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AIDS HELPLINE: 0800-0123-22 Prevention is the cure

CONTENTS

GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. 946 **27 June 2003**

MEDICINES CONTROL COUNCIL

MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965)

GUIDELINES WITH RESPECT TO THE MEDICINES AND RELATED SUBSTANCES ACT (ACT NO. 101 OF 1965, AS AMENDED)

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

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

A. Veterinary Medicines:

1. Guidelines on Pharmaceutical and Analytical Requirements for Veterinary Medicines
2. Guidelines on Maximum Residue Limits and Withdrawal Periods for Veterinary Medicines
3. Guideline on Reporting Veterinary Adverse Drug Reactions in South Africa
4. Guideline for Recall of Veterinary Medicines
5. Introduction and Scope of Guidelines f or Veterinary Medicines
6. Guideline for Veterinary Clinical Trial Application (Form VCTF 1)
7. Guideline to Complete Section 21 Application Forms for Veterinary Medicines

B. Inspectorate

8. Guidelines for Preparation of Site Master File

C. Clinical

9. Application Form for Change of Registered Package Insert (Form MRF 4)

D. General

10. Guideline on Generic Substitution
11. Guideline for Parallel Importation of Medicines in South Africa
12. PIF 1 – Application Form for Amendment of the Details of a Parallel Imported Medicine
13. PIF 2 – Notification Form for Procurement of a Parallel Imported Medicine

MS M.P. MATSOSO
Registrar of Medicines

P AND A FOR VETERINARY MEDICINES

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON PHARMACEUTICAL AND ANALYTICAL REQUIREMENTS FOR VETERINARY MEDICINES

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

These guidelines should be read in conjunction with Regulations 2, 22, 24, 42, 43, 44 and 48.

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

P AND A FOR VETERINARY MEDICINES

INDEX:

P AND A FOR VETERINARY MEDICINES

Comments pertaining to the Pharmaceutical and Analytical Requirements for Veterinary Medicines

General Comments.

1. *Information relating to the active ingredient and manufacturer thereof. (1.4/5)*

   1.1 Many suppliers of bulk or finished product are extremely reluctant to supply the details of the source of the active ingredient (a.i.).

   1.2 Many active ingredients coming from the Far East are supplied by vendors, who are also reluctant to supply the details of the manufacturer; hence CoAs for these materials are usually on the letterhead of the vendor/broker not the manufacturer.

   1.3 Numerous countries, including some first world countries, lack the necessary legislation which compels manufacturers of active ingredients to comply with GMP. Hence GMP certificates for these facilities are not available.

   1.4 While the reason for the need for the method of synthesis and stability data is understood, the suppliers of such information regard this information as highly confidential, as this is exactly the information that someone wishing to copy the ai would need. Hence they are extremely reluctant to supply such information. This raises two other questions:

      1.4.1 Should detailed method of syntheses be supplied, would Council possess the expertise to evaluate it? (As far as I know there are no organic chemists available to council).

      1.4.2 There are many documented complaints about data being lost at Council offices, this make it very difficult to convince the suppliers of such information that their data will be safe.

2. Pharmacopoeias (3 & 3.1)

   2.1 To the best of my knowledge there is only one veterinary pharmacopoeia, i.e. the BP Vet. The EP is rapidly superseding the BP.

   2.2 Many veterinary a.i.'s especially pesticides are not described in pharmacopoeias.

   2.3 The BP, EP and USP are now being updated annually, which makes complying with the latest edition very difficult for the following reasons.

      2.3.1 Realistically, one can only claim use of material complying with the latest pharmacopoeia once one has received material which complies with such monograph. Suppliers take about 6 months to change.

      2.3.2 Once this has occurred, one has to update one's batch records and registration information.

      2.3.3 By the time this has occurred a year may have passed, and the monograph may have changed again.

   2.4 A suggestion therefore would be to comply with a pharmacoepoeia reference which is not less than 3 years old.

P AND A FOR VETERINARY MEDICINES

3. Total Organic Carbon (TOC) (3.10)

3.1 The measurement of TOC can be measured on or off line, however:

3.1.1 On line measuring equipment is extremely expensive (±R300 000)

3.1.2 Off line measurement can lead to false positives, due to sampling errors, and the equipment required is also expensive.

3.1.3 Given the conditions in which oral or topical veterinary preparations are used, one questions the need for using water of almost injectable grade quality.

4. Batch Manufacturing records (BMRs) (5.3)

4.1 The supply of BMRs has long been a bone of contention, due to the confidentiality issues raised above.

4.2 A suggestion that the address where Council representatives may view such documents be included, or some arrangement whereby such documents are brought to council for viewing be included.

5. Dissolution (6.4)

5.1 The original reason for dissolution was to prove bioavailability. It has long since been proven that dissolution is not a good indicator of bioavailability, especially since the proposed media are designed to simulate human gastric fluid.

5.2 Another reason for measuring dissolution is to confirm batch-to-batch uniformity. If this is the justification to be used, then each batch's the result must be the same. It does not have to meet the normal standard of 70% - 80% in 30 to 60 minutes.

6. Analytical method validation. (6.10

6.1 Quantification of degradation products requires reference standards of such degradation products, which are very expensive and difficult to obtain.

6.2 It is suggested that the principle of mass balance be deemed acceptable, except where degradation products are known to be toxic in small amounts.

7. Pharmaceutical Expert.

7.1 Criteria are required as to what constitutes a pharmaceutical expert, as the areas to be covered cover a number of disciplines.

8. Process validation (9)

8.1 A clear distinction must me made between validation and R & D. The effect of various parameters on the formulation is an R & D function.

P AND A FOR VETERINARY MEDICINES

1. THE ACTIVE PHARMACEUTICAL INGREDIENT

1.1 The **approved name** (INN) or chemical description of the active pharmaceutical ingredient(s) must be stated including the structural formula, the empirical formula and the molecular mass.

1.2 The solubility of each active pharmaceutical ingredient must be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents must include water and the solvent(s) relevant to the formulation. Storage requirements of the raw material and retesting period must be stated.

1.3 The name and physical address of each manufacturer and vendors being applied for must be stated. No active ingredient from any source other that the approved source(s) may be used.

1.4 Active Pharmaceutical Ingredient File (APIF) should include the following information:

* The name and physical address of the manufacturer (Including any intermediate manufacturer)
* The approved name of the relevant active pharmaceutical ingredient
* The chemical name and chemical structure of the active pharmaceutical ingredient –
*

(The processes carried out by any intermediate manufacturer must be identified)

- Evidence of /GLP compliance of the laboratory where relevant or possible, for all tests and analyses must be submitted.
* Evidence occurrence of isomers and polymorphism where applicable
* Structure elucidation for New Chemical Entities (NCE)
* A description of impurities. Distinguish between actual and possible impurities
* A description of possible degradation products
* The physical and chemical properties of the active pharmaceutical ingredient
* The detailed methods used for identification and assay, including chromatograms wherever relevant
* CoA results of at least two batches
* Results of stability studies performed on the active pharmaceutical ingredient obtained by the above method of syntheses. The conditions under which degradation products are formed must be included. A stability-indicating assay method must be used in these studies, and must be described in full. Supporting chromatograms wherever relevant must be included.

  Stability data on new chemical entity active pharmaceutical ingredient must be generated according to the stability guidelines.

1.5 Certificates of analyses (CoA)

A valid CoA (a), of a batch of active pharmaceutical ingredient, purchased and received by the manufacturer of the final product must be submitted. Any test not included in the valid CoA as specified in Part 2C must be performed by or on behalf of the manufacturer of the final product. A valid CoA must be on the letterhead of the manufacturer of the active pharmaceutical ingredient.

1.6 Requirements for proof of chemical and physical equivalence of Active Pharmaceutical Ingredient:

When more than one manufacturer is being applied for or when different methods of synthesis are used in the manufacture of active pharmaceutical ingredient the following must be submitted in lieu of each manufacturer:

A. An Active Pharmaceutical Ingredient File (APIF)

Note that if the identical method of is used by each manufacturer (or the same parent company) or at different sites of the same manufacturer, a statement to this effect will suffice.

B. A communication pointing out the differences in the methods used, and the differences with regard to the impurity profiles.

C. A valid CoA issued by each manufacturer and the analytical reports issued by or on behalf of the manufacturer of the final product. For new sources the valid CoA is required.

D. Comparative critical tests e.g. Identification, assay, solubility, particle size, optical rotation, residual solvents and impurity profiles, performed on samples from each source to demonstrate physical and chemical equivalence, must be performed by the same laboratory (either the laboratory of the manufacturer or an independent laboratory). The same analytical methods and equipment must be used for these tests. These results must be presented in tabulated format.

2. FORMULATION

2.1 The formula must show the approved names (INN) and/or chemical names of all active pharmaceutical ingredients and approved names of **excipients** (inactive ingredients) including those that do not necessarily remain in the final product after manufacturing, such as granulating agents and gasses used for flushing, etc.

2.2 The name and the amount of the active pharmaceutical ingredient must correspond to that given under Composition in the package insert.

a) For excipients that do not appear in the final product, this must be so indicated
b) Each raw material must be listed together with its quantity per **dosage unit**. This would include the vehicle(s), solvent(s) or base(s). In the absence of an **approved name** (INN) or **chemical name**, a **chemical description** or characterization of the substance must be given. Special technical characteristics of the excipient, where applicable, must be indicated such as "lyophilised", "micronised", "solubilised", "emulsified", etc. the technical grade of excipients, where relevant, must be indicated.

Some excipients are single chemical entities while others are combinations. Some are chemically transformed, e.g. modified starch. For excipients that are mixtures of chemically related or unrelated components, e.g. Polyol esters (mixture of mono-, di- and trimesters), direct compression excipients or film coating material, or excipients that are chemically modified, the dossier must specify the nature and quantity of each component, where possible

P AND A FOR VETERINARY MEDICINES

2.3 A product may contain more than one active pharmaceutical ingredient provided that

i) each active pharmaceutical ingredient makes a contribution to the claimed indications;
ii) the effect of combining the active pharmaceutical ingredients in one product does not decrease the safety, stability or efficacy of the product; and
iii) the product provides rational concurrent therapy for a significant proportion of the target species

2.4 The purpose of each inactive ingredient must be stated briefly. If the excipient is used for multiple purposes in the formulation, each purpose must be mentioned.

2.5 Any overages for the active pharmaceutical ingredient must be stated separately and the reasons for it must be given. The label claim quantity must be stated and the excess quantity indicated as the actual amount or as a percentage. For example, 500mg*

*Use the asterisk to explain the amount, percentage and purpose of the overage.

2.6 Where a potency adjustment for the active pharmaceutical ingredient has to be made, a statement to the effect that the actual quantity of the active will depend on the potency, and the excipient(s) that will be used to adjust the bulk quantity must be included, as well as the manner in which the adjustment will be made. Potency calculations, formulae where applicable, must be included and must also be shown in the manufacturing procedure.

2.7 Where the vehicle is added up to the required volume or mass of the product, the actual or estimated quantity of that vehicle may be stated. However, expressions such as "add up to" and "q.s." are acceptable. Solutions added to adjust the pH must be described in terms of composition and strength (normality, molarity, etc) but it is not necessary to state the actual quantity added as none may be added or only minute quantities may be needed.

For biological medicines the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine that is offered for sale in a dried form shall be supplied.

2.8 *Toxicity levels per dosage unit must be indicated for all solvents and for other ingredients when required by Council.*

P AND A FOR VETERINARY MEDICINES

3. RAW MATERIAL SPECIFICATIONS AND CONTROL PROCEDURES

3.1 Specifications and the limits of all raw materials, including the active ingredient(s) must be listed and must at least be at the level of the latest editions of recognized pharmacopoeia reference books, (BP, USP, EP). Any deviation from such specifications and limits must be fully substantiated. More than one pharmacopoeia may be used for the raw materials, provided that each individual reference is used fully and not partially or selectively. For example, USP may be used for starch, and BP for lactose, etc One ingredient may be tested in accordance with alternative pharmacopoeias, depending on the site of manufacture.

3.2 In-house specifications must at least be at the level of an approved pharmacopoeia. Any in-house specifications that are at a lower quality standard than that of an approved pharmacopoeia must be fully motivated, subject to approval by the Council. (Cross-reference to a Pharmacopoeia is necessary).

3.3 Additional specification parameters, over and above those stipulated in the official compendia, such as a very accurate description of isomers, polymorphs, etc., must be submitted for all active ingredient(s) where required by the Council.

3.4 Control procedures for all raw material specifications shall be fully described, unless performed - in accordance with a recognised -pharmacopoeia. In the latter instance, reference to the - pharmacopoeia must be made as indicated in 3.1 above.

3.5 Specification limits and the control procedures for particle size of active pharmaceutical ingredients, which have a solubility of less than 1 part in 200 parts water, and for those which the Council may request, must be submitted. Particle size must be stated in SI units (μm). If the particle size is stated in sieve sizes, the corresponding size in SI units should be included. Exemption from this requirement may be applied for if the active ingredient is reconstituted into, or is administered as, a complete solution, or for any reason determined by the Council.

3.6 The following minimum requirements must be confirmed:

i) Identification and assay of the Active Pharmaceutical Ingredient will be performed irrespective of the possession of a certificate of analysis from the supplier;

ii) Identification of the inactive Ingredient will be performed irrespective of the possession of a certificate of analysis from the supplier; and that

iii) Any test not included in a valid* certificate of analysis will be performed.

* valid as defined by c GMP

3.8 For those inactive ingredients for which a conclusive identification test is not included, all those parameters, which are specific to the identification of that raw material, must be performed irrespective of the possession of a Certificate of Analysis from the supplier.

3.9 For all natural raw materials of organic origin, microbial limits and test procedures must be included.

3.10 Frequency of testing of water, if applicable shall be included. Water must be tested at least once a week for microbiological contaminants, and daily or just before use for conductivity, pH and oxidizing substances.

P AND A FOR VETERINARY MEDICINES

3.11 *For biological medicines:*

a) Specifications for the primary production lot used in the manufacture of the final filling lot of a biological medicine and specifications for all raw materials for the diluent must be listed.

b) Tests of a biological source material must include tests to confirm the identification, safety and potency of the primary production or bulk lot used in the manufacture of the final filling lot.

c) Parameters and criteria of acceptance to confirm the identification, safety and potency of the product must be provided.

4. CONTAINERS AND PACKAGING MATERIALS

4.1 Full details of the immediate container specifications and limits, including nature of material, dimensions and sketches where applicable, as well as ~~those of applicators and administration sets,~~ the closure system, wadding and any other component in direct contact with the product, where applicable, and the control procedures thereof must be supplied.

4.2 A brief description of the outer container, if any, must also be given. At least the nature of the material must be mentioned e.g. Outer cardboard carton.

4.3 The type of container described here must correspond to that described in the package insert under "Presentation" and in the stability studies.

4.4 If product is packed in bulk containers, the type of material of the container must be stated.

4.5 All pack sizes must be included.

P AND A FOR VETERINARY MEDICINES

5. THE MANUFACTURING PROCEDURES

5.1 The Inspection Flow Diagram must be included.

5.2 The batch manufacturing formula and the batch size(s) must be included. Where more than one batch size is indicated, the batch formula of the smallest batch size only may be given.

5.3 A copy of the Batch/Master manufacturing document or a comprehensive flow diagram and a description of the manufacturing procedures detailing the various stages of manufacturing must be submitted. Indicate the type of equipment (including sieve sizes in µm), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. Rotation speed or rpm) etc.

