

REVIEW ARTICLE

Pharmacokinetic scaling and pharmacokinetics/ pharmacodynamics for rational prediction of antibacterial dosage regimens in animals to mitigate antimicrobial resistance

Tridib Chaira^{1*}, Rashmi Kumari², Shailendra Chauhan^{3,4}, and Tarani Kanta Barman^{3,4*} 

¹Department of Pharmacology, Faculty of Pharmacy, Shree Guru Gobind Singh Tricentenary University, Gurugram, Haryana, India

²Department of Neuroscience and Experimental Therapeutics, College of Medicine, The Pennsylvania State University, Hershey, Pennsylvania, United States of America

³Department of Pathology, John Sealy School of Medicine, University of Texas Medical Branch, Galveston, Texas, United States of America

⁴Galveston National Laboratory, University of Texas Medical Branch, Galveston, Texas, United States of America

***Corresponding authors:**

Tridib Chaira
(tridib_fphs@sgtuniversity.org);
Tarani Kanta Barman
(tabarman@utmb.edu)

Citation: Chaira T, Kumari R, Chauhan S, Barman TK. Pharmacokinetic scaling and pharmacokinetics/ pharmacodynamics for rational prediction of antibacterial dosage regimens in animals to mitigate antimicrobial resistance. *Microbes & Immunity*. doi: 10.36922/MI026210055

Received: May 24, 2026

Revised: July 6, 2026

Accepted: July 9, 2026

Published online: July 27, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

The rapid emergence of antimicrobial resistance (AMR) has become a significant challenge in both human and veterinary medicine, largely driven by the misuse and overuse of antibiotics, including inappropriate cross-species dosage extrapolation. Empirical antimicrobial dosing can result in subtherapeutic exposure, disruption of the microbial ecosystem, and increased selective pressure, thereby accelerating the emergence and dissemination of resistant bacteria. Maintaining microecological homeostasis, particularly the stability of the commensal microbiota, is increasingly recognized as essential for limiting the development of resistance and preserving host health. Although interspecies scaling, Monte Carlo simulations, population pharmacokinetics (PK), and physiologically based PK models have been used to predict dosage regimens, their complexity and extensive data requirements restrict routine application in veterinary practice. In this context, PK/pharmacodynamic (PD) modeling provides a practical and scientifically robust framework for rational antimicrobial therapy. By integrating drug concentration–time profiles with antimicrobial effects, PK/PD-guided approaches enable species-specific dose optimization that improves therapeutic efficacy, minimizes ecological disruption, and reduces AMR selection pressure. This review highlights the application of modern PK/PD strategies in veterinary medicine as an essential tool for sustainable antimicrobial stewardship, AMR mitigation, and preservation of microbial ecosystem stability.

Keywords: Pharmacokinetic/Pharmacodynamic; Allometric scaling; Dose prediction; Antibacterial dosage; Physiological time

1. Introduction

The extensive use of antibiotics in livestock and poultry production has contributed substantially to the global rise of antimicrobial resistance (AMR), posing a major threat to both public health and ecological stability.¹ In modern animal agriculture, antibiotics have not only been used to treat and prevent diseases but also widely used in the livestock and poultry industries to efficiently produce pork, beef, poultry meat, and other animal products. When antibiotics are used at sub-therapeutic levels in feed, they improve growth rate and feed conversion efficiency, reduce mortality and morbidity, and enhance reproductive performance.² However, such practices exert continuous selective pressure on microbial populations, accelerating the emergence and dissemination of resistant bacteria across animal, human, and environmental interfaces. Compared with human pharmaceuticals, veterinary antimicrobial agents are often introduced with limited pre-approval pharmacokinetic (PK), pharmacodynamic (PD), and safety data. Consequently, inappropriate dosing regimens may lead to insufficient antibacterial exposure, poor PK/PD target attainment, and prolonged subinhibitory drug concentrations that favor the selection of resistant pathogens. An *in vivo* PK/PD modeling study of orally administered marbofloxacin in pigs demonstrated that a 2 mg/kg dose achieved effective bactericidal activity (90% target attainment) against *Escherichia coli*, providing an evidence-based approach for optimizing dosing regimens and reducing the risk of fluoroquinolone resistance.³ Beyond resistance development, indiscriminate antibiotic use can disrupt the intestinal microecological balance in animals, altering commensal microbial communities essential for host immunity, nutrient metabolism, and colonization resistance to pathogens. Such dysbiosis may further compromise animal health and productivity while facilitating the persistence and spread of antimicrobial-resistant organisms.

The amount of antibiotics consumed by livestock and poultry has increased significantly compared to that used by humans for medical purposes. Global sales data consistently indicate that food-producing animals account for approximately 73% of all antimicrobial consumption worldwide.^{4,5} Thus, the growing rate of antibiotic resistance has emerged as one of the greatest global public health threats in the 21st century.^{6,7} Antibiotic-resistant bacteria, for example, are responsible for about 33,000 fatalities in Europe and 4.95 million deaths globally each year, costing EUR 1.5 billion and lost productivity.

According to the World Health Organization (WHO), AMR is one of the 10 global public health threats facing

humanity, and it is expected to cause over 10 million deaths annually and more than USD 100 trillion in global losses by 2050.⁸ Additionally, the overuse or misuse of antibiotics results in toxicity, allergic reactions, and neurological and psychiatric problems, such as with the class of sulfonamides and fluoroquinolones.^{9,10} Common antibiotics (penicillin, beta-lactams, quinolones, gentamicin, and tylosin) are used extensively to treat the majority of recurring infections and as growth-promoting agents in cattle husbandry for meat production.¹¹ These antibiotics can promote the growth of pathogenic bacteria resistant to specific antibiotics, even though they are present in only trace amounts in effluent from secondary treatment.¹²

Effective AMR control, therefore, requires a transition from empirical antimicrobial administration to precision-based and ecologically conscious therapeutic strategies. Rational antimicrobial medication should aim not only to achieve clinical efficacy but also to preserve microbial homeostasis and minimize the selection pressure for resistance. In this context, determining an optimal dosage regimen is a central challenge in veterinary medicine because drug response varies considerably among animal species due to differences in anatomy, physiology, metabolism, plasma protein binding, and immune function. Interspecies variability in cytochrome P450 (CYP) enzymes and tissue distribution profiles further complicates the translation of antibacterial therapies across species. Thus, the primary difficulty for veterinarians is not about choosing a medication but determining the dosage schedule because variations in PK or PD of a drug account for variability in drug response both within and across species.¹³ We have graphically summarized the entire antibiotic discovery process, from *in vitro* PD and PK/PD integration to dose prediction, in [Figure 1](#) to help readers understand it.

Species-to-species translation, along with the use of effective therapies, may be challenging due to unfavorable PK properties and a poor PK/PD correlation at the pharmacological dose. The majority of lead molecules often fail to show the desired efficacy or safety profiles during species-to-species translation due to (i) differences in CYP isozymes responsible for drug metabolism and (ii) differences in plasma protein binding responsible for the distribution of drugs in different tissues. An improved understanding of absorption, distribution, metabolism, excretion (ADME), and toxicity, together with PK/PD relationships, provides a scientific basis for optimizing antimicrobial therapy in animals. PK/PD-guided dosing strategies can maximize antibacterial efficacy while minimizing unnecessary exposure, disruption of host-associated microbiota, and emergence of resistance.

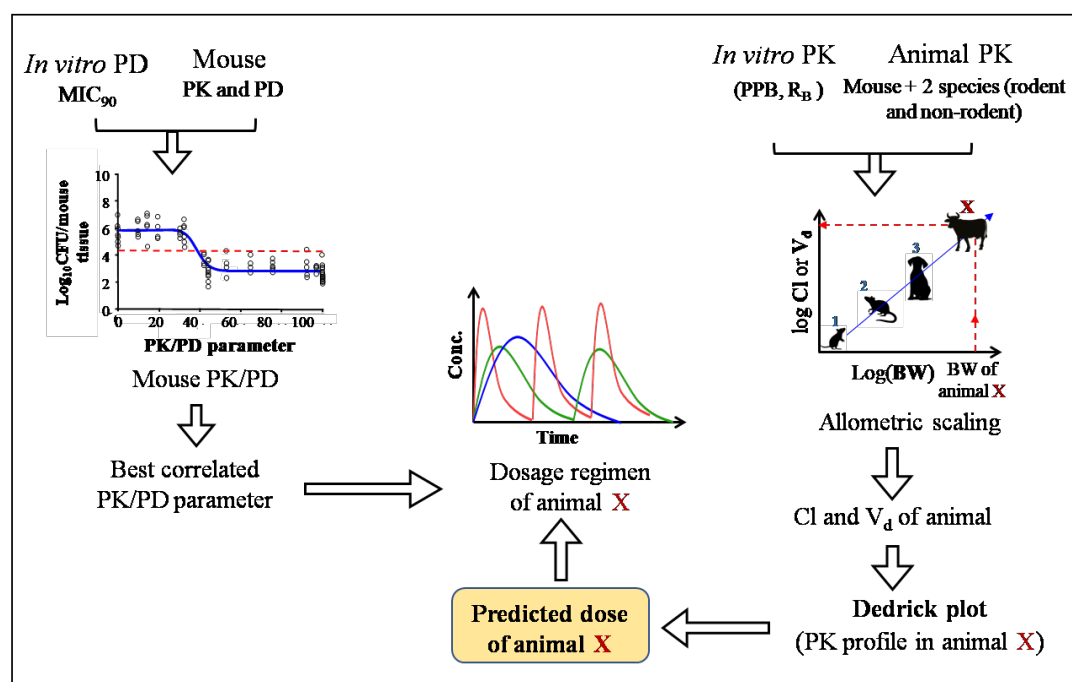


Figure 1. Schematic overview of the workflow for PK/PD-driven dose prediction, from *in vitro* assays to *in vivo* scaling. On the left-hand side (LHS), it shows how MIC_{90} and mouse PK/PD are used to derive PK/PD parameters. On the right-hand side (RHS), it shows how *in vitro/in vivo* PK with animal scaling is used to predict the dose. Both LHS and RHS converge at dosing regimens.

