American Academy of Veterinary Pharmacology and Therapeutics

20th Biennial Symposium
40th Anniversary

“The Role of Veterinary Pharmacology in One Health”

Bolger Conference Center, Potomac, MD
May 22-24, 2017
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20th Biennial of the American Academy of Veterinary Pharmacology and Therapeutics
“The Role of Veterinary Pharmacology in One Health”
Bolger Conference Center, Potomac, MD
Scheduled Program

Sunday, May 21, 2017
5:00-7:00 pm Nametag and ticket pickup [in the Hotel Check-In Building]
4:00-8:00 pm Poster set-up [Room 111, Osgood Building]

Monday, May 22, 2017
7:00- Nametag and ticket pickup [outside Stained Glass Ballroom, Osgood Building]
7:30-9:00 am AAVPT Business Meeting [Stained Glass Ballroom, Osgood Building]

SESSION 1: One Health [Stained Glass Ballroom, Osgood Building]
9:00-9:15 am Welcome and State of the Organization
9:15-10:00 Inaugural Tom Powers Keynote: Towards the Delivery of Personalized Medicine in Veterinary Oncology, Chand Khanna
10:00-10:15 Break
10:15-11:00 An Overview of One Health Activities, Bernadette Dunham
11:00-11:45 A One Health Vision on Antimicrobial Resistance, Johanna Fink-Gremmels
11:45-1:00 Lunch [Osgood Dining Room]

SESSION 2: Workshop [Stained Glass Ballroom, Osgood Building]
1:00-4:00 pm ACVCP/AAVPT Workshop on the Future of Clinical Pharmacology and the Clinical Pharmacologist

SESSION 3: Research [Stained Glass Ballroom, Osgood Building]
4:00-4:50 pm Student oral research presentations (Thungrat, Reinhart, Mays, Mzyk, and Visser)
5:00-7:00 pm Wine and Cheese Reception and Poster Session [Room 110/111 Osgood Building]
Tuesday, May 23, 2017

7:30-9:00 am  ACVCP Business Meeting [Stained Glass Ballroom/Osgood Building]

SESSION 4: Population Variability in Animal Health: Potential influence on dose-exposure response relationships or withdrawal times [Stained Glass Ballroom, Osgood Building]

9:00-9:20 am  Overview, Marilyn Martinez
9:25-9:50  Drug metabolism polymorphisms in dogs and cats, Michael Court
9:55-10:20  Age effects, Danielle Mzyk

10:20-10:45  Break

10:45-11:10  Companion animal transporter polymorphisms, Katrina Mealey
11:15-11:40  Food animal transporter polymorphisms, Johanna Fink-Gremmels

11:45-1:15  Lunch [Osgood Dining Room]

1:15-1:40 pm  Modeling and simulation: shifting gears to accelerate understanding of variability in animal health, Jonathan Mochel
1:45-2:10  Top down versus bottom up modeling approaches, Ronette Gehring
2:15-2:40  Modeling and simulation to understand diversity in residues, Jim Riviere
2:45-3:10  Modeling and simulation to improve clinical trials, Tomas Martin-Jimenez

3:10-3:30  Break

3:30-3:55  Understanding differences in dose-exposure relationships as a function of drug formulation and dog breed, Devendra Pade
4:00-4:25  Practical implications to industry, Ludovic Pelligand
4:25-5:00  Moderated panel discussion

5:30-8:30 pm  Veterinary Pharmacology Research Foundation Auction and AAVPT Awards Banquet with 40th Anniversary Celebration [Owney’s Fireplace Lounge/Overland Room, Hotel Check-In Building]

Wednesday, May 24, 2017

SESSION 5: Regulatory and Legislative Issues [Stained Glass Ballroom, Osgood Building]

8:00-8:50 am  Veterinary Drug-Related Legislation in 2017: Where We’re Headed and How We Get There, Ashley Morgan
8:55-9:40  Steven Solomon, Director, FDA Center for Veterinary Medicine
9:40-10:00  FDA Center for Veterinary Medicine Panel

10:00-10:15  Break

10:15-12:00  FDA Center for Veterinary Medicine Panel (continued)
SESSION 1: One Health

INAUGURAL TOM POWERS MEMORIAL KEYNOTE ADDRESS

TOWARDS THE DELIVERY OF PERSONALIZED MEDICINE IN VETERINARY ONCOLOGY
Chand Khanna, DVM, PhD, DACVIM (Onc), DACVP (Hon) 1,2

1Chief Science Officer- Ethos Veterinary Health, Woburn MA; President-Ethos Discovery, Washington DC;
2Professor Translational Genomics Research Institute (TGen), Phoenix, AZ

Foundations of Precision Medicine: The genetic basis of cancer
Cancer is a genetic disease that arises as a consequence of the stepwise accumulation of disruptive mutations in genes that regulate cell life and death. Clonal expansion of cell populations bearing cancer gene mutations fuels the formation of malignant tumors. This genetic model of cancer emerged in the latter 20th century as a product of advances in genetics, evolution, and cancer medicine. Through this mutational process, cancers acquire specific key properties including self-sufficient growth signaling, resistance to growth inhibitory signaling, invasion and metastasis, unlimited replication potential, angiogenic signaling, immune modulation, DNA instability, metabolic dysregulation, and immune evasion. The genetic model and its downstream phenotypes have since been validated in many cancer types and provide a framework for our growing genomic understanding of cancer.

Precision Medicine (PMed) for human and canine oncology
PMed is ushering in a new era in cancer therapy in which clinical and translational value are applied to advances in the genomic analysis of cancer. The discoveries and tools described above have provided new opportunities to tailor cancer therapy to the individual molecular characteristics of a specific cancer in a specific patient to guide diagnosis, prognosis, and treatment selection. In many cases, these genetic alterations can be matched to specific therapeutic agents as a means to uniquely improve outcomes for patients. Tumor samples and matched germline samples (from peripheral blood or cheek swabs) are collected, preserved, and then analyzed for genetic alterations in a core set of cancer genes which are ultimately matched to an individualized therapeutic recommendation.

How Precision Medicine differs from the current practice of oncology
The use of patient-specific information as a means to deliver precision medicine is not new to the treatment of cancer patients. In general through the history of cancer medicine, treatments have been administered in a patient-specific and personalized manner. Even in the modern era, it is the use of molecular data to guide the therapy of specific individuals with cancer is not entirely novel. The use of specific immunohistochemical or cytogenetic markers to guide diagnosis and prognosis has been a critical and routine practice in pathology laboratories for many decades. Further, in some cancers, molecular markers have been used to guide treatment selection as well. For example, in human breast cancer, it has been long-standing practice to define the expression of hormone receptors as a means to deliver specific therapeutics that alter downstream signaling pathways. More recently in veterinary medicine our understanding of the clinical and biological importance of c-kit mutations has directed distinct therapeutic plans for patients with and without such mutations,

Human cancer Precision Medicine
The potential success of Precision Medicine has received widespread recognition in the human field:
Cancer medicine is ultimately aimed at the recommendation of the most effective treatment for an individual patient based on supporting scientific evidence. The use of a PMed approach to cancer diagnosis and therapy may deliver a variety of outcomes related to this goal:

1. Improved outcomes for patients with a specific cancer.
2. Improved outcomes for patients with cancers that are not effectively managed with conventional treatment approaches.
3. Data that would support the grouping of patients in clinical trials that is agnostic to histology (i.e. “basket study designs”).
4. Data that provides an accelerated rationale for a conventional clinical trial of a specific therapy in a specific cancer (i.e. “accelerated reverse directional drug development”).

Although genomic data is expected to dramatically impact the above outcomes, genomic data have been slow to enter the clinic given the complexity of their implementation. One of the first pilot studies incorporating molecular profiling to guide therapy in advanced cancers was published by our collaborators in 2010:


This study faced considerable challenges, but found that 27% of 68 patients treated according to molecular profiling recommendations experienced a longer progression-free survival than during the most recent treatment on which they had progressed. Although perhaps intuitively beneficial to incorporate precise target identification into patient treatment, this approach still faces significant hurdles and it remains to be proven through prospective trials that treatment based on PMed outperforms physician’s choice of treatment. Now, multiple clinical trials incorporating genomics-guided therapy selection are underway to test this very hypothesis with some early results published in recent years. Trial designs include adaptive, basket, and umbrella trials. Adaptive trials such as I-SPY 2 (Investigation of Serial Studies to Predict Your therapeutic response with imaging and molecular analysis) modify treatment arms based on patient response. Basket trials such as the NCI MATCH (Molecular Analysis for Therapy Choice) trial assign patients with diverse cancers to treatment baskets based on mutation status. Umbrella trials incorporate study of multiple drugs in a single disease based on mutation signatures. One such trial - the Stand Up To Cancer and Melanoma Research Alliance Dream Team Clinical Trial is assessing molecularly-guided therapy in non-V600 BRAF metastatic melanoma. This is now an ongoing randomized treatment study. The non-treatment pilot study is described here:


Finally, beyond informing targeted treatment, cancer genomic studies in clinical contexts have also identified diagnostic and predictive biomarkers that have been rapidly commercialized.

Returning clinically relevant and actionable information based on genomic analysis within a window that enables effective treatment selection is a substantial challenge. Notable hurdles include those associated with patient consent, tumor biopsy, sample preservation and transport, nucleic acid extraction and quality control, genomic sequencing infrastructure and platform, data analysis and integration, generation of digestible genomic reports for physicians and scientists alike, and conduct of tumor board review to provide a treatment recommendation. These processes are not yet sufficiently streamlined to enable implementation beyond major academic research centers. Additional hurdles to the implementation of Precision Medicine in the clinic include:

1. Matching biological targets to drugs: A hierarchy of molecular events. Many gene expression (RNA) signatures have been hypothesized to predict treatment response, however few such
alterations have been validated in clinical studies. As such, the simple expression of a cancer
gene or its associated protein is not necessarily sufficient to be considered a highly valuable
target in the biology or therapy of that cancer. Conversely, we believe that mutations in DNA
that comprise the fundamental reducible phenomena behind oncogene activation or tumor
suppressor inactivation are often the gold standard for predictive capacity.

2. **Discrimination of driver versus passenger mutations.** Even though cancer is a fundamentally
genetic disease driven by mutations in cancer genes, not all mutations contribute to cancer
fitness (i.e. not all mutations are cancer “drivers”). Many mutations are “passenger” mutations.
They occur as collateral damage of normal replicative processes and/or mutational processes in
cancer cells, but do not directly contribute to the growth phenotype. It is not always
straightforward to identify the functional impact of a specific mutation, particularly if that
mutation has not been previously extensively characterized. Therefore driver/passenger
discrimination remains a key challenge for individualized genomic analysis.

3. **Context may influence the role of a driver.** In keeping with the above observation, driver
mutations may have variable clinical relevance depending on the presence or absence of other
mutations. For example, activating mutations in the *BRAF* oncogene are common in both
melanoma and colorectal cancer. In melanoma, these mutations confer sensitivity to selective
*BRAF* inhibitors. However, colorectal cancer has proven to be resistant to such drugs due to the
presence of concomitant activation of genes upstream of *BRAF*. Mutation status of single genes
has not always proven to be predictive across cancer types in diverse mutational backgrounds.