5.4 All in-process controls (analytical, microbiological and physical) shall be shown in the flow diagram.

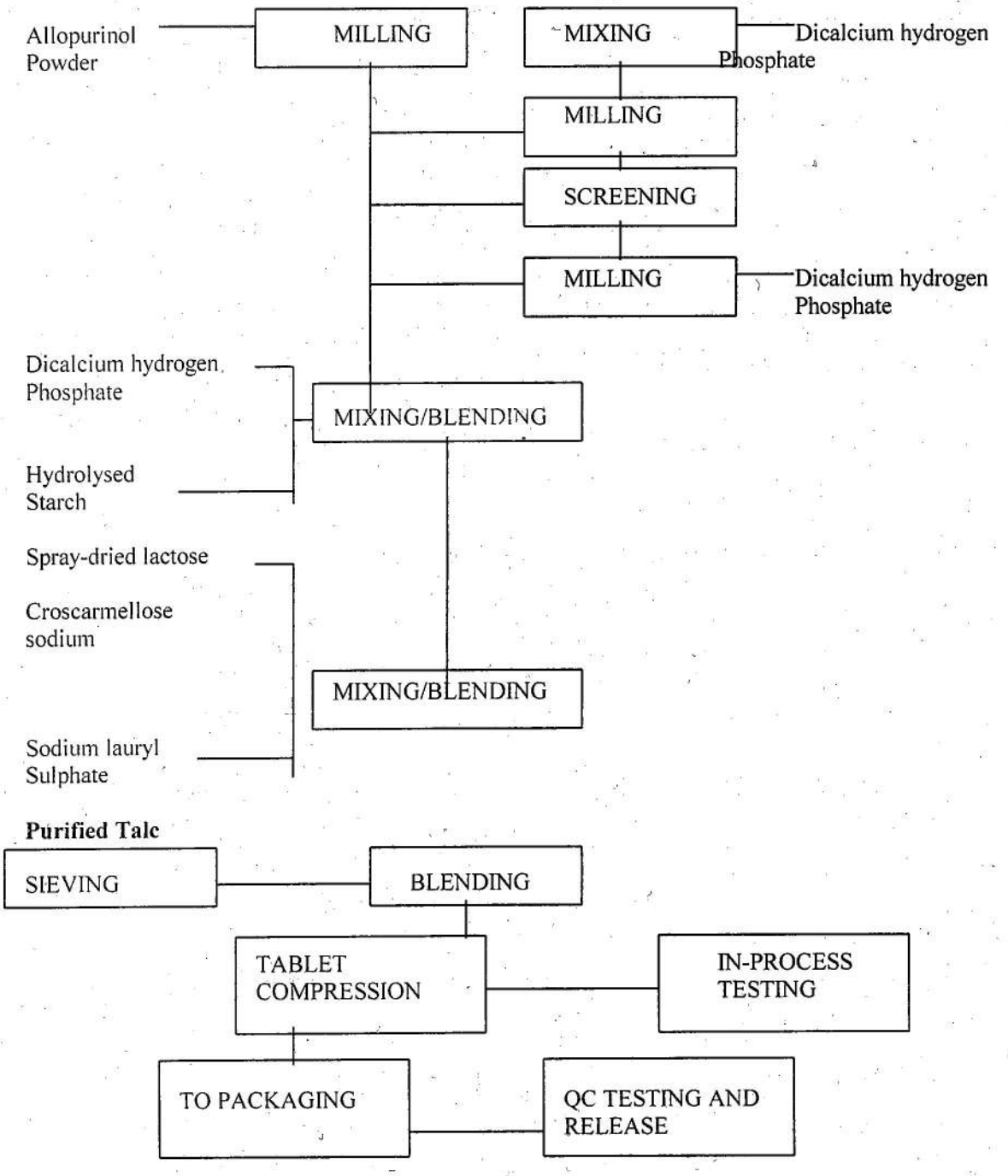
5.5 A copy of the Batch/Master Packaging document or a comprehensive description of the packaging procedures, detailing the various stages of packaging and labelling must be submitted. Indicate the type of equipment used in the packaging process. The in-process tests and control procedures carried out during the packaging process shall be included.

5.6 A process validation protocol must be submitted, and subsequent to this a validation report when available.

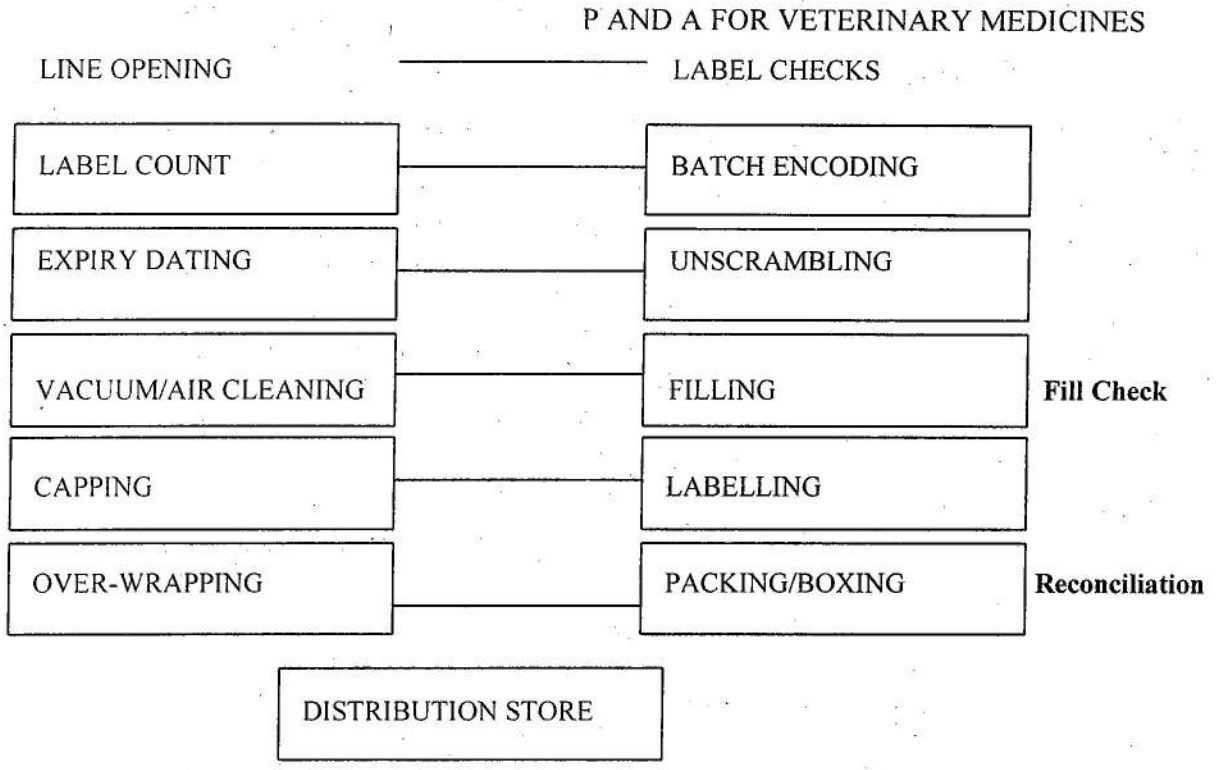
P AND A FOR VETERINARY MEDICINES

MANUFACTURING PROCESS FLOW DIAGRAM

PRODUCT NAME: ALLOPURINOL TABLETS (EXAMPLE)



PACKAGING PROCESS FLOW DIAGRAM



NB: Details of equipment and process conditions may be added in or next to each stage (box) or separately in an itemized paragraph.

6. THE FINISHED PRODUCT

6.1 Final product specifications and limits must be listed for in-process controls, final product controls, stability tests and the manipulated final product (if applicable).

6.2 The description of the final product must correlate to the description given under identification in the package insert.

6.3 Content uniformity must be specified and a control procedure must be submitted if the quantity of the active pharmaceutical ingredient is less than 2mg or less than 2 % mass per mass of the total mass of the dosage unit (e.g. tablet, capsule, etc), unless otherwise requested by Council. The active content assay need not be performed separately in the case where Uniformity of Content has already been performed for batch release purposes.

6.4 For quality control and batch release purposes, final product specifications for all solid oral dosage forms and suspensions shall include a requirement for dissolution of active pharmaceutical ingredient/s unless otherwise requested by Council.

6.5 Disintegration time, where relevant, for example for chew tablets, matrix tablets and soft gelatine capsules will be determined as a lot release requirement on all batches on which dissolution is not determined as a criterion for lot release. Disintegration time can be used as a lot release requirement for multivitamins and mineral preparation, unless a dissolution requirement for a specific product is included in the USP, in which case dissolution must be done as a lot release requirement.

6.6 For imported products, at least the identification and assay of the active pharmaceutical ingredient content must be performed after importation. This is intended to verify that the product has not been affected adversely during the transfer process. Exemption from this requirement may be applied for according to Addendum C (Guide on applying for exemption from re-identification and re-assay of imported products).

6.7 The final non-analytical release criteria must include the checking of the appearance of the dosage form, the container, the package insert, the label, the batch number, the expiry date of the product, the certificate of analysis and the batch release documents (FPRR functions).

6.8 All control procedures other than those from a recognized pharmacopoeia must be described in full.

6.9 A complete analysis report or certificate of analysis for one batch (pilot- or production) of the finished product must be submitted with the application.

6.10 The full validation data of the assay method of the active pharmaceutical ingredient related to batch release must be submitted. Chromatograms confirming the separation of the active from the degradation products, if relevant, must be included (See Addendum on Stability)

It must be demonstrated that the assay method is stability indicating, i.e. it must distinguish between the active pharmaceutical ingredient/s and the degradation product/s.

If the assay method used to determine the active pharmaceutical ingredient content is not stability indicating, then the validation data of the method/s used to determine the degradation product content must be submitted.

If the assay method (chromatographic) is taken from one of the latest recognized pharmacopoeias, then other validation data may be requested, e.g., system suitability where applicable.

If different assay method/s are used for stability testing, then a full description of the method and the validation thereof must be submitted.

Chromatograms confirming the separation of the active from the degradation products, if relevant, must be included.

6.11 All other quantitative assay methods (for preservatives, related substance, antioxidants etc) must be validated and the validation data included, except where such methods are from approved pharmacopoeias..

6.12 For a product from a non-biological origin, which has endotoxin levels, the validation data as required by the USP/BP/EP must be submitted, except where the dose is less than 2 mℓ/10kg, or standard LAL test is employed.

6.13 For products with a biological origin or any other products for which no endotoxin levels have been specified in a pharmacopoeia, the validation data must be submitted for evaluation.

7. STABILITY

7.1 All applications for registration of a medicine must be submitted with stability data in accordance with the minimum requirements stated in the **Guidelines for Stability**.

7.2 The stability program must be described in detail and must include the following information:

i) Conditions (temperature, humidity)
ii) Time points for testing e.g. 3 months, 6 months etc.
iii) - Tests to be determined
iv) How often - stability testing will be performed on future batches (should be in accordance with c GMP guidelines.)

7.3 Stability data must be presented in a tabulated format and must include the following:

i) Batch No. (Confirm that the formula is the same as the one applied for)
ii) Date of manufacture
iii) Date of commencement of stability study
iv) Name of manufacturer
v) Source of Active Pharmaceutical Ingredient (manufacturer not the supplier)
vi) Indicate whether production/pilot/experimental batch
vii) Container (Confirm that the container is the same as the one applied for)
viii) Storage conditions (must be controlled according to guidelines)
ix) Tests - and limits
x) Stability results

7.4 Discussion and conclusion of shelf life for each type of container must be provided.

P AND A FOR VETERINARY MEDICINES

8. PHARMACEUTICAL DEVELOPMENT

8.1 Any change or differences in the formulation during the development history must be indicated clearly.

8.2 A separate Pharmaceutical Expert Report (of not be more than 25 pages of A4 paper) must be submitted with each application and must include at least the following:

8.2.1 **Active Pharmaceutical Ingredient(s):**

a) Comment on the synthesis of the active pharmaceutical ingredient(s);
b) Discuss all physico-chemical properties, e.g. Solubility, water content, particle size, crystal properties, polymorphs, chirality, stability, etc. Reference may be made to the APIF;

8.2.2 **Formulation:**

a) Motivate and explain the function of the inactive ingredients;
b) Indicate the safety/toxicity profile of the inactive ingredients;
c) State any interactions likely to occur or that may occur under given circumstances;
d) Motivate/explain all overages;
e) discuss relevant physico-chemical parameters separately, e.g. pH, etc.;
f) Include pre-formulation studies and motivate;
g) Novel formulations and excipients must be discussed/explained.

8.2.3 **Production/Manufacture:**

a) Describe how the manufacturing method was derived;
b) Describe how in-process controls and validation plans were developed.

8.2.4 **Stability**

a) Discuss the stability of the final product formulation and the parameters used during stability and to confirm quality for lot release;
b) Discuss the containers used during stability studies;
c) Discuss dissolution;
d) Conclusion on stability.

8.2.5 Conclusion in Expert Report

8.2.6 Name, CV, Date and Signature of responsible person

8.2.7 A reference list used in the compilation of the report.

P AND A FOR VETERINARY MEDICINES

8.3 **Details relating to the premises on which primary production is undertaken and to the staff involved in production and testing of a biological medicine.**

A description of the premises where preparation of the primary production or bulk batch are carried out, names, qualifications, field and experience of the persons involved in preparation of the primary production and the final lot and details of the facility where the imported final filling lot is stored must be recorded.

i) A floor plan of the premises must be included.
ii) If the premises are used for other purposes such details must be supplied.
iii) Conditions under which the product is stored must be described.

P AND A FOR VETERINARY MEDICINES

9. GUIDELINES ON SUBMISSION OF VALIDATION PROTOCOLS AND VALIDATION REPORTS

This guideline intends to communicate to Industry, the policy and requirements in respect of validation protocols and validation reports to be submitted to the Medicines Control Council.

9.1 Important References:

Chapter 9 of the SA Guide to Good Manufacturing Practice (1996 edition)
Circulars
United States Pharmacopoeia (USP)
British Pharmaceutical Codex (BPC)
FDA Guidelines on Validation
ICH & VICH

9.2 Council resolution:
The standard to be used to assess compliance with current Good Manufacturing Practice, is the South African Guide to Good Manufacturing Practice (latest edition).

9.3 What is validation:

9.3.1 The SA Guide to GMP defines "validate" as follows:

"VALIDATE

To provide documented evidence that an item of equipment, process, system or method is in a state of control (i.e. That all assignable causes of variation have been eliminated) and is able to consistently deliver specified results."

9.3.2 Validation is an integral part of current good manufacturing practice; it is, therefore, also an element of the quality assurance programme associated with a particular product or process.

9.3.3 There should be levels where validation and qualification should be performed, and the level should determine the intensity of these products. It should be least for liquid preparations (solutions) and most for parenteral medicines, and for solid dosage forms it should depend on the criticality of the product as far as the patient is concerned.

9.4 When should validation be done?

9.4.1 Validation should be considered in the following situations:

* totally new processes
* new equipment
* processes and equipment, which have been altered to suit changing priorities
* processes where the end product test if poor and an unreliable indicator of product quality

9.4.2 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

9.4.3 The validation in the production unit mainly comprises the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.

9.4.4 At least three batches (including at least two production batches in the final batch size) should be validated, to show consistency. Worst-case situations should be considered.

9.4.5 When certain processes or products have been validated during the development stage, it is not always necessary to re-validate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process control and final product specifications.

9.4.6 There should be a clear distinction between in-process controls and validation. In-process tests are performed each time on a batch-to-batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously.

9.5 What does validation involve:

Validation involves the accumulation of documentary evidence relating to a process, item of equipment, or facility. This is achieved by means of **validation protocol** which should exist for every product and which details the tests to be carried out, the frequency of testing, and the results anticipated (acceptance criteria).

9.6 The Validation Protocol (VP)

The Validation protocol should clearly describe the procedure to be followed for performing validation. The protocol should include at least:

* the objectives of validation and qualification study;
* site of the study;
* the responsible personnel;
* description of equipment to be used (including calibration before and after validation);
* SOP's to be followed;
* standards and criteria for the relevant products and processes;
* the type of validation;
* time/frequency should be stipulated;
* processes and/or parameters to be validated (e.g. Missing times, drying temperatures, particle size, drying times, physical characteristics, content uniformity etc) should be clearly identified.

9.7 The Validation Report (VR)

9.7.1 A written report should be available after completion of the validation. The results should be evaluated, analysed and compared with acceptance criteria. All results should meet the criteria of acceptance and satisfy the stated objective. If necessary, further studies should be performed. If found acceptable, the report should be approved and authorized (signed and dated).

