

The Relationship Between Veterinary Pharmacology and Human Therapeutics

Marilyn N. Martinez, Ph.D.

*Pharmacologist, Food and Drug Administration
Center for Veterinary Medicine, Rockville, Maryland 20855*

To appreciate the extent to which veterinary drug development and regulation can influence human therapeutics, we first must examine the economics driving each of these two systems. In comparing recent reports published by the Animal Health Institute (AHI) and the Pharmaceutical Manufacturers Association (PMA), the latter representing both human and veterinary pharmaceuticals, it is evident that the financial foundation of the human and the veterinary drug industries are enormously different. These differences are expressed both in terms of sale revenues and research and development (R&D) allotments (Table 1). With the vast proportion of research funds being appropriated for human therapeutics, it's not surprising that veterinary pharmacology has had little opportunity to impact upon the progress of human medicine. Nevertheless, as technologies evolve and Guidelines are revised, new and valuable opportunities for research and regulatory harmonization are emerging.

Nearly half of all chemical entities approved for veterinary use also are approved for use in human patients (1993 FDA Approved Animal Drug Products; 1993 Physicians Desk Reference). The majority of this overlap involves anti-infective compounds. Of the nearly 300 chemical entities approved by the Center for Veterinary Medicine (CVM), over 21% can be classified as antimicrobials. Of these, approximately 60% are also the subject of approved human drug applications.

Both CVM and the Center for (human) Drug Evaluation and Research (CDER) generally require similar toxicology packages to verify product safety. However, CVM may request additional chronic toxicology data if an application is for use in a food-producing animal. Implementation of any additional requirements would be based on the perspective that drug residues contained within the edible tissues of food-producing animals act as chronically

administered, unintentional food additives (Somogyi, 1984).

CDER does not require chronic toxicity or carcinogenicity testing unless the drug is intended for chronic or chronic-intermittent administration (Goldenthal, 1968). In contrast, CVM requires chronic toxicity testing if the proposed level of residue in edible tissues exceeds 3 micrograms per ml. CVM requires carcinogenicity testing if the parent compound or any of its metabolites is a suspect carcinogen (CVM, 1986). Firms also voluntarily may provide chronic toxicity data if they wish to obtain a more liberal tolerance level for residues (thereby reducing their product's withdrawal time). Thus, CVM can be a repository of toxicology information which would be accessible to CDER in the event of unanticipated patient adverse reactions or when a firm seeks a chronic use indication for a drug previously approved solely on the basis of an acute exposure.

The science of veterinary pharmacology also can provide a wealth of information regarding the dose-response relationship of numerous anti-infective compounds. Of particular advantage in this regard is that a study involving naturally occurring infections bypasses many of the uncertainties associated with the extrapolation of data from animal models to human therapeutics (Barza, 1978). Such animal models often are employed during the preclinical phase of human drug development to help ascertain the biological activity of a drug against a targeted disease, to provide data for toxicity and safety evaluation and to provide the kinetic and dynamic data needed to assist in human dosing regimen evaluation and dose escalation strategies (Peck, *et al.*, 1992). Therefore, if the veterinary drug development data generated over a wide variety of diseases and animal species

TABLE 1
RELATIVE EXPENDITURES FOR HUMAN VS VETERINARY PHARMACEUTICALS

	Total Sales	R&D
AHI	\$2.3 billion (approx. \$1.3 billion of which were for pharmaceuticals)	\$400 million (\$252 million targeted at pharmaceutical preparations)
PMA	approximately \$57 billion	approximately \$10 billion

could be adequately captured, the resulting database could provide a practical tool for estimating an effective dosing regimen and would be applicable to both veterinary and human medicine.

Once an efficacious dose has been established, allometric scaling (based upon a comparison of intravenous pharmacokinetic data) may provide an inexpensive method of dose extrapolation to an alternative target host (Mordenti, 1985a,b). Although the host response to an invading pathogen is an important variable not factored into these equations, allometric scaling may be well suited to antimicrobials since the threshold response is dependent upon the invading organism rather than the host physiology.

CVM currently supports the efforts of Dr. J. E. Riviere and colleagues at the North Carolina State University to develop these allometric relationships. These analyses will be based upon information contained within the FARAD system (Riviere *et al.*, 1991; Craigmill *et al.*, 1994). The potential of a human therapeutic application for this endeavor is seen in the numerous examples where animal scale up has already successfully been employed to predict an effective drug dose in man (Kurihara *et al.*, 1992; McGovren *et al.*, 1988; Mitsuhashi *et al.*, 1990; Swabb & Bonner 1983).

