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VETERINARY MEDICINES CLINICAL GUIDELINE

This guideline is intended to provide recommendations to applicants wishing to submit clinical applications for the registration of veterinary medicines containing specified substances. In addition to this guideline, SAHPRA reserves the right to request any additional information to establish the quality, safety and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy.

Guidelines and application forms are available from the office of the website.

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LIST OF ABBREVIATIONS

ADI	Acceptable Daily Intake
API	Active Pharmaceutical Ingredient
APVMA	Australian Pesticide and Veterinary Medicinal Products
BCS	Biopharmaceuticals Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMC	Chemistry, Manufacture and Control
CoA	Certificate of Analysis
CTD	Common Technical Document
CVMP	Committee for Veterinary Medicinal Products of EMA
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRP	Good Regulatory Practice
HC	Health Canada
JMAFF	Japan Ministry of Agriculture Forestry and Fisheries
LOD	Limit of Detection
MRLs	Maximum Residue Limits
NCE	New Chemical Entity
P&A	Pharmaceutical & Analytical
PD	Product Dossier
Ph.Eur	European Pharmacopoeia
QOS	Quality Overall Summary
RSA	Republic of South Africa
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SmPC	Summary of Medicinal Product Characteristics

1 INTRODUCTION

The diversity across animal species' physiology and the numerous dosage forms used in veterinary practice result in unique formulations and dosage routes to be addressed during drug development for food producing and companion animals, and wildlife.

As such, technical requirements for registration of veterinary medicines are constantly evolving as a result of scientific developments and harmonisation of requirements with the more mature regulatory authorities such as the members of the VICH. SAHPRA endeavours to keep abreast of such developments and keep its application requirements and evaluation policies in line with “best international practice.”

This guideline outlines SAHPRA’s evaluation pathways for veterinary clinical applications and the associated data requirements to satisfy:

- Safety and Toxicology
- User safety
- Environmental risk assessment
- Food residues and withdrawal periods
- Establishment of maximum residue limits
- Efficacy and;
- The different review pathways and documents to be submitted.

The relevant guidelines for VICH, EMA and SAHPRA are quoted in each corresponding section of this guideline.

1.1 Replacement of "Summary Basis for Registration"

A key change in the submission format is that SAHPRA will no longer be requiring a Summary Basis for Registration (SBRA) document to aid clinical evaluation. The SBRA has been replaced by the clinical overviews and summaries, as well as the SCoRE document.

1.2 Revised Professional Information (PI)

The latest PI **format** is adopted from the EMA-CVMP SPC as-is, using both the stipulated EMA numbering and headings to " Holder of Certificate of Registration" in accordance with South African legislation. “Scheduling Status”, however, has not been covered in the EMA SPC. SAHPRA requires applicants to include this item above the “Name of the Medicine” section. Applicants to please note that the content may change according to South African requirements.

For “Pharmacological Classifications”, SAHPRA intends to adopt the Anatomical Therapeutic Chemical (ATC) Classification System in future. The ATC classification system divides medicines into different groups according to the organ or system on which they act and according to their chemical, pharmacological and therapeutic properties.

For PI content, SAHPRA will be using reliance wherever applicable. SAHPRA considers a PI previously approved by the EMA or VICH members as a default reference for reliance pathways.

2 PART 4/CTD MODULES 2.4, 2.6 & 4: NON-CLINICAL PHARMACO - TOXICOLOGICAL DATA

2.1 The information in this part is required for new pharmaceutical active ingredients. A new species indication, or an increased daily dose or different inactive pharmaceutical ingredients may result in the need for additional pharmaco-toxicological data. The objective of toxicological/safety studies is to define the pharmacological actions (pharmacodynamics and pharmacokinetics) and toxicological effects of the active ingredient in test animals and target species, users, consumers and the environment. This normally involves initial studies in laboratory animals and later on pre-clinical studies in the target species, which should take into consideration the following:

1.1 Selection of the relevant animal species

1.2 Age of the animals

1.3 Physiological state of the animals

1.4 The manner of drug delivery, including dose, route of administration and treatment regimen and the effect on the animals

1.5 Stability of the test medicine under the condition of use

1.6 Safety of personnel.

2.2 DATA PRESENTATION

The pre-clinical documentation should be presented in the following sequence:

1. Pharmacology
2. Toxicology
3. Discussions and conclusion
4. Expert report

The Toxicology of the medicine should be addressed.

a) A summary, or Expert Report, should be submitted for each animal species studied, with information on the sex of the animals, number of animals, dosage, route of administration, duration of study and toxic manifestations.

b) Important points to consider that pertain to pre-clinical toxicity, are:

- Dose-response relationship
- Time-response relationship
- Species specificity
- Consistency of findings across studies with different species
- Target organ specificity
- Reversibility/irreversibility of toxic effects.

2.3 PHARMACODYNAMICS

Provide a full description of tests performed to establish the pharmacological actions that are relevant to the proposed indication(s) and mechanism of action. Where possible it will be helpful to relate the pharmacodynamics of the medicine to available data (in terms of selectivity, safety, potency etc.) on other medicines in the same class.

2.4 OTHER ACTIONS (DESIRED/UNDESIRED)

Give an evaluation summary of action(s) other than those of therapeutic use. The results of two or three dosage levels studied should be submitted, with the lowest level representing the ED_{50} for the API's primary action on the animal species being investigated. For effects, which may be expected to have significant adverse reactions, attempts should be made to estimate the threshold levels. Due to the local climatic conditions, the phototoxic potential of a medicine should be considered.

2.5 PHARMACODYNAMIC INTERACTIONS

The applicant must submit data either to establish that such interactions do not occur or that they are clearly recognised and defined. Discuss the pharmacodynamic interactions and mechanisms of interaction of the API with other compounds/ other substances, which are relevant to the proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well explained. In cases of fixed dose combination or combination packs, appropriate data to justify the benefit of combination compared to a single API should be given. Special consideration must be given to antibiotic combinations in light of antibiotic resistance

2.6 PHARMACOKINETICS

Pharmacokinetics studies should be made with single dose by various routes. Repeated dose studies should also be performed when relevant, to establish the pharmacokinetics of chronic medicine administration. Metabolic studies should be conducted in the species used in toxicological and reproduction studies using the proposed clinical routes of administration. Where radioactive labelled materials are used in studies, the position of label stability and specificity of material should be stated.

Where the product contains a combination of medicines, the effect of use of two or more medicines on the pharmacokinetics of one or the other medicines should be established. Provide studies done to establish the pattern and time course of absorption, distribution, biotransformation, pharmacokinetic interactions and excretion of the API and/or its metabolites as described below.

2.7 ABSORPTION

Provide a summary of mechanism of absorption, factors affecting absorption, rate and extent of absorption, plasma levels of the API and metabolites (peak levels, half-life, etc.). This information should be discussed for different routes. Correlation between plasma levels and pharmacological effects should be discussed.

2.8 DISTRIBUTION OF THE API AND METABOLITES

Provide a summary and time course of distribution of the API and its metabolites in body fluids, tissues, and organs. Accumulation, retention of the medicine/metabolites in tissues, organs, penetration of blood-brain and placental barriers, plasma binding of all these parameters should be reported in quantitative form.

2.9 BIOTRANSFORMATION

Give the pattern and time-course of biotransformation of the medicine, i.e. sites of metabolism and their importance, metabolic pathway(s), nature and quantities of metabolites, rate of metabolism, pre-systemic metabolites enzyme inhibition or induction, activity of metabolites, if any.

2.10 PHARMACOKINETIC INTERACTIONS

Discuss the pharmacokinetic interactions and mechanisms of interactions of the API with other compounds (medicine or other substances), which are relevant to the proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well explained.

2.11 EXCRETION

Summarise the routes and extent of excretion of the medicine and its metabolites. State also its excretion in milk in case of lactating animals. Discuss the rate of elimination and factors influencing elimination.

