Review Article

International Veterinary Bioequivalence Guideline Similarities and Differences Between Australia, Canada, Europe, Japan, New Zealand and the United States

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Abstract. Considering the diversity in physiology between species and the numerous dosage forms that exist in veterinary drug products, there are numerous complex issues that arise from the development and regulation of veterinary drugs for food-producing and companion animals. Generic drugs are no exception. The main objective of this article is to illustrate the current important similarities and differences between international veterinary bioequivalence guidelines. It is concluded that since important differences are found, these may lead to barriers in international data exchange and scientific confusion, hence fostering the need for a harmonization effort in developing consistent guidelines based on sound pharmacological and statistical principles for the approval of veterinary generic drugs around the world.

KEY WORDS: bioequivalence; comparison; generic; international; veterinary drugs.

INTRODUCTION

Consistent with the diversity in physiology that exists across veterinary species and because of the unique formulations and methods of drug administration associated with veterinary drugs, there are numerous complex issues that are unique to the regulation of these drug products. Accordingly, the determination of product bioequivalence (BE) in animal species can present a host of statistical, logistical and regulatory challenges.

International differences in addressing these challenges and in defining the criteria for determining BE may lead to barriers in international data exchange and scientific confusion. In consideration of these scenarios, an effort to harmonize the critical BE parameters is necessary to establish consistency within the scientific and regulatory communities. In the foreshadowing of international harmonization, it is appropriate to demonstrate the numerous similarities and few differences in veterinary BE guidelines between the regulatory authorities around the world. Thus, the purpose of this article is to highlight, in a tabulated form, important international criteria for the consideration of granting biowaivers and for the demonstration of BE for veterinary drug products intended for both food-producing and companion animals.

MATERIALS AND METHODS

Tabulation of similarities and differences in veterinary BE guidelines between regulatory authorities was possible by referring to government websites (1–6) from Australia, Canada, Europe, Japan, New Zealand and the United States, and by consulting regulatory agents from each country.

RESULTS

Table I is a comparative table of the main criteria for granting biowaivers of *in vivo* BE studies by the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Health Canada's Veterinary Drugs Directorate (VDD), the European Medicines Agency (EMA), Japan's Ministry of Agriculture, Forestry and Fisheries/National Veterinary Assay Laboratory (MAFF/NVAL), New Zealand's Ministry of Agriculture and Forestry/Agricultural Chemicals and Veterinary Medicines (MAF/ACVM) and the US Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM).

Table II is a summary of the main similarities and differences in BE guidelines for the conduct of blood level studies between these same regulatory authorities.

DISCUSSION

Currently, as shown in the above tables, the registration requirements for demonstrating BE for veterinary

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Table 1. Summary of Criteria for Granting Waivers of *In Vivo* Bioequivalence Studies by Different Regulatory Authorities

