Any analytical processes carried out in a GLP accredited facility and carried out according to GLP do not need to supply any raw data records associated with the sample analyses.

Any analytical processes carried out in a GLP accredited facility and carried out according to GLP do not need to supply any raw data associated with the method of validation. It is sufficient to tabulate the performance specifications obtained during the validation.

Registrations under this option must provide copies of the laboratory's accreditation status, any audit reports and any action arising from deviations and amendments to the study plan.

A document detailing the study participants, their role and experience must be supplied (section 4, Annex II).

Analysis in non-GLP accredited facilities

Any analytical processes carried out according to GLP but not in a GLP accredited facility must supply the following:

- a complete copy of the method Standard Operating Procedure (SOP);
- a copy of the method SOP validation, the results of the validation and any algorithms used (with justification) in calculating and validation parameters;
- representative raw data records from within the validation. Where the analytical method involves an instrumental determination such as spectrophotometry, HPLC, or gas-liquid chromatography, specimen output charts showing blank determination and recovery determinations should be provided to assist in the evaluation of the method;
- all raw data pertaining to the samples/sample analysis;
- all records relating to traceability of physical measurements;
- all audits and results pertaining to the study;
- brief CV of study contributors.

If any component of the method SOP differs from that specified in the validation, any adverse impact on data quality must be discussed.

Applicants should note that after 1 January 2003 applications under 7.2 will not be complaint with ACVM policy. Applications under this option must be accompanied by a valid waiver application. Applicants are reminded that a waiver may not necessarily be accepted.

Analytical validation

The method must:

- be validated in accordance with the principles of GLP; or
- be validated according to ISO Guide 17025; or
- be validated according to, or equivalent to the procedures and specifications outlined in Eurachem/CITAC Guide *Quantifying Uncertainty in Analytical Measurement. 2nd Edition.*

Data supplied from analytical methods lacking documentation of appropriate validation will not be assessed.

Analytical methods

The method must:

- possess a high degree of specificity for the compound(s) reported under the residue definition;

- possess an acceptable accuracy for incurred residues for those residues that are specified as part of the residue definition.

This second point in 7.4.1 may be particularly difficult to demonstrate. Registrants using either:

- reference methods issued by CAC; or
- reference methods approved by the CVM (FDA) or EMEA

shall not be required to provide any further evidence. However, if the method reported in the registration application differs in any material way from the reference method, the validity of the change must be supported.

Registrants using 'in-house' methods supported by, or referenced to, radiometric tracer studies elaborating the disposition of residues shall not be required to provide any further evidence.

Registrants using 'in-house' methods not supported by the reference methods or radiometric evidence as described above must supply sufficient evidence that the method presented is capable of measuring the residues as specified in any of the regulations in 1.2.1.

The method should:

- have a Limit of Quantitation at a level considerably lower (at least ½ MRL) than any MRL (or MPL) proposed for finite residues. Where this is not possible for technical reasons, values reported as < LOQ may be interpreted as ½ LOQ unless the applicant provides a valid method for censoring data <LOQ. Where data is reported as < LOQ or less than < LOD registrants are encouraged to seek advice from a statistician for appropriate methods of data reduction;
- in respect of any sample analytical results made there from, be substantiated by adequate quality control evidence in the form of blanks, recovery and exhaustive extraction data, to show that the method was applied effectively for the determination of the residues in the substrates analysed, and at the levels under consideration.

Attribute data such as positive or negative response on a limit test, if supplied, as critical data at any level of residue testing is deemed of lower quality than numerical data. It may attract a more conservative WHP assessment than if quantitative data were to be supplied for the trade name product.

Analytical methods for compliance purposes

It is not proposed at this time as part of this standard to require and specify data requirements for methods suitable for compliance monitoring of the residues in question.

Storage stability tests for analytical samples

Where sample extracts have been stored prior to analysis, the stability of residues must be demonstrated with recovery studies performed under similar conditions. The results of stability tests for residues in stored analytical samples of representative substrates must be documented. The duration of the study must cover the interval between taking the samples and the end of the analytical phase.

In all cases samples with incurred residues are preferable and in some instances is the only way of showing the required stability of the marker residue.

Where a matrix with incurred residues cannot be provided a surrogate may be provided. Registrants should note that where a marker residue is not wholly the active ingredient then the study must include the other components in the form as specified in the residue definition.

The study conditions must reflect those to which the samples from the residue trials have been subjected.

8. LABORATORY DATA HANDLING AND STATISTICAL ANALYSIS

General requirements

The purpose of this section is to provide a means of analysing and reporting the residue data by a relatively simple and standardised procedure to enable the necessary residue conformance requirements to be met. A table of g' factors used to estimate upper conformance values from the mean and the SD are in Appendix 1.5.

The g' factor is a parameter used to obtain tolerance interval (a predictive interval) of a population from the mean of a restricted data set. It is a refined form of the t-statistic for confidence intervals of a mean for a data set.

If a different statistical procedure from that in this standard is used to estimate a WHP, then it should be fully documented to show that the WHP concluded from the statistical analysis will satisfy the conformance criteria for the MRL. In particular any different procedure should be sufficiently documented to show that it gives a conformance outcome not less than that obtained by the documented procedure.

Response parameters and units used to report any results must be consistent within the residue report. Where the option of a trial is to present a depletion curve and claim extrapolation the linearity of the curve with the data transform selected must be consistent with a correlation coefficient of 0.97 or more.