3 TOXICOLOGICAL STUDIES

The scope of toxicological evaluation should be described in relation to the proposed clinical use. Information obtained from experimental and biological studies of all aspects of toxicology (general toxicity, acute toxicity studies, sub-acute toxicity and long term toxicity studies including teratology, reproduction effects, carcinogenicity, genotoxicity, immunogenicity, Microbial affects (e.g. development of resistance), local tolerance (potential for adverse effects at site of administration, etc) is required to establish the safe use of the medicine and must be submitted for all new medicine applications.

The investigation should, if possible, include experiments conducted with the medicine in the vehicle intended for therapeutic application or its final pharmaceutical formulation (product).

3.1 GENERAL TOXICITY STUDIES

In general toxicity studies, at least three or more routes of administration should be used including one for therapeutic use and at least one other which ensures systemic absorption, i.e. intravenous, intramuscular or subcutaneous.

Different dose levels spaced logarithmically should be used. The maximum tolerated dose should be indicated. All animals dying during the experiment should be autopsied and cause of death determined where possible. Full post-mortem should be carried out on all animals and histopathological studies

undertaken on control and dosed groups. Results should be tabulated. Full data for all parameters measured, with mean, range for groups, should be included. If it is expected that the product will be used in young animals, studies should be conducted on both adult and young (weaning) animals. Due to the local climatic conditions, the phototoxic potential of certain medicines should be considered.

3.2 ACUTE, SUB-ACUTE AND LONG TERM TOXICITY STUDIES

Principles governing general toxicity studies shall be applicable to acute, sub-acute and long term toxicity studies and local tolerance studies.

3.3 GENERIC AND WELL ESTABLISHED DOSAGE FORMS

In case of generic or interchangeable multi-source medicines and established dosage forms, provide bioequivalence studies data corroborated with literature review.

3.4 PRESENTATION OF SAFETY STUDIES

All toxicity studies shall be properly presented under the following headings:

(i) Objectives

(ii) Experimental protocol including methodology and materials

(iii) Summarised results and related statistical analysis

(iv) Discussions and conclusion

(v) Proposed measures to minimise potential toxicity during use of the product

Toxicity and Safety Guidelines

EMA guidelines

- Assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products
- Regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches

VICH guidelines

- VICH GL22 Safety studies for veterinary drug residues in human food: reproduction studies
- VICH GL23 Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing
- VICH GL28 Studies to evaluate the safety of veterinary drugs in human: carcinogenicity testing
- VICH GL31 Safety studies for veterinary drug residues in human food: repeat-dose (90) toxicity testing

- VICH GL32 Studies to evaluate the safety of residues of veterinary drugs in human food: developmental toxicity testing
- VICH GL33 Safety studies for veterinary drug residues in human food: general approach to testing
- VICH GL37 Safety of veterinary drugs in human food repeat-dose (chronic) toxicity testing
- VICH GL54 Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish an acute reference dose (ARfD)

4 SAFETY TO USERS

Studies on potential harmful effects to exposure by various routes, e.g. inhalation, topical contact, oral ingestion, performed on laboratory animals, shall be presented. The implications to humans using the product should be described and, where appropriate, precautions during preparation and use of the product should be proposed.

EMA User Safety Guidelines

- User safety for pharmaceutical veterinary medicinal products
- User safety of topically administered products

5 RISK ASSESSMENT OF VETERINARY MEDICINES

5.1 TOXICITY TO THE ENVIRONMENT

Assessment of environmental safety should be given for all new veterinary medicinal products. Requirements for safety are important to avoid persistent damage to the environment.

Products requiring environmental assessment include:

(a) Antibiotics in poultry, pig and fish feeds

(b) Effluent from manufacturing plants

An assessment of the potential of exposure of the medicine and its active metabolites to the environment shall be made taking into account:

(i) The target species and likelihood of and method of excretion of the product and its active metabolites into the environment.

