8 REFERENCES

1. Draft copy: Guidelines pertaining to Regulation 12 (3) (a) to (i): Adverse drug reactions
2. Pharmacovigilance: Medicinal products for human and veterinary use, Eudralex, 2001,vol 9

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX 1

For all Adverse Drug Reactions associated with registered veterinary medicines:
The Veterinary Pharmacovigilance and Medicines Information Centre
Section of Pharmacology
Faculty of Veterinary Science
Private Bag X04
Onderstepoort
0110

APPENDIX II

1 Content/Required information for suspected serious adverse reactions reports
Applicants are expected to fully validate and follow-up all serious reactions reported by them to the authorities. It is essential for applicants to provide as complete as possible details, including all relevant clinical information for cases of suspected serious adverse reactions in order to facilitate assessment. The report of a suspected adverse reaction should as far as possible include the information below. The original words used by the reporter should be provided even if they are also classified or coded according to applicants or competent authority accepted terminology.

Applicant's details and original reporter's details

i) The name of the qualified person responsible for pharmacovigilance employed by the applicant.
ii) Address, telephone and fax number of the qualified person.

Unexpected Adverse Reaction: This means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of the product characteristics.

i) Applicants case reference number.
ii) Date of receipt of report by applicant
iii) Source of report e.g. spontaneous, clinical trial, post-authorisation study.
iv) Details of the original reporter – name, address, profession and speciality (if available).

Animal Details

i) Number treated
ii) Number of animals showing signs
iii) Number of animals dead
iv) Characteristics of animals showing signs:
- Species
- Breed
- Sex
- Age (in days/weeks/months/years)
- Weight (in kilograms)

Suspect Product details

i) Product name(s)/brand names(s)
ii) Approved Scientific Name(s) (INN - International Non-proprietary Name)
iii) Pharmaceutical form – if relevant
iv) Batch number
v) Expiry date of batch - if relevant
vi) Storage details - if relevant

5.3.4 Treatment details

i) The person who administered the product (e.g. animal owner, veterinary surgeon etc.) Include identifier (name/initials) and relevant occupation/qualification of person-if available
ii) Reason for treatment including diagnosis
iii) Dose (and frequency if relevant) of treatment given
iv) Route and site of administration used
v) Start date
vi) Stop date and/or duration of treatment
vii) Date of onset of reaction and reaction to the product
viii) Action taken after reaction (e.g. drug withdrawn, dose reduced)
ix) Previous reaction(s) to the product if occurred/reported, (re-challenge information) to include:

- Approximate date animal(s) previously treated with product
- Description of reaction including - were previous reaction signs similar to the present reaction signs
- Outcome including any treatment given

5.3.5 Other products used concurrently
All medicinal treatment over at least a one-week period preceding the suspected reaction should be provided when available. This should also include non-prescription medicines, magistral preparations and medicated feedstuffs if appropriate.

For each medication:
i) Product name(s)/brand names(s)
ii) Approved Scientific Name(s) (INN - International Non-proprietary Name)
iii) Pharmaceutical form-if relevant
iv) Batch number if relevant
v) Expiry date of batch if relevant
vi) Storage details - if relevant

Treatment details for other product(s) used concurrently
vii) The person who administered the product (e.g. animal owner, veterinary surgeon etc.) Include identifier (name/initials) and relevant occupation/qualification of person – if available
viii) Dose (and frequency if relevant) of treatment given
ix) Route and site of administration used
x) Start date
xi) Stop date and/or duration of treatment
xii) Other relevant information

5.3.6 Details of the animal suspected adverse reaction(s)
i) Description of reactions(s) including site and severity (intensity of the reaction). (The initial reporters words and/or phrases to be used where possible (with explanations if appropriate)
ii) Start date or onset of reaction
iii) Duration of reaction

iv) Specific treatments adopted against the observed adverse reaction
v) De-challenge information (e.g. any obvious effect of removal of treatment)
vi) If available the following information should be provided:
- Number of treated animals alive with sequelae
- Number of treated animals recovered

5.3.7 Other information
Any other relevant information available to facilitate assessment of the case should be provided, for example: disposition to allergy or changes in feeding habits, and/or production levels.

5.3.8 Investigation
- In a case of fatal outcome the cause of death should be provided and its relationship to the suspected reaction commented upon. Post-mortem examination findings or laboratory findings, if carried out, should be provided.
- Summary of product sample investigation (if relevant)
- Nature of applicants investigation (if relevant)

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX III

For Adverse Reactions in humans to veterinary drugs

Applicants details and original reporter's details

i) The name of the qualified person responsible for pharmacovigilance employed by the applicant.
ii) Address, telephone and fax number of the qualified person.

Adverse Reaction:

i) Applicants case reference number.
ii) Date of receipt of report by applicant
iii) Details of the original reporter – name, address, profession and speciality (if available).
iv) Details of health care professional involved – name, address, profession and speciality (if applicable)

Patient details

Details of person involved with the reaction – name, sex, age, date of reaction, nature of reaction

Adverse Event Details

i) Description of reactions(s) including site and severity (intensity of the reaction). (The initial reporters words and/or phrases to be used where possible (with explanations if appropriate)
ii) Start date or onset of reaction
iii) Duration of reaction
iv) Specific treatments adopted against the observed adverse reaction

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX IV

Tabulated Summary of Reporting requirements
Post-Registration ADR Reports (registered medicinal products)