9.7.2 The report should include at least:

* the title and objective of the study;
* refer to the protocol;
* detail of material;
* equipment;

* programmes and cycles used
* details of procedures and test methods
* results (compared with the acceptance criteria)
* recommendations on the limits and criteria to be applied to all future production batches (which could form part of the basis of a batch manufacturing document).

9.8 Re-validation:

As a rule re-validation is required under the following circumstances:

* change of formulae, procedures or quality of raw materials
* change of equipment, installation of new equipment, major revisions to machinery or apparatus and breakdowns. Re-validation in the case of breakdowns is only required if a motivation cannot be supplied that justifies that such breakdown will not influence product, quality, safety or efficacy.
* major changes to process parameters
* changes to facilities and installations, which influence the process
* on appearance of negative quality trends
* on appearance of new findings based on current knowledge, e.g. Sterilisation where the frequency of checking is dependent on sophistication of in-process methodology

NOTE: The extent of re-validation will depend on the nature and significance of the changes.

9.9 General notes

9.9.1 The following aspects could be considered during the validation of specific dosage forms.

9.9.2 **Validation of tableting:** In the case of an oral tablet manufactured by granulation and compression, the critical process parameters may include (but not be limited to):

* particle size distribution of the active
* blending time for the powder
* granulating time and speed
* amount of granulating fluid-binder concentration
* drying time – final moisture content
* granule particle size distribution
* granule active content and homogeneity
* blending time of external phase
* tablet hardness with respect to water content, friability, disintegration and dissolution
* lubrication level with respect tablet hardness, disintegration, dissolution ~~and die-ejection force~~
* tablet weight and thickness control uniformity of content

If the tablet is film coated, the following additional parameters may require validation:

* spray rate of coating solution
* inlet and outlet air temperatures
* coating weight of polymer with respect to table appearance, friability, disintegration and dissolution

P AND A FOR VETERINARY MEDICINES

9.10 Requirements

9.10.1 Each applicant should have a Validation Master Plan (VMP) (See SA Guide to GMP, Chapter 9)

9.10.2 Each product must have a Validation Protocol (VP), (where validation is required, i.e. for *inter alia* solid dosage forms, certain suspensions, sterile products etc or where major changes in formulation or manufacturing method is envisaged).

9.10.3 There should be a Validation Report (VR) following the complete validation.

9.10.4 Validation Protocols and Validation Reports should be available for inspection purposes by the inspectorate. The following is applicable:

A New Applications for registration:

A VP must be included in Annexure 11. (The VR should only be submitted when requested by the inspectorate).

B Applications for change in applicant/manufacturer/packer/laboratory

A VP must be submitted with each application for a change in manufacturer or laboratory, or change in applicant where it also involves a change in manufacturer.

[If the validation had already been done, it should be indicated as such in the application. A VR should only be submitted when requested by the inspectorate].

9.10.5 Applications will not be accepted if the Validation Protocol should be found to be incomplete.

9.10.6 Applicants should note that the submission of the VP or VR does not imply that the council or secretariat had approved the VP or VR.

P AND A FOR VETERINARY MEDICINES

10. EXEMPTION FROM POST IMPORTATION IDENTIFICATION AND TESTING OF REGISTERED MEDICINES

Imported veterinary medicines must be identified chemically, assayed through a stability-indicating method, and other relevant tests conducted before release, to prove that the product integrity has not been prejudiced during transport from sources in other countries.

10. Exemption from these requirements will be considered in the following circumstances:

10.1.1 When very small quantities are imported for "selected" patients, or groups of patients.
10.1.2 10.1.3 Any other reason deemed by the applicant as being of such nature as to qualify for consideration for this exemption.
10.1.4 Any exemption approved will be valid for three years, provided that all the requirements are complied with during the period of validity. Initially, post importation testing must be done and subsequently at specific intervals.

10.2 When requesting exemption the following must be submitted.:

10.2.1 A suitable motivation for the request, that is, a suitable projection as to the annual usage of the relevant project
10.2.2 Validation of transport, that is, evidence that the conditions during transport are continuously monitored by temperature and, where relevant, humidity recorders.

A tabulated summary indicated the method of transport utilized and the conditions during transport as indicated below must be submitted. A minimum of five printouts are required, giving an account of the same product or, five different products, provided that the products require the same storage conditions, and provided that the products are dispatched from the same site but by different shipments.

10.2.3 A copy of the accelerated stability data of the formulation being applied for, packed in the final container as specified in Part 2D [Annexure8] (to determine if the humidity must be monitored).

10.2.4 A copy of Part 2B [Annexure 2] as per the MRF 1.0 (Form.

10.2.5 An indication as to whether the request is for bulk products or for the product packed in the final container.

10.2.6 A certificate of GMP compliance, not older than 2 years, issued by a competent regulatory authority or in terms of the WHO certification scheme
10.2.7 A copy of the proposed master release document in accordance with Part 2F reflecting the specifications pertaining to the product in question (example attached).

a) The type of recorder used in transit
b) Specify that the received certificate of analysis: is valid, is complete (reflects the actual results of the tests performed) and reflects compliance with the registration requirements.
c) Visual identification of the product and dosage form
d) A consignment reference e.g. GRN (goods received notice) or invoice, etc. (Batch numbers on the invoice must concur with the batch numbers of the products).
e) Confirmation of the integrity of the containers, seals, and labels. Each aspect must be specified and controlled to ensure that no damaged articles are accepted.

P AND A FOR VETERINARY MEDICINES

10.3 Furthermore, the following must be ensured:

* The transport conditions (temperature and humidity, where relevant) of each shipment are recorded by a suitable device, which provides a printout that will form a permanent record of the specific shipment and is filed with the batch release documents.

* An SOP, specifying the details of inclusion of the recorders, must be available for inspection. The procedure must include amongst others, the number of recorders, position of placement, date of activation and inactivation (on leaving the place of dispatch i.e. Factory and or receipt by the applicant i.e. Warehouse) and evaluation of the printout with the reference to the stability data.

* The monitor must be validated and the validation data must be available for inspection.

* Please note that exemption is applicable only if each future shipment is monitored and subsequently evaluated for compliance with the stability profile.

* The submission must include the necessary supportive stability data. If previously submitted, a statement to this effect will suffice.

* The transport monitoring method, or transport conditions must be specified in the master release document. Applicants should note that any shipment received, not complying with these transport specifications, does not qualify for the exemption. These shipments must be assayed and identified as if exemption was not granted in the first instance.

NB 1) The Medicines Control Council reserves the right to withdraw the exemption, should the applicant give cause.

2) Applicants who have obtained permission for exemption previously from the MCC for their products must re-apply for exemption.

3) **NAME OF PRODUCT:**
REGISTRATION NUMBER:
DOSAGE FORM:
APPROVED STORAGE CONDITION:
QC FUNCTION TO BE AUTHORISED (point (v) below):
ASSURANCE: TEMPERATURE RECORDED IN EACH SHIPMENT

Name of Product	Batch Number	Maximum and minimum temperature recorded	Maximum humidity recorded (Where relevant)	Duration of transport (Date commenced and date terminated)	Mode of Transport	Signature of MD/responsible pharmacist who verified the printouts

P AND A FOR VETERINARY MEDICINES

MASTER RELEASE DOCUMENT

Product name and code		
Batch number		
Approved storage conditions		
Final product specification reference number		
Receiving notice number (GRN)		
Date of dispatch and of receipt		
Quantity dispatched		
Number of containers received		

P AND A FOR VETERINARY MEDICINES

Test	Specification	Result	Signature
Temperature printout (storage conditions)	Present, attached conforms to stability profile submitted		
Certificate of Analysis	Present, valid (batch specific), conforms to MBR1, complete		
Visual Identification	E.g. Product description, labelling, container, batch number, expiry date		
Shipping containers' condition	Clean, undamaged	Number approved, Number rejected	
Shipping container label	Untempered		
Shipping container seal	Present, intact		

Position/Function

Signature	Date

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON MAXIMUM RESIDUE LIMITS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit residue depletion data to substantiate the recommended withdrawal periods for veterinary medicines used in food – producing animals. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of veterinary medicines. The MCC is committed to ensure public safety in the use of medicines in food-producing animals. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

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

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

INDEX: **PAGE**

GUIDELINE FOR DETERMINATION OF A MAXIMUM RESIDUE LIMIT AND WITHHOLDING PERIOD FOR VETERINARY MEDICINES

1. INTRODUCTION

1.1 Purpose

This standard specifies the requirements for residue data for a veterinary medicine that must be supplied with an application for assessment and registration of certain trade name products under the Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965).

One purpose of assessment under Act is to determine the disposition of certain residues in the edible tissues of treated animals or other specified primary produce obtained from a treated animal

The relevant risks that lie within the scope of this standard are:

(a) risks to trade and market access for primary produce containing any substance, mixture of substances, or biological compound that forms part of the trade name product;

(b) risks to domestic food residue standards.

1.2 Scope

This document only applies to trade name products registered under Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965) with active ingredients that have either:

- an ADI and an MRL pursuant to the Food Act 1984;
- a PDE issued under the Hazardous Substances and New Organisms (HSNO) Act and an MRL pursuant to the Food Act 1984 from the relevant competent New Zealand authority and for which the active therapeutic or zootechnical substance has been previously assessed by the ACVM Group of the NZFSA. These are referred to as A2, B1, B2, C4 and C8 applications. Certain electable options in this standard do not apply to A2 applications;
- an MPL listed in the Meat Residue Regulations Notice 2000 and any amendments;
- a residue threshold specified in the NZFSA Dairy Standard D107.

Those products for which an MRL is required prior to registration will be subject to a separate Residue Standard in respect of data requirements.

This standard is compulsory in all cases where:

- residue data are required for registration of a trade name product; or
- an application is made to vary any condition of a registered trade name product which changes, or is likely to change, the residue risk as specified above;

and a data waiver or application for a default WHP has not been granted.

This standard must be followed by:

- all persons applying to register a trade name product or to vary the registration conditions on a registered trade name product where a WHP is required to be determined except where specific exemptions apply or waivers are granted;
- all persons accredited to undertake a technical assessment of applications made to register a trade name product that requires a WHP or to vary the WHP conditions on a registered trade name product.

This standard shall not apply for exempted active ingredients (see Annex III) or restricted substances (Annex IV)).

This standard shall not apply to applications for which the WHP is elected by the applicant and who then subsequently shows that product formulation lies within the specifications for a 'standardised WHP' (Annex V) for those active ingredients.

Waivers may be granted to reduce the number of studies or type of data that an application must submit. These waivers will be granted only in accordance with the prescribed ACVM standard and must accompany any application to which they apply.

- Where the guidelines have not been followed and no explanation noted in the dossier or there is no information waiver, the ACVM Group may return the application as incomplete.
- The ACVM Group reserves the right in such cases that are not returned as incomplete to interpret data that fall outside the traceability and veracity guidelines very conservatively.
- Registrants may elect to apply for the default WHP wherein no residue data of any kind needs to be supplied (see also 1.2.5). Default WHP options for full registration are documented in the ACVM standard *Information Requirements*.
- Registrants may nominate a WHP that is supportable by a mix of trial data and public information. In this option where all the required elements of the standard are not met and a waiver is approved, the ACVM Group will assess the proposed WHP supporting information conservatively (against a conformance standard higher than that specified for GLP audited trials).

Applicants should note that they are responsible for providing all information required by the ACVM Group of NZFSA to make a decision on the application. Applications that do not contain the required information may not be assessed or progressed. All data deficiencies and non-compliance with this standard will be documented by the data assessor and measures or risk management appropriate to the assessment will be assigned by the ACVM Group at the time of registration.

If further advice is required, applicants are advised to contract the services of an appropriate consultant prior to submitting the registration application to the ACVM Group. While much of the data specified in this document is also required for the determination of an MRL for a veterinary medicinal substance, the procedure to be followed and the specifications for supporting data for the elaboration of an MRL is specified in a separate ACVM standard, *ACVM Data Requirements for the Determination of an MRL (NZ Food Act) for a Veterinary Medicine and the Assessment of a WHP for that New Use.*

The standard documents a preferred method of data analysis for residues in edible animal produce. If applicants elect not to use this procedure then certain extra information as specified in the relevant section must be supplied.

This standard provides a recommended template for the:

- data assessor's report;
- data package summary.

Definitions and abbreviations

Active ingredient (a.i.)
The substance or substances in a formulated product that is/are responsible for the biological or other effects that make the product an agricultural compound or veterinary medicine.

ADME
Adsorption, Disposition, Metabolism, Excretion data in tissues, blood or plasma.

ACVM
The Agricultural Compounds and Veterinary Medicines Group within the NZFSA, responsible for the implementation of the ACVM Act.

ANOVA
Analysis of variance.

g'
A factor for calculating a one-sided tolerance estimate of conformance with a given threshold with a given confidence level (see **Population conformance**). The factors listed are based on the assumption of a normal distribution of data at any one time point although, for the small sample sizes specified in this standard, this cannot usually be proven for any particular sample set. The factor can be seen to be a special case of SD for application across different residue trials.

GAP
Good Agricultural Practice. Currently accepted 'best practice' standard that is applied to the use of veterinary medicines and agricultural compounds in animal husbandry and production, and consistent with the required residue threshold.

Good Laboratory Practice (GLP)
The organisation, process and conditions under which studies are planned, monitored, recorded and reported. The requirements for GLP are provided in the following documents:

OECD GLP Guidelines:

- Number 1 The OECD Principles of Good Laboratory Practice. Environment monograph No. 45, Paris (1992, as revised in 1997).
- Number 6 GLP Consensus Document. The Application of the GLP Principles to Field Studies. Environment monograph No. 50, Paris (1992).
- Code of Federal Regulations section 21 part 58, Sections A to K, USA.

Limit of Quantitation or Determination (LOQ)
The smallest measured content of an analyte in a given matrix using the specified analytical method above, which a determination of the analyte can be made with a specified degree of accuracy (usually ± 20%).

Marker residue
That chemical compound or aggregation of compounds to which the MRL applies.

Marker tissue
The edible tissue (kidney, liver, fat [+skin], meat, honey, milk or eggs) of highest residues at the assessed WHP.

Maximum permissible level (MPL)
The maximum concentration of an agricultural compound marker residue (expressed as mg/kg or ppm) legally permitted in food products as specified in the Meat Residue Regulations Notice 2000 (or any Notice that supersedes Notice 2000) or the Dairy Standard D107.

Maximum residue limit (MRL)
The maximum concentration of an agricultural compound marker residue (expressed as mg/kg) that is legally permitted in food products or agricultural produce as specified in Regulations pursuant to the NZ Food Act, Mandatory Food Standard Table of MRLs of Maximum Permissible Proportions.

Note that for compliance purposes a different marker tissue (e.g. urine, blood etc.) may be used in lieu of one of the marker tissues noted above. In this instance the MRL applicable to the tissue shall not apply to this surrogate substrate and the applicable thresholds will be issued under regulations pursuant to the Animal products Act or Dairy Act.

New Zealand Mandatory Food Standard (NZMFS)

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

The table of MRLs (and exemptions) for the active substances for various primary agricultural products as cited according to the requirements under the New Zealand Food Act and subsequent regulations.

Plant compound
Any substance, mixture of substances, or biological compound used or intended for use in the direct management of a plant. It also includes compounds used in the post-harvest treatment of unprocessed agricultural commodities of plant origin.

Population conformance
At the proposed WHP the population characteristic is to be that at a specified (upper) confidence level (UCL) bound of 100(1-ą) % (with ą being the significance level) and 100*p*%, where *p* is the fraction of the total population to be less than the MRL – estimated using g'. The factors *q* and *p* take into account that the desired conformance outcome relates to the cohort of the animal population as a whole presented for slaughter on any one day and not just the trial (treated animals).

Pre-Natal Treatment Interval (PNTI)
The elapsed time between application of an intrammary preparation or a sustained release dosage device to a non-lactating animal and when birth occurs and lactation commences within one season. The PNTI is the controlling interval to enable bobby calves to meet the required residue conformance and also to enable the residue conformance for milk to be met at the end of the current mandatory 8 milkings WHP.

QA
Quality assurance.

