GUIDELINE ON COMPLETING VETERINARY CLINICAL TRIAL APPLICATIONS

This guideline is intended to provide recommendations to applicants wishing to submit applications for veterinary clinical trial applications. It represents the South African Health Products Regulatory Authority's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

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

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SAHPRA ACTING CEO

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1 INTRODUCTION

The objective of this document is to guide applicants on the information to submit on the design and conduct of all clinical studies for veterinary products. It is intended to ensure that such studies are conducted and documented in accordance with good clinical practice. Any person who needs to conduct a clinical trial with an unregistered veterinary medicine, a new indication or new dosage regimen of a registered veterinary medicine requires approval from the South African Health Products Regulatory Authority. Additional approval from the Department of Agriculture is also required in terms of the Animal Diseases Act (Act 35 of 1984) for the conduct of clinical trials with veterinary biological medicines.

The attached template on "Completion of Veterinary Clinical Trial applications" should be completed in the presented format.

The following are requirements when submitting a veterinary clinical study application:

A Completed veterinary clinical trial application template

B Cover letter from the applicant

E Completed veterinary Section 21 application form to import an unregistered product

H Package Inserts of investigational products

I Material Safety Data Sheet of Test Product

J Signed CVs of key study personnel

K Signed Declaration by Study Director/Investigator

L Signed Protocol by Sponsor and Study Director/Investigator

M Local Animal Ethics Committee approval letter or proof of application

N Proof of application to Act 35 of 1984 (Section 20) to request for permission to import and use a veterinary biological for study purposes or approval letter (if applicable)

O Proof of payment (see Fees Gazette)

P Proof of registration for students if a trial will be conducted for study purposes towards publication

All documentation to be submitted as soft copy or by email.

NB: *Review of the study protocol by SAHPRA does not bind the authority to accept the data collected from a study conducted using such a study protocol.*

1 PURPOSE OF THE APPLICATION TEMPLATE

The purpose of the template is to assist the South African Health Products Regulatory Authority (SAHPRA) to determine the answers to the following questions:

- Does the proposed study contribute to new knowledge in a scientific way?
- Are all aspects of this proposed trial ethical?
- Can patient safety be assured?
- Has due regard been given to animal welfare, protection of personnel involved, the environment, and human and animal food chains.
- Should this trial be done in South Africa?

The template is divided into three sections.

Section A: The Cover Sheet and Checklist of documentation to be submitted by the applicant

Section B: Administrative and Supplementary Details

Section C: Applicant's Presentation

SECTION A COVER SHEET AND CHECKLIST

1.1 Complete the Cover Sheet

1.2 Complete the checklist to ensure that required documentation is compiled and submitted. At screening by the SAHPRA, if the documentation is incomplete, the application will not be processed and the applicant will be requested for more information

1.3 Declaration by the applicant: To be completed and signed by the Sponsor and or Study Director or Investigator

The Cover Page and Checklist should accompany the application. The Internal Evaluators will e-mail back the checklist to the applicant after screening to confirm receipt and outcome of screening.

SECTION B ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Cover letter

- *Apply to the Chief Executive Officer for the attention of the Veterinary Medicines Unit.*
- *State upfront what the aim of the study is and whether there is need to import any investigational products under Section 21 of the Medicines Act.*
- *Include a "Table of Contents" stating all the attachments submitted and the relevant page numbers.*

1. **Contact Details (Name, Address, Telephone, Cell and E-mail):**

1.1 Applicant (as in cover sheet)

1.2 Sponsor as in cover sheet. If no sponsor, give the details of the responsible person or organisation initiating, managing, and/or funding the clinical study

1.3 Name and details of monitor as appointed by the sponsor

1.4 Details of Study Director / Investigator

1.5 Details of trial site / CRO (where the study will be conducted)

1.6 Capacity of Site (number of study staff). All key personnel involved in conducting a clinical study should be qualified by education, training and expertise, to perform their respective tasks (include latest CVs).

