VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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CONCEPT PAPER

Establishment of an Expert Working Group to Elaborate the Requirements to Demonstrate Bioequivalence of Veterinary Pharmaceuticals by Blood Level Studies

1. Introduction

Following a proposal to establish an Expert Working Group (EWG) within VICH to develop a guideline on bioequivalence (BE) requirements, the 23rd VICH Steering Committee (SC) set up a Task Force (TF) to clarify the scope of such potential guideline so that the subcommittee could render a final decision on the merit of such a guideline

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 pharmaceuticals, there are numerous complex issues that are unique to the regulation of veterinary pharmaceuticals. Accordingly, the determination of 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 can lead to barriers in international data exchange and scientific confusion. Therefore, there is a great need for fostering a harmonization effort. [1] It is with an appreciation of the need for harmonization of these fundamental principles that has led to this proposal to establish an EWG within VICH to examine the similarities and differences among VICH member and observer countries/regions and to facilitate agreement between VICH member and observer countries/regions on these requirements. In the context of global outreach/strategic phase III, the SC may wish to reflect on the type of guideline that would also be beneficial to develop for use in non-VICH countries and on the process for development and consultation of such a guideline.

Within the context of the current VICH proposal, the first step in harmonization would be to ensure that a universal definition of BE is achieved and that all parties are in agreement with the underlying fundamental pharmacokinetic, statistical, and bioanalytical principles essential to all blood level BE assessments.

2. Problem:

Japan, EU, and U.S. have developed (or are developing or revising) BE guidelines for veterinary drugs. When comparing the requirements for documenting BE, there are several differences in the guidance

[1] The ICH Global Cooperation Group was formed on March 11, 1999 as a subcommittee of the ICH Steering Committee. Please see (http://www.ich.org/LOB/media/MEDIA4871.pdf).

documents. The magnitude of discrepancies have been documented in the Summary Report of International Bioequivalence Guidelines, authored by Chantal Lainesse, DVM, Ph.D., diplomate ACVCP (June 4, 2008; see appendix). Furthermore (and perhaps most importantly), the lack of a harmonized guideline has caused confusion in how BE will be assessed in numerous jurisdictions. For example, our current information indicates that there are no veterinary BE guidelines in India and Brazil: Argentina has a BE guidance in early development but many other countries in South America do not have veterinary pharmaceutical BE guidance; and Canada and China have final guidance documents, but China does not use the guidance at this time and this guidance is currently being revised and updated. Mexico is very close to a final guidance document.. A harmonized blood level BE guideline would serve to provide a single source, for VICH and non-VICH countries alike, on which to rely, thereby reducing or eliminating potential confusion.

The development of a grass-roots guideline will unify the global veterinary community understanding of the basic principles upon which blood level BE determinations are based.

3. Impact on Public Health, Animal Health, and Animal Welfare:

3.1 Animal Welfare: A harmonized guideline would minimize the number of failed studies, thereby reducing the number of animals that need to be employed in the demonstration of product BE.

3.2 Animal Health: A harmonized guideline would also ensure that regions employ comparable methods for bridging safety and efficacy across licensed/approved pharmaceutical formulations, thereby insuring that the medicated animal achieves the same clinical effect as would have been achieved if the reference pharmaceutical formulation was administered under the same set of conditions and at the same dose, frequency, and duration.

3.3 Impact on Public Health: The harmonization of principles and data requirements will ensure that efficacy and risks linked to the use of the bioequivalent pharmaceutical product are controlled in the same way as the reference pharmaceutical product. When dealing with veterinary pharmaceuticals, there are two areas of public health in which a sound approach to BE is critical:

3.3.1. Minimization of Drug Resistance Development

With regard to resistance development, there needs to be assurance that the effectiveness profile of the reference product successfully transfers to the test (alternative) formulation. Particularly in a global environment, the development of parasitic or microbial resistance within one jurisdiction can affect the safety and effectiveness of products in surrounding jurisdictions. Therefore, to minimize the risk of a dwindling effective therapeutic arsenal (which will impact both humans and veterinary species), there is a strong need to ensure that all alternative (test) formulations meet appropriate contemporary Quality Assurance standards.

3.3.2. Assurance of Human Food Safety

Antimicrobial safety is established on the basis of ensuring equivalent drug bioavailability for the test and reference formulations.

4. Anticipated Benefit:

The benefits that will be obtained through the development of a harmonized VICH BE Guideline are in keeping with the stated VICH objectives:

- *Establish and implement harmonized regulatory requirements for veterinary medicinal products in the VICH Regions, which meet high quality, safety and efficacy standards and minimize the use of test animals and costs of product development.*

Through an understanding of controllable factors that can minimize the residual error in a BE study, sponsors can achieve a higher power with fewer animals and lower cost. By ensuring that studies are done efficiently, the risk of failure and the need for repeat BE studies can be reduced.

- *Provide a basis for wider international harmonization of registration requirements.*

The proposed guideline will provide a framework upon which this international harmonization can be established. Thus, it is believed that it is essential for VICH (members and observers) to address the issue of BE study guidance and harmonization from a global perspective. Furthermore, the need to "Provide a basis for wider international harmonization of registration requirements" does not state VICH only, it says international, thus we believe that it has and is essential for VICH to address the issue of BE study guidance and harmonization from a global perspective.

- *By means of a constructive dialogue between regulatory authorities and industry provide technical guidance enabling response to significant emerging global issues and science that impact on regulatory requirements within the VICH regions.*

5. Discussion:

Currently, the registration requirements for demonstrating BE for veterinary pharmaceuticals varies from region to region (see “Problem” above). The fundamental principles, which unite requirements across jurisdictions, will be carefully laid out, providing the pharmacokinetic and statistical principles to form the basis for sound study designs. The proposed guideline will aim at harmonising the fundamental principles which underlie the demonstration of BE, including the validation of the bioanalytical method used to quantify the analyte upon which a determination of blood level BE is based. However, it is acknowledged that some aspects such as choice of reference product will vary between jurisdictions

As veterinary medicine and 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. There are new challenges for which global BE criteria cannot even be considered until we have resolved inconsistencies currently facing the most basic of BE assessments, the blood level BE study.

After the blood level BE study guidelines are established by the EWG, another concept paper may be developed for consideration by the SC, one that proposes to catalogue current and future challenges facing veterinary pharmaceutics, thus capturing the wisdom of the blood level BE EWG in hopes of facilitating future international dialogue (M.N. Martinez & R.P. Hunter (in press) Current Challenges Facing the Determination of Product Bioequivalence in Veterinary Medicine. *J. Vet. Pharmacol. Therap*.).

6. Recommendations:

VICH should establish an EWG to elaborate harmonized guidelines utilizing the basic principles underlying BE through blood level studies. The goals of the EWG include:

1. Obtain a harmonized definition of BE.

2. Define situations (e.g. through a decision tree) where it is appropriate to use blood level BE studies, biowaivers, and situations where exemptions are applicable.

3. Describe those factors/variables that need to be considered when developing scientifically sound BE blood level study designs. This section needs to expand upon the scientific and statistical rationale for these approaches and the scientific/statistical criteria that cannot be violated if the design is to remain valid (e.g., appropriate times and duration of blood sampling, species selection, reference product selection, dosing conditions, study power considerations, how to estimate number of subjects needed to achieve the necessary power for any given acceptable ratio of treatment means, replicate study designs, handling outliers, data transformation, statistical considerations, bioanalytical method validation, etc).

4. Determine the information that should be included in a blood level BE study report.

5. Determine the BE acceptance criteria and identify situations where the BE criteria may need to be adjusted due to safety and/or efficacy reasons.

6. Define situations where confirmation of blood level BE cannot ensure the comparability of withdrawal time (i.e., when do sponsors still need to conduct residue depletion studies).

