GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. 757 **6 June 2003**

MEDICINES CONTROL COUNCIL

MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965)

GUIDEINES WITH RESPECT TO THE MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965, AS AMENDED)

Guidelines for medicines regulation and control in South Africa as determined by the Medicines Control Council with reference to regulations published in regulation gazette number 7470 (1230).

The following guidelines are published for comment over a period four weeks from the date of publication this notice:

VETERINARY MEDICINES	
1	Application And Information Requirements
2	Guideline For Clinical Trials On Veterinary Medicines
3	Bioavailability And Bioequivalence For Veterinary Medicines
4	Guideline On Preclinical Safety Studies For Veterinary Medicines
5	Guideline On Efficacy For Veterinary Biological Medicines
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Ms M.P. MATSOSO
Registrar of Medicines

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON APPLICATION AND INFORMATION REQUIREMENTS - VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of veterinary medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

Version MCC2003/1

CONTENTS:

1. GENERAL INFORMATION

The Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965) requires that a application for registration of medicines including Veterinary Medicines must be submitted in prescribed format. These guidelines are for veterinary medicines and must be read in conjunction with th general guidelines for the application for registration of medicines.

A pre-screening process must be completed and the necessary form MRF 2.0 together with the pre screening fee must be submitted.

Once the pre-screening is complete the full application in the required format must be submitted.

2. STRUCTURE OF THE APPLICATION

The structure of the application should be as follows:

1. Cover/title page
2. Declaration by Applicant
3. Table of Contents
4. Summary
5. Body of Application
6. Other Relevant Information
7. Bibliography
8. Copies of referenced material
9. Appendices if required

3. NUMBER OF COPIES REQUIRED

Applicants must provide:

i. Four copies of the full application.

ii Fifteen copies of the Summary Basis of Registration Application of Veterinary Medicine (SBRAV) of the main application findings, abstracts of reference materials and ful bibliography/reference lists for distribution to committee members.

4. INFORMATION REQUIREMENTS AND APPLICATION FORMAT

4.1 COVER/TITLE PAGE

The cover / title page should indicate:

i. The subject of the application.
ii. The name and address of the applicant.
iii. The name of a contact person.
iv. The date on which the application was submitted.

4.2 DECLARATION BY APPLICANT

Applications for a rescheduling decision must contain a declaration by the applicant certifying that to th best of the applicant's knowledge all information relevant to the application has been submitted and i true and accurate.

4.3 TABLE OF CONTENTS

The table of contents should tabulate and correlate the titles of each section and major subsections of the application with their appropriate page numbers.

4.4 Summary Basis of Registration Application of Veterinary Medicines (SBRAV)

(i) The SBRAV is intended to be a very brief and concise document containing the core data on th basis of which the applicant intends to obtain registration for the veterinary product. It is to b presented as a summary only: therefore no articles, reports etc. are to be incorporated into th SBRAV nor should such papers be attached to it either, as these belong with the full submission.

(ii) Applicants must ensure that the general quality of the studies , proper cross referencing to th data, explanatory notes and the quality of photocopying and binding are of an appropriat standard. The SBRAV must be cross – referenced with the documentation submitted to th Medicines Control Council.

(iii) SBRAV format

Refer to the format below for details.

5. BODY OF THE APPLICATION

The body of the application should communicate the aims and justification of the proposal in a concise clear and logical manner. Appropriate data and information must be supplied to demonstrate that th substance or product will be safe for the public when supplied and used in the proposed manner. Whilst th format of each application may vary the Committee recommends the use of a standard framewor consisting of the following:

5.1 Purpose of the Application

A general statement of the purpose of the application (new, amendment, change in indications etc.) must be made.

5.2 General Background

5.2.1 Current Regulatory Status

Reference should be made to the current local regulatory status of the product or substance in terms of dosage forms registered, scheduling status and approved indications. If applicable, the registration number must be indicated.

5.2.2 International Regulatory Status:

Classification/ scheduling status in other countries where the drug is registered, including information of the approved indications and dosage forms. The availability status should be clearly indicated in terms of prescription only, pharmacy only, general sales outlets, etc. (The term OTC should distinguish between general sale and pharmacy, if relevant). It should be noted that recognized regulatory authorities include those in the USA, EU, Australia and Canada.

5.3 Technical Information

Additional information on the active ingredient that was not submitted during the registration of the original product. Data that was submitted during the registration process may be summarized.

.5.3.1. Physico-Chemical Properties of the Active Ingredient

i. Structural formula or any available information on the structure of the substance.
ii. All relevant chemical and physical properties.

5.3.2 Pharmacology

i. Any known information relating to the structural and pharmacological relationship to other drugs or chemicals
ii. The pharmacodynamic and pharmacokinetic profile
iii. Interactions, incompatibilities, side effects or adverse reactions
iv. Any recognized standard such as a pharmacopoeia monograph.

5.3.3 Clinical Data

i. Post-marketing reports
ii. Additional clinical reports
iii. Adverse drug reaction reports
iv. Epidemiology reports
v. Poisoning reports

5.3.4 Toxicology

i. Summary of the known toxicology of the product.
ii. Summary of the known metabolism of the product.
iii. Relevant details of any published or unpublished toxicological investigations of the product / substance

5.3.5 Safety Reports:

i. A summary of animal studies that show low general toxicity and no relevant reproductive toxicity, genotoxic, or carcinogenic properties relevant to the experience/ exposure of the product.
ii. Information from post-marketing surveillance studies, clinical trials and published literatur presenting the issue of drug safety. For OTC's: Considerable experience of patient exposure including at least 2 years of use in the relevant or similar population.
iii. Information on adverse drug reactions. In the case of OTC medication the information shoul include experience without medical supervision in other countries. Variables such as number of patients treated, demographic details, indications for use and dose should be provided an taken into account in providing and interpreting the data;
iv. Drug interactions with food or commonly prescribed drugs.
v. Consideration of the consequences concerning misuse.

5.3.6 Occupational Health and Safety Information: (If applicable)

A summary of occupational health and safety aspects.

5.3.7 Pharmaceutical Aspects:

Any intended change in formulation, pack size, packaging, etc should be indicated. However pharmaceutical data such as stability need not be included, this data must be evaluated as part of registration application or amendment to the registration application.

6. **Package Insert**

The under-mentioned information with regard to this medicine shall appear on the scientific packag insert. The information shall be presented in the format stipulated: Provided that the Council ma authorise any deviation from such information or such format. (Ref. Regulation 40)

1. Scheduling status.
2. Proprietary name
3. Dosage form
4. Composition.
5. Pharmacological classification
6. Pharmacological action. Pharmacokinetics
7. Indications.
8. Contra-indications.
9. Warnings.
10. Dosage and directions for use.
11. Side effects and special precautions
12. Interactions
13. Known signs of over dosage and particulars of its treatment.
14. Identification.
15. Presentation.
16. Storage instructions.
17. Registration number (or reference number).
18. Name and Business Address of the Holder of the certificate of registration.
19. Date of notification of approval of the scientific package insert.

