Introduction: A Welcome to the First Special Animal Health Issue of AAPS PharmSci

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Marilyn Martinez¹ and Stefan Soback²

¹Food and Drug Administration, Center for Veterinary Medicine, Rockville, MD 20855

²Kimron Veterinary Institute, Ministry of Agriculture, Beit Dagan 50250, Israel

ABSTRACT

The goal of this special volume is to provide veterinary scientists with state-of-the art reviews in animal health and to inform human health scientists of the various challenges and collaborative opportunities associated with their animal health counterparts. The contributors are highly respected experts, providing invaluable insights into current issues and state-of-the-art advances within veterinary medicine.

KEYWORDS: Veterinary medicine, harmonization

INTRODUCTION

Within the United States, research-based pharmaceutical companies spent an estimated \$30.5 billion in 2001 on research and development. Of this amount, only an estimated \$0.6 billion was spent on pharmaceuticals for veterinary use.¹ In addition to the challenge of small budgets and low profit margins, diverse anatomical and physiological characteristics make animals a very challenging target for achieving successful pharmaceutical product development.

The kinds of therapeutic interventions sought for veterinary species reflect the changing pressures exerted by modern society. For example, as companion animals take on a growing importance within the human household, clinical concerns are becoming increasingly similar to those of human medicine. These include the need for effective treatments against cancer,² anxiety,³ pain,^{4,5} and hypertension.⁶ Food-animal pharmaceutical demands closely follow changes in both consumer expectations and husbandry practices.⁷⁻⁹ With regard to aquaculture needs, given that more than 16% of the worldwide consumption of animal protein is derived from aquatic species,¹⁰ fish and shellfish farms have taken on a high level of importance.¹¹ Along with this demand comes the need for aquatic farming methods and the resulting need to control the outbreak of infectious diseases.¹²

One may ask, "Would the human pharmaceutical development benefit from interaction/harmonization with the veterinary health counterpart?" The answer lies, at least in part, in the similarity of certain disease conditions and the opportunity to explore the impact of species-specific physiological differences on the correlations between drug pharmacokinetics and pharmacodynamics. Such comparisons can provide the human health scientist with a rich appreciation of the impact of numerous variables on product safety and effectiveness. With this in mind, we have asked Prof Pierre-Louis Toutain to review ongoing research efforts aimed at understanding the pharmacokinetic and pharmacodynamic relationships supporting veterinary drug development and dose optimization.

The animal health scientist also has a unique opportunity to explore the relationship between dose, drug absorption, tissue kinetics, and cellular responses to specific pharmaceutical interventions. This is particularly important for drugs developed for use in food animals, where the drug sponsor must address not only target animal safety and effectiveness but also human food safety. Clearly, information on the tissue depletion of drug residues provides important insights into the relationship between a species' physiological characteristics and the corresponding differences in drug metabolism, distribution, and elimination. Drs Craigmill and Cartright have reviewed the state-of-the-art methods used to evaluate human food safety. They also explore current and future directions in the development of methods for extrapolating such information across target animal species and dosing regimens.

The importance of animal models in human medicine can be seen in their extensive use in product development. In this regard, PhRMA 2001 financial estimates indicate that 36% of human drug research and development expenditures are devoted to preclinical functions, and that about 18.7% is spent on preclinical biological screening, pharmacological testing, and continued evaluation of safety and toxicity.¹³ This includes the use of animal models as surrogates for the development of antidotes to bioterrorism attacks.¹⁴⁻¹⁵

There is a growing emphasis on the use of nonclinical safety studies to support the development of human pharmaceuticals. For this reason, the US Center for Drug Evaluation and Research (CDER), Center for Bio-

Corresponding Author: Marilyn Martinez, Food and Drug Administration, Center for Veterinary Medicine, Rockville, MD 20855. Telephone: (301) 827-7577; Facsimile: (301) 594-2298; E-mail: MMartin1@cvm.fda.gov

logic Evaluation and Research (CBER), and Center for Devices and Radiologic Health (CDRH) have issued guidances that include the use of preclinical data and animal models in the drug evaluation process.¹⁶⁻¹⁸ Animal models have also become an important mechanism for assessing the risk/benefit ratio of antiviral agents that are potentially immunotoxic or may otherwise result in adverse tissue effects. In this regard, it is of interest to note the current debate regarding whether or not recent advances in the development of a feline immunodeficiency virus vaccine may advance the development of a vaccine for the human counterpart (HIV).¹⁹