7. Timetable (for the initial BE guideline) and Milestones:

Step 1	Establish the EWG from VICH member and observer countries to actively participate in the development of the BE guidelines.	3 months
Step 2	The EWG develops a first draft of a blood level BE Guideline. A face-to-face meeting(s) of the EWG will be convened to facilitate successful harmonization on the scientific issues. The EWG submits the guideline to the Secretariat with the signatures of all experts.	12 months
Step 3	The draft Guideline is submitted to the SC for approving its release for consultation.	3 months
Step 4	Once adopted by the SC, the draft Guideline is circulated to all interested parties for consultation, applying the appropriate consultation period. The regulatory coordinators should inform VICH secretariat if the consultation process in their region is anticipated to be delayed.	6 months
Step 5	The comments received are directed to the EWG for consideration. At this step, the topic leader must be a representative of a regulatory authority. The EWG prepares a revised draft and submits it to the Secretariat with the signature of all experts. The signatures of industry experts are clearly separated from those of experts representing regulatory authorities.	6 months
Step 6	The revised draft Guideline is submitted to the SC for approval.	12 months
Step 7	Once approved by the SC, the final Guideline and a proposed date for its implementation are circulated to the regulatory authorities represented in the SC. Depending upon EWG recommendations, the SC may initiate discussions regarding the convening of an EWG to develop additional BE guidelines.	
Step 8	The SC members involved in the process report to the SC on the implementation of the Guidelines in their respective regions.	
Step 9	Monitoring, maintenance and review of Guidelines	Continuous, with

		formalised review 3 years after implementation

After the completion of the blood level BE guideline, the EWG may also make recommendations for developing a new concept paper to be considered by the SC that would address the list of additional BE challenges (i.e., Should the development of additional guidelines be considered). If the SC agrees that additional BE guidelines are to be developed, each will be treated as a stand-alone document within a set of VICH BE guidelines, thereby allowing for one guideline to undergo future revisions without disrupting the integrity of the other BE guidelines.

8. Impact Assessment:

Industry:

a. The guideline will provide clarity of the blood level BE requirements and therefore reduce the uncertainty and increase the competitive availability of generic pharmaceutical products.
b. The guideline will provide clarity of the requirements for blood level BE studies used to bridge between innovator formulations and therefore accelerate the availability of new, innovative formulations as line extensions.
c. Most importantly, this guideline will allow for global consistency in reviewing blood level BE studies.
d. By minimizing the number of failed studies, the unified requirements will lead to a reduction in number of studies needed to obtain global marketing. As a result, the numbers of test animals used should also decrease, resulting in an increase in animal welfare (3R principle).

Regulators:

a. This guideline will increase the clarity of the requirements in the regions, and therefore there will be less uncertainty expressed by Industry.
b. This guideline will lead to a consistent approach in interpretation and assessment by the competent authorities.
c This guideline will also decrease the submission of unacceptable studies and allow for timely reviews.

Appendix

VETERINARY DRUGS DIRECTORATE
CLINICAL EVALUATION DIVISION

BIOEQUIVALENCE GUIDANCE

Summary Report of
International Bioequivalence Guidelines

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Introduction

Bioequivalence (BE) is demonstrated when the rate and extent of absorption of two formulations of drugs (test and reference) are sufficiently similar, within allowable limits, when administered under similar experimental conditions. The underlying principle is that the products should be therapeutically equivalent if the products show BE with respect to each other and hence, be

interchangeable in a clinical setting. Thus, the rate and extent measures become surrogate indicators of therapeutic outcome (Rani, 2007).

A BE study is a useful tool to demonstrate comparable efficacy in several situations such as between generic and reference products, for registration of multiple products with the same active ingredient but in different concentrations, to support approval of an alternate route of administration or dosage form, of a minor formulation change or of a manufacturing change which may affect BA. Although it would be difficult to account for all situations, a common template to assess BE results is desirable.

Several problems associated with the current criteria for BE have given rise to international re-consideration of established guidelines by most regulatory agencies, in particular for highly variable drugs, drugs with a narrow therapeutic ratio or with a long half-life, and criteria for granting waivers. An international harmonization of BE Guidance for veterinary drugs would benefit both the pharmaceutical industry and government bodies, and be a testament to the continued collective effort toward progress in the design and interpretation of BE studies for food-producing and companion animal drugs.

The purpose of this report was to provide a detailed summary report of common international veterinary BE guidelines from the United States Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM), the European Medicines Agency Veterinary Medicines and Inspection/Committee for Medicinal Products for Veterinary Use (EMA/CVMP), the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products - trilateral program EU-Japan-USA (VICH), the Australian Pesticides and Veterinary Medicines Authority (APVMA) and available human BE guidelines from the Therapeutic Products Directorate (TPD) of Health Canada and FDA/Center for Drug Evaluation and Research (FDA/CDER). General current review practices of generic drug submissions by the Veterinary Drugs Directorate (VDD) are also included in this report.

General Considerations

Reference product selection

For all regulatory agencies, the reference product selected must be, as a general rule, the original approved pioneer product that is currently marketed by the innovator and approved in each of the respective countries, for the same indications (claims, target species) and identical concentration of the active ingredient(s), as intended for the generic product. Claims made may not be identical to the reference product but should not exceed those of the reference product without provision of additional data. If this pioneer product is no longer available, then the first approved generic equivalent product can be used as long as it is currently marketed in each of the respective countries.

According to the TPD, in cases where a non-Canadian reference product is presented, it must be demonstrated that it is the same as the product sold in Canada, and if slight differences existed, these differences should not have a therapeutic consequence. For example, a non-Canadian reference product would be acceptable if it was made by the same manufacturer as that of the product sold in Canada and had the same color, shape, size, weight, type of coating, dissolution

profiles, etc. The acceptance of a foreign reference product only applies to immediate release (IR) solid oral dosage forms (i.e. tablets or capsules). A cream or ointment for example, would be considered complex because they are multiphase systems and it would be very difficult to arrive at reliable quantitative comparison of formulations. In addition, grades of excipients (e.g. molecular weight of polymers) may have a profound effect on the physical properties of the formulation. Finally, there are no reliable *in vitro* tests which can be use as predictors of *in vivo* performance. The TPD thus has strict policies that outline specific requirements for the acceptance of foreign reference products.

According to the APVMA, if data is submitted from studies conducted overseas, using products that are registered in other countries than Australia, applicants must provide evidence or data to demonstrate that the overseas "reference" product is the same as the Australian-registered reference product.

Both the CVM and EMA, however, only accept a reference product that has been licensed by the FDA and EEA (European Economic Area, i.e. EU and Norway, Iceland and Liechtenstein) respectively.

Species selection

For all regulatory agencies, in order to minimize variability that would not be attributed to the different drug formulations, the animals should be clinically healthy and from a homogenous group (age, breed, weight, hormonal and nutritional status, level of production, etc). Since species is considered a factor that may potentially interact with the drug formulation, studies should be conducted for each major target species for which the reference product is approved for on the label and for which the generic product is seeking approval.

As a general rule, as long as BE has been confirmed in a major species, the minor species indication(s) is/are automatically granted without the need for a separate study.

Number of subjects

All regulatory agencies mention the importance of conducting studies using a sufficient number of subjects in order to demonstrate BE. However, as it is understood that requesting a large number of subjects would be cost prohibitive for the sponsors and perhaps unethical, and that a small number of subjects would lack statistical power, most regulatory agencies do not publish a "magic" number in their guidelines.

This is partly due to the fact that the probability that a study of a given size will pass the standards depends on two factors (sought *a priori* through a literature review or pilot studies): the expected mean difference between the test and the reference products of the pivotal parameters (AUC and Cmax) and the anticipated intra-subject coefficient of variation (CV) of these pharmacokinetic (PK) parameters (Toutain and Adams, 1997). The failure to show BE because of high variability may be due to the fact that not enough animals were used in the study.

Although several equations for sample size calculations have been recommended in the literature for the conduction of a two one-tailed study in BE, cross-over design, no selected equation has been specifically mentioned in the guidelines by most regulatory agencies, except for the TPD that includes in its Guidance for Industry, graphs for the determination of the appropriate sample size according to the probability of acceptance (90%), the ratio of the geometric means (%) and the estimated intra-individual variability (CV%). According to the TPD, although 12 is the minimum number of subjects recommended, a larger number is often required. Moreover, more subjects than the sample size calculation should be recruited into the study to allow for possible drop-outs and withdrawals.

Dose selection

For all regulatory agencies, BE studies should be conducted at the same dose for the test and reference products, as well as the highest dose (molar equivalent dose) approved for the reference drug for which the sponsor has demonstrated linear kinetics through literature or a pilot study. This applies for products labeled for a single claim or labeled for multiple claims involving different pharmacologic action (therapeutic and production claims). For drugs with an adequate margin of safety and linear kinetics, it is also possible to conduct the study at higher than approved dose (not more than 2-3 X the highest approved dose) in order to achieve measurable blood levels. In this case, the sponsor must conduct a tissue residue withdrawal study in food-producing animals.

According to the CVM, the potency of the pioneer and generic products should be assayed prior to conducting the BE study to ensure that FDA or compendial specifications are met. The CVM and APVMA recommend that the potency of the pioneer and generic lots should differ by no more than ± 5% for dosage forms products. Hence, normalization to account for any potency differences between the pioneer and generic product lots is not permitted. There is no specification however as to when the assay for potency (certificate of analysis) must be conducted in relation to the *in vivo* BE study.