4. **Drug matching rules, evidence, report generation, and molecular tumor boards.** The above
considerations all factor into the daunting task of cataloguing rules for matching drugs to specific
aberrations based on various levels of evidence from preclinical and clinical literature. Evidence
levels range from direct evidence of a positive predictive biomarker in prospective randomized
clinical trials to laboratory experiments assessing molecular alterations and drug sensitivity in cell
lines or animal models. An actively curated, literature-linked drug rule database must be
created, maintained, and intersected with genomic reports. Ultimately, these reports must be
automated, precise, and comprehensive enough to enable an expert team of clinicians and
scientists to interpret, discuss, and reach consensus on a treatment recommendation. The
molecular tumor board thereby necessitates a high degree of art, interpretation, and expertise.

An ever-growing array of tests designed to inform diagnostic and treatment decisions in the clinic is
available from more than 100 academic and 50 commercial laboratories. These tests range in scope
from single genes to gene panels, exomes, and even whole genomes. In everyday clinical practice, cost
is still prohibitive and the expertise and infrastructure that are required to bring them to bear on patient
care are also largely lacking. Finally, more comprehensive data showing improvements in genomics-
correlated clinical outcomes is needed to support the use of these tests and of off-label drug use.

**The path to PMed for canine cancer patients**

Although much work remains to be done to chart the genomic landscapes of canine cancers, the
precision medicine approach is nonetheless poised to make a dramatic impact on the care of canine
cancer patients. Indeed, we have published on the clinical feasibility of this approach in dogs:

*Paoloni M, et al. Prospective molecular profiling of canine cancers provides a clinically relevant
comparative model for evaluating personalized medicine (PMed) trials. PLoSOne. 2014 Mar
17;9(3)e90028.*
Precision medicine now represents a cutting edge opportunity in veterinary cancer care. In fact, not only would this approach make great headway in the care of canine cancer patients, but given the unique aspects of naturally occurring cancer in pet dogs as a comparative cancer model for humans, the veterinary profession on the whole may be able to provide key data validating this model and refining its implementation for human medicine, furthermore this approach to cancer medicine is more naturally aligned with the veterinary approach to medicine (the “what matters”; communicative approach) rather than the human approach to medicine (“what is the matter”; algorithmic approach).

As a means to change the biology of an important canine cancer problem, we have initiated a research agenda that will deliver personalized medicine for the canine cancer hemangiosarcoma through prospective clinical trials.

Acknowledgement: The lecture notes and the associated presentation were developed with input and assistance of Dr. Will Hendricks at TGen, and Drs. Fineman and Richter at Ethos Veterinary Health.
AN OVERVIEW OF ONE HEALTH ACTIVITIES
Bernadette Dunham, D.V.M., Ph.D.
Milken Institute School of Public Health

One Health is defined as the collaborative effort of multiple disciplines – working locally, nationally, and globally – to attain optimal health for people, animals, and our environment. Basically, one health links the well-being of humans, animals and the ecosystem. Today’s presentation will highlight a number of one health activities.

Today we face a number of global challenges such as emerging and re-emerging infectious diseases; climate change; food security issues (availability of safe and nutritious food); access to safe and abundant water supplies; antimicrobial resistance; and obesity. Worldwide, nearly 75% of all emerging human infectious diseases in the past three decades have originated in animals. Climate change, increased CO\textsubscript{2} levels, land-use changes, resource scarcity, decreased biodiversity, loss of pollinators, dams and irrigation projects, air and water pollution, and encroachment into wildlife habitat are just a few of the items impacting the ecosystem which in turn affects the health of humans and animals. Moreover, the world population is projected to grow from 7.4 billion in 2016 to 9 billion by 2050, further increasing humanity’s ecological footprint.

To provide adequate healthcare, safe food and safe water for the growing global population, a collaborative and trans-disciplinary approach is needed (e.g. agricultural scientists, anthropologists, economists, ecologists, educators, engineers, entomologists, epidemiologists, hydrologists, microbiologists, nutritionists, physicians, policy makers, public health professionals, sociologists, and veterinarians) where we work together to solve issues of mutual concern.

There are three major One Health organizations that serve as great resources for educational materials, news and ongoing research: the One Health Initiative\textsuperscript{2} the One Health Commission\textsuperscript{3} and the One Health Platform\textsuperscript{4}.

One of the most recent arthropod-borne infection that exemplifies a One Health approach is the Zika virus\textsuperscript{5}. It brings together entomologists, physicians, veterinarians, virologists, wild life biologists, environmental experts, universities, governments, public health organizations, world health organizations, just to mention a few, all seeking to help address the following needs:

1. Zika virus infection is usually asymptomatic or causes mild illness (e.g. fever, rash, muscle/joint pain), however, the Centers for Disease Control (CDC) has recently concluded that Zika virus infection during pregnancy can cause microcephaly and other severe fetal brain defects. 2. Commercial vaccines and specific antiviral drug treatment for Zika virus infection are needed. Funding for basic research, along with vaccine and drug development is required. 3. Diagnostic tests for Zika virus (e.g. blood, urine or saliva samples) need to be developed and then approved by the U.S. Food and Drug Administration (FDA). 4. Mosquito (\textit{Aedes} genus) vector control needs focused intervention (e.g. removal of water-containing sources; insecticide sprays; utilizing genetic engineering mosquitoes to suppress the mosquito population) and risk communication/education to help the public avoid mosquito exposure. 5. Enhanced surveillance systems are needed. Here, we can; take advantage of various smartphone apps to assist with collecting and analyzing data that can be used to develop public health strategies. 6. Determining whether there are non-human reservoirs for Zika virus needs to be established; studying the viral strains may help explain why the virus has demonstrated the capacity to spread exponentially in the human population in the Americas. 7. Medical care of new born infants with microcephaly is needed which means assessing the medical infrastructure at local and national levels; financial commitment; government engagement; and policy development at local, national, international levels.

Often we forget that animals are impacted, in similar ways as are humans, from environmental hazards. Take for example the case of lead in the water during the Flint Michigan water crisis\textsuperscript{6} of 2014. Using a
One Health approach, blood samples from pet dogs can be tested to monitor for a variety of hazardous metals such as lead, copper, mercury, iron and zinc to help serve as sentinels to guard against the poisoning of children.

Climate change has led to increased global temperatures which has led to melting glaciers and ice fields; rising sea levels; coastal flooding; more severe storms; more wild fires; more droughts; more red tide alae blooms; and worsened air quality (ozone, particulate matter and higher pollen counts). The encouraging news is that 195 countries adopted a global climate deal to limit global warming to less than 2°C (Paris Climate Conference in 12-12-2015; ratified in 10-7-2016)\(^7\).

In the USA, the warmer, shorter winters expand tick activity earlier and expand their geographical locations northward. Such is the case with the Ixodes sp. ticks that transmit the spirochete, Borrelia burgdorferi, the causative agent of Lyme disease, which, since 1995, is on the rise, as per the CDC\(^8\).

If we turn to the marine life we find similar indicators of harm related to climate change: the coral reef ecosystems\(^9\) are threatened by oceanic acidification due to increased levels of CO\(_2\), rising sea surface temperatures, sea level rise, and increased storm intensity and currents. Fibropapillomatosis is increasing in the Green Sea turtles\(^10\) where there is a strong link between this disease and the environmental health of the coastal habitat. Sea turtles are often considered sentinels of ecosystem health.

Moreover, there has been a loss of pollinators including honey bees – our Nation’s beekeepers lost 44% of bee colonies\(^11\) in 2015-2016 where a variety of factors may be the cause, such as pesticides, Nosema (a disease causing fungus), the Varroa mite, and changing land use patterns; and bats – White-nose Syndrome\(^12\) (caused by the fungus Pseudogymnoascus destructans, transported to N. America from Eurasia). The disease is estimated to have killed over six million bats in eastern North America since 2006, and can kill up to 100% of bats in a colony during hibernation.

Taking a look at translational biology, there is much to be learned from animals that can benefit human health. The Institute of Medicine (IOM), now the National Academy of Medicine, held a workshop in June 2015 entitled the The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research\(^13\) to examine the rationale and potential for an integrated comparative clinical trial approach to cancer drug development. Many canine tumors share similarities with human cancers in histologic appearance, tumor genetics, biologic behavior, molecular targets, therapeutic response, heterogeneity, acquired resistance, recurrence, and metastasis. Scottish Terriers are 19 more times more likely to develop bladder cancer (Transitional Cell Carcinoma (TCC) – a BRAF gene mutation) than the average dog breed, accounting for 2% of all canine tumors and it can affect up to 20,000 pets each year. This rate is similar to that seen in humans with TCC and they also have the same BRAF mutation. In the case of osteosarcomas, the gene expression profiles for canine and human osteosarcomas are almost indistinguishable, suggesting that findings from clinical drug trials in dogs would be informative for human patients, a win on both human patients and our pets.

The National Cancer Institute (NCI) followed up on the IOM workshop by funding eight supplements to the NCI-Designated Cancer Centers and Veterinary Medical Colleges, for P30 (Center Core Grants) in the fall of 2016. Cancers in these studies included bladder, mammary, melanoma, B-cell lymphoma, osteosarcoma, and glioma.

Building on the success of the IOM workshop, a symposium entitled Craniofacial Disorders and Solutions in Man and Animals, took place in November 2016 at the University of California - Los Angeles campus. Craniofacial reconstruction through regenerative technology benefits animals and people. For example, dogs may develop a malignant tumor of the mandible requiring a mandibulectomy or in the case of trauma, such as a car accident, they may need reconstructive surgery to restore function. FDA has approved two spinal fusion products for use in people consisting of recombinant human bone...
morphogenetic proteins (rh-BMPs) which are growth factors that help induce formation of bone and cartilage. Using titanium locking plates as a scaffold, rh-BMPs are combined with a collagen and calcium compression resistant matrix\(^4\) to achieve predictable and timely bone regeneration/reconstruction of the jaw in the dog, further demonstrating a link between human and animal health.

Another hot topic of global interest and an excellent example of One Health is antimicrobial resistance (AMR). Although we thought we had the magic bullet when Sir Alexander Fleming discovered penicillin, he cautioned that “resistance is a natural counterpart to antibiotics” and Louis Pasteur added that “the microbes will have the last word”. It would appear that both were correct because today we are facing a world where the microbes have indeed developed multiple pathways of resistance to antibiotics and there is little in the pipeline of new antibiotics. The need for everyone to become stewards of these important antibiotics is quintessential. A national strategy to combat antibiotic resistant bacteria laid out a One Health approach, as did the World Health Organization (WHO) – the World Organization for Animal Health (OIE) - the Food and Agriculture Organization (FAO) when they embraced the 2015 Global Action Plan on AMR\(^5\). In September of 2016 the United Nations\(^6\) also embraced the Global Action Plan stating they “Support a multi-sectoral and One Health approach to address antimicrobial resistance...”

By way of an example, and to further exemplify the engagement at the State level, the Minnesota Department of Health developed a One Health Antibiotic Stewardship Collaborative Five-Year Strategic Plan\(^7\). They developed human and animal antibiograms to serve as valuable tools in guiding therapy choices. It is quintessential that we take a One Health approach using global genomic surveillance data to enable our understanding of resistant microbial epidemiology and ecology.

As more and more examples of One Health in action are gathered, it behooves us to pass these along to others and encourage new success stories and experiences to be documented. By way of example the Association of American Veterinary Medical Colleges (AAVMC), the Association for Prevention Teaching and Research (APTR) and the Healthy People Curriculum Task Force (HPCTF) through the One Health Inter-professional Education Initiative developed 15 case studies\(^8\) for integration into degree programs of health profession curriculums.

Each one of us can embrace a One Health approach to issues of mutual concern by first, seeking to understand, then reaching out to other disciplines to “bring the needed expertise to the table” in a collaborative effort to address the health needs of animals, humans and our environment more efficiently, and often with an innovative approach not previously considered.