1.7 Details of the laboratories (Name / Address / Accreditation status)

SECTION C APPLICANT'S PRESENTATION

1.1 Include the Proof of Payment (Refer to SAHPRA Guideline on the website: "Fees Payable") and any other attachments stated in the "Table of contents).

2 Study details

2.1 If the study is to be conducted in South Africa and not in the host country of the applicant / sponsor, provide an explanation.

2.2 Name other Regulatory Authorities to which applications to do this trial have been submitted, but approval has not yet been granted. Include date(s) of application

2.3 Name other Regulatory Authorities which have approved this trial, date(s) of approval and number of sites per country.

2.4 If applicable, name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection

2.5 If applicable, give details of and reasons for this trial having been halted at any stage by other Regulatory Authorities

2.6 Give details if this trial is being undertaken in SADC, any other country in Africa, or any country where there is no regulatory control of clinical trials

2.7 Previous studies using this molecule, which have been approved by SAHPRA on your behalf:

- Study title
- SAHPRA approval number
- Date of approval
- Date of interim report
- Date of final report

3. Ethics Details

3.1 Local Animal Ethics Committee (AEC) approval letter for each study submitted should be attached.

3.2 The following information should be available

- Registration number of NHREC preferably in the approval letter
- Contact details of AEC
- Composition of AEC

Due regard should be given to the welfare of the study animals, the effects on the environment and the study personnel and to residues in the edible products derived from food-producing study animals.

4. Study Protocol

4.1 **Study title**

- Provide the full title.
- Include the protocol number, date of final protocol. Do not submit a draft protocol
- Check that the title is accurate and specific (e.g. if a drug being tested is actually an adjunctive treatment, this should be stated in the title).
- Make sure that no component is left out of the title – e.g. 'phase' of the study.

4.2 **Study Objective.** Ensure that, these are scientifically credible.

4.3 Study overview

4.3.1 Background information/Literature review

Discuss clearly the rationale for the conduct of the study. Describe all information where relevant to the understanding of the objective of the study (pre-clinical or clinical data published or otherwise available) that justifies the conduct of the clinical study. It could be the next logical component in a series of studies (e.g. phase II following phase I trial). Try to make sure that the answer to the question 'Why should this study be done at all?' is clear and logical.

4.3.2 Details of (VIP) Veterinary Investigational Product(s):

- Name(s) and details of test product(s) including controls to be used in study. Include formulation(s) and strength(s), dose and route of administration
- Registration number and date of registration (if applicable)
- Name(s) and details of concomitant medication(s) including reversal medicines which are required in the protocol.
- Submit package inserts or Summary of Products Characteristics or complete pharmacological information
- Estimates of quantity of all veterinary investigational products (VIP), batch number and expiry date or Certificate of Analysis if available
- If any of the above products are available in South Africa, give an explanation for not using what is available in South Africa.
- Details of supplier, storage conditions, dispensing, preparation and packaging of products should be documented and the products should be used in accordance with the study protocol only.

  Data derived from safety and pre-clinical studies may be requested by SAHPRA prior to authorisation of subsequent clinical studies.

4.4 Schedule of events

- Animal conditioning phase
- Commencement of animal phase
- Tissue sampling days
- Animal phase termination
- Anticipated withdrawal period (if applicable)
- Describe all activities and procedures to be conducted during the trial and post administration period
- Wash-out phase (if applicable)

4.5 Study design

Appropriate study designs are critical in contributing to answering scientific questions. Show that this study design is the correct scientific one to answer the stated objectives. Clearly describe and justify the components of the design with references. Discuss the type of control used.

4.6 Description of study animals

- Species
- Breed
- Number
- Age group
- Gender
- Physiological status
- Weight
- Source
- Animal identification

4.7 **Inclusion and exclusion criteria**

List the inclusion and exclusion criteria – and justify each of them in a sentence. Post inclusion removal criteria. Pay particular attention to how these criteria may or may not confound or invalidate the objectives of the trial.