7. SUMMARY BASIS FOR REGISTRATION APPLICATION OF VETERINARY MEDICINES (SBRAV)

1. THIS APPLICATION INVOLVES : a new application

2. DATE OF THIS SBRAV :

2.1 Submitted
2.2 Discussed(official use)
2.3 to applicant (official use)

3. PRODUCT DETAILS

Active ingredient(s) and quantity thereof
Proprietary name
Applicant :
Application / Registration No:
Pharmacological classification
Dosage form

4. **NAME(S)** of Registration Person and/or Medical Adviser responsible for compilation of this application, and telephone number where responsible individual may be contacted during office hours:

Name Position Qualifications Tel. No.

5. **PROVEN (ESTABLISHED) PHARMACOLOGICAL ACTION:**

(Only information concerning the clinical issues and indications claimed are relevant).
(MAXIMUM 100 WORDS).
(At least two key references in support, preferably published – see 13 below).

6. **EVIDENCE OF EFFICACY IN TARGET SPECIES:**

(Data should be summarized in tabulated format, preferably under the following headings, as applicable:

- Key trial(s) reference number: as listed under item 13 of SBRAV
- Trial design : indicate with abbreviations/symbols, e.g.
- 0 = open
- X = cross-over
- P = parallel groups
- R = randomised
- C = controlled
- PC = placebo-controlled
- MC = multi-centre
- LS = Latin square

- Indications/Diagnosis.

- Number of patients treated with each drug.

- Dosage range used.

- Duration of treatment.

- Reference/comparative drug(s).

- Parameters evaluated/findings.

- Statistical data

(Please indicate separately, the total (overall) number of patients treated with the product)

Indicate clearly which trials were done/not done with the formulation and dosage form, for which registration is being applied.

(Free comment, if required, MAXIMUM 200 WORDS, excluding tabulated data).

7. **MAIN SAFETY ISSUES AND TOXICOLOGY:**

(a) Target species studies:

i) (List side effects/adverse reactions/toxicological profile, with incidence figures and key references).
ii) Pre-clinical studies: (Animal and in vitro toxicology data)

(Free comment, if required: MAXIMUM 200 WORDS, excluding tabulated data).

8. EVIDENCE OF LONG TERM SAFETY/EFFICACY

Tabulate key long-term studies, their duration, indications, findings, tolerability, etc.; with references, where applicable).

(Free comment, if required: MAXIMUM 100 WORDS).

9. EVIDENCE OF BIOAVAILABILITY AND PHARMACOKINETICS OF THE ACTIVE COMPONENT (S):

Methods used and number of subjects studied to be clearly specified, where applicable. Pharmacokinetic data summarized in tabular or graphical form is essential. (MAXIMUM 100 WORDS).

For medicines containing more than one active component, provide a summary of evidence (with key references), that each contributes materially to the efficacy of the product. (MAXIMUM 100 WORDS).

10. REGISTRATION STATUS IN OTHER COUNTRIES:

Country	Date of registration

11. PROPOSED SCHEDULING STATUS:

(Provide reasons briefly, and illustrate structural formula)

12. LIST OF KEY REFERENCES:

(MAXIMUM 25)

(Directly applicable publications in referred scientific journals are preferred. Where suitable published scientific documentation is lacking, selected unpublished key scientific reports or in-house documents may be quoted, provided these are clearly indicated as such.

The "Vancouver Style" of setting out published references, entails the following*:

Author(s), title of article, names of journal (abbreviated according to Index Medicus), journal particulars (year, volume, page no.).

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DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR CLINICAL TRIALS ON VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for the conduct of clinical trials for veterinary medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for the conduct of clinical trials for veterinary medicines. The MCC is committed to ensure that all medicines available that are used in clinical trials are of the required quality, safety and efficacy. It is important for applicants to adhere to these requirements.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

INDEX:

1. SCOPE OF THE GUIDELINE

This document is intended to provide guidance for the conduct of clinical trials on veterinary medicinal products. It is intended to ensure that those trials are conducted and documented in according to International Guidelines.

2. INTRODUCTION

The objective of this document is to provide guidance for practice on the conduct of clinical trials on veterinary medicinal products. It is directed to all those involved in the conduct of such trials and is intended to ensure that those trials are conducted and documented in accordance with International Standards.

Pre-established systematic written operating procedures for the organisation, conduct, data collection, documentation and verification of clinical trials are necessary to establish the validity of data and to improve the ethical, scientific and technical quality of trials.

The welfare of the trial animals is ultimately the responsibility of the investigator for all matters relating to the trial. All investigators must demonstrate the highest possible degree of professionalism in the observation of animals in the trials and the reporting of such observations. Independent assurance that the trial animals and the human food chain are protected should be provided by the authorisation procedure of the competent authority and the procedure for informed consent of the owner of the animals. The approval of a competent Ethical Committee must be obtained. In certain basic trials this requirement may be waived. The authority should be consulted as to which trials are exempt from this requirement.

Safety and pre-clinical trials, including pharmacokinetic studies, are not included in the scope of this document since there are already such guidelines. Data derived from such trials must be submitted to the authority in order that the clinical trial or series of trials may be properly authorised prior to commencement.

In conducting clinical trials, due regard must be taken of the possible effects of the product on the environment, on residues in the produce of treated animals, and the eventual fate of animals used for food consumption.

3. RESPONSIBILITIES

Sponsor

1. Each Sponsor will confirm detailed Standard Operating Procedures (SOP) for the elements contained in the protocol.
2. With regard to trial protocols the recommendations contained in Chapter 2 of this guideline will be carefully followed during their construction.
3. Both the Sponsor and Investigator/Study director will sign the protocol as an agreement of the details of the clinical trial. Any amendments to the protocol must have the signed agreement of both Sponsor and Investigator/Study director.
4. All studies started after 2 May 2003 shall be carried out in accordance with this note for guidance
5. Furthermore, the Sponsor will:
   a) select the Investigator/Study director, and assure his/her qualifications, assure his/her availability for the entire duration of the study, ensure that he/she agrees to undertake the

study as laid down in the protocol according to this note for guidance of practice, including the acceptance of verification procedures; and

b) inform the Investigator/Study director of the relevant chemical, pharmaceutical, toxicological and clinical details as a prerequisite in planning the trial; and
c) submit notification/application to the relevant authorities where required; and
d) provide the investigational medicinal product(s) in suitable packaging and labelling, in conformity with the principles of GMP, and in such a way that any blinding procedure is not invalidated. The labelling should include the words
"For Veterinary Clinical Trial Only";
- A sample of each batch should be kept for reference for one year after the end of shelf life.
- Records of the quantities of medicinal product(s) supplied should be maintained with batch/serial numbers and Certificates of Analysis. Certificates of delivery of the medicinal product(s) signed by the investigator must detail the method and place of storage to identify the exclusive use of the product(s) in the trial. It will subsequently be used to account for unused supplies.
- Appropriate recommendations for disposal of unused test product/s should be given.

e) appoint appropriately qualified and trained Monitor(s); and
f) report all suspected Adverse Drug Reactions (ADR) in accordance with relevant requirements; and
g) inform the Investigator/Study director of any critical information that becomes available during a trial and ensure that when required the relevant authority is notified; and
h) ensure that a final trial report is prepared whether or not the trial has been completed; and
i) provide adequate indemnity for the Monitor and Investigator/Study director and compensation for animal owners in the event of injury or death of the animal or loss of productivity related to the trial.
j) ensure that an appropriate independent Ethical Committee approval is obtained prior to the commencement of the trial.