In contrast, calculations for AUC and Cmax ratio estimates based on correction for measured content must be provided, to the TPD, by the sponsor. First, a correction factor (CF) is calculated from ln values (% label claim Reference/ % label claim Test). Then, the CF is added to the PK estimate ratios on the logarithmic scale i.e. $(\ln X_T - \ln X_R) + CF$, for the calculation of the mean ratios as well as the lower and upper limits of the 90% confidence intervals.

Criteria for granting waivers of an* in vivo *bioequivalence study

Waivers

In general, there must be an *in vivo* demonstration of a limited acceptable difference in the rate and extent of drug availability associated with the generic and reference formulations when administered at the same molar dose and under similar conditions. However, for aqueous

solutions and for highly soluble/highly permeable, rapidly dissolving drug products, a waiver of the *in vivo* BE study may be considered.

For most regulatory agencies, the following formulations are considered for waivers of *in vivo* BE studies:

1) Simple aqueous solutions including parenteral (iv, sc, im), oral (including other solubilized forms), topical (local therapeutic use: dermatologic, ophthalmic, otic, nasal, inhalational) drugs, and inhalant volatile anesthetics (CVM, EMA, APVMA, TPD);

2) Solid oral dosage forms of multiple strengths (direct scales) of a same drug when BE has been demonstrated at the highest dose, and similar *in vitro* comparative dissolution profiles and same ratio of active to inactive ingredients in an identical formulation are confirmed (CVM, EMA, APVMA, TPD);

3) Topical drugs, other than solutions, for local therapeutic use only with the same active and inactive ingredients (food and non food-producing animals) (CVM) or the same active ingredients with "closely similar" (within 5%) (APVMA) or "essentially the same" (within 10%) (TPD) excipients which do not affect the rate of release of the active ingredient (non food-producing animals only) (CVM, EMA, APVMA);

4) Soluble powder oral dosage form products (CVM, APVMA) and Type A Medicated Articles (CVM), for highly soluble products mixed in drink and feed with the same active ingredients as the reference product and excipients unlikely to alter GI transit time, membrane permeability or drug metabolism or inactivate the active ingredients, and for low solublility products whose active and inactive ingredients and manufacturing process are the same as those of the reference product.

5) Products in oral dosage form not intended to be absorbed (eg antacids, radio-opaque material) (EMA, APVMA).

According to TPD, a request for a waiver is not appropriate for dosage forms intended for absorption in the oral cavity (e.g. sublingual or buccal tablets).

According to the CVM, in general, the generic product must contain the same active and inactive ingredients in the same dosage form and concentration and have the same pH and physicochemical characteristics (pH, crystalline form and particle size) as an approved pioneer product. However, the CVM will consider BE waivers for topical products intended for use in companion animals with certain differences in the inactive ingredients of the reference and test products. The generic product must be the same as the pioneer product in concentration and identity of active ingredients as well as in dosage form (i.e. ointment versus ointment, cream versus cream). For a change in dosage form for a topical product, an in *vivo* BE study will generally be required.

According to the EMA, if the test and reference formulations are identical i.e. same active and inactive ingredients, and physicochemical properties (concentration, dissolution profile, crystalline form, dosage form and similar particle size distribution with identical manufacturing process) and bioavailability (BA) has been adequately demonstrated in the target species, omission of the BE study would be justified, independent of the route of administration. Furthermore, generics that differ only by either coloring agents, flavoring agents or preservative recognized as having no influence on BA, are also considered for waivers.

According to the APVMA, repackaged products, change of site and/or standard of manufacture of active constituents, products with minor formulation changes, and vitamins/minerals and liniments (intended for companion animal use only) do not require BE data.

In all cases, the sponsor must be able to demonstrate pharmaceutical equivalence between the two formulations i.e. they must contain the qualitatively and quantitatively the same active substance(s) in the same dosage form, meet the same or comparable standards and intended to be administered by the same route. Pharmaceutical equivalence, however, does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.

The TPD suggests that the following important questions be answered when proposing a justification for the request for a waiver of the requirements to demonstrate *in vivo* BE when the test and reference products are not considered to be qualitatively the same and/or quantitatively essentially the same:

- *are there known or suspected bioavailability problems?*
- *does the drug exert therapeutic activity in a narrow therapeutic range?*
- *does the drug require careful dosage titration and patient monitoring?*
- *is the drug considered to be highly toxic?*"

(Health Canada Guidance for Industry - Pharmaceutical Quality of Aqueous Solutions 2005)

Table 1 shows similarities and differences in the international criteria for granting waivers of *in vivo* BE studies.

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	Certain differences in the inactive ingredients	Same dosage form and concentration	Same pH	Physico-chemical characteristics	Change of manufacturing site
	parenteral (i.v., s.c., i.m)	oral or other solubilized forms	inhalant volatile anesthetic	topical for local therapeutic use	other than solutions	special considerations	same ratio		required	required	pharmaceutical equivalence	
FDA/CVM	Yes	Yes	Yes	Yes	dermatologic, otic and ophthalmic; non-producing food animals only	soluble powder oral dosage forms and type A medicated articles; proportional formulations	food-producing animals, companion animals	companion animals only	Yes	Yes	Yes with same dissolution profiles (f2 must be equal or more than 50)	manufactured to same standard
EMA/VICH	Yes	Yes	Yes	unknown	unknown	local therapeutic effect i.e. not intended to be absorbed like antacids, radio-opaque material	Yes	no inactive ingredients that can significantly affect the absorption of the active substance (coloring or flavoring agents, preservatives)	Yes	Yes	Yes dissolution profiles, crystalline form, particle size distribution with identical manufacturing process	minimal modifications
APVMA	Yes	Yes	Yes	dermatologic, oral ophthalmic, otic	dermatologic, oral ophthalmic, otic; non-producing food animals only	antacids, radio-opaque material, vitamins, minerals, electrolytes, liniments (non-producing food animals only)	within ± 5%* (excipient) i.e. Category 6 drugs	minor formulation changes: no inactive ingredients that can significantly affect the absorption of the active substance i.e. Category 5 drugs	Yes	Yes	Yes direct scales (standard compendial); dissolution profiles, crystalline form, particle size	manufactured to same standard
TPD (human)	Yes	Yes	Yes	dermatologic, ophthalmic, otic, nasal, inhalational	dermatologic, ophthalmic, otic, nasal, inhalational	proportional formulations	within ± 10%** (especially for excipient that enhance absorption such as polysorbate 80, polyethylene glycol, ethanol; that inhibit absorption such as sorbitol, mannitol)	no inactive ingredients that can significantly affect the absorption of the active substance (coloring or flavoring agents, preservatives)	Yes	Yes	Yes within ± 10% partition coefficient, buffering capacity	manufactured to same standard

* considered closely similar
** considered essentially the same

Category 6 drugs (closely similar) have same active and non active ingredients (within ± 5%), same dosage form and same physico-chemical properties (pH, particle size, crystal form, dissolution profile) (APVMA).
Category 5 (similar) drugs have same active ingredients but may include differences in non-active ingredients and differences in product specifications and physico-chemical properties, but have the same dose form/formulation (APVMA).

Multiple strengths of solid oral dosage forms

For all regulatory agencies, consideration is given to the ratio of active to inactive ingredients, *in vitro* dissolution profiles of the different strengths (compared to the corresponding strengths of the reference product), the water solubility of the drug and the range of strengths for which approval is sought. One *in vivo* BE study with the highest strength product may suffice for product with multiple strengths that have the same ratio, are pharmaceutically equivalent, have the same dissolution profile and demonstrate linear kinetics (EMA, TPD).

It is recommended that the highest strength be used since potential differences between test and reference products are most likely to be elucidated at the high strength. However, the TPD will accept conduction of studies using a lower strength as long as a rationale justification is provided

a priori in the protocol. However, for some of the complicated drugs, such as those with a narrow therapeutic ratio, steep dose-response characteristics or with non-linear kinetics, the bioavailability at each strength of the drug should be established.

Types of Bioequivalence Studies

General study designs

For all regulatory authorities, there are three types of *in vivo* BE studies:

- Blood level studies
- Pharmacological end-point studies
- Clinical end-point studies

Blood level study

For all regulatory agencies, the blood level study is preferred as the most sensitive to differences in drug absorption, especially when drug concentrations can be readily measured in the blood and absorption is relevant to the drug action. It should then be chosen over the pharmacological and clinical end-point studies whenever possible. A single dose at the highest approved dose in mg/kg (or higher) is generally adequate for the demonstration of BE. Fasted subjects should be healthy animals representing the species, class, gender and physiological maturity for which the drug is intended to be approved and weight range should be kept to a minimum to allow for the same total dose to be administered across subjects. Splitting the tablet is generally not acceptable unless the tablet is scored and dosing by half (quarter) increments is representative of the clinical setting. The experimental subjects must be drug-free for a minimum of two weeks prior to the study.