Type of ADR report	Time frame for reporting	Format
Local Repons: (Spontaneous/ published/study0 All serious (expected and unexpected) Non serious (unexpected) Non serious (expected)	 15 days 15 days No report	 Complete form # Complete form Not required
Foreign Repons: (Spontaneous/published/ study) Serious	 PSUR only	 PSUR *
Periodic Safety Update Report (time frame as below)	30 Days	PSUR format as defined (see definitions)
Notification of Change in Nature, Severity or Frequency or Risk factors	15 days	Complete report and next PSUR*
New information impacting on risk-benefit profile of product including international regulatory decisions	3 days	Complete report (including actual publications)

Pre-Registration ADR/ ADE reports
(i.e. unregistered medicines being used under section 21 of Act 101, 1965)

Type of ADR report	Time frame for reporting	Format
Local Reports: Fatal or life-threatening (unexpected)	 i) 7+8** and ii) 6 monthly report	 i) ADR form # ii) line listing
Other serious (unexpected	i) 15 days ii) ii) 6 monthly report	i) ADR form # ii) line listing
Serious (expected) Non serious (unexpected)	 6-rnonthly report 6-monthly report	line listing line listing
Foreign reports Serious (unexpected) Serious (expected)	 6 monthly## 6 monthly##	 Line listing Line listing
Notification of Change in Nature, Severity or Frequency or Risk factors	15days and in 6 monthly report##	Complete report
New information impacting on risk-benefit profile of product or conduct of trial	3days and in 6 monthly report##	Complete report

** 7+8 - initial notification to Council as soon as possible but within 7 calendar days followed by a complete report Within 8 calendar days of the initial notification

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

PSUR- Periodic Safety Update Report (include most recent PI as well as English copy of UK PI, FDA PI, EU-SPC and steps to be taken) Submit PSURs under following circumstances

a) whenever requested by the Authority
b) when PSUR submission is a condition of registration These PSURs must be submitted within 30 calendar days of Initial receipt by the applicant from the parent company
c) as part of a submission for a PI amendment which Includes any changes relating to safety
d) routine submission from time of application for registration of new medicine until time of registration. These PSURs must be submitted within 30 calendar days of initial receipt by the applicant from the parent company
e) when a clinical trial under section 21 is being carried out with a product which is already registered in other countries

6 monthly progress report which should be submitted to Council during the entire duration of the clinical Investigation

The completed form should only be sent as an expedited report Line listings alone are acceptable when reported. In the periodic safety update report or 6 monthly progress report for clinical investigations.

APPENDIX 3

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

P.T.O

ADVICE ABOUT REPORTING SUSPECTED ADVERSE REACTIONS

This form should be completed whenever a suspected adverse reaction is observed during the use of a veterinary medicinal product in:

- animals (including birds and fish)
- incidents involving humans

Please complete the form in BLOCK LETTERS and send it to the **Department of Pharmacology and Toxicology, Faculty of Veterinary Science, University of Pretoria, Private Bag X 04, Onderstepoort, 0110 or fax to (012) 529-8304**

For further information write to the above address or telephone (012) 529-8239 or e-mail rgehring@op.up.ac.za.

What to report:

- Suspected adverse reactions to registered veterinary medicines, stock remedies and vaccines.
- Suspected adverse reactions to medicines used extra-labelly in animals
- Suspected adverse reactions to herbal, homeopathic or other alternative remedies
- Suspected lack of efficacy of a product.
- Suspected lack of efficacy of a vaccine.
- Misuse of products

We are particularly interested in:

- Adverse reactions to recently marketed products
- Serious reactions and interactions with all products
- Adverse reactions that are not clearly reflected in the package insert

Report even if:

- You are not certain that the product has caused the event
- You don't have all the details

Confidentiality:

- Identities of the reporter, client and patient will remain strictly confidential
- The report does not constitute an admission that the veterinarian or the product caused or contributed to the event

Tick box if extra report forms are required ☐

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

Veterinary Medicines – Report on Suspected Adverse Reactions **In Confidence**

SECTION ONE: REPORTER DETAILS

Name and address of reporter:

Code: _____ Tel: (___) _____

Name and address of veterinarian involved or, in the case of a human suspected adverse reaction, the doctor involved:

Code: _____ Qualifications: _____

SECTION TWO: ANIMAL DETAILS

No. of animals treated: _____ No. of animals reacting: _____ No. of deaths: _____

Species	Breed	Sex (M/F)	Age	Weight	Pregnant (Y/N)	Neutered (Y/N)

SECTION THREE: PRODUCT DETAILS

Please list **all** veterinary medicines, stock remedies and vaccines administered. Indicate the product suspected of causing the adverse effect by writing '(s)' next to the Trade Name.

Trade name	Batch No.	Actual amount administered	Route	Date started	Date stopped	Reason for use

Product administered by: Veterinarian ☐ Owner ☐ Paraveterinary professional ☐ Other ☐

Has the product registration holder been informed? Yes ☐ No ☐

SECTION FOUR: ADVERSE EVENT DETAILS

Date of onset:..... Duration of adverse event:.....

Description of event or problem (include relevant diagnostic test/ post mortem results)

If you need to continue on a separate sheet of paper, please attach and tick this box ☐

Are there any results to follow? Yes ☐ No ☐

SECTION FIVE: ADVERSE EVENT OUTCOME

☐ Died
☐ Euthanazed
☐ Congenital anomaly
☐ Intervention required to prevent permanent impairment
☐ Recovered
☐ Ongoing
☐ Other.....

