MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON VETERINARY DRUG ADVERSE EVENTS

This document has been prepared to serve as a guideline to those reporting adverse veterinary drug reactions. 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 safety data.

REGISTRAR OF MEDICINES
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CONTENTS:

1. GENERAL

These guidelines are intended to assist applicants in the reporting of adverse drug reactions (ADRs) associated with veterinary medicines and/or other medicines used in the management of animal health, and in the management of safety data which arise during clinical trials.

2. Scope

The scope of veterinary pharmacovigilance covers not only clinical safety, but also other aspects of post-authorisation surveillance.
The system takes into account any available information related to:

- lack of expected efficacy of a veterinary medicine
- off-label use
- reported violations of approved residue limits, possibly leading to investigations
- of the validity of the withdrawal period.
- potential environmental problems
- reactions in human beings related to the use of veterinary medicines

3. Items included within the scope of pharmacovigilance:

3.1 Reporting of lack of expected efficacy

Lack of efficacy in this context means: lack of expected efficacy of a veterinary medicinal product according to the indications claimed for.

It is incumbent for companies to investigate such reports. Where the conclusions drawn from the suspected adverse reaction reports differ from those in the dossier on which the authorisation was granted and which might normally be expected, the applicant should inform the competent authority.

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3.2 Off-label use (unlicensed use of products)

Off-label use: the use of a veterinary medicinal product that is not in accordance with the summary of the product characteristics, including the misuse and serious abuse of the product.

Reports of suspected adverse reactions may be obtained on products used outside the terms of the marketing authorisation e.g. use of a product in non-authorised species/indications, use at doses differing from those set out in the summary of product characteristics (SPC) and package insert.

While this practice is neither endorsed nor recommended, such reports can provide useful information on the safety of the product and should be recorded by the person responsible for pharmacovigilance and reported to the competent authorities in the normal way.

3.3 Medicated premixes

When medicated premixes that have been incorporated in the finished medicated feed are suspected of causing a reaction in animals or humans, both the premix and the medicated feed should be investigated without delay.

Among the factors that have to be examined are the composition of the finished medicated feed, the inclusion levels of active substances, the operation of the milling process(es) and, when possible, the actual dosage administered to individual target animals.

3.4 Investigation of the validity of the withdrawal period

[Reporting of violations of approved Maximum Residue Limits (MRL's)]

Where investigation of drug residues in tissues or produce of treated animals casts doubt on the validity of the withdrawal period in respect of a veterinary medicinal product, it is important that this information is brought to the attention of the competent authority responsible for authorisation of the veterinary medicinal product concerned. Such cases should be reported as suspected adverse drug reactions.

3.5 Use of human medicines in animals

Occasionally suspected adverse reaction reports may be obtained on human medicines having been used in animals. Such reports can provide useful information on the safety or otherwise of the product ingredients and should be recorded by the veterinary surgeon who used the product and, if appropriate, the veterinary representative of the company who holds the Marketing Authorisation for the human medicine concerned.

3.6 Reporting of human reactions to veterinary medicinal products

All suspected adverse reactions occurring in humans following use of veterinary medicinal products should be reported immediately by the applicant.

4. DEFINITIONS AND TERMINOLOGY

4.1 ADVERSE DRUG REACTION (ADR) or ADVERSE REACTION'

"adverse drug reaction" or "adverse reaction" is defined as a response to veterinary medicine which is noxious and unintended, and which occurs at normal doses.

This definition applies to registered veterinary medicines or medicines for which the applicant holds an application for registration. This definition includes any significant hazards to patients, such as lack of efficacy with vaccines and medicines used in life-threatening diseases.

In the case of unregistered orthodox medicines being used under section 21 of the Act, all noxious and unintended responses to a medicine related to any dose should be considered adverse drug reactions.

4.2 ADVERSE EVENT

"Adverse event/experience" is any untoward medical occurrence that may be present during treatment with a veterinary medicine but which does not necessarily have a causal relationship with this treatment.

For veterinary medicinal products, all suspected adverse reactions (serious or otherwise) should be reported when received from veterinarians, other animal health professionals, animal owners or users of the veterinary medicinal product.