All regulatory agencies recommend a two-period crossover design for blood level studies to eliminate the between subject (inter-individual) variability in the rates of drug absorption, drug clearance, and the volume of drug distribution. Assumptions in the crossover design are that of equal residual effects and no subject by formulation interaction.

A one-way parallel study is suggested for drugs that have a very long half-life (risk of carry-over) or sustained release products whose absorption continues over several days/weeks or even months, drugs that necessitate such a long washout period that it results in maturational changes in the subjects or studies in growing animals whose physiology can change significantly over a short period of time, drugs with flip-flop kinetics or studies with very small animals (e.g. poults, fish, chicks) (Martinez et al, 2002).

Pharmacological or physiological (APVMA) end-point study

This is second to the blood level study in preference by all regulatory agencies. It is used when a drug induces physiological changes related to its indications for use (e.g. antihypertensive drugs) and/or when the measurement of the rate and extent of absorption of a drug in blood can not be achieved or is unrelated to drug action. Subjects are as per the blood level study i.e. healthy and part of a homogeneous group.

A major disadvantage of this study is that a demonstrated BE between the test and reference products for a given pharmacodynamic effect does not guarantee the BE of other effects since concentration-response curves may be different for different drug effects (Toutain and Koritz, 1997).

A one-way parallel study is generally suggested for drugs that induce physiological changes

(eg. liver microsomal enzyme induction). More subjects are routinely required than for the cross-over design to ensure sufficient statistical power. Specific recommendations on how to conduct a pharmacological end-point study are sparse. Instead, sponsors are instructed to consult the regulatory body prior to the intended study in order to determine the appropriateness of this type of study for a particular drug.

Clinical end-point study

This study is the least preferred type because of a lack of statistical power, however it is used when pharmacological effects can not be monitored such as for ectoparasiticides (topical administration), anthelmintics (oral administration with *in situ* activity) and topically active drugs (ophthalmic and otic preparations). The dose and duration selection should reflect common clinical use of the reference product. Subjects are the target species (sex, class, body weight, health status, age) with feeding and husbandry conditions as labeled for the reference product. Generally, the experimental unit in this study is the pen not the individual animal. This type of study is generally conducted as a parallel group design with 3 treatment groups (placebo, test and reference). The purpose of the placebo is to confirm the sensitivity or validity of the study. In general, the response(s) to be measured should be based upon the labeling claims of the reference product and it may not be necessary to collect data on overlapping claims. As for the pharmacological end-point parallel study, more subjects are routinely required to ensure sufficient statistical power. As well, specific recommendations on how to conduct a clinical end-point study are sparse. Instead, sponsors are instructed to consult the regulatory body prior to the intended study in order to determine the appropriateness of this type of study for a particular drug.

Pharmacokinetic considerations in study design

Sampling times

The total number of sampling times will depend on the concentration-time profile curvature and the anticipated variability of the bioavailability data including PK variability, assay error and differences between the test and reference products in absorption kinetics. The sampling period should adequately define the peak concentration and the extent of the absorption and should extend to at least 3 terminal half-lives beyond Tmax. A pilot study may be needed to determine appropriate sampling times and duration depending on the drug mode of action. According to the TPD, twelve to 18 samples should be collected per subject per dose.

If the concentration in the blood is too minute to be detected and a substantial amount (> 40%) of the drug is eliminated unchanged in the urine, then the TPD suggests that the urine may serve as the biological fluid to be sampled. For a 24-hour study, sampling times of 0-2, 2-4, 4-8, 8-12 and 12-24 hours are usually appropriate.

If urine is sampled, the water intake and diet of the subjects must be carefully monitored in order to minimize the risk of fluctuations in the urine volume and pH (Toutain and Koritz, 1997).

Study design

To conduct a well controlled BE study, the following features should be part of the protocol:

i) blinding the investigators with respect to the identity of the drug products administered;
ii) blinding of the analyst with respect to identity of the treatments administered;
iii) standardization of physical characteristics of the subjects (age, weight, sex, physiological status, species);
iv) standardization of all meals and fluid intake during the study;
v) standardization of physical environment/activity (Dighe and Adams, 1991; McGilveray, 1991).

The duration of the washout period in a cross-over study should be approximately 10x the terminal half-life to ensure that 99.9% of the administered dose has been eliminated from the body. Longer washout periods should be used for drugs known to have prolonged tissue binding or potential carry-overs. However, according to the TPD, it should not exceed 3 to 4 weeks. In cases where a prolonged washout period would be necessary to avoid carry-over or could potentially cause maturational changes in the subjects, the CVM recommends a parallel design. Outliers are relatively small or large values that are considered to be different from, and not belonging to the main body of data for an individual subject. Outliers may be observed in plasma concentrations, AUC or Cmax. However, these outliers may not be arbitrarily discarded simply to narrow the AUC or Cmax confidence intervals for reasons other than a documented clinical problem or analytical error (Dighe and Admas, 1991; Toutain and Koritz, 1997).

According to the TPD, it is rarely acceptable to exclude more than 5% of the subjects or more than 10% of the data for a single subject-formulation combination. In fact, for BE studies, rejection of outliers is not acceptable unless for example, the patient has vomited the tablet and there are no measurable plasma drug levels. If the sponsor can not explain the presence of the outlier(s) and repeat analysis shows the same result, the TPD then recommends reformulation of the test product.

Generally, studies should be conducted according to the Good Laboratory Practices (GLP) for Non-Clinical Laboratory Studies, using Standard of Operation Procedures (SOPs), where most analytical errors are accounted for *a priori* in the protocol. Any study deviation must be indicated in the submission and its potential impact on the study evaluated by the principal investigator.

Design of multiple-dose *in vivo* BE studies

According to all regulatory agencies, a multiple dose study is required in the following conditions:

1) for drugs with non-linear kinetics (unpredictable drug accumulation and/or time-dependent kinetics);
2) for drugs with a narrow therapeutic ratio;
3) for drugs with prolonged or delayed absorption (flip-flop);

4) for when assay sensitivity is inadequate for quantification of drug out to 3 terminal elimination half-lives beyond Tmax;
5) when there is excessive intra-individual (within subject) variability in BA, studies should be carried out to steady-state (SS);
6) when the action of the product is dependent on SS concentrations of the investigated substance in the blood.

When linear kinetics cannot be assumed, the approved dosage regimen rendering the highest SS drug concentration must be selected. Blood (or urine) samples should be taken to establish that SS conditions are achieved by measuring three Cmax or Cmin, or by collecting 10 blood samples (including just prior to administration of the next dose) during a dosing interval. The characterization of the absorption and elimination phases is obtained after the administration of the last dose.

Statistical analysis

Blood level study

The earliest criterion used to demonstrate BE was based on a null hypothesis of equivalence between means of pivotal PK parameters of the test and the reference formulations, that was tested against an alternate hypothesis of nonequivalence (Midha et al, 1997). Two formulations were confirmed bioequivalent if the null hypothesis of no difference in means, tested by the *F* ratio from the Analysis of Variance (ANOVA) could not be rejected at a significance level of $\alpha = 0.05$, provided that the study had sufficient power to detect a ± 20% difference between these means (Midha et al, 1997). However, this statistical method was abandoned over the years in favor of the Two One-Sided test procedure in which the null hypothesis is one of nonequivalence or bioinequivalence. Hence, the rejection of H_0 at the 5% level and thereby acceptance of H_1 limits the type I error and patient risk to 5%. The following equations best represent the Two One-Sided test procedure:

H_0: $\mu_T-\mu_R \leq \theta_1$ or $\mu_T-\mu_R \geq \theta_2$;
H_1: $\theta_1 < \mu_T-\mu_R < \theta_2$,

where θ_1 and θ_2 are defined *a priori* as the acceptable difference limits i.e $-\theta_1 = \theta_2 = 0.2\mu_R$.

This method is operationally identical to the most common used method for veterinary drugs by regulatory agencies, termed the "average bioequivalence" (ABE) where an ANOVA (including formulation, period, sequence, and animal-nested-in sequence effects) is needed to estimate the error variance or within-subject error (s^2) for the calculation of a 90% confidence interval (CI). This 90% confidence interval is then used to evaluate BE as it applies to pivotal parameters on either untransformed or natural log-transformed (recommended) data. The final conclusion in favor of BE is taken only if the calculated confidence bounds fall within the allowable limits for all relevant parameters.

Pharmacological end-point study

For parameters which can be measured over time, a time versus effect profile is generated and equivalence is determined with a method of statistical analysis similar to the blood level study i.e. using a 90% CI. Unfortunately, there are no specific recommendations for the BE ranges of parameters derived from this type of study from any of the veterinary regulatory agencies.