Abbreviations: BW: Body weight; CFU: Colony-forming unit; Cl: Clearance; Conc.: Concentration; MIC_{90} : Minimum inhibitory concentration required to inhibit the growth of 90% of isolates; PD: Pharmacodynamic; PK: Pharmacokinetic; PPB: Plasma protein binding; R_B : Blood-to-plasma concentration ratio; V_d : Volume of distribution.

Mathematical and mechanistic PK/PD models therefore represent essential technical tools for designing evidence-based antimicrobial regimens tailored to specific animal species, pathogens, and clinical conditions. Thus, PK/PD improves treatment outcomes and slows the evolution of resistance.¹⁴

This review focuses on PK scaling and PK/PD integration as key approaches for rational antimicrobial use in veterinary medicine. Emphasis is placed on how predictive PK/PD modeling can support AMR mitigation, maintain microecological homeostasis, and facilitate the development of safer and more sustainable antibacterial dosing regimens across animal species.

2. Linkage between cross-species dosing and antibacterial resistance

In veterinary medicine, empirical cross-species dose extrapolation remains common because species-specific PK/PD data are often unavailable, leading to subtherapeutic antimicrobial exposure, treatment failure, and increased selection pressure for antimicrobial-resistant

bacteria.^{15,16} Species differences in drug ADME can lead to subtherapeutic exposure or toxicity.¹⁷ In livestock systems, indiscriminate antimicrobial use has been associated with resistant *E. coli*, *Salmonella*, and methicillin-resistant *Staphylococcus* species.¹⁸ Wildlife may also acquire and disseminate resistant bacteria through environmental exposure or contact with domestic animals, creating a major One Health concern.^{19,20} Recent reviews have highlighted enrofloxacin and ceftiofur as examples in which species-specific dosing recommendations differ because of significant PK variability across avian species.^{8,21} Therefore, species-specific dosage regimens, PK/PD-guided therapy, antimicrobial stewardship, and veterinary supervision are essential for rational antimicrobial use and AMR mitigation across animal species.

3. Variability of ADME physiology among different species

In veterinary medicine, changes in animal metabolism and protein binding frequently affect species differences in therapeutic effectiveness. The ADME of medications ultimately underpins the safety and efficacy of a

treatment.²² The CYP-mediated metabolism provides a better explanation for the differences in intestinal absorption and PK profile between humans and animals. Therefore, it is not appropriate to calculate animal doses from human doses in veterinary medicine solely based on total body surface area.²³

The DNA sequences of CYPs across different animals are often identical; however, differences do occur due to evolutionary adaptations. Therefore, unpredictable pharmacological effects arise from PK variability caused

by genetic differences in CYP isozymes. Differences in phase-I drug metabolism, resulting in inter-individual variability, depend on the polymorphic forms of three key CYP enzymes: CYP2D6, CYP2C19, and CYP2C9.²³⁻²⁵ The list of CYP orthologs between species is summarized in Table 1. Again, the rate of drug diffusion between plasma and tissues is greatly influenced by plasma protein binding, which in turn affects drug clearance, the volume of distribution (V_d) at steady state (V_{dss}), and the partitioning between plasma and tissues.^{26,27}

Table 1. Cytochrome P450 (CYP) orthologs between species²⁸⁻³³

CYP family	Mouse	Rat	Human	Bovine	Dog	Pig	Poultry
CYP1A	CYP1A1	CYP1A1	CYP1A1	CYP1A1	CYP1A1	CYP1A1	CYP1A1
	CYP1A2	CYP1A2	CYP1A2	CYP1A2	CYP1A2	CYP1A2	CYP1A4, CYP1A5
CYP1B	CYP1B1	CYP1B1	CYP1B1		CYP1B1	CYP1B1	
	CYP2B10	CYP2B1 CYP2B12	CYP2B6				
CYP2A	CYP2A4, CYP2A5, CYP2A12, CYP2A22	CYP2A1, CYP2A2, CYP2A3	CYP2A6, CYP2A7, CYP2A13		CYP2A13, CYP2A25	CYP2A	CYP2A6
CYP2B	CYP2B9, CYP2B10	CYP2B1, CYP2B2, CYP2B3	CYP2B6, CYP2B7	CYP2B6	CYP2B11	CYP2B22	
CYP2C	CYP2C38	CYP2C12	CYP2C9	CYP2C9	CYP2C21, CYP2C41	CYP2D21	CYP2C
	CYP2C29	CYP2C11	CYP2C8				
	CYP2C39, CYP2C55	CYP2C13, CYP2C55	CYP2C19				
CYP2D	CYP2D9, CYP2D10	CYP2D3	CYP2D6		CYP2D15	CYP2D45	CYP2D49
CYP2E	CYP2E1	CYP2E1	CYP2E1		CYP2E1	CYP2E	
CYP3A		CYP3A9	CYP3A4	CYP3A4	CYP3A12, CYP3A26	CYP3A22, CYP3A29	CYP3A37
	CYP3A25	CYP2A18	CYP3A5				

Beyond metabolic enzymes, membrane transporters are critical determinants of drug PK by regulating drug ADME. Uptake transporters, including organic anion-transporting polypeptides (OATPs), organic anion transporters (OATs), and organic cation transporters (OCTs), facilitate drug entry into hepatocytes and renal tubular cells, influencing hepatic uptake and renal secretion. In contrast, ATP-dependent efflux transporters, such as P-glycoprotein

(P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs), limit oral absorption, restrict tissue penetration, and promote biliary and renal excretion.^{34,35} Expressed predominantly in the intestine, liver, kidney, blood–brain barrier, and placenta, these transporters play a central role in determining systemic drug exposure, tissue distribution, and protection against xenobiotics (Table 2).

Table 2. Major membrane transporters involved in drug disposition and their pharmacokinetic roles

Transporter	Gene family	Transport mechanism	Major sites of expression	Primary physiological/ pharmacokinetic role	Representative drug substrates
P-glycoprotein (P-gp)	<i>ABCB1</i>	ATP-dependent efflux transporter	Apical membrane of intestinal epithelial cells, canalicular membrane of hepatocytes, renal proximal tubules, blood–brain barrier, placenta	Limits intestinal drug absorption, restricts brain penetration, promotes biliary and renal excretion, protects tissues from xenobiotics	Digoxin, ivermectin, enrofloxacin, doxorubicin, cyclosporine
Breast cancer resistance protein (BCRP)	<i>ABCG2</i>	ATP-dependent efflux transporter	Intestine, liver canalicular membrane, kidney, blood–brain barrier, placenta, mammary gland	Limits oral absorption, mediates biliary and renal excretion, restricts tissue distribution, contributes to drug secretion into milk	Fluoroquinolones, sulfasalazine, topotecan, methotrexate
Multidrug resistance-associated proteins (MRPs)	<i>ABCC</i> family	ATP-dependent efflux transporter	Liver, kidney, intestine, lung, blood–brain barrier	Efflux of drugs and conjugated metabolites into bile, urine, and intestinal lumen; detoxification; cellular protection	Methotrexate, glucuronide conjugates, bilirubin conjugates, antivirals
Organic anion-transporting polypeptides (OATPs)	<i>SLCO</i> family	Sodium-independent facilitated uptake	Basolateral membrane of hepatocytes, intestine, kidney	Hepatic uptake of endogenous compounds and drugs; influences hepatic clearance and systemic exposure	Rifampicin, statins, fexofenadine, certain β -lactam antibiotics
Organic anion transporters (OATs)	<i>SLC22</i> family	Facilitated uptake (anion exchange)	Basolateral membrane of renal proximal tubules, liver	Renal uptake of organic anions from blood for tubular secretion	Penicillins, cephalosporins, nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate
Organic cation transporters (OCTs)	<i>SLC22</i> family	Facilitated uptake of cations	Liver (OCT1), kidney (OCT2), intestine	Hepatic and renal uptake of cationic drugs; influences clearance and tissue distribution	Metformin, cimetidine, procainamide, trimethoprim
Multidrug and toxin extrusion proteins (MATE1/MATE2-K)	<i>SLC47</i> family	Proton/Drug antiporter (efflux)	Apical membrane of renal proximal tubules, liver canalicular membrane	Final step of renal and biliary excretion of organic cations	Metformin, oxaliplatin, cimetidine

In addition to CYP-mediated metabolism, membrane transporters are key determinants of drug disposition and interspecies PK variability. Species-specific differences in the expression, localization, and activity of major transporters, including P-gp, BCRP, OATPs, OCTs, and MRPs, influence drug absorption, tissue distribution, and biliary and renal elimination, thereby affecting systemic exposure, therapeutic efficacy, and toxicity. Genetic polymorphisms and transporter isoforms further contribute to variability in drug response.^{36,37}

Although optimizing the unbound drug fraction by modulating plasma protein binding or selecting appropriate doses can enhance target-site drug exposure, transporter-mediated uptake and efflux remain critical determinants of tissue distribution, particularly for

transporter substrates. Therefore, plasma protein binding and membrane transporter activity should be considered complementary factors when designing species-specific, evidence-based dosing strategies. Recent drug discovery efforts have emphasized strategies to optimize target-site drug exposure by considering plasma protein binding, as the high abundance of plasma proteins and the strong binding affinity of many drugs significantly influence the free drug concentration available for tissue distribution, target engagement, and therapeutic efficacy.

According to the principle of mass balance, the total mass (or amount) of the drug after absorption is equal to the sum of the mass in plasma (A_p) and various tissues (A_T). Mathematically expressed as:

$$\text{Total amount}(A) = A_p + \sum A_T \quad (1)$$

Using the definitions for V_d ($V_{ss} \times C_p$), plasma volume ($V_p \times C_p$), and tissue volume ($V_T \times C_p$), we can write **Equation 1** as follows:

$$V_{ss} \times C_p = V_p \times C_p + \sum V_T \times C_p \quad (2)$$

where V_p is the plasma volume, and V_T is the tissue volume.