Regulatory agencies	Solutions				Topically applied dosage forms		Oral dosage form	Same active and inactive ingredients	Same dosage form and strength	
	Parenteral (i.v., s.c., i.m.)	Oral or other solubilized forms		Inhalant volatile anaesthetic	Topical for local therapeutic use	Other than solutions				
		Yes	Yes			Yes				Yes
FDA/CVM (GFI # 35, 2006)	Yes	Yes	Yes	Yes	Dermatologic, otic and ophthalmic; non-food-producing animals only	Proportional formulations	Yes; usually same active and inactive ingredients	Yes		
EMA (EMA/CVMP/016/00-Rev.2, 2011)	Yes; aqueous i.v., same type of solution for i.m. or s.c. administration	Yes; aqueous	Yes	No mention	Only if formulations are identical (active substance and excipients as well as physicochemical properties)	Multiple strengths with proportional formulations; BCS Class I and III: solid and semi-solid immediate release dosage forms; pharmaceutical forms for in feed, drinking water or in milk	Yes; but may have different salt if BCS Class I	Yes; except different strengths may be used for i.v. solutions and BCS-based bioequivalents		
APVMA (GL #13, 2010)	Yes	Yes; aqueous	Yes	Yes; aqueous; dermatologic; oral ophthalmic, otic	Non-food-producing animals only	Some tablets and powders; and proportional formulations	Yes; products include vitamins, minerals, electrolytes, liniments, etc. antacids and radio-opaque media	Yes		
VDD (GFI ANDS, 2010)	Yes; aqueous	Yes; aqueous	Yes	Yes; simple topical solution category I (dermal, ophthalmic, otic and nasal)	Clinical endpoint studies preferred for ectoparasiticides, dermal/ophthalmic/otic, inhalant preparations, and intramammary products	Highly soluble soluble powder and medicated premixes; multiple strengths of proportional formulations	Yes; identical, usually same active and inactive ingredients	Yes		
MAF/ACVM (28 ACVM 08/02, 2000)	Yes; aqueous solutions/suspensions	Yes; aqueous solutions/suspensions	Yes	Yes; solution that do not contain any pharmacologically active ingredients, e.g., irrigation and cleaning solutions	Therapeutic equivalence can not be used as a method of fulfilling efficacy data requirements for intramammary preparations, estoparacitides or test dips	Highly soluble, highly permeable tablets, capsules, caplets, intratumoral delivery devices; multiple strengths of proportional formulations; antacid, radio-opaque media	Yes; active substance at same concentration; effects of excipients on absorption and/or GI transit time discussed; non novel excipients, same or comparable to reference product	Yes		
MAFF/NVAL (Notice 12 NVAL A No.418, Section 5, Appendix 8, GL 11-1, 2011)	Yes; aqueous only for i.v.	No	No	No	No	No	Yes same active substance at same concentration; no mention about inactive ingredients	Yes		
Regulatory agencies	Physicochemical characteristics		BCS criteria	Reformulated product		Change of manufacturing site	Tissue residue study			
	Same pH	Required		By original manufacturer	By original manufacturer		Required			
	FDA/CVM (GFI # 35, 2006)	Yes	Yes; correlate with specifications of the reference drug; comparative dissolution profiles for multiple strengths of solid oral dosage forms	No mention	No mention	No mention	No mention	Not generally required if <i>in vivo</i> BE waiver granted		
	EMA (EMA/CVMP/016/00-Rev.2, 2011)	No mention	Yes; highly soluble active substance; at 3 physiologically relevant pHs; product for in-feed use with insoluble excipients could be eligible for bioequivalence provided meet BCS criteria	Yes, species-specific defined criteria for waivers	Identical except for colouring/favouring agents or preservatives, or other excipients which are recognized as having no influence upon bioavailability	No mention	No mention	Local residues studies or a justification for their absence required		
APVMA (GL #13, 2010)	Yes	Yes; comparative dissolution profiles, crystalline form, particle size	No mention	No mention	Manufactured to same standard	Manufactured to same standard	Not addressed in guideline; applicants encouraged to read residues guidelines pertaining to their type of product			
VDD (GFI ANDS, 2010)	Yes	Yes; comparative dissolution profiles at 3 physiologically relevant pHs, crystalline form, particle size/distribution	No mention	Identical except for colouring/favouring agents or preservatives	Manufacturing process the same; minimal modifications; comparative dissolution profiles	Manufacturing process the same; minimal modifications; comparative dissolution profiles	Not generally required if <i>in vivo</i> BE waiver granted			

Table I. (continued)

Regulatory agencies	Physicochemical characteristics		BCS criteria		Reformulated product		Change of manufacturing site		Tissue residue study	
	Same pH	Pharmaceutical equivalence	Class I and III		By original manufacturer		By original manufacturer		Required	
MAF/ACVM (28 ACVM 08/02, 2000)	Yes	Yes; same particle size, crystal form, viscosity, water/oil miscibility; same dissolution profiles	No direct mention		Identical except for colouring/favouring agents or preservatives		Manufacturing process the same; minimal modifications; comparative dissolution profiles		May not be required if <i>in vivo</i> BE waiver granted	
MAFF/NVAL (Notice 12 NVAL A No.418, Section 5, Appendix 8, GL 11-1, 2011)	No mention	No mention	No mention		No mention		No mention		Not required if <i>in vivo</i> BE waiver granted	