Clinical end-point

For this type of study, the analysis is used to compare the test to the reference but also to compare the test and reference to the placebo separately in order to ensure that the study has adequate sensitivity to detect differences when they actually occur. If there is no significant differences ($p > 0.05$) between the placebo and the test or reference, then the study will not be considered adequate to evaluate BE. Assuming the test and reference products are superior to the placebo (or baseline if a placebo is not ethical and/or practical), then confirmation of BE is based upon the 90% CI of the difference between the two products. Unfortunately, there are no general recommendations for the BE ranges of parameters derived from this type of study.

Pharmacokinetic Calculation of the 90% Confidence Interval

Pivotal pharmacokinetic parameters for blood level studies

For most regulatory agencies, the pivotal PK parameters are the Area Under the Curve ($AUC_{0\text{-}LOQ}$, for a single dose study; $AUC_{0\text{-}t}$, for a SS/multiple-dose study) and the maximum concentration (Cmax). To be indicative of product equivalence, these pivotal parameters should be associated with a CI which falls within a set of acceptable limits. To avoid potential bias, pivotal parameter comparisons should be based upon observed rather than fitted data. The AUC reflects the extent of absorption in an ideal manner for most drugs, whereas Cmax is related nonlinearily to the rate of absorption on a nonspecific way, however, lacks sensitivity (Rani, 2007).

According to the TPD, only AUC is used to evaluate BE for uncomplicated drugs. A CI for Cmax is not required, but the ratio of the geometric means of Cmax (point estimate) must be in the range of 80-125%. Only drugs classified as Critical Dose drugs (see below) require both AUC and Cmax to fall within the acceptable limits of a 90% CI to confirm BE.

Area Under the Curve

The AUC is estimated by using the linear trapezoidal method. The relative AUC values generally change very little once the absorption of both products has been completed. However, on occasion, it is not possible to know if the product has been completely absorbed, in that case CVM recommends that $AUC_{0\text{-}LOQ}/AUC_{0\text{-}inf}$ be ≥ 0.80. This ratio is calculated to determine whether the ratio $AUC_{0\text{-}LOQ}$ adequately reflects the extent of absorption. If this is not the case, it is recommended that sampling time be extended or a multiple dose to SS be conducted to allow an accurate measurement of $AUC_{0\text{-}inf}$.

In a multiple-dose study, AUC should be calculated over one complete dosing interval AUC_{0-t} at SS. The average plasma concentration at SS i.e. Css = AUC_{0-t}/t can also be used to evaluate BE.

Rate and extent of absorption - Cmax

In general, for single and multiple dose studies, Cmax is extrapolated from the concentration-time curve of each subject and a mean is calculated for the test and reference formulations. For multiple dose studies, Cmin should also be calculated during a single dosing interval. Cmin however, is assessed by clinical judgment.

Rate of absorption - Tmax

For single dose studies, Tmax is extrapolated from the concentration-time curve of each subject. As it is subject to many variables including the sampling process, a 90% CI is not necessary. It is only assessed by clinical judgment.

Untransformed data

In all regulatory guidelines, the following equations are used in the calculations of the lower and upper bounds of the 90% CI around the mean difference in the PK parameters estimated from untransformed data.

$L = (\text{mean } X_T - \text{mean } X_R) - t_{nA+nB-2;\,0.05} \times s \times \sqrt{(1/n_A+1/n_B)}$;
$U = (\text{mean } X_T - \text{mean } X_R) + t_{nA+nB-2;\,0.05} \times s \times \sqrt{(1/n_A+1/n_B)}$ where,

L = lower confidence bound
U = upper confidence bound
T = test product
R = reference product
n_A = sample size for test product
n_B = sample size for reference product
X = pivotal PK parameter (AUC or Cmax)
s = root estimator of the error variance σ^2 from the ANOVA table

The acceptable confidence bounds are set at 0.80 - 1.20 or 80% and 120% where L/mean X_R x 100 and U/mean X_R x 100 should fall within ± 20%.

Natural logarithmic transformation

The following equations are used in the calculations of the lower and upper bounds of the 90% CI around the mean difference in the PK parameters estimated from natural log transformed data. Since AUC and Cmax estimates are not normally distributed, the transformation of the data in ln is recommended by all regulatory agencies.

$L = (\text{mean } \ln X_T - \text{mean } \ln X_R) - t_{nA+nB-2;\,0.05} \times s \times \sqrt{(1/n_A+1/n_B)}$;
$U = (\text{mean } \ln X_T - \text{mean } \ln X_R) + t_{nA+nB-2;\,0.05} \times s \times \sqrt{(1/n_A+1/n_B)}$, where

$\ln X_T$ and $\ln X_R$ = natural log of pivotal parameter (AUC or Cmax) of either test or reference product.

The acceptable confidence bounds must be backtransformed (e^L and e^U) in order to be expressed on the original scale of measurement. The backtransformed mean is called a geometric mean and is close but different to the arithmetic mean. The geometric mean ratio (GMR) should be close to 100% and the backtransformed confidence bounds around this GMR are set at 0.80 - 1.25 or 80% to 125%, where $(e^L - 1) \times 100$ and $(e^U - 1) \times 100$ should fall within - 20% and + 25%. For all regulatory authorities, rounding is not permitted.

Human Food Safety Considerations

Requirements for tissue depletion studies

According to all regulatory agencies, a tissue residue depletion study should be conducted for approval of a generic animal drug product in food-producing species. Two drug products may have the same plasma disposition profile at the concentrations used to assess product BE, but may have very different tissue disposition kinetics when followed out to the withdrawal time (WDT) for the reference product. Therefore, to show that the WDT of the generic drug is consistent with the tolerance for the reference product, a tissue residue depletion study is generally necessary. According to the EMA and APVMA, however, it is possible to request a spot confirmation of the residual marker in the target tissue following the administration of the generic drug at the withdrawal time approved for the reference product.

The results from one animal species can generally not be extrapolated to another species due to possible species differences in drug partitioning or binding in tissues that could magnify a small difference in the rate and extent of drug absorbed into a large difference in marker residue concentrations in the target tissue. Hence, for a reference product labeled for more than one food-producing species, a tissue depletion study will generally be requested for each major food-producing species on a label.

According to the CVM and APVMA, a tissue residue study is generally required in food-producing animals for the following dose forms: non-aqueous products for injection by s.c. and/or i.m. routes, intramammary infusions in dry cows, pour-on formulations, implants, intraruminal devices.

Calculation of withdrawal time for drugs used in food-producing animals

In a traditional withdrawal study, 20 animals are divided into 4 or 5 groups of 4 to 5 animals each. Groups of animals are slaughtered at pre-selected time points following the last administration of the test product and the edible tissues are collected for residue analysis. A statistical tolerance limit approach is used to determine when, with 95% confidence, 99% of treated animals would have tissue residues below the codified limits. Only the marker residue in the target tissue would be analyzed for the test product.

When an *in vivo* BE study waiver is granted, a tissue residue study waiver may also be granted. The generic animal drug is assigned the WDT supported by the residue depletion data, or the WDT currently assigned to the reference product, whichever is the longest. A shorter WDT must be supported by necessary data.

Validation Requirement for Analytical Methods

General considerations

For all regulatory agencies, a properly validated assay method is pivotal to the acceptability of any PK study. The submission should contain adequate information necessary to determine the validity of the analytical method used to measure the drug concentration in the biological matrix (blood or urine) within the acceptable limits. The determination of BE is dependent upon reliable, precise, and accurate measurement of the active ingredient, or its metabolites, or both, as a function of time (TPD).

Required data

The following data is requested when assessing the method performance:

1) Concentration range and linearity:
2) Limit of detection (LOD)
3) Limit of quantification (LOQ)
4) Specificity
5) Accuracy (recovery) (within ± 15%)
6) Precision (within 15% and 20% at the LOQ) (TPD)
7) Analyte stability
8) Analytical system stability
9) Quality control samples (a minimum of 6, composed of 3 concentrations)

Special Considerations

This section includes situations when BE demonstration may be complex. There appears to be no consensus among regulatory agencies on the study design and interpretation of BE, hence the need, by all regulatory bodies, to establish clear guidelines for these special considerations.

Excipients

In general, excipients or inactive ingredients are considered inert components of a dosage form, affecting only the physicochemical properties of the product, such as the dissolution and drug stability. These inactive ingredients would not be expected to alter the rate and extent of absorption of the active ingredient(s) (Martinez et al, 2002). However, some excipients are capable of exerting their own direct physiological effects. Mannitol, for example, decreases the GI transit via osmotic activity, surfactants such as polysorbate 80 and cremophor alter the

membrane characteristics of transporter pumps, whereas Vitamin E alters the activity of multi-drug resistant proteins. In cases where the inactive ingredients affect the solubility, permeability or elimination of the active ingredient, the conduction of an *in vivo* BE study should be adequate to detect these situations. However, if the excipient alters the safety and efficacy of the drug via mechanisms other than altering the systemic absorption of the active ingredient, unfortunately BE studies will not be adequate to detect this occurrence (Martinez et al, 2002).