Dividing through by the total plasma concentration (C_p), we obtain:

$$V_{ss} = V_p + \sum \left(V_T \times \frac{C_T}{C_p} \right) \quad (3)$$

Also, the unbound drug tissue-to-plasma partition coefficient ($K_{pu,T}$) is given by:

$$K_{pu,T} = \frac{C_{u,T}}{C_{u,P}} \quad (4)$$

where $C_{u,T}$ is the unbound drug concentration in the tissue and $C_{u,P}$ is the unbound drug concentration in the plasma. We know that total concentration relates to unbound drug concentration (C_u) and unbound drug fraction (f_u) as:

$$C = \frac{C_u}{f_u} \quad (5)$$

Substituting $K_{pu,T}$ and using **Equation 5**, $\left(\frac{C_T}{C_P} \right)$ in **Equation 3** can be expressed as:

$$\frac{C_T}{C_P} = K_{pu,T} \times \frac{f_{u,P}}{f_{u,T}} \quad (6)$$

Then, substituting **Equation 6** into **Equation 3**, we obtain:

$$V_{ss} = V_p + \sum \left(V_T \times K_{pu,T} \times \frac{f_{u,P}}{f_{u,T}} \right) \quad (7)$$

This derivation demonstrates that if $K_{pu,T} = 1$ (passive diffusion and equilibrium), the equation simplifies to the classic physiological model. However, for antimicrobials with active transport or sequestration, the $K_{pu,T}$ term serves as a necessary “correction factor” to account for the deviation from simple passive distribution. **Equation 7**

is the quantitative expression between V_d , plasma protein binding, tissue binding, and unbound drug tissue-to-plasma partition coefficient. It clearly shows that V_d is directly proportional to the free fraction of the drug in plasma and inversely proportional to its free fraction in tissue. Based on **Equation 7**, drugs with a high V_d have a propensity to leave the plasma and enter the extravascular compartments of the body, meaning that a higher dose of a drug is required to achieve a given plasma concentration. These drugs are more lipophilic and are transported more widely into tissues. Conversely, a drug with a low V_d is either too polar to disperse into tissue or has a greater tendency to bind to plasma proteins. These drugs have a propensity to remain in plasma, meaning a lower dose is required to achieve a given plasma concentration (**Figure 2**).³⁸

According to free drug theory (FDT), the free drug concentration in plasma equals the free drug concentration in the intracellular spaces of tissues after steady-state equilibrium is reached.^{39,40} This widely accepted hypothesis describes the relationship between pharmacological effect and plasma protein binding of a drug, namely the unbound drug portion. There is no relationship between the pharmacological effect and the overall drug concentrations in tissue. The remaining unbound drug is available to bind to the target receptor and, if present in pharmacologically relevant quantities, will exert the desired effect. A fraction of the unbound drug that penetrates the tissue is bound to tissue proteins. The concentrations of free drugs in various tissues are comparable at equilibrium, and the quantitative assessment of unbound drug in plasma reflects the free drug in tissues accessible to binding to cell membrane receptors at the target location (**Figure 3**). However, this concept has limitations for drugs that undergo active transport, intracellular accumulation, or extensive tissue sequestration, in which local drug concentrations at the site of infection may differ substantially from unbound drug plasma concentrations. Consequently, target-site PK, including tissue and intracellular drug exposure, has emerged as an important complement to plasma-based PK/PD indices for improving antimicrobial dose prediction.

The influx or efflux of drugs by transporters in veterinary animals is essential for drug disposition, pharmacological action, and organ-specific toxicity. Variations in the *in vitro* and *in vivo* effectiveness of potential test compounds necessitate a preliminary assessment for efflux transporter substrates, including P-gp, BCRP, and MRP1–6.⁴¹ These efflux transporters restrict intestinal absorption and the release of medication into the bloodstream. In addition to the modulation of metabolizing enzymes by genetic polymorphism and diseased conditions, which frequently result in changes in plasma and/or tissue exposure leading to changes in efficacy and/or toxicological effects, one

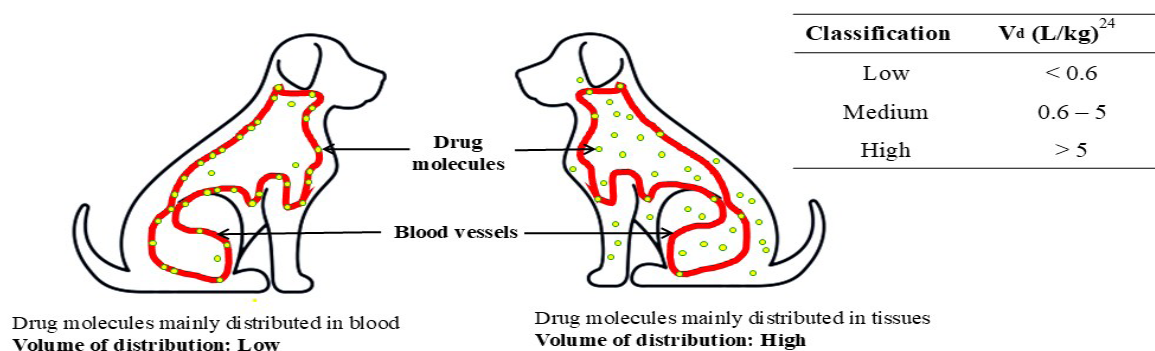


Figure 2. Distribution of drug molecules in the body of low- and high-volume of distribution (V_d) drugs. On the left, the figure shows a low V_d , where drugs are seen only in the blood circulation, whereas on the right, it shows a high V_d , where drugs are seen in both the blood and tissue compartments.

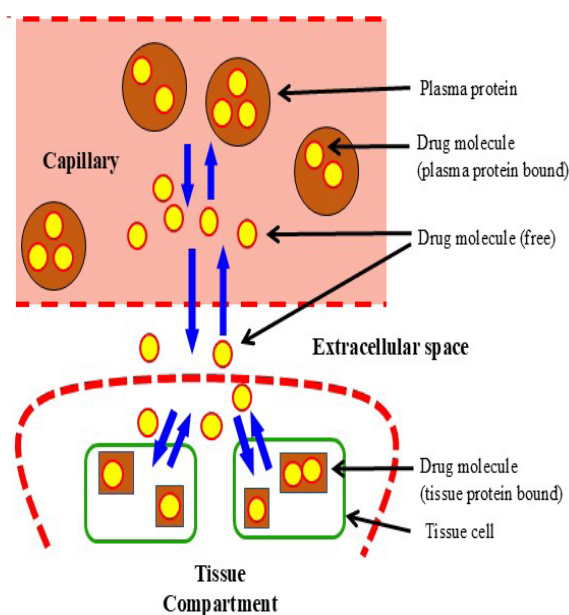


Figure 3. Distribution of unbound (free) drug across membranes at equilibrium. Both bound and free drugs are shown in the blood capillary and tissue compartments. The concentrations of free drugs in various tissues are comparable at equilibrium.

of the crucial criteria to be taken into consideration for understanding drug–drug interactions is the alteration of intestinal and/or hepatic transporters by the substrates.^{42,43}

4. Prediction of pharmacokinetic parameters using allometric scaling

Allometric scaling is a practical and widely used approach for predicting PK parameters across species based on body

weight and other empirical relationships. In contrast, physiologically based pharmacokinetic (PBPK) modeling employs a mechanistic framework that integrates species-specific anatomical, physiological, biochemical, and drug-related properties to simulate drug disposition. Although PBPK models require extensive experimental data and rigorous validation, they generally provide greater predictive accuracy for interspecies extrapolation, dose optimization, and regulatory decision-making than

traditional allometric scaling. Consequently, allometric scaling is well-suited for rapid first-pass predictions during early drug development⁴⁴, whereas PBPK modeling offers a more robust framework for species extrapolation, dose optimization, and regulatory decision-making when sufficient data are available.

As discussed above, the allometric connection enables the mathematical expression and generalization of similarities among animals. Based on the power-law function, the generalized allometric equation can be written as:

$$Y = a \times W^b \quad (8)$$

where Y is the PK parameter to be calculated, mainly clearance, W is the physiological parameter, primarily the average body weight of a species, and a and b are the allometric coefficient and exponent, respectively. The log-log transformation of this exponential equation makes it linear. The coefficient (a) and exponent (b) can be estimated using linear regression. The logarithmic transformation of **Equation 8** is written as:

$$\log(Y) = \log(a) + b \times \log(W) \quad (9)$$

Equation 9 is in the form of a line equation $y = mx + c$, where $\log(a)$ is the Y-intercept, and b is the slope of the straight line graph. The first primary PK parameter, plasma clearance, is computed for each species from an intravenous (IV) PK study. The plasma clearance (Cl_{plasma}) is converted to the blood clearance (Cl_{blood}) using the R_B (blood-to-plasma concentration ratio) value by the following equation:

$$Cl_{\text{blood,IV}} (mL/min) = \frac{Cl_{\text{plasma,IV}} (mL/min/kg)}{R_B} \times \text{body wt} (kg) \quad (10)$$

These IV blood PK parameters (clearance) from at least three species are plotted on a $\log(Y)$ versus $\log(W)$ scale to obtain a linear plot, and the a and b values are computed using **Equation 9**. Primary PK parameters of species of interest are then calculated using computed a and b values and the average adult body weight of the species of interest. However, when calculating these PK parameters using basic allometry, there is significant inaccuracy for drugs with a low hepatic extraction rate.⁴⁵ It should be noted that the common practice of scaling clearance based on body weight (mg/kg) alone may not always yield accurate predictions. To minimize prediction errors, the “rule of exponents” (ROE) method is used,

which provides selection criteria for the use of maximum lifespan potential (MLP) or brain weight (BrW) based on the values of the clearance exponents obtained from simple allometry.^{46–48} The ROE and associated correction factors have been successfully applied to improve allometric prediction of drug clearance across several mammalian species, including veterinary species, particularly for drugs undergoing hepatic metabolism. However, their predictive performance is drug- and species-dependent, and accuracy may decline for compounds exhibiting nonlinear PK, transporter-mediated disposition, or pronounced species-specific metabolic pathways. Consequently, external validation within individual veterinary species and drug classes remains necessary before these methods can be applied with confidence.^{46–48} It is also important to remember that the use of $Cl \times MLP$ and $Cl \times BrW$ correction factors should not be restricted to drugs that are extensively metabolized; they can be applied to drugs primarily excreted by the kidneys. In large animals, the use of correction factors frequently results in more errors than simple allometry, whereas in humans it does not. Extrapolating parameters, such as clearance, from small to large animals is often inaccurate due to several biological and physiological differences.⁴⁹ The predicted values were either substantially lower or higher. The projected clearance in cats, goats, and sheep was more accurate than in laboratory animals. However, for predicting drug clearance in large animals, including a large animal in the scaling can substantially improve prediction accuracy.⁴⁴