CVM Center for Veterinary Medicine, US FDA; EMA European Medicine Agency, Europe; APVMA Australian Pesticides and Veterinary Medicines Authority, Australia; VDD Veterinary Drugs Directorate, Health Canada; MAF/ACVM Ministry of Agriculture and Forestry/Agricultural Chemicals and Veterinary Medicines, New Zealand; MAFF/NVAL Ministry of Agriculture, Forestry and Fisheries/National Veterinary Assay Laboratory, Japan; BE bioequivalence

pharmaceuticals vary from region to region. It has been discussed among international veterinary industry and regulatory members that harmonization of BE guidelines may help provide several important advantages. These include (1) improved animal welfare by minimizing the number of *in vivo* studies needed for global approval; (2) improved animal health by ensuring that regions employ comparable methods for demonstrating BE between veterinary drug products, thereby ensuring that the bio-equivalent product achieves the same clinical effect as would have been achieved if the reference product was administered under the same set of conditions and at the same dose, frequency and duration and (3) may ensure that efficacy and risks linked to the use of the bioequivalent product are controlled in the same way as the reference product. Therefore, when dealing with veterinary pharmaceuticals, there are two areas of public health in which a sound approach to BE is critical: minimization of anti-infective (antimicrobial, antiviral and antiparasitic) resistance development and assurance of human food safety.

One of the important challenges noted within Table II is that even if the “identical” reference product is used across jurisdictions, generally, these products are uniquely manufactured for distribution within a specific region. In this regard, even if formulations are considered identical, international differences in product specifications, manufacturing equipment and manufacturing process could potentially lead to international variations in product quality and performance. Therefore, even though a sponsor's globally marketed product contains the same ingredients (active and inactive), dosage form and strength, and indications, there is a perceived potential for differences in the *in vivo* bioavailability characteristics of these products across the various geographic regions. For this reason, regulatory authorities within each jurisdiction generally require that BE studies be conducted using the reference product that is marketed within their own jurisdiction, necessitating an individual BE study for each country. However, it should be noted that there are no published studies that explore the *in vivo* similarities and differences between veterinary reference products marketed across various geographic locations.

A first step in this assessment could simply be the comparison of *in vitro* product performance and specifications. It is possible that international concerns about the quality and performance differences between globally marketed reference products far outweigh the reality of these concerns (7). At this time, Canada's VDD *Guidance for Industry: Preparation of Abbreviated New Drug Submissions: Generic Drugs* (2010) requests a side-by-side comparison of physicochemical properties between a foreign-registered reference product and the same marketed Canadian Reference Product (CRP) to assess the appropriateness of the use of that foreign reference product instead of the CRP in the conduct of a BE study for the purpose of a Canadian approval of a generic drug product. New Zealand's MAF/ACVM may also accept studies conducted on overseas reference products if acceptable evidence is provided that the reference

Table II. Summary of Main Similarities and Differences in BE Guidelines for the Conduct of Blood Level Studies from International Regulatory Authorities

General considerations							Blood level study			
	Reference product selection	Dose selection	Route of administration selection	Species selection	Sample size determination	Prandial state	Parallel <i>versus</i> crossover	Single dose <i>versus</i> multiple dose	Dose normalisation	
Regulatory agency	GCP or GLP required	Domestic original pioneer currently marketed	Highest labelled dose (or higher if considered safe)	All routes as approved for the reference product	Healthy, homogenous target population; all major species	Determined <i>a priori</i> with pilot studies	Generally fasted unless unsafe	Two-period, two-sequence cross over preferred	Single dose preferred	Acceptable
FDA/CVM (GFI #35, 2006)	✓	✓	✓	✓ Extrapolation to minor species possible	Cattle, swine, chickens, dogs, cats, horses and turkeys	✓	✓ Fasted and fed for modified-release products, nonlinear PK, NTR, known food effect	✓ Parallel if drug induces physiological changes, very long t½, long washout period resulting in maturational changes, or flipflop kinetics	✓ Multiple dose if drug with nonlinear PK, NTR, inadequate assay sensitivity or flipflop kinetics	No mention
EMA (EMA/CVMP/016/00-Rev.2, 2011)	✓	✓ Any approved mg/kg dose may be used	✓	✓ Extrapolation to minor species possible	Cattle, sheep (meat), swine dogs, cats, chickens and salmon	✓; 2-Stage design is possible if prespecified	✓ Fasted and fed for modified-release products in non-ruminants	✓ Parallel if very long t½ or growing animals	✓ Multiple dose if low sensitivity of bioanalytical method; some modified-release drugs with known accumulation	Possible in special cases, prospectively defined in protocol and linear PK for active substance
APVMA (GL #13, 2010)	✓	✓	✓	✓ Extrapolation between certain species possible	Cattle,sheep, swine, chickens, dogs, cats, and horses	✓	✓	✓	✓ Multiple dose when effect dependent on SS blood concentrations	No mention
VDD (GFI ANDS, 2010)	✓	✓ Foreign reference product may be acceptable if identical to currently marketed CRP	✓ In mg/kg	✓ Partial label may be acceptable	✓ Extrapolation to minor species possible	✓	✓ Fasted and fed for modified-release products, nonlinear PK, NTR, known food effect	✓ Parallel if very long t½, growing animals, limited blood sampling (fish, chicks, poultry)	✓ Multiple dose if difficulty in measuring blood concentrations, drugs with complex PK (modified-release, non linear PK) in addition to single dose	Not generally considered acceptable