Monitor

The Monitor will be the principal communication link between the Sponsor and the Study director/Investigator and will:

1. help the Sponsor to select the Study director/Investigator; and
2. work according to predetermined SOPs, visit the Investigator\Study director at critical time points during the trial to control adherence to the protocol and ensure that all data are correctly and completely recorded and reported and that informed consent is being obtained and recorded from the owner(s) of trial animals prior to including his/her animals; and
3. ensure that the trial site has adequate space, facilities, equipment, staff, and that an adequate number of trial animals is likely to be available for the duration of the trial; and
4. ensure that trial staff have been adequately informed about the details of the trial; and
5. be reasonably available to the Investigator/Study director for consultation, in person or via telephone, facsimile machine, telex, electronic mail etc.; and
6. check that the storage, dispensing and documentation for the supply of investigational medicinal product(s) are safe and appropriate, and ensure that any unused medication is returned by the owner(s) to the Sponsor or to an approved site; and
7. submit a written report to the Sponsor at agreed regular intervals to include the reporting of all telephone calls, visits, letters and other contacts with the Investigator/Study director (audit paper trail concept). These reports will form part of the trial documentation.

Investigator/Study director

The Investigator/Study director will:

1. agree the protocol with the Sponsor via the Monitor and confirm in writing that he/she will work according to the protocol, and adhere to this note for guidance; and
2. submit an up-to-date curriculum vitae in MCC format and other credentials to the Sponsor; and
3. obtain informed consent from the owners of trial animals where applicable. The animal owner must receive written information from the Investigator/Study director in advance; and
4. provide all relevant information to all staff members involved with the trial or with other elements of the management of the trial animals. This should include the local veterinarian that normally attends the animals; and
5. ensure that the investigational medicinal product(s) are correctly stored and safely handled. Ensure investigational medicinal products are dispensed to trial subjects in accordance with the protocol and to maintain a full inventory of receipt, usage and remaining stocks. At the end of the trial it must be possible to reconcile delivery records with those of usage and returns including accounting for any discrepancies; and
6. manage any code procedure and documentation (e.g. randomisation envelopes), with due professional care, and ensure that any treatment code is only broken in accordance with the protocol and with the Sponsor's/Monitor's knowledge and consent; and
7. collect and record data in accordance with protocol requirements; and
8. in the case of ADRs immediately notify the Sponsor and Monitor and, where required, relevant authorities; and
9. make all data available to the Sponsor/Monitor for the purposes of validation;
10. ensure the accuracy of any report drafted for him/her; and
11. forward signed Record Sheets to the Monitor. Collaborative Investigators and those responsible for the analyses (including statistical analyses) and the interpretation of the results should also sign the relevant Record Sheets. Where appropriate, all practice records will be clearly marked that the animal(s)/owner is participating in a clinical trial; and
12. observe the following points particularly related to animal care:
    a) the Investigator/Study director will be expected to give assurance that he/she has sufficient time to devote to the study, access to adequate staff and facilities for the conduct of the study, and that suitable equipment is immediately available in case of emergency;
    b) the Investigator/Study director is responsible for animals under his/her care for the purpose of the trial and, where the Investigator/Study director is not a veterinarian, will ensure that their care is maintained during and after the trial. The local veterinarian should be kept informed.
    c) the Investigator/Study director shall ensure the correct disposal of study animals at the completion of the trials. This should include compliance with appropriate withdrawal periods for animals that could enter the food chain as stipulated by the appropriate authority.

4. GUIDE FOR THE CONDUCT OF CLINICAL TRIALS

A well-designed trial relies predominantly on a thoroughly considered, well-structured and complete protocol, which should be completed and approved, by the Sponsor and Investigator/Study director before the trial is initiated.

The protocol will, where relevant, contain the information given in the following list of items, or this list should at least be considered whenever a trial is contemplated and reasons for any omissions given.

General information

1. Title of the study.
2. Each study will be given an identifier unique to the Sponsor.
3. The expected names and contact points of the Investigators responsible for the trial; the expected names of other possible participants and their professional background (e.g. veterinarian, biochemist, parasitologist, experimental animal attendant, statistician etc.) should also be made clear.
4. The name and any contact point of the Sponsor.
5. If known, the identity of the farm/department/group of veterinary practices where the trial will take place (affiliations, addresses).

Justification and objectives

1. The objective in conducting the study must be clearly established.
2. The essentials of the problem itself and its background, referring where appropriate to relevant literature.
3. Summary of the preclinical and relevant pharmaceutical data for NCE's.

Schedule

1. Description of the schedule of the trial, i.e. its expected date and time of commencement, investigation period, observation period and termination date where known.
2. Justification of the schedule, e.g. in the light of how far the safety of the medicinal product has been tested, the time course of the disease in question and expected duration of the treatment.
3. Justification of the withdrawal period before slaughter etc. Even if the post-medication period of observation of the live animal is in excess of this period, a withdrawal period must be proposed for all food-producing animals in the trial.

Design

1. Specification of the type of trial e.g. controlled study, pilot study.
2. Description of the randomisation method, including the procedures to be adopted and practical arrangements to be followed.
3. Description of the trial design (e.g. parallel groups, cross-over design) and the blinding technique selected.
4. Specification of other bias-reducing factors to be implemented.
5. Description and justification of the experimental unit(s).

Animal selection

1. Specification of the type of animal to be used, including species, age, sex, breed, category, reproductive status, prognostic factors etc.
2. The housing and management of the animals.

Inclusion/exclusion criteria

1. Provision of a clear statement of diagnostic admission criteria.
2. Detailed listing of the criteria for inclusion and, if possible, pre-admission exclusions and post-admission withdrawals of animals from the trial.

