Modern Approaches to Provide Data to Regulatory Agencies

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Major sections of drug approval

- Target animal safety
- Effectiveness
- Human food safety
- Chemistry, Manufacturing, Controls (CMC)
- Environmental assessment

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Target Animal Safety

- To identify any harmful side effects of the drug; and

- To establish a margin of safety for the drug. The margin of safety is usually determined by testing the drug at higher-than-labeled doses for a longer-than-labeled time period in the target animal species. The drug's margin of safety is like a "cushion" or "safety net" to make sure the drug will be safe when it is used in animals that may be sick or sensitive to the drug.

https://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm#Target_Animal_Safety

Target Animal Safety

- 0, 1X, 3X, 5X (8 animals per treatment, 32 animals total)
  - Dogs = HEALTHY Beagles
- 3 times the proposed duration up to a maximum of 90 d
  - longer duration studies may be recommended
- Tissues from all dose groups should be examined grossly and preserved for microscopic evaluation.

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052464.p

Target Animal Safety

- Is this an effective method for evaluating drug safety?
  - Carprofen NADA 141-053
    - 42 day study (48 dogs, 6 groups of 8 dogs)
    - Conclusions: Based on this study, the administration of carprofen was not associated with any clinically significant signs of toxicity when given orally at 1, 3 or 5 times the recommended daily dose for 42 consecutive days and at 10 times the recommended dose for fourteen consecutive days. Carprofen was well tolerated and is not expected to produce signs of toxicity when used as directed.

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052464.p

Target Animal Safety

- Carprofen NADA 141-053
  - 52 week study (72 dogs , 4 groups of 18 dogs)
  - Conclusions: Under the conditions of this study, dose levels of 2 and 7 mg/kg/day of Ro 20-5720 were clinically well tolerated by dogs during one year of treatment. At 25 mg/kg/day (approximately 5.7 times the recommended dose) the only clinical change observed, primarily in males, was an elevation of serum L-alanine aminotransferase. There were no gross necropsy or histologic changes that clearly distinguished treated from control dogs after one year of treatment.

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052464.p

Target Animal Safety

- Carprofen NADA 141-053
  - Extended use study (244 dogs, average duration 19 months (range 14d – 5 yrs)
  - Possible adverse events were reported in approximately 1.3% of the post-treatment evaluations…..the clinical signs most commonly reported were vomiting, lethargy, decreased appetite, diarrhea and increased appetite. One death, due to unexplained causes in a 20-year-old beagle, was listed as a possible adverse event. However, clinical signs did not relate to known signs of NSAID toxicity.

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052464.p

Target Animal Safety

- Carprofen NADA 141-053
  - 364 dogs with therapy at least 14 days
  - Dose from 0 to 25X approved dose
  - No GI ulcerations, GI perforations, hepatopathy, renal failure or death attributed to carprofen
  - Failed to identify GI, renal, hepatic adverse effects of carprofen in dogs

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052464.p

Target Animal Safety

- Is this an appropriate method for evaluating drug safety?
  - Fentanyl transdermal solution NADA 141-337
    - 0, 1, 2, 3X dosage (n=8 / group = 32 dogs) q 4 days for 3 doses
    - Deaths occurred
      - 2 dogs in 2X group; 1 dog 3X group
      - Sedation, hypothermia, bradycardia, anorexia, weight loss (7-11%), dehydration
      - Predictable opioid effects in dogs
      - No interventions (fluid administration, passive or active warming)
      - Deaths not due to opioids per se, but basic patient management
      - Does this predict clinical adverse effects / management?

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052464.p

Major sections of drug approval

- Effectiveness
  - "The drug sponsor must show that the drug works in the target animal species when it is used according to the label. One way for sponsors to prove that the drug is effective is by conducting a field study. "

https://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm#Target_Animal_Safety

Major sections of drug approval

- Effectiveness
  - Efficacy data must have, as a minimum, the following four attributes:
    - The data must be from adequate and well controlled studies
    - The data must demonstrate that the dose response relationship has been determined.
    - The data must be from adequate and well-controlled studies run in more than one location so that any geographical (or environmental) effects can be evaluated.
    - The pivotal data must come from studies in which the proposed dosage form was used

https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/PoliciesProceduresManual/ucm046648.pdf

Current Approaches to Drug Approval

- Where are we?