(ii) Pattern of use and therefore quantity medicine to be used (herd/flock medication or individual medication)

(iii) The method of administration and whether it may lead to direct entry of the product into the environment, e.g. sprays

(iv) The method of disposal of the unused, used products and containers

Studies on potential harmful effect of the product to the environment shall be provided. The environment shall include soil, water and air and such studies shall include:

(i) fate and behaviour in the soil

(ii) effects on soil organisms

(iii) fate and behaviour in water

(iv) effect on aquatic organisms

(v) effects of other non-target organisms
Proposed measures to minimise the above potential risks during use of the product shall be described.

Environmental Toxicity Guidelines

EMA guidelines

- Assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products
- Assessing the toxicological risk to human health and groundwater communities from veterinary pharmaceuticals in groundwater
- Determining the fate of veterinary medicinal products in manure

VICH guidelines

- Environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38
- Higher-tier testing of veterinary medicinal products to dung fauna
- Plant testing strategy in the risk assessment for veterinary medicinal products
- VICH GL6 Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I
- VICH GL38 Environmental impact assessments for veterinary medicinal products - Phase II

Additional Reference material

EMA Reflection papers

- Antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products
- Authorisation of veterinary medicinal products containing (potential) persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances
- Poorly extractable and/r non- radiolabelled substances
- Risk-mitigation measures related to the environmental risk assessment of veterinary medicinal products

EMA Concept papers

Assessing the toxicological risk to humans and the environment of veterinary pharmaceuticals in groundwater

5.2 RESIDUES IN FOOD OF ANIMAL ORIGIN: RESIDUE STUDIES

Residue study data should be provided to justify withdrawal periods for milk, meat, eggs for each species for which the product is indicated. Safety assessment of veterinary medicine residues in food of animal original should be performed for all new medicines. Relevant pharmacological, toxicological, and microbiological end points should be used to establish the acceptable daily intake. Maximum residue limits in food producing animals should be provided. The withdrawal period should be indicated on the labels. All the analytical methods used should be provided. Pre and post antimicrobial resistance surveillance should be performed on indicator pathogens e.g. *E.coli, Salmonella* spp. Quinolones - usage should be restricted to avoid resistance in zoonotic pathogens.

This section also provides guidance for situations or conditions under which waivers of the drug residue depletion studies could be granted. It also describes conditions under which the relevant studies will be required.

Overall, the information submitted on residues should be sufficient to confirm or establish that the withdrawal period of the generic product is identical to that of the reference product.

5.2.1 Situations and Conditions When the Residue Data Requirements Could Be Waived

For certain products for which the waivers of pharmaceutical equivalence and bioequivalence study requirements have been granted, residue data to confirm the withdrawal period assigned to the reference product *might not* be necessary.

There are situations where an abbreviated depletion study may be required even after granting pharmaceutical equivalence and bioequivalence of the generic products.

Requests for waiver of the residue depletion studies will be considered on a case-by-case basis. When an applicant requests a waiver for residue depletion study requirements, an assessment of the dossier is conducted to determine whether the generic product is identical to the reference product. When a waiver cannot be granted, the residue depletion studies to confirm or establish that the withdrawal period of the generic product is the same as approved for the reference product will be required.

If bioequivalence is granted based on blood-level studies, which should cover the absorption, distribution, and elimination phases of the active ingredients vs. the time profile, and the assay method used is sensitive enough to measure the residue levels in blood for the entire withdrawal period established for the reference product, the residue

depletion data requirements may be waived provided that the correlation data between the depletion of the drug residue from plasma and target tissue is known.

The waiver of residue data requirements may be granted to medicated premix products or soluble powder oral dosage forms that are pharmaceutically equivalent to the reference product.

5.2.2 Situations and Conditions When the Residue Data Requirements Cannot Be Waived

In various situations, the residue depletion data requirements cannot be waived.

The descriptions below specify the situations where applicants must submit the data from an abbreviated residue depletion study or a comprehensive residue depletion study.