Treatments

1. Clear, precise and detailed identification of the product(s) to be used. These should be fully formulated products likely to be proposed for marketing. There should be a justification of the doses to be used.
2. Description of treatment applied to the control group(s) or for control period(s) (placebo, other products, vehicle only, no treatment etc.).
3. Route of administration, dosing schedules, treatment period(s) for the test product(s) containing the active substance under investigation and for the comparative product(s).
4. Rules for the use of concomitant treatment.
5. Measures to be implemented to ensure the operator's safety whilst handling the test products prior to and during administration.
6. Measures to promote and control close adherence to the prescribed instructions/ordinances (compliance monitoring).

Assessment of efficacy/safety

1. Definition of the effects to be achieved before efficacy/safety can be claimed.
2. Description of how such effects are measured and recorded.
3. Times of and periods between, observations and concomitant recording of the effects.
4. Description of special analyses and/or tests to be carried out with times of sampling and interval before analysis/test.

Adverse events

1. Methods of recording and monitoring suspected adverse events.
2. Provisions for dealing with such events, e.g. treatment, changes to method of administration.
3. Information on where the trial code (for blinded studies) will be kept and how it can be broken in the event of an emergency.
4. Details for the reporting of suspected ADRs and all side effects, particularly the name of the individual designated to receive such reports.

Operational matters

1. A detailed plan should be drawn up of the various steps and procedures necessary to control and monitor the trial most effectively.
2. Definition of an instruction for anticipated deviations from the protocol.
3. The duties and responsibilities of the investigation team and their co-ordination.
4. Instructions to staff, including a trial description.
5. Addresses, telephone numbers etc. enabling any staff member to contact responsible members of the investigation team at any hour.

Handling of records

1. Procedures for handling and processing the records of various effects, including suspected ADRs, relating to the use of the product(s) under study should be defined.
2. Procedures for the maintenance of all the records for each individual (or test group) within the trial must be available. If animals are treated individually then the records must permit the identification of the individual concerned.
3. A copy of the test animal record sheet should be included.

Evaluation

1. Definition of the measure of test animals' response, e.g. a scoring system, and other measurements made in order to evaluate the clinical response.
2. Definition of the methods of computation and calculation of the effect of the medicinal product.
3. Description of how to deal with and report on animals withdrawn or otherwise removed from the trial.

Statistics

1. A thorough description of the statistical methods to be employed.
2. The planned number of animals to be included in the trial(s) and the reasoning for the choice of sample size, including reflections on (or calculation of) the power of the trial and the clinical justification, should be provided.
3. Description of the statistical unit/experimental unit.
4. The level of significance to be used.

Supplements

The protocol should comprise a comprehensive summary and relevant supplements (e.g. information to the owners of the animals, informed consent form, instructions to staff, description of special procedures).

References

A list of relevant literature, referred to in the protocol, must be included.

5. DATA HANDLING

General

1. The person recording an observation will sign and date or, in the case of the supervisor, each page of observations.
2. Data should be recorded on pre-established durable recording sheets. Record sheets should be diligently completed indelibly in ink or ball pen, with all the data points recorded as required in the protocol. However, when the Investigator/Study director considers additional observations necessary they should also be recorded on the record sheet together with a comment as to their perceived significance.
3. Units must always be stated, and transformation of units must always be indicated and documented.
4. All corrections on a record sheet and elsewhere in the raw data must be made by drawing one straight line through the erroneous values, which should still be legible. The correct data must be

inserted with date and signature or initials, if possible with reasons for change. An alternative would be to use a correction form.
5. Laboratory values should always be recorded on a record sheet or attached to it. The Investigator must certify values outside an accepted reference range. Normal reference values for the laboratory should be included.
6. If data are entered directly into a computer there will be adequate safeguards to ensure validation including a signed and dated printout. In this case the electronic record or the printout may be referred to as Raw Data.
7. If, for example, during (direct) data entry, data are transformed by coding, the transformation must be documented.
8. For electronic data processing only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions.

Investigator

The Investigator guarantees the correctness and completeness of the data with a signature and date on each record sheet.

Sponsor

1. The Sponsor will use properly documented and validated data entry handling and analytical systems/programmes.
2. The Sponsor will be able to identify each experimental unit (animal or group of animals) by unambiguous means.
3. SOPs will include systems for dealing with electronic data.
4. The Sponsor will ensure the greatest possible accuracy when converting data electronically. It should be possible to obtain a data printout that can be compared with the raw data.
5. Computer data systems will be designed to allow correction after loading but the correction must be documented and traceable by date and identity of the person making the correction.
6. The Sponsor will maintain a list of persons authorised to make corrections and protect the data by appropriate password systems.

Archiving of data

1. Wherever possible, the investigational centre should forward all raw data to the Sponsor for archiving. Where this proves impractical, the investigational centre must ensure adequate archive facilities and forward copies to the Sponsor. The Sponsor must ensure that the Trial Master File contains a listing of all information which is available and where it can be found.
2. The Protocol, documentation (including data on Suspected Adverse Events), approvals and all other documents related to the trial will be retained by the Sponsor in the Trial Master File for a period of five years after the product is no longer authorised.
3. All data and documents will be made available for inspection if requested by relevant authorities.

6. STATISTICS

1. Access to bio-statistical competence will be mandatory. Where and by whom the statistical analyses are carried out will be the responsibility of the Sponsor.
2. The type of statistical analysis to be used will be specified in the protocol and any subsequent deviations from the plan will be described and justified in the final trial report. Calculations and analyses will be confirmed by a named statistician.

3. The statistician and the Monitor will ensure that the data are of high quality at the point of collection and subsequent processing. The statistician will be expected to ensure the integrity of subsequent data processing by using proven and scientifically recognised statistical procedures. An account will be made of missing, unused and spurious data during statistical analysis. All exceptions will be documented for further review if required.

7. DATA VERIFICATION

1. Procedures for data verification will be applied to each stage of data collection, recording and processing.
2. The Sponsor/Monitor will be expected to perform the following functions before, during and after the study:

a) Monitor the trial site to ensure that the investigational product(s) and record keeping are being handled correctly and that Adverse Events are properly recorded and reported.
b) Account for the supply and use of investigational and reference substances.
c) Monitor the Investigator's procedures and facilities in accordance with the Protocol and SOPs. Any deviations will be documented and justified.
d) Verify data through each processing procedure.
e) Account for all relevant trial documents and have them available for future audit if required.

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MEDICINES CONTROL COUNCIL

BIOAVAILABILITY AND BIOEQUIVALENCE FOR VETERINARY MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of efficacy for veterinary medicines using bioavailablity/ bioequivalence studies. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy and in doing so reserves the right to make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
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1. INTRODUCTION

Adequate evidence/proof of efficacy and safety for all multisource products in the form of appropriate *in vivo* bioequivalence studies must be submitted with each application for the registration of a veterinary medicine.