Unfortunately, even if the targeted blood concentrations have been achieved, there remains an uncertainty regarding whether effective concentrations are present at the infection site. This issue begs the question of whether each infection site should constitute a new product indication. CDER's Division of Anti-Infective Drug Products poses this question in their POINTS TO CONSIDER document (CDER, 1992). They also raise the issue that firms potentially could be required to submit at least 2 adequate and well controlled clinical studies per infection site. Therefore, they leave open the possibility of integrating *in vitro* data,

pharmacokinetic data, pharmacodynamic data and relevant clinical data from comparable body sites as corroboration for certain effectiveness claims. Certainly, similar considerations constantly challenge the staff at CVM where clinical efficacy must be evaluated not only for each proposed label indication but also for each proposed host species.

In CVM's proposed Guideline for assessing animal therapeutics (1993), firms are requested to submit a detailed pharmacokinetic characterization of all new chemical entities and to assess blood drug concentrations during clinical efficacy trials. If implemented, integration of these data not only will provide the basis for characterizing the relationship between blood drug concentration, efficacy and toxicity but also will facilitate the development of pharmacokinetic models based upon the relationship between plasma drug concentrations and the corresponding drug concentration/time profiles in the various target tissues. It must be emphasized that we are not suggesting that efficacy be evaluated by comparing the drug concentration within whole tissue homogenates and an estimated bacterial minimum inhibitory concentration (MIC). The pitfalls associated with such an approach have been well documented (Cars, 1991). Rather, this is a summons for both the FDA and industry to explore ways of capturing and integrating the diverse wealth of information generated during the process of veterinary drug development.

To illustrate this point, let's consider a hypothetical veterinary compound which is manufactured for use in a food-producing animal. In this example, the drug entity exhibits little protein binding and is extremely well absorbed. For the sake of simplicity, we will assume that this particular compound undergoes little if any metabolism within any of the target tissues, that it acts extracellularly and that the MIC for the pathogen of interest (pathogen A) is 2 mcg/ml.

Using the blood and tissue pharmacokinetic data contained within this hypothetical submission, we will generate a four compartment body model consisting of a central (blood) compartment and three tissue compartments. In practice, it might be advisable to include a "sink" compartment which represents the drug concentrations within the other undefined body tissues. We also will assume that the tissue data demonstrate high concentrations of drug within tissues 1 and 3, that tissue 1 depletes very slowly and that the drug depletes very rapidly from tissue 3. Further, although the levels of drug are very low in tissue 2, its rate of depletion is somewhat slower than that of tissue 3.

The whole blood versus plasma data suggest that there is little partitioning of the drug across cell membranes. Therefore, its distribution would appear to be confined to the extracellular spaces. Accordingly, the concentrations of drug quantified in the whole tissue homogenates must be adjusted to the estimated percent fluid volume contributing to the overall wet weight of the tissue. These adjusted concentrations would then be integrated with the blood level data to establish a "therapeutic pharmacokinetic model".

Using this therapeutic pharmacokinetic model, we evaluated the potential clinical effects associated with four different dosing regimens: 250 mg b.i.d., 500 mg s.i.d., 500 mg t.i.d. and a reformulated sustained release (SR) 500 mg product administered s.i.d. Simulations were produced using the ADAPT II pharmacokinetic software package (1992) and the following pharmacokinetic estimates:

<u>Tissue to Blood</u>	<u>Blood to Tissue</u>
Tissue 1=0.001	Tissue 1=0.08
Tissue 2=2.0	Tissue 2=0.08
Tissue 3=2.5	Tissue 3=1.0
elimination rate constant (Kel)=1.0	
Volume of the central compartment=1	
Volume of tissue 1=1	
Volume of tissue 2=2	
Volume of tissue 3=1	

From the results of these simulations (Table 2) we constructed the following hypothesis:

- Since very little drug enters tissue 2, this drug most probably will not provide an effective treatment against infections caused by pathogen A in tissue 2.

- This drug should be highly efficacious in treating infections caused by pathogen A in tissue 1. However, due to the potential delay in reaching the MIC, a loading dose might be necessary if a 250 mg b.i.d. regimen is employed. Since the drug tends to accumulate in tissue 1, this tissue should be considered a potential site for adverse drug effects.