Current Approaches to Drug Approval

- Where are we?
- Compounding – customized, individual patient-specific medication

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*Quantity price breaks available.

Medication	Strength	Size	Dosage Form	Flavor	Regular Price	Special Price
Doxycycline (as Hyclate)	100mg	100ct	Quad tabs	Chicken	$55.00	$44.00*
Doxycycline (as Hyclate)	100mg	500ct	Quad tabs	Chicken	$237.00	$202.00
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Buprenorphine SR
Injectable

ZooPharm can provide sustained release Buprenorphine HCl by prescription in a proprietary, patent pending, sustained release system.

Buprenorphine SR releases over 72 hours and provides blood levels greater than 1 nanogram/ml in dogs and 0.5 nanogram/ml in cats for post operative analgesia. Buprenorphine SR can be injected subcutaneously through a 22-gauge needle.

Buprenorphine has produced excellent analgesic results in broad clinical applications for cats, dogs, exotic species and laboratory animals. It provides analgesia for management of perioperative / postoperative pain, as well as painful joint injuries, fractures, tissue inflammation due to infection, tissue necrosis and trauma resulting from wounds. Amelioration of postsurgical pain has been substantiated in a variety of species[1]. Due to its long duration of action, it is one of the most widely used opioid analgesics in veterinary clinical practices.[2,3,4]

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Current Approaches to Drug Approval

- Where are we?
- Compounding
- Unapproved drugs

Current Approaches to Drug Approval

- Where are we?
- Compounding
- Unapproved drugs – enforcement discretion

A systematic review of the safety of potassium bromide in dogs

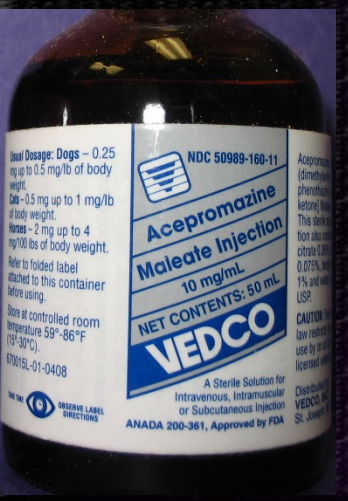
Hope E. Baird-Heinz, DVM; A'ndrea L. Van Schoick, DVM; Francis R. Pelsor, PharmD; D. Lauren Ranivand, MPH; Laura L. Hungerford, DVM, MPH, PhD

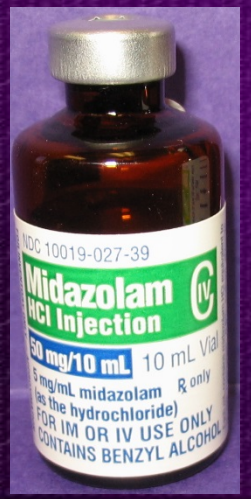
From the Center for Veterinary Medicine, US FDA, 7519 Standish Pl, Rockville, MD 20855 (Baird-Heinz, Van Schoick, Pelsor, Ranivand, Hungerford); and the Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD 21201 (Hungerford). Dr. Baird-Heinz's present address is Veterinary Relief Services, 3308 Westclarke Dr, Plano, TX 75093.

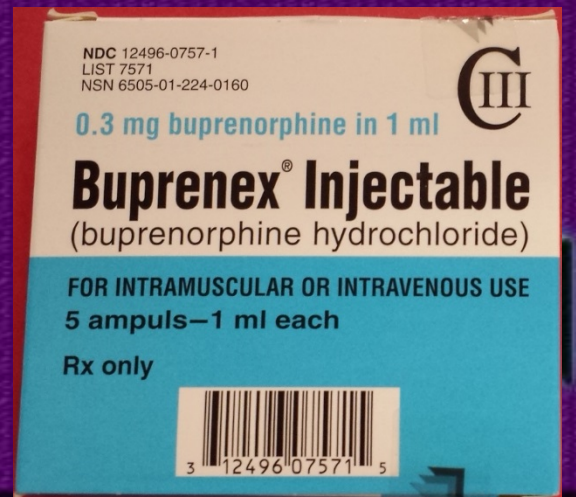
Unapproved Drugs

Unapproved Drugs / ELDU

- Dogs
  - Acepromazine (dose reduction)
  - Ketamine
  - Diazepam / midazolam
  - Morphine, hydromorphone, butorphanol, buprenorphine
- Cats
  - Acepromazine (dose reduction)
  - Diazepam / midazolam
  - Meloxicam cats (PO)
  - Morphine, hydromorphone, buprenorphine (Buprenex)