Understanding how product absorption characteristics may vary across species can provide important insights into the potential effects of human phenotypic variation or the impact of disease on oral drug absorption. For example, the interspecies differences in drug absorption caused by differences in gastric pH may be similar to bioavailability differences occurring in achlorhydric patients. Interspecies differences associated with the biliary recycling of compounds may reflect some of the differences that might occur in patients whose gall bladders have been removed.²⁰ Variability in gastrointestinal (GI) transit time may reflect differences that could occur in those diseases that induce GI motility changes in humans, such as Crohn's disease,²¹ villus atrophy,²² HIV infection,²³ stress,²⁴ and pain.²⁵ Therefore, improving the ability to predict species-by-formulation interactions in animal species may significantly improve our understanding of the adaptations needed to accommodate the changes in human drug absorption that may occur during medically relevant situations.

Clearly, to appreciate the correlation between dose, kinetics, and clinical effect, it is necessary to understand the relationship between a species' physiology, its normal progression of disease conditions, and its metabolic idiosyncrasies. The development of this understanding is the role of the veterinary clinical pharmacologist. The expertise of veterinary clinical pharmacologists is essential for tailoring therapeutic interventions to the specific needs of a given animal species. Such expertise also provides invaluable insights that can be applied toward the development of animal models that can bridge human and veterinary medicine. Despite their scientific and clinical importance, there is a critical shortage of board-certified veterinary clinical pharmacologists. Drs Langston and Clarke - 2 of the 36 within the United States - examine the likely reasons for this problem and explore potential solutions.

Antimicrobial resistance is another critical issue facing both human and veterinary medicine. In addition to concerns regarding the impact of drug use on the susceptibility of veterinary pathogens, veterinary medicine must also address public health concerns regarding the problems associated with zoonotic pathogens and human food safety. Drs Tollefson and Flynn describe the complexities of this problem and the FDA's multipronged ap-

proach for minimizing the human health risk associated with the veterinary use of antimicrobial compounds.

The flip side of the antimicrobial resistance issue is the role of vaccines in the fight against disease. Biologics are critical to animal health for combating both microbial and parasitic infections. Vaccinations have come a long way from the days when animals were injected with the processed tissues of diseased animals.²⁶ However, significant challenges remain. These range from the need for oral vaccines for use in herd animals to the need for vaccines that can be delivered to aquatic species. There is also the issue of interspecies difference in lymphatic uptake of substances. These can reflect species-related differences in the digestion of lipid substances (eg, it would be reasonable to expect better lymphatic uptake in carnivores or omnivores as compared to herbivores) and the distribution and density of intestinal lymphoid (eg, the species differences in the histology of the Peyer's patches).²⁷⁻²⁹ Dr Bowersock reviews the science of biologics, the utility of vaccines in veterinary medicine, and current challenges facing immunization efforts in veterinary medicine.

In addition to complex health issues, the veterinary pharmaceutical scientist must also address the chemistry and manufacturing challenges associated with development of the novel dosage forms (eg, the FDA-approved oral sulfadimethoxine 12.5-g bolus for use in cattle).³⁰ Until recently, there were no standardized in vitro test procedures that could be used either to ensure batch-to-batch uniformity or to examine the potential effect of formulation and manufacturing modifications on drug release. For this reason, Drs Fahmy, Marnane, Bensley, and Hollenback have reviewed the results of their landmark research in this area. Through the collaborative efforts of these scientific experts, there now exist in vitro test methods that not only employ the traditional USP apparatus II, but also require no more than 900 mL of dissolution media.

Finally, Drs Martinez and Rathbone provide a brief overview of several of the pharmaceutical outreach and harmonization efforts that are currently under way. These include workshops, Web-based networking opportunities, professional organizations, publications, and global resources. In keeping with the theme of this issue, the goal of this summary is to stimulate further interactions among the various areas of specialization within veterinary medicine and between the human and veterinary scientific communities.

Drs Martinez and Soback wish to express sincere gratitude to each of the authors for their outstanding contributions to this volume. We know that it will prove to be an invaluable source of information for both human and veterinary pharmaceutical scientists. It is our hope that by publishing these articles, we can enhance communication and encourage the formation of collaborative bridges between veterinary and human health counter-

parts. Similarly, it is our hope that animal health scientists unfamiliar with many of the human health issues will gain new insights by viewing other volumes of *AAPS PharmSci*.

It is our intent to publish additional animal health-themed issues of *AAPS PharmSci*. In fact, at this writing, our second issue is under development. Therefore, we welcome your comments on the contents of this issue and your suggestions regarding future veterinary-themed issues of *AAPS PharmSci*. You can contact Dr Marilyn Martinez at Mmartin1@cvm.fda.gov.

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