Residue
Any substance or mixture of substances in food for man or animals resulting from the use of an agricultural compound and includes any specified derivates, such as degradation and conversion products, metabolites, reaction products and impurities, which are considered to be of toxicological significance. They may be free or bound to cellular or sub-cellular components of tissue.

SD
Standard deviation of a statistically normal data set.

Significant residue components
Compounds other than the active ingredient(s) that are present in the trade name product and that may be toxicologically significant.

Supervised residue trials
Scientific studies conducted according to prescribed codes in which agricultural compounds are applied to target host species according to specified conditions that reflect the claimed use pattern and after which harvested crops or tissues of slaughtered animals are analysed for residues. Supervised means that a nominated person (of standing, experience and credibility), is responsible and accountable to the regulatory authority and sponsor for assurance that the trial protocols were followed.

Target species
Any organism that is subject to the intentional action of an agricultural compound or veterinary medicine or its residues.

Trade name product
An agricultural compound containing one or more active ingredient(s) normally mixed with non-active ingredients (such as surfactants, solvents, diluents, suspending agents), intended for application, with or without dilution prior to use, and which is labelled with directions for use.

UCL
The upper (confidence) level bounding the required population conformance statistic for compliance with the MRL.

Veterinary medicine
Any substance, mixture of substances, or biological compound used or intended for use in the direct management of an animal.

Withholding period (WHP)*
The WHP is a regulatory tool used by the ACVM Group as a condition of registration to manage compliance with the residue thresholds (section 1.21) as prescribed under the ACVM Act or at the direction of the Minister of Agriculture and Forestry.

WHP is that time for which a particular agricultural produce must be withheld before entering the food chain and is defined as the "minimum permissible time between the last application of that agricultural compound to an animal and either:

- its slaughter for human consumption
- the taking of eggs from treated poultry, for human consumption
- the taking of honey from treated hives, for human consumption
- the taking of milk from a herd of cows where the milk is aggregated after each milking"

For the purposes of assessment, the ACVM Group differentiates WHPs according to the manner by which they are determined:
Calculated WHP. The least amount of time calculated from the data set; or adjusted data set at which conformance with the MRL is met.
Proposed WHP. The WHP proposed by a prospective registrant according to their interpretation of the data.
Assessed WHP. The WHP determined by the ACVM Group after assessment of the trial data only according to the rules and guidelines specified within the ACVM Residue Standard and evaluation of the various residue risks identified.
Allocated WHP. The WHP determined by the ACVM Group to be appropriate to a reduced or non-existent data set but which takes into account other evidence supplied as part of a Waiver.
Default WHP. The set of predetermined WHPs that will be applied in the absence of any residue data (and a supportable residues information waiver).
Standardised WHP. A WHP assigned to a group of formulations with at least one active ingredient in common and with the same method(s) of administration. The standardised WHP will correspond to certain specifications attached. Future registrations of products within these specifications need supply no residue data (only) at all if the registrant elects to take the standardised WHP.

Notwithstanding any of the above, the product label will be annotated only with "WHP" irrespective of how it is derived.

In general "calculated WHP" ≤ "Assessed WHP" < "allocated WHP" << "default WHP"

Milking Animals not in Lactation

For cows not in lactation the expression of residue controls on milk is comprised of two parts the PNTI (see definition) and the milk WHP after calving/lactation commences. The former is the variable subject to product specific regulatory control while the latter is currently fixed and currently mandated at 8 milkings irrespective of product.

Z
The (statistical) normal variate in standard measure.

References

This standard and guideline is based on those for residue data developed by the FAO (JMPR), Australia, (National Registration Authority), USA (Environmental Protection Agency and the Food and Drug Administration), but modified according to the principles and requirements in the ACVM Act.

OECD series on Principles of Good Laboratory Practice and Compliance Monitoring, No. 1. The OECD Principles of Good Laboratory Practice, Environmental Monograph No 45, Paris, 1992 (as revised in 1997).

Number 6 GLP Consensus Document. The Application of the GLP Principles to Field Studies, Environment monograph No. 50, Paris (1992).

FAO. 1997. Manual on the submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed. FAO, Rome.

FAO. 1990. Guidelines on producing pesticides residues data from supervised trials. FAO. Rome.

FAO/WHO. 1993. Portion of Commodities to which Codex MRLs apply in Codex Alimentarius, 2nd ed., Volume 2. Pesticide Residues, Section 4.1. Joint FAO/WHO Food Standard Programme. FAO Rome.

FAO. 1986. Guidelines on pesticide residue trials to provide data for the registration of pesticides and the establishment of maximum residue limits. FAO. Rome.

Codex Alimentarius, Volume 3, 1994, Residues of Veterinary Drugs in Food, Part 3.

United States of America Code of Federal Regulations 21, Part 58, sections A to K.

Quantifying Uncertainty in Analytical Measurement. EURACHEM/ CITAC Guide, 2nd Ed.

Statistical Intervals. A Guide for Practitioners. Gerald Hahn and William Meeker. John Wiley and Sons, Inc, 1991.

Agricultural Compounds and Veterinary Medicines Act 1997.

ACVM Registration Standard-Information Requirements
ACVM Registration Standard-Information Waivers
ACVM Registration Guideline for Residue Data: Plant Compounds
ACVM Registration Standard and Guideline for Chemistry

This standard and guideline has been prepared to advise and assist applicants in the preparation of their application.

2. INFORMATION REQUIREMENTS

Each application to register a trade name product or to very the registration conditions on a trade name product where the MRL is already gazatted in the NZ Mandatory Food Standard Table of MRLS or the Table of maximum Permissible Levels (of residues) issued under the Animal Products Act, the Meat Act or the Dairy Act, must supply the information required to support a WHP determination at the prescribed

level of conformance. The applicant may propose a WHP based on their interpretation of the data and their evaluation of any deficiencies in the data set.

However, the ACVM Group will make the final assessment of a WHP based on an overall risk assessment which may include consideration of other issues and a different interpretation of the significance of any non-compliance with this standard.

The data assessment report must identify all non-compliances with the standard, preferably by section number.

The data assessment report may include comment on the perceived significance of any identified non-compliance and the effect that may have on any conclusion that could reasonably be obtained from the data contained in the residues dossier.

The residues dossier must contain an index of contents and an unambiguous page numbering that corresponds with the index of contents.

All waivers and or exemptions pertinent to the application for a WHP must accompany the application and copies must be included with the residue dossier.

2.1 **Standards**

2.1.1 All experimental trial data within applications but excluding:

- those research approvals that request a clearance for sale of produce into the human food; or
- when a default WHP is requested under the relevant ACVM standard must be collected according to the principles of GLP as specified in either of the codes specified under the definition of GLP in section 1.3 if the data is supplied with the intent of obtaining an assessed or allocated WHP.

This requires that all non-compliances with the code must be documented.

2.1.2 This standard refers to internationally accepted standards for the collection, reporting and interpretation of residue data. Where a dossier includes information collected and interpreted under any different standard it is the registrant's obligation to show equivalence to the standards and procedures herein.

3. PHYSICAL AND CHEMICAL PROPERTIES

Ancillary residue information

A summary of data elements from other dossiers is required as part of the WHP assessment. Information from the Chemistry, Efficacy and Safety dossiers is required.

Template

A data sheet summarising the separately required elements is documented in this standard (see Annex I) and is also available on the ACVM website under 'Forms'.

4. DATA ASSESSMENT REPORT ON RESIDUE TRIALS

Residues DA Template

A data sheet summarising the required elements is documented in this standard (see Annex II) and is also available on the ACVM website under 'Forms'.

(Applicants are advised that lack of availability to Assessors of these data in summary form may result in increased assessment costs owing to the extra time involved in data retrieval.)

5. PROPOSED USE PATTERN

The use pattern of a trade name product affects the level and nature of residues that will occur in food or primary produce. It is essential, therefore, that submissions include the complete and detailed use pattern proposed for the product, to supplement the proposed label directions.

The registrant must address any new risks arising from a new use of a substance in a registered trade name product. Examples of such new risks are:

- different metabolites with different quantitative relationships
- different marker compound.

The new use of a substance in regard to route of application shall require the registrant to furnish proof of the identity of both the marker residue and the marker tissue, and to identify any metabolites that may be relevant to the residue definition.

5.1 Use situation

The proposed use situation should be clearly identified, including an indication of the species, sex, growth stage(s) involved, e.g. weight ranges or age ranges of the animals involved and the situations or conditions/diseases for which the remedy is intended to be used. Details and characteristics of the individual animals used in the trial, their health, feed, housing and clinical status during the trial should be documented:

- for topically applied ectoparasiticides, description of the weather conditions at the time of application and for 5 days thereafter if housed outside;
- meteorological parameters required are temperature and range, RH, cloud cover, rainfall;

- the proposed prescription medicine status or other restricted access to, or proposed controls on, the trade name product where this may impact on the probability of conformance with the WHP.

5.2 **Application method**

The mode of application of the intended treatment must be described fully. The site or placement of the product on or in the animal must be described fully.

5.3 **Application rate**

The dosage for each animal must be reported in mg (of the active ingredient)/kg live body weight as well as total mass and/or volume of the trade name product administered. The ACVM Group shall not prescribe an upper limit to dose volumes/animal. Each case must be supported on its merits. Residue data must be reported on the largest volume of any range proposed; residue data must be reported on the largest dose of any range reported. All maximum dosages reported in the residue trials must also be reported in the safety and efficacy trials if the injection site lesion residues from those trails are to be used in WHP assessment.

Applicants may stratify WHP by dose regime and dose volume. Applicants should note that there exists evidence that residue persistence may increase significantly with dosage and dose volume, and is more marked with subcutaneous and intramuscular administration. However, this may not necessarily result in an increase of WHP in any particular instance.

5.4 **Application and timing**

The frequency and timing of repeat doses administered during the proposed treatment interval must be reported. If Good Agricultural Practice requires that cycles of application be used over the course of a year, then the timing (when) and frequency must be reported.

If the use of the product is such that it is likely to be used in conjunction with, or immediately following, the use of a different veterinary medicine this must be documented.

5.5 **Proposed withholding period**

For liver, kidney, muscle and fat (all species) WHP will be assessed from any of the following permissible WHP: days up to and including 21 days and in weekly intervals thereafter.

For eggs, WHP will be intervals of 1 day, commencing at day 0 (i.e. a nil WHP), thereafter in 1 day increments.

Milk WHP will ordinarily be expressed in hours. This is predicated on treatment being applied immediately after a milking. A nil milking WHP equates to a nominal 12 hr milk WHP, for example based on two milkings per day schedule.

PNTI will be in weeks only.

Any risks associated with practical or accidental non-compliance with proposed label directions should be noted. This includes, for example, studies done with subcutaneous injections (risk of intramuscular) on large animals or for whole herd treatments and injection at unusual sites, i.e. non-neck.

6. SUPERVISED RESIDUE TRIALS

Supervised trials serve as the primary source of information for determining residue levels. Specific information on the numbers of trials, time points, animals per time point and tissues required are specified in the tables or in footnotes to the tables in the appendices to this standard. The residue risks are considered different for pioneer uses and non-pioneer or generic uses. These are listed separately in Appendix 1.2 and 1.3.

Two trial options are possible:

Option 1. Three or more time points with the specified number of animals (see Appendix 1) at each time point. This option allows a limited extrapolation of data beyond the data time points supplied in the trial.

Option 2. One time point only. Election of a proposed WHP and selection of the specified number of animals (data points see Appendix 1.4) for the trial to enable ACVM Assessors to be assured that the required residue conformance is met at the assessed WHP. If this is so, then that time point (if it is between permitted WHP) or the next permissible one after it becomes the assessed WHP. No other extrapolation is permissible in this electable option. For example, if MRL conformance is not met at, e.g. a 5 day time point, then the ACVM Group will assess a suitable WHP based on a conservative interpretation of the data. It is very unlikely that the (long) default WHP would be offered but each case would be judged on its merits. Trial data presented under Option 2 with fewer than the specified number of animals will also be interpreted conservatively as specified for an "allocated WHP" and waiver situation unless the supplementary documentation in the waiver is sufficient to remediate the data deficiency.

Registrants should note that Option 1 must be followed for pioneer uses-with limitations (see section 12).

Where there is potential for plant compounds to produce residues in food producing animals through ingestion of treated fodder, feeds or soil then residue trials in crops and animals may need to be carried out. Refer to the *ACVM Registration Guideline for Residue Data: Plant Compounds* for trial procedures. Refer to the Meat Act Residue Regulations, Animal Products Act Regulations or the Dairy Act Regulations D 107 for the relevant MRLS or MPLs.

All trail design and execution must be conducted in compliance with GLP.

6.1 **Trials in GLP accredited facilities**

6.1.1 Any analytical processes carried out in GLP accredited facilities and carried out according to GLP do not need to supply full documentation of the procedure. A brief summary is sufficient. However, the actual formulation used, the interval elapsing between manufacture and use, and the storage conditions subsequent to manufacture must be documented.

6.1.2 Any 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 procedure.

6.2 **Trials in non-GLP accredited facilities**

6.2.1 Where any part of the study is not conducted in a GLP accredited facility the registrant must supply all of the following:

- Full documentation of all physical aspects of the facility;
- Full documentation of other accreditations held by the facility;
- Full documentation of the CV of any auditors employed for the study and the audit schedule;
- Full CV of all staff involved in the study;
- All raw data produced within the non-accredited facility pertinent to the study;
- Full documentation of any audits or peer reviews of the facility conducted within 1 year of the commencement of the study;
- The foregoing applies to all subcontractors who contributed to any element of the study;
- Documentation showing complete traceability of all relevant physical and observational data generated by the study.

6.2.2 Applicants should note that after 1 January 2003 applications under 6.2 will not be compliant 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.

Reporting requirements are much less onerous for trials in GLP accredited facilities.

6.3 **Residue trials and primary products**

Residue trials should aim at giving as accurate as possible a measure of the residues likely to occur in edible portions of the crop or in other food commodities such as products of animal origin (edible tissues, milk, milk products, eggs). A residue trial may be in the form of obtaining a residue decay curve (depletion over time) or residue measurements at one time point. In particular dose rates in the trial must not be less than label does rates. If it can be demonstrated that bioavailability is a direct and linear function of dose, then results from higher dose rates may be extrapolated to (inferred) levels at the label dose rate for doses not exceeding 3 times the label doses rate.

6.3.1 **Milk**

For milk residues the trial data must be generated on, and reported from, individual trial animals generally at the maximum dosage/animal. Where intra-mammary treatments do not in treat all teat canals or quarters then the following shall prevail:

- If milk is aggregated at milking then the assigned residue level for any sample so collected will be adjusted pro-rata for the proportion of teat canals treated in the animal.
- If teat canals are treated and milk collected and the residues analysed separately then the residue will be taken as the mean of those separate values.

Any factors such as partial udder treatment and partial herd treatment in a given situation, which could result in a reduction in the milk WHP (with suitable registration conditions), may be alluded to by an assessor and may be taken into account by NZFSA at the time the registration is granted.

For residue assessment and WHP purposes, milk will be assessed as pertaining to that bulked product obtained from the test group (i.e. a herd) at a given milking.

6.3.2 **Meat, (including fish), eggs and honey**
Analytical data must be reported on the produce from individual animals, eggs or hives* as the case may be.

* Honey from individual frames or combined from one hive

6.4 **Design of residue trials**

6.4.1 **Treatment frequency, dose and timing**
The dose and frequency of application and the interval between treatments should be the same as specified on the label. The dose should be the maximum of any electable dose specified on the label. If the trial conditions differ from those specified on the label or from those currently in farm practice in New Zealand, then this should be addressed in the report. All procedures applied to animals prior to application of the formulation must be documented in full (e.g. cleaning, clipping, sterilising).

6.4.2 **Field component of residue trials**
It is not required that residue trials are conducted on animals suffering from the disease for which the trade name product is (claimed to be) a remedy. The definitive residue depletion study must be conducted on animals certified as free of clinical disease. However, where pharmacodynamics and kinetics of the active ingredient(s) are known or suspected to be affected by disease states for which the veterinary medicine is indicated or by some unrelated disease, then this must be addressed in separate clinical/metabolism studies with reference to any published literature.

