Methods for Generated (G) and Real Data (R)**

Parameter	Metric (%)	Our method	LLaMA 70B	DeepSeek-R1 671B
Half-life (G)	Row-wise	87	44	-
	Cell-wise	93	65	-
Cmax (G)	Row-wise	94	81	-
	Cell-wise	96	89	-
Half-life (R)	Row-wise	74	67	53
	Cell-wise	87	75	82

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## *Session 4: Updates in Specialty Areas*

### **Advancing Veterinary Dermatology with Clinically Relevant *In vitro* Models**

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The global companion animal health market is undergoing rapid growth, with an estimated compound annual growth rate (CAGR) of approximately 7.58% [1]. Specifically, the global market size for veterinary dermatology drugs is estimated to be USD 8.20 billion in 2024 and is expected to reach approximately USD 19.28 billion by 2034, growing at a CAGR of 8.93% [2]. This expansion is linked to a variety of factors, including higher rates of pet ownership, advancements in veterinary technology—including improved treatments, vaccines, and diagnostic methods—as well as increasing demand for personalized pet care products like shampoos and creams. Additionally, the widespread availability of pet insurance is further driving expansion. Among companion animals, dogs remain the dominant contributors to market growth, accounting for the largest share of industry demand.

When compared to the human healthcare sector, the veterinary medical field benefits from more flexible regulatory pathways. For instance, in Europe, veterinary medicine approval requires the submission and review of a dossier assessing safety, quality, and efficacy [3]. However, these regulatory standards are less stringent than those applied to human medicine, enabling faster accessibility of treatments for animals. Additionally, certain human medications are adapted for veterinary use, underscoring the disparities in regulatory frameworks. Interestingly, drug development in veterinary dermatology has in some cases been ahead of what has been done in human dermatology. For instance, treatments for canine atopic dermatitis, like oral Janus kinase inhibitors and biologics targeting IL-31, were introduced in veterinary medicine prior to their approval for use in humans. [4].

Animal testing has long been a topic of discussion in both human and veterinary research. While animal models are undeniably valuable in the context of veterinary studies, they often fall short in human-focused research due to significant differences between animal and human biology, such as variations in skin structure. This has fueled the adoption of *in vitro* methods as a more refined alternative. Beyond addressing ethical concerns, these *in vitro* solutions enhance scientific accuracy by facilitating detailed and controlled testing environments. Through these techniques, researchers can accelerate the development of innovative medicines and high-quality pet care products.

At QIMA Life Sciences, we are committed to advancing research in companion animal health

through cutting-edge *in vitro* methodologies. Building on decades of experience in human dermatology and hair care research, we have refined our processes to align with the unique challenges of the veterinary sector. Many conditions, such as atopic dermatitis, are shared between humans and animals, providing a unique opportunity to leverage insights from human-focused dermatology to improve animal health solutions [5]. *In vitro* approaches not only drastically reduce the need for animal testing but also drive the innovation of safe, effective, and high-performing treatments for companion animals.

## **2D Canine *In vitro* Models**

2D *in vitro* models have proven to be invaluable tools for veterinary research due to their affordability and efficiency. They provide a cost-effective alternative to animal testing and the complexities of 3D models, making scientific research more accessible. These models are ideal for high-throughput screening, allowing researchers to test numerous compounds simultaneously. This accelerated process significantly aids early-stage research, helping scientists identify promising candidates before transitioning to more involved models.

At our facility, we've developed 2D assays using primary canine keratinocytes, primary blood cells and canine cell lines to measure the bioactivity of inflammatory cytokines involved in skin diseases (e.g. atopic dermatitis). A variety of readouts has been validated such as the phosphorylation of STATs, mRNA quantification by RT-qPCR or measurement of cytokine release. Additionally, methods validated using human cells are being transposed to animal cells to provide deeper insights into cell functions. These methods include phenotype screenings using CellPainting technology, wound-healing assays to explore cell migration behaviors and assessment of cellular metabolism through Seahorse® analysis.

## **3D Canine *In vitro* Models**

3D *in vitro* models offer unique advantages by closely mimicking the complexities of living tissues. One major benefit is their capacity to incorporate multiple cell types, fostering cellular interactions that simulate real tissue environments. An exception to this is the Reconstructed Canine Epidermis (RCE), which consists solely of keratinocytes. Nevertheless, these models support the study of tissue architecture and organization, revealing insights into structural arrangements and extracellular matrix composition, especially in epidermis layers where cell differentiation occurs. Their physiological relevance makes them crucial for evaluating drug efficacy, toxicity, and disease progression during early research stages [6].

We have developed a canine RCE to simulate atopic dermatitis by using a specific cytokine mix for tissue stimulation (RCE-AD). With this model, we analyze tissue alterations such as histological changes and keratinization patterns under cytokine stress. Additionally, our model measures the release of cytokines and chemokines such as IL-8, IL-10, and CCL2. Skin barrier properties are evaluated through metrics like Transepithelial Water Loss (TEWL) and Transepithelial Electrical Resistance (TEER). We also assess skin barrier components, including Natural Moisturizing Factors (NMFs), ceramides (both short- and long-chain), and filaggrin, leveraging techniques like immunofluorescence or western blotting.

Uniquely, the RCE model enables us to examine the canine skin microbiome. This is achieved using qPCR, colony-forming unit (CFU) counting, and scanning electron microscopy, which allows us to visualize and to quantify interactions between the microbiome and the epithelium. The effects of active ingredients applied systemically or topically can be measured with this model.

### **Non-invasive Canine Clinical Samples**

Our proprietary sampling kits make it easier to analyze non-invasive canine clinical samples for detailed skin marker evaluations. Featuring swabbing kits and tape-stripping kits, combined with mass spectrometry analyses, these tools assess epidermal lipids (ceramides and neutral lipids), hydration (via NMF components). Skin microbiota can be further characterized using qPCR. Additionally, they enable the examination of inflammatory markers, oxidative stress, and odor-related molecules, including volatile organic compounds. These kits facilitate comprehensive research while prioritizing the welfare of the animals involved.

### **Clinical Imaging Evaluation**

Advanced imaging technologies like the SkinCam Pro® allow us to perform detailed macro skin imaging, capturing factors such as pigmentation, pore visibility, porphyrins, dryness, redness, and even animal hair quality. Our expertise in human digital image analysis can be applied to animal studies to quantify treatment efficacy, providing insight into changes in skin texture (e.g., roughness and color uniformity), skin tone, and irritation levels (measured relative to hemoglobin levels).

Both SkinCam® and SkinCam Pro® are cloud-connected, enabling real-time image processing and analysis on demand. Additionally, these systems allow us to create image banks for documentation, illustration, and timeline tracking. This technological integration ensures that our clinical studies are accompanied by precise and actionable data.

By integrating these state-of-the-art *in vitro* models, non-invasive sampling, and imaging capabilities, we continue to advance veterinary research, offering innovative tools and insights to support professionals in animal health and the pet care industry.

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## Recent developments in veterinary oncology: supportive care and therapeutic approaches.

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New supportive care therapy in veterinary oncology includes the first conditionally approved drug to treat chemotherapy-induced diarrhea in the dog. Canalevia-CA1 (crofelemer delayed-release tablets) received conditional approval in 2021. Crofelemer is a proanthocyanidin extracted from the bark latex of the South American *Croton lechleri* that targets two distinct membrane transport proteins in the intestine. Inhibition of the cAMP-stimulated cystic fibrosis transmembrane regulator (CFTR) chloride channel and the calcium-activated chloride channel (CaCC) in the intestine are responsible for the inhibition of chloride hypersecretion, regulation of intestinal fluid transport and thus efficacy in secretory diarrhea in humans.<sup>1</sup> Crofelemer is FDA approved in humans for noninfectious, secretory diarrhea caused by HIV or its treatment with antiretroviral therapy (ART). Chemotherapy induced diarrhea (CID) in dogs is estimated to occur in a relatively small number of dogs (less than 70,000 annually) which constitutes a minor use in a major species and thus made canalevia eligible for conditional approval under the Minor Use and Minor Species Animal Health (MUMS) Act. With no clear standard of care for CID in dogs, the most commonly used treatments typically have been metronidazole or tylosin. Concern over recent increases in identification of metronidazole-resistant organisms in human medicine, as well as the lack of an infectious cause to CID, underscore the need to identify treatment options other than antibiotics/antimicrobials. The pilot study evaluating clinical field efficacy included 24 dogs (12 treated) with general acute diarrhea, not CID, but as both types include secretory diarrhea with similar pathophysiology the results of the pilot study were considered sufficient to extrapolate to support the reasonable expectation of effectiveness in CID. Canalevia-CA1 is administered as one

(1) 125 mg tablet twice daily for three days in dogs weighing less than 140 lbs. Two tablets twice daily are administered to dogs weighing more than 140 lbs.<sup>2</sup>

New treatment opportunities have included the first approved intratumoral therapy for canine mast cell tumors (MCT), Stelfonta (tigilanol tiglate; TT) in 2020. The active component of this medication is a phorbol ester that was initially extracted from the seeds of the *Fontainea picrosperma*, or bluishwood tree, endemic to rainforest areas of Australia. The drug is labeled for non-metastatic cutaneous MCT and non-metastatic subcutaneous MCT that are located distal to the elbow or the hock. The primary reason for not using TT for subcutaneous MCT above the elbow/hock is the risk of subcutaneous accumulation of necrotic debris from the very predictable formation of a wound at the injection site. While the direct tumor ablation caused by TT is thought to primarily occur via vascular disruption and necrosis at the injection site, an additional and critical component of the antitumor activity is the activation of  $\alpha$ ,  $\beta$ I,  $\beta$ II and  $\gamma$  forms of protein kinase C, as forms of TT that lack this activity show limited ability to eliminate tumors in animal models.<sup>3</sup> Structural similarities suggest that TT acts as a diacylglycerol (DAG) “mimetic” and as such can activate the conventional PKC group of proteins when also bound to calcium. Interestingly, this mechanism of action has

challenged the long-standing perception that the PKC family of proteins act as oncoproteins whose activity promote tumor formation and survival. Dosing of stelfonta is based on the volume of the tumor being treated, calculated as  $0.5 \times [\text{length (cm)} \times \text{width (cm)} \times \text{height (cm)}]$ . The label dose is 0.5 mL stelfonta (equivalent to 0.5 mg tigilanol tiglate) per cubic cm of tumor but not to exceed 0.25 mL/kg body weight or 5 mL per dog regardless of the tumor volume or body weight.<sup>4</sup> Because of a risk for systemic mast cell degranulation following tumor injection, all dogs should be administered a corticosteroid beginning two days prior to TT, and H1 and H2 receptor blocking agents starting on the day of TT treatment, all continuing for a total of 8 days. Systemic concentrations of TT have been evaluated in a small number of dogs (n=10) following intratumoral injection and estimated parameters for half-life (2.9 to 37 hours), maximum plasma concentration (0.4 to 14 ng/mL) and area under the plasma concentration-time curve (11 to 31 h\*ng/mL) were not found to have any relationship with tumor location or total dose administered (range of 0.05 to 3.4 mg/dog). The initial efficacy field study demonstrated a complete response in 75% of treated tumors and an objective tumor response in 80% of tumors. A later retrospective study of a larger number of tumors confirmed an initial CR rate of 75% that is durable (1 year) in 64% of animals.<sup>5</sup> The most prominent toxicity/side effect of TT is wound formation at the site of injection which occurs in over 94% of cases. The wounds are characterized by necrosis, swelling often well beyond the injection site, inflammation, pain, erythema, bleeding ulcerations, sloughing of tissue, open wounds and presence of granulation tissue. A comparison of wound sizes following TT injection with those that would be formed following surgical resection with standard surgical approaches found that TT “margins” were approximately half the size of surgical margins in about half of the cases, with a few cases having larger wounds from TT than surgery would have produced.<sup>6</sup> Due to the predictable formation of these wounds which can take 30 days or longer to heal, careful case selection and clear client education is required and stelfonta is uncommonly used by veterinary oncologists. Following approval in veterinary oncology, at least three human phase I/II clinical trials were initiated (head and neck cancer and two melanoma trials) which suggested safety but were terminated early due to insufficient patient recruitment rates.

Laverdia-CA1 (Verdinexor) received conditional approval as the first oral medication for the treatment of lymphoma in dogs in 2021. This approval came shortly after the first-in-class and structurally similar drug selinexor received accelerated approval for the treatment of multiple myeloma in humans in 2019. Verdinexor is a reversible, selective inhibitor of nuclear export (SINE) drug specifically targeting the nuclear export protein XPO1 (exportin 1)/CRM1 (chromosome maintenance region 1). Nucleocytoplasmic shuttling of proteins is a critical process for homeostasis of eukaryotic cells and cancer cells are thought to be particularly dependent on this process due to their heavy metabolic demand. Overexpression of XPO1 is seen in many cancers and plays a role in tumorigenesis, in part, by shuttling many tumor suppressor and cell cycle regulatory proteins out of the nucleus.<sup>7</sup> XPO1 shuttles over 220 cargo proteins that include p53, p21, retinoblastoma (RB), FOXO1, Cyclin B1/D1, survivin and BRCA1 and BRCA2.<sup>8</sup> In vitro, verdinexor has demonstrated activity against a number of canine cancers including lymphoma, mast cell tumors, osteosarcoma and melanoma at concentrations that are achievable in vivo following recommended dosing.<sup>9</sup> Pharmacokinetics of verdinexor have been described in

healthy beagle dogs and dogs with lymphoma showing similar results for a T<sub>max</sub> of around 4 hours and a half-life of approximately 5 hours.<sup>9,10</sup> Bioavailability is 3-5 fold greater in the fed state and thus a statement regarding feeding immediately before dosing is printed on the product insert. Dosing is initially 1.25 mg/kg administered twice per week, with doses at least 72 hours apart; increases to 1.5 mg/kg if well tolerated after two weeks or reductions to 1 mg/kg following adverse reactions are facilitated using charts provided on the package insert.<sup>11</sup> The reasonable expectation of effectiveness for conditional approval was evaluated in a 58-dog study that included any type of lymphoma that was either naïve to treatment or was relapsed or refractory to previous treatments. In this study, the overall response rate (ORR; defined as complete response + partial response) was 37% and a sustained benefit was seen as 40% of patients remained on the study for at least 8 weeks. The most commonly encountered toxicity with verdinexor seems to be a Grade 1 or 2 anorexia, with vomiting, diarrhea, lethargy and weight loss also encountered. Prednisolone has been found to be superior to other appetite stimulants in treating verdinexor-induced anorexia, and adequate control of anorexia is likely a critical component of therapy given the significant increase in drug bioavailability seen when administered with food. Verdinexor has a broad label indication (dogs with lymphoma) which allows treatment in numerous disease settings and lymphoma immunophenotypes. Preclinical evidence suggest that verdinexor may be rationally combined with other chemotherapeutic agents as a mechanism to prevent or reverse resistance to those drugs in cases where protein mislocalization impacts drug sensitivity. For example, one mechanism of resistance to doxorubicin, and other topoisomerase II inhibitors, is the aberrant cytoplasmic localization of TopoII $\alpha$  protein which is reversed upon exposure to SINE compounds resulting in restoration of sensitivity.<sup>12</sup> However, given the overlapping gastrointestinal toxicities between verdinexor and many cytotoxic chemotherapeutics, careful application of drug combinations will be required.

The most recent developments in veterinary cancer treatment have been in the immunotherapy space. Harnessing the immune system, specifically with immune checkpoint inhibitors (ICIs), to provide an anti-tumor response has transformed cancer treatment in human oncology. Following the first FDA approved ICI for humans in 2011, numerous monoclonal antibodies have been approved for over 20 different cancer types.<sup>13</sup> In 2023, the first caninized monoclonal antibody for the treatment of canine cancer became available following a conditional license from the USDA-CVB. Gilvetmab targets the immune checkpoint protein PD-1 (CD279), a co-inhibitory transmembrane protein expressed on antigen-stimulated T and B lymphocytes, natural killer (NK) cells and myeloid derived suppressor cells (MDSCs). Binding of PD-1 to its cognate ligand PD-L1 is a mechanism to modulate the intensity of an immune response. PD-L1 is expressed on many tumor types and the interaction of PD-1/PD-L1 results in inhibition of T-cell activation and proliferation followed by T cell exhaustion, preventing a meaningful antitumor immune response. Inhibition of PD-1 with Gilvetmab has the potential to reactivate the immune system to allow recognition and destruction of tumor cells. Gilvetmab is currently indicated for canine mast cell tumors (stage I, II or III) and melanoma (stage II or III). Clinical efficacy studies performed in canine mast cell tumors (n=26) demonstrated an overall response rate (CR + PR) of 46% with stable disease in an additional 27% of dogs. In canine melanoma patients (n=25), 20% of dogs had an objective response with an additional 40% having stable disease.

In these studies, lethargy/fatigue and gastrointestinal adverse events were most common with the majority being low grade. Infusion-related reactions, including anaphylaxis, are possible and premedication with an antihistamine is recommended to prevent or reduce severity of these potential reactions. Gilvetmab is administered as an IV infusion of 10 mg/kg over 30 minutes, every two weeks for up to 10 treatments. As with other monoclonal antibodies, Gilvetmab stays in circulation for several weeks and is eliminated through protein degradation pathways. While extensive pharmacokinetic data is not available, monoclonal antibodies to PD-1 in humans display PK properties typical of therapeutic antibodies such as target-mediated drug disposition and time-varying drug clearance that is impacted by the presence or absence of neutralizing antibodies.<sup>14</sup> Future studies utilizing receptor occupancy (RO) assays may provide for enhanced dosing guidelines.

In March of this year ELIAS Animal Health received full USDA-CVB approval for another immunotherapy in dogs targeting osteosarcoma, the first veterinary autologous prescription product to receive approval. This novel treatment involves autologous cancer cell vaccination, adoptive T-cell transfer and IL-2 treatment, termed “vaccine enhanced adoptive T-cell treatment with cytokine boost.” The procedure occurs over a period of 8 weeks following amputation: a small piece of tumor is sent to ELIAS for tissue dissociation/digestion and the isolated tumor cells are expanded and delivered 2 doses of 25 Gy radiation to halt replication. These radiated but viable tumor cells are combined with *P. acnes* as an adjuvant in autologous serum and then administered, intradermally, once per week over four anatomic locations for three vaccine visits. Two to three weeks following vaccination, leukapheresis is performed to isolate white blood cells which are then sent to ELIAS for expansion and stimulation using a proprietary “superantigen” cocktail. One week after leukapheresis the activated T-cells are infused back into the patient and recombinant IL-2 is administered 5 times at 48 hour intervals. Reported toxicities to this protocol initially included symptoms consistent with cytokine release which have been minimized with the incorporation of premedicants (diphenhydramine, maropitant and firocoxib). In one study evaluating 13 dogs undergoing the procedure, all dogs required additional calcium supplementation during leukapheresis and the majority of all other toxicities were gastrointestinal in nature, relatively low grade and occurred during the period of IL-2 administration.<sup>15</sup> This study had a 36% 2-year survival rate, similar to an older study utilizing a general immune stimulant (L- MTP-PE) in dogs with osteosarcoma.

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## ***Session 5: Antimicrobial Stewardship and One Health***

### **Developing Clinical Breakpoints for Veterinary Antibiotics – Essential for Antibiotic Stewardship –**

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The Clinical and Laboratory Standards Institute (CLSI) Veterinary Antimicrobial Susceptibility Testing (VAST) subcommittee has been active since 1993. Before VAST developed veterinary-specific breakpoints, all susceptibility testing for bacteria isolated from animals used human standards (M100, available from [www.CLSI.org](http://www.CLSI.org)). Testing standards for bacteria isolated from animals were needed to provide the best guidance for drug selection, interpretation, and monitoring programs. The latest published veterinary standard is the 7<sup>th</sup> edition (CLSI VET01(S), 2024). This document has tables with antimicrobial agents recommended for testing, interpretive categories and breakpoints, and quality control (QC) ranges. A new edition of this standard (8<sup>th</sup> Edition) will be published late 2025 or early 2026. The VAST subcommittee has developed breakpoints for 268 drug-bug combinations since 1999. Many of the breakpoints (40%) were developed by the Generic Drug Working Group to add and update older agents and add human antimicrobial agents used in animals extralabel to these tables.