Celebrate the annual One Health Day on November 3rd - *Promoting efforts around the world to bring together all human, animal, plant and environmental health disciplines.*

References:
\[1.\] American Veterinary Medical Association One Health Initiative Task Force 2008. [https://www.avma.org/KB/Resources/Reference/Pages/One-Health94.aspx](https://www.avma.org/KB/Resources/Reference/Pages/One-Health94.aspx)
\[3.\] One Health Commission. [https://www.onehealthcommission.org](https://www.onehealthcommission.org)
A One Health Vision on Antimicrobial Resistance
Johanna Fink-Gremmels, DVM, PhD, Dip ECVPT
Utrecht University, The Netherlands
SESSION 2: Workshop

ACVCP/AAVPT Workshop on the Future of Clinical Pharmacology and the Clinical Pharmacologist

1:00-1:10  Introduction to the Workshop
1:10-1:40  Breakout session #1
1:40-1:55  Report back and discussion
2:00-2:30  Breakout session #2
2:30-2:45  Report back and discussion
2:45-3:00  BREAK
3:00-3:30  Breakout session #3
3:30-3:45  Report back and discussion
3:45-4:00  Wrap-up: summarize and plan next steps
SESSION 3: Research

Oral Presentations

[Presented by graduate students who are eligible for the ACVCP/AAVPT Resident/Graduate Student Research Award]


4:10  A single nucleotide polymorphism in the cytochrome b5 reductase gene is associated with sulfonamide hypersensitivity and is overrepresented in Doberman Pinschers. Jennifer M. Reinhart.

4:20  Drug Testing in Livestock Show Animals. Travis Mays.


Pharmacokinetics of a selamectin and sarolaner topical combination parasiticide in cats

Wendy T. Collard, Ann E. Fielder, Steven P. Lesman, Vickie L. King, and Dawn A. Merritt
Zoetis, Inc., Veterinary Medicine Research and Development, Kalamazoo, MI 49007 US

The selamectin and sarolaner combination is a monthly, topical, broad spectrum parasiticide combining the endectocide and heartworm activity of selamectin with the ectoparasiticide activity of sarolaner for parasite control in cats. The pharmacokinetics and ADME of sarolaner and selamectin were characterized in the cat.

In cats, both sarolaner and selamectin were well absorbed following topical administration with bioavailability mean values of 57.9% and 40.5%, respectively. Both compounds were also low clearance compounds with the clearance of sarolaner and selamectin less than 1% of liver blood flow in cats. In cats the primary route of elimination for selamectin was via the feces, with the majority excreted as parent selamectin. The primary route of elimination for sarolaner was biliary elimination of parent sarolaner, with contributions by metabolic clearance. The decline of sarolaner drug-related residue concentrations from tissues and biofluids was consistent with the plasma elimination half-life. The half-lives of sarolaner and selamectin are long, 40 and 13 days respectively, which allows for efficacy following monthly dosing. Accumulation of sarolaner and selamectin following multiple monthly administrations was observed, with steady-state levels achieved following the fourth dose for sarolaner and following the second dose for selamectin. The accumulation was acceptable as the safety of the combination was evaluated following 6 monthly doses. Selamectin pharmacokinetics following topical administration of the standalone selamectin (Revolution®/Stronghold®) product and the selamectin sarolaner combination product were comparable based on the similar Cmax, AUC and t1/2 values. Therefore, there was no indication that sarolaner negatively impacts (i.e. decreases) the selamectin exposure.

Keywords: Pharmacokinetics, ADME, selamectin, sarolaner, cat
Meloxicam Residues in Eggs

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Keywords: Meloxicam, NSAID, analgesia, residues, eggs

One Health is the integrative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment. The importance of One Health is highlighted by many factors in our world today: including vigilant protection of our food supplies. With the increasing popularity of backyard poultry ownership, veterinarians are faced with how to treat these animals with regard to drug withdrawal times for egg consumption. A recent review describes allowable medications for use in egg-laying poultry; however, few drugs have recommended doses or withdrawal times for use in laying hens. Meloxicam is an NSAID that is commonly used in avian medicine. A commercially available liquid form is readily available and is easily administered to birds. A recent publication reported that the Food Animal Residue Avoidance Databank received more requests for egg withdrawal intervals for hens following meloxicam administration than for any other drug. In the study reported herein, we determined egg concentrations of meloxicam following a single oral dose and following oral dosing at 1 mg/kg Q12H for a total of 9 doses (5 days). Meloxicam was detected in egg whites (n = 30) up to 4 days and in egg yolks (n = 37) up to 8 days after single dosing. While drug was detected in egg whites (n = 46) up to 3 days and in egg yolks (n = 46) up to 8 days after multiple doses. Based on these results a 2-week withdrawal time should be adequate to avoid drug residues in eggs meant for consumption.
Florfenicol concentrations in different gastro-intestinal segments of pigs, after oral and intramuscular treatments

Joren De Smet, PharmD, Siska Croubels, PharmD, PhD, Patrick De Backer, DVM, PhD, DECVPT, Mathias Devreese, DVM, PhD
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Keywords: florfenicol, intestinal concentration, pigs, microbiota

The administration route and dose of antimicrobial drugs can have an impact on drug concentrations in the gastro-intestinal tract (GIT) and subsequently have a different influence on resistance selection in the gut microbiota.

The aim of present study was to evaluate intestinal concentrations of florfenicol (FF) after oral or intramuscular administration to pigs, using conventional dosing (leaflet) as well as over- and under dosing. Thirty-six pigs (12-week-old) were divided in six different groups. FF was given orally (5 or 10 mg/kg bodyweight (BW) once daily by oral gavage during 5 days in group 1 and 2, respectively; or via medicated feed during 5 days in group 3 and 4, respectively). Animals of group 5 and 6 received a total of two intramuscular (IM) administrations (15 or 30 mg/kg BW), with 48-hour-interval. Blood and manure were collected at different time points during treatment. Ten hours after the last FF administration, animals were euthanized and content of different intestinal segments (duodenum, jejunum, ileum, cecum, colon and rectum) was collected and analyzed for FF.

The results demonstrated substantial concentrations of FF in the GIT, remarkably independent of administration route (range 20 – 300 µg/g). There is a tendency towards higher FF concentrations in the proximal segments and lower concentrations in the distal segments. This pattern is to be expected after oral administration, for FF has high oral bioavailability in pigs. On the other hand, high intestinal FF concentrations after IM administrations were unexpected since FF is reported to be mainly renally excreted in pigs.

Acknowledgement
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Population pharmacokinetics opens new perspectives for pharmacokinetic studies in small and exotic avian species: the case of celecoxib, mavacoxib and meloxicam in cockatiels (*Nymphicus hollandicus*)

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**Keywords:** Celecoxib, Cockatiel, Mavacoxib, Meloxicam, Pharmacokinetics

In general, pharmacokinetic (PK) studies require structured sampling time schedules and frequent manipulation of the animals. These manipulations can cause a significant degree of distress. Sparse sampling in combination with nonlinear mixed effects (NLME) modeling gives the possibility to obtain robust estimates of PK parameters while minimizing distress and blood loss, which is of pivotal importance in small bird species. The objective is to describe the PK of selected NSAIDs in cockatiels using sparse plasma sampling and NLME modeling.

PK parameters and absolute oral bioavailability expressed as percentage (F%) of celecoxib (10 mg/kg BW), mavacoxib (4 mg/kg BW) and meloxicam (1 mg/kg BW) were determined following single oral and intravenous administration to 90 cockatiels (*Nymphicus hollandicus*) in total. The drugs were quantified in plasma by liquid chromatography-tandem mass spectrometry. Data were processed using the NLME approach.

In contrast to celecoxib ($T_{1/2\text{el}}= 0.88$ h) and meloxicam ($T_{1/2\text{el}}= 0.90$ h), mavacoxib has a prolonged elimination half-life ($T_{1/2\text{el}}= 135$ h) following oral administration of a commercial formulation. Complete oral absorption was observed following oral administration of celecoxib (F% = 110%) and mavacoxib (F% = 113%). In contrast, the F of meloxicam was low (F% = 11%). Based on the presented results, a less frequent dosing of mavacoxib is proposed compared to celecoxib and meloxicam. In conclusion, NLME analysis is a valuable tool for PK studies in small avian species.

**Acknowledgements**

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Impact of synthetic canine cerumen on the *in vitro* auricular skin penetration of florfenicol, terbinafine and betamethasone acetate in dogs.

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**Keywords**: Skin penetration, skin absorption, OSURNIA, synthetic canine cerumen

This study was designed to determine the skin pharmacokinetics of florfenicol, terbinafine and betamethasone acetate (OSURNIA) through dog auricular skin under the impact of synthetic canine cerumen.

Dogs with no visible signs for otitis externa qualified for this study. Ear skin of three female (status unknown) and three male neutered shelter dogs of mixed breeds, weighing ~15-30 kg and about ~1-5 years of age was taken. The skin distal to the ear canal was prepared for Bronaugh two-compartment teflon flow-through diffusion cell systems to evaluate the penetration of OSURNIA over 24 h.

Radiolabeled $^{14}$C-terbinafine hydrochloride and $^{3}$H-betamethasone acetate were added to OSURNIA gel to determine dermal penetration and skin distribution. Absorption of florfenicol was determined using HPLC-UV. Additionally, the effect of synthetic canine cerumen (SCC) was studied.

*In vitro* absorption through the auricular skin of dogs of the three drugs in OSURNIA was low during the 24 h experiment. The highest absorption in percentage of the dose was seen with 0.33 % (±0.07) $^{3}$H-betamethasone acetate, followed by 0.07 % (± 0.03) florfenicol and 0.06 % (± 0.01) $^{14}$C-terbinafine hydrochloride. The absorption profiles show no impact of SCC on skin absorption in all three components or on skin distribution of $^{3}$H-betamethasone acetate and $^{14}$C-terbinafine hydrochloride. *In vitro*, $^{3}$H-betamethasone acetate, $^{14}$C-terbinafine hydrochloride and florfenicol were all absorbed through healthy auricular skin within the first 24 h. SCC has a minor impact on dermal absorption of OSURNIA *in vitro*, but may serve as a temporary reservoir that prolongs the release of drugs.
POPULATION PHARMACOKINETIC MODELING OF THE GLOMERULAR FILTRATION RATE IN GROWING PIGLETS USING IOHEXOL

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Keywords: Piglet, glomerular filtration rate, iohexol, population pharmacokinetic modeling, animal model

ABSTRACT
Development of appropriate animal models that take growth and maturation into account is pivotal for pediatric preclinical pharmacokinetic (PK) research. To determine if the pig (Landrace x Large White) is such a potential animal model, the ontogeny of the different elimination processes need to be unraveled. In this study, the glomerular filtration rate (GFR) was determined and correlated with GFR data obtained in humans [1]. Iohexol (Omnipaque®, 64.7 mg/kg BW) was administered to piglets of four different age categories (8 days and 7 weeks: 16♂/group, 4 weeks and 6 months: 8♂/group [2]). Plasma concentrations were determined using a validated HPLC-UV method. Nonlinear mixed-effects modeling was conducted using Phoenix NLME® to determine the GFR based on iohexol clearance. The iohexol data were best described using a two-compartmental model with first order elimination. Body surface area (BSA determined by CT scans analyzed with VGStudioMax®) was included as covariate on volume of distribution and total body clearance. The population estimate of the GFR was 74.89 mL/min/m². The GFR for the individual in the different age groups (mean ± SD) was 41.59±16.98, 64.74±10.87, 99.00±21.69, 121.24±20.97 mL/min/m² for the 8 days, 4/7 weeks and 6 months old piglets, respectively. Iohexol plasma concentration data is best described using a two-compartmental model in pigs, with BSA as covariate. The GFR values obtained in the current study were comparable to humans. Therefore, the pig could be a convenient juvenile animal model for studying the GFR in the pediatric subpopulation, and to evaluate the PK of renally excreted drugs.