Table II. (continued)

	Blood level study		Blood level parameters 90% confidence interval				Human Food Safety	
	Blood sampling schedule	Defining the analyte	AUC	Cmax	Tmax	Cmin	Tissue residue study	Bioanalytical method
Regulatory agency	Determined through pilot studies to adequately capture peak and extent of absorption	Inactive prodrugs; enantiomers; endogenous substances	0.80–1.25	0.80–1.25	Assessed by clinical judgement	0.80–1.25	Required	Fully validated
APVMA (GL #13, 2010)	✓	No mention	✓	✓	✓	✓	Not addressed in this guideline; referred to residues	✓
VDD (GFI ANDS, 2010)	✓ AUC0-4/ AUC0-∞ >80%; 3X t½ past Tmax	No mention	✓ AUC0-INF, AUC0-LOQ or AUC0-τ (multiple dose); tighter if NTR	✓	✓ Cmax (single dose) or Cmax at SS (multiple dose); tighter if NTR	Tmax (single dose) or Tmax, ss (multiple dose)	Cmin at SS (multiple dose) transformed 0.80–1.25	✓ Comprehensive or abbreviated tissue residue study
MAF/ACVM (28 ACVM 08/02, 2000)	✓	No mention	Difference not more than 20%; flexible bounds	Difference not more than 20%; flexible bounds	Difference not more than 20%	No mention	✓	✓ Physiologically relevant pH conditions for target species; use of surfactant not acceptable; high solubility if 85% dissolved in 15 min
MAFF/NVAL (Notice 12 NVAL A No.418, Section 5, Appendix 8, GL 11-1, 2011)	✓ AUC0-4/ AUC0-∞ >80%; 3X t½ past Tmax; not less than 72 h if very long t½	Generally parent compound unless not measurable, active metabolite exceptionally; achiral bioanalytical method unless different PK between enantiomers	✓ AUC0-t (single dose) or AUCτ (multiple dose); calculated by trapezoidal method	✓ Use of an observed value; flexible bounds specific conditions	Reference only	No mention	✓ Single timepoint study	Not required

CVM=Center for Veterinary Medicine, US FDA; EMA= European Medicines Agency (veterinary medicines), Europe; APVMA=Australian Pesticides and Veterinary Medicines Authority, Australia; VDD= Veterinary Drugs Directorate, Health Canada; MAF/ACVM=Ministry of Agriculture and Forestry/Agricultural Chemicals and Veterinary Medicines, New Zealand; MAFF/NVAL= Ministry of Agriculture, Forestry and Fisheries/National Veterinary Assay Laboratory, Japan; CRP=Canadian Reference Product; PK=pharmacokinetics; NTR= narrow therapeutic ratio; IR=immediate-release; BE= bioequivalence; SS=steady-state; LOD=limit of detection; LOQ=limit of quantification; WDT= withdrawal time

product is equivalent to the NZ registered product. What constitutes acceptable evidence is dependent on the formulation type.

CONCLUSION

As pharmaceutical sciences move forward, the animal health industry is witnessing a rapid evolution in veterinary therapeutics and a growing need for ensuring international harmonization to accommodate the burgeoning global marketplace. The first step in support of this evolving therapeutic landscape is efforts to obtain a universal definition of BE, along with agreement on the underlying pharmacokinetic, statistical and bioanalytical principles essential to BE assessments. Such a harmonization process will serve as an important first step towards pharmaceutical globalization and will help reduce or eliminate potential confusion on the application of BE concepts to veterinary medicines.

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