All members of CLSI-VAST are volunteers. The committee is composed of representatives from industry, microbiology laboratories, device manufacturers (susceptibility testing companies), government (regulatory), and professions (academia). CLSI uses a consensus-driven process and open meetings to develop standards for testing. The committee is continuously evaluating existing interpretive categories and breakpoints for refinement and revision. The following sections define the activities of CLSI-VAST and explain how they develop antimicrobial susceptibility testing standards.

#### **Susceptibility Testing Interpretive Categories**

The primary mission of CLSI is to develop testing standards for bacteria isolated from animals and develop interpretive testing categories. Resistance and susceptibility (R and S) are determined by comparing the organism's MIC (or zone of inhibition) to the drug's breakpoint. In Table 2 of the CLSI VET01(S) standard, the interpretive categories for the MIC are shown, which defines the susceptible and resistant breakpoints. After a laboratory determines the MIC, it uses the “SIR” interpretive categories for breakpoints (S, susceptible; I, intermediate, R, resistant; or SDD, susceptible dose-dependent) developed by the Clinical Laboratory Standards Institute and reports the result to the user (the veterinarian). MIC data should not be used in isolation. By coupling the MIC from a laboratory report with CLSI interpretive categories and other important information such as the virulence of the bacteria and the pharmacology of the

antibiotics being considered, the clinician can make a more informed selection of an antibacterial drug. The following guidelines for interpretation apply:

- **Susceptible (S)** – a category based on a breakpoint that implies that isolates are inhibited by the usually achievable concentrations of antimicrobial agent when the dosage recommended to treat the site of infection is used. If the MIC for the bacterial isolate falls in the *susceptible category*, there is a greater likelihood of successful treatment (cure) than if the isolate were classified as resistant. It does not assure success; drug failure is still possible owing to other drug or patient factors (eg, underlying disease, or immunosuppression), and interactions.
- **Intermediate (I)** – a category based on a breakpoint that includes isolates with antimicrobial agent MICs that approach usually attainable blood and tissue levels and for which response rates may be lower than for susceptible isolates. Therapy with this drug using an accepted dosage is discouraged because there is a good likelihood that drug concentrations may be inadequate for a cure. The intermediate category implies clinical efficacy in body sites where the drugs are physiologically concentrated or when a higher-than-normal dosage of a drug can be used. (*Note* that the European equivalent of CLSI, EUCAST, uses “I” to mean “increased dose”.) This category also includes a buffer zone, which should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations, especially for drugs with narrow pharmacotoxicity margins.
- **Susceptible-Dose Dependent (SDD)** – This new category was added in the new edition of 2024 (Papich et al. 2023). This is a category defined by a breakpoint that implies that susceptibility of an isolate depends on the dosage regimen that is used in the patient. This category is used for some fluoroquinolones and applied to other agents in the next edition. To achieve levels that are likely to be clinically effective against isolates for which the susceptibility testing results (either MICs or zone diameters) are in the SDD category, it is necessary to use a dosage regimen (ie, higher doses, more frequent doses, or both, or extended infusion) that results in higher drug exposure than that achieved with the dose that was used to establish the susceptible breakpoint. Consideration is given to the maximum safe dose the manufacturer has reported.
- **Resistant (R)** – a category based on a breakpoint that implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or that demonstrate MICs that fall in the range in which specific microbial resistance mechanisms are likely, and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies. Bacteriologic failure is more likely because of specific resistance mechanisms or inadequate drug concentrations in the patient. However, a patient with a competent immune system may sometimes eradicate an infection even when the isolate is resistant to the drug based on a susceptibility test.

## Wild Type vs Non-Wild Type

- **Wildtype (WT)** – a category based on an epidemiological cutoff value (ECOFF) that describes isolates with no mechanisms of acquired resistance or reduced susceptibility for the antimicrobial (antibacterial or antifungal) agent being evaluated.
- **Non wildtype (NWT)** – a category based on an epidemiological cutoff value that describes isolates with presumed or known mechanisms of acquired resistance and reduced susceptibility for the antimicrobial (antibacterial or antifungal) agent being evaluated.

The distinction is that wild-type (WT) describes bacteria isolates with no phenotypically detectable mechanisms of acquired resistance or reduced susceptibility for the antimicrobial agent being evaluated. Non-wild-type (NWT) bacteria describes isolates with presumed or known mechanisms of acquired resistance and reduced susceptibility for the antimicrobial agent being evaluated. These are defined by phenotypic characteristics (MIC values) not through genetic testing. The wild-type cutoff does not necessarily align with the clinical breakpoint, although sometimes they may agree. The MIC value is the lowest concentration of an antimicrobial agent that inhibits visible bacterial growth in a susceptibility test. The epidemiological cutoff values (ECV, used by CLSI, or ECOFF used by EUCAST), distinguishes between the wild-type and non-wild-type bacterial populations. The ECV is not the breakpoint. The ECV should not be used as the breakpoint, clinical decision making. The ECV does not account for pharmacokinetic-pharmacodynamic (PK-PD) or clinical response correlations.

## How are Standards Developed?

The most important information for the clinician to guide treatment is the report that informs them which drugs have an “S” and which ones have an “R”. What goes into this interpretation? The paper by Turnidge and Paterson (2007) describes the process of setting breakpoints. The CLSI-VAST uses a published guideline (VET02) to develop their standards and establish breakpoints. Sponsors (pharmaceutical companies) submitting breakpoints to CLSI follow these guidelines and submit data to support a proposed breakpoint. The data includes pharmacokinetic data in the target species, MIC distributions for the pathogens targeted, clinical data from the drug used under field conditions at the approved dose, and pharmacokinetic-pharmacodynamic (PK-PD) analysis, using Monte Carlo Simulations (Ambrose, 2006) to show that, at the approved dose, the drug attains PK-PD targets for the labeled pathogen. For older drugs that do not have active sponsors (referred to as “generic drugs” in the guidelines), or human-labeled antimicrobial agents used frequently in animals, the Generic Drug Working Group has developed breakpoints. This group developed most of the breakpoints that are listed in Table 2 for the past 20 years. For these drugs, the committee will consider less rigorous detail. For example, results from clinical use of the agent under controlled field conditions may not be available.

## *Are These Standards, or Guidelines?*

The CLSI is a consensus-driven process and after approval by the subcommittee, the standards become public documents. The consensus process involves the development and public open review of documents, revision of documents in response to discussion, and finally, the acceptance of a document as a consensus standard or guideline.

The CLSI documents used for culture and susceptibility testing should be regarded as a public standard, not a guideline. A Standard is a document developed through the consensus process that clearly identifies specific, essential requirements for materials, methods, or practices for use in an unmodified form. A *Standard* may, in addition, contain discretionary elements, which are clearly identified. A *Guideline* is a document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

To improve the safe and effective use of antimicrobial agents for treatment of animal bacterial infections, The Clinical and Laboratory Standards Institute (CLSI, [www.CLSI.org](http://www.CLSI.org)) continually analyzes existing breakpoints and re-evaluates the accuracy based on new pharmacokinetic, clinical, or microbiologic data. This review is needed to support a revision of the antimicrobial susceptibility testing (AST) breakpoints. This was recently done for enrofloxacin, marbofloxacin, and chloramphenicol for use in dogs in the 7<sup>th</sup> Edition of VET01(S) (CLSI, 2024). There are new changes pending – a revision of these fluoroquinolone breakpoints for cats, and revision of the ampicillin breakpoints for dogs that have been proposed to the CLSI-VAST subcommittee, and if approved, will appear in

<b>Table 1. New Interpretive Categories for Antimicrobial Agents in Dogs and Cats</b>				
	<b>Breakpoints (µg/mL)</b>			
	<b>S</b>	<b>I</b>	<b>SDD</b>	<b>R</b>
<b>Dogs</b>				
Enrofloxacin (Old)	≤ 0.5	1–2		≥ 4
Enrofloxacin (New) <sup>a, b</sup>	≤ 0.06		0.12–0.25	≥ 0.5
Levofloxacin	≤ 0.5	1		≥ 2
Marbofloxacin (Old)	≤ 1	2		≥ 4
Marbofloxacin (New) <sup>a, b</sup>	≤ 0.12		0.25	≥ 0.5
Pradofloxacin	≤ 0.25	0.5–1		≥ 2
Chloramphenicol (Old)	≤ 8	16		≥ 32
Chloramphenicol (New) <sup>c</sup>	≤ 2	4		≥ 8
Ampicillin (human)	≤ 8	16		≥ 32
Ampicillin (proposed) <sup>d</sup>	≤ 0.25	0.5		≥ 1
Ampicillin (proposed) <sup>e</sup>	≤ 2		4	≥ 8
<b>Cats</b>				
Enrofloxacin (Old)	≤ 0.5	1-2		≥ 4
Enrofloxacin (New) <sup>a</sup>	≤ 0.12	0.25		≥ 0.5
Marbofloxacin (Old)	≤ 1	2		≥ 4
Marbofloxacin (New) <sup>a, b</sup>	≤ 0.25	-	0.5	≥ 1
Pradofloxacin	≤ 0.25	0.5–1		≥ 2
a. Susceptible fluoroquinolone dose: 5 mg/kg once daily, enrofloxacin; 2.75 mg/kg once daily, marbofloxacin. b. SDD fluoroquinolone dose: 10-20 mg/kg once daily, enrofloxacin; 5.5 mg/kg once daily marbofloxacin. c. Chloramphenicol dose: 50 mg/kg, oral, q8h. d. Ampicillin dose: 20 mg/kg IV, q8h (or ampicillin-sulbactam) e. Ampicillin SDD dose: 100 mg/kg IV q8h.				

the next (8<sup>th</sup>) edition of CLSI standard document VET01(S), scheduled for publication in 2026.

Because these revised susceptibility testing breakpoints are different than those used previously, laboratories should ensure that they are using the latest CLSI approved standard for interpretation. Device manufacturers (the companies that make testing plates) need to update their testing methods and software. Other groups that use susceptibility testing data for monitoring and surveillance also must be aware of these changes to avoid misinterpretation of data. Revising the breakpoints to values that more accurately reflect current understanding of PK-PD and antimicrobial resistance may improve the effective use of these antimicrobial agents and reduce the risk of selecting resistant bacterial strains. This continual review and revision of CLSI breakpoints will contribute to antimicrobial stewardship and Ambrose, et al 2020.

### Recent Breakpoint Revisions

The 7<sup>th</sup> edition of the CLSI VET01(S) standard includes new breakpoints that will replace old ones developed many years ago. The canine breakpoints have been published (Papich et al. 2023) and the cat breakpoint publication is pending. These changes from the prior breakpoints reflect more current understanding of the PK-PD properties of fluoroquinolones, more pharmacokinetic data, and a large database of microbiology data not available previously. These changes are shown in Table 1.

This table shows the new SDD category, which requires a higher dose. These breakpoints apply to *Staphylococcus* spp., Enterobacterales (for example, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp.), *Pasteurella multocida* (cats), and *Pseudomonas aeruginosa*. Note that isolates that previously may have tested S, will now be interpreted as R. This table does not show the breakpoints for *Streptococcus* spp. which are one dilution higher.

A new breakpoint was also included in the 7<sup>th</sup> edition of the VET01(S) standard for chloramphenicol. This was developed to reflect current understanding of PK-PD principles for chloramphenicol, and new data on MIC distributions. The new breakpoint for dogs is S,  $\leq 2$   $\mu\text{g/mL}$ ; I, 4  $\mu\text{g/mL}$ ; and R,  $\geq 8$   $\mu\text{g/mL}$ . This replaces the old breakpoints of S,  $\leq 8$   $\mu\text{g/mL}$ ; I, 16  $\mu\text{g/mL}$ ; and R,  $\geq 32$   $\mu\text{g/mL}$ . At this new breakpoint, very few isolates from dogs will test susceptible.

Other breakpoints under revision, or yet to be approved by the CLSI committee are the breakpoints for ampicillin (IV), orbifloxacin, and meropenem.

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## Lessons in One Health: An Update on Antimicrobial Stewardship in Companion Animals

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### Introduction to antimicrobial stewardship

Antimicrobial stewardship is a multipronged effort to improve antimicrobial prescribing to preserve this group of critical medications for future use. Antimicrobials save lives and are among the most important medical discoveries to date. Unfortunately, the pipeline of antimicrobial development has slowed with few new classes discovered in recent decades. This fact coupled with the increasing number of multidrug-resistant infections has led some to caution that we are already entering the “post-antibiotic era” where antimicrobials are no longer as effective for the infections they once treated. Veterinary prescribers often report a desire to practice good stewardship but feel pressured by pet owners to prescribe antimicrobials.<sup>1-2</sup> Pet owners often poorly understand the concept of antimicrobial resistance and the potential risks of antimicrobial overuse including increased difficulty and cost of treating future infections in their pet.<sup>2</sup> Antimicrobial resistance is a true “One Health” problem and there is a clear need to mindfully use antimicrobials in every species.

### *The need for companion animal antimicrobial stewardship*

While not an initial focus of veterinary stewardship, companion animal medicine is increasingly recognized as a priority area to target improved antimicrobial prescribing. Pets and their owners are in close contact and can share antimicrobial-resistant flora,<sup>3-4</sup> and one report documented resistant organism transmission between a dog and the veterinary staff.<sup>5</sup> In addition, many of the same drug classes and even exact medications are used in companion animals and humans. Several resources are now available to guide antimicrobial stewardship efforts in small animal hospitals (see Resources below) and it is critical to engage the entire team, including veterinarians, veterinary staff, and the pet owner, in the effort. Our hospital has also benefitted from partnering with a human antimicrobial stewardship team. Antimicrobial stewardship programs (ASPs) are required in all human hospitals, and there is a wealth of experience and expertise that can be adapted to companion animal settings.

### *What is an Antimicrobial Stewardship Program (ASP)?*

The Centers for Disease Control and Prevention (CDC) has clearly defined the components of ASPs to help guide human hospital program implementation. As mentioned above, it is required for human hospitals to have an ASP and they have been shown to reduce healthcare costs and improve patient outcomes such as reducing length of stay and decreasing mortality. The 7 “Core Elements” of human ASPs as defined by the CDC are<sup>6</sup>:

- 1) Hospital Leadership Commitment: Dedicate necessary human, financial, and information technology resources.
- 2) Accountability: Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes.
- 3) Pharmacy Expertise: Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antimicrobial use.
- 4) Action: Implement interventions, such as prospective audit and feedback or preauthorization, to improve antimicrobial use.
- 5) Tracking: Monitor antimicrobial prescribing, impact of interventions, and other important outcomes, like *C. difficile* infections and resistance patterns.
- 6) Reporting: Regularly report information on antimicrobial use and resistance to prescribers, pharmacists, nurses, and hospital leadership.
- 7) Education: Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antimicrobials, antimicrobial resistance, and optimal prescribing.

As shown, several of these components rely on prescription tracking to assess the effects of interventions. The CDC also allows human hospitals to submit their antimicrobial use data and receive a calculated “Standardized Antimicrobial Administration Ratio” or SAAR, which compares their facility’s actual antimicrobial use to expected use determined based on hospital-level factors such as the number of beds and presence of certain care units like a neonatal intensive care unit. A ratio  $>1$  prompts investigation for over-prescribing, and a ratio  $<1$  may indicate antimicrobial underutilization.<sup>7</sup>

Efforts to benchmark antimicrobial use in companion animal hospitals are just beginning. There are now several published studies of antimicrobial prescription rates with some describing stewardship/education programs that have resulted in reduced prescribing in participating hospitals.<sup>8-10</sup> Many metrics have been proposed to capture veterinary antimicrobial use, but none is used standardly and automatic data extraction from medical records systems is not yet available to most veterinary practices. A national point-prevalence survey of antimicrobial use led by the University of Minnesota was conducted in 2021 where participating general and referral practices input their prescribing data for patients seen on one calendar day and identified “limited use of bacterial culture and susceptibility testing, the frequent prescribing of third-generation cephalosporins and imidazoles, and the common use of prophylactic antibiotics for clean surgical procedures.”<sup>11</sup> As this and similar efforts proceed, it is important to consider the idea of adjusting rates for factors like illness severity and services offered when attempting to compare use rates between facilities. Antimicrobial use reporting is an active area of research and will likely be routinely possible for practices in coming years.

### *Guidelines, education, and other approachable stewardship elements*

Antimicrobial use tracking has tremendous potential but is considered a more advanced stewardship activity. Basic, intermediate, and advanced companion animal stewardship activities

are described in the Handbook of Antimicrobial Stewardship in Companion Animal Veterinary Settings (<https://arsi.umn.edu/handbook-antibiotic-stewardship-companion-animal-veterinary-settings>). The American Veterinary Medical Association also has produced resources for veterinary practices and identified the following 5 Core Principles of antimicrobial stewardship in veterinary medicine<sup>12</sup> which mirror the CDC Core Elements:

- 1) Commit to stewardship: Engage all practice members and stakeholders, identify a leader and provide accountability
- 2) Advocate for a system of care to prevent common diseases: Adopt preventative strategies to minimize the need for antimicrobials and consider alternatives to antimicrobial drugs
- 3) Select and use antimicrobial drugs judiciously: Use evidenced-based approaches to determine whether to use an antimicrobial and when needed, make informed selections and refer to guidelines for judicious use
- 4) Evaluate antimicrobial drug use practices: Develop a program to evaluate prescribing and provide feedback to prescribers; engage clients in implementation of programs
- 5) Educate and build expertise: Keep up-to-date and critically appraise and implement guidelines for antimicrobial use; provide client education and support research on antimicrobial use

By applying checklists and recommendations from available resources, increasing numbers of companion animal hospitals are successfully practicing antimicrobial stewardship. There are also organized efforts within corporate practice networks to support antimicrobial stewardship within their hospitals.

#### *Companion animal antimicrobial stewardship: Current status and next steps*

There is a globally recognized need for antimicrobial stewardship within veterinary medicine, but unsurprisingly, continental efforts proceed at variable rates. Various groups including the World Health Organization, the World Organisation for Animal Health, and the World Small Animal Veterinary Association have all endorsed and developed resources to support antimicrobial stewardship in production and companion animals. The European Union (EU) is a leader in antimicrobial stewardship and in 2018 adopted Regulation 2019/6 that set a requirement for member nations to develop the ability to monitor antimicrobial use in all animals by 2030.<sup>13</sup> In 2023, the EU restricted the use of certain high priority antimicrobials such as carbapenems and glycopeptides to use in humans only.<sup>14</sup> The European Network for Optimization of Veterinary Antimicrobial Treatment (ENOVAT) has evaluated available evidence and produced guidelines in key areas such as canine acute diarrhea and surgical antimicrobial prophylaxis.<sup>15-16</sup> Investigators in Australia have performed large scale analyses of antimicrobial prescriptions using natural language processing to evaluate antimicrobial prescription patterns.<sup>17</sup>

In the United States, The Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) includes recommendations encouraging veterinary antimicrobial stewardship in some of its reports.<sup>18-19</sup> As described above, the AVMA created core principles and various resources to advance antimicrobial stewardship in veterinary medicine.<sup>20</sup> Recently, individuals from US veterinary schools met to identify priorities to support companion animal stewardship.<sup>21</sup> We created a group called the Companion Animal Antimicrobial Stewards (CAAMS) which is now a committee of the International Society for Companion Animal Infectious Diseases (ISCAID). CAAMS holds a monthly antimicrobial stewardship and infection prevention and control seminar series and plans to continue biennial workshops intended to foster national and international companion animal antimicrobial stewardship efforts.