Scaling of V_d , the second primary PK parameter, from animal species is predicted using simple allometry, as mentioned in **Equation 9**, using the Adolph Dedrick method⁵⁰:

$$\log\left(\frac{V_{\text{dss,blood,IV}} \times R_B}{f_u}\right) = \log(a) + b \times \log(W) \quad (11)$$

where f_u is the fraction of the unbound drug in plasma; $V_{\text{dss, blood, iv}}$ is the V_{dss} in blood following IV administration, and R_B is the blood-to-plasma concentration ratio. The $\left(\frac{V_{\text{dss,blood,IV}} \times R_B}{f_u}\right)$ value in humans is then calculated using a and b values derived from at least three species, and the average adult human weight is estimated. $V_{\text{dss, blood, IV}}$ of the animal species of interest is calculated by multiplying by human f_u/R_B . As with clearance, including one large animal in the scaling, along with small laboratory animals, can substantially improve predictions of V_d in large animals. However, further investigation is needed in this direction.⁴⁴ The predicted human elimination half-life is estimated using the predicted human clearance and V_{dss} .

5. Prediction of plasma concentration–time profiles in veterinary animals (species-invariant time method [Dedrick plots])

Predicting PK/PD correlation, estimating an adequate dosage, and determining the dosing frequency in animals all depend on the plasma concentration–time profile of a drug candidate, which can be predicted using modeling and simulation in conjunction with animal PK characteristics.

The physiological species-invariant time technique originates from the allometric approach. The allometric correlations among PK parameters across species determine prediction accuracy. For example, compared to long-lived, larger animals, short-lived, small animals often clear drugs from their bodies at a higher rate (chronological time) per unit body weight (rate/body weight). All animals, regardless of species, tend to clear drugs at a comparable rate if the biological clock of each species is used to quantify drug clearance from the body. The species-invariant time technique is based on the principle that plasma concentration–time curves should be normalized by body weight and converted from chronological time to physiological time.⁵¹ Chronological time is the actual elapsed time measured after drug administration, whereas physiological time is normalized according to body size and physiological processes. Chronological time was initially normalized to species-specific equivalent time.^{51–}

⁵⁴ Later, Boxenbaum and Ronfeld⁵³ introduced new units of PK time, incorporating MLP and BrW into the Dedrick plot. In the Dedrick plot, using kallynochrons and apolysichrons as time units, b and c are the allometric scaling exponents for Cl and V_{dss} , respectively.^{53,55,56} The transformed concentration–time curves of various species are superimposed and then back-transformed to estimate predicted IV plasma concentration–time profiles at a 1 mg/kg dose for the species of interest (Figure 4). The predicted IV profile, along with the estimated mean absorption rate constants and bioavailability, is used to simulate the oral PK profile at a 1 mg/kg oral dose. The Dedrick plot methodology is a valuable tool for interspecies PK extrapolation when PK processes are conserved across species. However, its predictive accuracy may be limited for drugs exhibiting nonlinear PK, saturable metabolism, transporter-mediated disposition, or species-specific differences in absorption, plasma protein binding, and tissue distribution.⁵⁷ Mahmood and Yuan⁵⁸ compared the accuracies of transformations via equivalent time, kallynochrons, and apolysichrons (complex Dedrick plot) for predicting human clearance, V_{dss} , and half-life. The derived complex Dedrick equations are as follows:

$$C_p = \frac{D}{V_{dss}} \times e^{-\left(\frac{Cl}{V_{dss}}\right) \times t} \quad (12)$$

where D is the dose in mg. Dividing both sides of Equation 12 by D/W , we obtain:

$$\frac{C_p}{D/W} = \frac{1}{C \times W^c / W} \times e^{-\left(\frac{B \times W^b}{C \times W^c}\right) \times t} \quad (13)$$

where B and C are coefficients, and b and c are the exponents of clearance and V_d , respectively, in a simple allometric equation where $Cl = B \times W^b$ and $V_d = C \times W^c$. On rearranging Equation 13, we obtain:

$$\frac{C_p}{D/W} = \frac{1}{C \times W^{c-1}} \times e^{-\left(\frac{B}{C}\right) \times W^{b-c} \times t} \quad (14)$$

By plotting the concentration scale, e.g., $\frac{C_p}{D/W} = C_p'$, on the y-axis and the time scale, e.g., $W^{b-c} \times t = t'$, on the x-axis, the above equation can be rewritten as:

$$C_p' = \left(\frac{1}{C \times W^{c-1}} \right) \times e^{-\left(\frac{B}{C}\right) \times t'} \quad (15)$$

Equation 15 is called the complex Dedrick equation. The area under the complex Dedrick curve (AUC_{DC}) is assumed to be equivalent for all species (Figure 4) and is given by:

$$AUC_{DC} = \int_0^\infty \left(\frac{C}{D/W} \right) \times d\left(t / W^{1-b}\right) \quad (16)$$

$$\Rightarrow AUC_{DC} = \left(\frac{1}{D/W} \right) \left(\frac{1}{W^{1-b}} \right) \int_0^\infty C \times dt \quad (17)$$

$$\Rightarrow AUC_{DC} = \left(\frac{W^b}{D} \right) \int_0^\infty C \times dt \quad (18)$$

Incorporating the first-order absorption rate constant (K_a) into an IV PK equation (Equation 14) enables the prediction of the plasma concentration–time profile following oral administration.

6. Pharmacokinetic/Pharmacodynamic analysis

Understanding the PK/PD characteristics of any drug is crucial for effective treatment.^{45,59} The idea of PK/PD was

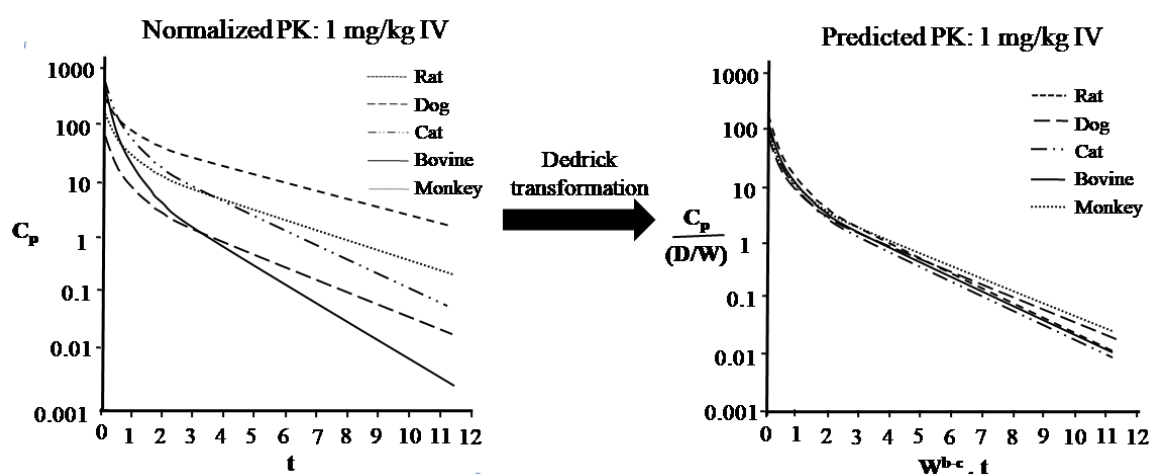


Figure 4. Dedrick transformation of pharmacokinetic (PK) profiles in various species
Abbreviation: IV: Intravenous.

first proposed in the 1940s and then tested experimentally in the 1990s, demonstrating a repeatable association between animal models and human clinical data.^{47,60,61}

6.1. Pharmacokinetic/Pharmacodynamic integration

Currently, PK/PD analysis has become increasingly critical for anti-infective drugs, as identifying optimal PK/PD parameters and adjusting the dosage regimen accordingly, through modeling and simulation of the predicted oral plasma profile, is crucial for reducing the emergence of resistance.^{24,56,62} The PK/PD of antibiotics is studied thoroughly, and the correlation of preclinical data among small animals (mainly mammals) has been studied more compared to large mammals, birds, and other veterinary species because of the high costs of the studies, the number of animals needed, and the difficulty in working with many of these species.⁶³ Three PK/PD indices are used to describe the concentration-dependent and time-dependent antibacterial activity of antibiotics. The minimum inhibitory concentration (MIC) of an antibiotic, which prevents observable bacterial growth in a test tube, is used to calculate these indices.⁶⁴ The area under the concentration–time curve (AUC) and peak concentration or maximum serum concentration ($C_{\max}$) are crucial PK metrics utilized in PK/PD studies. By combining PK and PD parameters (MIC, AUC, and $C_{\max}$), PK/PD indices that serve as indicators of effectiveness are derived: AUC_{0-24h}/MIC , $C_{\max}/MIC$, and $T_{>MIC}$ (time above MIC). General classification of antimicrobial drugs according to PK/PD indices is presented in Table 3.