Event reappeard on rechallenge
Yes ☐
No ☐
Rechallenge not done ☐

Treatment given, if any _____

Were there any sequelae? Yes ☐ No ☐

If yes, please describe sequelae _____

SECTION SIX: ADVERSE REACTIONS IN HUMANS

Names/ Initials	Sex	Age	Date of reaction	Nature of reaction

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

Required on all reports
Protocol #:_____
Patient #:_____

CLINICAL TRIAL SERIOUS ADVERSE EVENT/ REACTION REPORTING FORM

- Complete in English - Refer to Reporting Guidelines for advice on reporting
- When reporting dates report as (dd/mm/yy) - Indicate estimated dates with an asterisk (*)
- Submit SAE reports to: Clinical Trials Unit: c/o Registrar of Medicines, Pvt Bag X828, Pretoria, 0001, S. Africa
- Fax: (012) 326 2528 Tel: (012) 312 0287

1.

Species:	Sex (Mark with X)		Study Design (mark with X)		
Breed:	MALE	FEMALE	Open	Single Blind	Double-Blind
Date of Birth	Or age at event		Development Phase of trial		
Weight at time of event: _____kg					
Neutered (y/n)			Randomisation No.		

Required on all reports
☐ Initial ☐ Follow-up
Date company notified _____
Protocol # _____ Patient # _____

2.

Investigator name : _____MCC's Investigator Number:_____
Study Site Address: _____email:_____
City:_____ Postal code: _____
Province:_____ Country:_____
Sponsor Name: _____

3.

Investigational Medicines History

Name of study medication	Causality (see below)	Medicine identity known? Y/N	Dose & Frequency	Route	Start Date	Stop Date (Mark X if ongoing)	Indication for use

* Causality : 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown

4.

Concomitant Medicines History (Non Investigational concomitant Medicines)
Asterisk any suspected medicines

Name of medication	Causality* (see below)	Dose & Frequency	Route	Start Date	Stop Date (Mark X if ongoing)	Indication for use

- Causality: 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown
-

Required on all reports
Protocol #:_____
Patient #:_____

5.

Adverse Event Terms (reported terms):					
Onset Date: _____	Improved/ Resolved?	Yes	No	N/a	If Yes enter Date: _____

6.

Event Description: (including dates of hospitalisation)
_____

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

Relevant Medical History - continue on Supplementary Information Sheet		Signature (reporting investigator)
Date	Disease / Surgery	
		Name:
		Title:
		Phone No:
		Fax No:
		Date:

CLINICAL TRIAL SERIOUS ADVERSE EVENT (SAE) REPORTING FORM Page 3 of 3

11.

SUPPLEMENTARY INFORMATION
Please indicate the section to which supplementary Information refers:

VETERINARY DRUG RECALLS

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR RECALL OF VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants regarding the recalls of veterinary medicines, and the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. 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 which has been submitted regarding any recalls. The MCC is committed to ensure that all medicines that are registered 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: 27/06/2003

VETERINARY DRUG RECALLS

INDEX: PAGE:

WITHDRAWAL OR RECALL OF VETERINARY PHARMACEUTICAL PRODUCTS BY THE APPLICANT

1. DEFINITIONS

Withdrawal: is the removal or total withdrawal of the product from the market.

Recall: is the removal from the market of a specific batch or batches of product.

Patient: is the animal patient/s to which the veterinary medicine is administered.

Client: is the owner of the patient treated by the veterinarian.

End – user: is the person administering the veterinary medicine to the patient be this the veterinarian or the veterinarian's *bona fide* client.

Consumer: is a person ingesting foods of animal origin. The relevant issue here is potentially harmful veterinary drug residues in animal products.

2. REASONS FOR A RECALL

An applicant may be required to recall a particular batch or batches of a veterinary product from the market due to:

- a report of an adverse drug reaction to a particular batch of a product by the end – user, patient or consumer,
- product deficiencies identified as result of ongoing stability studies,
- technical complaints experienced regarding the printed packaging material, contamination, mislabelling, counterfeit, etc or
- when requested or instructed by the Medicines Control Council.

3. PROCEDURE

3.1. The following procedure provides some guidelines on the withdrawal or recall of a defective or possible harmful veterinary medicine from the market. These guidelines serve to remind the Pharmaceutical Industry that the Council expects the applicant to take full responsibility for product recalls, including follow-up checks to ensure that the recalls are successful. When initiating a recall, the applicant should consider the following aspects: the extent of public warnings and the success of the recall.

3.2 All recalls shall be categorized into three classes according to the level of health hazard involved (risk to the patient / end – user / consumer). On determining the level of hazard to the patients' / end – users' / consumer's health the depth or extent to which a product should be recalled from the distribution chain level could also be categorized into one of three types of recalls.

CLASS OF RECALLS

Class I
Class I recalls are for dangerous or defective products that predictably or probably could cause serious adverse health consequences or death to the patient / end - user / consumer.

Class II
Class II recalls are for products that possibly could cause a temporary or medically reversible adverse health problem.

Class III
Class III recalls are for defective products that are unlikely to cause any adverse health reaction or which do not comply with the requirements of Act 101 of 1965 in terms of the requirements for printed packaging material, product specifications, labelling etc.

TYPES OF RECALL (i.e. the depth of the recall).

Type A
A Type A recall is designed to reach all the suppliers of veterinary medicines (all distribution points) i.e. wholesalers throughout the country, distributors, veterinary medicine suppliers, private and academic veterinary hospitals and clinics, Animal Welfare Organisations, pharmacists working in private and academic veterinary clinics / hospitals, veterinarians, veterinary nurses, Animal Welfare Assistants, individual clients and consumers through press release (radio, television, regional and national press). [Recall letter to all distribution points plus press release]

Type B
A Type B recall is designed to reach wholesalers throughout the country, private and academic veterinary hospitals and clinics, veterinarians, veterinary nurses, pharmacists working in private and academic veterinary clinics / hospitals, [Recall letter to all distribution points]

Type C
A Type C recall is designed to reach wholesale level and other distribution points (e.g. veterinarians, private and academic veterinary clinics/hospitals) This could be achieved by means of representatives calling on wholesalers. If it is known where the product in question had been distributed, specific telephone calls or recall letters to arrange for the return of the product must be made.