### *Conclusion*

ASPs are not required in companion animal veterinary hospitals, but they are urgently needed. Given the frequency of antimicrobial use in cats and dogs, veterinary hospitals are encouraged to implement antimicrobial stewardship practices today. There is an emerging and vibrant community dedicated to sharing resources and advancing veterinary antimicrobial stewardship making this an exciting One Health space.

### *Resources*

- AVMA Antimicrobial Use Resources
- University of Minnesota CVM Antimicrobial Resistance and Stewardship Initiative
- Guidelines
- ISCAID: ISCAID Guidelines for Treating Urinary Tract Infections, ISCAID Guidelines for Treating Respiratory Disease, ISCAID Guidelines for Treatment of Superficial Bacterial Folliculitis
- BSAVA PROTECT ME Resources

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## **Antimicrobial stewardship in food animals: Idealism increases in direct proportion to one's distance from the problem.**

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### **Introduction**

In 1935 medical practitioners began using the first truly effective, modern antimicrobial. The sulfas were soon being prescribed by physicians for illnesses such as the common cold and the flu. And so started our tumultuous 90-year relationship with antimicrobials and our struggle to get their use right, a struggle we today know as antimicrobial stewardship (AMS).

Writing papers that generalize AMS is easy. It is a much bigger challenge to provide practical AMS guidance that balances antimicrobial efficacy with animal welfare and (in the case of food animals) an efficient use of resources to produce food. Add to this the current environment of a mistrust of science, widespread disinformation (of which we all have our own definition), and downright belligerence in attempted scientific discourse and it is easy to see how we have a difficult time drawing concrete conclusions related to AMS and including antimicrobial resistance into our decision-making process.

Antimicrobial resistance is the reason we discuss AMS. Antimicrobial resistance is the result of two components: (1) the antimicrobial exposure and (2) the genetic resistance and epidemiological characteristics of the exposed bacterial populations. Because both resistance components are different depending on the situation, it becomes problematic when we generalize from a successful AMS program in, for example, a human hospital environment, to the widely varied situations in veterinary medicine. In addition, too often we discuss only the antimicrobial exposure component of resistance while failing to acknowledge the importance of the nature of both the pathogen and normal flora resistance characteristics.

### **Antimicrobial stewardship in human medicine**

If someone suggests that human medicine is not being held accountable for AMS, they are ignorant of a huge body of work. Just like in veterinary medicine, human-medical professionals struggle with the tension between the big picture of preserving antimicrobials for future generations and personal autonomy. AMS programs can be most directly initiated in acute care and critical-access human hospitals where there are central record systems and potentially central dispensing units that can be used as control points. But having an AMS program and having a *functional* AMS program are two entirely different things. The difference became apparent during the Covid pandemic in the struggle to allocate available human resources when the needs of responding to the pandemic resulted in many AMS programs being present in name only.

The body of literature related to antimicrobial use in humans is overwhelming, with substantial efforts in categorizing antimicrobial use as appropriate or inappropriate in individual case scenarios. Antimicrobial-use monitoring is also gaining momentum in human medicine, with all acute and critical access hospitals required to report through the National Healthcare Safety Network—Antimicrobial Use Reporting (NHSN AUR) system at the start of fiscal year 2024.<sup>1</sup> This is due to changes in the Center for Medicare and Medicaid Services (CMS) Promoting Interoperability Program. The Standardized Antimicrobial Administration Ratio (SAAR) is the base metric for evaluating antimicrobial use in that system, though

experts caution against using this metric for public reporting.<sup>2</sup> Human medicine has the advantage of standardized disease and drug codes, something that doesn't exist for veterinary medicine.

The Centers for Disease Control and Prevention (CDC) has issued extensive guidelines for implementing AMS programs in human hospitals.<sup>3</sup> As mentioned above, there is significant tension between AMS programs and physicians when restrictions are put in place (such as requiring pre-authorization for the use of some especially critically important antimicrobials). The core elements of these guidelines outline the basic components of an AMS program:

- Hospital Leadership Commitment
- Accountability
- Pharmacy Expertise (previously “Drug Expertise”)
- Action
- Tracking
- Reporting
- Education

The primary challenges in antimicrobial resistance in human medicine are well characterized as reported by the CDC.<sup>4,5</sup> Many of the characterized pathogens, including the fungus *Candida auris*, are, themselves, the inciting factors for extensive AMS and infection-control programs in the human setting.

### **Antimicrobial stewardship in veterinary medicine**

The AMS definition and core principles from the American Veterinary Medical Association (AVMA) are about as good as any AMS definition gets.<sup>6</sup> The core principles are a good overview of a reasonable approach to antimicrobial use in veterinary medicine. According to the AVMA,

“Antimicrobial stewardship involves maintaining animal health and welfare by implementing a variety of preventive and management strategies to prevent common diseases; using an evidence-based approach in making decisions to use antimicrobial drugs; and then using antimicrobials judiciously, sparingly, and with continual evaluation of the outcomes of therapy, respecting the client’s available resources.”

As experienced by the author, in the United States there is a general rejection of the precautionary principle and the associated mandated formularies. As defined by the European Parliament, “The precautionary principle enables decision-makers to adopt precautionary measures when scientific evidence about an environmental or human health hazard is uncertain and the stakes are high.”<sup>7</sup> This principle has resulted in multiple formularies in other countries which require that first veterinary use consideration be given to antimicrobials which are categorized as being less important in human medicine, as well as limiting use of those considered critically important.

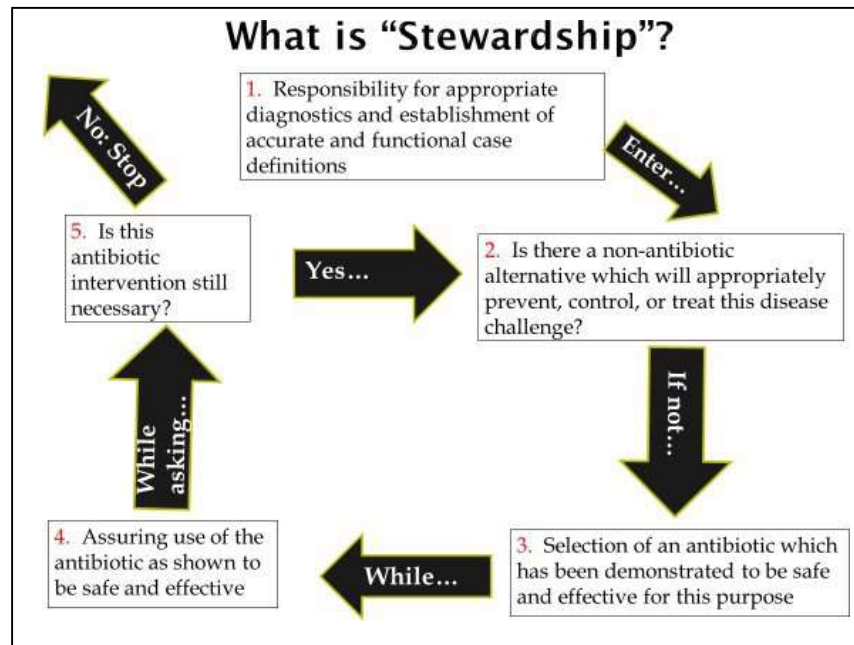
There are published antimicrobial-use guidelines for skin, urinary tract, and respiratory diseases in small animals from an international working group.<sup>8-10</sup> In addition, the AVMA has recently made documents available which contain recommendations for when a dog or cat may not need antimicrobials for common diseases.<sup>11,12</sup> As with any guidelines, these documents might be debated by practitioners, but they are a good-faith effort to provide meaningful support to veterinarians striving to make the best antimicrobial use decisions. At a minimum, they bring forward the most important points of discussion.

And, of course, almost every veterinary organization has a document or two on AMS and antimicrobial use in their particular species. Most of these documents, though, don't translate to clear direction on how to make antimicrobial-use decisions.

## The components of antimicrobial stewardship in food animals

Food animal production takes us directly to the application of antimicrobials in populations, including for the uses of prevention and control of disease. The FDA Center for Veterinary Medicine (CVM) considers the use of medically important antimicrobials for prevention and control purposes to be a therapeutic use as noted in Guidance for Industry (GFI) #209, for which the final version was published in 2012.<sup>13</sup> This guidance also established that all uses of medically important antimicrobials for growth promotion should be discontinued, and that all remaining uses of medically important antimicrobials in animal feed or water should be authorized by a veterinarian through a Veterinary Feed Directive (VFD) or prescription, respectively. These transitions occurred in 2017, taking in-feed and water-soluble medically important antimicrobials out of the farm stores in the U.S. unless they were willing to process VFDs and prescriptions. The last transition of all medically important antimicrobials to prescription status occurred in June of 2023, as directed in GFI #263 which was finalized in June of 2021.<sup>14</sup>

The result is that all uses of medically important antimicrobials in food animals in the U.S. must be authorized by a veterinarian. Here is my concept of how this would ideally work.



1. It is a common theme among food animal veterinarians that our surety of diagnosis is lacking for many of our diseases. The application of a case definition is likely applied by a lay person who is in a veterinary-client-patient relationship (VCPR) with a veterinarian. The actual nature of the VCPR varies. Diagnostics take time as well as money, and our basic disease threats remain fairly constant, so while diagnostics are still conducted for surveillance and characterization of disease challenges, they are not conducted prior to every antimicrobial exposure. In some species with lower cost per individual animal (e.g., poultry, small swine), routine diagnostic surveillance may be conducted on acute cases through euthanasia and necropsy.

2. Common alternatives to antimicrobials for prevention or control of disease in food animals are vaccines, nutrition, and environmental management. When considering treatment of acute disease, it is

hard for this author to consider alternative therapies (e.g., immune system drugs, botanical compounds) to be anywhere near the efficacy of an antimicrobial which is effective against a bacterial disease.

When expecting a veterinarian to only authorize alternative approaches to disease control and treatment, we must consider the financial aspect of assuming the risk of not using an antimicrobial. As of this writing in May 2025, a 500 lb steer calf may cost in the range of \$4.00/lb, or around \$2000. Depending on the drug purchasing situation, a feedlot is currently able to use tulathromycin for control of bovine respiratory disease (BRD) in this calf on arrival for well under \$5.00 total cost. Several years ago, it would have been closer to \$22-23.00 before the tulathromycin generics hit the market.

In high-risk calves, we expect to prevent a subsequent BRD case in 1 out of every 6 calves in which we use an antimicrobial for control of respiratory disease. Given the usual range of overall morbidity in these calves, control is considered to cut our morbidity in half. Using an expected case-fatality rate of around 10% in challenging respiratory disease outbreaks, cutting morbidity by just 10% in 100 animals saves one calf. Therefore, saving a \$2000 animal costs \$500 to administer an antimicrobial to the entire group.

Administering chlortetracycline in the feed will be less effective, with the limited available data suggesting we may cut morbidity by 25% (25% of total morbidity, so 40% morbidity becomes 30%) with a 5-day pulse of chlortetracycline at 10 mg/lb of bodyweight per day, although it may require repeated pulses to potentially achieve this reduction. These studies are quite old and PK/PD modeling does not support this effect using MIC distributions of bovine respiratory disease pathogens.<sup>15</sup> This administration will require 25 grams of CTC, or ½ lb of 50 g/lb type A chlortetracycline medicated article. Current cost of this product at catalogue pricing puts this regimen at around \$1.80 per head. A superficial look at the situation results in the conclusion that we can “cover” a \$2000 animal with 5 days of an antimicrobial for \$1.80.

Consider this scenario. A semi-truck hauls 50,000 lbs. That is 100 calves weighing 500 lbs, so around \$200,000 today. Extensive resources (facilities, labor, feed) will be put into these calves over the next 280 days or so to bring their individual value to around \$3,250 (A \$1500 lb steer at \$2.17/lb live). They could be pulsed with CTC in the feed for around \$180 total for the 100 head, or 0.09 % of the initial investment. Or, injectable tulathromycin for control of BRD for around \$500 for the group (0.25% of the initial investment). Here’s the question; at what expected morbidity (and therefore, subsequent mortality) would you as a veterinarian accept the risk of saying that antimicrobials are not necessary to control BRD in this shipment of cattle? Hence, part of the title for this presentation.

**Idealism increases in direct  
proportion to one’s  
distance from the problem.**

**John Galsworthy  
1867 - 1933**



3. We have very limited approved and well-researched options for some food animal species, while there is a variety of approved drugs proven to be safe and effective for others (e.g., bovine respiratory disease). One clear option to improve stewardship is to provide guidance to mixed-animal veterinarians who work with food animals but may not have the continuing education options or contacts available to other veterinarians. An example of guidance from a food animal practitioner group related to a specific issue is the American Association of Bovine Practitioners (AABP) position statement on medically important antimicrobials in the prevention of calf diarrhea. This statement reports “the scientific literature does not provide enough evidence to support the use of short-term, intermittent or chronic use of medically important antimicrobials in milk, milk replacers or other routes of administration to prevent calf diarrhea.”<sup>16</sup> This organization also has multiple guidelines addressing antimicrobial stewardship.<sup>17,18</sup> Similar guidance may be accessed through the American Association of Small Ruminant Practitioners (AASRP) and the American Association of Swine Veterinarians (AASV). These documents generally provide a broader overview of AMS approaches.

4. Of all the components of an AMS program in food animals, this is the part that, in the author’s opinion, is the best indicator of whether a true VCPR is present. It is one thing to establish a “VCPR” for the purpose of dispensing and another to truly be involved in a food animal operation and be aware of how case definitions and treatment protocols are actually being applied.

5. Deciding when to stop a prevention or control practice is one of the hardest things to do in a food animal protocol. The “risk” word pops up again in consideration of when to stop a practice. The example of antimicrobials in the milk replacer cited in the AABP position statement is a good example. Another example is the ceasing of in-ovo injections in chicken hatcheries. One of the biggest things we can do as regulatory and veterinary organizations is to support food animal veterinarians in taking these risks.

### **Monitoring our way to stewardship?**

So, the answer is to monitor antimicrobial use in food animals, right? There has been extensive work on antimicrobial use monitoring in food animals both here in the U.S. and internationally. The FDA recently sponsored two cooperative agreements addressing antimicrobial monitoring in swine, dairy cattle, feedlot cattle, chickens, and turkeys.<sup>19-24</sup> Two of our team’s most recent publications took the data to the point of matching antimicrobial use with the morbidity driving the use.<sup>25,26</sup> This author’s conclusions related to antimicrobial use monitoring encompass several key points.

- Antimicrobial use data used to drive stewardship is the most relevant when put in the hands of people with “boots on the ground” in the individual production sites being monitored.
- How do overall numbers for an entire industry based on total kg of active compound drive stewardship? Use needs to be linked to the morbidity driving the use.
- If I had a choice between antimicrobial use data and morbidity data to drive an antimicrobial stewardship program, I would rather have the morbidity data.

### **The minimum components for a food animal antimicrobial stewardship program**

In food animal veterinary medicine, I propose the following minimal components to prepare ourselves to make the best antimicrobial-use decisions possible:

- Be able to describe the anticipated effects of our antimicrobial uses and the strength of evidence for these effects.

- Understand the language of antimicrobial decision making, and why some terms are actually harmful when misused, such as narrow or broad spectrum, bacteriostatic and bactericidal, or synergism and antagonism.
- Antimicrobial susceptibility testing (AST) can be controversial, but we should understand the correct and incorrect applications of AST to inform our decisions.
- Resistance can have multiple implications. We must understand these implications and how they apply to our future use of antimicrobials.
- Our antimicrobial regimens must be based on some semblance of science...
  - Duration of therapy?
  - Should we routinely rotate antimicrobials?
  - Adjusting antimicrobial regimens to address resistance?
- Optimal order of antimicrobials when addressing non-responders?
- Combination therapy? (improving clinical response or accelerating resistance?)
- Ancillary therapies?
- Other effects of antimicrobials masquerading as antibacterial effects?
- Post-treatment intervals for deciding success or failure?
- Effect of resistance on clinical outcome?

In preparing the above list I was guilty of the over-generalizations that I have accused other sources of committing. However, each of these points is worth considering in specific antimicrobial-use decisions; the biggest sin is an antimicrobial regimen with no beneficial effect.

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# Keynote Presentation

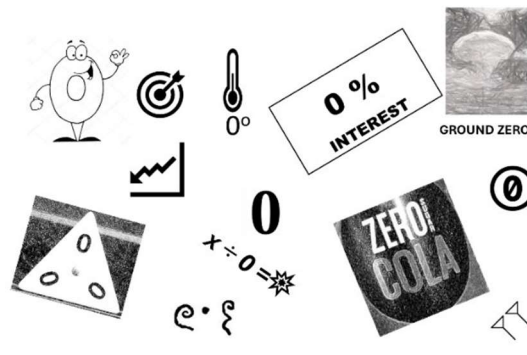
Thinking About Nothing: Zero and its Implications in Veterinary Pharmacology

Jim E Riviere, DVM, PhD, ATS, DACVCP

Distinguished Professor Emeritus

North Carolina State and Kansas State Universities

I have always been fascinated by the concept of and definition of *zero*. The idea of *nothing*, as well as its assignment to the specific number  $0$ , is encountered in many fields ranging from philosophy to mathematics, and the pure sciences of physics and chemistry to its practical application in areas including toxicology, food safety, statistics, and the law. We are constantly exposed to zero in areas far beyond math where we are tempted with zero calorie soda to credit cards with 0% interest. In gambling, the placement of “0” and “00” on the Roulette wheel ensures that the House has the advantage since common bets such as *red* or *black* and *even* or *odd* lose when the ball lands on a zero. Other counting numbers do not share this unique aura. The non-integer numbers  $\pi$  and  $\infty$  come close, but as we will see, zero easily assumes prominence and consternation in wide ranging swaths of human endeavour.



Zero everywhere.

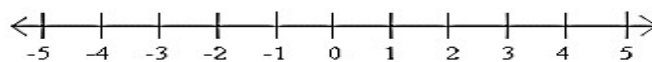
Seems like such a simple question; what does zero mean? Why would anyone care if people can't agree on a definition? Zero is a misfit amongst the normal so-called counting numbers. It defies definition as it reflects nothing, emptiness, or a void. The ancient Greeks abhorred the concept of emptiness and the void. Zero causes headaches when first encountered in arithmetic, where one is forbidden to divide by it. Zero occupies a unique position in our numbering system as it is the only counting integer that does not relate to any actual quantity. It came into existence centuries after all the counting numbers were introduced in civilizations around the world. It originated in first millennium India and only migrated to Europe in the 13th century.

Nothingness and emptiness were and remain central constructs of major schools of both Eastern and Western philosophies and religions. Psychologically they can be the drivers of both anxiety and depression in the west or the enlightened goals of a meditative Nirvana in the East. These discordant perspectives still affect the interpretation of using the digit 0 today. When interpreting 0 as *nothing* or *empty*, all sorts of contexts derived from numerous encounters subconsciously infuse our cognitive processes affecting our perspective on the issue at hand and influence how we arrive at a conclusion. This powerful meme suggesting cautiousness still hangs on. *The major issue is understanding how zero is to be measured, interpreted, and employed relative to the problem one is working on.* Are we discussing the absence of pharmacologic or toxicologic effect, or the limit of quantitation or detection in analytical chemistry? This sorting process requires great discipline and effort to parse out the different baggage (vocabulary, definition, methods, sensitivity, rules, purpose) associated

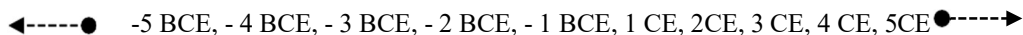
with zero or nothing as applied to the different disciplines involved in the analysis, to get the contexts involved straight, and to achieve a rational and deliberative solution. This in fact is the true goal of philosophic reflection.