Pharmacokinetics

- Not a required element
- Standard two-stage (STS)
- Determine individual PK, then calculate descriptive stats
- 6-8 animals, 10-15 samples per animal (young, healthy Beagles)
  - Small number of animals; intensive sample
  - Not the target population
- Adequate to describe mean PK parameters in THAT population
- Does not describe variability, breed differences, drug interactions, disease, anesthesia, surgery, organ function

Pharmacokinetics

- Test population (1-3 year old, healthy Beagle dogs)
- Emphasis on gender inclusion (4 Male / 4 Female)
- Intact (spay /neuter effects on PK?)
  - Polymorphisms identified in Beagles
  - Greyhounds, Alaska Malamutes, Labrador retrievers
  - Chihuahuas vs. Great Danes
  - Greyhounds vs. Scottish Deerhounds vs. Whippets vs. Irish Wolfhounds

https://www.mnn.com/earth-matters/animals/stories/9-of-the-worlds-largest-dog-breeds

Other Approaches?

- Pharmacokinetic-Pharmacodynamic modeling (PK-PD)
- *In vitro* drug metabolism repository (consortium?)
- Physiologically Based Pharmacokinetic Modeling (PBPK)
- Physiologic Based Pharmacokinetic-Pharmacodynamic Modeling (PBPK-PD)
- Population pharmacokinetics (Pop PK)
  - Nonlinear mixed effects modeling
- Population Pharmacokinetic-Pharmacodynamic modeling (Pop PK-PD)

Pharmacokinetic-Pharmacodynamic (PK-PD)

- Integration of pharmacokinetics (ADME) with pharmacodynamics (effects)
- Used to predict drug effects of PK changes: dosages, clearance (disease effects), drug interactions, breed differences
- NSAIDs, opioids, antimicrobials

In vitro drug metabolism repository

- Species-specific (dogs)
- Beyond commercially available Beagle microsomes
- Hepatic cell culture / tissue bank?
  - Phase I and Phase II metabolism
  - Battery of cell lines / tissue banks – breeds, genders
    - phenotypic metabolism differences
  - Polymorphisms: Beagles (CYP2D15, 1A2, 2C41); Greyhounds, others?
  - Drug interaction screens (phenobarbital, ketoconazole, chloramphenicol, fluoxetine, etc.)