By virtue of the fact that the veterinarian is making a report to an applicant, he/she is indicating that the observed event may be caused by the veterinary medicine: i.e, the veterinarian suspects that the medicine may be responsible for the event, All spontaneous reports are therefore suspected adverse drug reactions,

In the case of pre- and post-marketing studies adverse "'events" are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction. it is better to treat the event as a reaction, **For the purpose of clinical investigations registered under Section 21 of the Act an adverse drug reaction includes any adverse event where the contribution of the study veterinary medication, concomitant veterinary medication or other intervention of the clinical trial cannot be ruled out.**

A reaction contrary to an event is characterised by the fact that a causal relationship between the drug and the occurrence is suspected. i.e, judged possible by the reporter or a reviewing veterinarian. If a reaction is spontaneously reported, this usually implies a positive association from the reporter. If the sponsor of a clinical trial or the applicant does not agree with the causal association assigned by the reporter or investigator the reaction should still be reported.

4.3 SERIOUS ADVERSE DRUG EVENTS OR ADVERSE DRUG REACTION

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- **results in death,**
- **is life-threatening,**

requires patient hospitalisation or prolongation of existing hospitalisation,
results in persistent or significant disability/incapacity, or
is a congenital anomaly/birth defect.

In veterinary medicine the existence of a variety of animal species and husbandry conditions require a modified approach to the classification of a ’serious adverse reaction’ (‘serious ADR’).

For example in intensive animal production with species such as poultry, fish or bees, a certain level of mortality rate is considered as 'normal' or 'expected'. These species are usually treated as a group and only an increased incidence of mortality, or severe signs, or variations of animal production levels exceeding the rates normally expected should be considered as a 'serious ADR'.

However, in species like dogs, cats or horses a single death constitutes a 'serious ADR'. This also applies to cases of individual deaths in cattle, sheep, pigs, goats and rabbits even if they are kept in herds or flocks in intensive animal production because treatment is often performed on the individual animal and therefore a single death or severe symptoms have to be considered on an individual basis

NOTE: For all species if they are kept as an individual animal, a single death constitutes a ‘serious ADR'.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical and scientific judgement should be exercised in deciding whether other situations are serious, such as important medical events that may not be immediately life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples include blood dyscrasias or convulsions not resulting in hospitalisation.

4.4 UNEXPECTED ADVERSE REACTION

For the purposes of this regulation an "unexpected" adverse reaction is an adverse reaction, the nature, specificity, severity and outcome of which is not consistent with the applicable product information (i.e. Investigator's Brochure or other product information for unregistered medicines being used under section 21 of this Act or the approved package insert for registered medicines).

4.5 Reporters

For the purposes of reporting suspected adverse reactions reporters includes veterinarians, specialist practioners, pathologists, pharmacists, veterinary nurses, and animal owner(s), as well as health care professionals reporting suspected adverse drug reactions which occur in people following use of veterinary medicines.

When reports originate from pharmacists, animal owner or veterinary nurses. Further information about the case should be sought from a qualified veterinarian responsible for the patient or patients if possible. Furthermore if there is more than one reporter, the veterinarian directly involved in the patient's care who provides the most complete and clinically relevant information will be considered the primary reporter.

For the accuracy and usefulness of the information reported, it is recommended for animal owners and users to seek veterinary advice prior to reporting

4.6 ADVERSE DRUG REACTION REPORT

An adverse drug reaction report is a detailed record of all relevant data associated with the use of a drug in a subject or patient.

4.7 SPONTANEOUS REPORT OR SPONTANEOUS NOTIFICATION

A spontaneous report is a communication to a company, regulatory authority or other organisation that describes an adverse drug reaction in a patient given one or more medicines and which does not derive from a study.

4.8 REPORTABLE ADVERSE REACTION REPORTS-MINIMUM INFORMATION

Minimum requirements for any suspected adverse reaction (serious/non-serious/) to be reported to the VP & MIC should include:

(i) An identifiable source, wherever possible this should include the name and address of the reporter (e.g. veterinarian, pharmacist, animal owner)
(ii) animal details: species, sex, age
(iii) suspect product(s)
(iv) Suspected reactions (see appendix II)

The reference point for deadlines for submission of reports is the time of receipt of the minimum information. It should be stressed that these are minimum requirements and that companies should endeavour to provide all the information necessary for a full evaluation.