8.1.1 For sample concentrations where analytical data points are reported as 'zero', 'nil' or 'negative' in the analytical record, registrants must set these at ½ of the LOQ reported in the method validation. This 'data censoring' is not required if a probabilistic method of estimating the tolerance level is used. Where a regression curve is the chosen mode to determine WHP extrapolation of individual animal data, to complete a data set where some elements are < LOD or < LOQ is permissible if the requirements of the last paragraph of section 8.1 are met. Extrapolation is permissible for only 1 time point* beyond the last data point. Registrants should note that trial data must be tabulated as found. If in the WHP calculation interpolated data (or amended data) is used then that detail should be noted separated with the substitutions clearly noted.

* In this context the permissible extrapolated time is the least of any of the time intervals over which linearity is established (see 8.3.5).

8.1.2 Where a sample is analysed more than once in the same batch, the analytical results are recorded separately but the sample value used shall be the average of the replicates. Where two replicates of the sample are analysed in two separate batches, the foregoing applies unless the results differ by more than 2 SD (as cited in the validation document) when the measurement obtained first is to be used in the WHP calculation unless there is a reason specified why it is invalid. If three replicates are done and any one differs from the mean by more than 2 SD as per the validation document, then that recorded data point is not used in the WHP calculation but an explanation for the aberration should be included.

8.1.3 If an internal standard and/or surrogate standard is used to normalise the analytical (concentration) data and to compensate for any unanticipated mechanical, extractive or derivatisation losses, then the analytical results should report both corrected and uncorrected data. Whichever set gives the better correlation coefficient for the calibration curve should be used to calculate the sample residue concentrations.

8.1.4 Mathematical transforms of individual data time point sets for regression analysis must document the validity of the transform in the particular application, with literature reference where applicable.

8.1.5 In general it is preferable that the time points selected bound the proposed WHP but this standard recognises that this is sometimes impossible to achieve. However, with the expectation that registrants understand the properties of their formulation extrapolation of residue data using a supportable regression relationship to proposed WHP 1 relevant time unit (see list of permissible WHPs) beyond the last data point is permissible.

8.1.6 For animals in a feedlot situation where medicated feeds may be administered the minimum first sampling time must reflect current industry practice, e.g. in the poultry industry a first slaughter time of 3 hrs is possible and will be taken to represent a 'nil' WHP.

Meat, eggs and honey

The treated population conformance characteristics are:

- Meat, liver, kidney, fat, edible offal of ruminants and horses; honey
  - *P* is 0.9
  - 100 (1-a) is 95%
- Meat, liver, kidney, fat, edible offal of poultry, pigs, emus, ostriches; meat, liver, fat of farmed fish; eggs
  - *P* is 0.95
  - 100 (1-a) is 95%

For data analysed by regression the minimum number of time points and analytical data points specified in tables A1.1-1.4 must be met or a waiver supplied. For WHP data reliant on one time period only the animal numbers specified in table A1.3 are applicable. It will be assumed for tissue and egg analytical data sets that all the data points corresponding to any one time point are distributed normally.

Data reduction includes (one tailed) application of the g' parameter to the standard deviation. The relevant value is entered into the equation:

$$UCL = mean + g'*SD$$

The factor g' is obtained from tables of statistical intervals but a selection for different values of N, *p* and a are listed in Appendix 1.5. The upper confidence value for each of the time point sample means is calculated. This will generate a new set of concentration data for entering into the regression equation. The locus of the curve will intercept the concentration axis equal to the MRL at the minimum time for withholding. This time can be calculated by entering the MRL value into the equation and solving for time parameter and gives the *calculated WHP* (note extrapolation restrictions above). This is not the *assessed* WHP, which is the next specified time after this value. Registrants should note that this assessed WHP is not necessarily that which will be allocated to the trade name product; peer review and other external risk factors considered after assessment may result in an adjustment to the assessed WHP.

The time/ UCL data set should be analysed to determine if it fits a linear or linear transformed (e.g. log) depletion model. A regression equation relating residue concentration and time is of the form:

$$T = m*c + b$$

at the upper conformance level and T is the time. The correlation coefficient for the association must be documented. If the transformed equation does not give a linear relationship, then the predictive power of the relationship must be justified by reference to relevant literature or the mathematical model used.

Registrants should note that this equation is written in the reversed form from the way it is conventionally expressed. T is the independent variable to be estimated.

Non-finite data such as that bounded by LOQ and or LOD may be analysed by a probabilistic risk assessment process to determine the (probable) residues present at the required conformance or conversely show that the required conformance is met at a particular WHP.

Milk

The treated population conformance characteristics are:

- p is 0.99
- 100 (1-a) is 95%

Applicants should note that where part herd treatment can be justified in terms of New Zealand farm practice for that trade name product then where a limiting proportion of a herd can be identified, documented and supported assessment may take that (dilution) into account when assessing whole herd residues. Product registration conditions will then specify any such maximum proportion for users to manage.

General requirements for milk data

Milk WHPs are assessed on pooled milk from a treated cohort. In principle analytical samples could be prepared for each time point and consist of milk aliquots from each cow mixed according to each cow's milk yield at that milking as a proportion of the total for the treated cohort at that treatment time. However, while this would give only the required one value per time point the pooling loses information on variance as only the mean value is computed. Thus while milk pooled in this fashion may be used to track residue depletion prior to the time points of interest (see table A1.4) it will not be used for assessing the residues at the final WHP. For this individual cow, information on volumes and residue concentrations are required. Time at which herd milkings occur post-treatment must be reported as hours not numbers of milkings.

The ACVM Group requires that individual animal data are required for the time points used in the determination of the WHP, whether by regression or single point.