In vitro drug metabolism repository

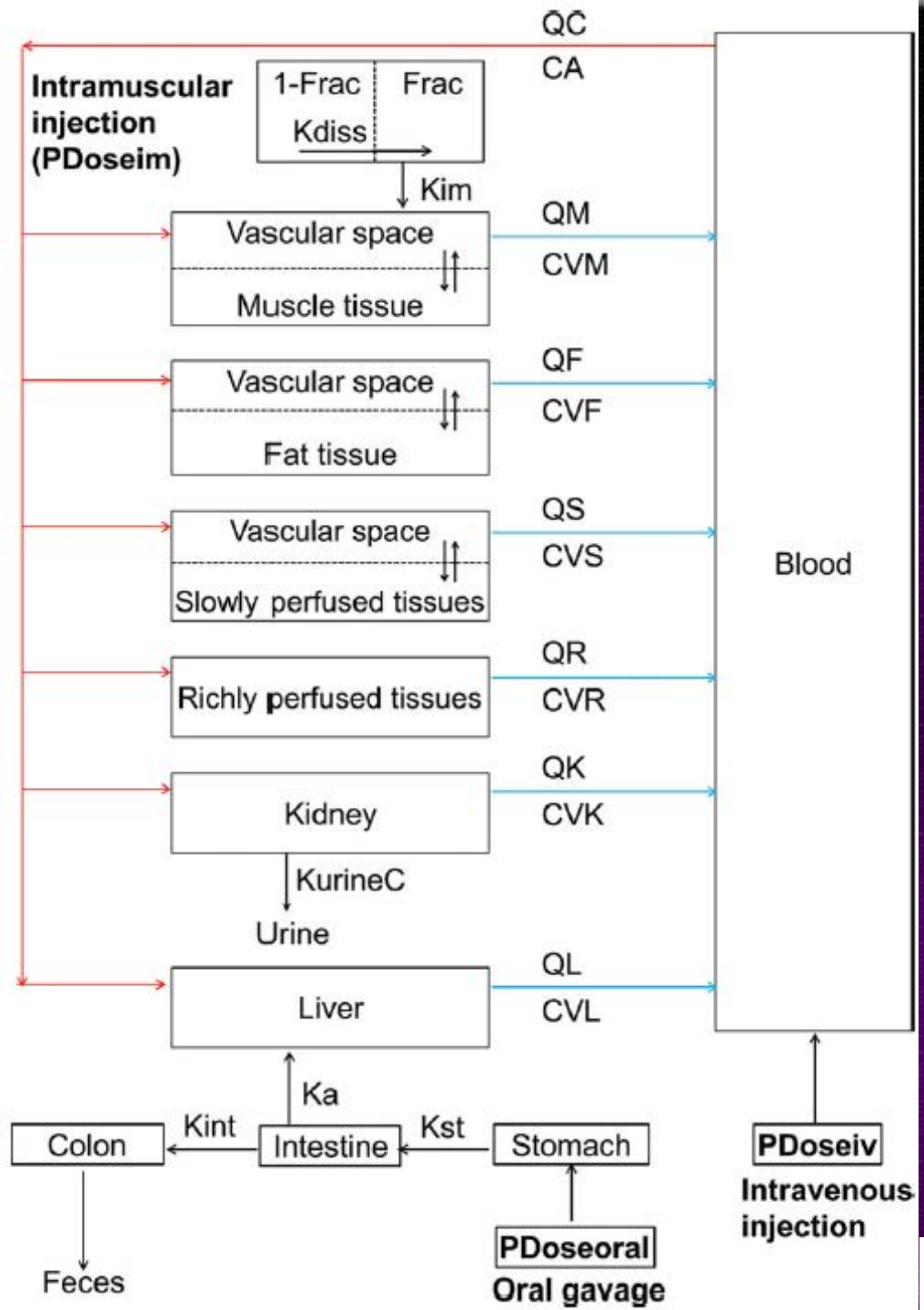
- May not be viable individually, consortium?
  - Kansas State University Animal Metabolism Program for dogs (KSU AMP'd)?
  - Fee for service?
    - Confidential results
      - Could results be made public after exclusivity/patent expiration?
    - Drug interaction screen (CYP inhibitors/inducers)
    - Polymorphism screen (e.g. 50 dog breeds, polymorphisms)
    - Industry and academia interest
  - FDA response (GLP vs. non-GLP)?
    - GLP ≠ better results

In vitro drug metabolism repository

- What to do with the data?
  - Drug interaction warnings / studies
  - Metabolite profiling – active or toxic metabolites?
  - Used to predict pharmacokinetics and variability
    - Input data for PBPK modeling
- Replace preclinical pharmacokinetic studies?
  - Not in addition
  - Cost compared to GLP pharmacokinetic study?
    - Probably could be done for a similar cost, maybe less

In vitro drug metabolism repository

- Should this really be a metabolism & transporter repository?
  - P-glycoprotein (ivermectin sensitivity)
  - Organic cation transporters (OCTs)
  - Organic anion transporters (OATs)
  - Breast Cancer Resistance Protein (BCRP)
  - Multidrug And Toxin Extrusion (MATE) protein
- Drug metabolism, interaction and transporter screen?