Although one can endlessly debate the impact and significance of a number relating to nothing, problems arise when one must measure zero and attest that nothing is there. A simple example from the above figure illustrates this concept. Zero sugar cola is easily defined as sugar simply is not used in the soda's manufacture. However, if a natural beverage is to be labelled as such, there must be proof that analysis would yield a result of zero. But how precise does that need to be, what type of sugar is being assayed and how much variability is there in natural beverages? This analytical zero is also the focus of its role in veterinary pharmacology.

Zero is a crucial number in mathematics. The simplest definition is that it is the origin point of the number line, dividing positive and negative numbers.



Note that in the historic timeline of dates, there is no year zero separating the current (CE) from ancient (BCE) eras.



The most serious issue with zero is its limitations and unique properties in certain mathematical operations. These are listed below.

- *Addition:*  
 Zero added to itself gives zero. [ $0 + 0 = 0$ ].  
 Zero added to any number yields the original number. [ $a + 0 = a$ ]  
 Adding a number to its opposite yields zero. [ $-a + a = 0$ ]
- *Subtraction:*

Zero subtracted from a number equals that number.  $[a - 0 = a; 0 - a = -a]$

Subtracting a number from itself equals zero.  $[a - a = 0; -a - (-a) = 0]$

- *Multiplication:*

Zero times any number equals zero.  $[a * 0 = 0]$

- *Division:*

Zero divided by any non-zero number is zero.  $[0 \div a = 0]$

Dividing by zero is undefined and thus is forbidden.  $[a \div 0 = \text{⊘}]$

If the denominator of a fraction is 0, then the fraction is also undefined.

- *Exponents:*

Anything raised to the power of 0 equals 1.  $[a^0 = 1]$

Zero raised to any power is zero.  $[0^a = 0]$

Square root of zero is zero.  $[0^{1/2} = \sqrt{0} = 0]$

- *Logarithms:*

$\log_{10}$  of zero is not defined.

$\log 1$  is 0 and thus the antilog of 0 is 1.

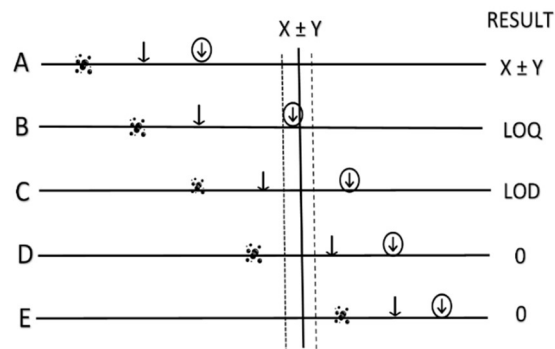
- *Factorials:*

$0! = 1$

- *Euler's Identity*

$e^{i\pi} + 1 = 0$  (where  $e$  is Euler's number and  $i = \sqrt{-1}$ )

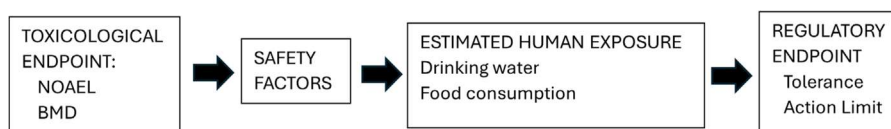
Zero also has important roles in physics and cosmology, topics well beyond the scope of this discussion. The primary issue that is encountered in veterinary medicine is when 1st order exponential pharmacokinetic equations, solved using logarithms, prohibits the use of zero concentration. This limitation prohibits the lowest concentration in a drug depletion experiment from being zero. To remedy this, the lowest concentration is replaced with the analytical limit of quantitation (LOQ) or limit of detection (LOD), or a combination of both. There is not a consistent definition for LOQ and LOD across regulatory agencies. The issue is to determine the legal allowable concentration permitted in food relative to the sensitivity of the analytical method being used. In the schema below, X is the legal food safety threshold such as tolerance (TOL) or maximum residue level (MRL). With a sensitive assay such as A, TOL can be accurately measured. Issues occur when TOL is below LOQ and LOD.



A, B, C, D and E represent Different Assays with Decreasing Sensitivities  
 ✖ = Instrument Noise ↓ = LOD ⊕ = LOQ  
 X = Concentration Y = Standard Deviation

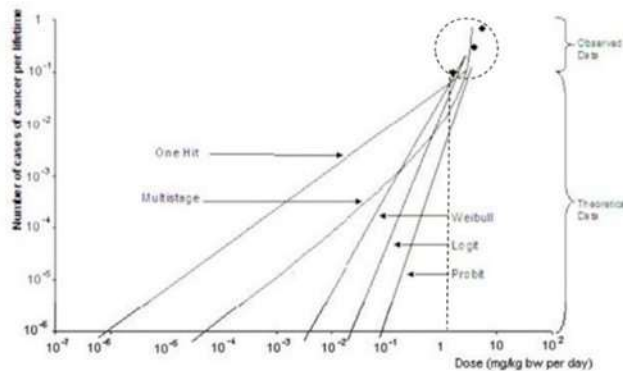
At low concentrations near LOQ and LOD, estimation errors also increase and add to the uncertainty. Difficulties remain in interpreting values at LOD or below because although not quantifiable, they do indicate less compound or even no compound may be present. They are essentially zero, but zero can't be entered into the mathematical equations that use exponential decay to calculate risk factors. A non-zero concentration is then often entered. This remains a computational and statistical quagmire.

The next issue is in deriving the concentrations that define the TOL or MRL. This again brings us to the issues of what is no biological effect, that is nothing happens, when exposed to this concentration of chemical in food. The LOD and LOQ define detectability while TOL and MRL define absence of biological effect. It is a prediction of safety based on experimental studies generally conducted in animal toxicology trials. Toxicology and Food Safety texts should be consulted for further details.



The endpoint is different when drug assays are used to regulate sports doping. Here *detection proves exposure and thus potentially illegal drug use*. There is no safety endpoint. In detection of alcohol in people, there is alcohol detection in a minor (which is illegal) versus quantification in an adult (which only prohibits levels related to intoxication), because adults are allowed to consume alcohol at levels determined not to affect driving ability. In sports, drug testing is a detection issue.

In toxicology risk assessment, threshold concentrations are based on estimations using various risk assessment models that extrapolate to lower concentrations from the available experimental data obtained at higher concentrations. The wide variety of potential extrapolations for potential carcinogens is illustrated below.

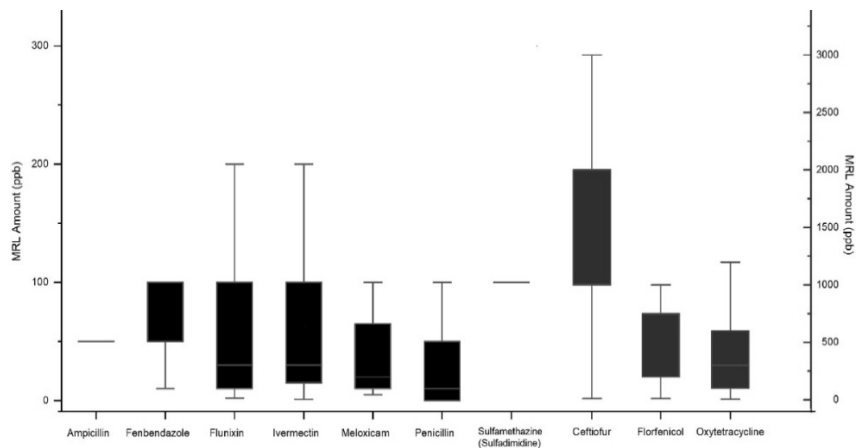


Low dose extrapolation for a carcinogen. Dotted circle encompasses the data-defined inference space. The dotted line is the lowest dose actually tested. Everything below is an extrapolation.

Depending on the nature of the chemical being regulated and the jurisdiction involved, numerous safe and action levels are employed. Unfortunately, all have different approaches to extrapolate safety factors involved and use different assumptions to estimate allowable daily intake (ADI) which in veterinary medicine is the basis of MRL and TOL. These include:

- Bench Mark Dose (BMD)
- Biological Exposure Indices (BEIs)
- De Minimis Level – < 0.5 to 1 ppb
- Minimal Toxic Level (MTL)
- Minimum Level of Applicability (MLA)
- Permissible Exposure Limit (PEL)
- Reference Concentration (RfC)
- Reference Dose (RfD)
- Threshold Limit Value (TLV)
- Threshold of Toxicological Concern (TTC) (< 1.5 µg/day intake)

The figure below illustrates how different MRLs are across different regulatory jurisdictions for a few commonly used drugs in veterinary medicine.



Distribution of the range of MRLs of 10 drugs across multiple global jurisdictions and species ranging from 0 to 3,500 ppb. (Zad et al., Food and Chemical Toxicology, 2023). The right three drugs use the right y-axis concentration scale.

## Discussion.

This brief overview of zero and nothing illustrates the differences between zero in analytical chemistry and the absence of biological or toxicological effect. The tension is between detection versus effect.

This tension arises when a chemical, such as a pesticide, is found in food at levels below the acceptable tolerance but still at a measurable amount. There is no quantifiable biological risk to exposure at this concentration. Regulatory agencies acknowledge this in their definition of a threshold, which already incorporates multiple safety factors and assumes lifetime consumption.

Yes, it may be detected, but there are hundreds of other natural compounds and toxins that may be present at higher levels in food that are not even looked for and do not produce an adverse effect. It's even worse when a very low concentration is detected (LOD) but below the quantifiable level (LOQ). The media often report this as “dangerous chemicals were detected in the food.” Many of these are agricultural chemicals, such as pesticides, that are important to large-scale agriculture and are used to improve crop production, ward off plant diseases, or kill true toxin-producing fungus. A hazard may be present to the manufacturer or pesticide applicator, but the minuscule level present in food is safe.

The issue fueling the public concern about chemical exposure in food and the environment is one of communication. There is not a universal definition of zero. Both the context in which it was determined and the problem to which it will be applied must be defined. The proper approach is to operationally define what is meant by zero and the conditions under which it is assigned. This definition ideally should be tagged to this value. However, when recorded in a data table, missing values or empty entries, as well as values originally entered as LOQ or LOD, may just end up being recorded as zero. This also occurs when these same data are then “scraped” from the web by various machine learning algorithms that compile them into a secondary database.

Grocery surveys often only report detection independent of what the allowable limits may be. Internet searches determine that the chemical detected may be harmful, but no one looks at the dose that any adverse effect was detected versus the level of contamination detected. This is termed “regulation by hazard”. The public must be made aware of this as the situation will only worsen with increasingly sensitive analytical methods. The chemicals haven't changed. Focus should be on issues with a higher positive public health impact. Unfortunately, in today's political climate, these issues are not openly and freely debated.

In conclusion, zero is a unique number both mathematically and how its interpretation affects everyday life. In some scenarios, zero simply means nothing or empty. No apples, no money. In other cases, it is an analytical determination based on measurement, and interpretation of its meaning is dependent upon extrapolations from experimental models. All these steps are steeped in uncertainty.



***Session 6: Fostering Leadership in  
Veterinary Pharmacology***

## Insights Gleaned By A Seasoned Scientist

Marilyn N. Martinez, Ph.D.  
Senior Biomedical Research and Biomedical Product Assessment  
Service Expert  
Fellow AAPS, Fellow Controlled Release Society,  
Distinguished Fellow AAVPT  
Office of Generic Animal Drug/Center for Veterinary  
Food and Drug Administration

*The information in this presentation is not a formal dissemination of information by FDA and does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.*



In this presentation, I would like to share some of the experiences and insights I acquired over my scientific career.

### 1. Don't cloister yourself with like-minded people.

Many of the insights I have gleaned over the years have evolved from conversations with scientists across a range of disciplines. For example:

Formulation chemists: provided the basis for appreciating the relationship between drug physicochemical properties, its in vivo behavior, and some of the approaches used to alter in vivo drug absorption through product composition and manufacture (both parenteral and oral). In addition, interactions supported my understanding of how excipients can alter drug solubilization, membrane permeability, and in some cases, exert their own biological effect.

### Don't cloister yourself

Statisticians: Our numerous interactions helped me appreciate the problems we can encounter if we ignore potential sources of outcome bias (i.e., any instance that creates a difference between an expected and true value of the population parameter being estimated). For example:

- How outcomes are expressed
- Selection of a time frame supporting a clinical outcome.
- Adequacy of the power of the study
- Number of samples taken from the same subject
- Under-representation of certain types of subjects.
- Non-random sampling
- Inadequatemasking


<https://builtin.com/data-science/types-of-bias-in-statistics>  
<https://www.scribbr.com/statistics/statistical-tests/>  
Fernstrom JD, Choi S. doi: 10.1016/j.pharmthera.2007.09.001.

### Don't cloister yourself

Statistical vs clinical relevance: Alerted me to situations where although a treatment effect may be statistically significant when compared to a placebo control, the size of that effect can be without clinical relevance.

This can happen when a large sample size exhibits a small but clinically insignificant effect. For example, in a clinical trial with 10,000 participants, a 0.5 kg improvement in weight loss for the treatment group reached a level of statistical significance but that differences had little to no clinical impact.

## Don't cloister yourself



**Recognizing the difference between Absolute and relative change:**

"Absolute change" refers to the simple difference between two values, while "relative change" expresses that difference as a percentage of the original value, essentially showing how relevant that change is in relation to the starting point.


Example: **RELATIVE:** The use of alendronate for the treatment of osteoporosis leads to a 50% decrease in the risk of new hip fractures vs placebo –**VERY IMPRESSIVE.**

BUT..... The actual **ABSOLUTE** change was only 1.1% (2.2% risk on placebo vs 1.1% risk on alendronate)!


Authors may report relative vs absolute change to make their product/study results look more impressive!

Black DM, et al., Lancet. 1996. doi: 10.1016/s0140-6736(96)07088-2.  
www.fda.gov

## Don't cloister yourself




**PBPK modelers:** through these interactions, I've become keenly aware of the importance in understanding the mechanistic basis of dose-exposure-response relationships (e.g., the multitude of factors influencing oral drug absorption & impact of population polymorphisms on drug PK [and PD]) and recognizing that a model with incorrect assumptions can still be made to fit a single set of observed data [**DANGER!**].




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## 2. The importance of exploring "what if" scenarios using in silico models



The 2 types of in silico modeling tools I will discuss are Population Pharmacokinetics (**PopPK**) and Physiologically Based Pharmacokinetic (**PBPK**) models.


Pharmacokinetic models



Population PK models

VS

In silico physiologically based pharmacokinetic models (PBPK)




In silico physiologically based pharmacokinetic models (PBPK)

<https://singaporepharmacometrics.com/2024/04/09/top-down-vs-bottom-up-pharmacokinetic-pk-modeling-a-soft-intro/>

**To decide which is the most appropriate, one needs to determine their modeling objective.**

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## Exploring "what if" Two traditional types of in silico models




**PopPK models:** PopPK models **rely upon the use of compartmental models** and these compartments do not have a physiological meaning. These models are typically used to explore the shape of dose-exposure-response relationships in a population without the need to explain the specific mechanisms through which the population variability may occur. However, variability can be segregated into an analysis of "covariates" which have a basis in patient characteristics and help support an understanding of how a drug will behave in a patient population.

PopPK models can be divided into parametric (P) and nonparametric (NP) approaches, each differing primarily in the **statistical distributional properties** of the PK parameters

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## Two traditional types of in silico models




**PopPK models:**

**Parametric** assumes parameters follow a normal probability distribution (fixed effect = average and the random effect = variability). Therefore, P models are often used to provide a general description the population and of significant covariates.

**Nonparametric** there are no distributional assumptions but rather the PK parameters are described in terms of their joint probability distribution with "support points" for each parameter. This allows for improved detection of subpopulations or outliers that could be missed by parametric methods. At least in part, the nonparametric approach is **highly efficient for individual dose optimization** (refer to the many publications by Roger Jelliffe, Goutelle et al., 2022, J Clin Pharm, DOI:10.1002/jcph.1993), de Velde et al., 2018).

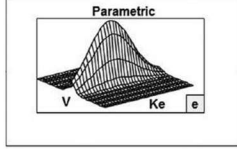
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## Parametric vs nonparametric Population PK approaches

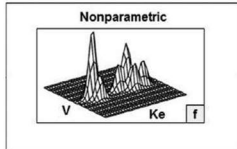


The parametric method assumes that the data are normally distributed whereas the nonparametric method identifies the 2 subpopulations. e) and f).

Parametric



Nonparametric



de Velde et al, 2018.  
doi.org/10.1016/j.phrs.2018.07.005  
www.fda.gov

## Two traditional types of in silico models



• **PBPK Models:** Unlike PopPK, these models describe the PK of a drug in terms of variables influencing its absorption, distribution, metabolism, and clearance (ADME), the drug's physicochemical properties, and the physiological attributes of the patient population.

Through a granular examination of the drug's PK, these models provide an opportunity to predict dose-exposure-response relationships under a range of clinically relevant situations.

[www.fda.gov](http://www.fda.gov)

Tsamandouras et al., 2013, BJCP, doi: 10.1111/bcp.12234

## PBPK: invaluable to truly understand drug PK in the targeted patient population. E.g.,



- Predicting influence of metabolic and transporter polymorphisms across a patient population (e.g., Mdr1 mutation in dogs (e.g., Collies), Cyp polymorphism in certain breeds (e.g., Greyhound))
- Impact of breed differences in lean body mass.
- Age (e.g., changes in liver function, renal function and blood flow in the elderly or pediatric population).
- Potential impact of food, drug-drug interactions, etc.

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## Selecting the best modeling approach



Consider the following: an investigator wants to predict the potential for a drug-drug interaction (DDI) in a patient population. How does one determine the modeling approach to use?



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Victim drug = amlodipine (AML, a calcium channel blocker used to treat hypertension).  
Perpetrators = several drugs that are strong CYP3A4 inhibitors.



When patient concentration-time data are available for AML with and without potential perpetrators (including drugs that are NOT strong CYP3A4 inhibitors or CYP3A4 inducers), the PopPK model can be used to identify significant covariates (e.g., patient characteristics) and the relationship between AML dose-exposure relationship and the co-administered drug. Providing this information in the package insert can be helpful to the clinician.

Courlet et al., European Journal of Clinical Pharmacology, 2021 doi: 0.1007/s00228-020-03060-2

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## Developed PBPK/PD model to simulate changes in SBP due to the dynamic changes in amlodipine plasma exposures with and without RTV.



Victim drug = amlodipine (AML).

Perpetrator = ritonavir (RTV)

- Based on a similar question, a PBPK model was developed utilizing published information on AML physicochemical properties, ADME parameters, and CYP3A4 Michaelis-Menten kinetics.
- The PBPK model was linked to an AML PD model for its effects on systemic blood pressure (SBP) to explore the dose adjustments that may be needed when AML is co-administered with RTV, a reversible CYP3A inhibitor and moderate inducer.
- In this case, published AML concentration-time profiles were used for model verification rather than model development.
- Once verified, the model could be used to explore a range of "what-if" scenarios, including changes in dosing regimens or patient polymorphisms.
- Efforts to understand and predict the consequences of co-administering these two drugs is challenging without the use of a mechanistic modeling approach.

Mukherjee et al., J Pharmacokinetic Pharmacodyn., 2018. doi: 10.1007/s10928-018-9574-0.

## 3. Examples of perspectives to avoid – know your drug and your patient



- "I have access to data collected in a colony of young, healthy Beagle dogs (both genders). Therefore, I can tell you about the PK of drug in a potential patient population."
- CAUTION: This may not be the case as drug dose-exposure-response relationships can differ as a function of:
  - Breed variability
  - Age variability
  - Disease
  - Formulation and route of administration
  - Duration of treatment

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**For example: breed and disease effects:**



**Breed:**

- There can be tremendous differences in the activity of drug metabolizing enzymes, not only across breeds but also across mixed dog breeds. For example, a 14-fold variance in Cyp2b11 activity was observed in mixed breed dogs.
- Breed differences were also reported in large intestinal transit time and in fecal quality (multiple potential reasons for the latter).