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Aspects in controlled-release dosage forms in veterinary medicine

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Early development of controlled-release drug delivery systems was aimed at serving the challenges of human medicine. Around the mid-1970s, the technology of controlled-release dosage form (CRDF) began to be applied for veterinary medicine purposes. The development of CRDF is highly desirable, from both a convenience and a compliance perspective. One of the biggest advantages of such formulations over the conventional ones is their ability to release a drug at a pre-prescribed rate, leading to relatively constant and stable serum concentrations. Another benefit is their ability to administer medications in infrequent mode. The use of CRDFs reduces adverse affects and thereby assists in optimizing therapy. During recent years, our team developed and evaluated several kinds of CRDFs based on a drug-delivery system producing a polymeric matrix for various indications in animals. These include parenteral controlled-release antibiotic formulation models in goats, pigs, calves, dogs, pigeons, and parrots; a topical sustained release varnish for treatment of dental disorders in dogs and kangaroos; a topical sustained release formulation for udder health in dairy cows; a gastro-retentive dosage form (GRDF) in dogs, and coated catheters with a sustained release varnish for prevention of urinary tract infections in dogs. In many of these trials, by using a single administration, we achieved the ability to provide a constant serum drug level for several days that is higher than the MIC. To summarize, there appears to be enormous potential for controlled-release drugs for many animal species as well as for human beings.

Keywords: Veterinary Medicine, Controlled-Release, Drugs
Modeling of Medicated Food Intake in Swine
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Keywords: Modeling and Simulation, Population Variability, Medicated Feed, Swine

Medicated feeds are a common method for administering drugs to farm animals. The concentration of drug administered in feed is typically based upon the targeted dose and assumptions regarding average daily feed intake. Such estimates need to account for the sources of variability in food intake, including pig-specific variables (e.g., inherent behaviors, body weight, age), pen variables (e.g., pen, feeder design), barn variables (e.g., barn density, stocking protocol, air quality), or farm protocols (which will influence the selection of breed, gender, and food materials). Each of these factors can influence the magnitude and pattern of food intake within and between animals, on a farm and between farms. As a result, this method of drug delivery leads to variability in the exact dosage received by the individual animal at any given point in time, rendering it important to develop models that can describe within- and between-farm variability in individual feed intake. Which sources of variability are the primary determinants of population variability in feed intake can be explored in this model.

We will provide a diagrammatic presentation of the model developed to date with the hope that it will stimulate discussions, thereby leading to further model refinement. Ultimately this feeding behavior model will be connected to population pharmacokinetic models to predict variability in drug exposure in swine.
Modeling Medicated Feed Intake in Swine
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2017 AAVPT Biennial Symposium

This handout is an accompaniment to the poster, Modeling Medicated Feed Intake in Swine, and is included in the 2017 AAVPT Biennial Symposium Abstract Book as a mechanism for soliciting comments and suggestions for model refinement. Please see accompanying abstract and the poster which will be presented at the 2017 Biennial Symposium. We welcome post-meeting discussions. Please contact Craig.Lewis@fda.hhs.gov with comments or questions.

Diagrammatic Representation of Interacting Factors Influencing Feed Intake in Swine: This is a high-level (left) and more detailed (right) diagrammatic representation of interacting factors influencing feed intake in swine, based on published literature. Swine production systems are composed of individual animals, typically housed in groups within pens which are in turn enclosed within barns. The industry can be further organized by "companies" (including large-scale integrators as well as small-scale independent farmers), which may consist of multiple barns at potentially different geographic locations.
Farm protocols represent the attempt of human management to influence a variety of system factors, and are adjusted based on expectations and measures of outcome success. For our purposes, feed intake is identified as the primary measure of success; the red arrows indicate a feedback loop, where farm protocols indirectly influence feed intake through a number of factors (including animal, dietary, social, and environmental), success is evaluated in the context of expectations, and protocols are potentially adjusted. External influences are identified as an uncharacterized effect on success.

**Overall Objectives**

To use modeling and simulation as a tool for exploring the influence of within- and between farm factors on the intake of medicated feed in swine; and, when combined with the known pharmacokinetic characteristics of the specific compounds administered in medicated feed, to predict the resulting between-swine variability in systemic drug exposure.

**Specific Aims**

- Identify factors known or believed to influence feeding behavior in swine
- Create a hierarchical random effects covariance distribution model using these factors
- Simulate feeding behavior in populations of swine using this covariate model
- Verify the ability of the model to predict concentration-time profiles for drugs administered in medicated feed using oxytetracycline and tiamulin as model compounds (using data previously generated by JRE del Castillo)
- Publish manuscript of methods and results
- Potentially adapt to medicated feeds administered to other food animal species (e.g., cattle, poultry)

**Current List of Factors Known or Suspected to Influence Swine Feeding Behavior**

**Animal factors** (individual-level, although likely correlated at pen and barn level)
- Genetics: categorical, indicating breed composition
- Gender: categorical (barrow, gilt, sow, boar)
- Age: days
- Body weight: kilograms
- Health status: categorical/descriptive
- Physiological status: e.g., pregnancy/lactation

**Social factors** (pen-level, although likely correlated at barn and even company level)
- Group size: number of animals in group

**Dietary factors** (pen-level, although likely to likewise be correlated at the barn and company level)
- Space allocation/stocking density: horizontal surface area per animal in group
- Feeder design/space: linear length (per animal in group)
- Regrouping and restocking protocols: categorical, but linked to parameters allowing simulation of regrouping

- Ingredients: percent by type (e.g., corn, soybean, etc.)
- Additives: e.g., drug; inclusion rate (e.g., g/ton)
- Contaminants: level (e.g., ppm); by specific contaminant
- Nutrient density: percent, by nutrient
- Feed presentation: categorical, indicating method feed is delivered to animals
- Availability of good quality drinking water: binomial (Y/N)

**Environmental Factors** (pen-level, although likely to likewise be correlated at the barn level)
- Air temperature: degrees
- Humidity: percent
- Air circulation: unit volume per unit time
- Radiation: heat from sun or environment
Implications of Canine Cytochrome P450 Oxidoreductase Genetic Polymorphisms in Drug Metabolism

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Two variants in canine cytochrome P450 oxidoreductase (POR), the sole electron donor for all microsomal cytochrome P450 (CYP) enzymes, have recently been discovered in our laboratory resulting in either one (POR-H2) or two (POR-H3) amino acid changes in the coding region of the gene. Breed screens using our Hospital DNA Bank revealed that greyhounds had the highest allele frequency for POR-H3. Due to the necessity of POR for CYP-function, metabolism of xenobiotics and endogenous compounds may be affected by these mutations. The purpose this study is to determine whether POR genetic variants impact CYP-mediated drug metabolism in an isoform-dependent manner and to elucidate how these interactions are mediated. A baculovirus expression vector system was selected for recombinant protein generation using Sf9 insect cells. Wild-type POR-H1, POR-H2 and POR-H3 were independently expressed. The effect of POR-H2 and –H3 variants on intrinsic electron transport activity was assessed through an NADPH-P450 reductase assay using cytochrome c as a surrogate electron acceptor. All expression experiments were repeated at least three independent times. Initial results suggest no significant differences among POR variants in cytochrome c reduction indicating that the mutations may not affect the enzyme’s innate ability to transport electrons. Experiments are ongoing in our laboratory to continue to elucidate how POR variants affect CYP metabolism in an isoform-dependent manner through co-expression with major drug metabolizing CYP enzymes.

Keywords: P450 oxidoreductase, Cytochrome P450, Pharmacogenomics, Recombinant Proteins, Drug Metabolism
A novel, selective HPLC method for the determination of ponazuril concentrations in green turtle (Chelonia mydas) plasma

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Keywords: high-performance liquid chromatography, solid-phase extraction, toltrazuril sulphone, sea turtle, reptile

Ponazuril is a triazine antiprotozoal drug that is approved in the U.S. for the therapy of Sarcocystis neurona infection in horses. A related apicomplexan parasite, Caryospora cheloniae, is associated with severe enteritis and encephalitis in immature wild and farm-raised green turtles (Chelonia mydas) in Australia and Florida. Therefore, an effective therapeutic agent should be both orally absorbed and well-distributed to the central nervous system of green turtles. Since ponazuril is administered to bearded dragons (Pogona spp) with coccidiosis and is broadly active against apicomplexans, we selected ponazuril for assessment in green turtles. Initial HPLC analysis of green turtle plasma revealed large endogenous peaks that co-eluted with ponazuril. Therefore, solid-phase extraction (Oasis HLB, Waters Corp. Milford, MA) cartridges were utilized to remove the interfering compound. The final method used toltrazuril as an internal standard, a SymmetryShield RP18 5µm column (Waters Corp.), and a mobile phase of 0.1% formic acid in 61% of 1:1 acetonitrile:methanol with ultraviolet detection at 255 nm. It was simple, sensitive, and specific in turtle plasma. The limit of quantitation was 0.05 mg/l. The intraday accuracy and CV was 95% and 4% at 0.5 mg/l and 108% and 5% at 25 mg/l, whereas the interday accuracy and CV were 99% and 4% at 0.5 mg/l and 106% and 2% at 25 mg/l, respectively. The method successfully demonstrated that ponazuril was absorbed after oral administration to a green turtle at a dose rate of 50 mg/kg, so appropriate use of ponazuril in this species is worthy of further study.
Drug Testing in Livestock Show Animals

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Keywords: drug testing, analytical chemistry, drug residues

Livestock shows and county fairs utilize drug testing programs to ensure animal welfare and fairness among exhibitors. TVMDL has served as a drug testing laboratory for many programs since 1999. Summarizing test data could provide trends about the evolution of drug testing over the last seventeen years. The authors are not aware of any similar published data on drug testing in livestock show animals.

Drug analysis was performed by various methods over the years, including thin layer chromatography (TLC), enzyme-linked immunosorbent assay (ELISA), gas chromatography – mass spectrometry (GC-MS) and liquid chromatography – mass spectrometry (LC-MS). Sample matrices tested included urine, serum, feces, retina, liver, kidney, and muscle tissue. Animal species included cattle, sheep, goats, pigs, horses, chickens, turkeys and rabbits. More than 30,800 drug tests have been performed on show animals at TVMDL since 1999. The total number of tests performed annually ranged from 154 to 3,507. The mean annual number of tests performed by species was 452 bovine tests, 301 caprine tests, 294 ovine, 468 porcine, 99 chickens and turkeys, 14 equine, and 12 rabbits. The annual percent positive (% POS) rate ranged from approximately one to 16%. The mean % POS from 1999 – 2014 was approximately 3%. In 2015, drug screening was transitioned from TLC and ELISA to LC-MS which significantly increased detection sensitivity. As a result, the mean % POS from 2015 – 2016 was approximately 15%. The most frequently confirmed drugs since 1999 were ractopamine, flunixin, dexamethasone, zilpaterol, sulfamethazine, and caffeine.