The AUC_{0-24h}/MIC is defined as the ratio of the area

under the concentration–time curve to the MIC; $C_{\max}/MIC$ is the maximum concentration divided by the MIC; and the $T_{>MIC}$ is the percentage of time during the dosing interval that the drug concentration sustains above the MIC (Figure 5). These indices are generally calculated as free drug concentrations based on serum protein binding of the drug.^{50,65-67}

The mathematical expression of AUC from time 0 to infinity is given by:

$$AUC = \int_0^{\infty} C_p \cdot dt = \int_0^{\infty} \left[\frac{Fk_a D_0}{V_d (k_a - k_{el})} \{ e^{-k_{el}t} - e^{-k_a t} \} \right] dt \quad (19)$$

Hence, the mathematical expression of the PK/PD index $fAUC/MIC$ from time t_1 to $(t_1 + T_{>MIC})$ can be written as:

$$\frac{fAUC}{MIC} = \int_{t_1}^{(t_1 + T_{>MIC})} fC_p \cdot dt - (MIC \times T_{>MIC}) \quad (20)$$

Substituting C_p in Equation 20, we obtain:

$$\frac{fAUC}{MIC} = \int_{t_1}^{(t_1 + T_{>MIC})} \left[\frac{f \cdot Fk_a D_0}{V_d (k_a - k_{el})} \{ e^{-k_{el}t} - e^{-k_a t} \} \right] dt - (MIC \times T_{>MIC}) \quad (21)$$

Similarly, the mathematical expression of $C_{\max}$ is given by:

$$C_{\max} = \frac{Fk_a D_0}{V_d (k_a - k_{el})} \left[e^{-k_{el}t_{\max}} - e^{-k_a t_{\max}} \right] \quad (22)$$

Table 3. General classification of antimicrobial drugs according to pharmacokinetic/pharmacodynamic indices

Characteristic	Time-dependent	Concentration-dependent	Exposure dependent (AUC_{0-24}/MIC)
Relationship with efficacy	Efficacy of the drugs directly correlates with the duration of free drug sustained above the minimum inhibitory concentration	Efficacy of the drugs directly correlates with the peak free drug concentration	Efficacy of the drugs directly correlates with the total amount of drug exposure over 0–24 h
Antimicrobial classes and examples	(i) Beta-lactams: <i>Penicillin</i> (penicillin G, ampicillin, amoxicillin) & <i>Cephalosporins</i> (cefalexin, cefovecin, ceftiofur, cefquinome) (ii) Macrolides: Erythromycin, tylosin, tilmicosin (except azithromycin) (iii) Lincosamides: Lincomycin, clindamycin (iv) Carbapenems: Meropenem (v) Phenicol: Florfenicol, chloramphenicol (vi) Sulfonamides & diaminopyrimidines: Sulfadiazine, sulfamethoxazole, trimethoprim (vii) Pleuromutilins: Tiamulin, valnemulin	(i) Aminoglycosides: Amikacin, gentamicin, kanamycin, neomycin, tobramycin, streptomycin, apramycin (ii) Fluoroquinolones: Enrofloxacin, marbofloxacin, danofloxacin, orbifloxacin, pradofloxacin (iii) Nitroimidazoles: Metronidazole Macrocyclic: Rifamycins	(i) Fluoroquinolones: Enrofloxacin, marbofloxacin, danofloxacin, orbifloxacin, pradofloxacin (ii) Tetracyclines: Oxytetracycline, doxycycline, chlortetracycline (iii) Aminoglycosides: Amikacin, gentamicin Polypeptides: Colistin (iv) Lincosamides: Lincomycin, clindamycin (v) Glycopeptides: Avoparcin, teicoplanin, vancomycin (vi) Macrolides: Tylosin, tulathromycin, gamithromycin, tildipirosin

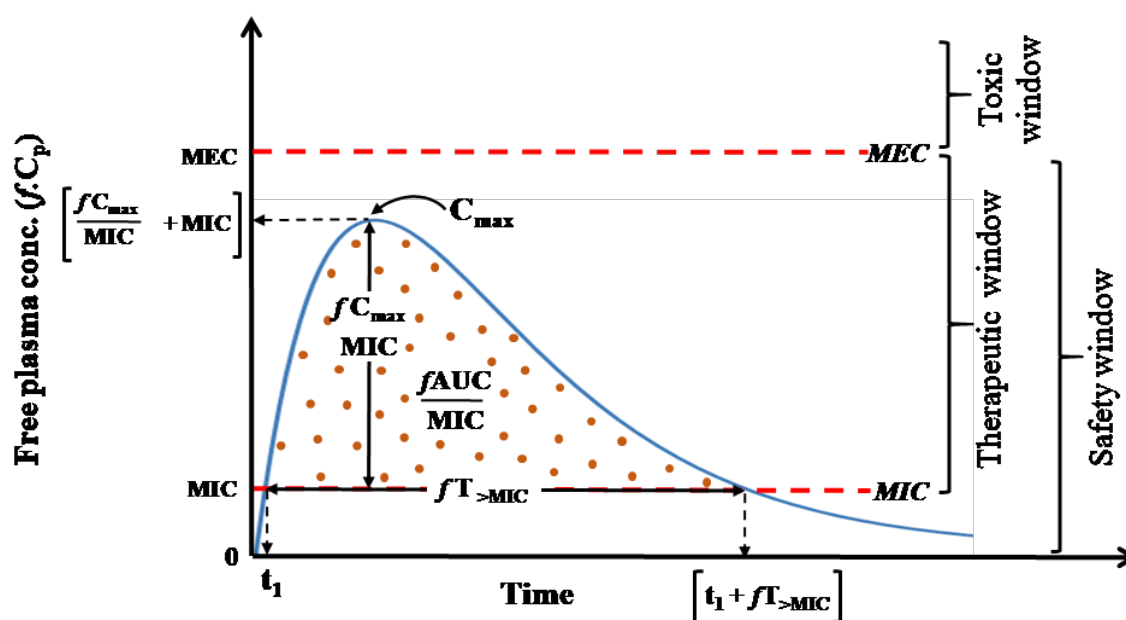


Figure 5. Graphical representation of pharmacokinetic/pharmacodynamic (PK/PD) indices of efficacy. The figure shows all three PK/PD parameters along with therapeutic, safety, and toxic windows.

Abbreviations: $fAUC$: Area under the curve of the free drug; fC_{max} : Maximum plasma concentration (C_{max}) of the free drug; fC_p : Plasma concentration of the free drug; $fT_{>MIC}$: Percentage of a dosage interval in which the free drug plasma level exceeds the MIC; MEC: Maximum effective concentration; MIC: Minimum inhibitory concentration.

Therefore, the mathematical expression of the PK/PD index $fC_{\max}/MIC$ can be written as:

$$\frac{fC_{\max}}{MIC} = \frac{f \cdot F k_a D_0}{V_d (k_a - k_{el})} \left[e^{-k_{el} \cdot t_{\max}} - e^{-k_a \cdot t_{\max}} \right] - MIC \quad (23)$$

6.2. Estimation of predicted efficacy dose using pharmacokinetic/pharmacodynamic parameters

Out of the three PK/PD indices, the PK/PD parameter used for predicted efficacy dose (PED) estimation is the one from the PK/PD analysis with the highest coefficient of determination (r^2), i.e., the best-fit value. If $fAUC/MIC$ shows the highest r^2 on the PK/PD graph, then the PED of the veterinary animal of interest is estimated from general mathematical deduction as:

$$F \times \text{Dose}_{\text{vet}} = AUC_{\text{vet}} \times Cl_{\text{total, vet}} \quad (24)$$

On the incorporation of PK/PD indices as alternatives to AUC_{vet} , **Equation 24** is written as:

$$F \times \text{Dose}_{\text{vet}} = \left(\frac{fAUC}{MIC_{90}} \right) \times \frac{MIC_{90}}{f_{u, \text{vet}}} \times Cl_{\text{total, vet}} \quad (25)$$

The numerical value for $fAUC/MIC_{90}$ is derived from the mouse PK/PD graph.

Therefore, on rearranging **Equation 25**, PED is given by:

$$\text{Predicted dose}_{\text{vet}} = \left[\left(\frac{fAUC}{MIC_{90}} \right) \times \frac{MIC_{90}}{f_{u, \text{vet}}} \times Cl_{\text{total, vet}} \right] \div F \quad (26)$$

If $fC_{\max}/MIC$ shows the highest r^2 on the PK/PD graph, then the predicted $C_{\max}$ is estimated from **Equation 27**:

$$\text{Predicted } C_{\max} = \left(\frac{fC_{\max}}{MIC_{90}} \right)^* \times \frac{MIC_{90}}{f_{u, \text{vet}}} \quad (27)$$

The PED is determined from a simulated veterinary oral PK profile using the Dedrick plot upon incorporation of the absorption rate constant. Using a simulation of the predicted free (unbound) drug oral plasma PK profile, the dose at which the free drug plasma concentration–time curve reaches the predicted $C_{\max}$ value is the dose of interest (PED dose).

If $fT_{>MIC}$ shows the highest r^2 on the PK/PD graph, then the PED is estimated graphically, assuming that the magnitude of $T_{>MIC90}$ is equal for the mouse and veterinary animal of interest, similar to $fC_{\max}/MIC$. The PED is

determined from a simulated veterinary oral PK profile. Using a simulation of a predicted free drug oral plasma PK profile, the dose at which the free drug oral concentration–time curve intersects the horizontal MIC_{90} line at $T_{>MIC}$ time is the PED dose, as shown in **Figure 6**.

Murine infection models are widely used to establish PK/PD targets because they provide a controlled and reproducible framework for defining the relationship between drug exposure and antibacterial efficacy. Although physiological, immunological, and pathological differences between mice and veterinary species may influence the direct translation of these targets, numerous studies have demonstrated that PK/PD indices, such as AUC/MIC , $C_{\max}/MIC$, and $\% \text{ of } fT_{>MIC}$, are generally conserved across species for a given antimicrobial class.^{68,69}

6.3. Optimized pharmacokinetic/pharmacodynamic strategies to mitigate resistance development

The present work proposes a novel cross-species PK/PD-guided framework that integrates AMR prevention with microbial ecology to optimize antimicrobial dosing while preserving microbial stability across animal species. Unlike conventional approaches that focus primarily on therapeutic efficacy, this framework emphasizes species-specific PK/PD targeting to minimize selective antimicrobial pressure, maintain microbiome integrity, and suppress the emergence of resistance.^{17,70} Evidence from veterinary pharmacology and metagenomic ecology indicates that inappropriate dose extrapolation across rodents, dogs, pigs, cattle, buffaloes, and wildlife disrupts commensal microbiota and accelerates the emergence of resistant bacterial populations.^{18,36} Integrating PK/PD indices, such as AUC/MIC , $C_{\max}/MIC$, and $T_{>MIC}$, into microbial ecology enables dosing strategies that achieve pathogen clearance while limiting collateral microbial damage and amplification of resistance genes.⁷⁰ Supported by population PK modeling, Monte Carlo simulations, and microbiome surveillance, this One Health-oriented framework advances precision antimicrobial therapy, the preservation of microbial diversity, and sustainable AMR containment.