In general, when the waivers for pharmaceutical equivalence or bioequivalence cannot be granted, a waiver for the residue depletion study requirements will not be considered.

In most cases, data from an abbreviated residue depletion study will be required to confirm the withdrawal period of the generic products.

An abbreviated residue depletion study is generally required in food-producing animals for the following product formulations:

- Non-aqueous products for injection by subcutaneous and/or intramuscular routes;
- Intra-mammary infusions in dry cows;
- Pour-on formulations;
- Implants; and
- Intra-ruminal devices.

For products where the formulation (e.g., pH, vehicle, excipients, etc.) differs from that of the reference product, and concerns about residue depletion are evident, data from residue depletion studies to confirm the withdrawal period may still be required even though the generic product is considered to be pharmaceutically equivalent and the waiver of bioequivalence study requirements has been granted.

Some generic drug products may have the same plasma disposition profile as the reference product at the concentrations used in bioequivalence studies, but may have very different tissue disposition kinetics when followed out to the withdrawal period for the reference product. In these cases, the submission must include data from the residue depletion study.

Similarly, differences in the location of injection sites or evidence of significant injection site tissue reaction might lead to an altered tissue residue depletion pattern, which may result in the submission requiring data from an abbreviated residue depletion study.

In generic drug submissions where residue depletion studies are not waived, and when the reference is indicated for use in more than one food-producing species, an abbreviated tissue residue depletion study will generally be required for each major food-producing species on the label. This is because the data derived from one animal species generally cannot be extrapolated to another species due to possible species differences in drug partitioning or binding in tissues. These differences could magnify a small variation in the rate and extent of drug absorbed into a large variation in marker residue concentrations in the target tissue.

For a reference product approved for use in major and minor species, data from a residue depletion study from a major species on the label is generally sufficient for confirmation of withdrawal periods for all related minor species on the label.

In all cases where no residue data are available on file for the reference product, the submission must contain data from the tissue residue depletion studies to meet the current standards of the guidelines.

An applicant seeking a shorter withdrawal period for the generic product must provide the data from a comprehensive residue depletion study to support the proposed shorter withdrawal period.

5.2.3 Residue Depletion Study

The purpose of a residue depletion study is to confirm the withdrawal period of a generic version of the reference product. This study should be conducted in a minimum of 6 animals (evenly mixed by sex) for large and medium sized animals (e.g., cattle, swine, sheep, etc.), 12 birds for poultry, 15-20 for fish, and 20 lactating dairy animals (e.g., cows, goats, and sheep), treated with the product at the same dose and using the same route and frequency of administration as recommended for the reference product.

The study should include a control (non-treated) animal. The concentration levels of the marker residue or residues in the target tissue, if known, at the recommended withdrawal period for the reference product, will need to be determined by using the validated analytical method (regulatory method).

A single-point statistical procedure will be used to determine the upper tolerance limit of residue concentrations with 95% confidence for 99% of the animal population, which should be below the established maximum residue limit (MRL) at the established withdrawal period for the reference product. In case the residue levels in target tissue, if known, at the established withdrawal period for the reference product, exceed the established MRL, data from a comprehensive residue depletion study.

5.2.4 Comprehensive Residue Depletion Study

The purpose of a comprehensive residue depletion study is to establish a withdrawal period for the generic product. This study should be conducted in a minimum of 20 animals, divided into either four or five groups of four or five animals each.

The study should include at least one control (non-treated) animal. Groups of animals are slaughtered at each of either four or five appropriately distributed and pre-selected time point intervals following the last administration of the test article. Edible tissues are then collected for marker residue analysis.

For the purpose of establishing the withdrawal period, only marker residues in the target tissue, if known, will be analysed.

A statistical procedure will be used to calculate the withdrawal period. The upper tolerance limit residue concentrations with 95% confidence for 99% of the animal population will be determined, which should be below the established MRL. It is noted that to meet the current standards of the guidelines, data from a comprehensive residue depletion study in all the edible tissues may be requested where the MRL in tissues other than the target tissue are not available.