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

Comparison of therapeutic performances of two pharmaceutical products containing the same active substance is a critical means of assessing the possibility of using either the innovator or a multi-source (generic) pharmaceutical product. Assuming that in the same subject a similar plasma drug concentration time course will result in similar drug concentrations at the site of action and thus in a similar effect, pharmacokinetic data instead of therapeutic results may be used to establish bioequivalence.

The objectives of this guideline are to:

i. Define when bioavailability or bioequivalence data will be required in order to prove safety and efficacy.

ii. Provide guidance on the design and conduct of studies and the evaluation of data.

iii. Provide guidance when *in vitro* instead of *in vivo* data may be used.

iv. Provide guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.

For pharmaceutical products where the active ingredient is not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied. Under these conditions availability (local) may be assessed by quantitative measurements which appropriately reflect the presence of the active ingredient at the site of action.

2 DEFINITIONS

2.1 Active Pharmaceutical Ingredient (API)

A substance or compound used or intended to be used in the manufacture of a pharmaceutical product and which is expected to have a medicinal or pharmacological effect when administered.

2.2 Pharmaceutical Product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

2.3 Pharmaceutical Equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same active pharmaceutical ingredient(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 bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in the product performance.

2.4 Therapeutic Equivalence

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.

2.5 Bioavailability

Bioavailability refers to the rate and extent to which the active pharmaceutical ingredient, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

2.6 Bioequivalence

Bioequivalence is defined as the absence of a significant difference in the bioavailability between two pharmaceutically equivalent products under similar conditions in an appropriately designed study.

Comparative studies using clinical or pharmacodynamic end points may be used to demonstrate bioequivalence.

2.7 Pharmaceutical Dosage Form

A pharmaceutical dosage form is a pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution etc.) suitable for administration to human and animal subjects.

2.8 Multi-Source (Generic) Pharmaceutical Product

Multi-source pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

2.9 Proportionally Similar Dosage Forms/Products

Pharmaceutical products are considered proportionally similar in the following cases:

i. When all active pharmaceutical ingredients and inactive components are in exactly the same proportion between different strengths (e.g. a 100mg strength tablet has all active and inactive pharmaceutical ingredients exactly half of a 200mg strength tablet and twice that of a 50mg strength tablet).

ii. When the active and inactive ingredients are not in exactly the same proportion but the ratios of inactive pharmaceutical ingredients to the total weight of the dosage form are within the limits defined by the Guideline for Major and Minor Amendments.

iii. When the pharmaceutical products contain high potency active pharmaceutical ingredients and these products are of different strengths but are of similar weight.

The difference in API content between strengths may be compensated for by weight changes in one or more of the inactive pharmaceutical excipients provided that the total weight of the pharmaceutical product remains within 10% of the weight of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same inactive pharmaceutical excipients must be used for all strengths, provided that the changes remain within the limits defined by the Guideline for Major and Minor Amendments.

Exceptions to the above definitions may be considered provided justification is submitted.

3. DESIGN AND CONDUCT OF STUDIES FOR ORALLY ADMINISTERED PHARMACEUTICAL PRODUCTS

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound alternatively well-established designs such as parallel designs for very long half-life substances could be considered.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required and must be justified.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of Cmax and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80% is covered before 72 hours.

3.2 Trial Animals

3.2.1 Number of Animals

It is recommended that the number of subjects should be justified on the basis of providing at least 80% power of meeting the acceptance criteria.

The minimum number of animals should not be less than 8. If 8 animals do not provide 80% power more subjects should be included.

A minimum of 12 animals is required for modified release oral dosage forms.

The number of animals required to provide an 80% power of meeting and passing the acceptance criteria for the 0,8 - 1,25 acceptable interval can be determined from Table 1 below (Reference 1).

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Table 1 Sample sizes to attain a power of 70%, 80% and 90% in the case of the multiplicative model: $\alpha = 5\ \%$, $\theta_1=0.8$, $\theta_2=1.25$ and various CVs.

CV	Power	μ_T/μ_R							
(%)	(%)	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	70	10	6	4	4	4	4	6	16
7.5		16	6	6	4	6	6	10	34
10.0		28	10	6	6	6	8	16	58
12.5		42	14	8	8	8	12	24	90
15.0		60	18	10	10	10	16	32	128
17.5		80	22	12	12	12	20	44	172
20.0		102	30	16	14	16	26	56	224
22.5		128	36	20	16	20	30	70	282
25.0		158	44	24	20	22	38	84	344
27.5		190	52	28	24	26	44	102	414
30.0		224	60	32	28	32	52	120	490
5.0	80	12	6	4	4	4	6	8	22
7.5		22	8	6	6	6	8	12	44
10.0		36	12	8	6	8	10	20	76
12.5		54	16	10	8	10	14	30	118
15.0		78	22	12	10	12	20	42	168
17.5		104	30	16	14	16	26	56	226
20.0		134	38	20	16	18	32	72	294
22.5		168	46	24	20	24	40	90	368
25.0		206	56	28	24	28	48	110	452
27.5		248	68	34	28	34	58	132	544
30.0		292	80	40	32	38	68	156	642
5.0	90	14	6	4	4	4	6	8	28
7.5		28	10	6	6	6	8	16	60
10.0		48	14	8	8	8	14	26	104
12.5		74	22	12	10	12	18	40	162
15.0		106	30	16	12	16	26	58	232
17.5		142	40	20	16	20	34	76	312
20.0		186	50	26	20	24	44	100	406
22.5		232	64	32	24	30	54	124	510
25.0		284	78	38	28	36	66	152	626
27.5		342	92	44	34	44	78	182	752
30.0		404	108	52	40	52	92	214	888

Note: Less than 8 subjects should not be used even if the above table indicates that a power of 80% can be attained with less than 12 subjects.

To determine the number of animals required, proceed as follows:

i. Determine the CV% of the appropriate BA/BE parameter for the drug under investigation from published literature or an appropriate pilot study.

ii. Choose an appropriate mean test/ reference ratio that is envisaged for the BA/BE parameter (μ_T / μ_R). Ideally this value will be 1.00, however, in practice this is seldom the case so the choice of this ratio is at the discretion of the Sponsor/Applicant.

iii. Determine from the table the number of animals required for the appropriate CV%, Power and μ_T / μ_R.

For example, if the drug under investigation has an AUC CV of 20% and if a μ_T/μ_R of 0.95 or 1.05 is selected, then a minimum of 20 and 18 animals respectively will be required for a power of 80%.

Alternatively, the sample size can be calculated using appropriate power equations, which must be presented in the protocol.

Add-ons will be permitted but the number of animals in the add-on should not excee d the initial number of animals in the study, unless fully justified. The applicant must show that the data are homogeneous using appropriate statistical tests. The provision for add-ons must be made in the protocol *a priori*.

3.2.2 Selection of Animals

The animal population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy animals.