All animals must be treated to the maximum of the recommended dose regime on the label. Cows treated at less than the maximum dose rate will have residue data adjusted pro-rata the dose and the number of quarters treated.

The WHP is based on the residues that are determined in the pooled milking from the treated. If the regression method is used then the animal numbers as specified in table A1.2 or table A1.3 are applicable. If the single time point option is elected then the animal numbers specified in table A1.4 are required.

Milk WHP will be set in hours with a nil WHP as the first possible WHP. This is predicated on treatment being applied immediately after a milking. A nil milking WHP equates to a nominal 12 hr milk WHP, e.g based on two milkings per day schedule.

Time dependent trial data must be manipulated to establish the relationship between the marker residue concentration and time. If the relationship is linear, a degree of extrapolation to an assessed WHP is permissible. Anova and regression analysis will provide an estimate of the distribution of residues in treated herds by concentration and time from which the WHP can be assessed with the required conformance and confidence.

For milk samples at the three critical time points the mean residue concentration is the sum of the individual animal residue concentration multiplied by the corresponding milk yield, and this total is divided by the total milk yield for that milking from the treated animals, that is:

$$C_m = (\sum Ca*Va+Cb*Vb \ldots\ldots Cn*Vn)/(\sum Va+Vb+\ldots Vn)$$

Where Ca, Cb are the residue concentrations of cow # *a, b* etc. and Va, Vb are the milk volumes from that milking which correspond with the respective concentrations of cow # *a, b* etc.; the sample trial mean is denoted by C_m, then the upper conformance level of herd milk residue concentration is:

$$UCL = C_m+g'*SD/\sqrt{(N)}$$

Where g' is the factor relating N, SD and the mean at the conformance level of 'C_m' (%) using a one tailed test. A table of g', N, *p* and α are listed in table A1.5.

Registrants should note that the manipulations required in 8.3.4 may be conveniently done using a spreadsheet such as EXCEL.

The mean data points and the upper conformance values (UCL) are displayed as a continuous graph and the point of intersection with the MRL located. This is the minimum calculated WHP. The minimum assessed WHP is the next multiple of 12 hrs (or one milking) after this time (the WHP is the time at which milk may be taken). The allocated WHP is that to be applied to the product after consideration of any other risk factors. The time/ UL data set should be analysed to determine if it fits a linear or linear transformed (e.g. log) depletion model. A regression equation relating residue concentration and time is of the form:

$$T = m*UCL+b$$

The correlation coefficient for the association must be documented. Note that time should not be expressed in milkings in this equation as the interval may not be the same between milkings.

Registrants should note that this equation is written in the reversed form from the way it is conventionally expressed. T is the independent variable to be estimated.

Extrapolation of the regression curve to the MRL (or MPL) but which embraces one extrapolated data set time point is permissible; that is, if the reported points are in weeks then extrapolation is one week, if days then one day, if in milkings then one milking. If the intervals are not equal then extrapolation will be restricted to the least interval.

Non-finite data such as that bounded by LOQ and or LOD may be analysed by a probabilistic risk assessment process to determine the (probable) residues present at the required conformance or conversely show that the required conformance is met at a particular WHP.

Calves

Treatment of pregnant dams can result in calves being born with residues acquired pre-natally that may exceed the residue thresholds. Registrants should also note that calves feeding on treated dams may also acquire residues from the colostrums. Both sources of residues must be evaluated for an application for registration involving calves and particularly bobby calves. Trial data sets shall consist of tissue analyses of at least 4 days old calves (3 days old calves are acceptable) with tissue concentrations stratified according to PNTI as per sections 8.2.2 – 8.2.4. A trend of decreasing tissue residues with increasing PNTI will be apparent from which

an appropriate PNTI for the trade name product for that use may be estimated. It is not required that there be an equal number of calves attributable to any particular PNTI in the trials because of the accepted practical difficulty in predicting birthdates.

To enable an acceptable degree of confidence in the estimation of the PNTI it is required that not less than 20 calves contribute residue data and are more or less spread over the interval of interest. The same data extrapolation restrictions apply as outlined in section 8.

Applicants should note that a PNTI to meet residue thresholds for both meat and milk should be estimated. The greater of these shall be the one presented for approval.

Dry cow therapy

Treatment of dry cows prior to commencement of milking may also result in violative residues in the milk, even after 4 days of mandatory withdrawal. In this case the trial data set will as in 8.3.1 above consist of milk analyses with the results stratified according to pre-natal treatment time. A trend of residue depletion with increasing pre-natal interval will be apparent from which the required pre-natal withholding time to achieve acceptable milk residues can be estimated as per the method specified under 8.3. Assessed PNTI for dry cow treatments must always be done by trials reporting residue depletion. Extrapolation to a quantised WHP beyond the last data point is permissible.

This standard does not specify the exact number of animals to be included in such a trial but some general guidelines can be outlined (see table A1.3). As the PNTI is specified in weeks only the number of animals in any one week spread of brithdates should not be less than 7. With a minimum of 3 time points to be reported, a minimum of 21 successful mother/neonate births must be reported. However, often due to practical difficulties in managing birthdates these may not be evenly spread or, as is preferable, for these clustered proportionately closer to the proposed PNTI

Each application will be examined on its merits with weight given to trial design, birhtdate distribution over the trial interval and the degree of clustering around the proposed PNTI.

To enable an acceptable degree of certainty in the estimation of the WHP it is required that not less than 20 cows take part in the trial and that the withholding period claimed lies within the pre-natal treatment interval range.