Follow-up information should be actively sought and submitted as soon as it becomes available.

4.9 PERIODIC SAFETY UPDATE REPORTS

A periodic safety update report (PSUR) is an update of the world-wide safety experience of a medicine at defined times post-registration. Each safety update report should cover the period of time since the last update report. The PSUR should fulfil the format and content described in the Final Report of the CIOMS Working Group II. (Ref 1)

4.10 LINE LISTINGS

A line listing provides key information but not necessarily all the details customarily collected on individual cases.

Reactions are classified by body system for the most serious presenting sign or symptom. The columns include:

Country
Source (physician, literature, etc.)
Number of animals treated
Number of animals involved
Age or Age group
Species and Breed
Sex
Dose of drug or drugs
Duration of treatment (prior to event);
Time to onset
Description of reaction (as reported)
Outcome (e.g. fatal, resolved etc.) Comment
Company Reference Number

Depending on their type or source, some ADR cases should be presented as line listings. It serves to help the Authority to identify cases which they might wish to examine more completely by requesting full case reports.

4.11 Authority

For the purposes of these guidelines, "Authority" refers to the Medicines Control Council.

The VP & MIC refers to the Veterinary Pharmacovigilance and Medicines Information Centre.

5. GENERAL PRINCIPLES

5.1 Who to report to:
All reportable adverse drug reactions should be sent to the Authority at the address reflected in Appendix I

5.2 Route of Notification
All reports, unless perceived to be extremely urgent, should be mailed and not faxed. (Electronic transmission of reports, may be accepted in the future)

5.3 Follow-up reports: After initial notification of an adverse reaction, a notice of acknowledgement will be sent to the applicant citing the adverse reaction number assigned to that case report in the VP & MIC Adverse Drug Reaction Information (ADRI) database. Any follow-up correspondence relating to the same case report should be cross-referenced, where possible to the ADRI database number (if one has already been assigned) or to an appropriate unique number assigned by the applicant (relating specifically to the initial notification.) This is the only reliable way to minimise the duplication of reports submitted by the applicant.

5.4 Internal pharmacovigilance system: The applicant should ensure that it has an appropriate system of pharmacovigilance in place in order to assure responsibility for its registered products and to ensure that appropriate action can be taken, when necessary.

It is strongly recommended that the applicant has permanently and continuously at its disposal in South Africa, a qualified person/s responsible for pharmacovigilance, both for pre- and post-marketing surveillance. This person/s should have experience and training in all aspects of pharmacovigilance and if not a veterinarian , should have access to a veterinary qualified person.

Applicants should inform the VP & MIC in writing of the applicant's contact person/s for all matters pertaining to pharmacovigilance The postal address, email address and telephone and fax numbers of this person should be submitted in this correspondence as well.

The responsibilities of the applicant's pharmacovigilance officer should include:

The establishment and maintenance of a system which ensures that informationabout all suspected adverse reactions which are reported to the staff of the companyor organisation including medical representatives and clinical research associates, is collectedand collated so that it is accessible at a single point.

- Serving as a contact person for Council and in particular the VP & MIC for any matters relating to pharmacovigilance.
- The preparation of the following for submissions to the Authority
  - All adverse drug reaction reports
  - Periodic Safety Update Reports (PSURs), when necessary
  - Company-sponsored pre- and post-registration study reports
  - Ongoing pharmacovigilance evaluation during the post-registration period.
- Ensuring that any request for additional risk-benefit information from the Authority is reported to the Authority promptly and fully.

5.5 Report Format and Details:

Post-registration: Reporting can be done using the white form available from the VP & MIC. Applicants may use their in-house report forms to submit reports, provided all the necessary data elements are included on the form in a readable format (Appendix 2). **It is essential that the original report (or copy thereof), submitted by the reporter is sent to the Authority**.

Pre-registration: A separate pre-registration ADR reporting form is included in Appendix 3 for reporting of clinical trial adverse reaction reports. Applicants may use their in-house Adverse Event report forms to submit such reports, provided all the necessary data elements are included on the form in a clearly readable format. **The original report (or copy thereof), submitted by the reporter must be sent to the** Authority.