3.3 The aforementioned information implies that a specific recall initiated could be identified as a specific Class combined with a specific Type Recall e.g. Class I, Type C for a product that could result in a possible health hazard to the patient where the product was distributed to only one veterinarian for the treatment of a few specific patients etc.

VETERINARY DRUG RECALLS

TYPE	A	B		C
CLASS				
I				X
II				
III				

3.4 Note that the Class and Type of recall to be initiated shall be decided by the Medicines Control Council, Registrar of Medicine or the Deputy-Director: Medicines Control in consultation with the Applicant and shall be as far as possible based on documented evidence and/or expert opinion of the Council and Applicant. In the event of greater urgency e.g. after hours or over weekends, the decision to recall a veterinary product from the market should be initiated by the applicant concerned following the abovementioned guidelines.

3.5 Should the performance of the applicant responsible for the recall be deemed to be inadequate, the Medicines Control Council may take appropriate action to remove the veterinary product from sale or use. An applicant's recall does not preclude enforcement actions being taken by the regulatory authority as deemed appropriate, either during, or following the completion of the recall.

4. INFORMATION TO BE SUBMITTED

The basic information that would be required by the Registrar for the decision on the status of the initiated recall would include the following:

1. The name and strength of the veterinary product to be recalled, pack size, batch/lot number, any means of identification, and the registration number of the product.

2. The total quantity of the recalled veterinary product batch originally in the applicants possession prior to the distribution.

3. The date distribution began of the recalled veterinary product.

4. Area of distribution of the recalled veterinary product and, if exported, the country to where it was exported.

5. The total quantity of the recalled veterinary product that had been distributed up to the time of the recall.

6. Suggested action to be taken and its urgency.

7. Indication of the health risk to the patient/end – user / consumer together with reasons.

This Information could be provided verbally but it should be confirmed in writing within 3 days.

5 RECALL COMMUNICATION GUIDELINES

The Recall communication from the Applicant to the distribution chain should be written in accordance with the following guidelines;

1. Should be on a letterhead from the Applicant of the product and signed by the Managing Director (or Responsible Pharmacist in terms of the Pharmacy Amendment Bill when proclaimed);

2. State the name, strength and registration number of veterinary product, pack size, and any other pertinent descriptive information of the product;

3. Nature of the defect (be brief and to the point);

4. Urgency of the action;

5. Reason for the action (must accurately describe the problem);

6. Indication of the health risk; and

7. Provide specific instructions on what should be done in respect of the recalled veterinary product.

8. The recall communication should not contain irrelevant qualifications, promotional materials, or any other statement that may distract from the message. Where necessary, follow-up communication should be sent to those who fail to respond to the initial recall communication.

14.6. POST RECALL PROCEDURES

The Medicines Control Council must be furnished with a written report within 30 days of the recall or withdrawal having been instituted. The report shall contain the following;

1. Name of the product;

2. Strength of the product;

3. Registration number

4. Pack size and Batch/lot number

5 Nature of the defect;

14 Action taken (taking into account the area of the distribution of the recalled product), and if exported confirmation of the notification of the Regulatory Authority and Applicant for the product in the country of export;

15 Urgency of the action taken;

16 Reason for the action;

17 Indication of the health risk to the patient/end–user/consumer and reported clinical problems;

18 Copies of all the recall correspondence including reference to previous correspondence to the council regarding the recall;

19 Steps taken to prevent a re-occurrence of the problem and

20. Fate of the recalled product (including the decision taken).

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

INTRODUCTION AND SCOPE OF GUIDELINES FOR VETERINARY MEDICINES

This document has been prepared to serve as an introduction to applicants wishing to submit applications for registration of veterinary medicines. 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: 27/06/2003

INDEX :

1. INTRODUCTION

1.1 SCOPE OF THE GUIDELINES

These guidelines are intended to provide information and guidance on the procedures, criteria and policies adopted by the Veterinary Clinical Committee, Veterinary Products Policy Committee, Pharmaceutical and Analytical Committee and the Secretariat of the Medicines Control Council for evaluating veterinary medicines.

The guidelines should be read in conjunction with the Medicines and Related Substances Control Act (Act 101 of 1965) as amended, and its supporting Regulations.

As these guidelines are constantly evolving due to harmonisation initiatives as well as due to new scientific developments, applicants are advised to always consult the latest information available. The Medicines Control Council endeavours to keep abreast of such developments and to keep its application requirements and evaluation procedures and policies in line with "best international practice".

1.2 GENERAL INFORMATION FOR APPLICANTS

The processing of applications may only proceed once all requirements, outlined in this document, are complied with. The application will be considered complete only if the submission is in the proper format, with the required data, the correct number of copies and the prescribed application fee.

All applications must be accompanied by a duly completed screening form, which should be used by the applicant as a checklist for completeness before submitting an application.

Once an application has been received, it will be logged, acknowledged, and processed for evaluation. From this point onwards, time lines will be followed, as determined by the Medicines Control Council, for the evaluation process and these will be communicated to the applicant.

All applications will be subjected to an in-house screening process, from where the application will be forwarded to an in-house or external evaluator depending on the nature of the application.

Any additional information that may be required for completion of the evaluation of the application will be communicated to the applicant, together with the time lines set for response.

At no stage will the applicant be permitted to communicate directly with the evaluator. All queries and concerns must be communicated through the regulatory authority to allow for these to be logged and processed.