Injection site residues (ISRs)

Although there is no CAC standard for the reporting and assessment of ISRs, the ACVM Group requires reporting of such data. Where the ISRs are less than 10 times the meat MRL, ISRs will not at the present time be used by the ACVM Group to set a WHP. Where some ISRs reported show residues in excess of 10 times the meat MRL the ISRs may be used in conjunction with the other tissue residues to set a WHP. This data is required only for intramuscular or subcutaneous administration. Risk assessment on the significance of any ISR above the ACVM threshold is contingent on the number of data points supplied and the proportion of those below the threshold. Applications are advised to supply as many ISR data points at the proposed WHP as possible. This is especially so if any ISR >10X MRL (meat) where the final decision WHP will take frequency and concentration into account although this knowledge is often available only from post-registration residue surveys.

Registrants must identify any factors associated with their product that may impact on the incidence of ISR arising from the field use of the product.

9. SUMMARY AND CONCLUSIONS

The registrant of the trade name product must comment in the application, with reference to the withholding period claim, on:

- the significance of the statistical variation in the data;
- the effect of sampling procedure on the analytical results;
- the effect of storage and transport of samples on the analytical results;
- the interpretation of outliers, the method and validity of that method for dealing with them;
- the significance of variability within the analytical method itself on the reported residue concentrations;
- the extent to which any departure from the guidelines affects the estimation of the withholding period; and
- any deviations and amendments to the study plan and all other non-compliances with this standard.

FOR MILK WITHHOLDING TIMES NO ALLOWANCE SHOULD BE MADE FOR APPLICATION OF TRADE NAME PRODUCTS TO LESS THAN 100% OF A HERD IN THE APPLICANT'S REPORT OR SUMMARY UNLESS THE APPLICANT DEMONSTRATES THAT THIS IS 'GOOD AGRICULTURAL PRACTICE' AND THAT AN APPROPRIATE RESTRICTIVE CONDITION ON THE LABEL IS PRESENTED FOR APPROVAL.

10. MAXIMUM RESIDUE LIMITS OR MAXIMUM PERMISSIBLE LEVELS

The MRL or MPL relevant to each application must be reported from the New Zealand Mandatory Food Standard Table of MRLS for the named substance or the Meat Residue Regulations Notice 2000 of MPLs or the Dairy Residue Regulations, as appropriate. The residue definition (marker residue) must be listed opposite that named substance as well as the primary product to which these pertain.

11. PROCEDURE TO BE FOLLOWED FOR REGISTERED TRADE NAME PRODUCTS WHERE THE MRL (OR MPL) IS CHANGED

Increased MRL (or MPL)

Where the MRL (or MPL) is increased and notified through the New Zealand Mandatory Food Standard Table of MRLs or the Meat Residue Regulations or Dairy regulations, registrants may apply to the ACVM Group for a change of WHP. In these instances only data that has been generated in accordance with this residue standard may be used to support the application. A reduction in WHP will be granted only where the existing data in support of the application is primarily that of Option 2 (see section 6), i.e. by a depletion curve. However, no extrapolation to a WHP which is outside the data range is permissible. (Outside in this context means to an assessed WHP shorter than the first time point, or outside the linear range of extrapolation of the regression relationship to an MRL [or MPL] higher than found for the UCL of the sample sets.) Applicants are advised to note this when designing any residue trials.

Decreased MRL (or MPL)

Where the MRL (or MPL) is decreased and notified through the NZ Mandatory Food Standard Table of MRLS or the Meat residue Regulations or Diary Regulations, then the registrant has a number of options available. Otherwise, the ACVM Group will assess the existing data held on file and make an allocated WHP.

Option A:

The existing data set supporting the current registration consists of a trial, conducted according to the ACVM standard, with the data analysed as a residue depletion curve. The UCL of the penultimate or last data point must be less than the new MRL (or MPL) and then WHP assessment is facile and an assessed WHP can be easily determined.

Option B:

The new MRL (or MPL) is less than the last data point but linearity of the depletion curve is demonstrated whereby extrapolation of the depletion curve (UCL) according to the requirements of this standard will give the necessary residue conformance at the next permissible WHP.

Option C:

The existing data does not meet the requirements of the depletion curve of Options A or B above. In this case, trial data to support the claim must be supplied. If the data to support the existing registration with the superseded MRL (or MPL) was generated according to the ACVM standard, then only the absent data sets need to be supplied.

The applicant may elect to use Option 2 specified under section 6 for trial data – single time point data.

The applicant may elect to support an ACVM allocated WHP based on a combination of data supporting the current registration and/or a mix of new data and published information supplied with a data waiver. However, data supplied under this option will be assessed conservatively by the ACVM Group for the allocation of a WHP as specified in this standard.

12. A2 APPLICATIONS: PROCEDURES TO BE FOLLOWED

New use patterns for active ingredients that have an MRL are considered to present a residue risk no less than if they were in a pioneer substance. Although formulations of this type will have an MRL for the active ingredient entered into the NZMFS where one is required, they pose significantly more risks than B1 or B2 applications or C8 and C4 applications.

Residue trials for these applications must be conducted according to this standard but also and only to the particular requirements in sections 6.1, 7.1 and 8 but noting that the single time point trial option is not permissible for trials under A2 applications.

Data extrapolation by means of regression analysis is <u>not</u> permissible under A2 applications.

The sampled time points must bracket the proposed WHP. Extrapolation only to fill data points at <LOQ or <LOD is permissible on individual animals for one time point past that for which finite residue data is obtained. Confidence parameters for the extrapolation must be documented.

Residues in all edible tissues (kidney, liver, muscle and fat) must be presented unless a supportable waiver is presented.

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

No waivers in respect of minimum trial numbers and time points will be accepted in respect of A2 applications except for horses where a default WHP is electable.