Any research results obtained for other purposes and which shows any interaction or otherwise between the ADME of the active substance and the disease state for which it is a remedy or any other disease present in New Zealand livestock will assist assessors in ascertaining a more accurate risk profile of the residues.

While in general the time points selected should cover the rise, plateau and decay phases of the residue depletion curve for WHP assessment, only the depletion phase is significant for the purpose of setting a withholding time.

Bioequivalence trial results normally used to demonstrate *equivalent bio-effectiveness* (e.g. by comparative measurements on plasma) between a reference and a test product may, by themselves, be insufficient to show that, in the case where bioequivalence is proven, the WHP of the reference product is applied directly to the test product. The *power* of the data analysis is usually insufficient to obtain the required degree of conformance for residues.

6.5 **Samples and sampling**

6.5.1 **Sampling procedures**
The procedure for taking samples for residue analysis must be fully documented with particular attention to the practical avoidance of contamination of samples. Failure to comply fully with this provision may result in inclusion of outlying (high and possibly arising from contamination) data points unnecessarily in the evaluated data set. This may result in the imposition of an unnecessarily conservative WHP.

6.5.2 **Sample storage**

The storage of the samples must be fully documented from the time of removal from the animal to receipt within the laboratory, up to and including analysis, and then for storage until the study is completed. The sample packaging must be shown to be free from components that interfere with the residue analysis.

Samples taken in non-GLP accredited facilities must supply all raw data sheets, sampling protocols, and freezer and transport logs.

6.5.3 **Sample types**

Tissues are on a wet weight basis.

For residue studies:

- meat is muscle (voluntary, e.g. not heart) obtained from any of the major muscles; the correct anatomical name is required (e.g. *latissimus dorsi)* from a specified part of the animal;
- fat is omental or renal fat;
- kidney is homogenised whole kidney with fat trimmed;
- liver is any part of the liver;
- eggs are homogenised whole eggs without shell;
- muscle is with fat trimmed off;
- fish meat is without skin/scales.

It is not required to report (residues) on kidney of fish or poultry.

A minimum of 100 g of any one tissue must be homogenised from which the requisite subsample must be taken (excluding eggs). Where this condition cannot be met because of the immaturity of the animal or small organ size, the organ mass must be reported.

A minimum of 100 ml of milk must be taken from each animal from which the requisite subsample is taken. In the case of trade name products for application into or on the udder, then the milk must be identified as either originating from either specified quarter(s) (treated udder) or combined with milk from untreated quarters from the same animal.

All samples should be taken in duplicate (the second as a reserve sample).

6.6 **Residue data from other countries**

Registration data in support of a withholding period for a veterinary medicine does not necessarily have to be generated from trials conducted in New Zealand **except** in the case of topically applied parasiticides on sheep. One New Zealand trial on cross-bred sheep is required for each of the claimed use patterns, e.g. off-shears and or long-wool use.

7. METHODS OF RESIDUE ANALYSIS

Analysis in GLP accredited facilities

Any analytical processes carried out in GLP accredited facilities and carried out according to GLP do not need to supply full documentation of the method. A brief summary is sufficient.

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-q) 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-q) 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 q 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 C*a*, C*b* are the residue concentrations of cow # *a, b* etc. and V*a*, V*b* 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 not 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
Intramammary Lactating Animal Preparations	3	3 See 8.5.1 (PNTI)	NA	NA	NA		NA
Intramammary (Dry) Animal Preparations	3 1	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 1	NA	NA	NA		NA
Gaseous Anaesthetics	1		1	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 Preparations	9	19	0	*	0	0	0
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**

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: _____

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	

MRLS AND WITHDRAWAL PERIODS FOR VETERINARY MEDICINES

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

CONTENTS:

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.

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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.

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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.

8 REFERENCES

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

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX 1

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

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX II

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

Applicant's details and original reporter's details

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

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

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

Animal Details

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

Suspect Product details

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

5.3.4 Treatment details

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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

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

5.3.5 Other products used concurrently

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

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

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

5.3.6 Details of the animal suspected adverse reaction(s)

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

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

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

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

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX III

For Adverse Reactions in humans to veterinary drugs

Applicants details and original reporter's details

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

Adverse Reaction:

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

Patient details

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

Adverse Event Details

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

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

APPENDIX IV

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

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

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

Type of ADR report	**Time frame for reporting**	**Format**
Local Reports: Fatal or life-threatening (unexpected) 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

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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

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

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

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

APPENDIX 3

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

P.T.O

ADVICE ABOUT REPORTING SUSPECTED ADVERSE REACTIONS

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

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

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

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

What to report:

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

We are particularly interested in:

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

Report even if:

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

Confidentiality:

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

Tick box if extra report forms are required ☐

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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

SECTION ONE: REPORTER DETAILS

Name and address of reporter:

Code: _____ Tel: (___) _____

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

Code: _____ Qualifications: _____

SECTION TWO: ANIMAL DETAILS

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

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

SECTION THREE: MEDICINE DETAILS

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

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

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

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

SECTION FOUR: ADVERSE EVENT DETAILS

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

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

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

Are there any results to follow? Yes ☐ No ☐

SECTION FIVE: ADVERSE EVENT OUTCOME

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

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

Treatment given, if any _____

Were there any sequelae? Yes ☐ No ☐

If yes, please describe sequelae _____

SECTION SIX: ADVERSE REACTIONS IN HUMANS

Name/ Initials	Sex	Age	Date of reaction	Nature of reaction

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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

CLINICAL TRIAL SERIOUS ADVERSE EVENT/ REACTION REPORTING FORM

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

1.

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

Required on all reports

☐ Initial
☐ Follow-up

Date company notified _____

Protocol # _____
Patient # _____

2.

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

3.

Investigational Medicines History

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

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

4.

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

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

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

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

5.

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

6.

Event Description: (including dates of hospitalisation)

REPORTING OF VETERINARY ADVERSE DRUG REACTIONS

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

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

11.

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

VETERINARY DRUG RECALLS

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR RECALL OF VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants regarding the recalls of veterinary medicines, and the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data which has been submitted regarding any recalls. The MCC is committed to ensure that all medicines that are registered are of the required quality, safety and efficacy. It is important for applicants to adhere to these requirements.

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

VETERINARY DRUG RECALLS

INDEX: **PAGE:**

WITHDRAWAL OR RECALL OF VETERINARY PHARMACEUTICAL PRODUCTS BY THE APPLICANT

1. DEFINITIONS

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

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

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

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

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

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

2. REASONS FOR A RECALL

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

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

3. PROCEDURE

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

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

CLASS OF RECALLS

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

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

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

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

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

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

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

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

VETERINARY DRUG RECALLS

TYPE	A	B		C
CLASS				
I				X
II				
III				

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

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

4. INFORMATION TO BE SUBMITTED

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

1. The name and strength of the veterinary product to be recalled, pack size, batch/lot number, any means of identification, and the registration number of the product.
2. The total quantity of the recalled veterinary product batch originally in the applicants possession prior to the distribution.
3. The date distribution began of the recalled veterinary product.
4. Area of distribution of the recalled veterinary product and, if exported, the country to where it was exported.
5. The total quantity of the recalled veterinary product that had been distributed up to the time of the recall.
6. Suggested action to be taken and its urgency.

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

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

5 RECALL COMMUNICATION GUIDELINES

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

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

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

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

4. Urgency of the action;

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

6. Indication of the health risk; and

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

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

14.6. POST RECALL PROCEDURES

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

1. Name of the product;

2. Strength of the product;

3. Registration number

4. Pack size and Batch/lot number

5 Nature of the defect;

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

15 Urgency of the action taken;

16 Reason for the action;

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

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

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

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

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

INTRODUCTION AND SCOPE OF GUIDELINES FOR VETERINARY MEDICINES

This document has been prepared to serve as an introduction to applicants wishing to submit applications for registration of veterinary medicines. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

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

INDEX : PAGE

1. INTRODUCTION

1.1 SCOPE OF THE GUIDELINES

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

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

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

1.2 GENERAL INFORMATION FOR APPLICANTS

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

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

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

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

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

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

1.3 LANGUAGE

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

1.4 WHERE TO SEND APPLICATIONS

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

1.5 CONFIDENTIALITY

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

VCTF 1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDE TO VETERINARY CLINICAL TRIAL APPLICATION

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

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

TABLE OF CONTENTS:

VCTF 1 I

1. INTRODUCTION

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

2. APPLICATION PROCEDURE

CLINICAL TRIAL APPLICATION – VETERINARY MEDICINES

SECTION 1 – CHECK-LIST OF REQUIRED DOCUMENTATION

To be completed by Applicants for all Clinical Trials

COVER SHEET

Study Title:

Protocol No:

Version No: **Date:**

Study Drug(s):

MCC Ref number (if applicable):)

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

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

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

Applicant:

Contact Person:
Address:

Telephone Number: **Fax Number:**

Cell Number:

E-mail address:

VCTF 1 I

To be completed by MCC

Date original application received:

Tracking No:

Proposed Clinical Trials Committee Meeting Date if applicable:

Signature: **Date:**

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

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

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

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

VCTF 1 I

CHECKLIST

Applicant's
MCC
check list
double-check

COVERING LETTER

FULLY COMPLETED APPLICATION (SECTIONS 1–3)

PROTOCOL (INCLUDING RELEVANT QUESTIONNAIRES ETC.)

INFORMATION LEAFLET(S) AND INFORMED CONSENT(S)

INVESTIGATOR'S CV(s) IN MCC FORMAT

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

ETHICS APPROVAL OR

COPY OF LETTER APPLYING FOR ETHICS COMMITTEE APPROVAL

WITHDRAWAL PERIOD APPROVAL (Where appropriate) OR

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

APPROVAL FROM VETERINARY SERVICES (Biologicals) OR

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

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

LABELLED DISKETTE/CD-ROM (MSWORD OR RICH TEXT FORMAT)
List of files submitted on diskette/CD-ROM:

VCTF 1 I

SECTION 2 – ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title:

Protocol Number/identification:

Date of protocol (final):

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

1.1 Applicant: (as in Section 1)

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

1.2 Sponsor: (as in Section 1)

Address :
Tel No :
Fax No :

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

1.4 Local Contact Person for correspondence:

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

Phone:
Fax:

1.6 International Principal Investigator: (if applicable)

1.7 Regional Monitor: (as in Section 1)

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(s)

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

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

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

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

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

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

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

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

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

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

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

Principal Investigator:
Address:
Phone:
Fax:
E-mail

Sub – Investigators:

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

Principal Investigator:
Address:

Telephone. No:
Fax No:
E-mail

Contact person:

VCTF 1 I

Telephone No :
Fax No :
E-mail :

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

Part 4: STUDY ANIMALS

4.1 Number of animals:

Part 5: OTHER DETAILS

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

5.2 Estimated duration of trial:

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

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

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

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

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

5.7 Details if this trial is being undertaken in SADC, any other country in Africa, or any country where there is no regulatory control of clinical trials:

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

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

Part 6: ETHICS

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

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

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

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

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

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

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

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

Reviewer's comments on Section 2:

SECTION 3 – APPLICANT'S REPORT / PRESENTATION

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

1 Title:

CTC Reviewer's comment:

2 **Protocol Number/identification:**

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

CTC Reviewer's comment:

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

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

Mode of action:

Toxicology:

Mutagenicity:

Carcinogenicity:

Teratogenicity:

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

Pharmacokinetics

Clinical studies in target species

Safety

Efficacy

Adverse reactions

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

CTC Reviewer's comment:

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

Objective elements	Justification
	•
	•

CTC Reviewer's comment:

VCTF 1 I

Study design (clearly described and each component justified)

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

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

CTC Reviewer's comment:

Inclusion and exclusion criteria:

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

CTC Reviewer's comment:

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

CTC Reviewer's comment:

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

Treatment	Justification
	•
	•

CTC Reviewer's comment:

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

Primary and secondary Variables	Justification
	•
	•

CTC Reviewer's comment:

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

CTC Reviewer's comment:

9 Statistical measures:

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

Sample size	Justification
	•

CTC Reviewer's comment:

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

Statistical Analysis	Justification
	•
	•
	•

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

Procedure

Data validation:

Closing of the data base

Statistical analyses of the data

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

CTC Reviewer's comment:

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

Explanation of which GCP guidelines are or are not being followed

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

Comment on monitors and monitoring plan
Comment on Informed Consent

Comment on ethics of the publication policy

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

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

CTC Reviewer's comment:

11 Other relevant information not included above

E.g.

Are references adequate and dates of references current?
Yes

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

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

Other comments on this trial.

CTC Reviewer's comment:

For office use:

VCTF 1 I

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

CTC Reviewer's recommendation:

Declaration of conflict of interests by CTC reviewer:

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

MCC decision (date):

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

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

3.1. TRIAL PROTOCOL

A well designed trial relies predominantly on a thoroughly considered, well structured and complete protocol which should be completed and approved by the Sponsor and Investigator/Site Supervisor before the trial is initiated.
The protocol will, where relevant, contain the information given in the following list of items, or this list should at least be considered whenever a trial is contemplated and reasons for any omissions given.

VCTF 1 I

General information

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

Justification and objectives

1. The objective in conducting the study must be clearly established.
2. The essentials of the problem itself and its background, referring where appropriate to relevant literature.

Schedule

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

Design

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

Animal selection

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

Inclusion/exclusion criteria

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

Treatments

1. Clear, precise and detailed identification of the product(s) to be used. These should be fully formulated products likely to be proposed for marketing. There should be a justification of the doses to be used.

2. Description of treatment applied to the control group(s) or for control period(s) (placebo, other products, vehicle only, no treatment etc.).
3. Route of administration, dosing schedules, treatment period(s) for the test product(s) containing the active substance under investigation and for the comparative product(s).
4. Rules for the use of concomitant treatment.
5. Measures to be implemented to ensure the operator's safety whilst handling the test products prior to and during administration.
6. Measures to promote and control close adherence to the prescribed instructions/ordinances (compliance monitoring).

Assessment of efficacy

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

Adverse events

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

Operational matters

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

Handling of records

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

Evaluation

1. Definition of the measure of test animals' response, e.g. a scoring system, and other measurements made in order to evaluate the clinical response.

2. Definition of the methods of computation and calculation of the effect of the medicinal product.
3. Description of how to deal with and report on animals withdrawn or otherwise removed from the trial.

Statistics

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

Supplements

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

References

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

3.2 DATA HANDLING

General

1. The person recording an observation will sign and date it or, in the case of the supervisor, each page of observations.
2. Data should be recorded on pre-established durable recording sheets. Record sheets should be diligently completed indelibly in ink or ball pen, with all the data points recorded as required in the protocol. However, when additional observations are considered necessary by the Investigator/Site Supervisor they should also be recorded on the record sheet together with a comment as to their perceived significance.
3. Units must always be stated, and transformation of units must always be indicated and documented.
4. All corrections on a record sheet and elsewhere in the raw data must be made by drawing one straight line through the erroneous values, which should still be legible.
The correct data must be inserted with date and signature or initials, if possible with reasons for change. An alternative would be to use a correction form.
5. Laboratory values should always be recorded on a record sheet or attached to it. Values outside an accepted reference range must be certified by the Investigator. Normal reference values for the laboratory should be included.
6. If data are entered directly into a computer there will be adequate safeguards to ensure validation including a signed and dated print-out. In this case the electronic record or the print-out may be referred to as Raw Data.
7. If, for example, during (direct) data entry, data are transformed by coding, the transformation must be documented.
8. For electronic data processing only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions.

Investigator

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

Sponsor

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

6. The Sponsor will maintain a list of persons authorised to make corrections and protect the data by appropriate password systems.

Archiving of data

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

4. STATISTICS

1. Access to biostatistical competence will be mandatory. Where and by whom the statistical analyses are carried out will be the responsibility of the Sponsor.
2. The type of statistical analysis to be used will be specified in the protocol and any subsequent deviations from the plan will be described and justified in the final trial report. Calculations and analyses will be confirmed by a named statistician.
3. The statistician and the Monitor will ensure that the data are of high quality at the point of collection and subsequent processing. The statistician will be expected to ensure the integrity of subsequent data processing by using proven and scientifically recognised statistical procedures. An account will be made of missing, unused and spurious data during statistical analysis. All exceptions will be documented for further review if required.