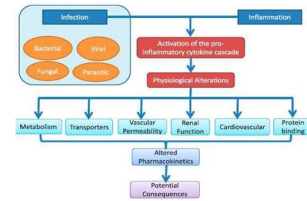
Fleischer et al., AAPS J. 2008; doi: 10.1208/s12248-008-9011-1.  
 Hay Kraus et al., Xenobiotica, 2000. doi: 10.1080/004982500406417. PMID: 10923860.  
 Zoran et al., Am J. vet Res, 1993.  
 Oswald et al., European Journal Pharm Biopharm, 2015 doi: 10.1016/j.ejpb.2015.09.009.  
[www.fda.gov](http://www.fda.gov)

**Breed and disease effects:**



**Disease:** Numerous examples of altered drug PK by infection and inflammation in veterinary species.

This can differ as a function of the type of infection (bacterial species, parasitic species), host species, and in companion animals, the potential for inflammation associated with physiological diseases such as heart failure.



Reviewed by Martinez et al., DRUG METABOLISM AND DISPOSITION, 2020,  
[doi.org/10.1124/dmd.120.090704](https://doi.org/10.1124/dmd.120.090704)

[www.fda.gov](http://www.fda.gov)

**4. Using in vitro dissolution data: how and when**



- Know your drug (solubility, permeability – if available)
- Understand the relationship between the in vitro dissolution test conditions versus what will be encountered in vivo.



[www.fda.gov](http://www.fda.gov)

**Need for caution when interpreting data: essential to understand the factors influencing outcome.**



For example, take the case where Brand A and B were compared in vitro to determine the likelihood of bioequivalence.

Are these two products bioequivalent?

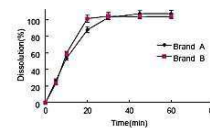


Fig. 3. Dissolution of two brands of simvastatin tablets in pH 4.5 acetate buffer contain 0.3% (w/v) of SDS (mean ± S.D., n = 6).

[www.fda.gov](http://www.fda.gov)  
[www.fda.gov](http://www.fda.gov)

He, et al., Eur J Pharm Sci. 2004. doi: 10.1016/j.ejps.2003.11.009.

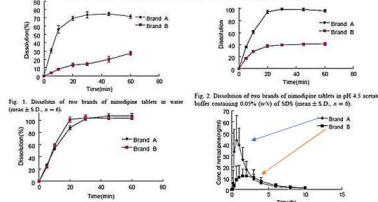
**Need for caution when interpreting data: essential to understand the factors influencing outcome.**



Now, let's look at the rest of the data!

These two products are clearly NOT bioequivalent!

**Developing Biologically Relevant In Vitro Dissolution Test Methods**



[www.fda.gov](http://www.fda.gov)

He, et al., Eur J Pharm Sci. 2004. doi: 10.1016/j.ejps.2003.11.009.

**5. Look for original research articles: don't rely upon reviews!**

- Another challenge is the tendency to rely upon review articles or research abstracts as information sources. Such practices can lead to serious scientific flaws!

- When citing abstracts, you need to know how the study was designed, executed, and analyzed. Were there biases introduced into the investigator data interpretation?

Agarwal et al., World J Mens Health. 2023. doi: 10.5534/wjmh.230001

[www.fda.gov](http://www.fda.gov)

## Don't simply rely upon reviews!



Citing reviews: the **ECHO** effect. There was a case where one research paper with an exciting outcome and conclusion was cited in reviews by multiple authors. In turn, those reviews were further cited by authors who neglected to examine the original research article. Ultimately, hundreds of publications stated the same thing, leading to that cited outcome becoming an accepted scientific fact (I'm calling this the "ECHO" effect). However, when someone *finally* questioned the basis for that scientific "fact", they discovered that everything led back to a single **FLAWED** research article which in fact was later retracted!



www.fda.gov

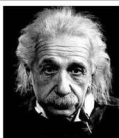
## 6. Relying on AI: aye yai yai!



- AI is the current buzz word.
- It can be invaluable for identifying and developing new medications.
- It minimizes the need for trial-and-error experimentation and for high-throughput screening.
- It processes large amounts of data in a highly efficient manner.
- It can also predict drug toxicity.
- **HOWEVER:** "The major underappreciated challenge in developing robust and predictive AI models is the impact of the quality of the input data on the model accuracy. Indeed, poor data reproducibility and quality have been frequently cited as factors contributing to the crisis in biomedical research, as well as similar shortcomings in the fields of toxicology and chemistry."
- For example, similar compounds with minor modification of a parent molecule can have very different toxicity, efficacy, or inter-individual variability. These similar compound structures with very different activities can raise significant challenges to Quantitative Structure-Activity Relationship (QSAR) modeling.
- QSAR models can also be biased by errors during the data curation process (errors in drug structure).

Alves et al., Altern Lab Anim 2021; 49(3): 73-72. doi:10.1177/02611929211029635

www.fda.gov



## 7. "Not everything that can be counted counts"



In a world where data is king, it can be easy to get so locked in on the power of numbers that we lose sight of what really matters. Rather, it is important to focus on the real-time concentration of a free drug (the form exerting a biological effect) and how disease, nutrition, and polypharmacy can influence these unbound drug concentrations.

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## "Not everything that can be counted counts" Avoid misinterpreting ramifications of altered *fu*!



- Depending upon the binding site, polymorphic variations in amino acid sequences can markedly influence binding characteristics of dogs (Costa et al., DMD, 2019, doi: 10.1124/dmd.119.087304) and humans (Kragh-Hansen U. Biochem J. 1985. doi: 10.1042/bj2250629).
- Similarly, changes in concentration of the binding protein can influence *fu* (Boffito AIDS Res Hum Retroviruses. 2003 doi: 10.1089/088922203769232629.)

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## Impact of plasma protein binding on AUCinf-u and AUCinf total

- **HOWEVER**, It is the **unbound** drug concentrations that are typically responsible for dose-exposure-response relationships.
- Under most circumstances, changes in the unbound fraction (*fu*) will **not** influence the unbound drug total systemic exposure (AUCinf-u). Nevertheless, *fu* does influence the **total** (bound + unbound) drug exposure (AUCinf Total).
- Problem: typically, it is the **total drug** concentrations that are measured.
- Therefore, we need to understand how to translate total to unbound total drug exposure to avoid biased efficacy predictions.

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## Avoid misinterpreting ramifications of altered *fu*!



Since these sources of population variability are unlikely to alter the unbound drug concentrations, we need to correctly interpret the therapeutic ramifications of altered total drug concentrations. For example:

- When setting clinical breakpoints (based upon a PK/PD target). (Toutain et al. 2023, CPT Pharmacometrics & Systems Pharmacology, and Martinez et al., 2025, JVPT).
- When interpreting patient information obtained during therapeutic drug monitoring where changes in total drug concentrations may lead to unnecessary dose adjustments.

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## 8. The “poor me” syndrome



Let’s take a lesson from a great inventor: Thomas Edison, whose records show that he failed to create a workable lightbulb 2,774 times before having a success. When asked about it, it is claimed that he said: "I have not failed 2,774 times—I've successfully found 2,774 ways that will not work".



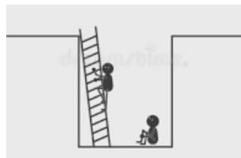
www.fda.gov

## The “poor me” syndrome



“My study failed to confirm my hypothesis or gave me an unexpected outcome. Therefore, there was either an error in my study design, a problem with the study execution, or my null hypothesis was way off base and I should discard the whole idea.”

If that is you, **it’s time to climb out of that hole!**



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## “My results are wrong, I know they are wrong!”

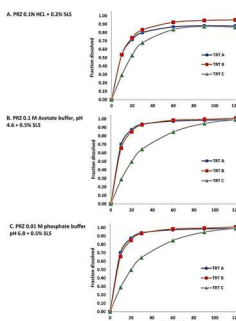


- When  $F > 100$ , there must be a mistake somewhere in the data generated/analysis, right?
- How many times have you seen published studies where the bioavailability after oral administration exceeds 100%. Clearly, this is due to experimental error, right?
- **NO** – THERE CAN BE VALID PK REASONS WHY ORAL BIOAVAILABILITY CAN EXCEED 100%. There are examples where the observed  $F > 100\%$ , e.g., the presence of **interfering metabolites, PK non-linearities, or enterohepatic recycling**.

Thanks to Dr. Tomas Martin-Jimenez for permitting me to use this information which he gathered and presented to CVM review staff.

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## The “poor me” syndrome: In vitro dissolution results: PRZ



A = PF/IF  
B = PF/IM  
C = PM/IF

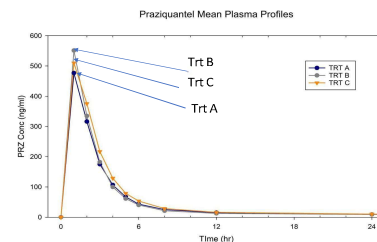
Based on these in vitro results, we expected that Trt A PRZ would be the best and fastest absorbed while C would be the slowest. Trts A and B were expected to be bioequivalent.

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## The “poor me” syndrome: In vivo results did not match expectations



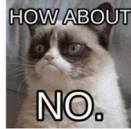
A = PF/IF  
B = PF/IM  
C = PM/IF



While the in vitro and in vivo results were consistent for PRZ TRT B and C comparative bioavailability, unexpectedly, Trt A had the lowest in vivo bioavailability.

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Since I failed to prove my original null hypothesis, was my study a failure?



This study served as an important tool, reinforcing that reliance on in vitro comparative product dissolution should proceed with caution and only after having a thorough understanding of product differences and the variables that can affect tablet in vivo product performance. Subsequent modeling and simulation (GastroPlus®) was used to narrow the potential causes for this unexpected outcome.

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9. Understand the issues and assumptions before trying to interpret published data or trying to solve your own research questions!



Be fully versed in what others have already done and the assumptions they and others have relied upon.




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10. Lastly, keep in mind that everything changes with time – including our understanding of drug PK and PD, the tools available for gaining the technical insights necessary to address the questions and issues at hand, and the approaches and treatment options available to support human and animal health. BE AMENABLE TO CHANGE!



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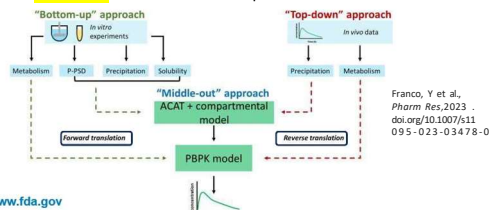
THANK YOU FOR YOUR ATTENTION



**EXTRA SLIDE: PBPK Models:** The three modeling approaches are



- **top-down:** modeler uses published PK profiles to describe outcomes in a patient population to better understand factors influencing drug absorption as a function of dose, administration route or prandial state
- **bottom up:** the population profiles are predicted based on information such as patient physiology, drug physicochemical properties, membrane permeability, metabolism and transport, Michaelis Menten kinetics, etc.
- **middle out:** a combination of top-down and middle out.



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# Organizational Leadership in Veterinary and Scientific Contexts

AAVPT 23rd Biennial Symposium, May 18 - 21 2025

*Michela Cantiello, DVM, PhD, MBA*  
 Managing Director of Preclinical and Clinical Research – QIMALS  
 Adjunct Lecturer in Leadership – IU, Kelley School of Business

## Our Journey Today

- Foundation**  
Leadership definitions, models, and contexts
- Challenges**  
Communication, decision-making, teaming
- Growth**  
Failure, innovation, mindfulness
- Final Thoughts and Q&A**  
Wrap up and open discussion

## Foundations

Leadership definitions, models, and contexts

## Defining Leadership

Leadership	Management
Vision, influence, culture creation	Execution, structure, processes
Requires strategic and emotional intelligence	Focuses on implementation and control
<i>Connection</i>	<i>Incentiv. &amp; Control</i>

## Leadership Models That Matter

- Transformational**  
Inspires change and aligns with mission
- Transactional**  
Provides structure and clear expectations
- Servant**  
Empowers experts and fosters trust
- Adaptive**  
Flexible response to regulatory shifts

**Four distinct Leadership styles**

- Visionary
- Protective
- Collaborative
- Supportive

**VUCA**

Bass, B.M., & Riggio, R.E. (2006). Transformational Leadership(2nd ed.)  
 Heifetz, D.A., et al. (2009). The Practice of Adaptive Leadership.

## Leadership Contexts Compared

Academia	Independence, intellectual influence, tenure
Industry	Metrics, timelines, commercialization
Regulatory	Compliance, public trust, risk management

## Cross-Sector Stakes

- Academic PI**  
Publication focus, intellectual property concerns
- Industry Sponsor**  
Commercial timeline, ROI pressure
- Regulatory Advisor**  
Safety standards, public interest
- Resolution**  
Role clarity, shared goals, transparency

## Challenges

Communication, decision-making, teaming

## Communicating Across Expertise

- Translate Complexity**  
Adjust language without losing precision
- Listen Across Silos**  
Understand lab, legal, financial, logistics, clinical and preclinical ops concerns
- Evolve Writing Skills**  
From technical reports to vision documents

## The Importance of Communication in Leadership

Why communication is critical:

- Trust and Transparency:** Builds team credibility.
- Team Alignment:** Helps team understand goals and vision.
- Conflict Resolution:** Key to navigating team dynamics.
- Decision-making:** Facilitates sound and inclusive choices.

Goleman, D., Boyatzis, R., & McKee, A. (2013). *Primal Leadership*.

## The L.E.A.D. Communication Framework

- L:** Listen actively.
- E:** Empathize with team members.
- A:** Adapt to context and audience.
- D:** Deliver messages clearly and concisely.

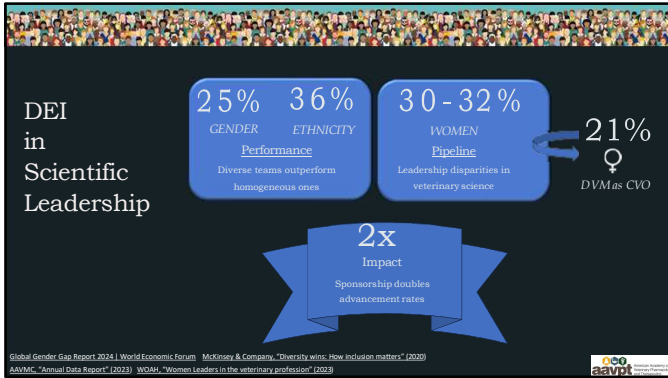
The L.E.A.D. framework simplifies and structures key communication skills for leaders.

Goleman, D., Boyatzis, R., & McKee, A. (2013). *Primal Leadership*.

## Decision-Making Under Uncertainty

- Psychological Safety**  
Foster debate and welcome dissent; appoint a 'devil advocate'
- Ethical Leadership**  
Navigate regulatory ambiguity with integrity
- Risk-Informed Approach**  
Balance caution with progress

Edmondson, A. C. (2019). *The Fearless Organization: Creating Psychological Safety in the Workplace for Learning, Innovation, and Growth*. Wiley



### Generational & Work Dynamic Changes

**Generational Styles**  
Boomers vs. Millennials  
leadership approaches

**Work Evolution**  
Remote/hybrid shifts in  
leadership expectations

### Growth

Failure, innovation, mindfulness

### Leadership and Failure

**Scientific Progress**  
Failure is essential to discovery

**Risk Balance**  
Distinguish acceptable risk from negligence

**Team Culture**  
Leaders' response defines environment

**Learning Process**  
Normalize, debrief, improve rapidly

Frontiers | Medical Errors Cause Harm in Veterinary Hospitals

### Leadership for Innovation

- Create Safety**  
Psychological safety enables idea flow
- Protect Risk-Takers**  
Shield innovators from premature criticism
- Build Structure**  
Provide clear goals, time, trust, autonomy, tolerance for exploration

Huang, C., & Jiang, P. "Exploring the Psychological Safety of R&D Teams: An Empirical Analysis in Taiwan." *Journal of Management & Organization* 18 (2017): 171-92.

### The reality check...

...innovation is hard

- LARGE ORGANIZATIONS
- Often SLOW, COMPLEX, CUMBERSOME
- IDENTIFYING GOOD, SCALABLE SOLUTIONS is EVEN HARDER



### Mindfulness in Leadership

- Present Engagement**  
Full attention to current challenges
- Improved Decisions**  
Mindful pharma leaders report better choices
- Emotional Regulation**  
Enhanced resilience and team engagement
- Burnout Prevention**  
Reduces stress and improves culture


*Pharmaceutical Executive "Developing Mindful Leaders in the Pharmaceutical Industry"*  
<http://www.pharmexec.com/ViewArticle.aspx?id=1140004>



### Closing Thoughts


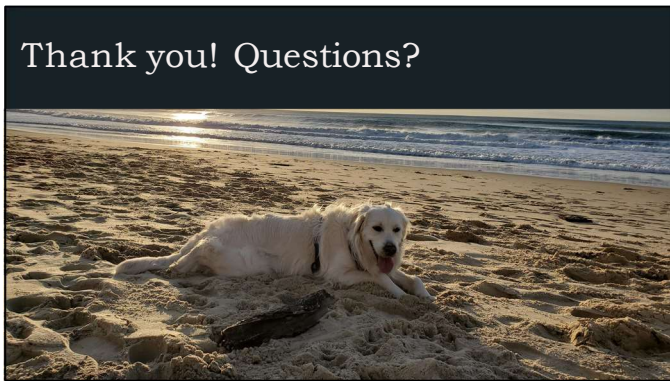
**Everyone Leads**  
Leadership is influence, not just title

**Be Inclusive**  
Diverse perspectives drive better outcomes



**'Science Shaped by Leadership**  
How we lead affects what we discover

**Be Intentional**  
Lead with purpose and clarity

The Veterinary Information Network: The Veterinary Community For Veterinarians By Veterinarians

Dawn Merton Boothe (VIN #0034)

Alumni Professor Emerita, Auburn University

Veterinary Information Network Consultant, Editor and all around Druggie

<https://www.vin.com/vin/default.aspx?pId=130&id=8286005>

A series of Queries answered by Perplexity.ai, Boothe and VIN.

• **Query: What is the Veterinary Information Network (VIN)?**

- ❖ AI Answer: A comprehensive, online community and resource platform designed exclusively for veterinary professionals. VIN connects tens of thousands of veterinarians worldwide, fostering collaboration through interactive forums, case discussions, and peer consultations. This collegial network enables practitioners to seek advice, share experiences, and consult with hundreds of veterinary specialists on complex cases.
- ❖ Boothe: The best re-wirement ever! (Okay, an n of 1). An apolitical, safe (for all), science-driven, caring, collaborative environment / experience. 114,000 members worldwide, largest veterinary information database (journals, conference proceedings, webinars (rounds), message board discussions, drug resources, calculators, videos, MedFAQs, textbooks and much more)

• **Query: What is VIN's mission?**

- ❖ AI Answer: VIN's mission is to empower veterinarians with the resources, education, and community support needed to provide the highest standard of care for their patients and to foster professional growth within the veterinary field.
- ❖ VIN Answer: to inspire and facilitate excellence within the worldwide veterinary community. (Help veterinarians, elevate level of veterinary medicine, lead by example, bring colleagues together)

• **Query: What titles would you use to describe the Veterinary Information Network?**

- ❖ AI Answer: These titles highlight the collaborative, expert-driven, and resource-rich nature of the Veterinary Information Network, reflecting its reputation as a comprehensive support and information hub for veterinary professionals and students
  - "VIN: Your Gateway to Veterinary Expertise"
  - "Unlock Veterinary Wisdom with VIN"
  - "VIN: Where Vets Connect and Collaborate"
  - "Veterinary Information Network: The Powerhouse for Pet Professionals"
  - "VIN: Empowering Vets, Enhancing Care"

• **Query: What services does VIN offer to its members?**

- ❖ AI Answer: (red = additions by Boothe)

Service Category	Description
Clinical Information	Medical library (Textbooks, journals and companion articles), drug handbooks (VVDH), VINyclopedia) case studies, video resources, research articles, calculators and tools, 3D

	Anatomy, Virtual Clinic Simulator, and much more all available as searchable and (saveable)/retrievable databases
Community & Support	Peer-to-peer forums, access to specialists, global networking for case management and personal/career growth, including opportunities for everyone to provide input/perspective Member Feedback What are Collaborative Rounds?
Continuing Education	Online CE courses (real-time and your-time), live rounds, specialty lectures
Practice Management	Business resources (legal compliance, financial advice), workflow tips, ancillary support for career development
Client Education	Veterinary Partner® articles, drug info sheets, printable/emailed client resources
Industry Updates	News Service providing up-to-date, relevant information on diseases, treatments, technologies
Interactive Discussions	Case presentations, clinical discussions, problem-solving sessions
Student Education	Anatomical, Diagnostic Imaging, Lectures, Study tools
Student/Post Graduate Support	Student Debt, Virtual Veterinary Internship

- **Query: What is VIN’s history (VINstory); Where has VIN been?**

- ❖ Answer:

- Cofounded by Paul Pion, Duncan Ferguson, starting as the Pet Care Forum on American Online. Conversations among participating veterinarians led to an organization for veterinarians.
    - Nicky Mastin of the Quarterly Index brought the journal information expertise to the effort, beginning the VIN data base. By 1999, the community had grown to ≈4200 members
    - Mismatch between AOL interests and VIN’s goals led to moving complete web-based community
    - During this “dot.com” period, a decision was made to decline offers of partnerships based on financial interest. The decision to “go it alone” rather than “sell the soul” of the community meant no longer accepting advertising or sponsorship, a philosophy that is emphasized and followed today. (Thank goodness!)
    - Emergence of VIN 10 Commandments (which pretty much rule the present and future).