7. Discussion

In both human and veterinary medicine, antibiotics are among the most essential treatment options. Inappropriate cross-species antimicrobial dosing in veterinary medicine promotes AMR by causing subtherapeutic exposure and selective pressure on bacteria. Species differences in PK can accelerate the emergence of resistant *E. coli*, *Salmonella*, and Methicillin-resistant *Staphylococcus aureus* in livestock and wildlife.^{18,71} Continuous low-dose

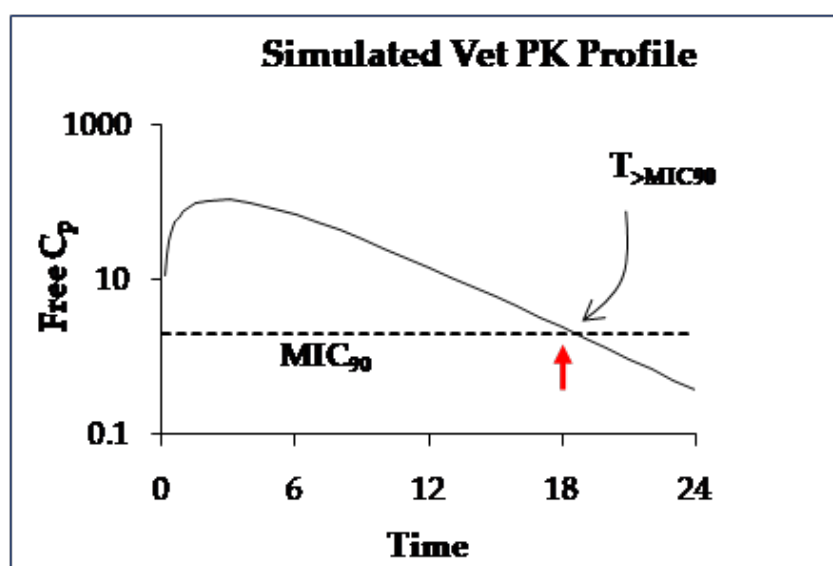


Figure 6. Graphical representation of $T_{>MIC90}$
Abbreviations: MIC: Minimum inhibitory concentration; PK: Pharmacokinetic; Vet: Veterinary.

exposure enhances horizontal gene transfer and multidrug resistance⁷⁰, highlighting the need for PK/PD-guided, species-specific antimicrobial stewardship and veterinary supervision. In veterinary medicine, two PK/PD indicators are often employed: (i) the time that the free drug plasma concentration surpasses the MIC during the dosing interval ($fT_{>MIC}$) and (ii) the ratio of the area under the curve of the free drug plasma concentration to the MIC ($fAUC/MIC$).⁴⁸ The primary goal of interspecies scaling is to determine an appropriate therapeutic dose and to offer preliminary estimates of the expected clinical therapeutic dose and half-life of a new drug during the drug discovery process. Two critical PK parameters, clearance and V_d , are necessary to model temporal drug profiles and predict half-life by integrating estimated clearance and V_{dss} . This approach generally provides more accurate half-life predictions than the direct correlation of half-life across different animal species.⁵⁰ In recent years, interspecies scaling of PK parameters and the prediction of human PK profiles through PK/PD analysis have gained considerable attention in anti-infective drug development. However, the extrapolation of animal PK data for veterinary dosing remains relatively under-explored. Consequently, dose extrapolation without appropriate validation may result in suboptimal therapeutic regimens, potentially contributing to treatment failure and the emergence of AMR. Furthermore, predictive performance should be supported by uncertainty analyses, including sensitivity analyses and confidence intervals, to assess the influence of variability in

physiological, PK, and microbiological parameters. These approaches may also be less reliable for drugs exhibiting nonlinear PK, species-specific metabolism, transporter-mediated disposition, variable oral absorption, or marked differences in plasma protein binding, highlighting the need for validation using target-species PK and clinical efficacy data.

In our previous work²⁴, the primary objective was to develop a robust approach for predicting human doses from rodent and non-rodent animal data. That study focused mainly on translating animal PK data into predicted human concentration–time profiles by incorporating human physiological parameters and interspecies scaling principles. In contrast, the present review focuses on interspecies dose prediction within veterinary species. Specifically, the current review transforms PK data from one animal species to another by generating predicted concentration–time profiles using the species-specific physiological parameters of the target veterinary animal. Accordingly, the methodological framework has been extended from animal-to-human extrapolation to animal-to-animal dose prediction in veterinary medicine.

In addition, the present review introduces a novel dimension by highlighting the potential role of accurate antibacterial dose prediction in veterinary species in reducing inappropriate dosing and, consequently, mitigating AMR. Therefore, although both our previous work²⁴ and the current review employ physiology-based translational principles, the present review differs

substantially in its application, target species, and clinical significance, and provides new insights into veterinary antibacterial dose optimization.

Ahmad *et al.*⁶⁷ described conventional PK/PD dose-optimization equations that directly calculate dosage regimens from established PK/PD indices, such as AUC/MIC and $T_{>MIC}$, using standard PK parameters, including clearance, bioavailability, and V_d . In contrast, the present review introduces a translational PED framework in which PK/PD targets are first derived from mouse infection models, the optimal PK/PD index is selected based on the highest coefficient of determination (r^2), and the veterinary dose is subsequently predicted through interspecies PK transformation and simulated veterinary PK profiles. Therefore, the current approach represents not merely a dose-optimization equation but a translational cross-species efficacy-prediction methodology.

Furthermore, Ahmad *et al.*⁶⁷ presented generalized equations for standard PK/PD indices without incorporating a statistical selection procedure. In the present review, however, PED estimation explicitly depends on selecting the PK/PD index that yields the highest r^2 from PK/PD modeling. This best-fit, statistically driven selection of the governing PK/PD index is not reported by Ahmad *et al.* While their approach relies on conventional PK/PD equations based on observed PK parameters, such as clearance and bioavailability, the present review uniquely integrates: (i) Dedrick plot-based interspecies scaling, (ii) transformation of animal PK data into veterinary species concentration–time profiles, and (iii) simulation of oral veterinary PK curves for PED determination.

Moreover, the current review determines PED graphically using simulated veterinary concentration–time profiles. Specifically, PED is defined as the dose at which the simulated free drug plasma concentration attains the predicted C_{max} value, or at which the simulated concentration–time curve intersects the MIC_{90} threshold for the required $T_{>MIC}$ duration. Ahmad *et al.*⁶⁷ did not describe the graphical determination of PED using simulated interspecies PK profiles. Although our proposed PED framework provides a rational approach for cross-species antibacterial dose prediction, its accuracy depends on the availability of reliable species-specific PK parameters and robust in vivo MIC or epidemiological susceptibility data for target pathogens. Predictions may also be influenced by assumptions regarding interspecies similarities in plasma protein binding, tissue distribution, and pathophysiology of host–pathogen interactions, highlighting the need for prospective clinical validation.

Overall, Ahmad *et al.*⁶⁷ provided a broad overview of

PK/PD principles, antimicrobial dose optimization, and resistance prediction in veterinary medicine. In contrast, the present review develops a specific translational methodology for predicting efficacious veterinary doses from mouse PK/PD data by integrating PK/PD target attainment, interspecies scaling, and simulated veterinary exposure profiles. Thus, although both studies involve PK/PD-guided dose estimation, the methodology proposed in the present review is mechanistically, statistically, and mathematically distinct from the generalized dose-optimization framework described by Ahmad *et al.*

8. Future perspective

Advanced PK/PD modeling is a cornerstone of modern veterinary pharmacology, providing a rational framework for optimizing antimicrobial therapy across diverse animal species. Traditional one-size-fits-all dosing approaches often overlook interspecies variability in drug ADME, which can compromise both therapeutic efficacy and safety.⁷² By integrating PK parameters (e.g., clearance, V_{dss} , half-life) with PD indices (e.g., MIC, time- or concentration-dependence of killing), advanced models enable the tailoring of dosage regimens that achieve the desired therapeutic targets while minimizing toxicity.

Importantly, PK/PD-guided strategies are pivotal in addressing AMR. Optimized dosing regimens can maximize bacterial kill, reduce the window of subtherapeutic exposure, and thereby decrease the selective pressure for resistant strains.⁷³ Numerous strategies have been proposed over time to enhance the predictive capabilities of time-course profiles; however, no strategy is without its shortcomings.⁷⁴ To improve the predictive outcome from animal data to veterinary species or from one veterinary species to another, a specific extrapolation method should be considered based on the physicochemical properties of drugs, such as renal secretion or biliary excretion, experimental design, species, and analytical errors, as all these factors may affect allometric extrapolation. Beyond PK/PD-based dose predictions, more powerful techniques are available for dose prediction in veterinary pharmacology, but their high data requirements, complexity, and time demands limit their routine use in clinical practice. In essence, advanced PK/PD applications provide not only a logical but also an efficient framework for improving drug efficacy, animal welfare, and public health protection by curbing the emergence and spread of AMR. Their broader adoption in veterinary medicine is therefore not just desirable, but essential.