- For infections located within tissue 3, the optimal dosing regimens will be highly dependent upon the drug's mechanism of action. For example, if its activity is dependent upon peak concentrations (C_{max}), such as that seen with the aminoglycosides and fluoroquinolones (Zhanel & Ariano, 1992; El Bahri & Blouin, 1991; Drusano *et al.*, 1993), neither the 500 mg sustained release product nor the 250 mg b.i.d. dose should be employed. If peak concentrations are less critical than is the area above the MIC (AUC_{MIC}), then the 250 b.i.d. and the 500 mg s.i.d. may be equally efficacious. However, if the time above MIC (T>MIC) is most important, the 250 b.i.d. regimen will be superior to that of 500 s.i.d. dosing. This will be particularly true for a beta-lactam since these agents tend to have little or no post-antibiotic activity (Drusano, 1988). In fact, if little or no post-antibiotic activity is present, the 500 mg SR product should be chosen to treat infections caused by pathogen A in tissue 3. Finally, due to the potential toxicity associated with drug accumulation within tissue 1, the 500 mg t.i.d. regimen should be chosen only if AUC_{MIC} must be maximized (such as in the case of a highly resistant bacterial strain).

It is well recognized that blood and tissue kinetics in healthy tissues differ from those encountered under pathological conditions (Barza & Cuchural, 1985; Bergogne-Berezin, 1988; Clarke *et al.*, 1989; Decre & Bergogne-Berezin, 1993). Nevertheless, tissue drug depletion data can assist in the development of pharmacokinetic models superior to those based solely on the integration of MIC estimates and blood level profiles (Kays, *et al.* 1991). Optimally, dose determination for both human and veterinary drug products (particularly, new indications and new animal species) will be assisted by integrating therapeutic pharmacokinetic models with such pivotal information as pathogen sensitivity, disease response, the modality of the bacteriocidal effects, host defense response, duration of a postantibiotic effect, blood flow to

the infection site, species-specific differences in drug metabolism and the life cycle of the invading microbe (Barza & Cuchural, 1985; Bergeron, 1992; Bergogne-Berezin, 1988; Brown, 1987; Calabrese *et al.*, 1992; Caldwell, 1992; Carbon, 1992; Clarke *et al.*, 1989; Craig & Gudmundsson, 1986; Drusano, 1988; Koritz & Bevill, 1991).

In the recent past, CDER and CVM have collaborated in such areas as manufacturing chemistry, environmental chemistry, microbiology, toxicology and pharmacokinetics. Ultimately, these cooperative efforts will increase the efficiency of both veterinary and human drug approval processes and will lead to safer, more efficacious and more cost-effective dosing regimens.

TABLE 2
Data Simulation: Results Over a 24 Hour Dosing Interval

	Blood day 1-4	Tissue 1 day 1	Tissue 1 day 4	Tissue 2 day 1-4	Tissue 3 day 1-4
250 MG BID T>MIC	15 hrs	11.5 hrs	24 hrs	0	12
AUCmic	480	19	310	0	182
CMAX	90 µg/mL	4 µg/mL	16 µg/mL	1.4 µg/mL	31 µg/mL
500 MG SID T>MIC	9 hrs	22 hrs	24 hrs	1.5 hr	7
AUCmic	480	34	310	1.0	182
CMAX	181 µg/mL	4 µg/mL	15 µg/mL	2.8 µg/mL	62 µg/mL
500 MG TID T>MIC	24 hrs	22 hrs	24	4.5 hr	21 hrs
AUCmic	1440	117	930	3.0	546
CMAX	181 µg/mL	12 µg/mL	45 µg/mL	2.8 µg/mL	62 µg/mL
500 MG SR, day 1: T>MIC	24 hrs	8 hrs	-----	0	23 hrs
AUCmic	287	2.5287	-----	0	85
CMAX	20 µg/mL	2.6 µg/mL	-----	0.4 µg/mL	8 µg/mL
500 MG SR day 4: T>MIC	24 hrs	-----	24 hrs	0	24 hr
AUCmic	441	-----	235	0	148
CMAX	30 µg/mL	-----	13 µg/mL	0.6 µg/mL	12 µg/ml

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**SESSION 2: Veterinary Pharmacology in
Animal Health Pharmaceuticals**

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