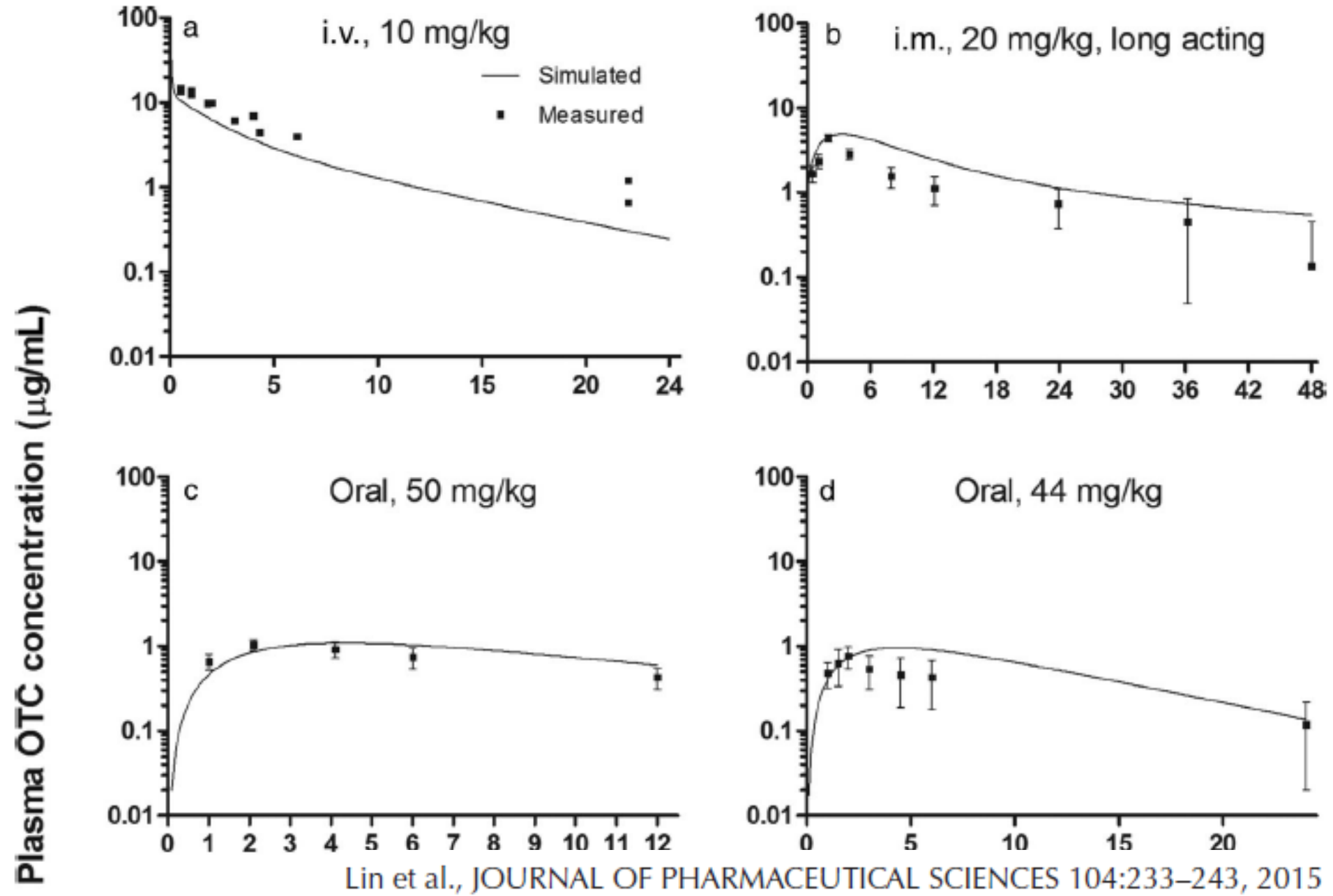


Physiologically Based PK

- PBPK commonly used in rodents, humans and toxicology studies
- Simulates ADME using computer models
- Simulate multiple routes, repository formulations, drug interactions
- Predicts tissue specific concentrations
  - PBPK-PD modeling
  - Drug residues (food animals)

Lin et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:233–243, 2015

Oxytetracycline in dogs – proof of concept



Lin et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:233–243, 2015

Population Pharmacokinetic Studies

- Large population of animals (100-200+)
- Target population
  - Clinical trials (if trials fail maybe PK component explains why)
- Small sample numbers per patient
  - 1-4 samples depending on specifics of the drug
- Patient demographics recorded and correlations to PK assessed
  - Breed, age, concurrent drugs, diseases, organ dysfunction
- Different doses can be administered
  - Replace dose ranging studies?
  - Replace pivotal pharmacokinetic studies?
- Correlation with clinical outcomes / variables (Pop PK-PD)

Population Pharmacokinetic Studies

- Mavacoxib
  - NSAID with long half-life
    - Beagles (laboratory) ~14 days
  - 286 patients enrolled from clinical trials (1317 plasma samples)
  - Trough plasma concentrations obtained
  - Clearance (/F) and volume of distribution (/F) correlated with body weight
  - Clearance (/F) negatively correlated with age (↑ age = ↓ Cl/F)
  - Breed: Labrador retrievers and German Shepherd = ↑ Cl/F