The inclusion/exclusion criteria should be clearly stated in the protocol.

3.3 Standardisation of the Study Conditions

The test conditions should be standardised in order to minimise the variability of all factors involved, except that of the products being tested. Therefore standardisation of the diet, fluid intake and exercise is recommended.

3.4 Sample Collection and Sampling Times

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the drug. In most cases the drug may be measured in serum or plasma, however, in some cases, whole blood may be more appropriate for analysis.

When blood is collected:

i. The duration of blood sampling in a study should be sufficient to account for at least 80% of the known AUC to infinity (AUC_∞). This period is approximately three terminal half-lives of the

drug.

ii. For most drugs 12 including a pre-dose sample should be collected per animals per dose.

iii. Sample collection should be spaced such that the maximum concentration of drug in blood (C_{max}) and the terminal elimination rate constant (K_{el}) can be estimated.

iv. At least three to four samples should be obtained during the terminal log-linear phase to estimate K_{el} by linear regression analysis.

v. The actual clock time when samples are collected as well as the elapsed time relative to drug administration should be recorded.

If drug concentrations in blood are too low to be detected and a substantial amount (> 40%) of the drug is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

When urine is collected:

i. The volume of each sample must be measured immediately after collection and included in the report.

ii. Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life so that the amount excreted to infinity (Ae_{∞}) can be estimated.

iii. Sufficient samples must be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours are usually appropriate.

3.5 Characteristics to be Investigated

3.5.1 Blood/Plasma/Serum Concentration *versus* Time Profiles

In most cases evaluation of bioavailability and bioequivalence will be based upon measured concentrations of the parent compound (i.e. the API) where the shape of and the area under the plasma concentration *versus* time curves are generally used to assess the rate and extent of absorption.

In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound.

i. If the concentration of the active substance is too low to be accurately measured in the biological matrix.

ii. If there is a major difficulty with the analytical method.

iii. If the parent compound is unstable in the biological matrix.

iv. If the half-life of the parent compound is too short thus giving rise to significant variability.

Justification for not measuring the parent compound must be submitted by the applicant and

bioequivalence determinations based on metabolites should be justified in each case.

Sampling points should be chosen so that the plasma concentration *versus* time profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. AUC_t, AUC_∞, C_{max}, t_{max} for plasma concentration *versus* time profiles.

ii. AUC_τ, C_{max}, C_{min}, fluctuation (%PTF) and swing (%Swing) for studies conducted at steady state.

iii. Any other justifiable characteristics (cf. Appendix I).

iv. The method of estimating AUC-values should be specified.

3.5.2 Urinary Excretion Profiles

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug input. However, justification must also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. Ae_t, Ae_∞ as appropriate for urinary excretion studies.

ii. Any other justifiable characteristics (cf. Appendix I).

iii. The method of estimating AUC-values should be specified.

3.5.3 Pharmacodynamic Studies

If pharmacodynamic parameters/effects are used as bioequivalence criteria, justification for their use must be submitted by the applicant. Bioequivalence determinations based on these measurements should be justified in each case. In addition:

i. A dose response relationship should be demonstrated.

ii. Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.

iii. The complete effect curve should remain below the maximum physiological response.

iv. All pharmacodynamic measurements/methods must be validated with respect to specificity, accuracy and reproducibility.

3.6 Chemical Analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and cGMP.

Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix. Validation should therefore address the following characteristics of the assay (Reference 2):

i. Stability of stock solutions.

ii. Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

iii. Specificity.

iv. Accuracy.

v. Precision.

vi. Limits of detection and quantitation.

vii. Response function.

viii. Robustness and ruggedness.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run.

A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).

All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed.

Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation and all modifications should be reported and the scope of revalidation justified.

3.7 Reference Product

N.B. Products that are not registered in South Africa cannot be used as reference products in bioequivalence studies submitted in support of an application e.g. a product approved for marketing in another country(s) but not approved for marketing in South Africa cannot be used as a reference product.

3.7.1 Reference Products Registered and Marketed in South Africa

The reference product must be an innovator product registered with the Medicines Control Council (MCC) and must be procured in South Africa except that an "OLD MEDICINE" may be used as a reference product when no other such product has been registered and provided that it is available on the South African market. If more than one such product is available, then the product that is the market leader in South Africa should be used as the reference.

3.7.2 Reference Products Registered but not Procured inside South Africa.

1. A foreign reference product can be used provided that the following evidence is submitted:

   i. The reference product has an identical formulation (the same in all respects) as the innovator product marketed in South Africa.

   ii. The reference product is manufactured by the same method as the innovator product marketed in South Africa.

   iii. The reference product is manufactured at the same site as the innovator product marketed in South Africa.

   The intention of the above clause is to provide for the use of a reference product where that innovator product has been imported for use in South Africa.

2. As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in SA and must meet the f_2 requirements when tested in dissolution media of pH 1.2, 4.5 and 6.8, using an appropriate dissolution apparatus (see Guideline for Dissolution Testing).

   The intention of the above clause is to make provision for dossiers submitted prior to the implementation of this guideline.

3.7.3 Reference Products Registered in South Africa but not Marketed (Available) in South Africa

If a reference product is registered in SA but cannot be procured (i.e. is not available) in South Africa, then the reference product used can be obtained from outside South Africa provided that the product meets the following criteria:

i. The reference product must be a conventional, immediate-release oral dosage form.

ii. There is no documented evidence of bioavailability problems related to the active pharmaceutical ingredient(s) or the pharmaceutical product, or ingredients or products of similar chemical structure or formulations.

iii. It must be documented that the pharmaceutical product is authorised for marketing by the health authority of a country with drug registration requirements acceptable to the MCC. In such instances the registration requirements of the country where the reference product was approved must be submitted.

iv. It must be documented that the pharmaceutical product is marketed in the country of origin by the same innovator company or corporate entity which currently markets the same active pharmaceutical ingredient in the same dosage form in South Africa; or, that it is marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity which currently markets the product in South Africa. The country of manufacture must be stated.

v. Copies of the labelling for the reference as well as the innovator product marketed in South Africa, together with Certificates of Analysis for both products, analysed using the specifications for description, assay, content uniformity and dissolution proposed in the submission for the multi-source product, must be provided.

vi. The active pharmaceutical ingredient is uncomplicated i.e. it does not exhibit any of the following:

- A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
- A steep dose / response relationship.
- A risk of serious undesired effects.
- Complicated or variable pharmacokinetics e.g.:
  - non linear pharmacokinetics
  - variable or incomplete absorption
  - an absorption window, i.e. site specific absorption
  - substantial first-pass metabolism (>40%)
  - an elimination half life of 24 hours or more

vii. The active pharmaceutical ingredient must not be a pro-drug.

viii. The dosage form:

- Contains a single API.
- Contains the same quantity of medicinal ingredient as the innovator product registered in South Africa.
- Is the same as the dosage form registered in South Africa with respect to colour, shape, size, weight, type of coating and other relevant attributes.