5. DATA VERIFICATION

1. Procedures for data verification will be applied to each stage of data collection, recording and processing.
2. The Sponsor/Monitor will be expected to perform the following functions before, during and after the study:
a) Monitor at the trial site to ensure that the investigational product(s) and record keeping are being handled correctly and that Adverse Events are properly recorded and reported.
b) Account for the supply and use of investigational and reference substances.
c) Monitor the Investigator's procedures and facilities in accordance with the Protocol and SOPs. Any deviations will be documented and justified.
d) Verify data through each processing procedure.
e) Account for all relevant trial documents and have them available for future audit if required.

6. ETHICS APPROVAL

Refer to Section 6 on page 10.

7. CLINICAL TRIAL ADVERSE DRUG EVENTS

MONITORING OF POTENTIAL SIDE-EFFECTS IN CLINICAL TRIALS

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

7.1 Experimental conditions

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

VCTF 1 I

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

DEPARTMENT OF HEALTH

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

CLINICAL TRIAL SERIOUS ADVERSE EVENT/ REACTION REPORTING FORM

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

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

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

Investigator name : _____ MCC's Investigator Number:_____

Study Site Address: _____ email:_____

City:_____ Postal code: _____

Province:_____ Country:_____

Sponsor Name: _____

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

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

VCTF 1 I

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

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

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

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

Adverse Event Terms (reported terms):

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

Event Description: (including dates of hospitalisation)

_____
_____
_____
_____
_____
_____

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

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

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

Description of treatment: _____

VCTF 1 I

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

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

CLINICAL TRIAL SERIOUS ADVERSE EVENT (SAE) REPORTING FORM

Page 3 of 3

11.

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

Reporting Investigator (Print Title and Name): _____

Telephone Number: _____ Fax Number: _____

Signature: _____ Date: _____

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

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

9. **FOOD SAFETY REQUIREMENT**

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

VETERINARY SECTION 21 APPLICATION

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDE TO COMPLETING SECTION 21 APPLICATION FORM FOR VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for Section 21 exemptions for unregistered veterinary medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for Section 21 exemptions for veterinary medicines. It is important for applicants to adhere to these requirements.

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

TABLE OF CONTENTS :

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Policy

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

4.2 All applicants must submit the following information:

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

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

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

4.5 The officer designated must confirm the authorisation in writing.

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

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

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

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

4.10 All adverse events or unexpected events must be reported immediately to Council and the supplier.

4.11 At the termination of treatment, a full case report shall be submitted to Council.

4.12 Council may in writing withdraw any such authorisation.

4.13 All unused, unregistered products shall be returned to the supplier for disposal, according to the requirements of Council.

4.14 Information about the basic efficacy, safety and quality about the product must be supplied to Council.

4.15 Where the product is used for a clinical trial, the MRF1.0 form must include the formula of the final product in terms of a dosage unit.

a) Specifications of a final product, namely the name of the specification, limits of criteria of acceptance of all physical, chemical and where applicable microbial parameters;
b) The laboratory responsible for the final lot release locally. At least an identification and assay must be done if the product is imported.
c) Stability data derived from the product stored at room temperature (at least nine (9) months), and elevated condition (three (3) months) in tabulated form. The data of manufacture batch number, batch size and container must be stated.

4.16 The Registrar of medicines shall, when Council is not sitting, refer as far as possible, all matters and report thereon at the next meeting of Council.

4.17 An exemption will be given for investigational and comparator medicines which:

a) are new chemical entities;
b) are new or different dose forms, delivery systems or formulations of established medicine; which
c) do not have consent to be sold in the Republic of South Africa.

The Medicines Control Council may grant the approval after receiving approval from an accredited ethics committee for the study protocol and the justification and validity of the study protocol.

4.18 Copy of Authorisation Form

1. APPLICANT DETAILS

a) Name
b) Street Address
c) Telephone number/Cell phone
d) Fax number
e) E-mail address
f) Designation
g) Qualification
h) Registration number

2. PATIENT DETAILS

a) Name
b) Address
c) Age
d) Diagnosis
e) Current regimen

3. DRUG / PRODUCT INFORMATION

a) Generic name
b) Trade name
c) Indications
d) Dose, route. Frequency and duration of administration
e) Concomitant medication
f) Has the product been approved for use in other countries?
g) If approved, specify countries and conditions of authorisation
h) If so specify major side effects of this product.

4. MOTIVATION FOR THE USE OF UNAUTHORISED MEDICINE

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5. REASON FOR NOT USING A SIMILAR REGISTERED PRODUCT OR CURRENT REGIMEN

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6. PATIENT / GUARDIAN'S INFORMED CONSENT AND PROCEDURE

7. AUTHORISED BY:

8. AUTHORISATION NUMBER:

4.18 COPY OF AUTHORISATION FORM

Medicines Control Council

APPLICATION FOR THE USE OF AN UNREGISTERED MEDICINE IN TERMS OF SECTION 21 OF ACT 101 OF 1965

A. **APPLICANT DETAILS**

1) **Name:**.....

2) **Postal / street address:** ....

.....

3) **Telephone number/Cell phone number** .....

4) **Fax number :** .....

5.) **E-mail address**.....

6) **Qualification :** .....

7) **SAVC (South African Veterinary Council) Registration number** .....

B. **OWNER AND PATIENT DETAILS**

1) **Name of owner:**.....

2) **Physical address**.....

.....

..

3) **Patient data:**

Name of patient / Description of group of animals: .....

.....

i) **species:**.....

ii) **breed:**.....

iii) **sex and age :** .....

4.) **Diagnosis / purpose**.....

.....

.....

5.) **Current treatment :** .....

.....

.....

C. **UNREGISTERED DRUG/PRODUCT INFORMATION**

1) **Generic name :** .....

2) **Trade name :** .....

3) **Quantity required:** .....

4) **Indication:**.....

.....

5) **Dose, route, frequency and duration of administration :**.....

.....

6.) **Concomitant medication:**.....

.....

7.) **Has the product been approved for use in other countries :** .....

8) **If approved specify countries and conditions of authorisation :** .....

.....

9) **Specify major side effects of this product if it is approved for use in any other country:**.....

.....

D. **MOTIVATION FOR THE USE OF UNAUTHORISED MEDICINE:**

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VETERINARY SECTION 21 APPLICATION

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E REASON FOR NOT USING A SIMILAR REGISTERED PRODUCT OR CURRENT REGIMEN:

.....

.....

.....

F. OWNERS CONSENT (YES/NO)

G. PREVIOUS APPROVAL NO. (for repeat of treatment):.....

H. Is a six monthly progress report attached in the event of previous authorisation to use the unregistered product ? YES / NO

If "NO" above , motivate

:.....

.....

.....

.....

.....

.....

Signature of Applicant :..... Date.....

Annexure 1

GUIDELINES FOR SECTION 21 APPLICATIONS FOR VETERINARY MEDICINES

1. Enquiries for the acquisition of unregistered veterinary products may be made by fax, telephone and letter to the Secretariat of the Veterinary Clinical Committee (VCC).

2. Applications must be made on the specific application form for veterinary Section 21 applications as per Attachment 1 (Section 21 application form) and then faxed/ posted to the Secretariat of the VCC.

3. In the case of a Section 21 application for the use of the unregistered veterinary product in a clinical trial the protocol for the clinical trial to be conducted in South Africa must be attached to this application (see guidelines for clinical trials).

4. The Secretariat may request other information from the Applicant concerning the specific application. This application will only be processed further once this information has been forwarded to the Secretariat.

5. The Applicant may contact the Secretariat should the Applicant not receive any decision in respect of the application within five working days of having submitted the application.

6. The Secretariat shall inform the Applicant of the decision by letter and will attach a progress report form as per attachment 2. This progress report is to be completed by the applicant in due course (+/- 6 months). No further approvals will be given to the Applicant for the acquisition of a specific product if any progress reports are outstanding.

7. In the case of an emergency request (i.e. the patient has a life–threatening condition) for an unregistered medicine, the Secretariat may verbally supply the authorisation number to the Applicant. However, the written application for the unregistered medicine must be forwarded to the Secretariat within three days of this verbal authorisation.

7. Approval of Section 21 applications may be subject to the issuing of an import permit for products of animal origin in terms of the Animal Diseases Act 35 of 1984. This will be stated in the letter from the Secretariat to the Applicant.

8. The acquisition of certain products may be subject to other conditions with which the Applicant must comply. These will be stipulated in the authorisation letter.

9. The approval number quoted in the letter to the Applicant shall be derived in the following manner e.g. SP/40/2003 :SP = special permission ; 40 = fortieth application for approval ; 2003 = year of 2003.

11. The Applicant shall then obtain the unregistered medicine through the relevant veterinary supplier or directly from the Registration Holder of the product.

12. The application as well as the letter of approval must be tabled at the next VCC meeting for confirmation by the committee of the approval given as well as for information. The decision taken by the committee must be ratified at the next Council meeting.

CONTACT DETAILS FOR THE VETERINARY CLINICAL COMMITTEE SECRETARIAT:

National Dept. of Health
Sub – Directorate: Veterinary Medicines Unit - Code for Applications **RUM**
Private Bag x 828
Pretoria
0001

Telephone: 012 312 0301
Fax : 012 312 3106

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR PREPARATION OF SITE MASTER FILE

This document has been prepared as a guide to assist applicants to comply with the requirements for Site Master Files with regard to all sites for pharmaceutical business. The MCC is committed to ensure that all sites where medicines are manufactured, stored or tested are of good standard and that all premises where pharmaceutical business is conducted comply with statutory requirements. Applicants must endure that all administrative requirements are adhered to.

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

INDEX

1. INTRODUCTION

The Site Master File is prepared by the manufacturer and contains specific information about the quality assurance, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a
pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc.

When submitted to a regulatory authority, the Site Master File provides information on the manufacturer's operations and procedures that can be useful in the efficient planning and undertaking of a GMP inspection.

These guidance notes have been set out in such a manner that each chapter and the paragraphs noted under "REQUIREMENT" is followed by "GUIDANCE" to provide details of how the requirements should be interpreted.

A Site Master File should be succinct and, as far as possible, not exceed approximately twenty-five to thirty A4 pages.

The Site Master File should have an edition number and an effective date.

Wherever possible, simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans *etc.* should fit on A4 sheets of paper. A deliberate limit has been set on the length of the narrative. If more detailed information is required, then this will be taken up by the Inspector in his/her part of the report.

2. PURPOSE

The aim of these Explanatory Notes is to guide the manufacturer of medicinal products in the preparation of a Site Master File that can be useful to the regulatory authority in planning and conducting GMP inspections.

3. SCOPE

These Explanatory Notes apply to the preparation of the Site Master File. Refer to national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File.

4. SITE MASTER FILE

Refer to Annex for the format to be used.

5. PREPARATION OF SITE MASTER FILE

REQUIREMENT

C.1. GENERAL INFORMATION

C.1.1. Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understand the manufacturing operations.

GUIDANCE

C.1.1. In not more than 250 words (one A4 page) outline the firm's activities, other sites, in addition to the site which is the subject of this report.

REQUIREMENT

C.1.2 . Pharmaceutical manufacturing activities as licensed or approved by the Competent Authorities.

GUIDANCE

C.1.2.Quote the relevant document as issued by the Competent Authority. State period of validity of licence document (if the validity of the document is given in the country concerned). Any conditions and/or restrictions should be stated.

REQUIREMENT

C.1.3. Any other manufacturing activities carried out on the site.

GUIDANCE

C.1.3. This covers both pharmaceutical and non-pharmaceutical activities. NB: See para C.1.6

REQUIREMENT

C.1.4. Name and exact address of the site, including telephone, fax and 24 hrs telephone numbers.

GUIDANCE

C.1.4. Name and Address of Site
C.1.4.1. Name of Company (and trading style if different). Postal Address including. Code (street address if different).
C.1.4.2. Telephone No. of contact person.

C.1.4.3. Fax No. of contact person.
C.1.4.4. hour contact Telephone No.

REQUIREMENT

C.1.5. Type of actual products manufactured on the site (see list at Appendix), and information about specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).

GUIDANCE

C.1.5. Type of Actual Products Manufactured

C.1.5.1. Quote the type of actual products as described at Appendix.
C.1.5.2. Note any toxic or hazardous substances handled e.g. antibiotics, hormones, cytostatics. Note whether the products are manufactured in a dedicated facility or on a campaign basis.
C.1.5.3. Mention if human and veterinary products are both prepared on the site.

REQUIREMENT

C.1.6. Short description of the site (size. location and immediate environment and other manufacturing activities on the site).

GUIDANCE

C.1.6. A Short Description of the Site (not more than 250 words/one A4 page)

C.1.6.1. The location and immediate environment.
C.1.6.2. The size of the site, types of buildings and their ages.
C.1.6.3. Other manufacturing activities on the site.

REQUIREMENT

C.1.7. Number of employees engaged in the quality assurance, production, quality control, storage and distribution.

GUIDANCE

C.1.7. (Note: Include employees working only part-time on full-time equivalent basis. Give the rate of the academic and non-academic persons.)

C.1.7.1. Quality Assurance
C.1.7.2. Production
C.1.7.3. Quality Control
C.1.7.4. Storage and distribution

C.1.7.5. Technical & Engineering Support Services
C.1.7.6. Total of the above

REQUIREMENT

C.1.8. Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.

GUIDANCE
C.1.8. For each outside contractor give:
C.1.8.1. Name and address of the company.
C.1.8.. Telephone No.
C.1.8.3. Fax No.
C.1.8.4. Brief outline of the activity being undertaken in not more than 100 words (half an A4 page).

REQUIREMENT

C.1.9. Short description of the quality management system of the firm responsible for manufacture.

GUIDANCE

C.1.9. (Not more than 750 words or three A4 pages)

C.1.9.1. State the firm's Quality Policy.
C.1.9.2. Define the responsibility of the Quality Assurance function.
C.1.9.3. Describe the elements of the QA system e.g. organisational structure, responsibilities, procedures, processes;
C.1.9.4.Describe the audit programmes (self inspection or audits by external organisations undertaken).
C.1.9.5. Describe how the results are reviewed to demonstrate the adequacy of the quality system in relation to the objective i.e. quality efficacy and safety of the product. See also paragraph 6.1.2
C.1.9.6. Record if standards such as ISO 9001-9004 are used by the company to assess its suppliers.
C.1.9.7. When suppliers of critical starting materials and packing materials - actives, excipients, containers and closures and printed materials are assessed, give details of how this is done.
C.1.9.8. Describe the release for sale procedure for finished products.

SITE MASTER FILE

REQUIREMENT

C.2. PERSONNEL

C.2.1. Organisation chart showing the arrangements for quality assurance, including production and quality control. (see also C.1.9.3)
C.2.2. Qualifications, experience and responsibilities of key personnel.
C.2.3. Outline of arrangements for basic and in-service training and how records are maintained.
C.2.4. Health requirements for personnel engaged in production.
C.2.5. Personnel hygiene requirements, including clothing.

GUIDANCE

C.2. PERSONNEL (500 words/two A4 pages)

C.2.1. Organisation chart

C.2.1.1. Organogram for quality assurance including production and quality control. Record senior managers and supervisors only.

C.2.2. Qualifications, Experience and Responsibilities of Key Personnel.

C.2.2.1. Brief details of academic qualifications and work related qualifications and years relevant experience since qualifying.

C.2.3. Outline of Arrangements for Basic and In-service Training and how Records are maintained

Give brief details of the training programme and include induction and continuous training, as follows:

C.2.3.1. Describe how training needs are identified and by whom.
C.2.3.2. Give details of training relative to GMP requirements.
C.2.3.3. State the form of training e.g. in-house, external, and how practical experience is gained and which staff are involved.
C.2.3.4. Explain how the efficacy of the training is assessed e.g. by questionnaires.
C.2.3.5. Explain how retraining needs are identified.
C.2.3.6. Give brief details of records kept.

C.2.4. Health Requirements for Personnel Engaged in Production

C.2.4.1. Who is responsible for checking health of employees?
C.2.4.2. Is there a pre-employment medical examination?