1.3 LANGUAGE

In terms of Regulation 22 of Act 101 of 1965, all applications and supporting data submitted to the Medicines Control Council must be presented in English. Any documents in languages other than English must be accompanied by a translation.

1.4 WHERE TO SEND APPLICATIONS

Applications may be posted to Private Bag X 828, Pretoria 0001 or delivered to Room 233, Hallmark Building, 237 Proes Street, and Pretoria, where they will be logged and acknowledged. All correspondence should be addressed to the Registrar of Medicines. Applications received in any other manner other than as stated above will not be considered for processing.

1.5 CONFIDENTIALITY

Section 34 of Act 101 of 1965 preserves the confidentiality of information submitted to the Medicines Control Council. In terms of this section, no member of Council, its Committees or the secretariat may disclose to any person any information relating to the acquisition, supply, marketing, importation, export, development, manufacture or research of any medicine, complementary medicine, veterinary medicine or medical device or any other matter related thereto, except for the purpose of exercising his/her powers or for the performance of his/her functions under the Act or when required to do so by any competent court or under any law, or with the written authority of the Director-General of Health.

VCTF 1 I

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDE TO VETERINARY CLINICAL TRIAL APPLICATION

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for the conduct of veterinary clinical trials. 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. 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: 27/06/2003

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VCTF 1 I

1. INTRODUCTION

Any person wanting to initiate or conduct any clinical trial with an unregistered veterinary medicine, a new indication or new dosage regime of a registered veterinary medicine requires approval from the Medicines Control Council. Application is made on a form determined by Council. Approvals from the Department of Agriculture are also required in terms of the Animals Diseases Act for the conduct of clinical trials with unregistered veterinary biologicals and in terms of the Abattoir Act for unregistered veterinary medicines used in food producing animals. The guideline is intended to provide guidance on the application procedure, good clinical practice for the conduct of clinical trials on veterinary medicines, the format of the clinical trial protocol, ethics approval for conduct of clinical trials in animals, reporting of clinical trial adverse drug events and approvals required form the Department of Agriculture.

2. APPLICATION PROCEDURE

CLINICAL TRIAL APPLICATION – VETERINARY MEDICINES

SECTION 1 – CHECK-LIST OF REQUIRED DOCUMENTATION

To be completed by Applicants for all Clinical Trials

COVER SHEET

Study Title:

Protocol No:

Version No: **Date:**

Study Drug(s):

MCC Ref number (if applicable):)

MCC Ref number(s) of comparator drug(s) (if applicable):

MCC Ref number(s) of concomitant drug(s) (if applicable):

Date(s) MCC approval of previous protocol(s):
Sponsor: **International:**
Local:

Applicant:

Contact Person:
Address:

Telephone Number: **Fax Number:**

Cell Number:

E-mail address:

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To be completed by MCC

Date original application received:

Tracking No:

Proposed Clinical Trials Committee Meeting Date if applicable:

Signature: **Date:**

ACKNOWLEDGEMENT OF RECEIPT OF CTA (Contact details to be completed by the applicant). Whole cover sheet to be faxed to applicant once details in block above are completed.

Contact Details: Name: **Fax No.:**

Receipt of new applica tion is hereby acknowledged. **Date:**

Signature (of MCC recipient): **Name:**

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CHECKLIST

Applicant's
MCC
check list
double-check

COVERING LETTER

FULLY COMPLETED APPLICATION (SECTIONS 1–3)

PROTOCOL (INCLUDING RELEVANT QUESTIONNAIRES ETC.)

INFORMATION LEAFLET(S) AND INFORMED CONSENT(S)

INVESTIGATOR'S CV(s) IN MCC FORMAT

CERTIFICATE(S) OF ANALYSIS (May be submitted with ethics approval letter)

ETHICS APPROVAL OR

COPY OF LETTER APPLYING FOR ETHICS COMMITTEE APPROVAL

WITHDRAWAL PERIOD APPROVAL (Where appropriate) OR

COPY OF LETTER APPLYING FOR APPROVAL FOR USE OF EXPERIMENTAL PRODUCTS IN FOOD PRODUCING ANIMALS

APPROVAL FROM VETERINARY SERVICES (Biologicals) OR

COPY OF LETTER APPLYING FOR APPROVAL FOR USE OF EXPERIMENTAL BIOLOGICALS UNDER FIELD CONDITIONS IN SOUTH AFRICA

Electronic versions of the application form (Sections 1 –3), the protocol and/or other relevant documents:

LABELLED DISKETTE/CD-ROM (MSWORD OR RICH TEXT FORMAT)

List of files submitted on diskette/CD-ROM:

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SECTION 2 – ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title:

Protocol Number/identification:

Date of protocol (final):

Part 1: CONTACT DETAILS (NAME/ADDRESS/TEL/CELL/FAX/E-MAIL)

1.1 Applicant: (as in Section 1)

Physical Address:
Tel No :
Fax No :
E-Mail:

1.2 Sponsor: (as in Section 1)

Address :
Tel No :
Fax No :

1.3 If no sponsor – person or organisation initiating, managing, and / or funding the clinical trial:

1.4 Local Contact Person for correspondence:

1.5 National Principal Investigator/Coordinator: (or equivalent person)

Phone:
Fax:

1.6 International Principal Investigator: (if applicable)

1.7 Regional Monitor: (as in Section 1)

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(s)

2.1 Name(s) and details of investigational product(s) to be used in trial: [Formulation(s) and strength(s) (e.g. 10 mg/ml–10ml amp.)] Include MCC registration number and date of registration if applicable.