- **Query: And where is VIN going ?**

- ❖ Answer: The VIN 10 Commandments

1. VIN shall always be For Veterinarians, By Veterinarians and other great people who strongly believe in the importance of that standard.
2. VIN shall make choices based upon what is best long-term for VIN Members..... not what is best for the short-term, for VIN or for "profit"
3. VIN shall encourage its members to be critical, questioning, caring veterinarians, and shall strive to provide or generate the highest level of clinical evidence available.

4. VIN shall support the future of the veterinary profession; the development of the people who join our profession and the information upon which our profession is based.
5. VIN shall support the independence of the veterinary profession and the veterinarians, veterinary clinics, and veterinary schools that make up the profession.
6. VIN shall fairly reward the individuals who generate information resources available on VIN
7. VIN shall honor the privacy of all colleagues and never share any colleague's information with others without the explicit permission of those who have entrusted VIN with their information
8. VIN shall never enter into a "partnering" relationship with another entity who is unwilling to sign and be bound by the Governance Document
9. VIN shall have the "spine" to speak out against injustices even when it may not be in VIN's best interest or when there is threat of litigation for doing so.
10. VIN shall never betray the trust of the VIN membership in any way.
- (11. Thou shalt answer the question)
- (12. And do so by not making a VINner feel stupid)
- (13. \***“We”** is largely a forbidden word (Your is better than our)

- **Query: Who can join VIN (and who pays)?**

- ❖ Answer: A dynamic situation with caveats. In the words of Harry Potter (and Griphook), “It’s complicated”. But, one can refer back to the 10 commandments to predict eligibility.
- ❖ VIN is for Veterinarians by Veterinarians. Only graduate veterinarians and veterinary students can join.
  - Current cost is \$65/month. 30 day free trial membership. Membership includes all access, including VVDH app.
  - There are exceptions to the veterinary only rule for persons who can or are willing to bring something back to VIN. A good example are Veterinary Pharmacists in a veterinary teaching environment.
  - A reflection of the goal to support career development and education, membership is free to:
    - Veterinary students (national and international)
      - Membership is discounted to \$19.50 for the first year post graduation and \$39 for the second year.
    - Veterinary school faculty (veterinarians and other with significant student teaching exposure)
    - Veterinarians in training programs (interns at universities, all residents, some fellowships) are provided free. Private practice interns heavily discounted
    - Military (free for those in active combat zones)
    - No group/hospital memberships
  - Veterinary technicians can join VSPN (Veterinary Support Personnel Network)

- **Query: What does the current membership of VIN look like?**

- ❖ Answer: As of April 2025, 114,069 members: 63,321 veterinarians ( $\approx$  12,000 members outside US representing 114 countries) and 50,473 students ( $\approx$  36000 student members outside US representing 103 countries )

- **Query: So, like, what is VIN?**

- ❖ Answer:

Message Boards      Content Rounds      Learning tools      Clinical Tools      Search  
 tools      VIN tools      CE/CPD      (Membership Services, Security)

- **Query: What are the VIN message boards?**

- ❖ VIN Answer: The heart of the community, supported by Consultants, Editors and Reps. Both Medical and Life.

- ❖ Boothe Answer: A vehicle for serving and learning (and occasionally squirming).

**Life**

\* News that's fit to Click

- Dealing with the Situation
- Ethics
- Humor in Veterinary Medicine
- Issues and Answers
- Issues and Arguments
- LGBTQIA
- Life Away From The Office
- Military Veterinarians
- Personal Financial Issues
- Prof Communication - Stress
- Prof Motivators/Mentorship
- Student Debt/Repayment Issues
- Student Issues
- The Commons — General
- Veterinary Trivia
- Women Veterinarians

**Medical**

- |                                      |                                         |                                   |                            |
|--------------------------------------|-----------------------------------------|-----------------------------------|----------------------------|
| Alternative Medicine                 | Endocrinology                           | Neurology                         | Shelter Medicine           |
| Anesthesia/Analgesia                 | Equine                                  | Oncology                          | Surgery - Orthopedic       |
| Aquatic Animal Medicine              | Ethics                                  | Ophthalmology                     | Surgery - Soft Tissue      |
| Association of Shelter Veterinarians | Hematology - Hemostasis                 | Parasitology                      | Swine                      |
| Avian                                | Hospice/Palliative Med/End of Life Care | Pediatrics and Geriatrics         | Telemedicine               |
| Behavior                             | Immunology                              | Physiology - Pathophysiology      | Toxicology                 |
| Cardiology - Pulmonology             | Infectious Dz - Immunology              | Practice Tips                     | Urology - Nephrology       |
| Clinical and Anatomic Pathology      | Interesting Cases                       | Prof Communication - Stress       | Veterinary Trivia          |
| Clinical Nutrition                   | Internal Medicine - Canine              | Prof Motivators/Mentorship        | Vets Only                  |
| Clinical Pharmacology                | Internal Medicine - Feline              | Rehab/Sports Med/Chronic Pain     | Wacky Cases                |
| Dealing with the Situation           | Issues and Answers                      | Reproduction and Genetics         | Zoonoses and Public Health |
| Dentistry                            | Life Away From The Office               | Reptiles/Amphibians/Invertebrates |                            |
| Dermatology                          | Mammals Small and Exotic                | Ruminants Large and Small         |                            |
| Diagnostic Imaging - Radiology       | Military Veterinarians                  |                                   |                            |
| Emergency Medicine                   |                                         |                                   |                            |

- **Query: What is VIN Content?**

- ❖ Answer: Name a resource you need to answer a question and it likely will be there and if not, likely obtainable.

- VIN Core Materials:

- Library: Journal abstracts and articles of 686 individual journals and since collecting, over 3.3 million veterinary /animal (at least 60 veterinary journals (plus an article request), 67 textbooks (including Merck Veterinary Manual), Conference proceedings from 76+ organizations (close to 100,000 proceedings articles), and Formularies (BSAVA, Camelid, NACA)
      - Specialty centers with slides, reference documents
      - Forms, handouts including MSDS/SDA forms, Client Information Sheets

- From Community Activities (and see Search below)

- \*Message Board Archives, \*Rounds (collaborative, every day, every time zone, but also recorded for replays and transcripts, many RACE approved for CE credit, linked to message board discussion so conversation can continue and documents can be shared.)

- VIN generated Surveys, Clinical Studies
- Others
- Built by VIN for everyone:
  - For Veterinarians: \*VINcyclopedia, \*VIN Veterinary Drug Handbook: web based and Mobile based and VDDH App; Companion Notes (to journal articles), Medical FAQs; VINNews; Guidelines, notes, case studies; Veterinary Nerdbook (4<sup>th</sup> ed), Low Stress Handling Textbook (2<sup>nd</sup> ed)
  - Hugely popular with students worldwide (and others): 3D Anatomy
  - Guidelines, notes, VINNews,
  - For Clients: \*Veterinary Partner
  - For Veterinary Staff: VSPN
  - VIN \*Front Page
- **Query: What are the VIN Learning Tools?**
  - ❖ Answer: Although student-centric, not surprisingly, these are tools that are sufficiently informative that they support learning at all levels
    - VIN Student Center
    - Anatomy in 3D, Virtual Clinic, Procedure Videos, multiple choice questions, flashcards, case studies, VINcyclopedia diseases to consider.
- **Query: What are the VIN Clinical Tools?**
  - ❖ Answer: user friendly, really neat tools that empower VINners to provide improved patient care.
    - Learning tools
    - Calculators: Doses (including CRI [single vs multiple, unit conversions], (also in the VVDH) dilutions, bromide loading dose; Toxicity (chocolate, NSAID, rodenticide, ethylene glycol), emergency drugs, fluid therapy, transfusion volumes Conversions (glucocorticoids, iron salts, units, body surface area), Topical Therapy Product finder, Flea and Tick product Finder, Veterinary Feed Directive
    - Anesthesia protocols, Companion Notes, Medical FAQs, Diseases to Consider, Algorithms
- **Query: What are the VIN tools?**
  - ❖ Answer: All the things that make VIN easy to use .
    - Message boards: Signalments always included, diagnostics are generally included as needed. Tools allow cross-posting to other message boards, pulling experts in from multiple disciplines on complex cases (and blind copying to other consultants if needed); ability to link stuffy such as related message board discussions to current one, FAQs, websites, articles outside of VIN, photos, blood work etc. VINner (reaching out) information. Most of these message boards are archived and can be searched.
    - Your MyActivities: favorite things can be ear-marked and saved; your contributions to message boards can be searched.
    - Feedback! (also really neat) allows VINner to identify problems (errors, poorly worded or difficult to understand verbiage) or make suggestions. This has proven to be a very effective tool for making things better.
    - Member profiles

- **Query: What is VIN CE/CPD?**
  - ❖ Answer: What do you want to learn today (interactive, non-interactive)?
    - VINCE/VSPNCE
    - Drip Vet
    - CE Credit Rounds
    - Focused: Cattle Dog, Low Stress Handling
- **Query: What can be searched?**
  - ❖ Answer: What can't be?
    - Search + filter = very robust / successful searching effort
    - "My Stuff" sites for saving

**Focus on the VVDH**

- > 1000 drugs
- Searchable by categories
- US, plus AU, CA, EU, UK
- Coordinated with VINcyclopedia
- All referenced (Journals, Proceedings)
- "Clinical Pearls" = clinicians pointers
- Includes Dose Calculator
- Coming: Ability to add notes
- Updated & Full Reviews



- **Query: What is the VIN Foundation?**
  - ❖ AI Answer: is a nonprofit organization (501(c)(3)) focused on supporting veterinarians, veterinary students, and pre-veterinary students through free programs addressing critical challenges in the profession. Established in 2005, it operates under the principle that a healthy animal community depends on a robust veterinary community
  - ❖ VIN Answer: The [VIN Foundation](#) (a 501c3 nonprofit) believes a healthy animal community depends on a healthy veterinary community. The [VIN Foundation provides tangible resources](#) for pre-veterinary students, veterinary students, and veterinarians, available at no cost (VIN membership not needed) thanks to individual donors like yourself.
  - ❖ VIN Answer: The VIN Foundation is a 501(c)(3) nonprofit made possible through generous gifts by individual donors and grants. [All gifts made to the VIN Foundation are tax-deductible.](#) The VIN Foundation is a four-star rated charity through Charity Navigator, and has received the highest level rating from nonprofit tracker Candid (formerly GuideStar) annually since 2017. Less than 2% of the nonprofits tracked receive this level of recognition.
  - ❖ The Future Home / Owner of VIN

**Wrap up Queries:**

## What can ACVCP'ers (and other veterinarians) bring to VIN?

1. Message Boards: As consultants (financial reimbursement), associated editors (financial reimbursement ) or as VIN member. There is no barrier to anyone sharing their expertise or reaching out for more
2. Content: Information documents: Helping with VP, FAQ and especially VVDH
  - a. Monographs: new monographs, updating monographs, innovative approaches (applying principles of antimicrobial stewardship)
  - b. Drug Interactions project
  - c. Adverse Event Project
  - d. Describe it and it shall be considered.
3. Teaching tools
  - a. Adding to MCQ, Flash Cards
  - b. Describe it and it shall be considered and you probably can get support
4. Clinical tools:
  - a. help with antimicrobial decision making tool would be great.
  - b. Describe it and it shall be considered and you probably can get support
5. Continuing Education
6. Rounds
7. VINternships
8. Probably lots of other places

## How might VIN support ACVCP?

1. Use of Teaching tools in classrooms: VVDH, anatomy 3D, imaging, MCT, flash cards, clinical cases, virtual clinic etc etc
2. Service: message boards
3. Clinical Research? Survey based? Others (be careful here: the 10 commandments will rule).
4. Residency training
  - a. Message boards as a mechanism of exposure to clinical medicine
  - b. Availability of study materials resources
    - i. Library
    - ii. Teaching tools above
    - iii. FAQ etc etc
  - c. Contributing to
    - i. VVDH monograph updates, reviews, new monographs
    - ii. FAQ
    - iii. Calculators
    - iv. Protocols
  - d. A repository (future?) for study materials
5. Others?

# Veterinary Medicine and USP

Why Veterinary Professionals Should Volunteer for  
USP Standard Setting

Gigi Davidson, BSPHarm, DICVP, FAVCP, FSVHP

## Learning Objectives

1. Identify significant USP quality standards that impact veterinary pharmaceuticals and compounded therapies.
2. Explain how the USP Expert Committees develop standards
3. Identify USP initiatives that would benefit veterinary medicine.
4. Describe professional benefits received from volunteering for USP.
5. Describe the relationship between the USP Nomenclature and Labeling Expert Committee in publishing veterinary drug standards

### USP history in US law

1820:

- 11 physicians met at the US Capitol to standardize the best known medicines of the time (they were all compounds) which became USP 1

1848:

- USP Standards called out in federal law in the Drug Importation Act to intercept substandard and adulterated drugs from being shipped to the US

1906:

- USP quality monographs called out in the Pure Food and Drug Act

1938:

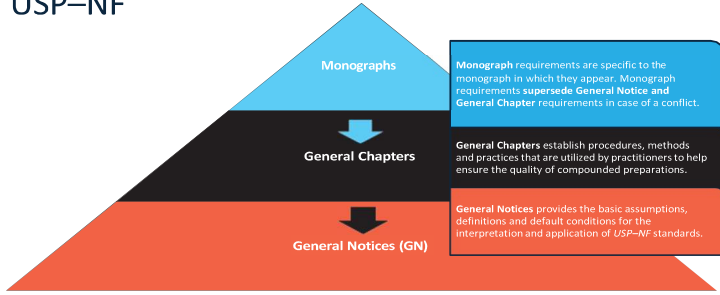
- Food, Drug, and Cosmetic Act mandated that all manufactured drugs must meet the standards in USP monographs

## Mission

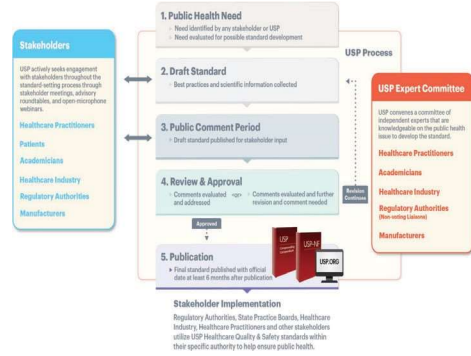
To improve global health  
through public standards  
and related programs that  
help ensure the quality,  
safety and benefit of  
medicines and foods



**USP Monographs, General Chapters and General Notices**  
**USP-NF**



**How USP works**



**USP Collaborative Groups**



Biologics	Small Molecules	Excipients	General Chapters	Healthcare Quality & Safety	Dietary Supplements & Herbal Medicines, Food Ingredients
<p><b>Biologics Monographs 1- Peptides &amp; Oligonucleotides</b> Michael Dai Falopp</p> <p><b>Biologics Monographs 2- Plasmids</b> Tapan Das (pro temp)</p> <p><b>Biologics Monographs 3- Complex Biologics &amp; Vaccines</b> Earl Jabackas</p> <p><b>Biologics Monographs 4- Antibiotics</b> Matthew Boren</p> <p><b>Biologics Monographs 5- Advanced Therapies</b> Mahmoud Jaz</p>	<p><b>Small Molecules 1</b> Mary Seibel</p> <p><b>Small Molecules 2</b> Justin Pennington</p> <p><b>Small Molecules 3</b> Eric Krasner</p> <p><b>Small Molecules 4</b> Kim Huynh Da</p> <p><b>Small Molecules 5</b> Amy Geron</p> <p><b>Over-The-Counter (OTC) Methods &amp; Approaches</b> Rachael Ornel</p>	<p><b>Simple Excipients</b> Eric Munson</p> <p><b>Complex Excipients</b> Celia Koo</p> <p><b>Excipients Test Methods</b> Citra Alonson</p>	<p><b>General Chapters-Dosage Forms</b> Martin Coffey</p> <p><b>General Chapters-Chemical Analysis</b> Nancy Lovell</p> <p><b>General Chapters-Microbiology</b> Mark Schaeffer</p> <p><b>General Chapters-Packaging &amp; Distribution</b> Renaud Janssen</p> <p><b>General Chapters-Measurement &amp; Data Quality</b> Jane Vintner</p> <p><b>General Chapters-Statistics</b> Charles Tan</p> <p><b>General Chapters-Physics</b> Analytica Kath Houck</p>	<p><b>Nomenclature &amp; Labeling</b> Stephanie Crawford</p> <p><b>Healthcare Safety &amp; Quality</b> Melody Ryan</p> <p><b>Healthcare Information &amp; Technology</b> Joanna Tuttle</p>	<p><b>Botanical Dietary Supplements &amp; Herbal Medicines</b> Robin Marten</p> <p><b>Non-Botanical Dietary Supplements</b> Bernadette Leutenber (pro temp)</p> <p><b>Dietary Supplement Administration, Evaluation, &amp; Labeling</b> Amy L. Rice</p> <p><b>Food Ingredients</b> Jon DeVries</p>

**2025-2030 USP Expert Committees**

Small Molecules	Biologics	Excipients	Dietary Supplements & Herbal Medicines, Food Ingredients	Healthcare Quality and Safety	General Chapters
<p><b>Small Molecules Therapeutic Area 1</b> (Antibiotics, Antivirals &amp; Anticancer)</p> <p><b>Small Molecules Therapeutic Area 2</b> (Cell, Drug &amp; Biologic)</p> <p><b>Small Molecules Therapeutic Area 3</b> (Gastrointestinal, Sens, Endocrine &amp; Oncology)</p> <p><b>Small Molecules Therapeutic Area 4</b> (Psychiatric, Psychotropic, Neurotransmitter, Radiopharmaceutical &amp; Non-Radiotracer Imaging Agents)</p> <p><b>Small Molecules Therapeutic Area 5</b> (Pulmonary, Anesth, Inhalation &amp; Steroids)</p> <p><b>Small Molecules Therapeutic Area 6</b> (Cardiovascular, Ophthalmology, OTC, Dermatology &amp; Veterinary Products)</p>	<p><b>Therapeutic Peptides, Oligonucleotides and Complex Carbohydrates</b></p> <p><b>Vaccines</b></p> <p><b>Cell &amp; Gene Therapies</b></p>	<p><b>Excipient Monographs 1</b> (Simple Organic Monographs, Lipids, Essential Oils and Fixed Oils, Fats &amp; Steroids)</p> <p><b>Excipient Monographs 2</b> (Natural, Synthetic, Semi-synthetic Polymers, Celluloses, Gums &amp; Chitos)</p> <p><b>Excipient Chapters</b> (Excipients Test Methods &amp; more)</p>	<p><b>Botanical Dietary Supplements and Herbal Medicines</b></p> <p><b>Non-botanical Dietary Supplements</b></p> <p><b>Dietary Supplement Administration, Evaluation, &amp; Labeling</b></p> <p><b>Food Ingredients</b></p>	<p><b>Healthcare Safety, Quality &amp; Nomenclature</b></p> <p><b>Compounding</b></p> <p><b>Healthcare Information and Technology</b></p> <p><b>Personalized Medicines</b></p>	<p><b>Dosage Forms</b></p> <p><b>Chemical Analysis</b></p> <p><b>Microbiology</b></p> <p><b>Packaging and Distribution</b></p> <p><b>Statistics</b></p> <p><b>Pharmaceutical Analysis, Lifecycle and Data Science</b></p> <p><b>Materials Physical Properties Characterization</b></p>