APPENDIX
SPECIFICATIONS FOR TRIALS AND ANIMAL NUMBERS FOR ASSESSMENT OF WHP

Table A1.1
Minimum trial sets to establish a residue depletion curve

Category	Number of Trials
Topical parasiticides (long wool)	2 (sheep only/goats)
Topical parasiticide (off shears)	1 (sheep only)
All other trade name products	1

Notes

1 Trials to establish a meat WHP must be carried out on each of merino and cross-bred sheep for long wool application. One New Zealand trial on cross-bred sheep is required for the claimed use pattern, e.g. long wool. No substitution for this is permissible. Applicants would be advised to use a climatic zone significantly different from that in any one of an overseas sourced residue data report.

2 Pre-ruminant animals under one month of age are considered to be a separate category of stock for orally administered trade name products. Residue data cannot be extrapolated from the 'adult' category. Separate residue trials are required.

3 Bobby calves are a separate category of pre-ruminant animals. Residue trial data cannot be extrapolated from the 'adult' or 'pre-ruminant' categories. Separate trials are required for bobby calves and for pre-ruminant animals where a use is claimed.

4 Default withholding periods have been set for food producing animals (including horses as food producing animals). Where applicants consider these to be inappropriate for their trade name product, trial data must be supplied (see following tables). Waivers for significant elements of this standard for a WHP application must meet the ACVM Standard for Waivers.

5 An application for a trade name product requiring a milk withholding time will always require that a meat withholding time also be set and trial data to support the meat withholding time must be submitted unless the applicant elects the default WHP or can support an allocated WHP shorter than the default WHP.

Table A1.2
Minimum number of data sets (time points) to establish a residue depletion curve

Table A1.2 specifies the minimum number of data sets or time points that must be reported upon at a given time point in a residue depletion trial for meat, edible offal, fat, eggs and milk. The requirements are specified according to the model of application of the trade name product.

	Number of Time Points						
	Ruminants/Deer/ pre-ruminants	Ruminants	Pigs	Horses	Birds		Fish
Model of application	Meat	Milk	Meat	Meat	Meat Eggs		
Oral Systemic	4	4	4	3	4	4	3
Oral Non Systemic	4	4	4	2	3	3	3
Topical Systemic	4	4	4	3	4	4	3
Topical Non Systemic	3	3	3	2	3	3	3
Parenteral Preparations[2]	4	4	4	2	3	3	0
Intrauterine Preparations	2	3	NA	NA	NA NA		NA
Intramammary Lactating Animal Preparations	3	3 See 8.5.1	NA	NA	NA		NA
Intramammary (Dry) Animal Preparations	3 1	(PNTI) 1	NA 1	NA *	NA		NA 0
Gaseous Anaesthetics					NA NA 0	0	

Notes

1 Pre-ruminant animals, e.g. bobby calves and, separately, calves under 1 month of age, for the purposes of this guideline are treated as a separate class of stock from 'ruminants' (refer notes 3 and 4 attached to table A1.1). This particularly applies when prenatal treatment is applied to dams (see section 8).

2 Trade name products subject to WHP restrictions and administered by subcutaneous injection must generate a data set where administration is by intramuscular injection. However, for this aspect of residues **only the marker tissue residues** are required at the claimed WHP.

3 For intramuscular and subcutaneous administration injection site residue data must be supplied particularly for those samples that bracket the proposed or assigned WHP.

4 Waiver from these requirements may be applicable where ADME data is highly temporally compressed.

Table A1.3
Minimum number of data elements at one time point to establish a residue depletion curve.

Table A1.3 specifies the minimum number of animals that must be included and reported upon at any sampling given time point in a residue decay trial for meat, edible offal, fat, eggs and milk. The requirements are specified according to the mode of application of the trade name product.

	Ruminants/Deer/ pre-ruminants	Ruminants	Pigs	Horses	Birds		Fish
Model of application	Meat	Milk	Meat	Meat	Meat Eggs		
Oral Systemic	5	9	5	1	5	3	3
Oral Non Systemic	4	5	3	1	4	3	3
Topical Systemic	5	9	4	1	5	3	3
Topical Non Systemic	4	4	3	1	4	3	3
Parenteral Preparations[2]	5	9	5	2	3	3	0
Intrauterine Preparations	3	5	NA	NA	NA NA		NA
Intramammary Lactating Animal Preparations	3	9	NA	NA	NA		NA
Intramammary (Dry) Animal Preparations	3	= 7 per week (PNTI) see 8.5.1	NA	NA	NA		NA
Gaseous Anaesthetics	1	1	1	NA	NA NA NA		NA

Notes

1 Pre-ruminant animals, e.g. bobby calves and separately calves under 1 month of age, for the purposes of this guideline are treated as a separate class of stock from 'ruminants' (refer notes 2 and 3 attached to table A1.1). This particularly applies when prenatal treatment is applied to dams (see section8).

2 Trade name products subject to WHP restrictions and administered by subcutaneous injection must generate a data set where administration is by intramuscular injection. However, for this aspect of residues **only the marker tissue residues** are required at the claimed WHP.

3 See section 12 for exceptions.

Table A1.4
Minimum number of data points for single time point assessed WHP

Table A1.4 specifies the minimum number of animals that must be included and reported upon at a given time point in a residue decay trial for meat, edible offal, liver, kidney, fat, eggs and milk. The requirements are specific according to the mode of application of the trade name product.