2.2 Name(s) and details (as above) of comparator product(s) and MCC registration number(s) and date(s) of registration if applicable: [Ensure package inserts or complete pharmacological information been included (Section 1).]

2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and

MCC registration number(s) if applicable: [Ensure package inserts or complete pharmacological information has been included with application (Section 1).]

2.4 Estimated Quantity of Trial Material (each drug detailed separately) for which exemption will be required:

2.5 If any of the above drugs are available in South Africa, give an explanation for not using what is available in South Africa:

2.6 Details of receiving of drugs from supplier, storage, dispensing, packaging of drugs:

2.7 Date MCC registration applied for – or envisaged date of application for trial medication. Explain if registration is not envisaged:

2.8 Registration status of entity, for the indication to be tested in this trial, in other countries: (i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority) [Attach as an appendix if necessary.]

Part 3: DETAILS OF TRIALIST(s) AND SITE(s)

3.1 Details of Investigator(s): [designation, title: (i.e. principal investigators / investigators) Include Name/Address/Tel/Cell/Fax/E-Mail]

Principal Investigator:
Address:
Phone:
Fax:
E-mail
Sub – Investigators:

3.2 Details of Site(s) (Name of site, physical address, contact details, contact person, etc.)

Principal Investigator:
Address:

Telephone. No:
Fax No:
E-mail

Contact person:

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Telephone. No :
Fax No :
E-mail :

Names of staff assigned to study qualifications and experience				
Name of site	Names	Qualifications	Function	Experience in clinical research (years)

Part 4: STUDY ANIMALS

4.1 Number of animals:

Part 5: OTHER DETAILS

5.1 If the trial is to be conducted in SA and not in the host country of the applicant / sponsor, provide an explanation:

5.2 Estimated duration of trial:

- Start of clinical study:
- Completion of clinical study:

5.3 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:

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

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

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

5.7 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:

5.8 Previous studies using this agent which have been approved by MCC:

5.9 If any sub studies are proposed as part of this protocol, indicate whether or not they will also be done in South Africa. If not, please explain.

Part 6: ETHICS

6.1 Ethics Committee responsible for each site, date of approval or date of application:

6.2 Attach copy of response(s) made by, and/or conditions required by ethics committee(s) if available. Ensure that date of EC response is legible.

6.3 State which Good Clinical Practice (GCP) guidelines are being followed. (Particular reference to the South African guidelines required):

6.4 Details of capacity building component of the trial, if any:

6.5 Details of the training of investigators, monitors, study co-ordinators in terms of carrying out this trial and in terms of GCP:

6.6 Detailed safety and monitoring plan for each site: [May be attached. Label as 'Section 2 Item 6.6']

6.7 Details of trial insurance certificate: (e.g. title, protocol, dates, policy #, amount)

6.8 Details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial:

Reviewer's comments on Section 2:

SECTION 3 – APPLICANT'S REPORT / PRESENTATION

[Please use Black 12 point Arial Font, using MSWord or rich text format (rtf) for electronic version]

1 Title:

CTC Reviewer's comment:

2 **Protocol Number/identification:**

3 **Rationale for study summarized: (Why should this trial be done at all?) Include statement about South African contribution, if any, to the development of this protocol.**

CTC Reviewer's comment:

4 **Background information (summarised – essential points that apply to this trial) [1-2 sentences max for each point]:**

Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity)

Mode of action:

Toxicology:

Mutagenicity:

Carcinogenicity:

Teratogenicity:

Clinical findings (e.g. phases; PK; PD; dose-finding; ADRs, NNT/NNH, other)

Pharmacokinetics

Clinical studies in target species

Safety

Efficacy

Adverse reactions

Systematic review(s) and/or citations per year-group on a Medline search

CTC Reviewer's comment:

5 **Objectives of study (clearly listed and justified)**

Objective elements	Justification
	•
	•

CTC Reviewer's comment:

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Study design (clearly described and each component justified)

[includes phase, use of placebo, dosages, randomisation, blinding, duration, etc.]

Study design elements	Justification
Animals	•
Type of study	•
Dose, period of exposure	•
Randomisation, Blinding	•
Safety	•

CTC Reviewer's comment:

Inclusion and exclusion criteria:

Inclusion criteria	Justification
1.	•
2.	•
3.	•
4.	•

CTC Reviewer's comment:

Exclusion Criteria	Justification
1.	•
2.	•
3.	
4.	•

CTC Reviewer's comment:

6 **Treatment modalities and regimens, drug accountability [clearly explained and justified for all participant groups/arms e.g. in terms of route of administration, dose, etc. Drug accountability clearly described.]**

Treatment	Justification
	•
	•

CTC Reviewer's comment:

7 Outcome measurements/variables (each clearly stated and justified)

Primary and secondary Variables	Justification
	•
	•

CTC Reviewer's comment:

8 Adverse events (prevention, definitions – including causality assignment, recording, reporting, time-lines, action to be taken, all clearly described)

CTC Reviewer's comment:

9 Statistical measures:

Determination of sample size correct, clear and justified (with and/or without stratification)

Sample size	Justification
	•

CTC Reviewer's comment:

Statistical method(s) and analysis of quantitative measures appropriate, clear and justified

Statistical Analysis	Justification
	•
	•
	•

Data processing (how, where, when, who) clearly described and justified. If a SA person will be involved in data processing, please identify that person

Procedure

Data validation:

Closing of the data base

Statistical analyses of the data

Interim analysis envisaged or not (justify) and stopping rules if applicable (explain)

CTC Reviewer's comment:

10 Ethical Issues: justification of 'Section 2 part 6' including:

Explanation of which GCP guidelines are or are not being followed

Comment on need for, appropriateness of, and relevance of GCP training / updating / for staff involved in this trial

Comment on monitors and monitoring plan
Comment on Informed Consent

Comment on ethics of the publication policy

Comment on treatment and/or management of participants and their disease condition(s) after completion of trial

Comment on ethics committee capacity to monitor site if not a local ethics committee

CTC Reviewer's comment:

11 Other relevant information not included above

E.g.