According to Martinez and collegues (2002), "the potential for species-specific excipient effects underscores the need for an inactive ingredient guide that provides information on excipients with respect to dose, route, amount administered and target animal species."

Minor formulation changes

According to the APVMA, formulation changes only include alterations to the excipients and not to the active ingredients. These alterations produce no significant change in the physical or chemical characteristics of the product and no consequent improvement or reduction in performance. Thus, there is no significant change in the basic activity of the product. Where a non-active constituent is different from that in the reference product, tissue irritancy studies may be required and confirmation of the margin of safety may be necessary. The following examples of minor formulation changes are found in the APVMA guidelines (Residue Guideline 18, February 2000).

Dip concentrates

In general, any change to a dip concentrate formulation that does not alter the physical and chemical characteristics of the diluted dip will not require residue data.

Pour-on formulations

In the case of pour-on formulations that claim a systemic effect, such as ivermectin products, acceptable changes to components such as dyes and stabilizers do not require residue data. Changes to other components such as solvents, dispersants, emulsifiers and surfactants involving a different chemical and physical profile will generally require residue data as they may influence absorption through the skin.

Oral formulations

In general, only very major changes to oral formulations (tablets, capsules, granules, oral liquids, oral powders, premixes) will affect the residue profile of the active constituents to a significant degree. Exceptions to this position would be where an excipient is known to affect the bioavailability of actives such as for example polysorbate 80, sorbitol, mannitol, or when the amount of the excipient is in excess of the expected standard concentration.

Intramammary infusions

Generally, apart from very minor formulation changes to intramammary infusions and parenteral preparations, data will be required to confirm that the bioavailability and injection site reaction have not been significantly altered from the original formulation.

Lotions and creams

For lotions, creams, gels, ointments, pastes, powders, pessaries and suppositories, the release of the active ingredient from the constituent is the most critical factor when considering the need for residue data for a formulation change. Findings from PK profiles, transdermal penetration and dissolution would determine the need for residue data in these formulations.

Eye formulations

Additional residue data is not required for approval of formulation changes to eye drops and eye ointments because while there is some potential for active ingredients to enter the systemic system, this is generally only a minor extent.

For topical formulations

A quantitative and qualitative comparison of inactive ingredients between the test and reference products is required. Differences within 5% are acceptable by the TPD.

Changes in dosage form, route of administration, manufacturing or indications

If the immediate release (IR) test and reference products do not have the same dosage form, the TPD accepts a comparable dosage form such as a tablet and a hard gelatine capsule and vice versa for the conduction of an *in vivo* BE study, but does not accept a BE comparison between any other formulation differences.

According to the CVM, under a suitability petition, the applicant can request a change in active ingredient (in combination products only), dosage form, strength, and route of administration. The request may include one or more of these allowable changes. The current CVM policy is that if new safety and effectiveness studies are required, it would allow the applicant to get the generic approval first (exact copy of reference drug) and then submit a supplement requesting the change that would require the additional studies, generally reserved for innovative products. Bioequivalence is required because the original generic application still relies on the safety and effectiveness studies of the reference product.

According to the EMA, a different dosage form or route of administration to the reference product can be compared in *in vivo* BE studies.

Measurement of metabolites

The international perspective on measurement of metabolites for drugs intended for human use, is that since the parent compound is most sensitive to differences in formulations, it is accepted that the BE studies should be solely based on the parent drug as long as the active metabolite(s) concentration time profile is, at all time points, less than 10% of the comparable value of the parent drug, the type of pharmacological or toxic responses produced by the parent drug and active metabolite are similar, both parent and metabolite(s) possess linear PK processes and the drug is not an extended-release product (Rani, 2007).

However, in certain circumstances, the measurement of metabolites could be required, such as when a prodrug is administered, if the plasma concentration of the parent drug is too small to be measured, if the parent drug is unstable or if its half-life is very short (Rani, 2007).

Fed versus fasted subjects

For all regulatory agencies, a fasted state is preferable if no specification is indicated on the label of the reference product. However, both fasted and fed states (small studies to evaluate meal effects) are necessary for enteric coated and oral sustained release products, for drugs known to have a high bioavailability in the fed state (from literature or pilot study), for drugs exhibiting non-linear kinetics or a narrow therapeutic ratio (NTR).

According to the TPD, administration of food and fluid should be carefully controlled regarding the timing and the content. The purpose is to select a test meal that can challenge the formulation where a meal has the greatest potential to demonstrate altered BA. The meal should be given within a pre-determined, constant time of administration of the drug.

A standard meal, either for food-producing or companion animals, for the conduction of a BE study has not yet been defined in the published guidelines of the veterinary regulatory agencies.

Highly variable drugs

A highly variable drug (HVD) is defined as a drug for which the intra-individual (within subject) variability or ANOVA-CV contained in the residual variance is greater than 30%. The ANOVA-CV is the square root of the residual variance (also known as the error mean square) multiplied by 100. Replicate study designs are recommended to estimate the intra-individual variability of a particular formulation to distinguish it from HVD products of poor pharmaceutical quality.

According to the EMA and the TPD, for certain products, greater variance in BA can be tolerated because of the intended therapeutic use or because the product does not require careful patient dosage regimen. These products include the HVDs that are generally safe with flat dose-response curves, where application of the present preset BE limits of 80-125% may impose more rigorous BE requirements for these drugs than for lower variability drugs.

For drugs with a large safety margin and a large efficacy window, AUC differences exceeding the allowable limits of 80-125% may be tolerated by the EMA when pre-specified *a priori*. However, no numerical value for this widening of the bounds is available as these drugs are reviewed on a case-by-case basis. This is contrary to the present guidelines from the CVM, CDER, TPD and EMA (human) that appear nonflexible regarding this pivotal parameter.

The generally accepted limits for the 90% CI of Cmax are 80-125%. However, as this parameter may exhibit a greater variation, limits of 70% to 143% (75-133% for EMA human) could be acceptable for the EMA, as long as it is based on clinical evidence and when pre-specified, *a priori* through appropriate pilot studies, in the protocol.

For uncomplicated drugs, the TPD requires a 90% confidence limit of 0.8 - 1.25 for AUC, however, a limit (0.8-1.25) is placed only on the GMR (a point estimate) for Cmax except for Critical Dose drugs (see below Drugs with a Narrow Therapeutic Ratio).

Unfortunately, one of the consequences of high intra-individual variability is that a large number of subjects may be required to provide adequate statistical power to the study even though the formulations may be bioequivalent. Another suggestion that has recently gained some popularity is the broadening of the BE limits, also called "scaling", according to the within-subject variability of the reference formulation. This is achieved by dividing the natural log limit (± 0.225) by the within-subject standard deviation at which the limits are to be permitted to be broadened (suggested $\sigma_{W0} = 0.25$) and multiply by the standard deviation of the reference formulation (σ_{WR}), generally obtained from a replicate study design i.e. $0.225 \times \sigma_{WR}/\sigma_{W0}$.

The TPD prefers "add-on study" where the study is repeated (identical protocol) and results are added to the original study. If this option is chosen, however, it must be stated *a priori* in the study protocol. In addition, two important criteria must be followed: the same protocol as the original study (minimum of 12 subjects) must be used and consistency tests, such as (homoscedasticity and formulation by study interaction) must be met at an α error of 5%. These add-on studies are acceptable in cases where the power of the study was underestimated, but are not recommended in cases where outlier(s) skew the data.

For the CVM, however, exceeding the limits of 80-125% for any drug, for either AUC or Cmax, is not acceptable and the use of add-on studies is not permitted.

Drugs with a narrow therapeutic ratio

A drug has a narrow therapeutic ratio (NTR) when there is less than a two-fold difference between the median lethal dose and the median effective dose or if there is less than a two-fold difference between the minimum toxic concentration and the minimum effective concentration in the blood (Rani, 2007), and safe and effective use of the drug products require careful titration and patient monitoring. Therefore, considerably small changes in the drug levels can lead to marked change in the pharmacodynamic effects and current evaluation guidelines may not be appropriate for the assessment of NTR drugs.

Much controversy has risen from this issue and present guidelines are being reviewed to better represent this type of drugs. It has been suggested by the EMA that the 90% confidence limits be tightened; whereas the FDA (CVM and CDER) does not recognize that the NTR drugs may belong to a separate group of drugs since scientific evidence is presently not available to justify narrowing the bounds for these NTR drugs.