	Ruminants/Deer/ pre-ruminants	Ruminants	Pigs	Horses	Birds		Fish
Model of application	Meat	Milk	Meat	Meat	Meat	Eggs	
Oral Systemic	9	19	9	3	9	9	5
Oral Non Systemic	4	10	4	2	5	5	5
Topical Systemic	9	19	9	3	9	9	5
Topical Non Systemic	4	19	4	2	5	5	5
Injectable Preparations[2]	9	19	9	4	9	5	0
Intrauterine Preparations	5	5	0	*	0	0	0
Intramammary	9	19	0	*	0	0	0
Preparations Gaseous Anaesthetics	2	1	21	*	0	0	0

Notes

1 Pre-ruminant animals, e.g. bobby calves and separately calves under 1 month of age, for the purposes of this guideline are treated as a separate class of stock from 'ruminants'. This particularly applies when prenatal treatment is applied to dams.

2 Trade name products subject to WHP restrictions and administered by subcutaneous injection must generate a data set where administration is by intramuscular injection. However, for this aspect of residues **only the marker tissue residues** are required at the claimed WHP.

Table A1.5

Factors* g' (1-α, *p*, N) for calculating normal distribution one-sided 100(1-α)% tolerance bounds

	p = 0.90			*p* = 0.95			*p* = 0.99		
1-α	0.9	0.95	0.99	0.9	0.95	0.99	0.9	0.95	0.99
N									
2	10.025	20.581	103.02	13.09	26.26	131.43	18.5	37.094	185.62
3	3	6.155		5.311	7.656	17.37	7.34	10.553	
4	4.258	4.162	13.995	3.957	5.144	9.083	5.438	7.042	23.896
5	3.188	3.407	7.38	3.4	4.203	6.578	4.666	5.741	
6	2.724	3.066	5.362	3.092	3.708	5.406	4.243	5.062	12.387
7	2.494	2.755	4.411	2.894	3.399	4.728	3.972	4.642	8.939
8	2.333	2.582	3.859	2.754	3.187	4.285	3.783	4.354	7.335
9	2.229	2.454	3.497	2.65	3.031	3.972	3.641	4.143	6.412
10	2.133	2.355	3.240	2.568	2.911	3.738	3.531	3.981	5.812
	2.066		3.048						5.389
									5.074

*Hahn and Meeker, Statistical Intervals. Wiley and Sons, 1991.

ANNEX 1
TEMPLATE FOR OTHER DATA ELEMENTS SUMMARY

1 CHEMISTRY DOSSIER

1.1 Formulation: ingredients and content in % or g/L (or ml/L); purpose of ingredient

1.2 Formulation type
(if a suspension, median particle size and range)

1.3 Specific gravity, freezing temperature of formulation

1.4 Viscosity in centipoise units at a specified temperature (any information on viscosity-temperature relationship)

1.5 Impurities chemically related to any component of the marker residue; identity and concentration over the proposed shelf life claimed

2 EFFICACY DOSSIER

2.1 Dose rates at which efficacy is established

2.2 Label dose rates

2.3 Relevant environmental conditions over the duration of the efficacy trial (place, month, weather, sunlight)

3 SAFETY DOSSIER

3.1 Numbers and proportion of treated animals showing injection site lesions (for parenteral products)

3.2 Documentation on size and persistence of lesions (for parenteral products)

3.3 Any other adverse effects noted, including numbers and proportion, that will impact on residues conformance at a proposed WHP, e.g. skin irritation (increased permeability), photo-sensitivity (increased permeability)

3.4 Relevant environmental conditions over the duration of the safety trial (place, month, weather, sunlight)

ANNEX II
DATA ASSESSMENT TEMPLATE FOR WHP RECOMMENDATION

1 **Identity**

1.1 Applicant

1.2 Trade name of product

1.3 Registration number

1.4 Formulation details

1.5 Active ingredient(s) and impurities related to residue definition

1.6 Status and application type

2 **Proposed use pattern**

2.1 Use situation

2.2 Condition(s) being treated

2.3 Application/administration method and site

2.4 Application rates/dosage

2.5 Number and timing of treatments

2.6 Applicant's proposed withholding period

2.7 Changes to agricultural practice (if any)

3 **MRLs**

Insert the exact MRL statement for the stated active ingredient as documented in the New Zealand Mandatory Food Standard Table of MRLS or the Meat Residue Regulations or the Dairy Residue Standard.

4 **Residue trial data supporting information**

Provide a concise statement on the quantity, quality, validity and completeness of the supporting data. Record that the appropriate marker residue was determined. Note the appropriateness and validity of any procedure in the residues dossier report. Note any deviations and amendments to the study plan that may adversely affect the residue profile as documented. Note any non-compliances with GLP or GAP that may impact on the validity of any individual data points, the trial and residues profile as a whole, and which includes any break in traceability of any data elements.

Report on each study separately, according to the number of studies the registrant elects to supply.

Document the accrediation status of all organisations participating in the residue studies. Identify the principal individuals together with their roles and qualifications. Report all audits carried out that relate to the residue study. Identify the auditors. Document the method validation parameters.

5 **Residue trial data**

Tabulate the uncorrected data points. Having noted the comments in section 4 above document any adjustments, corrections or manipulations to the data points and tabulate. Note the particular reason(s) for any data point adjustment. Using the method as described in the standard construct either a depletion curve or a table of the UCL. If a different data reduction method is used the additional information as documented in the Standard must be included. Note the relationship of the UCl to the MRL at time points of interest. Report on all methods used.

Tissue Residue Study No XXX
Tissue Residue Study No XYZ
Milk Residue Study No AAA
Eggs Residue Study No ABC

Within each study comment on the clinical and analytical phase separately.