Are references adequate and dates of references current?
Yes

Are there discrepancies between protocol and IB or package inserts? Are there specific explanation(s) for these discrepancies?

Are the explanations for not following the SA 'GCP guidelines' acceptable?

Other comments on this trial.

CTC Reviewer's comment:

For office use:

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CTC Reviewer's questions and concerns to be considered and/or forwarded to applicant:

CTC Reviewer's recommendation:

Declaration of conflict of interests by CTC reviewer:

CTC recommendation (date): 1A, 1B, 2, 3, 4, 5

MCC decision (date):

CLASSIFICATION	COMMENT	ITEMS OUTSTANDING
1	Approved	No item outstanding
1B	Approved	One item outstanding (Ethics Committee Approval)
2A	Not Approved. For in-house approval	Ethics Committee approval plus two or more items as deemed by the Committee are outstanding, that is, minor concerns
2B	Not Approved For in-house plus original evaluator approval	Ethics Committee approval plus two or more items as deemed by the committee are outstanding, that is minor concerns
3	Not Approved	Items outstanding to be referred back to full CTC meeting at the next cycle due to major scientific concerns
4	Not Approved	For referral for specialist opinion before approval
5	Nor Approved For resubmission	Not approved with following reasons

3. GOOD CLINICAL PRACTICE FOR CONDUCT OF CLINICAL TRIALS ON VETERINARY MEDICINES

3.1. TRIAL PROTOCOL

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/Site Supervisor 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.

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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.

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

1. Definition of the effects to be achieved before efficacy 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 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.

3.2 DATA HANDLING

General

1. The person recording an observation will sign and date it 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 additional observations are considered necessary by the Investigator/Site Supervisor 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. Values outside an accepted reference range must be certified by the Investigator. 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 print-out. In this case the electronic record or the print-out 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 print-out which 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.

4. STATISTICS

1. Access to biostatistical 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.

5. 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 at 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.

6. ETHICS APPROVAL

Refer to Section 6 on page 10.

7. CLINICAL TRIAL ADVERSE DRUG EVENTS

MONITORING OF POTENTIAL SIDE-EFFECTS IN CLINICAL TRIALS

Efficacy studies and field trials enable to potentially observe side effects in a much larger number of animals, although a more limited number of parameters than in tolerance studies are evaluated. These suspected adverse drug reactions or side effects occurring following the use of the product in clinical trials should be documented and evaluated.

7.1 Experimental conditions

The purpose is here to evaluate the incidence of potential side effects at the intended dose level in a much larger number of animals in the conditions very close to or identical to those in which the product is intended to be.
The protocols for efficacy studies and field trials shall take due consideration of the monitoring of these effects and facilitate their record. Positive findings from pharmacodynamic studies (mostly carried out in laboratory animals) and from tolerance studies, carried out in the target animal(s), shall warrant more specific clinical monitoring of particular organ systems. The following techniques may be relevant for this purpose:
– detailed physical examination of relevant organ systems;
- blood chemistry;
– haematology;
– (fine needle) aspiration biopsy cytology;
– electrodiagnosis (e.g. ECG);
– imaging techniques (X-rays, scanner, echography);
– behavioural analysis.
The experimental conditions shall be those required for the efficacy trial in question. The composition of the product, the dose level, the route of

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administration, treatment duration shall be identical to the product intended to be marketed. Any deviation shall be duly justified.

Required on all reports
Protocol #:_____
Patient #:_____

CLINICAL TRIAL SERIOUS ADVERSE EVENT/ REACTION REPORTING FORM

- Complete in English - Refer to Reporting Guidelines for advice on reporting
- When reporting dates report as (dd/mm/yy) - Indicate estimated dates with an asterisk (*)
- Submit SAE reports to: Clinical Trials Unit: c/o Registrar of Medicines, Pvt Bag X828, Pretoria, 0001, S. Africa
- Fax: (012) 326 2528 Tel: (012) 312 0287

Patient Initials:	Sex (Mark with X)		Study Design (mark with X)		
Race:	MALE	FEMALE	Open	Single Blind	Double-Blind
Date of Birth	Or age at event		Development Phase of trial		
Weight at time of event:	_____kg				
Height at time of event	_____cm		Randomisation No.		

Required on all reports
☐ Initial ☐ Follow-up
Date company notified
Protocol # _____ Patient #

Investigator name : _____MCC's Investigator Number:_____
Study Site Address: _____email:_____
City:_____ Postal code: _____
Province:_____ Country:_____
Sponsor Name: _____

Name of study medication	Causality (see below)	Medicine Identity known? Y/N	**Dose & Frequency**	**Route**	**Start Date**	**Stop Date (Mark X if ongoing)**	**Indication for use**

- **Causality : 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown**

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Concomitant Medicines History (Non-Investigational concomitant Medicines)
Asterisk any suspected medicines

Name of medication	Causality* (see below)	Dose & Frequency	Route	Start Date	Stop Date (Mark X if ongoing)	Indication for use

- **Causality: 1=Definite, 2=Probable, 3=Possible, 4=Unlikely, 5=Unknown**
-

Required on all reports
Protocol #:_____
Patient #:_____

Adverse Event Terms (reported terms):