Nowadays, the use of artificial intelligence (AI) in PK/PD dose prediction for veterinary animals is gaining significant attention. By integrating biological, physiological, and

drug-specific data, AI models surpass the limits of traditional interspecies extrapolation. Machine learning identifies ADME patterns in drug behavior to optimize and individualize dosing. This enhances treatment efficacy, minimizes toxicity, and simultaneously reduces the risk of AMR. However, it may still be several years before user-friendly AI tools are fully integrated into routine clinical practice for cross-species dose prediction.

9. Conclusion

This review presents a cross-species PK/PD-guided antimicrobial framework integrating microbial ecology and AMR prevention. By optimizing species-specific dosing and preserving microbiome stability, it minimizes selective pressure and the emergence of resistance while maintaining therapeutic efficacy. The approach supports One Health principles through precision antimicrobial therapy, preservation of microbial diversity, and sustainable AMR containment.^{17,70}

The integration of allometric scaling, Dedrick plots, and PK/PD-based PED estimation provides a practical framework for the early prediction of oral PK profiles and dose selection in veterinary species. Published studies have shown that these approaches can achieve reasonable predictive accuracy when the underlying assumptions of linear PK and conserved physiological processes are met. Nevertheless, model performance should be evaluated through external validation using observed PK and efficacy data from the target species. Uncertainty analyses, including sensitivity analyses and confidence intervals for key parameters, are also important for quantifying the effects of variability in physiological, PK, and microbiological inputs on model predictions. Furthermore, these methods may be less reliable for drugs exhibiting nonlinear PK, species-specific metabolism, transporter-mediated disposition, variable oral absorption, or marked differences in plasma protein binding. Therefore, model-derived dose predictions should be regarded as an evidence-based starting point and refined using target-species PK studies and, when available, clinical efficacy data.

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Conceptualization: Tridib Chaira, Tarani Kanta Barman

Visualization: All authors

Writing—original draft: All authors

Writing—review & editing: Tridib Chaira, Rashmi Kumari, Tarani Kanta Barman

All authors have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Van Boeckel TP, Brower C, Gilbert M, *et al.* Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA*. 2015;112(18):5649–5654.
doi: 10.1073/pnas.1503141112
2. Cromwell GL. Why and how antibiotics are used in swine production. *Anim Biotechnol*. 2002;13(1):7–27.
doi: 10.1081/ABIO-120005767
3. Lei Z, Liu Q, Xiong J, *et al.* Pharmacokinetic and Pharmacodynamic Evaluation of Marbofloxacin and PK/PD Modeling against *Escherichia coli* in Pigs. *Front Pharmacol*. 2017;8:542.
doi: 10.3389/fphar.2017.00542
4. Van Boeckel TP, Glennon EE, Chen D, *et al.* Reducing antimicrobial use in food animals. *Science*. 2017;357(6358):1350–1352.
doi: 10.1126/science.aao1495
5. Tiseo K, Huber L, Gilbert M, Robinson TP, Van Boeckel TP. Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. *Antibiotics*. 2020;9(12):918.
doi: 10.3390/antibiotics9120918
6. Sartorius B, Gray AP, Davis Weaver N, *et al.* The burden of bacterial antimicrobial resistance in the WHO African region in 2019: a cross-country systematic analysis. *Lancet Global Health*. 2024;12(2):e201–e216.
doi: 10.1016/s2214-109x(23)00539-9
7. Ferdinand AS, McEwan C, Lin C, *et al.* Development of a cross-sectoral antimicrobial resistance capability assessment framework. *BMJ Glob Health*. 2024;9(1):e013280.
doi: 10.1136/bmjgh-2023-013280

8. Caneschi A, Bardhi A, Barbarossa A, Zaghini A. The Use of Antibiotics and Antimicrobial Resistance in Veterinary Medicine, a Complex Phenomenon: A Narrative Review. *Antibiotics*. 2023;12(3):487.
doi: 10.3390/antibiotics12030487
9. MacGowan A, Macnaughton E. Antibiotic resistance. *Medicine*. 2017;45(10):622-628.
doi: 10.1016/j.mpmed.2017.07.006
10. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47(6):735-743.
doi: 10.1086/591126
11. Cameron A, McAllister TA. Antimicrobial usage and resistance in beef production. *J Anim Sci Biotechnol*. 2016;7:68.
doi: 10.1186/s40104-016-0127-3
12. Mithuna R, Tharanyalakshmi R, Jain I, et al. Emergence of antibiotic resistance due to the excessive use of antibiotics in medicines and feed additives: A global scenario with emphasis on the Indian perspective. *Emerg Contam*. 2024;10(4):100389.
doi: 10.1016/j.emcon.2024.100389
13. Barman TK, Arora P, Rao M, Bhadauriya T, Upadhyay DJ. Utilization of Bombyx mori larvae as a surrogate animal model for evaluation of the anti-infective potential of oxazolidinones. *J Infect Chemother*. 2008;14(2):166-169.
doi: 10.1007/s10156-008-0586-3
14. Boffito M, Back D, Stainsby-Tron M, et al. Pharmacokinetics of saquinavir hard gel/ritonavir (1000/100 mg twice daily) when administered with tenofovir diproxil fumarate in HIV-1-infected subjects. *Br J Clin Pharmacol*. 2005;59(1):38-42.
doi: 10.1111/j.1365-2125.2004.02240.x
15. Lees P, Shojaee Aliabadi F. Rational dosing of antimicrobial drugs: animals versus humans. *Int J Antimicrob Agents*. 2002;19(4):269-284.
doi: 10.1016/s0924-8579(02)00025-0
16. Prescott JF. Antimicrobial use in food and companion animals. *Anim Health Res Rev*. 2008;9(2):127-133.
doi: 10.1017/S1466252308001473
17. Toutain PL, Ferran A, Bousquet-Melou A. Species differences in pharmacokinetics and pharmacodynamics. In: Cunningham F, Elliott J, Lees P, eds. *Comparative and Veterinary Pharmacology*. Handbook of Experimental Pharmacology, vol 199. Berlin, Heidelberg: Springer; 2010:19-48.
doi: 10.1007/978-3-642-10324-7_2
18. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Rev*. 2011;24(4):718-733.
doi: 10.1128/CMR.00002-11
19. Allen HK, Donato J, Wang HH, Cloud-Hansen KA, Davies J, Handelsman J. Call of the wild: antibiotic resistance genes in natural environments. *Nat Rev Microbiol*. 2010;8(4):251-259.
doi: 10.1038/nrmicro2312
20. Meier H, Spinner K, Crump L, Kuenzli E, Schuepbach G, Zinsstag J. State of Knowledge on the Acquisition, Diversity, Interspecies Attribution and Spread of Antimicrobial Resistance between Humans, Animals and the Environment: A Systematic Review. *Antibiotics*. 2022;12(1):73.
doi: 10.3390/antibiotics12010073
21. Soh HY, Tan PXY, Ng TTM, Chng HT, Xie S. A Critical Review of the Pharmacokinetics, Pharmacodynamics, and Safety Data of Antibiotics in Avian Species. *Antibiotics*. 2022;11(6):741.
doi: 10.3390/antibiotics11060741
22. Ahmed H, Bohmdorfer M, Eberl S, Jager W, Zeitlinger M. Interspecies variability in protein binding of antibiotics basis for translational PK/PD studies-a case study using cefazolin. *Antimicrob Agents Chemother*. 2024;68(4):e0164723.
doi: 10.1128/aac.01647-23
23. Zhou SF, Liu JP, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev*. 2009;41(2):89-295.
doi: 10.1080/03602530902843483
24. Chaira T, Subramani C, Barman TK. ADME, Pharmacokinetic Scaling, Pharmacodynamic and Prediction of Human Dose and Regimen of Novel Antiviral Drugs. *Pharmaceutics*. 2023;15(4):1212.
doi: 10.3390/pharmaceutics15041212
25. Prueksaritanont T, Tang C. ADME of biologics-what have we learned from small molecules? *AAPS J*. 2012;14(3):410-419.
doi: 10.1208/s12248-012-9353-6
26. Avery LB, Zarr MA, Bakshi RP, Siliciano RF, Hendrix CW. Increasing extracellular protein concentration reduces intracellular antiretroviral drug concentration and antiviral effect. *AIDS Res Hum Retroviruses*. 2013;29(11):1434-1442.
doi: 10.1089/AID.2013.0031
27. Fischl MA, Richman DD, Flexner C, et al. Phase I/II study of the toxicity, pharmacokinetics, and activity of the HIV protease inhibitor SC-52151. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;15(1):28-34.
doi: 10.1097/00042560-199705010-00005
28. Antonovic L, Martinez M. Role of the cytochrome P450 enzyme system in veterinary pharmacokinetics: where