*Eligible for ACVCP/AAVPT Resident/Graduate Student Research Award
Comparison of minimum inhibitory concentration of veterinary tetracyclines in broth and serum microdilution

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Keywords: Minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC),
Tetracycline, *Pasterurella multocida*, *Mannhaemia haemolytica*

Tetracycline is commonly used as reference for susceptibility testing before initiating treatment with
another drug from the family (oxytetracycline, doxycycline). This study investigates the differences in MIC
between three tetracyclines and the effect of using serum for the determination of MIC and minimum
bactericidal concentration (MBC) for bovine respiratory pathogens (*Mannhaemia haemolytica* [MH] and
*Pasterurella multocida* [PM] field isolates). Tetracycline, oxytetracycline and doxycycline potencies were
determined using non-standard methodology (adapted from CLSI guidelines) involving five overlapping
sets of two-fold dilution series in cation-adjusted Mueller-Hinton broth and foetal bovine serum. Free drug
MIC and MBC were compared between media and drugs using ANOVA and Tukey post-hoc analysis.
Doxycycline broth MICs (0.18 mcg/mL PM, 0.31 mcg/mL MH) were significantly lower than oxytetracycline
(0.34 mcg/mL PM, 0.35 mcg/mL MH) and tetracycline (0.38 mcg/mL PM, 0.52 mcg/mL MH), except for *M.
haemolytica* MIC in broth (only lower than tetracycline MIC). Doxycycline broth MBCs (0.53 mcg/mL PM,
0.86 mcg/mL MH) were significantly lower than oxytetracycline (1.27 mcg/mL PM, 1.58 mcg/mL MH) and
tetracycline (1.14 mcg/mL PM, 1.38 mcg/mL MH), oxytetracycline MIC for *M. haemolytica* were
significantly lower than tetracycline, regardless of matrix. Serum increased MIC for tetracycline,
oxytetracycline and doxycycline 6.67-, 6.93- and 1.35-fold (p<0.001) for *P. multocida* and 5.46-, 9.38- and
1.15-fold, for *M. haemolytica* respectively. The MBC tetracycline and oxytetracycline were also
significantly higher in serum than in broth. In conclusion, use of a more biologically relevant media could
present an extension to current methods and a more relevant PK/PD target for dosage determination.
The ontogeny of hepatic cytochrome P450 enzymes in conventional pigs using enzyme activity and proteomics
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Keywords: Pig, ontogeny, cytochrome P450, proteomics, enzyme activity

Development of appropriate animal models taking growth and maturation into account is pivotal for pediatric preclinical pharmacokinetic and pharmacodynamic (PK/PD) research. Literature reports have demonstrated a high homology between human and porcine CYP450 enzymes in adults, suggesting the pig as a suited animal model for PK/PD and safety studies [1]. However data regarding the ontogeny of porcine hepatic CYP enzymes are lacking. The in vitro CYP450 enzyme activity of the following probe substrates was measured in microsomes: midazolam, tolbutamide and chlorzoxazone. The microsomes were prepared of each time 16 pigs (8 ♂ and 8 ♀, Hybrid sow x Piétrain boar) aging 2 days, 4 weeks, 8 weeks and 6-7 months. Furthermore, the microsomal protein per gram liver (MPPGL) was determined [2]. In addition to these in vitro activity experiments, the CYP isoenzymes in the same microsomes were determined by high definition data directed analysis (HD-DDA) mass spectrometry. The data analysis was performed using Progenesis QI. The microsomal activity of the three substrates increased with age. Significant sex differences were observed at 8 weeks of age for the three substrates and at 6 months of age for chlorzoxazone. The activity per gram liver, as calculated with the MPPGL, also showed a maturation profile. The increase in microsomal activity is reflected in an increase in CYP450 proteins in the microsomes. A total of 17 CYP isoenzymes was identified from which 10 had 2 or more unique peptides. These results show similar trends with human CYP ontogeny.

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References

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The effect of age on the pharmacokinetics and distribution of tulathromycin in interstitial and pulmonary epithelial lining fluid in calves

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The aim of this study was to determine the influence of age on the pharmacokinetics (PK) and distribution of tulathromycin into the plasma, interstitial fluid (ISF) and pulmonary epithelial lining fluid (PELF) of healthy holstein calves following the administration of a single subcutaneous administration of a 2.5 mg/kg dose of Draxxin™ (tulathromycin). Plasma concentrations were determined using UPLC-MS-MS. The PK parameters associated with the plasma concentration versus time profiles were analyzed via non-linear mixed effect model. PELF concentrations were calculated by a urea dilution assay of the bronchoalveolar lavage fluids. Plasma protein binding was measured using a microcentrifugation system.

The maximum concentrations in the plasma greater in 3-week old calves (1.34 ± 0.45 μg/mL) as compared to that of the 6-month old calves (0.82±0.45 μg/mL). Clearance values (CL/F) were significantly lower in 3-week old calves but the volume of distribution significantly increased in 6 month old calves. A downward trend in the fraction bound to plasma proteins was observed in plasma derived from 6-month old calves (63% to 39% for concentrations ranging from 0.1 to 1.0 μg/mL) but lower and relatively constant fraction bound observed in 3-week old calves (22% - 24% bound at concentrations ranging from 0.1 to 1.0 μg/mL). The older calves maintained higher ISF concentrations throughout the study period compared to those seen in younger calves. An age-associated difference in plasma and ISF concentration time curves are consistent with maturational changes in calf physiology, which results in altered tulathromycin exposure characteristics in the plasma, lungs and ISF.

Keywords: Macrolide, Calves, Age, Pharmacokinetics, Tulathromycin

*Eligible for ACVCP/AAVPT Resident/Graduate Student Research Award
A single nucleotide polymorphism in the cytochrome b₅ reductase gene is associated with sulfonamide hypersensitivity and is overrepresented in Doberman Pinschers

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Doberman Pinschers appear to be predisposed to hypersensitivity reactions to sulfonamide antibiotics; however, the genetic basis for this predisposition is unknown. Cytochrome b₅ reductase (encoded by CYB5R3) is a known detoxification enzyme for sulfonamide antibiotics, and we have previously found a single nucleotide polymorphism (SNP) in CYB5R3 (729A>G) to be significantly over-represented in dogs with sulfonamide hypersensitivity. This variant is predicted to decrease CYB5R3 protein expression. The aim of this study was to determine whether CYB5R3 729G is associated with sulfonamide hypersensitivity in a larger population of dogs, and whether this SNP is overrepresented in Doberman Pinschers relative to other dog breeds. Genomic DNA from dogs hypersensitive (n=24), tolerant (n=20), or naïve (n=60) to sulfonamide antibiotics, along with drug-naïve Doberman Pinschers (n=24), were genotyped for CYB5R3 729A>G. The 729G allele was overrepresented in sulfonamide hypersensitive dogs (allele frequency 0.792) relative to tolerant dogs (0.550; p=0.022). All Doberman Pinschers were homozygous for the 729G allele, and frequencies for the 729G allele and 729GG genotype were significantly higher in drug-naïve Dobermans compared to drug-naïve non-Doberman dogs (1.00 vs. 0.567 and 1.00 vs. 0.417, respectively; p<0.001). These data suggest that the CYB5R3 729G variant may confer genetic risk to sulfonamide hypersensitivity in the general dog population as well as in the Doberman Pinscher breed.

Keywords: pharmacogenetics, pharmacogenomics, idiosyncratic, adverse drug reaction, dog

*Eligible for ACVCP/AAVPT Resident/Graduate Student Research Award
Exercise training normalizes excitability of pre-sympathetic neurons by increasing GABAergic transmission in rats with heart failure

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Sympathetic hyper-activation is a hallmark of heart failure (HF). Recent studies showed that exercise training (ExT) decreases sympathetic nerve activity in HF rats, which may explain the beneficial effects of Ext on HF patients. Here, we investigated the mechanisms of ExT-induced decrease in sympathetic nerve activity in HF rats. We measured electrical activity of the paraventricular nucleus neurons projecting to rostral ventrolateral medulla (PVN-RVLM) using slice patch technique combined with retrograde labeling, and heart rate using telemetry technique. The HF was induced by ligating the left descending coronary artery. Neuronal activity or heart rate variability was recorded at the 8th week after the ligation. The rats were exercised on a motor-driven treadmill for 3 weeks before recording. ExT decreased the firing rate of PVN-RVLM neurons in HF rats (3.40 vs. 1.98 Hz), and increased the frequency of spontaneous IPSCs (1.13 vs. 3.14 Hz) without affecting EPSC. Replacement of Ca²⁺ with Mg²⁺ in recording solution reduced miniature IPSC frequency more in HF-ExT than in HF group (71.4 vs. 40.4%). GABA-A receptor blocker (bicuculline, 20 μM) increased the firing rate more in HF-ExT than in HF group (10.3 vs. 93.0%). ExT also increased the amplitude of circadian fluctuation in heart rate and sympatho-vagal activity in HF rats. Collectively, the results indicate that ExT-induced increase in GABA release normalizes the elevated excitability of the hypothalamic pre-sympathetic neurons and the blunted circadian rhythm in sympatho-vagal balance in HF rats. Our findings newly provide a synaptic mechanism of ExT-induced beneficial effect in HF patients.

Keywords: paraventricular nucleus, slice patch clamp; firing rate; heart rate variability, circadian fluctuation

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Pharmacodynamics and PK-PD modeling of danofloxacin against *Pasteurella multocida* in bovines.

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The objective of this study was to predict rational dosage schedule of danofloxacin (DFL) using PK-PD modeling approach for *Pasteurella multocida* in bovines. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of DFL were determined in Mueller Hinton Broth (MHB) and buffalo calf serum for four isolates of *P. multocida* according to CLSI guidelines, using five overlapping sets of doubling dilutions. The mutant prevention concentration (MPC) was determined in MHB by the method described by Blondeau et al. (2004). *In vitro* time-kill kinetics against *P. multocida* were determined in MHB and serum to generate information on the time course of DFL action, understanding the mode of antibacterial activity (as time-, concentration- or co-dependent in their killing) and determination of PK/PD breakpoints by PK/PD modelling. The ranges of MIC and MBC of DFL in broth were narrow, 0.045-0.065 and 0.060-0.080µg/ml, respectively, for *P. multocida*. In serum, MIC ranged from 0.055-0.70µg/ml and MBC was 0.060-0.090µg/ml. For *P. multocida* the range of MPC was 0.80-1.30µg/ml. *In vitro* time-kill studies demonstrated concentration dependent bactericidal activity of DFL in MHB and serum. The viable count decreased by 3-log colony forming units (cfu)/ml after 1h and 3h of incubation at 2×MIC for isolates of *P. multocida* and viable count was 33 cfu/ml at 4×MIC. PK-PD modelling will be used to determine, AUC\(_{24h}/\text{MIC}\) ratios required for bactericidal action and eradication of bacteria. Based on PK-PD modelling a dosage schedule of DFL will be calculated for bactericidal activity and eradication of *P. multocida* in buffalo species.

Key words: Danofloxacin, Pharmacodynamics, Time-kill kinetics, *Pasteurella multocida*, PK-PD modelling.

Acknowledgements: Authors would like to thank Professor Peter Lees for gifting the drug danofloxacin and Certara for providing the software Phoenix-winnonlin for PK-PD modelling.