5.2.5 Analytical Methodology

When choosing analytical methods to determine marker residue concentration levels, applicants should consider the approved method. If an analytical method other than the approved method of analysis is used, the applicant of a generic product should provide method validation data with consideration of the analytical methodology requirements.

Withdrawal period and MRL Guidelines

EMA guidelines

- Approach towards harmonisation of withdrawal periods
- Determination of withdrawal periods for milk
- Injection-site residues
- Setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

VICH Guidelines

- VICH GL46 studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: metabolism study to determine the quantity and identify the nature of residues
- VICH GL47 studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: laboratory animal comparative metabolism studies
- VICH GL48 studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: Marker-residue-depletion studies to establish product withdrawal periods
- VICH GL49 studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: validation of analytical methods used in residue depletion studies

- VICH GL56 studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: study design recommendations for residue studies in honey for establishing MRLs and withdrawal periods
- VICH GL57 on studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing species: marker residue depletion studies to establish product withdrawal periods in aquatic species

Additional Reference Material

EMA Reflection papers

- Injection-site residues: considerations for risk assessment and residue surveillance

EMA Concept papers

- Introducing a review and update of existing EU guidelines on residues studies to bring these into line with the VICH metabolism and residues guidelines GL46 to 49

Establishment of maximum residue limits: Guidelines

EMA guidelines

- Approach to establish a pharmacological acceptable daily intake (ADI)
- Data to be provided in support of a request to include a substance in the list of substances considered as not falling within the scope of regulation (EC) No 470/2009
- Risk-analysis approach for residues of VMPs in food of animal origin

VICH guidelines

- VICH GL36 Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI

Additional reference material

EMA Reflection papers

- Assessment of bioavailability of bound residues in food commodities of animal origin in the context of Council Regulation (EEC) No 2377/90
- Consideration of adjuvants and preservatives under Council Regulation (EEC) No 2377/90 laying down a community procedure for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin
- New approach developed by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives for exposure and maximum residue limit assessment of residues of VMPs

EMA Concept papers

- Approaches on how to consider excipients in the context of Regulation 2377/90

EMA Position papers

- Definition of substances capable of pharmacological action in the context of Council Directive 2001/82/EC as amended, with particular reference to excipients and manufacturing materials
- Establishment of maximum residue limits for milk considering the daily intake by children

- Antimicrobial resistance in the environment: considerations for current and future risk assessment of veterinary medicinal products

6 PART 5/CTD MODULES 2.5, 2.7 & 5: EFFICACY DATA

This section shall only be applicable to new chemical entities. Original efficacy data will be required for all veterinary medicinal products containing new chemical entities (NCE) whether mono or in fixed dose combination with another NCE or a well-known medicine substance. A summary of well presented, controlled blinded clinical trials conducted in target animals investigating the pharmacological and therapeutic properties, and adverse reactions is required. Pharmacological studies are only required if the biological studies were not done in target animals. The principles of Good Clinical Practice (GCP) should be adhered to during the study.

The clinical data should be presented in a manner that allows easy cross-referencing to the index, other studies and the professional information. Clinical trials should be conducted with the formulation as applied for. Where studies have been conducted with different formulations, comparative equivalence studies are required to enable extrapolation to the formulation intended for the market.

6.1 PHARMACODYNAMIC STUDIES (TARGET ANIMALS)

Describe the study protocol including the study design, pharmacological or biochemical response measured, measuring instruments, results, statistical methods used and their justification. Tabulation and graphical illustration of results and conclusion.

Please note:

a) A cross-over design is preferred and where it is not appropriate a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.

b) Studies should be done in healthy animals or in sick animal if the disease affects the actions/responses studied.

c) Inclusion/exclusion criteria must be stated and non-responders should be identified and excluded prior to the study commencement

d) Measured pharmacological response should be relevant to the claimed therapeutic uses and where there are more than one therapeutic uses, studies should be done to demonstrate the therapeutic use for each indication.

e) Measurement of responses should as far as possible be quantitative, measured under double blinded conditions and be recorded in an instrument producer/instrument recorded fashion.
f) The methodology must be validated for precision, accuracy, reproducibility and specificity.

g) Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.