## Where Does USP Overlap with Veterinary Medicine?

<b>Veterinary medications</b>	<ul style="list-style-type: none"> <li>• Create standards for veterinary drug products and compounds, ensuring that they reflect the unique needs of non-human patients</li> </ul>
<b>Improving drug quality and safety</b>	<ul style="list-style-type: none"> <li>• Advocating for high-quality veterinary medicines</li> <li>• Helping to reduce risks associated with poor-quality drugs in veterinary practice</li> <li>• And enhancing non-human patient care</li> </ul>
<b>Access to scientific expertise</b>	<ul style="list-style-type: none"> <li>• Access to a global network of experts in pharmaceuticals, including veterinary drugs</li> <li>• USP is at the forefront of scientific developments, regulatory changes, and trends in veterinary pharmacology</li> </ul>
<b>Collaboration with stakeholders</b>	<ul style="list-style-type: none"> <li>• USP staff and volunteers collaborate with key stakeholders from government agencies, pharmaceutical companies, compounding pharmacies, healthcare providers, and academia</li> <li>• Fosters partnerships and innovations that benefit both the veterinary sector and public health, especially in areas like antimicrobial resistance and compounded medications for animals</li> </ul>
<b>Contribution to public and animal health (One Health Medicine)</b>	<ul style="list-style-type: none"> <li>• USP standards can help improve not only the health of animals but also public health.</li> <li>• Veterinary drugs can impact the human food chain, zoonotic disease, and antimicrobial resistance</li> </ul>

## How Do Veterinary Professionals Benefit from Volunteering for USP?

### Advocacy for Veterinary-Specific Issues

- USP gives veterinary professionals a platform to advocate for veterinary-specific standards (e.g. drug products, biologic products, compounded preparations) ensuring that the needs of veterinarians and non-human patients are met

### Global Recognition

- USP standards are recognized internationally, being a volunteer for USP enhances the individual volunteer's credibility and influence globally.

### Educational and Professional Development

- USP provides educational resources and professional development opportunities, such as workshops, webinars, and conferences, allowing volunteers to stay updated on best practices and the latest advancements in the field.

## How Does USP Benefit from Veterinary Volunteers?

- Providing Expertise in Veterinary Pharmacology
- Advocating for Species-Specific Standards
- Driving Innovation in Veterinary Medicine
- Enhancing Public Health through Animal Health
- Shaping Standards for Veterinary Compounding
- Addressing Environmental and Ethical Concerns Surrounding Use of Animal Drugs
- Supporting Educational Initiatives
- Fostering Multidisciplinary Collaboration

## USP Expert Committees in Need of Veterinary Input—Dosage Forms

- Responsible for naming and standard-setting for all dosage forms (found in USP Chapter <1151>)
- No veterinary representation of any kind
- Examples:
  - "transdermal gel" is definition
    - Varies for veterinary vs human
    - "topical creams or ointments" in USP standards (inaccurate)
  - compounding standards for this dosage form cannot be developed until it exists in USP language

## USP Expert Committees in Need of Veterinary Input—Small Molecules 3

- Responsible for writing standards for veterinary drug products and bulk drug substances
- Currently, no veterinary representation of any kind
- If there are no monographs for veterinary products or bulk chemicals (e.g. trilostane, marbofloxacin, enrofloxacin) then:
  - quality (eg, purity, identity, strength) is left to the manufacturer/compounder
  - Drives importation of bulk drug substances from countries that have pharmacopeial monographs for those substances

## USP Expert Committees in Need of Veterinary Input—Biologics

- 5 different Biologics Expert Committees
- No veterinary representation of any kind
- Biologics are storming on to the veterinary marketplace, but are currently regulated by USDA, not by FDA as for humans
- Without strong quality standards the veterinary biologics market is at risk
- Biologics standards set for humans will strongly impact veterinary biologics
- Examples:
  - Consider consequences of compounded or pirated veterinary mAb (lokivetimab, frunevetmab, or bedinvetmab)

## USP Expert Committees in Need of Veterinary Input—Compounding

- Responsible for setting all compounding practice standards and developing compounding preparation monographs (formulas)
- Responsible for chapters <795> Nonsterile Compounding, <797> Sterile Compounding, <800> Hazardous Drug Compounding, and <825> Radiopharmaceutical Compounding
- The one veterinarian on this committee for the current cycle has largely been absent due to health reasons
- Veterinary input and perspective largely come from a veterinary pharmacist and CVM FDA liaisons; a veterinary clinical perspective is needed

## USP Expert Committees in Need of Veterinary Input—Nomenclature and Labeling

- Responsible for...
- Found in chapters...
- Dawn Boothe has contributed with impact to this committee for decades
- This Expert Committee is the safety and naming gauntlet through which all USP Standards must pass
- It is a critical step in ensuring that drug products and substances that are standardized by USP....

## USP Expert Committees for which Veterinary Input might become important—

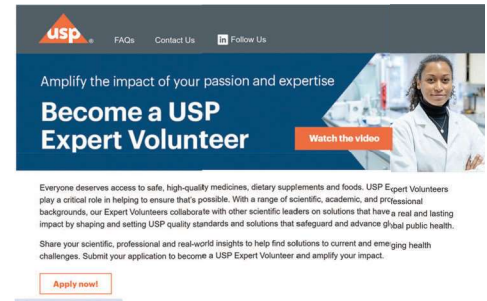
- Health Information and Technology
  - Digitalized medicine
  - New responsibility will include a focus on artificial intelligence
- Personalized medicine
  - Standardizing information regarding pharmacogenomics
  - Digital Therapeutic Oversight

## How To Apply For a USP Expert Committee

Known as "The Call for Candidates"

Watch video here:

<https://callforcandidates.usp.org/>



The image shows a recruitment banner for USP Expert Volunteers. At the top left is the USP logo. To its right are links for 'FAQs', 'Contact Us', and 'Follow Us'. The main text reads 'Amplify the impact of your passion and expertise' followed by 'Become a USP Expert Volunteer' in large, bold letters. A 'Watch the video' button is positioned to the right of the main text. Below this is a photograph of a woman in a white lab coat. Underneath the photo, there is a paragraph of text explaining the role of USP Expert Volunteers and their impact on public health. At the bottom of the banner is an 'Apply now!' button.

Everyone deserves access to safe, high-quality medicines, dietary supplements and foods. USP Expert Volunteers play a critical role in helping to ensure that's possible. With a range of scientific, academic, and professional backgrounds, our Expert Volunteers collaborate with other scientific leaders on solutions that have a real and lasting impact by shaping and setting USP quality standards and solutions that safeguard and advance global public health.

Share your scientific, professional and real-world insights to help find solutions to current and emerging health challenges. Submit your application to become a USP Expert Volunteer and amplify your impact.

[Apply now!](#)

## Identifying the core competencies of advanced veterinary pharmacology training

Virginia Fajt, Martin Hawes, and Arno Werners

(From Texas A&M University, University of Surrey, and St. George's University)

A competency-based approach to educating veterinarians in training has been implemented at a number of institutions. Competencies are observable abilities related to a specific activity that integrates knowledge, skills, values, and attitudes (<https://cbve.org/terminology>). This approach starts with the desired outcomes, sometimes called backwards design, with assessments and then learning activities designed to lead to the desired outcomes. In veterinary education, this approach is embodied in the Competency Based Veterinary Education (CBVE) Framework, which provides the high-level competencies new graduates should have acquired by the end of their training program.<sup>1</sup> These program-level competencies are used to develop subcompetencies, which can then be mapped onto courses or smaller subunits of education. The authors have been working to provide connections between the CBVE framework and pharmacology competencies for day-one veterinarians, and we propose adapting this approach to provide a framework for advanced veterinary pharmacology training.

As background, the steps that we and colleagues have been using to develop veterinary pharmacology learning outcomes and curricular aids for veterinary training programs started with the AAVPT-sponsored Teaching Workshop in 2012. After that workshop, working groups developed lists of desired knowledge; this list was prioritized using a Delphi methodology and published in 2021.<sup>2</sup> The prioritized list has since been mapped to the CBVE domains of competence.<sup>3</sup> Data from a workshop sponsored by the University of Surrey UK in 2024 was used to develop learning objectives and milestones, which are being incorporated into a draft of a complete curriculum. This curriculum includes pharmacology competencies mapped to the CBVE, with each competency fleshed out to include key concepts and learning objectives that are suitable for creating lesson plans for lectures, small group activities, or laboratories.

Advanced veterinary pharmacology training is a more complicated and diverse array of educational institutions and programs than veterinary education. However, we assert that the AAVPT and other organizations with an interest in veterinary pharmacology as a discipline would be well served to agree about the end points of advanced veterinary pharmacology training, with or without a veterinary degree. AAVPT has previously supported this effort with a workshop in 2007, which resulted in a publication of a “blueprint” for graduate pharmacology education (see Appendix).<sup>4</sup> These competencies included those that are common to all workplaces as well as those that differ for industry as compared with academia. At the 2019 Biennial, there were sessions addressing advanced training, but no plans were made to revise or update the blueprint, and there was limited interactive discussion to develop consensus about updates.

Based on our experiences developing endpoints for new veterinarians, we propose an approach that includes overlapping areas of endpoints for outcomes of advanced training that leads to work in research/industry and in clinical arenas of veterinary pharmacology. These endpoints would be

the targets for training applicable to MSc/PhD training programs as well as clinical pharmacology residencies.

In this session, we will obtain input from meeting attendees as the starting point for adaptation of the previously published blueprint for veterinary graduate education. Modernization of training programs to include workplace-based learning and modular approaches to resident training are crucial to attract and maintain an adequate number of residents. Additional input will also need to be sought from other stakeholders such as all members of AAVPT and diplomates of ACVCP and ECVPT. We contend that having a unified set of competencies that includes those that are unique to segments of the discipline will aid in graduate training program development. It could also improve understanding about the relevant and unique skills and knowledge that advanced training in veterinary pharmacology provides, leading to additional career opportunities.

### References

1. AAVMC Council on Outcomes-based Veterinary Education, Chaney KP, Hodgson JL, et al. CBVE 2.0 Model. 2024. Accessed June 12, 2024. <https://cbve.org/cbve-20>
2. Werners A, Fajt V. What a veterinary graduate should know about basic and clinical pharmacology: A Delphi study to finalize day-1 competencies. *J Vet Pharmacol Ther.* 2021;44(4):568-574. doi:10.1111/jvp.12920
3. Hawes M, Fajt V, Werners AH. Mapping Disciplinary Competencies and Learning Outcomes to the Competency-Based Veterinary Education Framework Using Veterinary Pharmacology as an Example. *J Vet Med Educ.* Published online December 9, 2024:e20240097. doi:10.3138/jvme-2024-0097
4. Fajt VR. Skills and competencies required by veterinary pharmacologists: a blueprint for graduate education in veterinary pharmacology in North America. *J Vet Pharmacol Ther.* 2008;31(1):22-30. doi:10.1111/j.1365-2885.2007.00920.x

APPENDIX – Competencies identified as important for careers in both academia and industry by attendees of an AAVPT workshop in 2007

<p><b>Professional skills</b></p>	<p>Communication skills</p>	<p><i>Writing</i></p> <ul style="list-style-type: none"> <li>- <i>Technical and scientific writing</i></li> <li>- <i>Based scientific literacy</i></li> </ul> <p><i>Formal oral presentations</i></p> <ul style="list-style-type: none"> <li>- <i>Including effective use of presentation software</i></li> </ul> <p><i>Informal interactive communication</i></p> <ul style="list-style-type: none"> <li>- <i>Able to talk up and down the organizational levels</i></li> <li>- <i>Informal interactions with colleagues, lab personnel, etc.</i></li> </ul> <p><i>Listening skills</i></p>
	<p>People management skills</p>	<p><i>Recognizing/managing personalities</i>  <i>Participate in solving problems</i>  <i>Challenge and motivate</i></p>
	<p>Personal management skills</p>	<p><i>Time management</i>  <i>Prioritization</i>  <i>Organizational skills</i>  <i>Task completion</i>  <i>Planning/preparatory skills</i>  <i>Initiative</i>  <i>Deal with success/failure</i></p>
<p><b>Professional skills specific to industry</b></p>	<p>Personal characteristics</p>	<p><i>Personality fit, culture fit</i>  <i>Humility, ability to take feedback</i>  <i>Self-awareness of introversion vs extroversion</i></p>
	<p>External focus</p>	<p><i>Willingness to learn and broaden horizons</i>  <i>Ability to understand big picture (small companies)</i>  <i>Ability to focus intensely on specific details (large company)</i>  <i>Ability to do both (large companies)</i>  <i>Willing to do what is best for organization, not just project</i></p>

		<i>Abilities in scenario-planning, strategic thinking, multi-dimensional planning (including risk analysis)</i> <i>Business acumen</i>
	Interactions with others	<i>Actively engage in scientific debate without getting personal</i> <i>Team player</i> <i>Consensus building</i> <i>Managing meetings</i> <i>Influence and motivate to make own decisions</i> <i>Appropriate level of delegation</i>
<b>Professional skills specific to academia</b>	Grantsmanship	
	Teaching experience/ concepts	
	Responsibility for publication	
	Increasing independence and initiative	
	Employment negotiation	
<b>Technical skills</b>	Study design and analysis	<i>Capable of designing studies</i> <i>Ability to generate hypotheses and test them</i> <i>Knows statistical methods and has performed based statistical analysis</i>
	Subject knowledge	<i>Understanding of clinical relevance</i> <ul style="list-style-type: none"> <li>- <i>Clinical background/ ability to grasp clinical relevance of work</i></li> <li>- <i>For DVMs: has clinical experience with knowledge of species-specific diseases and conditions</i></li> <li>- <i>Exposure to whole-animal work</i></li> <li>- <i>Advanced comparative pharmacology</i></li> </ul> <i>Research techniques</i> <ul style="list-style-type: none"> <li>- <i>Able to perform needed research techniques</i></li> <li>- <i>Basic laboratory skills, including chromatographic separation techniques (understanding of concepts)</i></li> <li>- <i>Analytical chemistry and assay validation</i></li> </ul>

		- <i>Understands and can perform PD (ADME) analysis</i> <i>Understands and can perform basic PK analysis, including able to use appropriate software</i>
	Knowledge and experience in research compliance issues	<i>Exposure to GLP/ GCP</i> <i>Safety/ compliance/ IACUC/ IRB/ QA</i>
<b>Technical skills specific to industry</b>	Flexibility in research area	
	Exposure to industry via externships	
<b>Technical skills specific to academia</b>	Knowledge of molecular and cellular biology	



# Speaker Bios

**Michael D. Apley, DVM, PhD, DACVCP**  
**College of Veterinary Medicine, Kansas State University**

Dr. Apley is a veterinarian with a PhD in physiology (pharmacology). He is a Diplomate of the American College of Veterinary Clinical Pharmacology. His practice background includes general practice in central Kansas and a feedlot consulting/contract research practice based in Colorado. Dr. Apley was on the College of Veterinary Medicine faculty at Iowa State University for 9 years through 2005. He is currently a professor in the Department of Clinical Sciences at the Kansas State University College of Veterinary Medicine. Dr. Apley works with veterinarians and producers throughout the United States concerning the use of drugs in food animals and also in the area of beef cattle health.

Dr. Apley teaches in multiple courses related to food animal medicine, clinical pharmacology, and antimicrobial resistance. His research interests include infectious disease, antibiotic efficacy and resistance, antibiotic stewardship, drug residues, and applications of drugs in food animals. In 2022, he and collaborators completed a 5-year cooperative agreement with the FDA Center for Veterinary Medicine which focused on quantifying antibiotic use in feedlots and dairies. In 2022, the team started on a 3 year FFAR ICASA funded grant to further advance antimicrobial use monitoring in beef feedlots in conjunction with a wide array of stakeholders.

In 2015, Dr. Apley was appointed as a voting member of the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria. He completed his two terms on the council in March of 2023, serving as vice chair. Dr. Apley currently serves as an alternate member on the American Veterinary Medical Association Committee on Antimicrobials, as a member of the American Association of Bovine Practitioners Committee on Pharmaceutical and Biological Issues, as a member of the American Association of Swine Veterinarians Committee on Pharmaceutical Issues, and as an advisor to the Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee.

**Dawn M. Boothe, DVM, MS, PhD**  
**Auburn University College of Veterinary Medicine**

Dr. Boothe received her DVM degree from Texas A&M in 1980, completed a small animal internship at Auburn University in 1980, received an MS degree from Texas A&M in 1985, completed a residency in small animal medicine in 1985, completed a PhrMA Fellowship in 1989, and received a PhD degree in 1989. In 1990, she joined Texas A&M in the Department of Veterinary Physiology & Pharmacology and became a professor. In 2003, she joined the Departments of Anatomy, Physiology and Pharmacology and Clinical Sciences at Auburn in 2003, where she directs the Clinical Pharmacology Laboratory. Dr. Boothe has authored or coauthored approximately 125 peer-reviewed

scientific publications, 60 book chapters, and 2 textbooks. She received the Texas A&M University Achievement Award in Teaching, the Jack Mara Scientific Achievement Award for contributions in clinical pharmacology of the critical care patient, Auburn University Outstanding Graduate Student Mentor Award, the Zoetis Award for Excellence in Research, and an Alumni Professorship.

**Michela Cantiello, DVM, Ph.D., MBA, AAVPT President  
QIMA Life Sciences**

Dr. Michela Cantiello is currently the Preclinical and Clinical Research Managing Director at QIMA Life Sciences. An Italian professional in Veterinary Medicine from the University of Bologna, Italy, she brings over two decades of experience in Animal and Human Health academic research and industry.

Michela holds an MBA from the Kelley School of Business, Bloomington, Indiana, USA, with a focus on Strategy and Leadership. Her academic journey includes a Master's in Executive Profession from Toulouse Business School, Toulouse, France, and a PhD in Pharmacology & Toxicology from the University of Veterinary Medicine, Turin, Italy. Fluent in Italian, French, and English, in her last working experience she has led for 3 years the French and the Italian Business Units of Eurofins Professional Scientific Services, the consulting branch of the company. Prior to that, Dr. Cantiello has spent over 12 years at Avogadro LS and played a pivotal role in delivering profitable growth in the space of preclinical in-vivo testing.

Dr. Cantiello is an Adjunct Professor at the Kelley School of Business, Bloomington, Indiana, USA, teaching leadership, organizational behavior and organizational excellence.

Dr. Cantiello serves as the President of the American Academy of Veterinary Pharmacology and Therapeutics. Outside her professional life, she enjoys running, skiing, walking her Golden Retriever, and cooking.