Critical Dose Drugs (CDD) are defined by the TPD as those drugs where comparatively small differences in dose or concentration (NTR drugs/highly toxic drugs) lead to dose- and concentration- dependent serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible or life threatening, which could result in inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death.

Bioequivalence studies for CDD should be conducted according to the TPD general guidelines with the exception of the following:

i) BE should be demonstrated under both fasting and fed conditions;
ii) the 90% CI of the relative mean AUC of the test and the reference formulations should be between **90-112%** (fasted and fed states), whereas the relative mean Cmax should be between 80-125%;
iii) if SS is required, 90% CI of the relative mean Cmin should also be between 80-125%;
iv) due to the nature of these drugs, it may be necessary to conduct studies in patients rather than in healthy subjects;
v) ethical considerations may also dictate that these studies be conducted in parallel groups rather than by a crossover design.

Critical Dose Drugs include cyclosporine, digoxin, flecainide, lithium, phenytoin, sirolimus, tacrolimus, theophylline and warfarin.

Modified release formulations

Modified-release (MR) dosage forms are drug formulations that differ from conventional formulations in the rate at which the drug is released (disintegration, de-aggregation, dissolution, absorption). They require guidelines that differ from those for immediate release (IR) formulations because of a greater likelihood of an increase in inter-individual variability in BA (including the possibility of dose-dumping), an increase in the risk of adverse effects such as GI irritation, or of an accumulation when the drug is given in repeated doses at the recommended dose intervals.

In the case of enteric-coated drugs, a BE study can be performed provided that the only difference between the enteric-coated drug and the corresponding IR drug is a time shift in the concentration-time curve (i.e. no other modification of release occurs). Studies must be carried out in both fasted and fed states.

Second entry (generic) MR drugs require BE studies (fasted and fed) using an appropriate reference product.

For formulations that are likely to accumulate ($AUC_t/AUC_{inf} < 0.8$), safety requires that SS studies, generally fasted only with pivotal parameters being AUC_τ, Cmax, Tmax, Cmin and fluctuation, be performed in addition to the single-dose studies (fed and fasted). To establish SS, at least 3 consecutive Cmin (pre-dose concentrations), generally at the same time of the day,

must be determined. Fluctuation is expressed as a %, determined as the range of concentrations divided by the average SS concentration i.e. (Cmax -Cmin)/(AUC_{τ}/τ) x 100.

Drugs exhibiting non-linear kinetics

A drug is considered to exhibit non-linear PK when a change in dose results in a disproportional change in the concentration of the drug in the blood. According to the TPD, the drug may be treated in the same way as those exhibiting linear kinetics, if evidence is provided to show that dose-normalized AUC values deviate (increase or decrease) by less than 25% over the practical clinically recommended single dose range.

The BE requirements should be met in single dose studies in both the fasted and fed states. The requirements for studies under fed conditions may be waived if scientific evidence is provided to show that the non-linearity is not related to a capacity-limited process such as absorption or pre-systemic metabolism, such as first pass effect.

For drugs that demonstrate greater than proportional increases in AUC with increasing dose, it has been suggested by the TPD (July 2003) that the comparative bioavailability studies should be conducted on at least the highest strength, or for drugs that demonstrate less than proportional increases in AUC with increasing dose, the comparative bioavailability studies should be conducted on at least the lowest strength.

In general, the total concentration is measured, however, in cases of non-linear kinetics, both free and total concentrations should be measured. If the drug is known to enter erythrocytes, potential non-linearity from uptake into erythrocytes should also be addressed. The magnitude of protein binding and type of blood protein to which it binds should be provided in the report.

Drugs with a long half-life

According to the TPD, drugs which exhibit a terminal half-life > 24 hours, BE standards should be applied to $AUC_{0\text{-}72}$. For the purpose of BE assessment, it is not necessary to sample for more than 72 hours post-dose, regardless of the half-life, however, alternate designs such as parallel studies should be considered. There is currently no provision made for drugs with a long half-life in the published guidelines of the EMA, CVM and APVMA.

Rapid onset drugs

This section includes drugs for which an early time of onset or rapid rate of absorption is important as for example the analgesic drugs. Current TPD BE guidelines apply for rapid onset drugs. In addition, the relative mean $AUC_{RefTmax}$ of the test to the reference formulation should also be within 80-125%, where $AUC_{RefTmax}$ for a test product is defined as the AUC to the time of the maximum concentration of the reference product, calculated for each study subject. Failure to fall within these limits for this parameter results in a conclusion of bioinequivalence.

Submissions in support of superiority claims, such as time to onset of effect is important, may need additional PK/PD or clinical data.

There is no provision made for drugs with a long half-life in the published guidelines of the EMA, CVM and APVMA.

Identification of adverse reactions and side effects

For all regulatory agencies, the incidence, severity and duration of adverse reactions and side effects observed during the BE study must be reported in the submission. The probability that an adverse effect is drug-induced is to be judged by the principal investigator.

Dissolution Tests

Drug absorption from a solid dosage form after oral administration depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug under physiological conditions, and the permeability across the GI tract.

Design of* in vitro *equivalence studies for oral dosage forms

Bioequivalence studies and comparable *in vitro* dissolution data along with chemistry, manufacturing and controls (CMC) assessment are required in order to characterize the performance and quality of the test product. Dissolution profile comparisons are useful for accepting product sameness, to waive BE requirements for lower strengths of a dosage form or to support waivers for other BE requirements.

Study conditions

Conditions of testing should be clearly defined (pH, temperature, dissolution medium, stirring, etc.) in the protocol. For drugs intended for human use, at least three pH conditions is indicated in order to give some confidence to the extrapolation from the *in vitro* to the *in vivo* conditions especially when pharmacopeia specifications are unknown (CDER, TPD). The Biopharmaceutics Classification System (BCS) is used as a basis for setting *in vitro* dissolution specifications and can also provide a basis for predicting the likelihood of achieving a successful *in vivo-in vitro* correlation. Compendial pharmacopeia standards (US or European) should be carefully followed for official specifications of *in vitro* testing whenever possible.

Experimental design

Replicates of measures should be taken in order to take into account the variation inherent to the analytical method. A validated analytical method should be used with accuracy and precision within acceptable limits. For rapidly dissolving products, generation of an adequate profile, sampling at 5 or 10 minute intervals may be necessary. Twelve (CDER) or six (TPD) units each of test and reference products should be used at each strength.

The most common measure of similarity between dissolution profiles is the model independent approach using the similarity factor (f_2) according to the following equation:

$f_2 = 50 \times \log \{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$,

where n = number of time points, R_t is the dissolution value for the reference batch at time t and T_t is the dissolution value of the test batch at time t. Only one measurement should be considered after 85% dissolution of both products. The percentage of the coefficient of variation (CV%) should not be > 20% at earlier points i.e. at less than 15 minutes, and > 10% for all other time points (CDER).

Other approaches for measuring the degree of similarity in the dissolution profiles between two products include f_1 (the difference factor), the model independent multivariate confidence region procedure and the model dependent approaches. These methods are beyond the scope of this report.

Waivers/Exemptions

An exemption or waiver of *in vivo* studies is only possible when results of *in vitro* studies could lead to the deduction of similar PK behavior between the two products compared. The BE study may be performed at the highest strength and waivers of *in vivo* studies may be granted on lower strengths, based on adequate dissolution tests, provided the lower strengths are proportionally similar in composition.

General Current VDD Practices

In the past years, the VDD has been following the CVM Guidance for Industry #35 in the review of ABNDS of generic drugs, with the influence of TPD and EMA guidelines. In general, decisions have been made on a case-by-case basis, based on sound pharmacological and biostatistical principles. Table 2 represents a general comparative view of the differences and similarities between the current VDD practices and the international established guidelines.

Table 2 - Summary of selected current international bioequivalence guidelines.