6 **Results from data reduction**

7 **Comments**

8 **WHP**

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

List assessed, allocated or default WHP for meat, lactating cows, dry cows, chickens, eggs, fish, honey separately; list PNTI separately.

9 **Conformance**

Estimate the degree of conformance of the treated population with the MRL using the method as outlined in the standard if more than 99/95%.

10 **Further advice to the applicant**

Note any inconsistencies and non-compliances in the dossier.
Include any explanatory notes in support of the recommendation or conclusion.

11 **Further advice to the ACVM Group**

Note any inconsistencies in the dossier.
Note any inconsistencies in the standard.
Note any issues or areas not addressed by ACVM standards as a consequence of this review.

Assessor's name/organisation: _____
Signature: _____
Date: _____

Peer reviewed/organisation: _____
Date: _____

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

ANNEX III
ACTIVE INGREDIENTS WITH WHP EXEMPTION

LIST OF SUBSTANCES FOR WHICH NO RESIDUE THRESHOLD IS SPECIFIED WHEN USED ACCORDING TO THE CONDITIONS OF REGISTRATION UNDER THE ACVM ACT. (THESE HAVE TO BE GAZETTED TO TABLE 3 OF THE NZMFS AND THE USE RESTRICTION SPECIFIED.)

Named substance*	Therapeutic/Zootechnical Use
Oestradiol-17β and its esters or conjugates	To aid in initiation of cycling in cattle Anoestrus in sheep, goats, sows, metrits, pyometra, dystocia, retained placenta in cows
Testosterone and its esters or conjugates	In all food producing animals for aging, debility, crypto-orchidism, deficient sex drive
Prostaglandin $F_{2\alpha}$	To control and synchronise oestrus, sub-oestrus, pregnancy termination, chronic endometritis in cattle
Androstendione and its esters or conjugates	
Epidermal growth factor for sheep	De-fleecing of sheep
Progesterone, alpha-hydroxyprogesterone (deoxycortisone)	Control of oestrus, anoestrus, induce cycling
Norgestomet	Oestrus synchronisation in cows
Zinc Sulphate/Zinc oxide/Zinc	Facial eczema
Salicylic acid or any of its esters	Topical keratolytic, pruritis
Oxytocin	Aid in parturition, uterine prolapse, milk letdown, post-partum haemorrhage in pigs, goats, horses and cows Farrowing fever in pigs
Buserelin/buserelin acetate	Anoestrus, cystic ovaries, induction of ovulation, increase conception rate
Isoxsuprine	
Gonadorelin, Deslorelin	Treatment of cystic ovaries, prevention of delayed ovulation, improve fertility rate in cattle Induction of ovulation in horses Induction of spawning in finfish
Gonadotrophins	Induction of superovulation in cattle, anoestrus, treatment of cystic ovaries Induction of superovulation in sheep and goats Industion of superovulation and anoestrus in horses
Ovine and porcine FSH	

Propantheline	Oestrus induction in pigs
Eugenol	Spawning induction in finfish
	Sedative for finfish

* Trade name products with any of the named substances as the active ingredient will not attract a WHP when the claim for use is as listed against that named substance.

Note: The ACVM Group will issue a procedure by which substances are evaluated for entry to this list.

ANNEX IV

RESTRICTED SUBSTANCES

LIST OF SUBSTANCES FOR WHICH SPECIAL REGULATORY PROVISIONS APPLY

Any **cattle, deer, goats, sheep, llamas, ostrich, emu** or **fish** treated with the following substances or any product derived from any of the cited animals that has been treated with the following listed substances may never be sold for entry into the human food trade where it cannot be assured that the animals or their edible tissues do not enter a market where the substances are prohibited from use on food producing animals. Prospective registrants should seek advice from the ACVM Group on the likely restrictions that would apply and the registrant's responsibilities in the management of these substances.

- Chloramphenicol
- Colchichine
- Chloroform
- Nitrofurans (including but not limited to nitrofurazone, nihydrazone, furazolidone, furaltodone)
- Nitroimidazoles (including but not limited to dimetridazole, ronidazole, metronidazole, carnidazole)
- Chlorpromazine
- Dapsone
- Substances with the pyrazolidone moiety within the chemical makeup for example, but not restricted to, phenylbutazone, ramifenazone, dipyrone
- Arsenilic acid
- Nandrolone

ANNEX V
STANDARDISED WHP SPECIFICATIONS

Standardised WHPs apply for the products that meet the stated criteria provided the dose rates for the active ingredient for which efficacy is claimed do not exceed 105% of the reference product. Applicants are not obliged to accept the default WHP for their product but if they elect not to do so they must comply with all provisions of this residue standard. Standardised WHPs are a subset of previously assessed WHPs falling within the general framework of pharmaceutical equivalence. The specification applies to the meat of all species intended for human consumption except horses and bobby calves or where specific exceptions are noted.