**Charlotte Cross, BSc, MSc  
Certara UK Ltd**

Charlotte Cross is an Associate Research Scientist working at Certara UK Ltd. (Simcyp division, Certara Predictive Technologies), a biosimulation company that develops physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modelling platforms to support model informed drug development. Charlotte graduated from the University of Nottingham, UK, with an Animal Science BSc in 2018 and completed a Biological Sciences MSc at the University of Manchester, UK, in 2020. In her research, she has combined her passions for animals and using biosimulation software. Her most recent CRADA-work (manuscript currently under review) examined canine

pharmacology beyond its usual role in drug development as a human preclinical model, by considering the veterinary applications. For studying the impact of breed variation, particularly the delta-MDR1 mutation frequently found in Collies, she developed a virtual Collie population with P-glycoprotein and Cyp3a12 functionality. Charlotte has also worked on PBPK models for several compounds to evaluate transporter-mediated drug-drug interactions in humans and monkeys.

**Gigi Davidson, BSPHarm, DICVP, FACVP, FSVHP**

Gigi Davidson is the former Director of Clinical Pharmacy at the NC State University College of Veterinary Medicine where she practiced veterinary pharmacy for 35 years. Ms. Davidson received a pharmacy degree from UNC Chapel Hill in 1983 and earned Diplomate status in the International College of Veterinary Pharmacy in 2001. She was inducted into the Phi Zeta Honor Society in 2006 as an honorary member for distinguished advancement of veterinary science. Gigi is a past President of the Society of Veterinary Hospital Pharmacists and of the American College of Veterinary Pharmacists. Ms. Davidson is the ACVP delegate to the American Pharmacists Association House of Delegates where she has championed the cause for recognition of animals as patients and for veterinary pharmacy education. Ms. Davidson was the Chair of the United States Pharmacopeia Compounding Expert Committee from 2010-2020 and continues to serve as a member on that committee. Gigi is the recipient of USP's Beal Award when in 2015 she became the first female and first veterinary recipient of that award. She has many publications in peer-reviewed scientific journals, and her primary area of research interest is stability, safety, and efficacy of compounded therapies in non-human species. Her research interests in retirement include drug disposition in honey bees and pharmacological action of plant pollens and nectars on honey bee colonies.

**Jérôme Dellacasagrande, PhD**  
**Qima Life Sciences Labège**

Dr. Jérôme Dellacasagrande is an accomplished scientist with extensive experience in immunology and biotechnology. He currently serves as the R&D Head and Senior Study Director at Qima Life Sciences Labège, where he manages in vitro assay activities and R&D programs in the fields of inflammation and skin biology related to human and veterinary medicine. Dr. Dellacasagrande founded Blood Assay Solutions, a contract research organization specializing in wholeblood assays, and has held key positions at Opsona Therapeutics, Invivogen and the Institute of Immunology at the National Hospital in Oslo.

He holds a Ph.D. in "Transmissible Diseases & Tropical Pathologies" from Université de la Méditerranée and has a background in genetics, cell biology, and immunology. Dr.

Dellacasagrande has contributed to the field through various publications and patents, including research on Toll-like receptors and anti-tumoral immunity. He is committed to mentoring and leading within the scientific community.

**Virginia R. Fajt, DVM, PhD, DACVCP**  
**Texas A&M University**

After receiving her DVM at Auburn University, Dr. Fajt did a food animal internship and served as a clinical instructor at Kansas State University, followed by a PhD in Physiology at Iowa State University. She is a diplomate of the American College of Veterinary Clinical Pharmacology. Since joining the Department of Veterinary Physiology and Pharmacology at Texas A&M University, she has taught pharmacology courses and concepts of evidence-based veterinary medicine to undergraduates, graduate students, and DVM students. She also collaborates with clinical veterinary faculty, epidemiologists, microbiologists, and librarians to study drug disposition and other aspects of clinical drug use, such as drug safety, storage, and decision-making. Dr. Fajt serves as the chair of the DVM Curriculum Committee at Texas A&M, and she has held many roles in organized veterinary medicine in the American Association of Bovine Practitioners, the American Association of Small Ruminant Practitioners, the American Veterinary Medical Association, the American Academy of Veterinary Pharmacology and Therapeutics, the Veterinary Pharmacology Research Foundation, and the Evidence-Based Veterinary Medicine Association. She is also a voting member of PACCARB, the Presidential Advisory Council on Combatting Antibiotic Resistance.

**Claire Fellman, DVM, PhD, DACVIM (SAIM), DACVCP**  
**Cummings School of Veterinary Medicine at Tufts University**

Dr. Claire Fellman is an associate professor in the small animal internal medicine service at Tufts University, Massachusetts, USA. Claire earned her bachelor's degree in biological engineering prior to her veterinary training at Mississippi State University. She then completed residencies in small animal internal medicine and clinical pharmacology also at Mississippi State University, while doing a PhD investigating the effects of cyclosporine on immune function in dogs. Following her residencies, Claire began her work at Tufts where she leads a One Health collaboration with physicians and pharmacists from Tufts Medical Center with the goal to bring successful antimicrobial stewardship strategies from human medicine to companion animal veterinary settings. Claire's clinical interests include infectious and immune-mediated diseases.

**Jonathan Hare, DVM, PhD, Dipl ACVCP**  
**Telemark Veterinary Consulting**

Jonathan is a veterinarian with a PhD in immunopharmacology. He has worked in the animal health industry in technical support, regulatory affairs, and business development. He was co-founder and president of an animal health contract research organizations in North America for 14 years. Most recently he has been an independent animal health product development consultant and a visiting scholar at the University of Guelph. In 2021 he became a Diplomate of the American College of Veterinary Clinical Pharmacology.

**Martin Hawes BPharm(Hons), MBA, MSc, BVetMed**  
**School of Veterinary Medicine, University of Surrey**

Martin originally trained as a hospital pharmacist before moving to the pharmaceutical industry, where he spent 20 years in human drug discovery and development. In 2012, he took a career break to read veterinary medicine, and graduated from the Royal Veterinary College, University of London, UK in 2016. Martin worked as a companion animal vet before joining the University of Surrey, UK in 2018 part-time to teach veterinary pharmacology and therapeutics. Martin was awarded the British Pharmacological Society Student Choice Award for Excellence in Pharmacology Teaching in 2021, the British Small Animal Veterinary Association Amoroso Award for Teaching in 2022, and the British Pharmacological Society Rang Prize for Outstanding Achievement in Teaching in 2024. Martin is active in Health Professions Education research.

**Majid Jaber-Douraki BSc, MSc, PhD**  
**Kansas State University**

Dr. Majid Jaber-Douraki is a professor of mathematics and data science at Kansas State University, where his research focuses on computational modeling, machine learning, artificial intelligence (AI), and predictive models with applications in healthcare. He is also affiliated with the Johnson Cancer Research Center at Kansas State University. Dr. Jaber-Douraki leads the 1Data collaboration between K-State and the University of Missouri-Kansas City, a consortium dedicated to cleaning, standardizing, and making preclinical human and animal health data accessible for researchers developing new therapeutics.

His work involves advanced in-silico approaches to assessing drug interactions, drug-disease effects, and residue limits for veterinary medicines, contributing significantly to improving therapeutic safety and efficacy. Dr. Jaber-Douraki is also known for his development of machine learning algorithms that support predictive modeling and decision-making in the context of drug development. His research also includes enhancing knowledge in LLMs by improving the accuracy of semantic extraction from

table PK data and development of machine learning algorithms to predict unestablished PK parameters including clearance and maximum residue limits for veterinary medicines.

**Robbin Koenig, PhD**  
**Rumin8**

Robbin received her PhD in Biochemistry from the University of Missouri - Columbia with a primary research focus in host-microbe interactions. Her graduate and postdoctoral work centered around elucidating the underlying molecular mechanisms of host-microbe interactions in symbiosis and disease in both plant and animal systems.

She started her professional post-graduate career as research scientist at the USDA-ARS in New Orleans and moved into veterinary drug development in 2005 after Hurricane Katrina forced an unexpected change of career path. For eight years she worked for a contract research organization planning and executing efficacy and safety studies for animal drug approval, and developing successful regulatory strategies for clients to gain approval of veterinary drugs in both companion and food animals under FDA-CVM. This was followed by over five years as a team leader and as a Sr. Product Development Manager for Ceva Sante Animale and three years as Global R&D Director for Milk Quality and Animal Health for DeLaval. She has since worked as Director of Development and Regulatory Affairs for the companion animal start-up company Verté Therapeutics, LLC, and is currently Head of Development for Rumin8, a company dedicated to providing methane-reducing solutions to the global cattle industry.

**B. Duncan X. Lascelles, BSc, BVSC, PhD, FRCVS, CertVA, DSAS(ST), DECVS, DACVS**  
**NC State College of Veterinary Medicine**

Dr. Lascelles is the Dr. J. McNeely and Lynne K. DuBose Distinguished Professor of Musculoskeletal Health, and Professor of Translational Pain Research. Since his PhD training at Bristol, UK, he has devoted his professional career to improving our ability to recognize and treat pain in animals. His research program (Translational Research in Pain [TRiP]) develops methods to measure pain associated with spontaneous disease in animals and seeks to understand the underlying neurobiology. Leveraging these measurement techniques in proof of concept studies his work improves our understanding of how to control pain in companion animals, and facilitates analgesic development in human medicine, and discovery of relevant pain signaling mechanisms. He has a particular interest the measurement of movement in relation to pain, the effects of exercise and diet on pain, and in the role of neurotrophins and neurotrophic factors, and downstream signaling, in pain states.

He is director of the Comparative Pain Research and Education Centre (CPREC). He has authored over 230 peer reviewed research papers and reviews, ~400 research abstracts, and ~ 30 book chapters.

**Marilyn Martinez, MS, PhD**  
**Food and Drug Administration**

Marilyn is a Senior Biomedical Research Scientist for the US FDA, CVM. She is also a CLSI voting member, chaired the development of a VICH bioequivalence guidance, is an adjunct professor in the College of Veterinary Medicine, NCSU, and is a Federal Liaison to OrBITO. Marilyn is on the Editorial Board of the JVPT and is an Associated Editor of the AAPS Journal. She received the 2015 Lloyd Davis Lifetime Achievement Award from the AAVPT and is a Fellow of the AAPS and the Controlled Release Society. Marilyn is the FDA PI on a Cooperative Research and Development Agreement with Simcyp for the purpose of expanding the utility of the canine in silico physiologically based pharmacokinetic models and for the development of breed-specific in silico populations. The latter will be invaluable for exploring sources of pharmacokinetic variability in dogs and for supporting the use of the dog as a preclinical species in human drug development. Currently, much of Marilyn's research focuses on the use of in vitro methods for predicting in vivo product performance, extrapolating pharmacokinetic information between dogs and humans, and the use of in silico models for predicting in vivo product performance

**Katrina L. Mealey DVM PhD, DACVIM , DACVCP**  
**College of Veterinary Medicine, Washington State University**

Dr. Katrina Mealey earned a B.S. in Pharmacy from the University of New Mexico, and a DVM from Colorado State University. She then completed a small animal internship at the University of Minnesota. She continued her training at Texas A&M University where she completed two residencies, one in Small Animal Internal Medicine and the other in Veterinary Clinical Pharmacology. She also earned a PhD in pharmacology from Texas A&M University.

Dr. Mealey is currently a Regents Professor and Endowed Chair at Washington State University and is the Founder and Director of the Program in Individualized Medicine (PrIME) in the College of Veterinary Medicine. Because of her strong foundation in pharmacy and pharmacology she pioneered the field of veterinary pharmacogenetics. She holds several patents which have been licensed by 9 different companies on four continents. Her discoveries have dramatically improved drug safety in dogs and cats. She has authored over 100 peer-reviewed research articles and has authored a book (Pharmacotherapeutics for Veterinary Dispensing). She is the recipient of the Pfizer Award for Research Excellence, Lloyd Davis Award, and numerous other national, regional, and university-level awards. Dr. Mealey was elected a Fellow of the U.S. National Academy of Inventors in 2017, a Fellow of the Washington State Academy of Sciences in 2020 and as a Fellow of the American Association for the Advancement of Science in 2021.

**Mark J. Novotny, DVM, MS Pharmacology, PhD, DACVCP**  
**Boehringer Ingelheim Animal Health Global Pharmacovigilance Academic**

Qualifications:

Doctor of Veterinary Medicine (Iowa State University)  
Master's Degree, Pharmacology (University of Missouri)  
Doctor of Philosophy, Cardiovascular Physiology (University of Missouri)  
Diplomate of the American College of Veterinary Clinical Pharmacology

Current Position and Responsibilities:

Principal Scientist, Boehringer Ingelheim Animal Health Global  
Pharmacovigilance (PV)  
Responsibilities include safety surveillance, signal detection, and signal  
management for marketed products; analysis of PV data; benefit-risk analyses and  
risk management activities.

Industry Positions:

30 years of pharmaceutical industry experience in both animal and human health.  
Roles mostly in drug safety and pharmacovigilance, but also exploratory and full  
product development positions.

Companies: Pfizer Animal Health, Pfizer Human Health, Zoetis, Elanco, and  
Boehringer Ingelheim Animal Health.

Academic Position: (prior to Industry)

Assistant/Associate Professor, Pharmacology and Clinical Pharmacology, Atlantic  
Veterinary College, University of Prince Edward Island, Canada

Clinical Practice: (prior to Academia)

Companion Animal Medicine and Surgery (Massachusetts and Rhode Island)

Pre-Professional Activity:

Native of South Dakota

Commercial cow-calf ranch

**Jane Owens, DVM, PhD, Dipl ACVCP**  
**JGO Consulting**

Accomplished scientist with 30 years of multi-disciplinary expertise in all stages of animal health R&D. Demonstrated delivery of commercially successful global products for companion and food animals. Proven success in designing and implementing comprehensive project plans to deliver innovative veterinary products, including small molecules and biotherapeutics using traditional and accelerated approaches. Known for creating collaborative partnerships with contract research organizations, academia, startups, external funding sources and key opinion leaders. Deep expertise in veterinary clinical pharmacology, pharmacokinetics, and development of pre-clinical efficacy models in all major veterinary species. Recognized as a leader who is committed to advancing the science of veterinary pharmacology by developing alliances with academia, government, and industry to solve key problems in drug development.

**Mark Papich, MS, DVM, DACVCP**  
**North Carolina State University College of Veterinary**

Dr. Mark G. Papich is a Professor of Clinical Pharmacology and the Burroughs Wellcome Fund Professorship in Veterinary Pharmacology at North Carolina State University. He is the Supervisor of the Clinical Pharmacology Laboratory in the College of Veterinary Medicine at North Carolina State University. He is a diplomate in the American College of Veterinary Clinical Pharmacology (ACVCP), and has served as president of ACVCP. He has served on various Expert Committees: the Council of Experts, and Chairman for the Veterinary Drugs Expert Committee for the United States Pharmacopeia (USP), and is a current member of the USP Expert Committee on Antibiotics. He is a member of the AVMA Committee on Antibiotics (CoA). He is a member and past Chairholder of the Clinical Laboratory Standards Institute (CLSI) Veterinary Antimicrobial Susceptibility Testing subcommittee (VAST) and chair of CLSI working groups. He served as a member of the Veterinary Medicine Advisory Committee of the Food and Drug Administration (FDA). He has taught veterinary pharmacology for over 30 years.

He has authored/edited eight books on veterinary pharmacology and is one of the editors of the 9th and 10th editions of Veterinary Pharmacology and Therapeutics. He is author or co-author of over 275 research papers published in refereed journals and has authored over 135 book chapters, and review papers (h-index 56). He has several awards including the Zoetis Distinguished Veterinary Teacher Award and the Faculty Award presented to the outstanding teacher by veterinary classes. He was also awarded the Pfizer Award for Research Excellence, the Excellence in Consensus Management by the Clinical and Laboratory Standards Institute (CLSI), the Lloyd E. Davis Award by the AAVPT, the Distinguished Fellow Award from AAVPT, and the Huffman Leadership Award from NC State University. He has also delivered hundreds of presentations on veterinary pharmacology at national and international veterinary meetings, conferences and symposia.

**Jim E Riviere, DVM, PhD, DSc(hon), DACVCP**  
**Distinguished Professor Emeritus**  
**North Carolina State University and Kansas State University**

Jim E Riviere, DVM, PhD is Distinguished Professor Emeritus from North Carolina State University and Kansas State University. He is an elected member - National Academy of Medicine, Fellow - Academy of Toxicological Sciences and Honorary Diplomate - American College of Veterinary Clinical Pharmacology. Dr. Riviere, an NCSU faculty member for 31 years, founded the Center for Chemical Toxicology Research and Pharmacokinetics and directed the Biomathematics Graduate Program, retiring both as Alumni and Burroughs Wellcome Fund Distinguished Professor. At KSU, he was the McDonald Chair of Veterinary Medicine, University Distinguished Professor, Kansas Bioscience Authority Eminent Scholar, Director of the Institute of Computational

Comparative Medicine and co-founder of the KSU/UMKC 1Data Consortium. He co-founded the Food Animal Residue Avoidance and Depletion (FARAD) program, supported by USDA from 1981 to present. Riviere holds six patents, authored/edited 23 books/editions and 640 scholarly publications in pharmacokinetics, toxicology, food safety and nanomaterials. He was Principal Investigator on 21 million dollars of extramural research grants. Honors include the AVMA *Lifetime Excellence in Research Award*, American Pharmaceutical Association *Ebert Prize*, FDA *Harvey W. Wiley Medal*, UNC System *O Max Gardner* award, as well as *Lifetime Achievement Awards* from the American and European Associations of Veterinary Pharmacology and specialty sections of the Society of Toxicology. Riviere earned his BS in biology *summa cum laude* and MS in endocrinology with distinction from Boston College; a DVM and PhD in pharmacology from Purdue University as well as an honorary DSc from Purdue in 2007. Dr. Riviere had 3 children and lives with his wife Nancy of 48 years in Raleigh. He continues to collaborate with colleagues in pharmacokinetic, nanotoxicology and AI research topics as well as FARAD.

**Arno Werners DVM MEd PhD DECVPT  
St. George's University School of Veterinary Medicine**

Professor of veterinary pharmacology and toxicology, Assistant Dean of Academic Programs (as of 1 January 2023), St. George's University, School of Veterinary Medicine. Arno graduated from Utrecht University in 1999, received his PhD and board certification in veterinary pharmacology and toxicology in 2005. He worked part-time in private equine practice from 1999 until 2005. In 2005 he joined to the Equine Science Department at Utrecht where he undertook an equine medicine residency and contributed to the ambulatory service. He left Utrecht University in 2010 and moved to Cambridge University, Department of Veterinary Medicine.

In 2011 he joined St. George's University. He obtained a Master of Education in 2019. Arno has served the European College of Veterinary Pharmacology and Toxicology (ECVPT) in several roles and is currently the ECVPT President.

**Luke Wittenburg, D.V.M, Ph.D, DACVCP  
UC Davis School of Veterinary Medicine**

Dr. Wittenburg received his DVM from Colorado State University in 2004 and went on to complete an internship in small animal medicine and surgery at a private practice in Los Angeles, California. Following this internship, he returned to Fort Collins and began a graduate program in Cancer Biology through the Program in Cell and Molecular Biology at Colorado State University. Luke received his PhD in 2010 and continued at CSU as a post-doctoral researcher in the Cancer Pharmacology Shared Resource while completing the residency in Veterinary Clinical Pharmacology, becoming a diplomat of the American College of Veterinary Clinical Pharmacology in 2013. Luke joined the faculty at University of California, Davis in 2016 where he started the Developmental

Cancer Therapeutics Laboratory, formed the Veterinary Pharmacology Research Core and serves as the Assistant Program Leader for the Comparative Oncology Group at the University of California, Davis Comprehensive Cancer Center. Research in the Developmental Cancer Therapeutics Laboratory currently focuses on the role of transcription factor complex protein interactions in the malignant phenotype of canine and human osteosarcoma, and the pharmacokinetics of chemotherapeutics in veterinary species.