3.7.4 Reference Products for Combination Products

Combination products should in general, be assessed with respect to bioavailability and bioequivalence of individual active substances:

i. Either individually (in the case of a new combinations), or

ii. Using an existing combination as the reference.

iii. In the former instance, immediate release oral dosage forms containing a single API can be used as the reference. These reference products may include "OLD MEDICINES".

Bioequivalence testing of such products will be permitted only for those products approved by the MCC.

3.8 Study Products and Batch Size

3.8.1 Study Products

The following information on test and reference products must be submitted:

i. Assay of test and reference product.

ii. Comparative dissolution profiles of the test and the reference product.

iii. A CoA of the API used in the test product bio-batch as well as quality control data demonstrating compliance with the specifications.

In addition, the test and reference products must conform to the following:

i. Test and the reference product should not differ by more than 5% in assay.

ii. A sufficient number of retention samples of both test and reference products used in the bioequivalence study must be kept by the study sponsor for one year in excess of the accepted shelf life or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by the MCC.

iii. A complete audit trail of procurement, storage, transport and other use of both the test and reference products must be recorded.

3.8.2 Batch Size

The bio-batch used in the bioequivalence study must satisfy the following requirements:

i. The bio-batch must be a minimum of 10 000 units or at least 10% of the production batch which ever is greater.

If the bio-batch is less than 10 000 the applicant must motivate and justify the use of a smaller batch.

ii. If the production batch is smaller than 10 000 units, a full production batch will be required.

iii. A high level of assurance must be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale -up, this should be validated appropriately.

3.9 Data Analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the test and reference products and to demonstrate that any clinically important difference is unlikely.

3.9.1 Statistical Analysis

The statistical method for testing relative bioavailability (i.e average bioequivalence) is based upon the 90% confidence interval for the ratio of the population means (Test/Reference) on the log-transformed scale, for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t, AUC_∞, C_{max} should be analysed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation.

If appropriate to the evaluation, the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data.

In addition to the appropriate 90% confidence intervals, summary statistics such as geometric and arithmetic means, SD and %RSD as well as ranges for pharmacokinetic parameters (minimum and maximum) should be provided.

3.9.2 Acceptance Range for Pharmacokinetic Parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

3.9.2.1 Single-Dose Studies

In single-dose studies designed to determine average bioequivalence, acceptance criteria for the main bioequivalence parameters are as follows:

i. AUC_t - ratio

The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

In certain cases an alternative approach may be acceptable.

Justification for the use of alternative methods e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs has been described in the literature (Reference 2 and 3). Use of alternative methods MUST be stated *a priori* in the protocol and cannot be added retrospectively.

ii. C_{max} - ratio

The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133% calculated using log transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125% will apply.

In certain cases e.g. in the case of highly variable API's, a wider interval or other appropriate measures may be acceptable but must be stated *a priori* and justified in the protocol (See references 3 and 4).

3.9.2.2 Steady-State Studies

i. Immediate Release Dosage Forms

The acceptance criteria are the same as for single dose studies but using AUC_τ instead of AUC_t

ii. Controlled/Modified Release Dosage Forms

The acceptance criteria are as follows:

- AUC_τ - ratio

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

- $C_{max\,(ss)}$ and $C_{min\,(ss)}$

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.75-1.33 (75 - 133%) calculated using log transformed data.

- %Swing and %PTF

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

3.10 Reporting of Results

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP, GLP and cGMP.

3.10.1 Clinical Report

In addition to the protocol etc., the clinical section of the bioequivalence study report should include the following:

i. A statement indicating the independence of the ethics committee.

ii. Documented proof of ethical approval of the study.

iii. A complete list of the members of the ethics committee, their qualifications and affiliations.

iv. An independent monitor's report on the study.

v. Names and affiliations of the all investigator(s), the site of the study and the period of its execution.

vi. The names and batch numbers of the products being tested.

vii. The manufacturing sites (address of the manufacturer of both the reference and the test product).

viii. Expiry date of the reference product and the date of manufacture of the test product used in the study.

ix. Assay and comparative dissolution profiles for test and reference products.

x. CoA of the API used in the test product bio-batch.

xi. A signed statement confirming that the test product used in the bio-study is the same as the one that is submitted for registration.

xii. A summary of adverse events which must be accompanied by a discussion on the influence of these events on the outcome of the study.

xiii. A summary of protocol deviations (sampling and non-sampling) which must be accompanied by a discussion on the influence of these adverse events on the outcome of the study.

xiv. Animals who are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

3.10.2 Analytical Report

The analytical section of the bioequivalence report should include the following which must be clearly presented:

i. The full analytical validation report.

ii. All individual subject concentration data.

iii. All individual plasma concentration *versus* time profiles presented on a linear/linear as well as log/linear scale (or, if appropriate, cumulative urinary excretion data presented on a linear/linear scale).

iv. Calibration data i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters for the entire study.

v. Quality control samples for the entire study.

vi. Chromatograms from analytical runs for 20% of all subjects (or a minimum of 4 subjects) including chromatograms for the associated standards and quality control samples.

vii. Analytical data from subjects who dropped out of the study due to an adverse drug event should also be presented.

viii. A summary of protocol deviations which must be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations must be justified.

3.10.3 Pharmacokinetic and Statistical Report

The pharmacokinetic and statistical section of the bioequivalence report should include the following, which must be clearly presented:

i. All drug concentration *versus* time data from the bio-study. This data must be submitted in hard copy and also formatted on a diskette in a format compatible for processing by SAS software. Individual subject data should be in rows and arranged in columns which reflect the subject number, phase number, sequence, formulation and sample concentration *versus* time data (Appendix 2).

ii. The method(s) and programs used to derive the pharmacokinetic parameters from the raw data.

iii. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.

iv. Tabulated summaries of pharmacokinetic and statistical data.

v. The statistical report should contain sufficient detail to enable the statistical analysis to be repeated, e.g. individual demographic data, randomisation scheme, individual subject concentration vs. time data, values of pharmacokinetic parameters for each subject, descriptive statistics of pharmacokinetic parameters for each formulation and period.

vi. Drug concentration data of any subject withdrawn from the study due to an adverse drug event should also be submitted, but should not be included in the statistical analysis.

3.10.4 Quality Assurance

i. The study report should be accompanied by a signed QA statement confirming release of the document.

ii. A declaration must be made by the applicant to indicate whether the site(s) (clinical and analytical) where the study was performed was subjected to a pre-study audit to ascertain the status of GCP and GLP &/or cGMP conditions at the site(s). All audit certificates should clearly indicate the date of audit and the name(s), address(es) and qualifications of the auditor(s).

iii. The applicant should submit an independent monitor's report on the clinical portion o f the study.