In using pharmacodynamic methods, the following requirements must be satisfied:
a) The response can be measured precisely over a reasonable range
b) The response can be measured repeatedly to obtain time-course from the beginning to the end of the response.

6.2 PHARMACOKINETICS AND BIOAVAILABILITY OF THE MEDICINE IN TARGET ANIMALS

The summary should outline;

a) Particulars of principal investigators (name, curriculum vitae, affiliation and signature)
b) Product information, batch details, batch number, manufacturing site and date, expiry date, specifications. The product must be identical to the intended commercial product in every respect; same manufacturing site and same composition (qualitative and quantitative). Samples should be the same as the commercial scale production batch
c) Protocol and study design; (objectives, animal selection, conduct of the study, medicine administration, food intake, sample collection, storage, bio-analytical methods and validation results, pharmacokinetics parameters measured and results. Justifications for the chosen design (e.g. cross over or replicated design), measures taken to minimise intra and inter-animal variability and elimination of bias must be stated. All possible factors that may influence the product pharmacokinetics must be standardised e.g. fluid intake, food intake, exercise/confinement, etc.
d) Population:
Population size of 8 – 24 (sample size shall depend on the animal co-efficient of variation CV if low say < 15%; n = 14, > 30%; n = 44) healthy young animals. A minimum of 12 animals is required for modifies release oral dosage form studies.
e) The results, data and statistical procedures should be detailed enough to allow for repeat analysis if required.

6.3 EFFICACY CLINICAL END POINT STUDIES IN TARGET SPECIES

Describe in detail the study protocol, which should, include:
a) the title of the study
b) Particulars of principal investigator(s), location, justification and objectives, dates, time, duration, observation periods and justification thereof,
c) study design (randomization methods description of design e.g. cross-over or parallel etc), inclusion, exclusion, criteria, animal housing and feeding, methods and treatments, dosage used, concurrent treatments,
d) specifications of the test product and placebo,
e) response variables – precise clinical endpoints measured, and recording clinical response (measurable scoring system for endpoints).

f) analysis of results including statistical methods used and their justification.
g) Discussions and conclusion on efficacy and safety, including but not limited to:
adverse drug reactions observed and their relationship to the administered dose.

General: Guidelines

EMA guidelines

- Conduct of bioequivalence studies for veterinary medicinal products
- Conduct of pharmacokinetic studies in target animal species
- Demonstration of palatability of veterinary medicinal products
- Statistical principles for veterinary clinical trials

VICH guidelines

- VICH GL9 Good clinical practices
- VICH GL52 Bioequivalence: blood level bioequivalence study

SAHPRA

- 3.03: Quality, Bioavailability and Bioequivalence of veterinary medicines
- 2.48: Veterinary medicines exemptions from certain medicine registration requirements

Additional reference material

EMA Reflection Paper

Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action

Target animal safety guidelines

VICH GL43 Target animal safety: pharmaceuticals

EMA Specific guidelines

- Conduct of efficacy studies for non-steroidal anti-inflammatory drugs (NSAIDs)
- Demonstration of target animal safety and efficacy of veterinary medicinal products intended for use in farmed finfish

- Dossier requirements for anticancer medicinal products for dogs and cats
- Veterinary medicinal products for fluid therapy in case of diarrhoea

EMA Antimicrobials guidelines

- Guideline on the summary of product characteristics for antimicrobial products
- Demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

EMA Products for intramammary use guidelines

- Conduct of efficacy studies for intramammary products for use in cattle
- Local tolerance of intramammary preparations in cows
- SAHPRA guidelines on antimastitis products

ADDENDUM

1. SAFETY AND EFFICACY REVIEW PATHWAYS

A clinical application will follow one of the following review types, namely:

a) Full Review

b) Abridged Review

c) Verification Review

d) Mutual Recognition

e) Notifications (Variations)

Review types (b), (c) (d) and (e) represent reliance pathways, which SAHPRA will be implementing to reduce evaluation times. To qualify for a reliance pathway, an application must have received prior approval from a recognised regulatory authority Reliance pathways are applied independently for clinical and quality sections based on the quality of documents submitted.