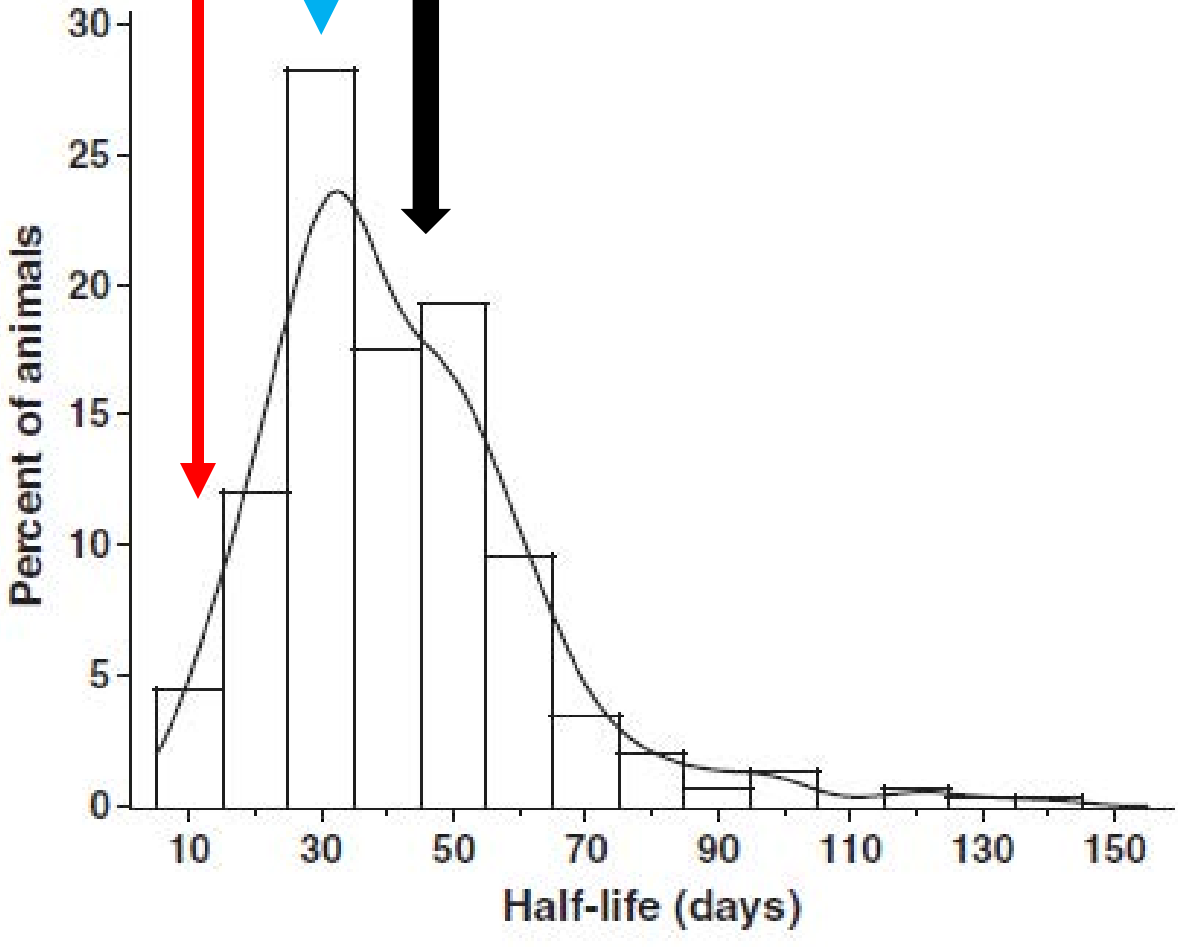
Mavacoxib in dogs

Labrador retrievers
GSD

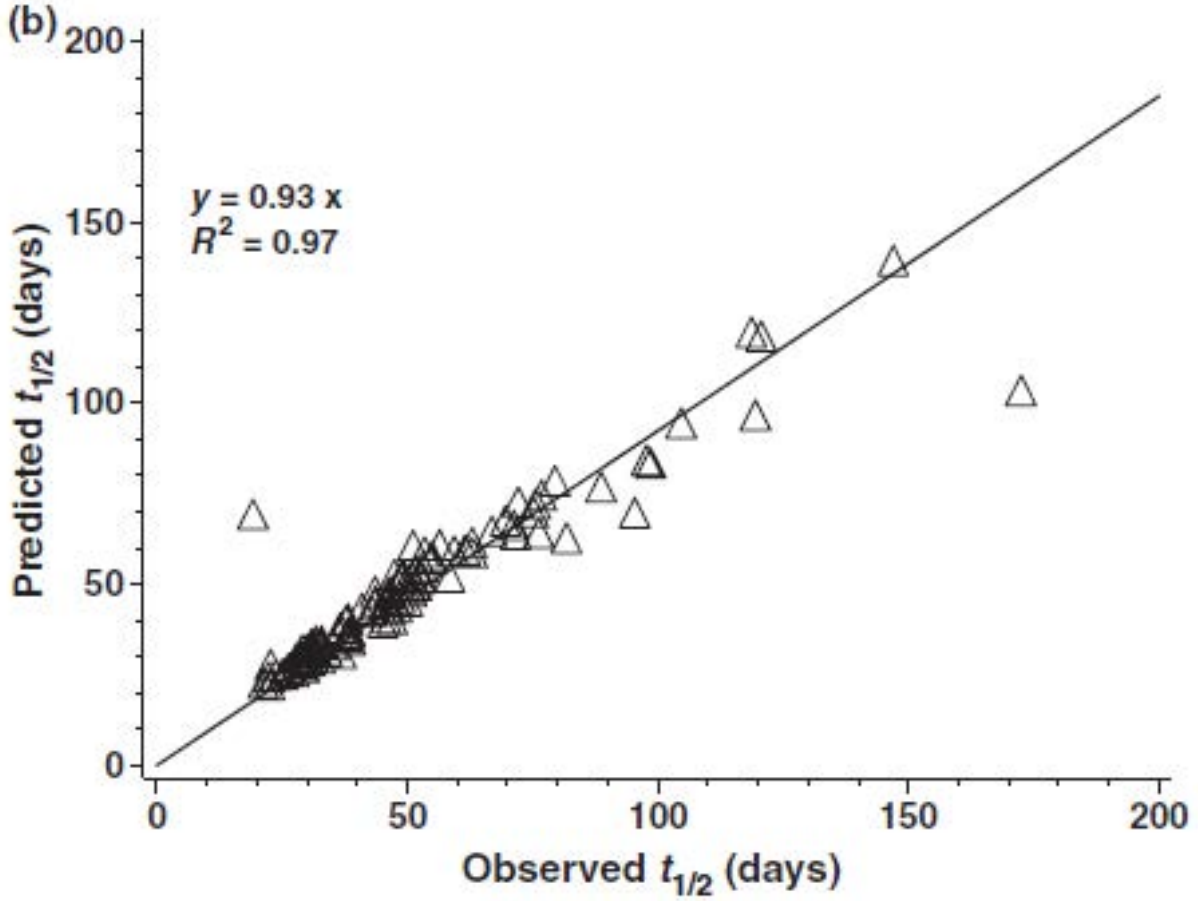
Other geriatric dogs

Young
Beagles

J. vet. Pharmacol. Therap. 34, 1–11.



S. R. Cox et al. *Population pharmacokinetics of mavacoxib*



Mavacoxib in dogs

- Population PK revealed age and breed differences of mavacoxib in dogs
- Dosage decreased to account for differences between research dogs and clinical dogs – approved dosage lower than expected
- Essentially replaced dose ranging studies, was more accurate than pivotal PK studies, combination with pharmacodynamic measurements (Pop PKPD) allowed revised dosages

Future considerations

- Avoidance of drug approval processes is occurring
  - Compounding, unapproved drugs, extralabel drug use
  - Alternative pathways for “grandfathered” drugs (e.g. diazepam) with accepted/documented safety and efficacy – straight to clinical trials?
- Current drug approval processes have limitations
  - Safety/dose finding in NON-target populations
  - Animal welfare and public opinion concerns
- Alternative pathways may provide better data without enhanced burden
  - *In vitro* metabolism/transporter assays
  - Physiologically based PK, PK-PD, Population PK