1 Oxytetracycline crèmes, gels, oblets, pessaries, solutions or suspension formulations for intra-uterine use not exceeding 2 g of active within a 10 day period, containing no other active ingredient(s) for intra-uterine use:

10 days meat WHP for cattle

Oxytetracycline formulations for oral use at dosages less than 25 mg/kg bw for sheep and goats, 45 mg/kg bw/day for pigs, and 12 mg/kg for calves, and containing no other active ingredient(s) regulated by an MRL:

10 days meat WHP for cattle, sheep, goats, pigs, poultry

2 Tetracycline crèmes, gels, oblets, pessaries, solutions or suspension formulations for intra-uterine use not exceeding 2 g of active within a 10 day period and containing no other active ingredient(s) regulated by an MRL:

10 days meat WHP for cattle

Tetracycline formulations for oral use at dosages less then 25 mg/kg bw for sheep and goats, 45 mg/kg bw/day for pigs, 20 mg/kg bw/day for poultry and 12 mg/kg for calves and containing no other active ingredient(s) regulated by an MRL:

10 days meat WHP for sheep, goats, pigs, poultry and calves

3 Chlortetracycline crèmes, gels, oblets, pessaries, solutions or suspension formulations for intra-uterine use not exceeding 2 g of active within a 10 days period and containing no other active ingredient(s) regulated by an MRL:

10 days meat WHP for cattle

Chlortetracycline formulations for oral use at dosages less than 25 mg/kg bw for sheep and goats, 45 mg/kg bw/day for pigs, 20 mg/kg for poultry and 12 mg/kg for calves for oral use, and containing no other active ingredient(s) regulated by an MRL:

10 days meat WHP for sheep, goats, pigs, poultry and calves

Chlortetracycline formulations for oral use at dosages less than 45 mg/kg bw/day for pigs, containing no other active ingredient(s) regulated by an MRL except tiamulin at less than 6.75 mg/kg as the hydrogen tartrate salt:

10 days meat WHP for pigs

4 Xylazine aqueous solutions by parenteral administration for sedation at dose rates not exceeding 4 mg/kg bw for deer, 0.4 mg/kg for sheep and goats, and 0.35 mg/kg for cattle and containing no other active ingredient(s) regulated by an MRL, nor any excipient added to prolong persistence:

3 days meat WHP for cattle, sheep, goats and deer
nil WHP for cattle, milk

5 Dexamethazone sodium phosphate aqueous solution by parenteral administration. The formulation must contain no other active ingredient(s) regulated by an MRL, no liquid other than water and no excipient intended to prolong persistence:

1 day meat WHP for cattle and deer
2 milkings WHP for cattle

6 Praziquantel oral solutions or suspensions for sheep to be given at dose rates not exceeding 7.5 mg/kg bw. The formulation must contain no other active ingredient regulated by an MRL and no excipient intended to prolong persistence:

7 days meat WHP

7 Fenbendazole oral formulations at dose rates to not exceed 7.5 mg/kg bw for cattle and 5.0 mg/kg for sheep, goats and deer and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:

- Febantel, oxfendazole and fenbendazole sulphone at a.i. inclusion rates within limits required by the *ACVM Chemistry Standard*;
- Levamisole at concentrations to not exceed 8.1 mg/kg bw as the base;
- Praziquantel at concentrations to not exceed 7.5 mg/kg bw:

10 days meat WHP for cattle, sheep, goats, deer

8 Oxfendazole oral formulations at dose rates to not exceed 7.5 mg/kg bw for cattle and 5 mg/kg bw for sheep, goats and deer and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:

- Fenbendazole, its sulphone and febantel at a.i. inclusion rates within limits as required by the *ACVM Chemistry Standard*;
- Levamisole at concentrations to not exceed 8.1 mg/kg bw as the base;
- Praziquantel at concentrations to not exceed 7.5 mg/kg bw:

10 days meat WHP for cattle, sheep, goats, deer

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

9 Levamisole oral formulations for sheep and goats at dose rates to not exceed 8.1 mg/kg bw (as levamisole base) and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:

- Albendazole or albendazole sulphoxide at concentrations to not exceed 10 mg/kg bw for cattle and deer and 5 mg/kg for sheep and goats;
- Fenbendazole or oxfendazole at concentrations to not exceed 7.5 mg/kg bw for cattle and deer and 5.0 mg/kg bw for sheep and goats;
- Praziquantel at concentrations to not exceed 7.5 mg/kg bw:

10 days meat WHP for cattle, sheep, goats, deer

10 Albendazole oral formulations at dose rates to not exceed 10 mg/kg bw for cattle and deer or 5 mg/kg bw for sheep and goats and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:

- Albendazole sulphoxide, the sulphone and hapasil at a.i. inclusion rates within limits as required by the *ACVM Chemistry Standard*;
- Levamisole at concentrations to not exceed 8.1 mg/kg bw (as the base);
- Praziquantel at concentrations to not exceed 7.5 mg/kg bw:

10 days meat WHP for cattle, sheep, goats, deer

11 Albendazole sulphoxide oral formulations as dose rates to not exceed 10 mg/kg bw for cattle and deer or 5 mg/kg bw for sheep and goats, and containing no excipient intended to prolong persistence in the alimentary tract and no other active ingredient(s) except:

- Albendazole, its sulphone and Hapasil at a.i. inclusion rates within limits as required by the *ACVM Chemistry Standard*;
- Levamisole at concentrations to not exceed 8.1 mg/kg bw as the base;
- Praziquantel at concentrations to not exceed 7.5 mg/kg:

10 days meat WHP for cattle, sheep, goats, deer

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

REPORTING VETERINARY ADVERSE DRUG REACTIONS IN SOUTH AFRICA

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
MS. M.P. MATSOSO
DATE: 27/06/2003

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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.

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 III)**

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 worldwide 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 3)

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 addresses 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 information
  about all suspected adverse reactions which are reported to the staff of the company
  or organisation including medical representatives and clinical research associates, is collected
  and 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.

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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. 5.2.(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.

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 5.3) 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 1.1 and 1.2 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 5.1 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 reaotion, 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 3.3 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.

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7. 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.

7.1 Adverse Drug Reaction reporting for Cljnica1 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.

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7.2 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

7.3 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.

7.4 Medicines being used under section 21 not within a clinical 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.

7.5 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.