RRAs for registration of veterinary medicines include: US-FDA (CVM), EMA (CVMP), Japan Ministry of Agriculture, Forestry and Fisheries (JMAFF), Health Canada (VDD), Australia, (APVMA), UK (VMD), and New Zealand (APVMA). In order for an application to be considered for the reliance evaluation, additional documentation must be submitted with the application.

The data requirements are listed in this addendum.

The final evaluation pathway decision for an application is at the discretion of SAHPRA, and will depend on the type of molecule, species, legibility for minor use/minor species, indications, including availability and quality of reliance documentation submitted.

SAHPRA will share screening queries with applicants regarding insufficient reliance documentation to ensure that as many applications as possible qualify for abridged and verified reviews. Where applicable, applications will default to a Full Review in the absence of a suitable reliance pathway.

Whilst the medicine is under review, applicants should inform SAHPRA of any prohibition and restriction imposed by the RRAs of any country in which the medicine is marketed and of any other information which might influence the evaluation of the benefits and risks of the medicine concerned.

1.1 FULL REVIEW

A full review involves a thorough review of all aspects of the dossier, particularly the pre-clinical and clinical data submitted under PARTs 4 and 5/CTD and Modules 4 and 5 respectively (and summarised in PART 2E/Module 2).

All NCE applications, generic applications with clinical data, Type II variations and line extensions that lack adequate reliance documentation or prior approval from a RRA will default to full review.

A full review is indicated specifically for the following types of applications**:**

1.1.1 Monocomponent medicines

- For a monocomponent NCE (new chemical entity) not registered by a RRA
- For a monocomponent multisource medicine/generic/API not registered by a RRA, and where clinical data generated with the generic has been supplied in support of the application
- All veterinary biological medicines not registered by a RRA.

1.1.2 Multicomponent medicines

- For a multicomponent fixed dose combination of two or more chemical entities, where the combination is not registered by SAHPRA or by a RRA.

1.1.3 Type II variations

- For Type II variations where the amendment applied for has not been approved by a RRA,

1.2 ABRIDGED REVIEW

The Abridged Review is initiated to limit the evaluation time of medicines that are registered by a RRA.

The abridged review is based primarily on the overviews of pre-clinical and clinical data. All supporting documents as stipulated in this addendum should be included in order to qualify for the abridged review. The abridged review process **does not** involve an abbreviated application – the full application should be submitted by the applicant. Evaluators may still wish to review pre-clinical and clinical data in Modules/PARTs 4 and 5 as required.

Applicants need to draft and sign a Letter of Access, allowing SAHPRA to request un-redacted reports from the associated RRA(s). The Letter of Access must also be signed by the marketing authorization holder in the associated RRA country or by the principal from whom the dossier is purchased. This is a minimum requirement in order for an application to be considered for an abridged review. However, there is one exception to this requirement: The Letter of Access does NOT need to be provided if the applicant supplies SAHPRA with the un-redacted reports directly.

All NCE and biological applications, generic applications with clinical data**,** Type II variations and extensions that have prior approval from a RRA will be considered for an abridged review.

An abridged review is indicated specifically for the following types of applications**:**

1.2.1 Monocomponent medicines

- For registration of a new medicine/NCE already approved by a RRA.
- For registration of a new medicine /NCE based on a well-established use (relying on literature), where the medicine has already been registered on the same basis by a RRA
- For a monocomponent multisource medicine/generic/API registered by a RRA, and where clinical data generated with the generic has been supplied in support of the application

- Biological medicine registered by a RRA

  Multicomponent medicines

- For a multicomponent fixed dose combination of two or more chemical entities, where the combination is not registered by SAHPRA, but registered by a RRA