References

Exenatide as a Safe and Efficacious Treatment for Laminitis in Horse

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Keywords: Insulin Resistance (IR), Equine Metabolic Syndrome, Hyperinsulinemia, Laminitis

Today the general veterinary public recognizes that “equine metabolic syndrome (EMS)” is a similar disease to the metabolic syndrome in humans. While the onset of the metabolic syndrome in humans is associated with abnormalities in the coronary vessels, horses suffer from increased risk of laminitis, inflammatory condition in tissues of the horses hoof. However, while the manifestation may be different, there is a growing consensus that the underlying causes of metabolic syndrome in humans and horses are similar. Metabolic syndrome is associated with the inability of the organism to effectively use insulin, termed insulin resistance (IR). The aim of this study is to assess safety and efficacy of Exenatide in healthy horses. We hypothesize that Exenatide will decrease IR and as such lead to a decrease in hyperinsulinemia, major risk factor for laminitis. In 6 normal horses (3 mares, three geldings) the current high human dose of Byetta subcutaneous injection of 10 mcg/per dose can be safely used with no adverse effects observed. While this dose translates into much smaller concentration normalized per kg of body weight, it nevertheless showed to be efficacious and resulted in statistically significantly reduction of postprandial insulin secretion by 20% (P=0.034). This study is the first evidence that Exenatide, GLP-1 mimetic, can be safely used in horses. Furthermore, we provide evidence that this dose resulted in decreased postprandial insulin secretion. The observed effect is likely extra-pancreatic related to decreased hepatic IR.
Patterns of Antimicrobial Prescribing Practices for Treatment of *Escherichia coli* Infections in Dogs and Cats in the United States

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To effectively control resistance, medical communities need to monitor and limit antimicrobial use. The objective of this study was to describe patterns of veterinary antimicrobial prescribing behaviors and investigate any associations between MDR infections, antimicrobial use, and clinical outcomes of antimicrobial therapy. A retrospective study was conducted from January 2008 through January 2013 of spontaneous *E. coli* canine and feline infections (n=823) diagnosed in veterinary practices in the US. A questionnaire was sent to veterinarians that had submitted samples with isolates that were subjected to antimicrobial susceptibility testing. Collected information included signalment, history of infection, and antimicrobial information (drug and dosing regimens). Univariate analyses were performed to describe the patterns of antimicrobial use. Risk factors for MDR *E. coli* infections were polymicrobial infections and non-urinary tract infections. Antimicrobials most frequently used and the proportions of isolates resistant to that drug were amoxicillin-clavulanic acid (AMC; 25% [190/760] use, 24% [46/190] resistance), enrofloxacin (22% [170/760] use, 6% [10/170] resistance), 1st generation cephalosporins (9% [68/670] use, 99% [67/38] cephalothin-resistance), and amoxicillin (9% [66/760] use, 21% [14/66] resistance). The proportions of appropriate dosing regimens used were 0.6% of AMC, 23% of enrofloxacin, 26% of 1st generation cephalosporins, and 3.5% of amoxicillin for treatment of urinary tract infections. Proportions of success versus failure were not demonstratively different among drugs except for 1st generation cephalosporins (*P*=0.03). Dose and duration could be related to success only for AMC. Our study suggests that the inappropriate use of antimicrobials is not the only cause of therapeutic failure.

**Keywords**: Antimicrobials, Prescribing, *E. coli*, Infection, Dogs, Cats

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*E. coli* associated urinary tract infections (UTI) that cause varying severities of clinical signs, ranging from absent to severe, are based on the presence of selected virulence factors. In humans, asymptomatic bacteriuria (ABU) is indicated not to use antimicrobial therapy since treatment may lead to multidrug resistant (MDR) infection. The purpose of this study was to characterize *E. coli* from canine UTIs (n=96) based on the relationships between virulence and resistance in terms of phylogenetics, multi-locus sequence typing (MLST), virulence genotype, antimicrobial resistance, and clinical signs. Of the 96 canine *E. coli* UTIs, symptoms were classified as ABU in 19 patients (20%) and symptomatic UTIs in 77 patients (80%). Thirty-five MLSTs were identified with 15 being unknown. The most frequent MLST was a community based strain ST372 (n=25) followed by ST961 (n=7), ST12 (n=5), a global UTI epidemic strain ST131 (n=4). ST372 was represented by 19 non-multidrug resistant (SDR) isolates and 6 MDR isolates. ST131 included 1 SDR and 3 MDR isolates, all carrying the highest number of virulence genes. *pap* genes were most commonly identified among 32 virulence adhesin genes in symptomatic UTIs and *afa/draBC* for ABU. Twenty-three MLSTs (66%; 23/35) in this study have previously been reported in human infections, implying that these MLSTs may be shared with human owners. These results suggest that the complexity of the relationship between virulence and resistance should be taken into consideration before antimicrobial therapy.

**KEY WORDS:** *E. coli*, infection, dogs, virulence, MLST

*Eligible for ACVCP/AAVPT Resident/Graduate Student Research Award*
RNA-Seq comparison of canine and feline cytochrome P450 gene expression across liver, kidney, blood, duodenum and lung

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Cytochrome P450 (CYP) enzymes are important for metabolism of pharmaceuticals. In humans, extensive knowledge regarding CYP impact of drug metabolism and the variation in drug metabolism has led to the development of genetic testing. This extensive knowledge is lacking in canine and feline medicine, with only a few CYP identified in targeted tissues. This study identified CYP in canine and feline and determined the difference in expression between the species. RNA-seq of canine (n=8) and feline (n=4) liver, kidney, duodenum, lung and kidney was mapped to the annotated ENSEMBL canine and feline genome, and unique transcripts quantified. A total of 38 CYP families were identified in canine and 37 CYP families in feline. Pearson correlation in each tissue indicates a strong correlation present in the lung (r=0.98) and blood (r=0.98), a weaker correlation in duodenum (r=0.87) and weakest in liver (r=0.69) and kidney (r=0.68). The highest expressed CYP families in the canine (liver: 2E, 3A, 2C; duodenum: 3A, 2B, 27A) and feline (liver: 2E, 2A, 3A; duodenum: 3A, 2C, 4B), function in drug metabolism. Comparison of lung tissue between canine (2B, 4B, 27A) and feline (2B, 4B, 2F) show a combination of drug metabolism and homeostatic function. Expression in the kidney indicates homeostatic function as prevalent in the feline (4F, 4A, 27A), while canine (4A, 4V, 3A) had a mixture of drug metabolism and homeostatic function. CYP expression in blood varied between canine (4F, 27A, 4V) and feline (4F, 2J, 4V), but all expressed families function in homeostasis.

Keywords: RNA-seq, cytochrome P450, canine, feline

*Eligible for ACVCP/AAVPT Resident/Graduate Student Research Award
Preliminary Population Pharmacokinetics of Meloxicam in Lion (*Panthera leo*), Cheetah (*Acinonyx jubatus*), and Tiger (*Panthera tigris*)

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Nonsteroidal anti-inflammatories (NSAIDS) are a group of drugs commonly used in the treatment of both acute and chronic inflammation and pain in human and veterinary medicine. The most common meloxicam indications in non-domestic felids include control of both acute pain, such as post-operative, as well as chronic pain from degenerative osteoarthritis. Very limited information is available regarding efficacy, safety and adverse events in non-domestic felids. The purpose of this study was to compare and contrast the population pharmacokinetics (PPK) between lion (*Panthera leo*; n=22), cheetah (*Acinonyx jubatus*; n=9) and tiger (*Panthera tigris*; n=6). At their respective zoological institute, each subject received a dose of oral meloxicam (0.1-0.2mg/kg), and up to three blood samples collected at 2-4hrs, 8-12hrs, and 20-24 hours. An appropriate PPK model established based on the AIC and 2-LLC score. In lions, the maximum concentration (Cmax) was 817.9ng/ml at a time (Tmax) of 2.1hr, and a half-life (t1/2) of 5.92hr. In cheetah, Cmax was 1412.14ng/ml at a Tmax of 10.03 hrs, and t1/2 was 8.11hrs. Tiger Cmax was 613.7ng/ml at Tmax of 2hr, and t1/2 was 6.31hr. The absorption in cheetahs appears slower compared to lion and tiger, but they can reach higher therapeutic concentrations. All three species were able to achieve therapeutic concentrations based on the domestic felid pain model. However, cheetahs may take longer to reach therapeutic efficacy due to the prolonged absorption time. This is the first use of PPK and sparse data collection to report pharmacokinetics in non-domestic felids.

**Keywords**: meloxicam, population pharmacokinetic, cheetah, lion, tiger
Registration of Veterinary Medicinal Products under conditional license – differences to EU

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Keywords: Veterinary Medicines Regulation, conditional license

Since 2004 the Minor Use and Minor Species (MUMS) Animal Health Act¹ allowed conditional licenses (CNADA)². This is a very effective way to bring products to market more quickly especially in the area of specific needs and for products that fall under the minor use – minor species (MUMS) categories. Hence further safety and efficacy data in the field can be gathered whilst initially starting to sell the product. While this pathway provides faster and easier access to novel and niche products and promotes the availability of VMPs, thorough marketing including advertising to achieve market penetration is usually not possible. In contrast to the expectations, the significant sales are mostly not reached.

In the European Union (EU) the current legislation of Directive 2001/82/EC³ as amended does not foresee exceptional licenses for limited markets except for some vaccines under emergency use. However, in many countries of the EU national conditional/exceptional licenses are possible. These are not extendable to other Member States (MS) unless the data can be updated to a full dossier. The proposed new regulation⁴ however considers also exceptional licenses applicable for centralised and decentralised procedures for MUMS products. Unfortunately, the implementation of this regulation may be still a few years away. However, with good planning, a full marketing authorisation in the European market may be reached in a similar timeline. Thus, an applicant has to consider carefully which may be the fastest way to reach return of investment.

References:
3. Directive on the Community code relating to veterinary medicinal products as amended (Dir 2001/82/EC)
4. Draft Regulation of the European Parliament and the Council on veterinary medicinal products in the current form
Updated guidance for registration of Veterinary Medicinal Products (VMPs) under MUMS (minor use - minor species) in the European Union

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Keywords: Veterinary Medicines Regulation, MUMS, Minor Use, Minor Species

With effect of 01JUL2017, several revised guidelines for Minor Indication – Minor Species (MUMS) come into force in the European Union (EU). There is a list of species generally classified as major species (cattle, sheep, pig, chicken, salmon, dog, cat). All other animal species are by default, classed as minor species. Respective classification guidance is provided for minor or limited markets in a separate document (EMA/CVMP/388694/2014).

The guideline on quality data requirements for VMP intended for MUMS reflects that where an EU authorised veterinary medicine already exists a full part II dossier (CMC, chemistry, manufacturing and controls) in support of an application to add a minor species to the authorisation is not required.

The guideline for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin are based on regulation (EC) No 470/2009 permitting only very limited scope for reduction of data requirements under MUMS. Nevertheless, there may be scope for data reductions, e.g by use of extrapolation.

The guideline on efficacy and target animal safety (TAS) data requirements for VMPs for MUMS allows for data reduction where this can be justified. Tolerance may be demonstrated in the field and/or based on literature data.

Overall some further clarifications are given with a focus on known substances and products for extension to minor species. However there are no major improvements for new VMPs for MUMS compared to previous guidance. Therefore the impact on availability of VMPs for these categories in the EU is questionable.