SITE MASTER FILE

C.2.4.3. Are employees routinely checked from time to time depending on nature of their work?
C.2.4.4. Is there a system for reporting sickness or contact with sick people before working in a critical area?
C.2.4.5. Is there a system of reporting back after illness?
C.2.4.6. Are those who work in clean areas (grade A-D) subject to additional monitoring?

C.2.5. Personnel Hygiene Requirements Including Clothing

C.2.5.1. Are there suitable washing, changing and rest areas?
C.2.5.2. Is the clothing suitable for the activity undertaken? Briefly describe the clothing.
C.2.5.3. Are there clear instructions on how protective clothing should be used and when it should be changed? Detailed procedures are not needed. Is in house or external laundry used?

REQUIREMENT

C.3. PREMISES AND EQUIPMENT

Premises

C.3.1. Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required).

C.3.2. Nature of construction and finishes.

C.3.3. Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for manufacture of sterile products should be mentioned.

C.3.4. Special areas for the handling of highly toxic, hazardous and sensitising materials.

C.3.5. Brief description of water systems (schematic drawings of the systems are desirable) including sanitation

C.3.6. Maintenance(description of planned preventive maintenance programmes and recording system).

Equipment

C.3.7. Brief description of major production and control laboratories equipment (a list of equipment is not required).

C.3.8. Maintenance (description of planned preventative maintenance programmes and recording system).

SITE MASTER FILE

C.3.9. Qualification and calibration, including recording system. Arrangements for computerized systems validation.

Sanitation

C.3.10. Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

GUIDANCE

C.3. PREMISES AND EQUIPMENT

C.3.1.Premises
C.3.1.1. Provide a site plan highlighting production areas.

C.3.1.2. Provide a simple plan of each production area with indication of scale. Label areas and annotate plan with names.

C.3.1..3. Plans should be legible and on A4 sheets of paper. Plans could be on A3 sheets of paper if considered necessary.

C.3.1.4. For sterile product areas indicate room and area classification and pressure differentials between adjoining areas of different classifications.

C.3.2. Nature of Construction and Finishes (500 words/two A4 pages)

C.3.2.1. To reduce narrative for a large complex plant, the details should be limited to critical areas.

C.3.2.2. These areas must include all processing and packaging and critical storage areas.

C.3.2.3. A narrative format is preferred.

C.3.3. Brief Description of Ventilation Systems etc. (500 words/two A4 pages)

Note 1: More details should be given for critical areas with potential risks of airborne contamination. This will include sterile product areas as well as areas for processing powders, granulation and tabletting. For sterile product areas a summary of the results of the most recent qualification/requalification should be given.

Note 2: To reduce the narrative, schematic drawings should be used.
The following data should be given: -

C.3.3.1. Design criteria e.g.
- Specification of the air supply

- Pressure differentials and air change rate
- Simple pass or recirculation (%)
-Temperature
- Humidity

C.3.3.2. Filter design and efficiency e.g.
- Bag 99% eff.
- Hepa 99.997% eff.
Details of any alarms on the ventilation system should be given.

C.3.3.3. The limits for changing the filters should be given.
C.3.3.4. If DOP (dioctyl-phthalate) is introduced, the point must be shown.
C.3.3.5. Give the frequency of revalidation of the system.

C.3.4. Special Areas for the Handling of Highly Toxic Hazardous and Sensitising Materials
C.3.4.1. Follow the same layout as 3.1 above.

C.3.5. Brief Description of Water Systems, including sanitation (500 words / two A4 pages)

Schematic drawings of the systems are preferred. The following information must appear:

C.3.5.1. The schematic must go back to the city supply system.
C.3.5.2. The capacity of the system (maximum quantity produced per hour).
C.3.5.3. Construction materials of the vessels and pipework.
C.3.5.4. Specification of any filters in the system must be given.
C.3.5.5. If water is stored and circulated, what is the temperature at the point of return.
C.3.5.6. The specification of the water produced
a) chemical
b) conductivity
c) microbiological
The sampling points and frequency testing.
The procedure and frequency for sanitation.

C.3.6.Maintenance (250 words/one A4 page)

Note: For the purpose of this guide "Maintenance" is carried out by the manufacturer and "servicing" by an outside contractor.

C.3.6.1. Describe the planned preventative maintenance programme.
C.3.6.2. Are there written procedures and suitable reporting forms for maintenance and servicing? Do the documents record type frequency of services/checks, details of service, repairs and modifications?
C.3.6.3. Are the maintenance routines that could affect product quality clearly identified?
C.3.6.4. Are the reports made known to the users?

Equipment (250 words/one A4 page)

C.3.7. Brief Description of Major Production and Control Laboratory Equipment

Note: Makes and model numbers equipment are not required. However the following points should be addressed:

C.3.7.1. Is the equipment designed with ease of cleaning in mind?

C.3.7.2. Only a general description is required e.g. a rotary tablet press etc. If the equipment has additional devices, these should be recorded e.g. automatic weighing machines with printer; a labeller incorporating a bar code reader for the label; a lot number and expiry date over printer; a freeze drier equipped with a steam sterilisation facility.
C.3.7.3. In the quality control laboratory only general descriptions such as pH meters, chromatographic equipment GLC (gas-liquid chromatography), HPLC (high performance liquid chromatography) with computer systems, particle size analysers.
C.3.7.4. Is the machinery constructed of appropriate material (e.g. AISI grade 316 stainless steel for product contact equipment?)*
C.3.7.5. Have other materials been suitably validated e.g. polypropylene, chrome-plated brass, PVC (poly vinyl chloride), non-reactive plastic materials?
C.3.7.6. In microbiology use general descriptions such as incubators (temperature ranges) facilities for LAL (limulus amebocyte lysate) testing, membrane filtration sterility testing, antibiotic assay, etc.
C.3.7.7. In particular give brief information on the use of computers, microprocesors etc. in the factory.

C.3.8. Maintenance (250 words/one A4 page)

C.3.8.1. Who is responsible for maintenance and servicing?
C.3.8.2. Are there written procedures and contractual details for outside work?
C.3.8.3. Are maintenance routines which could affect product quality clearly identified?
C.3.8.4. Are records kept of:
1 .type and frequency of service/check;
2. details of service repairs and modifications?

C.3.8.5. Are reports made known to the users?

C.3.9. Qualification, validation and Calibration (750 words/three A4 pages)

C.3.9.1. Briefly describe the Company's general policy and protocols for qualification and validation (prospective and retrospective).
C.3.9.2. Is there regular revalidation of critical equipment?
C.3.9.3. Describe equipment calibration policy and records kept. (
C.3.9.4. An outline of process validation may be given here or cross-referenced to production para 5.4
C.3.9.5. What are the arrangements for computer validation, including software validation?

C.3.9.6. Describe the system for the release for sale or supply of development and validation batches.

C.3.10. Sanitation
Cleaning procedures for manufacturing areas and equipment (250 words/one A4 page)

C.3.10.1. Are there written specifications and procedures for cleaning, cleaning agents and their concentration for the method of cleaning and the frequency?
C.3.10.2. Are cleaning agents changed from time to time?
C.3.10.3. Have the cleaning procedures been validated and what was the method of evaluating the effectiveness of cleaning?
C.3.10.4. Are cleaning methods monitored routinely by chemical and/or microbiological methods?
C.3.10.5. What are the cleaning methods (and their frequency) for the water supply system, air handling system and dust extraction system?

REQUIREMENT
C.4. DOCUMENTATION

C.4.1. Arrangements for the preparation, revision and distribution of necessary documentation for manufacture.

C.4.2. Any other documentation related to product quality which is not mentioned elsewhere (e.g. microbiological controls on air and water).

GUIDANCE

C.4. DOCUMENTATION (500 words/two A-4 pages)

Note: This section refers to all documentation used in manufacture. Manufacture involves all activities relating to the production and control of pharmaceutical products.

C.4.1. Arrangements for the Preparation and Revision and Distribution of Documentation

C.4.1.1. Is there a description of the documentation system?
C.4.1.2. Who is responsible for the preparation revision and distribution of documents?
C.4.1.3. Where are the master documents stored?
C.4.1.4. Is there a standard format and instruction of how documents are to be prepared?
Are there documents for:
1. Product/process specification
2. Raw material specifications
3. Packaging component specifications
4. Standard process instructions including packaging
5. Batch records including packaging
1. Product/Process Specifications

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6. Analytical methods
7. QA release procedures.

C.4.1.5. How is the documentation controlled?
C.4.1.6. For how long are documents kept after release of the batch?
C.4.1.7. Detail any arrangements for electronic or microfilmed records.

C.4.2. Other Documentation related to Product Quality

Are the following documents available and in use?
C.4.2.1. Specifications for disposables i.e. cleaning materials.
C.4.2.2. Standard operating procedures.
C.4.2.3. Equipment specifications.
C.4.2.4. Quality Control Procedures.
C.4.2.5. Training procedures.
C.4.2.6. Computer program specifications.
C.4.2.7. Documentation control of process deviations.
C.4.2.8. Calibration and test documents (see para 3.9.5)
C.4.2.9. Validation documents (see paras 3.9 and 5.4)
C.4.2.10. Reconciliation of batches of raw materials, major packing components i.e. product-contact and printed materials.
C.4.2.11. List and briefly explain the use of any additional standard documentation used routinely.

REQUIREMENT

C.5. PRODUCTION

C.5.1. Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters (see at Appendix the list of products manufactured).

C.5.2. Arrangements for the handling of starting materials. packaging materials, bulk and finished products, including sampling quarantine, release and storage.

C.5.3. Arrangements for reprocessing or rework.

C.5.4. Arrangements for the handling of rejected materials and products.

C.5.5. Brief description of general policy for process validation.

GUIDANCE .

C.5.PRODUCTION

This narrative should be kept to a minimum and generalized schematic layouts used where possible. The following points should be addressed:

C.5.1. Describe the operations capable of being carried out at the site with the existing facilities and specify the types of pharmaceutical products. (See para 1.5.1 and the Appendix for types of products manufactured).

When packaging only is undertaken, give a brief description only, e.g. labelling, filling etc, and the nature of containers used e.g. sachets, tamper evident glass containers.

If cytotoxic or radio-active substances are handled give details of the products.
Describe the production operations using flow charts if possible. Technical details are not required.

Describe how products are identified during production and how in-process storage is organized.

C.5.2. Arrangements for handling Starting Materials, Packing Materials, Bulk and Finished Products including Sampling Quarantine Release and Storage

Identification of suppliers lot number with the company's lot number. Status labelling e.g. by using labels or by computer. Issue of materials to manufacture and package. The control of weighing.

Sampling plans.

How are materials being used for manufacture identified and released?
Checking methods

C.5.2.1. Control of Bulk Manufacture

Checks on key parameters during manufacture e.g. blend times, filter integrity tests. Records of key parameters.
Records of in-process checks.
Compliance with the Marketing Authorisation.
In-process checks.

C.2.2. Packing

Release of bulk, semi-finished products, packing materials;
Confirmation of identity and line clearance checks;
In-process checks.

C.5.2.3. Quarantine and release of finished products; compliance with the Marketing Authorisation.

C.5.2.4. Explain the role of the Authorized Person(s).

C.5.3. Arrangements for Reprocessing or Rework

C.5.3.1. What arrangements are in place for reprocessing or reworking batches of products?

C.5.4. Arrangements for Handling Reject Materials and Products

C.5.4.1. Are reject materials and products clearly labelled? Are they stored separately in restricted areas?
C.5.4.2. Describe arrangements for sentencing the materials and disposal. Is destruction recorded?

C.5.5. Brief Description of the General Policy for Process Validation

An outline of process validation protocol only is required. (See para 3.9.3)

REQUIREMENT

C.6. QUALITY CONTROL

C.6.1. Description of the Quality Control system and of the activities of the Quality Control Department Procedures for the release of finished products.

GUIDANCE

C.6. QUALITY CONTROL
C.6.1. Activities of the Quality Control Department

C.6.1.1. (a) Describe the elements of the QC system e.g. specifications, test methods, and other quality related data collection.
(b) Briefly describe the activities of analytical testing, packaging, component testing, biological and microbiological testing.

C.6.1.2. If the review of batch documentation and release of final documentation takes place in this department, give details. (See also para 1.9.5)
C.6.1.3. Outline the involvement in the arrangements for the preparation, revision and distribution of documents in particular those for specification test methods and release criteria if not mentioned elsewhere. (See also para 1.9 and , Documentation)

REQUIREMENT

C.7. CONTRACT MANUFACTURE AND ANALYSIS

C.7.1. Description of the way in which the GMP compliance of the contract acceptor is assessed.

GUIDANCE

C.7. CONTRACT MANUFACTURE AND ANALYSIS
C.7.1. Describe briefly the details of the technical contract between the contract giver and acceptor and the way in which the GMP compliance is assessed to ensure product compliance with the Marketing Authorization.

REQUIREMENT

C.8. DISTRIBUTION, COMPLAINTS AND PRODUCT RECALL

C.8.1. Arrangements and recording system for distribution.

C.8.2. Arrangements for the handling of complaints and product recalls.

GUIDANCE

C.8. DISTRIBUTION
C.8.1. A Description of Storage and Distribution Practices

C.8.1.1. Is the warehouse secure?
C.8.1.2. Is it environmentally controlled?
C.8.1.3. Is there refrigerated storage?
C.8.1.4. How are the materials stored e.g. pallet racking?
C.8.1.5. How is the status of products controlled e.g. by computer, by label?
C.8.1.6. What are the methods of distribution to customers?
C.8.1.7. Does the despatch order ensure first in/first out and identify the lot number?

C.8.2. Records of Distribution
Do the retained records permit full batch traceability from the factory to the customer, in terms of the date of sale, customer details and quantity despatched?

Complaints

C.8.2.1.1. Is there a written complaints procedure?
C.8.2.1.2. Who is responsible for:
1. Logging;
2. Classifying;

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3. Investigating complaints.

C.8.2.1.3. Are written reports prepared?
C.8.2.1.4. Who reviews these reports?
C.8.2.1.5. For how long are complaints records kept?

C.8.2.2. Product Recalls

C.8.2.2.1. Is there a written procedure which describes the sequence of actions to be followed including:
1. Retrieval of distribution data;
2. Notification of customers;
3. Receipt/segregation/inspection of returned product;
4. Investigation/reporting of cause;
5. Reporting corrective action.

C.8.2.2. Who is responsible for coordinating product recalls?
C.8.2.3. Who notifies the Competent Authority of complaints and recalls.
C.8.2.4. Is the Competent Authority involved in complaints and the decision to recall?
C.8.2.5. Can recalls be effected below wholesale level?

REQUIREMENT

C.9. SELF INSPECTION

C.9.1. Short description of the self inspection system See also para 1.9.4.).

GUIDANCE

C.9.1.1. Describe how the self inspection system verifies that those activities that have a bearing on quality comply with the planned arrangement.
C.9.1.2. Are the quality systems effective?
C.9.1.3. Are there documented procedures for the self inspection system and for the follow-up actions?
C.9.1.4. Are the results of the self inspection system documented, brought to the attention of the personnel having responsibility for the area and activities inspected?
C.9.1.5. Does the system ensure that those responsible for the area or activity take timely corrective action on the deficiencies found?