Applicants should submit **ALL** the relevant information available at the time of initial notification of an adverse drug reaction report i.e. not only the Minimum Information required for a report. The attachment of discharge summaries, post-mortem reports, relevant laboratory data, and other concise clinical data is encouraged.

The applicant is required to submit the name, address and telephone number of the initial reporter on the adverse drug reaction case report form. In the case of a report from a clinical investigation, the investigation site at which the reaction occurred needs to be submitted in addition to other information requested.

5.6 Overdose:

Reports of overdose should be submitted only when the overdose was associated with an adverse reaction. The adverse reactions associated with an overdose should be reported, as are other serious reactions.

5.7 Teratogenicity and congenital anomalies

For reports on congenital anomalies or teratogenicity:

- Give age and sex of the animal species involved
- The number of neonates involved.
- Follow-up reports for the neonate should be considered a follow-up to the initial report. This will include either natural outcome or euthanasia.
- Follow-up for the mother will be considered a new initial case report on a separate report form
- The birth date or the date pregnancy was terminated should be the event onset date.

5.8 Product defects: If a product defect results in an adverse experience, these reactions should be reported in the routine manner. Applicants should reflect whether the implicated products have been tested for product quality and what (if any) corrective actions are being taken.

5.9 Drug Interactions: Any drug interaction which results in an adverse reaction should be reported as an adverse reaction in the prescribed manner.

5.10 Another Applicant's Product:

Reports of reactions or events in which the initial reporter identifies the suspect drug as one marketed by another applicant should be promptly forwarded to that applicant. The applicant to whom the event was originally reported should not report such reports to the Authority.

An applicant who receives such a report about its medicine from another applicant is required to submit the report to the Authority with time constraints applicable to any other report.

An exception is when serious, unlabeled experiences are found for another applicant's drug during the conduct of a clinical trial of a registered medicine. In this instance the applicant conducting the study should submit such a report directly to the Authority.

In the case of multiple drug utilisation, where the cause of the ADR may be due to interactions, involving products from different applicants, the report should be forwarded to the authority by the applicant initially receiving the report, as well as to the other applicants, together with the reference number assigned by the VP & MIC. This will prevent confusion when the other applicant submits the same report.

5.11 Confidentiality:

The VP & MIC will maintain strict confidentiality regarding the identities of the person(s) utilising the reported veterinary medicinal product(s) and the reporter. Details on the adverse drug reactions themselves are in the public domain.

6 POST-REGISTRATION ADVERSE DRUG REACTION REPORTS

6.1 Reactions occurring in South Africa

(i) Applicants must report all serious, suspected adverse drug reactions occurring in South Africa with any medicine, as soon as possible, within 15 calendar days after first knowledge by the applicant.

(ii) Applicants must report all non-serious, unexpected, suspected adverse drug reactions occurring in South Africa with any medicine, within 15 calendar days after first knowledge by the applicant.

(ii) Applicants must report any change in the nature, severity or frequency of expected adverse drug reactions or when any new risk factors are identified within 15 calendar days. The basis on which these assessments are made should be included.

6.2 Reactions occurring outside South Africa

(i) Foreign individual case reports should not be forwarded to the Authority on a routine basis but should be reported in the context of a specific safety issue, periodic safety update reports or on specific request by the Authority.

(ii) The Authority should be advised of any significant safety issue or action which has been taken by a foreign agency including the basis for such action within 3 days of first knowledge by the applicant.

(ii) This guideline [i.e. 13.6.2.(i) and (ii)] also applies to veterinary medicines for which the applicant holds an application for registration

6.3 Periodic Safety Update Reports

(i) Applicants must submit periodic safety update reports (see definitions for details on product safety update reports) on that medicine as deemed appropriate by Council.

(ii) Period Safety Update reports should **only** be submitted in the following situations:

a. Whenever requested by the Authority.
b. When the submission of PSURs is a **condition of registration** for a new medicinal product or range of medicinal products. 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 package insert amendment which includes any changes relating to safety.
d. When a new medicinal product is **submitted to Council for registration** and where the product has already been marketed elsewhere, PSURs should be sent routinely to the Authority during the evaluation period prior to 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.