References:
1. EMA/CVMP/388694/2014: Classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market
2. EMA/CVMP/QWP/128710/2004-Rev.1: Guideline on quality data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market.
4. EMA/CVMP/EWP/117899/2004–Rev.1: Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market
Pharmacokinetics of mequindox and its marker residue 1,4-bisdesoxymequindox in swine following repeated oral and intramuscular administration: an experimental study coupled with population physiologically based pharmacokinetic modeling

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Mequindox (MEQ) is a quinoxaline-N,N-dioxide antibiotic used in food-producing animals in China. MEQ residue in animal-derived foods is a food safety concern. To establish a quantitative model to simulate the disposition of MEQ and its marker residue 1,4-bisdesoxymequindox (M1), a flow-limited physiologically based pharmacokinetic (PBPK) model was developed in swine. Residue depletion data were collected in swine exposed to MEQ via oral gavage (10 mg/kg) or intramuscular (IM) administration (5 mg/kg) twice daily for 3 consecutive days. The model was calibrated with oral exposure dataset, extrapolated to simulate IM exposure, and further evaluated with published independent data. The model predictions correlated with available swine data well, including M1 concentrations in liver, kidney, muscle, fat and plasma. Monte Carlo analysis was applied to predict times needed for M1 concentrations to fall below the limit of detection (LOD, 5 µg/kg) in the liver for the 99th percentile of the population, which were 32 and 34 days after the 3-day twice daily oral and IM administrations, respectively. This population PBPK model can be used to predict depletion kinetic profiles and tissue residues of MEQ and its marker residue M1 in swine, and as a foundation for scaling to other quinoxaline-N,N-dioxide antibiotics and to other animal species.

Keywords: mequindox, physiologically based pharmacokinetic (PBPK) modeling, swine, food safety, withdrawal period
SESSION 4: Population Variability in Animal Health

Population Variability in Animal Health: Influence on Dose-Exposure-Response Relationships or Withdrawal Times

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There is an increasing effort to understand the many sources of population variability that can influence drug absorption, metabolism, disposition and clearance in veterinary species. This growing interest reflects recognition that this diversity can lead to systemic drug (or drug metabolite) concentrations that are greater or lower than anticipated based upon well-controlled pharmacokinetic (PK) studies. For example, a 17-fold increase in parent compound concentrations (experimental drug) and a 32-fold increase in an intermediary metabolite were observed in those dogs carrying a specific CYP1A2 polymorphism (Kamimura, Arch Toxicol, 2006). Similarly, in an investigation of ivermectin sensitive collies, average S-fexofenadine concentrations (area under the curve from hr zero to last) was more than 10-fold greater in those animals homozygous for the MDR1a mutation as compared to wild type dogs (Meyers et al., submission in progress).

To appreciate the PK diversity that may exist across a population of potential drug product recipients, both endogenous and exogenous variables need to be considered. Exogenous factors include:

• Food effects
• Environment/housing
• Concomitant medications
• Amount of water administered (PO drugs)
• Injection site and volume
• Stress
• Drug formulation

Endogenous factors include:

• Age
• Gender
• Body composition
• Genetic variability in enzyme systems and drug transporter systems
• Disease
• Breed/species idiosyncrasies such as GI transit time, licking behavior, coprophagia)

These are only highlights of the sources of population variability that have been observed across veterinary species.
During the Tuesday AAVPT session, the issue of population variability in animal health will be explored from the perspective of what is known and the tools available to evaluate this variability. Sessions include the following topics:

- Drug metabolism polymorphisms in dogs and cats, Michael Court
- Age effects, Danielle Mzck
- Companion animal transporter polymorphisms, Katrina Mealey
- Food animal transporter polymorphisms, Johanna Fink-Gremmels
- Modeling and simulation: shifting gears to accelerate understanding of variability in animal health, Jonathan Mochel
- Top down versus bottom up modeling approaches, Ronette Gehring
- Modeling and simulation to understand diversity in residues, Jim Riviere
- Modeling and simulation to improve clinical trials, Tomas Martin-Jimenez
- Understanding differences in dose-exposure relationships as a function of drug formulation and dog breed, Devendra Pade
- Practical implications to industry, Ludwig Pelligand

These talks will be summarized for publication as a review article to be submitted to the Journal of Veterinary Pharmacology and Therapeutics. Therefore, separate abstracts for these presentations were not requested from the speakers.
Veterinary Drug-Related Legislation in 2017:
Where We're Headed and How We Get There
Ashley S. Morgan, DVM
American Veterinary Medical Association
May 24, 2017

AVMA Governmental Relations Division
The AVMA’s mission is to lead the profession by advocating for its more than 89,000 member veterinarians and seeks to advance the science and practice of veterinary medicine to improve animal and human health. The AVMA Governmental Relations Division actively promotes the Association’s federal legislative and regulatory priorities, monitors legislative developments, keeps members updated on activities, educates congressional lawmakers and policymakers working for federal agencies, and liaises with strategic partners.

The GRD team, based in Washington, DC, is comprised of a director, three assistant directors/lobbyists, an administrative manager, a communications manager, a program manager, a staff assistant, an administrative assistant, and two consultants – one for lobbying and the other to manage the AVMAPAC.

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- Federal Budget
- Federal Appropriations
- Veterinary Education
- Student Financial aid
- Small Business
- Tax issues
- Veterinary Workforce
- Association issues

- Animal Welfare
- Animal Transportation
- Farm Bill issues
- Zoo & Wildlife issues
- Endangered Species Act
- Aquatic Veterinary Medicine
- Environment, conservation & EP?
- Guardianship and Ownership
- Human Animal Bond

- Animal Health & Research
- Pharmaceuticals & Veterinary Biologics
- Public Health
- Food Safety
- Biotechnology
- Bio- & Agro-terrorism
- Emergency Response
- Homeland Security
Pharmacology Issues in the 115th Congress

Compounding
The AVMA updated its policies on compounding, both the overarching and compounding from bulk ingredients in nonfood and food animals, in June 2013. This was necessary and timely, given the fungal meningitis outbreak in humans in the fall of 2012 and resulting legislative action. The Drug Quality and Security Act (P.L.113-54) was signed into law in Nov. 2013, however it was not intended to change animal drug compounding or impact animal drug compounding in any way.

In Feb. 2014, AVMA established a Task Force on Veterinary Compounding Legislation to develop a legislative proposal pursuant to AVMA’s revised policies on compounding. The Task Force delved into topics of importance to the profession: maintaining office stock, compounding from bulk ingredients, adverse event reporting, and quality assurance. They also considered the role that drug shortages and the preservation of the Food and Drug Administration’s (FDA) approval process play in the access to compounded preparations. The Task Force sent recommendations for legislation to the AVMA Board of Directors’ meeting in June 2016, which were approved. Legal counsel has finalized draft legislative language and it is currently being reviewed by AVMA entities, state veterinary medical associations and allied constituent associations. Once approved by the Board, we hope to have it introduced in the 115th Congress.

FDA published draft guidance for compounding animal drugs from bulk drug substances in May 2015. This notice called for public comment, which closed in mid-Nov 2015. AVMA appreciates the feedback we received from members, allied organizations, and state veterinary medical associations. FDA has informed us that they made changes to the draft guidance after reviewing the comments and publication is forthcoming; there is no known projected date for publication of another draft or finalization of the guidance.

Antimicrobial Resistance & Antimicrobial Use in Food Animals
Legislation has been introduced for a number of the past congresses to limit the use of medically important antimicrobials in food animals. AVMA has fervently opposed previous bills that attempt to restrict veterinarians’ ability to appropriately treat their patients.

Legislation introduced in the 115th Congress:
- H.R. 1587, Preservation of Antibiotics for Medical Treatment Act of 2017
  To amend the Federal Food, Drug, and Cosmetic Act to preserve the effectiveness of medically important antimicrobials used in the treatment of human and animal diseases.
- S. 629, Preventing Antibiotic Resistance Act of 2017
  To amend the Federal Food, Drug, and Cosmetic Act to ensure the safety and effectiveness of medically important antimicrobials approved for use in the prevention, control, and treatment of animal diseases, in order to minimize the development of antibiotic-resistant bacteria.

FDA published a proposed rule to amend its animal drug regulations regarding VFD drugs in December, 2013. FDA published the Final Rule on the Veterinary Feed Directive (VFD) in June 2015 and it went in to effect in January 2017. AVMA has been very engaged with FDA throughout this revision and has recently developed VFD resources related to the new rule.
Former President Obama released an Executive Order on Combating Antibiotic-Resistant Bacteria in Sept. 2014 and called for $1.2 billion in funding for FY 2016 for activities related to antibiotic resistance. The use of antibiotics in food animals is a component of this discussion. AVMA is supportive of new funding for FDA and USDA to implement components of this strategy.

**Coalitions**

**S-FAR - U.S. Stakeholder Forum on Antimicrobial Resistance**

S-FAR is a national partnership convened by the Infectious Diseases Society of America (IDSA). Over 100 national health organizations have joined the partnership to ensure that any U.S. government strategy to address antimicrobial resistance involve sustained and meaningful engagement with non-government experts and stakeholders throughout the policy development and implementation process.

**Animal Agriculture Coalition**

The AAC is comprised of most major animal and animal-related commodity organizations as well as allied organizations representing veterinary medicine, animal science and various livestock or animal agricultural interests in the U.S.
Speakers and panel members from the FDA Center for Veterinary Medicine

OFFICE OF SURVEILLANCE AND COMPLIANCE
Division of Surveillance
   Neal Bataller
   Dorothy McAdams
Division of Compliance
   Eric Nelson
   Dillard Woody
Division of Animal Feeds
   Dragan Momcilovic

OFFICE OF NEW ANIMAL DRUG EVALUATION
Division of Generic Animal Drugs
   Matt Lucia
   Charli Long
   Dave Longstaff
   Gypsi Feeney
   Sharon Ricciardo

Division of Therapeutic Drugs for Non Food Animals
   Steve Fleischer

Division of Production Drugs
   Crystal Groesbeck
   Suzanne Sechen
   Danielle Sholly
   Linda Wilmot

Division of Therapeutic Drugs for Food Animals
   Cindy Burnsteel
   John Mussman

Division of Scientific Support/Biometrics Team

Division of Scientific Support/Clinical Pharmacology Team
   Eden Bermingham
SPEAKER BIOGRAPHIES

Michael Court, BVSc, PhD, DACVAA, is the William R. Jones Endowed Chair in Companion Animal Medicine/Surgery and a researcher in the Program in Individualized Medicine at Washington State University. He is also the director of the Pharmacogenomics Laboratory. Dr. Court’s research focuses on determining how genetics affects the way in which companion animals metabolize medications, with the ultimate goal of improving drug safety and effectiveness. He is the recipient of an NIH Special Emphasis Research Career Award, Ramsey Invited Lectureship, and a Zoetis Award for Research Excellence.

Bernadette Dunham, DVM, PhD, is currently a Visiting Professor with the Milken Institute School of Public Health at George Washington University where her focus is on One Health issues. From 2008-2016 she served as Director of the Center for Veterinary Medicine (CVM) at the U.S. Food and Drug Administration (FDA) where she was responsible for ensuring the safety and effectiveness of animal drugs, and the safety of animal feed, including pet food. Prior to joining FDA in 2002, Dr. Dunham was Assistant Director with the American Veterinary Medical Association's Governmental Relations Division in Washington, D.C; from 1995-2002. She served as Director of Laboratory Animal Medicine and Adjunct Professor of Pharmacology at the State University of New York Health Science Center, Syracuse, N.Y. from 1987-1995. Dr. Dunham received her D.V.M. degree from the Ontario College of Veterinary medicine, University of Guelph, Canada and her Ph.D. from Boston University, MA.

Johanna Fink-Gremmels, Dr.med.vet., PhD, Specialist DPhGT, Dip ECVPT, is qualified as a veterinarian and as a specialist in veterinary pharmacology and toxicology. She is a Diplomate in the ECVPT and senior vice president of EAVPT. She was for several years European partner of Jim Riviere as Editor of JVPT. Next to her academic career at Utrecht University, she served as an expert EU Commission services, including the EFSA (European Food Safety Authority) for more than 2 decades now.