4.8 **Randomisation method**

- Group or category or experimental unit allocation and justify procedure (Tabulated)
- Blinding procedures

4.9 **Treatment regimen**

A brief summary of the actual administration of medications. Ensure that dosage regimens are consistent with the package insert if applicable.

- Dosing regimen, route and justification
- Administration of test and control products
- Concomitant treatment
- Reversal / rescue treatment
- Adverse drug events: Describe the reporting procedures of adverse events. Any adverse events established should be reported using the "Adverse events reporting form for veterinary medicines" that is on the website.
- Prandial state

4.10 **Safety precautions**

- State user safety precautions and rescue treatment if applicable.

4.11 **Animal Management and Housing**

- Holding facilities and environmental control
- Permissible and non-permissible therapy and care
- Animal feeds

4.12 **Statistics**

- Ensure that all components are adequately addressed. Answer the question, 'Is this the best statistical approach / method for the outcome measures / objectives?'
- Determination of sample size (clearly stated and justified)
- Statistical method(s) and analysis of quantitative measures appropriate (clearly stated and justified)
- Data processing (how, where, when, who): clearly described

4.13 **Deviations from the Protocol**

Study protocol deviations should be recorded, signed and dated by the investigator describing the deviation and the reason for its occurrence.

4.14 **Laboratory and Assays**

Give details of sample collection and method of transportation

4.15 **Assessment of outcomes**

- Clearly describe the effects to be achieved and the clinical end-points. If surrogate markers are being used when the drug is intended to decrease mortality, etc., they should be justified.
- Define any scoring system that is necessary to objectively measure the targeted responses of the study animal and evaluate the clinical response.

Ensure that no intended measurements are likely to be of more risk to the study animals, than they are likely to provide useful information.

4.16 **Pathology Outcomes**

- Post mortems of any dead animals involved in the study should be documented including histopathological results

4.17 **Quality Control/Assurance**

- Provide information as to how the sponsor and study director / investigator will ensure quality control
- List the SOPs (Should be available in full upon request during inspection)

4.18 **Disposal of Study Animals, Chemical Waste and Effluent management plan**

Describe the proposed disposal of the study animals.

State the conditions for use of edible tissues from food producing animals.

Describe the proposed disposal of the investigational and control veterinary products that must be followed.

4.19 **Record keeping and documentation**

Specify procedures for recording, processing, handling, and retaining raw data and other study documentation. If data are entered directly into a computer system, the electronic record is considered the raw data. A computerised system should ensure that the methods for record keeping and retention afford at least the same degree of confidence as that provided with paper systems. To be validated.

- List all data capture forms (DCF)
- Provide information on data capturing and archiving of records (SOP)
- List records to be retained by Investigator

5 **Changes/amendments to the study protocol**

A written change or modification of the study protocol effected prior to the implementation of the changed or modified task should be approved by SAHPRA. Study protocol amendments should be signed and dated by the investigator and sponsor and incorporated into the study protocol once approved.

6 **Final Study Report**

- The final study report (FSR) is a complete and comprehensive description of the study written after the study has been completed.
- It includes a description of the materials and methods, a presentation and evaluation of the results, statistical analyses and a critical clinical, scientific and statistical appraisal.
- The report should follow the format of the study protocol

7 REFERENCES

1. Medicines and Related Substances Act (Act 101, 1965)
2. VICH GL9. (GCP) June 2000 for Implementation at Step 7
3. OECD Principles on Good Laboratory Practice (as revised in 1997)
4. Animal Diseases Control Act (Act 35 of 1984)
5. Farm Feeds, Fertilisers and Stock Remedies Act (Act 36 o 1947)
6. Foodstuff, Cosmetics and Disinfectant Act (Act 54 of 1972)
7. National Health Act (Act 61 of 2003)
8. Ethics in Health Research, Second Edition (2015)