All PSURs must be accompanied by a copy of a package insert approved by a reputable international regulatory authority (e.g. Unites States-FDA, EU -SPC or British package inserts) as well as the currently approved South African package insert.

(iii) The applicant should inform the Authority of any steps which are to be taken with regard to safety concerns raised in the periodic safety update report at the time of the submission.

(iv) The applicant should submit any consequential amendments (e.g. package insert changes) simultaneously with the PSUR at the time of its submission, in order to prevent any unnecessary duplication of effort. Further amendments may, however, also be required subsequently by the Authority.

(v) This guideline (section 13.6.3) also applies to veterinary medicines for which the applicant holds an application for registration. Periodic safety update reports of unregistered medicines or medicines for which no submission for registration has been made must not be routinely submitted for registration unless requested by the Authority.

6.4 Case reports from published scientific literature

I. Applicants should report published suspected adverse drug reactions related to the active substance(s) of their veterinary medicinal products, as relevant to the categories identified in 13.6.1 and 13.6.2 above. A copy of the relevant published article should be provided.

II. An adverse drug reaction form should be completed for each identifiable patient (with an identifiable adverse drug reaction). For instance. if an article describes 6 patients with a given adverse experience, 6 adverse drug reaction forms should be submitted to the Authority. Please refer to annexure I for the description when single or multiple reports need to be submitted.

III. If multiple drug products are mentioned in the literature report. only the applicant whose drug is the suspect drug is required to submit a report. The suspect drug is usually that mentioned as such by the author or stated in the article's title. (See 1.11)

6.5 Reports from post-registration studies

(i) All suspected adverse reactions from post-registration studies taking place in South Africa must be reported according to 13.6.1 above. This applies to reports from any type of clinical or epidemiological investigation independent of design or purpose.

(ii) Investigators involved in post-registration studies should be aware of the definition of what constitutes a serious adverse drug reaction as well as the distinction between 'reactions' and 'events'.

(iii) In the case of post-marketing studies adverse "events" are usually systematically solicited. In cases where there is uncertainty as to whether or not an event is a reaction, it is advisable to report the case as an adverse reaction. Events that are clearly unrelated to the medicine should not be reported.

(iv) If the manufacturer receives a report of a serious adverse drug reaction from the investigator who is blinded to individual patient treatment, the guidelines outlined in section 13.7.3 below should be adhered to.

6.6 On-going Pharmacovigilance evaluation

(i) Applicants must inform the Authority within 3 calendar days of first knowledge by the applicant, whenever new evidence becomes available which may significantly impact on the benefit/risk assessment of a veterinary medicine or which would be sufficient to consider, changes in the conditions of registration of the medicine.

(ii) Additional pharmacovigilance data such as actual case reports, drug usage figures, the regulatory status of the product in other countries, independent pharmaco-epidemiology studies, pre-clinical studies or significant product quality data may be requested by the Authority as the situation warrants. This will be requested for submission within a time period specified by the Authority.

6.7 Consumer Reports

If an applicant receives a report from a consumer, the applicant is encouraged to advise the consumer to report this reaction through his or her veterinarian If this approach fails, the applicant should attempt to obtain as much information as possible from the patient. If the minimum information for reporting has been met, and the report is deemed to be relevant by a health care professional within the company, the case is considered reportable.

6.8 PRE-REGISTRATION ADVERSE DRUG REACTION EVENT REPORTS

This applies to reports from any type of clinical or epidemiological trials, independent of design or purpose. being conducted under Section 21 of the Act.

6.8.1Adverse Drug Reaction reporting for Clinical Trials

(i) **All fatal and life-threatening, unexpected** adverse drug reactions occurring in clinical investigations in South Africa, registered under section 21 of the Act, should be reported within 7 calendar days after first knowledge by the applicant (i.e. the investigator), followed by as complete a report as possible within 8 calendar days of the initial information.

This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicines.

(ii) **Serious, unexpected reactions that are not fatal or life-threatening,** occurring in clinical trials in South Africa, registered under section 21 of the Act must be reported as soon as possible but no later than 15 calendar days after first knowledge by the applicant.