Steven Fleischer, DVM, joined the FDA in 2002. He has worked in premarket review in both the Center for Veterinary Medicine and Center for Biologics Evaluation and Research. He is currently the Director of the Division of Therapeutic Drugs for Non-Food Animals.

Ronette Gehring, BVSc, MMedVet (Pharm), MRCVS, Dipl. ACVCP, is Associate Professor at Kansas State University and Midwest Director of the Food Animal Residue Avoidance Databank. Her research interests lie with the use of mathematical modeling and simulation to optimize therapeutic dosage regimens in veterinary medicine. She is the current president of the AAVPT and one of the founding members of the AHM&S.

Chand Khanna, DVM, PhD, DACVIM (Onc), DACVP (Hon), is the chief science officer Ethos veterinary health, a new national specialty medicine company and president of its non-profit incubator of scientific innovation. He is a credentialed scientist (metastasis biologist), with full tenure as a Senior Investigator at the National Institutes of Health National Cancer Inst., pediatric oncology branch. Dr. Khanna is an active clinician and board certified veterinary oncologist,
**Marilyn Martinez**, PhD, is a Senior Biomedical Research Scientist for the US Food and Drug Administration, Center for Veterinary Medicine (CVM). In addition to her responsibilities at the CVM, her activities and include her role as a voting member of the VAST, Adjunct Professor in the College of Veterinary Medicine, North Carolina State University, Federal Liaison to OrBITO, and is an Associate Editor of the AAPS Journal. She is the recipient of the 2015 Lloyd Davis Lifetime Achievement Award, and is a Fellow of the AAPS and of the Controlled Release Society.

**Tomás Martin-Jiménez**, DVM, PhD, DACVCP, DECVPT, is Associate Professor of Pharmacology at The University of Tennessee. He earned y DVM in University of Madrid, 1987 and my PhD in North Carolina State university in 2000. I have held faculty positions at NCSU, University of Illinois and University of Tennessee. His research interests involve the population modeling and simulation of drug disposition and effect in animals, particularly anticancer and antimicrobials.

**Katrina L. Mealey**, DVM, PhD, DACVIM, DACVCP, is currently a Professor and holds the Richard Ott Endowed Chair at Washington State University and is the Director of the Program in Individualized Medicine in the College of Veterinary Medicine. Her research focuses on the pharmacogenetics of drug transporters. Dr. Mealey was recently elected a Fellow of the National Academy of Inventors.

**Jon Mochel**, DVM, MS, PhD, DECVPT, obtained his DVM from the National Veterinary School of Alfort. He holds several Masters in Pharmacology and Pharmacokinetics and a PhD in PKPD modeling from the University of Leiden (Netherlands). He is a board-certified veterinary pharmacologist and toxicologist, and currently chairs the Education and Residency Committee of the European College of Pharmacology and Toxicology. In 2012, he co-founded the Animal Health Modeling & Simulation (AHM&S) Society, together with Prs. Jim Riviere and Johan Gabrielsson. Dr. Mochel spent several years in the Modeling and Simulation group of Dr. Don Stanski (Novartis) and Thierry Lave (Roche). He is currently an Associate Professor in the Department of Biomedical Sciences at Iowa State University. His research, which falls under the scope of the One Health initiative, pertains to the analysis of clinical data obtained from spontaneous animal models of human diseases to bridge the knowledge gap between experimental models and patients.

**Ashley Morgan**, DVM, has been with the AVMA since August 2008 where she has spent her time, until recently, advocating to Congress and the federal government on public health, animal health, and pharmaceutical issues. In May, Ashley shifted roles and will lead the AVMA’s State Advocacy Division. Prior to joining the AVMA staff, Ashley was in equine practice and completed an AVMA Congressional Science Fellowship in U.S. Senator Richard Burr’s office.

**Danielle Mzyk** is a current DVM/PhD dual degree student at North Carolina State University College of Veterinary Medicine studying ruminant pharmacology and large animal medicine. Her research focuses on pharmacokinetics and drug distribution in dairy calves and is currently a responder for the Food Animal Residue Avoidance Databank. Her primary clinical and research interests revolve around clinical medicine of ruminants with a specific focus on calf health and ruminant pharmacology.
Devendra Pade, PhD, is a Senior Research Scientist at Simcyp-Certara since 2009 and works in the Modelling and Simulation department. He is also part of the Simcyp-FDA,CVM CRADA partnership on the application of canine PBPK models to aid veterinary drug approvals and study drug exposure in dogs. Prior to joining Simcyp, Deven has worked with Watson Pharmaceuticals (now Allergan) on orally inhaled drug products. He received his PhD in Prediction of Oral Drug Absorption and Pre-Clinical Pharmacokinetics from The University of Texas at Austin.

Ludovic Pelligand, Docteur Veterinaire, Cert. VA, Dip. ECVAA, Dip. ECVPT, PgCert(VetEd), FHEA, PhD, MRCVS, is a senior lecturer in Veterinary Clinical pharmacology and anaesthesia in the RVC, London. He graduated from the École Nationale Vétérinaire d'Alfort (Paris, France) in 2001. He then completed an anaesthesia residency at the RVC where he gained his European Diploma of Veterinary Anaesthesia and Anaesthesia in 2006. He gained the European Diploma in Veterinary Pharmacology and Toxicology in 2014. He is developing research programs in pharmacology and pain management (acute and chronic), particularly in the area of pharmacokinetics and mathematical modeling (PK-PD). He is promoting the use of pharmacometrics to help resolve clinical questions at the level of the individual animal or for more global questions, as in the field of antimicrobial use and resistance.

Jim Riviere, DVM, PhD, is presently Emeritus Distinguished Professor at both Kansas State and North Carolina State Universities. He is Editor of the Journal of Veterinary Pharmacology and Therapeutics and was one of the original co-founders of the FARAD program.

Danielle Sholly, MS, PhS, is a reviewer on the Swine and Poultry Drugs Team, Division of Production Drugs. She received her MS and PhD from Purdue University. Dr. Sholly has been with CVM for 8 years and is the lead for the Office of New Animal Drug Evaluation’s Outreach Working Group.

Steven Solomon, DVM, MPH, was appointed Director of the Food and Drug Administration’s Center for Veterinary Medicine in January 2017. Dr. Solomon previously served as the Deputy Associate Commissioner for Regulatory Affairs within the Food and Drug Administration’s Office of Regulatory Affairs. He joined FDA in 1990 as a Veterinary Medical Officer in the Center for Veterinary Medicine, and has served in various policy and leadership positions in the Office of Regulatory Affair’s Office of Enforcement, Office of Regional Operations and as the Assistant Commissioner for Compliance Policy. He also served in the Office of Global Regulatory Operations and Policy. Dr. Solomon has a Doctor of Veterinary Medicine from Ohio State University and a Master’s in Public Health from Johns Hopkins University.
Meeting Registrants

Mahmoud Abouraya, FDA/CVM
Paul Adams, Merck Animal Health
Karin Allenspach, Iowa State University
Elias Awji, FDA/CVM/ONADE
Wolfgang Baeumer, North Carolina State University College of Veterinary Medicine
Ronald Baynes, North Carolina State University College of Veterinary Medicine
Eden Bermingham, FDA/CVM/ONADE
Stephen Bienhoff, AlcheraBio, LLC
Dawn Boothe, Auburn University College of Veterinary Medicine
Joseph Boucher, Zoetis
Tina Burgess, FDA/CVM
Thomas Burnett, Elanco Animal Health
Michela Cantillio, AMATSIGROUP
Alan Chicoine, Veterinary Drugs Directorate / Western College of Veterinary Medicine
Cynthia Cole, Mars Veterinary
Wendy Collard, Zoetis
Michael Court, Washington State University College of Veterinary Medicine
Sherry Cox, University of Tennessee College of Veterinary Medicine
Jennifer Davis, Virginia Maryland Regional College of Veterinary Medicine
Keith DeDonder, Veterinary and Biomedical Research Center, Inc
Jerome del Castillo, Universite de Montreal
Mathias Devreese, Ghent University
Bernadette Dunham, George Washington University Milken Institute School of Public Health
Sarah Ehling, North Carolina State University College of Veterinary Medicine
Virginia Fajt, Texas A&M University College of Veterinary Medicine & Biomedical Sciences
Claire Fellman, Cummings School of Veterinary Medicine, Tufts University
Johanna Fink-Gremmels, Utrecht University
JD Foster, Friendship Hospital for Animals
Joy Rachel Ganchingco, North Carolina State University College of Veterinary Medicine
Ronette Gehring, Kansas State University
Joe Gloyd, Elevate DVM, Inc.
Jonathan Hare, Kingfisher International Inc
Mark Heit, Elanco Animal Health
Kyle Horlen, InCube Labs
Mirja Huhtinen, Research and Development
Rob Hunter, One Medicine Consulting
Chad Johannes, Iowa State University
Carl Johnson, Prairie Diagnostic Services, Inc.
Leslie Kenna, FDA/CVM/ONADE
Chand Khanna, Ethos Veterinary Health
Lindsey Kissell, FDA/CVM/ONADE
Robbin Koenig, Ceva Animal Health LLC
Jeffrey Lakritz, The Ohio State University
Cory Langston, Mississippi State University
Eran Lavy, Koret School of Veterinary Medicine, The Hebrew University of Jerusalem
Anthony Lucas, Dechra
Marilyn Martinez, FDA/CVM
Stephanie Martinez, Washington State University College of Veterinary Medicine
Tomas Martin-Jimenez, University of Tennessee College of Vet Medicine
Beasley Mason, Kindred Biosciences, Inc.
Lara Maxwell, Oklahoma State University
Travis Mays, Texas Veterinary Medical Diagnostic Laboratory
Katrina Mealey, Washington State University College of Veterinary Medicine
Kristen Messenger, NC State College of Veterinary Medicine
Bipin Mistry, FDA/CVM/ONADE
Kemmy Mizinga, Elanco Animal Health
Jonathan Mochel, Iowa State University
Tomislav Modric, FDA/CVM
Ashley Morgan, American Veterinary Medical Association Governmental Relations Division
Ben Moses, Dechra
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Jeff Norris, Midwestern University College of Veterinary Medicine
Jane Owens, Elanco Animal Health
Devendra Pade, Simcyp Certara
Mark Papich, North Carolina State University
S. Craig Parks, Virbac AH
Carly Patterson, Texas A&M University College of Veterinary Medicine & Biomedical Sciences
Ludovic Pelligand, Royal Veterinary College University of London
Melinda Poole O'Banion, KindredBio
Jennifer Reinhart, UW Madison-School of Veterinary Medicine
Jim Riviere
Mary Robinson, University of Pennsylvania
Pan Dong Ryu, Seoul National University College of Veterinary Medicine
Maya Scott-Garrard, Merial
Pritam Sidhu, Kansas State University
Emma Stafford, NC State College of Veterinary Medicine
Darko Stefanovski, School of Veterinary Medicine, University of Pennsylvania
Stephen Sundlof, Kindred Biosciences, Inc.
Emily Sundman, Kindred Biosciences, Inc.
Kamoltip Thungrat, Auburn University
Lisa Troutman, FDA/CVM
Lilly Tsirulnikov, Kingfisher International Inc
Kyle Van Riper, Charles River Laboratories
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Feli Walther, Merck Animal Health
Jessica Wofford, Aratana Therapeutics, Inc
Regina Wolf, Klifovet AG
Dongping Zeng, South China Agricultural University

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