	CVM	EMA	APVMA	TPD	VDD
General Considerations					
Reference Product	FDA approved only	EEA[1] approved only	APVMA approved, foreign exceptionally	Health Canada approved; foreign exceptionally oral dosage form only	Health Canada approved; foreign exceptionally oral dosage form only
Species Selection	target (all major)	target (all major)	target (all major)	N/A	target (all major)
Dose Selection	same dose; highest dose; highest strength; within 5% potency difference	same dose; highest dose; highest strength; within 5% potency difference	same dose; highest dose; highest strength; within 5% potency difference	same dose, highest dose in mg/kg	same dose, highest dose in mg/kg
Waivers					
Aqueous Solutions	parenteral (iv, sc, im); oral; topical (local effect only); volatile anesthetics	iv (same active); parenteral & oral (same active and excipient -or excipients not affecting BA); volatile anesthetics	parenteral (iv, sc, im); oral; topical (local effect only); volatile anesthetics	parenteral (iv, sc, im); oral; topical (local effect only including inhalational); volatile anesthetics	parenteral (iv, sc, im); oral; topical (local effect only); volatile anesthetics
Identical Formulations	same active, inactive ingredients, same dosage form and concentration & same pH and physico-chemical properties	same active, inactive ingredients, same dosage form and concentration & same pH and physico-chemical properties	within 5% (excipients) i.e. Category 6 drugs	within 10% (excipients)	same active, inactive ingredients, same dosage form and concentration & same pH and physico-chemical properties
Oral Dosage Forms	direct scales[2], soluble powders and Type A medicated articles	direct scales[2]; not intended to be absorbed (local action only); identical except for different coloring, flavoring agent, preservative, from original manufacturer	pharmaceutical equivalence; direct scales[2]; not intended to be absorbed (antacids, radio-opaque agents); no inactive ingredients that can affect BA i.e. Category 5 drugs	direct scales[2]; no inactive ingredients that can affect BA	direct scales[2]; no inactive ingredients that can affect BA
Minor Formulation Change	no effect on BA	minimal modifications	including repack and change in manufacturing site (with same standard)	no effect on BA	no effect on BA
Pivotal Parameters and Acceptable Confidence Interval					
AUC	0.8-1.25 (no exception)[3]	0.8-1.25	0.8-1.25	0.8-1.25* except for Critical Dose Drugs** (0.90-1.12)	0.8-1.25*
Cmax	0.8-1.25 (no exception)[3]	0.8-1.25 (widening acceptable to 0.7-1.43 for certain safe drugs)	0.8-1.25 (widening acceptable to 0.7-1.43 for certain safe drugs)	point estimate only (0.8-1.25)***	0.8-1.25*
Tmax	clinical judgment only	clinical judgment only	clinical judgment only	not relevant unless rapid onset claim where T/R ratio of AUCrefTmax: 0.8-1.25 ****	clinical judgment only

[1] European Economic Area (EU, Norway, Iceland and Liechtenstein);

[2] proportional formulations (similar dissolution profiles);

[3] rounding not permitted

* correction for potency difference required

** Critical Dose Drugs: cyclosporine, digoxin, flecanaide, lithium, phenytoin, sirolimus, tacrolimus, theophylline, warfarin

*** Point estimate= mean lnCmaxTest/mean lnCmaxReference

**** T/R ratio of AUC refTmax = Test to Reference product ratio of AUC up to the Tmax of reference product

Major similarities between the VDD and its international veterinary regulatory counterparts include the selection of the target species, types and preference of study designs for BE studies, use of transformed data for the calculation of the 90% CI in the determination of BE, most

criteria for granting waivers (BE and tissue residue studies), and the requirements for fed/fasted studies and dissolution testing.

General differences include the selection of the reference product, the selection of the appropriate dose for multi-strength formulations, potency correction of the calculated 90% CI limits, and interpretation of BE results for Cmax and AUC (the acceptability of widened confidence bounds), especially for complicated drugs.

Conclusion

The purpose of this report was to summarize international published BE guidelines and compare them to the VDD's current approach. A particular challenge to this task, however, was the fact that at the present time, the VDD does not have any specific written guidelines for submissions of generic drugs, for veterinary use, intended to be marketed in Canada. In general, the review process of generic submissions by the VDD has been comparable to the international approach. The lack of a common BE template for the evaluation of these submissions, however, may have resulted in minor inconsistencies and a long reviewing process.

As guidelines have evolved over the years with the increasing understanding of the application of BE concepts to uncomplicated as well as complicated drugs, it has become necessary for the VDD to develop Guidance for Industry in order to standardize the review process within the regulatory agency as well as provide guidance to the pharmaceutical industry of VDD's requirements. Furthermore, in the foreshadowing of international harmonization, it seems appropriate for the VDD to implement written basic and concise guidelines at this time, reflecting international scientific understanding of BE issues. Although sound PK and biostatistical principles will continue to be used to assess BE of generic veterinary drug formulations, the proposed new guidance will help bridge the present gap between the pharmaceutical industry and the VDD, and assist in processing and evaluating ABNDS in a timely matter.

The present report was compiled from the CVM, EMA, APVMA and TPD's respective public information websites, numerous consultations with regulatory reviewers and authorities on general and specific issues of BE studies presently conducted for human and veterinary drugs, and a literature review. Summarized guidelines reflect a general consensus among the above regulatory authorities.

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Pharmaceutical Glossary

http://www.worldpharmaceuticals.net/glossary.htm

Appendix

List of abbreviations

ABE: Average Bioequivalence
ABNDS: Abbreviated New Drug Submission
ANOVA: Analysis of Variance
APVMA: Australian Pesticides and Veterinary Medicines Authority
AUC: Area Under the Curve
BCS: Biopharmaceutics Classisfication System
BA: Bioavailability
BE: Bioequivalence
CVM: Center for Veterinary Medicine
CDER: Center for Drug Evaluation and Research
CED: Clinical Evaluation Division of the VDD
CI: Confidence Interval
Cmax: maximum plasma concentration
CMC : Chemistry, Manufacturing and Controls
Cmin: minimum plasma concentration
CR: Correction Factor
CRP: Canadian Reference Product
Css: plasma concentration at steady-state
CV: Coefficient of Variation
EMA: European Medicines Agency Veterinary Medicines and Inspection
f_2 : similarity factor
FDA: Food and Drug Administration
GCP: Good Clinical Practice
GI: Gastrointestinal
GLP: Good Laboratory Practice
GMR: Geometric Mean Ratio
h: hour
HPLC: High Performance Liquid Chromatography
HSD: Human Safety Division of the VDD
HVD: Highly Variable Drug
i.m. : intramuscular
INF: Infinity
IR: Immediate Release
i.v.: intravenous
L: Lower 90% confidence bound
ln: natural logarithmic
LOD: Limit of Detection
LOQ: limit of Quantification
MCED: Manufacturing and Chemical Evaluation Division of the VDD
MR: Modified Release

n: sample size
NSAIDs: non-steroidal anti-inflammatory drugs
NRA: National Registration Authority
NTR: Narrow Therapeutic Ratio
PD: Pharmacodynamic
PK: Pharmacokinetic
PSUR: Periodic Safety Update Report
R: Reference product (pioneer/innovator)
s^2: error variance
s.c.: subcutaneous
SOP: Standard of Operation Procedure
SS: Steady-State
t: time
T: Test product (generic)
Tmax: time to achieve maximum concentration
TPD: Therapeutic Product Directorate
Tmax: Time to maximum concentration
U: Upper 90% confidence bound
US: United States
USP: United States Pharmacopeia
VDD: Veterinary Drugs Directorate
WDT: Withdrawal Time

Important definitions

Closely similar: According to the APVMA, two drug formulations are closely similar if they have the same active and same inactive ingredients (within 5%), in the same dosage form and same physico-chemical properties (pH, particle size, crystal form and dissolution pofiles). These drugs are classified as Category 6 drugs.

Dissolution: a drug is considered to be highly dissolving when no less than 85% of the labeled amount of the drug dissolves within 30 minutes using USP apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 mL or less in (1) 0.1 N HCL or simulated gastric fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or simulated intestinal fluid USP without enzymes. The dissolution characteristics of the drug product should be developed based in consideration of the pH solubility profile and pKa of the drug substance.

Essentially the same: two products are quantitatively essentially the same when the concentration of each excipient in the test product is within 10% of the concentration of each excipient in the reference product (TPD).

Interchangeability: An interchangeable pharmaceutical product is one that is therapeutically equivalent to a comparator (reference) product.

Permeability: a drug is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

Pharmaceutical equivalents: Products are pharmaceutical equivalents if they contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standards; and if they are intended to be administered by the same route. Pharmaceutical equivalence does not necessarily imply therapeutic equivalence, as differences in the excipients and/or the manufacturing process can lead to differences in product performance.

Similar: According to the APVMA, two drug formulations are similar if they have the same active ingredients in the same dosage form, and have the same physicochemical properties, including pH, particle size, crystal form and dissolution profile. These drugs are classified as Category 5 drugs.

Simple aqueous solution: a homogeneous mix (solute in molecular dimensions) that contains the active ingredient(s), water and buffers, preservatives, coloring or flavoring agent and no other excipients. It excludes emulsions and suspensions.

Solubility: a drug is considered highly soluble when the highest dose strength of an IR product is soluble in 250 mL or less of aqueous media over the pH range of 1 - 7.5.

Therapeutical equivalents: Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Type A medicated article: Also called a medicated premix, it is a veterinary medicinal product consisting of a mixture of one or more drug substances, generally with a carrier (edible material to which drug substances are added to facilitate uniform incorporation into feed), that is prepared to facilitate oral administration of the drug to animals when mixed in feed.