Onset Date: _____	**Improved/ Resolved?**	**Yes**	**No**	**N/a**	**If Yes enter Date:** _____

Event Description: (including dates of hospitalisation)

_____
_____
_____
_____
_____
_____

If necessary please continue event description on Supplementary Information Sheet ☐ Mark (x) if used

Why was the event serious (mark ALL that apply (X)		**Outcomes at the time of the report**	
Fatal		Resolved/ Improved	
Life-threatening		Recovered with long term sequelae	
New/prolonged in-patient hospitalisation		Condition worse	
Persistent or significant disability/incapacity		Not available	
Congenital anomaly / birth defect		Fatal	
Medically significant		If Outcome was Fatal: Date of Death: _____	
Required intervention to prevent one of the above outcomes		Cause of Death: _____	

Treatment of Event: **Yes , described below** ☐ **None** ☐ **Unknown** ☐

Description of treatment: _____

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Relevant laboratory/ diagnostic tests: Yes , described below ☐ None ☐ Unknown ☐			
Date	**Test**	**Results**	**Mark (X) if Pending**

Relevant Medical History - continue on Supplementary Information Sheet		**Signature (reporting Investigator)**
Date	**Disease / Surgery**	
		Name:
		Title:
		Phone No:
		Fax No:
		Date:

CLINICAL TRIAL SERIOUS ADVERSE EVENT (SAE) REPORTING FORM

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11.

SUPPLEMENTARY INFORMATION
Please indicate the section to which supplementary Information refers:

Reporting Investigator (Print Title and Name):_____

Telephone Number: _____ Fax Number:_____

Signature: _____Date: _____

8. **APPROVAL IN TERMS OF ANIMAL DISEASES ACT 35 OF 1984**

Approval for the use of all veterinary biologicals must be obtained from Veterinary Services at the National Department of Agriculture in terms of the Animal Diseases Act 35 of 1984.

9. **FOOD SAFETY REQUIREMENT**

Where applicable , withdrawal period approval must be obtained or a copy of the letter applying for approval for use of experimental products in food – producing animals must be submitted.

VETERINARY SECTION 21 APPLICATION

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDE TO COMPLETING SECTION 21 APPLICATION FORM FOR VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for Section 21 exemptions for unregistered 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 Section 21 exemptions for veterinary medicines. It is important for applicants to adhere to these requirements.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 27/06/2003

TABLE OF CONTENTS :

21.1 COUNCIL'S RESPONSIBILITIES AND LIABILITY WHEN PERFORMING ITS FUNCTION IN TERMS OF SECTION 21 OF ACT 101 OF 1965

In terms of this Section, Council may authorise the sale of unregistered medicine, complementary medicine and veterinary medicine or device for certain purposes.

21. (1) The council may in writing authorise any person to sell during a specified period to any specified person or institution a specified quantity of medicine, complementary medicine, veterinary medicine or device, which is not registered.

21. (2) Any medicine, complementary medicine, veterinary medicine or device sold in pursuant to any authorisation under sub-section (1) and in such a manner and during such a period as Council may in writing determine.

21. (3) Council may at any time in writing by notice in writing withdraw the authorisation granted in terms of subsection (1) if effect is not given to any determination made in terms of subsection (2).

An applicant who wishes to use an unregistered medicine must be fully informed and be able to respond if his request is not successful.

Section 21 mandates Council to approve the use of unregistered medicine. Council therefore, is required to address the following requirements of Section 30

21(1)
- Authorise sales
- Specify the period of sale
- Specify the purchaser or institution
- Specify the quantity of medicine

21(2)
- Determine the purpose for the use of such a medicine
- Determine the manner of use
- Determine the period of use

21(3)
- Withdrawal of the authority to sell or use.

21.2 THE AUTHORISATION OF THE USE OF AN UNREGISTERED MEDICINE UNDER SECTION 21 OF ACT 101 OF 1965

1. Objective. The objective of Section 21 of this policy is to determine how an unregistered medicine can be authorised under Section 21.

2. Responsibility. Council shall delegate the administration of the control and execution to the appropriately qualified person (Clinical Pharmacologist or Medicine Control Officer).

3. Source document Section 21 of Act 101 of 1965.

4. Policy

4.1 Council shall in writing authorise any person to sell during a specific period up to (six months) to any specified person or institution, a specified quantity of any medicine, which is not registered.

4.2 All applicants must submit the following information:

a) Name, street address and telephone number of the applicant/medical practitioner;
b) Registration number of the prescriber;
c) Name and address of the patient;
d) Diagnosis of the patient;
e) Dose frequency and route of administration of the product;
f) Number and frequency of repeats;
g) Concomitant medication;
h) Name (generic) of the unregistered product;
i) Motivation why an unregistered product is to be used;
j) Reason for not using a similar registered product/current regimen; and
k) Urgent applications can be handled by telephone in case of an emergency but the above-mentioned information must be supplied before an authorisation number is supplied. A telephonic request must be followed up in writing within 48 hours.

4.3 Request can only be repeated after follow-up reports have been submitted to the supplier and Council.

4.4 In case of long-term treatment, a follow-up report must be submitted every six months. A new authorisation number must be obtained every six months.

4.5 The officer designated must confirm the authorisation in writing.

4.6 The patient must be fully informed that the drug is not registered with the Medicines Control Council.

4.7 The patient must be fully informed about the possible benefits and risks of the product.

4.8 The patient must sign an informed consent. In the case of a minor, the parent or guardian must sign the informed consent.

4.9 If approved, the product shall only be used for the treatment of the patient in such a manner and for the approved period only. No other patient may receive the authorised unregistered medicine.