This report should clearly indicate the date of monitoring and the name, address and qualifications of the monitor and should be included in the study report.

3.11 Expiry Dates of Biostudies

The bioavailability/ bioequivalence study must have been completed not longer than three years prior to the date of submission.

4 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4.1 Orally Administered Drug Products Intended for Systemic Action

4.1.1 Solutions

A bioequivalence waiver may be granted for oral solutions, elixirs, syrups or other solubilized forms containing the same active pharmaceutical ingredient(s) in the same concentration(s) as the South African reference product and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).

4.1.2 Suspensions

Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

4.1.3 Immediate Release Products – Tablets and Capsules

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vivo* dissolution profiles on all strengths of each product. Waivers for *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on comparative dissolution studies may be acceptable (see Guideline for Dissolution Testing).

4.1.4 Modified Release Products

Modified release products include delayed release products and extended (controlled) release products. In general bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

4.1.5 Miscellaneous Oral Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE. Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because they might be swallowed by an animal without proper chewing. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same active ingredient/moiety.

4.2 Orally Administered Drugs Intended for Local Action

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required.

4.3 Parenteral Solutions

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently approved product.

In the case of other parenteral routes other than i/v., e.g. intramuscular or subcutaneous, if the test product is of the same type of solution (aqueous) as the reference product, contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required provided that the formulation does not contain an excipient(s) known to significantly affect absorption of the active ingredient(s).

For all other parenterals bioequivalence studies are required.

For intramuscular dosage forms monitoring is required until at least 80% of the AUC_{∞} has been covered.

4.4 Topically Administered Products

4.4.1 Locally Acting

Topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test) is recommended to prove bioequivalence. Validated visual and/or chromometer data will be necessary.

Topical formulations, other than a simple solution, with bacteriostatic, bactericidal, antiseptic and/or antifungal claims, clinical data (comparative clinical efficacy) will be required. Microbial growth inhibition zones will not be acceptable as proof of efficacy. Simple solutions however, may qualify for a waiver based on appropriate *in vitro* test methods.

Proof of release by membrane diffusion will not be accepted as proof of efficacy unless there has been data to show the correlation between release through a membrane and clinical efficacy data.

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

4.4.2 Systemically Acting

For locally applied products with systemic action e.g. transdermal products, a bioequivalence study is always required.

4.5 Products Intended for Other Routes of Administration

Products for local use (oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration.) intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. However, pharmacokinetic studies may be required as measures of safety.

4.6 Variations or Post Registration Amendments

For all post registration changes that require proof of efficacy the requirements of this guideline will be applicable.

5. WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

Bio-waivers will be considered under the circumstances detailed below.

5.1 Immediate Release Products

5.1.1 Class 1 Drug Substances

When the drug product contains a Class 1 drug substance(s) (based on the Biopharmaceutics Classification System, BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients a bio-waiver may be acceptable.

The drug substances must be highly soluble, highly permeable and the dosage form rapidly dissolving (see Guideline for Dissolution Testing).

The applicant must provide relevant information to prove that the drug substance falls within the Class 1 classification (Reference 5).

5.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (See Section 2.9) in its active and inactive ingredients, a bio-waiver may be acceptable.

In such cases the demonstration of bioequivalence *in vivo* of one or more of the lower strength/s may be waived based on dissolution tests (see Guideline for Dissolution Testing) and an *in vivo* study on

the highest strength.

1. **For Multi-source pharmaceutical products**, conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength when an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

   i. Linear elimination kinetics has been shown over the therapeutic dose range.

   ii. The higher strength is proportionally similar to the lower strength.

2. **For New Chemical Entities** with questions on toxicity, bio-wavers for a higher strength will be determined to be appropriate based on:

   i. Clinical safety and/or efficacy studies including dose desirability of the higher strength, and

   ii. Linear elimination kinetics over the therapeutic dose range, and

   iii. The higher strength being proportionally similar to the lower strength, and

   iv. The same dissolution procedures being used for both strengths and similar dissolution results obtained.

Dissolution profiles are required for all strengths. The f_2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f_2 value <50, it may be necessary to conduct an *in vivo* study. The difference factor, f_1, must also be submitted but will not be used as an acceptance criterion (Reference 6).

Note: Details on the performance of dissolution studies are described in the Guideline for Dissolution Testing and not in the BA-BE guideline.

5.2 Modified Release Products

5.2.1 Beaded Capsules - Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A bio-waiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a bio-waiver should be generated for each strength using the recommended dissolution test methods described in the Guideline for Dissolution Testing.

5.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

i. In the same dosage form but in a different strength, and

ii. Is proportionally similar in its active and inactive ingredients, and

iii. Has the same drug release mechanism,

an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

For Section 5.2.1 and 5.2.2 above, the f_2 factor should be used to compare profiles from the different strengths of the product. An f_2 value of ≥ 50 can be used to confirm that further *in vivo* studies are not needed (see Guideline for Dissolution Testing).

6 References

1. Sample size determination for bioequivalence assessment by means of confidence intervals. International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29 No. 1 (1991) 1-8, E. Diletti, D. Hauschke and V.W. Steinijans.

2. Workshop Report: Shah, V.P. et al., *Pharmaceutical Research*: 2000; 17:1551-1557.

3. Evaluation of the Bioequivalence of Highly-Variable Drugs and Drug Products. Pharm. Res. 18:6 (2001) 728-733, L. Tothfalusi, L. Endrenyi, K.K. Midha, M. J. Rawson and J.W. Hubbard.

4. Limits for the Scaled Average Bioequivalence of Highly-Variable Drugs and Drug Products. Pharm. Res. 20:3 (2003) 382-389, L. Tothfalusi and L. Endrenyi.

5. Guidance for Industry. Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

6. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

APPENDIX 1 - Abbreviations and Symbols.

C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
$C_{max\,(ss)}$	maximum plasma concentration at steady-state
$C_{min\,(ss)}$	minimum plasma concentration at steady-state
C_{av}	average plasma concentration
t_{max}	time to C_{max}
AUC_t	area under the plasma/serum/blood concentration-time curve from time zero to time t where t is the last time point with measurable concentration.
AUC_∞	area under the plasma/serum/blood concentration-time curve from time zero to time infinity
AUC_τ	AUC during a dosage interval at steady state
MRT	mean residence time
Ae_t	cumulative urinary excretion from drug administration until time t
Ae_∞	Amount of unchanged drug excreted in the urine at infinite time (7 -10 half lives).
$t_{1/2}$	elimination half-life
%PTF	$(C_{max\,(ss)} - C_{min\,(ss)}) / C_{av} \cdot 100$
%Swing	$(C_{max\,(ss)} - C_{min\,(ss)}) / C_{min} \cdot 100$