- are we now? Where are we going? *Future Med Chem.* 2011;3(7):855-879.
doi: 10.4155/fmc.11.37
29. Court MH. Canine cytochrome P-450 pharmacogenetics. *Vet Clin North Am Small Anim Pract.* 2013;43(5):1027-1038.
doi: 10.1016/j.cvsm.2013.05.001
 30. Hammer H, Schmidt F, Marx-Stoelting P, Potz O, Braeuning A. Cross-species analysis of hepatic cytochrome P450 and transport protein expression. *Arch Toxicol.* 2021;95(1):117-133.
doi: 10.1007/s00204-020-02939-4
 31. Martignoni M, Groothuis GM, de Kanter R. Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. *Expert Opin Drug Metab Toxicol.* 2006;2(6):875-894.
doi: 10.1517/17425255.2.6.875
 32. Trepanier LA. Cytochrome P450 and its role in veterinary drug interactions. *Vet Clin North Am Small Anim Pract.* 2006;36(5):975-985.
doi: 10.1016/j.cvsm.2006.05.003
 33. Watanabe KP, Kawai YK, Ikenaka Y, *et al.* Avian cytochrome P450 (CYP) 1-3 family genes: isoforms, evolutionary relationships, and mRNA expression in chicken liver. *PLoS ONE.* 2013;8(9):e75689.
doi: 10.1371/journal.pone.0075689
 34. Nigam SK, Granados JC. OAT, OATP, and MRP Drug Transporters and the Remote Sensing and Signaling Theory. *Annu Rev Pharmacol Toxicol.* 2023;63:637-660.
doi: 10.1146/annurev-pharmtox-030322-084058
 35. International Transporter C, Giacomini KM, Huang SM, *et al.* Membrane transporters in drug development. *Nat Rev Drug Discov.* 2010;9(3):215-236.
doi: 10.1038/nrd3028
 36. Chu X, Bleasby K, Evers R. Species differences in drug transporters and implications for translating preclinical findings to humans. *Expert Opin Drug Metab Toxicol.* 2013;9(3):237-252.
doi: 10.1517/17425255.2013.741589
 37. Virkel G, Ballent M, Lanusse C, Lifschitz A. Role of ABC Transporters in Veterinary Medicine: Pharmacotoxicological Implications. *Curr Med Chem.* 2019;26(7):1251-1269.
doi: 10.2174/0929867325666180201094730
 38. Hann E, Malagu K, Stott A, Vater H. Chapter Three - The importance of plasma protein and tissue binding in a drug discovery program to successfully deliver a preclinical candidate. In: Witty DR, Cox B, eds. *Progress in Medicinal Chemistry.* Amsterdam: Elsevier; 2022:163-214.
doi: 10.1016/bs.pmch.2022.04.002
 39. Bohnert T, Gan LS. Plasma protein binding: from discovery to development. *J Pharm Sci.* 2013;102(9):2953-2994.
doi: 10.1002/jps.23614
 40. Li P, Fan Y, Wang Y, Lu Y, Yin Z. Characterization of plasma protein binding dissociation with online SPE-HPLC. *Sci Rep.* 2015;5:14866.
doi: 10.1038/srep14866
 41. Rosa B. Equine Drug Transporters: A Mini-Review and Veterinary Perspective. *Pharmaceutics.* 2020;12(11):1064.
doi: 10.3390/pharmaceutics12111064
 42. GollaBala A, Ahad H, Chintaginjala H, Chapidi SR, Kodi K. A technical view on transporters-the drug pharmacokinetics dictators. *MOJ Bioequiv Bioavailab.* 2019;6(4):47-53. Accessed February 1, 2026. <https://medcraveonline.com/MOJBB/MOJBB-06-00134.pdf>
 43. Liu H, Sahi J. Role of Hepatic Drug Transporters in Drug Development. *J Clin Pharmacol.* 2016;56(Suppl 7):S11-S22.
doi: 10.1002/jcph.703
 44. Mahmood I. Application of allometric principles for the prediction of pharmacokinetics in human and veterinary drug development. *Adv Drug Deliv Rev.* 2007;59(11):1177-1192.
doi: 10.1016/j.addr.2007.05.015
 45. Huang Q, Riviere JE. The application of allometric scaling principles to predict pharmacokinetic parameters across species. *Expert Opin Drug Metab Toxicol.* 2014;10(9):1241-1253.
doi: 10.1517/17425255.2014.934671
 46. Jairam RK, Mallurwar SR, Sulochana SP, *et al.* Prediction of Human Pharmacokinetics of Fomepizole from Preclinical Species Pharmacokinetics Based on Normalizing Time Course Profiles. *AAPS PharmSciTech.* 2019;20(6):221.
doi: 10.1208/s12249-019-1434-8
 47. Mahmood I, Balian JD. Interspecies scaling: predicting clearance of drugs in humans. Three different approaches. *Xenobiotica.* 1996;26(9):887-895.
doi: 10.3109/00498259609052491
 48. Tang H, Mayersohn M. A novel model for prediction of human drug clearance by allometric scaling. *Drug Metab Dispos.* 2005;33(9):1297-1303.
doi: 10.1124/dmd.105.004143
 49. Martinez M, Mahmood I, Hunter RP. Interspecies allometric scaling: prediction of clearance in large animal species: part II: mathematical considerations. *J Vet Pharmacol Ther.* 2006;29(5):425-432.
doi: 10.1111/j.1365-2885.2006.00787.x

50. Sawada Y, Hanano M, Sugiyama Y, Iga T. Prediction of the disposition of beta-lactam antibiotics in humans from pharmacokinetic parameters in animals. *J Pharmacokinet Biopharm.* 1984;12(3):241-261.
doi: 10.1007/BF01061720
51. Gong Y, Haque S, Chowdhury P, *et al.* Pharmacokinetics and pharmacodynamics of cytochrome P450 inhibitors for HIV treatment. *Expert Opin Drug Metab Toxicol.* 2019;15(5):417-427.
doi: 10.1080/17425255.2019.1604685
52. Oitate M, Nakayama S, Ito T, Kurihara A, Okudaira N, Izumi T. Prediction of human plasma concentration-time profiles of monoclonal antibodies from monkey data by a species-invariant time method. *Drug Metab Pharmacokinet.* 2012;27(3):354-359.
doi: 10.2133/dmpk.dmpk-11-sh-059
53. Boxenbaum H, Ronfeld R. Interspecies pharmacokinetic scaling and the Dedrick plots. *Am J Physiol.* 1983;245(6):R768-R775.
doi: 10.1152/ajpregu.1983.245.6.R768
54. Yagura H, Watanabe D, Kushida H, *et al.* Impact of UGT1A1 gene polymorphisms on plasma dolutegravir trough concentrations and neuropsychiatric adverse events in Japanese individuals infected with HIV-1. *BMC Infect Dis.* 2017;17(1):622.
doi: 10.1186/s12879-017-2717-x
55. Mahmood I. Role of fixed coefficients and exponents in the prediction of human drug clearance: how accurate are the predictions from one or two species? *J Pharm Sci.* 2009;98(7):2472-2493.
doi: 10.1002/jps.21597
56. Chaira T, Barman T, Samuel Raj V. In Vitro ADME, Preclinical Pharmacokinetics and Prediction of Human Pharmacokinetics of RBx14255, a Novel Ketolide with Pharmacodynamics Against Multidrug-Resistant Bacterial Pathogens. *J Pharm Pharm Sci.* 2020;23:206-219.
doi: 10.18433/jpps30942
57. Mordenti J. Man versus beast: pharmacokinetic scaling in mammals. *J Pharm Sci.* 1986;75(11):1028-1040.
doi: 10.1002/jps.2600751104
58. Mahmood I, Yuan R. A comparative study of allometric scaling with plasma concentrations predicted by species-invariant time methods. *Biopharm Drug Dispos.* 1999;20(3):137-144.
doi: 10.1002/(sici)1099-081x(199904)20:3<137::aid-bdd165>3.0.co;2-i
59. Tuntland T, Ethell B, Kosaka T, *et al.* Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at Novartis Institute of Biomedical Research. *Front Pharmacol.* 2014;5:174.
doi: 10.3389/fphar.2014.00174
60. Ambrose PG, Bhavnani SM, Rubino CM, *et al.* Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. *Clin Infect Dis.* 2007;44(1):79-86.
doi: 10.1086/510079
61. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm.* 2016;7(2):27-31.
doi: 10.4103/0976-0105.177703
62. Barman TK, Kumar M, Mathur T, *et al.* In Vitro and In Vivo Activities of DS-2969b, a Novel GyrB Inhibitor, and Its Water-Soluble Prodrug, DS11960558, against Methicillin-Resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 2018;62(6).
doi: 10.1128/AAC.02556-17
63. Kukanich B. Clinical interpretation of pharmacokinetic and pharmacodynamic data in zoologic companion animal species. *Vet Clin North Am Exot Anim Pract.* 2011;14(1):1-20.
doi: 10.1016/j.cvex.2010.09.006
64. Pandya M, Chakrabarti A, Rath S, *et al.* Activity of a novel series of acylides active against community-acquired respiratory pathogens. *Int J Antimicrob Agents.* 2010;36(2):169-174.
doi: 10.1016/j.ijantimicag.2010.03.026
65. Zhang H, He Y, Davies Forsman L, *et al.* Population pharmacokinetics and dose evaluations of linezolid in the treatment of multidrug-resistant tuberculosis. *Front Pharmacol.* 2023;13:1032674.
doi: 10.3389/fphar.2022.1032674
66. Asin-Prieto E, Rodriguez-Gascon A, Isla A. Applications of the pharmacokinetic/pharmacodynamic (PK/PD) analysis of antimicrobial agents. *J Infect Chemother.* 2015;21(5):319-329.
doi: 10.1016/j.jiac.2015.02.001
67. Ahmad I, Huang L, Hao H, Sanders P, Yuan Z. Application of PK/PD Modeling in Veterinary Field: Dose Optimization and Drug Resistance Prediction. *Biomed Res Int.* 2016;2016:5465678.
doi: 10.1155/2016/5465678
68. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis.* 1998;26(1):1-10;quiz 11-2.
doi: 10.1086/516284
69. Craig W. Pharmacodynamics of antimicrobial agents as a

- basis for determining dosage regimens. *Eur J Clin Microbiol Infect Dis*. 1993;12(Suppl 1):S6-S8.
doi: 10.1007/BF02389870
70. Andersson DI, Hughes D. Microbiological effects of sublethal levels of antibiotics. *Nat Rev Microbiol*. 2014;12(7):465-478.
doi: 10.1038/nrmicro3270
71. Lin JH. Species similarities and differences in pharmacokinetics. *Drug Metab Dispos*. 1995;23(10):1008-1021.
doi: 10.1016/S0090-9556(25)06742-X
72. Caffrey AR, Borrelli EP. The art and science of drug titration. *Ther Adv Drug Saf*. 2020;11:2042098620958910.
doi: 10.1177/2042098620958910
73. Onita T, Ishihara N, Yano T. PK/PD-Guided Strategies for Appropriate Antibiotic Use in the Era of Antimicrobial Resistance. *Antibiotics*. 2025;14(1):92.
doi: 10.3390/antibiotics14010092
74. Toutain PL, Pelligand L, Lees P, Bousquet-Melou A, Ferran AA, Turnidge JD. The pharmacokinetic/pharmacodynamic paradigm for antimicrobial drugs in veterinary medicine: Recent advances and critical appraisal. *J Vet Pharmacol Ther*. 2021;44(2):172-200.
doi: 10.1111/jvp.12917