(iii) All suspected **serious, unexpected** adverse drug reaction reports originating from world-wide clinical sites **outside South Africa** for clinical trials conducted with the same medicine under section 21 of the Act, should be reported as part of the 6-monthly progress reports in a line listing format.

(iv) The Authority must be notified within 15 calendar days after first knowledge by - the investigator when there is a suggestion of a change in the nature, severity or, frequency of expected adverse drug reactions or when new risk factors are identified. The basis on which these assessments are made should be included.

(v) All serious suspected adverse events must be included as part of the 6-monthly progress reports in a line listing format.

(vi) All reports originating from South Africa must be signed by a clinical investigator that has been approved by the Authority as such. A single copy of the original report (or photocopy thereof) should be submitted to the Authority.

In the case of *pre-registration clinical trials* expedited reporting will be inappropriate for serious events from clinical investigations that are considered not related to the study product. Causality

assessment is required for clinical investigation cases. All cases judged by the clinical investigator or the sponsor as having a reasonable suspected causal relationship to the medicine qualify as ADRs. For the purpose of clinical investigations registered under Section 21 of the Act an adverse drug reaction includes any adverse event where the contribution of the study medication or other intervention of the clinical trial cannot be ruled out.

6.8.2 Other observations

Any information, including individual case reports, which may in any way influence the benefit-risk assessment of a medicine or that would be sufficient to consider changes in the administration of the medicine or in the overall conduct of a clinical investigation. must be reported to the Authority. e.g. a major safety finding from a newly completed study (such as carcinogenicity). This must be submitted to the Authority within 3 calendar days of first knowledge by the investigator

6.8.3 Managing Blinded Therapy Cases

(i) When a suspected serious, unexpected adverse drug reaction occurs which results in death or is life-threatening occurs, and is therefore judged reportable on an expedited basis it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that when possible and appropriate. the blind be maintained for those persons, such as biometrics personnel responsible for analysis and interpretation of results at the study's conclusion.

(ii) When a fatal or other serious outcome is the primary efficacy endpoint in a clinical trial, the integrity of the clinical trial may be compromised if the blind is broken. Under these and similar circumstances, agreement should be reached in advance with the Authority concerning serious events that would be treated as disease-related and not subject to routine expedited reporting. Only when an independent data safety monitoring board or committee is in place will such a condition be considered.

6.8.4 Medicines used under Section 21 not in a clinical trial trial

(i) This pertains to veterinary medicines approved for use under section 21 of the Act for patients not enrolled in a clinical trial (e.g. Capture drugs).

(ii) The prescriber of the medicine, as approved by the Authority, must report any serious adverse drug reaction occurring with the use of the medicine, in the specified patients within 15 calendar days of first knowledge by such individual.

6.8.5 Protocol design details:

(i) Each clinical trial protocol submitted to Council. should include a risk management procedure for dealing with serious, unexpected events or reactions which may arise, during the conduct of the trial and which could significantly impact on the safety of the study subjects.

Post Registration ADR Reports Format

Type of ADR report	**Time frame for reporting**	**Format**
Local Reponse (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)

7 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) Other serious (unexpected Serious (expected) Non serious (unexpected)	 i) 7+8** and ii) 6 monthly report i) 15 days ii) ii) 6 monthly report 6-rnonthly report 6-monthly report	 i) ADR form # ii) line listing i) ADR form # ii) line listing 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

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.

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

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.

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.

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

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

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

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

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.

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)

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

REPORT FORM FOR SUSPECTED ADVERSE REACTIONS

Veterinary Medicines-Report on Suspected Adverse Reactions

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: Medicine Details
Please list all veterinary medicines, stock remedies and vaccines administered. Indicate the product suspected 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 ☐ Recovered
☐ Euthanazed ☐ Ongoing
☐ Congenital anomaly ☐ Other:……
☐ Intervention required to prevent permanent impairment

Event reappeared on rechallenge
Yes ☐
No ☐

Treatment given, if any_____

Were there any sequelae? Yes ☐ No ☐
If yes, please describe sequelae:_____

Section Six: Adverse Reactions in Humans

Name/Initials	Sex	Age	Date of reaction	Nature of reaction