6. APPENDIX

TYPE OF PRODUCTS MANUFACTURED (referred to in paragraph C.1.5)

A. Sterile products

A.1 Liquid dosage forms (large volume solutions, including LVP and rinsing solutions)

A.1.1 Aseptically prepared

A.1.2 Terminally sterilized A.2

A.2. Liquid dosage forms (small volume solutions, including SVP and eye drops)

A.2.1 Aseptically prepared

A.2.2 Terminally sterilized

A.3 Semi-solid dosage forms

A4 Solid dosage form

A.4.1 Solid fill

A.4.2 Freeze-dried

B. Non-sterile products

B.1 Liquid dosage forms
B.2. Semi-solid dosage forms
B.3. Solid dosage forms
B.4. Unit dose form (tablet, capsules, suppositories, pessaries)
B.5 Multi dose form (powder, granules)

C. Biological products

C.1. Vaccines C.
C.2 Sera C.
C.3 Blood products
C.4 Others (describe)

D. Specifically toxic and hazardous substances

D.1 Penicillins
D.2 Cephalosporins
D.3. Hormones

D.4. Cytostatics
D.5. Others (describe)

E. Packaging only

E.1 Liquid dosage forms
E.2 Semi-solid dosage forms
E.2 Solid dosage forms

F. Contract manufacturing (kind of products)

F.1. Firm reported upon is:
F.2. Acceptor .
F.3. Giver

G. Contract analysis

Firm reported upon is:

F.1. Acceptor
F.2. Giver

H. Drugs for clinical trials

I. Others
(e.g. veterinary products, cosmetics, etc)

7. REFERENCES

Circular 34/93
PIC/S guide

8. CONTACT DETAILS

1. Ms J. Gouws
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SITE MASTER FILE

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9. GUIDELINE UPDATE HISTORY

Date	Reason for update	Version
April 2003	New	MCC2003/1

MRF 4

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FORM FOR AMENDMENTS TO APPROVED PACKAGE INSERTS

Version MCC2003/1

MRF 4

APPLICATION FORM FOR AMENDMENT TO A PACKAGE INSERT OF REGISTERED ORTHODOX MEDICINES

DETAILS OF PRODUCT: PROPRIETARY NAME: ..... REGISTRATION NUMBER: .....

INCOMPLETE APPLICATIONS AND APPLICATIONS WHICH DO NOT COMPLY TO THE PRESCRIBED FORMAT WILL RESULT IN THE APPLICATION BEING RETURNED TO THE APPLICANT FOR CORRECTION.

The submission should be presented as follows:

I. three (3) suitably bound copies of the following documents submitted in the order:

(i) covering letter reflecting **ALL** proposed changes and a motivation for the changes;
(ii) Proposed cross – referenced package insert typed in double spacing and in black print only;
(iii) Approved package insert (unmarked);
(iv) Package insert/SPC approved with other regulatory authority, whenever listed as a reference;

2. two (2) copies of supporting data or references suitably bound. A copy of the covering letter should be bound into each set of the supporting data or references.

Note:

(a) **Each copy referred to in 1 and 2 above should be bound separately**
(b) Bound copies should not be bigger than A4 size.
(c) Back – to –back printing is not acceptable.

MRF 4

Tick the appropriate box	Yes (Y)	No (N)
Are all additions in the proposed package insert indicated by underlining with a solid line?	☐	☐
Are all deletions in the proposed package insert indicated by bolded square brackets?	☐	☐
Are all rephrasing in the proposed package insert denoted by a broken line?	☐	☐
Are all proposed amendments in the package insert properly cross referenced to the relevant substantiating data?	☐	☐
Are three (3) unmarked copies of the current approved package insert included?	☐	☐
Are three (3) copies of the proposed package insert included?	☐	☐
Are two (2) bound copies of supporting data / references submitted?	☐	☐
Type of amendment		
1) Does this amendment include a new indication ?	☐	☐
2) Does this amendment include an amendment to a current indication?	☐	☐
3) Does this amendment include a new dosage instruction?	☐	☐
4)Does this amendment include an amendment to a current dosage instruction?	☐	☐
5) Does this submission contain a complete safety update?		
Has the proposed package insert been checked for grammatical and typographical errors?	☐	☐

MRF 4

I declare that the application has been checked and that the information supplied herewith is complete and complies to the prescribed requirements.

.....	.....
Name in block letters	Signature
.....	.....
Designation	Date

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR PARALLEL IMPORTATION OF MEDICINES IN SOUTH AFRICA

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for a permit to parallel-import medicines. It represents the Medicines Control Council's current thinking on access to safe and quality medicines that are cost effective. It is not intended as an exclusive approach. Council reserves the right to request additional information to establish the safety, quality and efficacy of a medicine and to make amendments in keeping with current knowledge at the time of consideration of data accompanying applications for a permit or for amendment of the registration of a parallel imported medicine. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements of the MCC to avoid delays in the processing of applications.

These guidelines should be read in conjunction with Regulation 7 of the Medicines and Related Substances Act No. 101 of 1965, as amended.

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

Version MCC2003/1

TABLE OF CONTENTS

1. INTRODUCTION

Medicines form a critical part of an effective healthcare system. The challenge facing most health departments today is to provide the public access to medicines that are of good quality, safety and efficacy and that are economically affordable. This is in fact one of the key objectives of the South African National Drug Policy which has also assumed special importance in the face of the HIV/AIDS pandemic and other related emerging and opportunistic infections.

2. BACKGROUND

An important component of the transformation process of the healthcare services in South Africa is its expansion to reach even the most remote part of the country to ensure that all people, particularly those previously disadvantaged, have access to good quality healthcare. This key objective is, however, being constrained by the escalating costs of services, facilities and medicines. In an attempt to address the issue, the South African government introduced the Medicines and Related Substance Control Amendment Act in 1997 (Act No. 90 of 1997) as a means to facilitate, among other things, access to affordable medicines by all. This Act allows for the importation and registration of medicines which are under patent, are already registered in South Africa, and which originate from any site of manufacture approved by Council, regardless of any existing patent rights.

3. LEGISLATIVE PROVISIONS

The Minister of Health is empowered by section 15C of the Medicines and Related Substances Control Act of 1965, as amended (Act No. 101 of 1965), to prescribe the conditions on which any patented medicine may be parallel imported into South Africa regardless of the provisions of the Patents Act, 1978 (Act 57 of 1978). A parallel imported medicine must have the same formulation, meet the same quality standards and is intended to have the same proprietary name as the medicine already available and registered in South Africa. In addition, any person or company, other than the person or company that is the holder of the registration certificate of that medicine, may import such a medicine. It may also be obtained from any manufacturing site used by the original manufacturer and which is approved by Council in accordance with the current technical requirements.

Thus, to procure a cost-effective or less expensive medicine than the one already registered and available in the Republic, the Minister may authorise, through a permit, the importation of the same medicine manufactured by, or on behalf of, the approved manufacturer from any other country and the restrictions imposed by the Patent Act shall not apply.

Parallel importation is defines in the Regulations as

"the importation into the Republic of a medicine protected under patent and/or registered in the Republic that has been put onto the market outside the Republic by or with the consent of the patentee in respect of such medicine"

The expressions "*parallel importer*", "*parallel imported medicine(s)*", "*parallel imported*", "*to parallel import*", "*to be parallel imported*" and "*parallel importation permit*" shall have the corresponding meanings to 'parallel importation'.

4. CONDITIONS FOR PARALLEL IMPORTATION OF A MEDICINE

4.1 Any patented medicine may be imported in terms of Section 15C and Regulation 7 of the Act if it is already registered in South Africa.

4.2 A person or company that wishes to import a patented medicine must apply to the Minister of Health for a permit to parallel import a medicine.

4.3 The holder of a certificate of registration for a medicine in South Africa shall not be entitled to prevent its importation into South Africa, nor its sale, on account of such registration or on account of the existence of a patent on such a medicine.

4.4 The parallel importer shall be responsible and liable for the parallel imported medicines, for example, in the event of a recall or adverse event, and must notify the Council of these situations.

4.5 The parallel importer shall be liable for destruction of any expired, parallel imported medicines still remaining on stock after the expiry date, whether during the duration of the permit or after the parallel importation permit has expired.

5. PROCEDURE FOR OBTAINING A PERMIT TO PARALLEL IMPORT MEDICINES

5.1 The application for a permit to parallel import a medicine must be submitted to the office of the Minister of Health. The application must be accompanied by the following:

i) Written confirmation of the lowest price at which the medicine is currently sold by the holder of the certificate of registration in South Africa dated not more than one month before the date of submission of the application for a parallel import permit;

ii) The price at which the parallel imported medicine will be sold in South Africa by the importer;

iii) A declaration by the importer that the medicine to be imported is a medicine under patent in South Africa;

iv) The prescribed application fee;

v) A certified copy of his or her identity document, or in the case of a juristic person, a certificate of registration as such in the Republic;

vi) A certified copy of his, her or its registration in terms of the Pharmacy Act, 1974, where applicable;

vii) A certified copy of the licence in respect of the premises in terms of: -

a) Section 19 of the Customs and Excise Act, 1964 (Act No. 91 of 1964); and

b) Section 22 of the Pharmacy Act, 1974;

viii) An undertaking that he, she or it will ensure the continued safety, efficacy and quality of the medicine; and

ix) Any other information the Minister may require.

5.2 The Minister may, upon consideration, approve with or without conditions, or reject, such an application.

5.3 If a permit is issued, it shall be valid for a period of 24 months.

5.4 The permit holder must, at least three months before the expiry date, apply to the Minister for its renewal in accordance with the procedure prescribed by the Minister.

5.5 The Minister may, at any time and on good cause shown, cancel the permit to import any medicine.

6. PROCEDURE FOR OBTAINING REGISTRATION OF A MEDICINE THAT IS TO BE PARALLEL IMPORTED

6.1 After being issued with a permit to import a medicine, the importer must apply to Council for: -

i) Authorisation to import a sample of the medicine to be submitted together with the application for registration of the medicine; and

ii) Registration of the medicine, using Form MRF 1 (provided by the Registrar of Medicines).

6.2 An application for the registration of a parallel-imported medicine must be accompanied by the following:

i) Copies of the package insert and patient information leaflet, where available, which must be translated into English and verified;

ii) An appropriately labelled sample of the medicine in accordance with the requirements of Regulation 8 or Regulation 48;

iii) Information on the exporter, stating whether it is a manufacturer, packer, re-packer, wholesaler or broker;

iv) A cGMP Certificate from a recognised authority, which must be specific for the manufacturer, packer, re-packer, laboratory, distributor, wholesaler or broker of the imported medicine;

v) Real-time stability data for the duration of shelf-life using a stability-indicating method for the active pharmaceutical ingredient, according to the requirements of the Guideline for Stability Studies - Addendum 4;

vi) Comparative dissolution data against the MCC-approved product (same formulation, same name, same dosage form, etc.) that has been procured in South Africa, in terms of the requirements for proof of efficacy (Also Refer to the Guidelines on Dissolution Testing) and using f_2 values.

6.3 The following is the minimum information required for the registration of a parallel imported medicine:

i) Administrative Data (section A and B).

ii) Parts 1A, 1B and 1C.

iii) Part 2B.

iv) Part 2D for repackaged medicines and if the packaging material is different from that used by the patent holder.

v) Part 2E (b) (i) and (c); for repackaged medicines only.

vi) Part 2F (a), (b), (d) and (e).

vii) Part 2G for repackaged medicines only.

6.4 Council will only consider approval of registration of the medicine if the importer has: -

i) been issued with a permit to parallel import the medicine;

ii) a registered office in South Africa;

iii) a storage facility approved by Council for such medicine;

iv) a responsible pharmacist as required in terms of the Pharmacy Act, 1974 (Act No. 54 of 1974);

v) undertaken to be responsible for ensuring that such medicine meets the safety, quality and efficacy standards as determined by Council and accepts liability for any consequences arising from the distribution and use of the medicine;

vi) in place recall procedures as determined by Council,

vii) complied with any other conditions as Council may determine; and

viii) an MCC-approved manufacturing site in the case where the imported medicine is to be repackaged.

6.5 The parallel importer may proceed with the sale of the medicine only after the medicine has been registered.

7. REGISTRATION OF MEDICINES TO BE PARALLEL IMPORTED

7.1 The evaluation and registration of medicines intended for importation will follow the same procedure as provided for in Section 15 of the Act and as prescribed in the regulations, except as specified under item 6.3 above.

7.2 Council may impose any conditions necessary for the registration of the medicine.

7.3 The Registrar shall keep a separate register for parallel imported medicines.

8. CANCELLATION OF REGISTRATION OF PARALLEL IMPORTED MEDICINES

Council may, on good cause shown and in consultation with the Minister, cancel the registration of any parallel imported medicine.

9. INFORMATION TO BE PROVIDED TO THE PATENT HOLDER OR HOLDER OR THE CERTIFICATE OF REGISTRATION

The importer must, within 30 days after registration of the medicine, inform the patent holder or the holder of the certificate of registration in South Africa, of this fact and submit a copy of the letter to the Registrar.

10. IMPORTATION OF MEDICINES

10.1 The parallel importer must inform the holder of the certificate of registration at least four weeks prior to importation, on a form determined by Council, of his or her intention to parallel-import the medicine. The requirements for post-importation identification and testing of medicines, as described in Addendum 2 of the *Guidelines for the Registration of Medicines in South Africa*, will apply.

10.2 The parallel importer may not manufacture or re-export any medicine registered in South Africa as a parallel imported medicine.

11. REPACKAGING AND RELABELING OF PARALLEL-IMPORTED MEDICINES

11.1 Where the medicine is to be repackaged in South Africa after importation, this must be done at a site approved and licensed by the Council for this purpose.

11.2 The medicine must be labelled, packaged and have a package insert and patient information leaflet as prescribed in terms of regulations 8, 9 and 10.

11.3 The parallel importer may use the proprietary name approved in South Africa as well as any trade marks applicable to the medicine in order to ensure the public health interests.

11.4 The words "Parallel imported medicine" or the abbreviation "PIM" must be included on the label of each distribution pack.

11.5 The batch numbers of repackaged medicines must be identical to those of the original medicines and all original packaging material must be destroyed.

12 INFORMATION TO BE PROVIDED TO THE MEDICINES CONTROL COUNCIL

The following information must be supplied to Council by the parallel importer:

12.1 Any change in the conditions under which the medicine was registered;

12.2 Any adverse drug reactions or events arising from the use of the medicine;

12.3 Any report of risks associated with the medicine that may affect its quality, safety or efficacy.

13. TRANSFER OF CERTIFICATE OF REGISTRATION

A certificate of registration for an imported medicine may only be transferred to another person or company with the approval of the Minister.

14. AMENDMENTS TO THE DETAILS OF A PARALLEL IMPORTED MEDICINE

The importer must apply to Council on form PIF 1, available from the office of the Registrar, for approval of any change in the conditions of registration of an imported medicine or change in the storage conditions or change in any of the particulars of the medicine.

15. FEES PAYABLE

An applicant for the registration of a medicine to be parallel imported shall pay an application fee and a registration fee as determined by Council.

16. FORMS TO BE COMPLETED

The following forms, obtainable from the office of the Registrar, must be completed in respect of an application for amendment to the details of a parallel imported medicine and for informing the patent holder of the intention of the parallel importer to import a medicine, respectively: PIF 1 and PIF 2.

PIF 1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION TO AMENDMENT THE DETAILS OF A PARALLEL IMPORTED MEDICINE

PIF 1

1. Details of the importer

Name:

Business Address:

Postal Address:

Tel:

Fax:

Wholesale Distribution License Number:
(Issued in terms of Regulation 19)

Responsible Pharmacist (To be contacted in case of safety and quality problems of the medicine):

Name:

Address:

Registration number (in terms of Act No. 54 of 1974):

Cell phone number:

Fax:

E-mail:

2. Details of the medicine

Proprietary Name:

INN or Approved name:

Strength:

Pharmaceutical Dosage Form:

Pack size(s):

Registration number:

Date of MCC notice submitted:

3. Scope of the change(s)

☐ Change(s) resulting from amendments to the MCC Decision

☐ Change(s) proposed by the importer not related to the MCC Decision

Provide details of change and Parts of dossier affected:

_____

_____

_____

_____

_____

_____

_____

_____

☐ It is certified that the original condition of the product has not beendirectly or indirectly affected by the proposed change (Submit transport validation data where applicable).

5. Submission of copies of inner and outer labels and package insert

Copies of the amended outer and/or inner package labels and/or package insert of the medicine must be enclosed where applicable together with an electronic version in Microsoft Word (on diskette or by E-mail).

	YES	NO remains unchanged
Copy of the amended outer package label enclosed	☐	☐
Copy of the amended inner package label enclosed	☐	☐
Copy of the amended package insert enclosed	☐	☐

_____ Signature

_____ Name

_____ Designation

_____ Place

_____ Date

Note: Please return the form and its required annexes to:
The Registrar of Medicines
Medicines Control Council
Private Bag X828
Pretoria 0001

PIF 2

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

NOTIFICATION FORM – PARALLEL IMPORTED MEDICENES

Version MCC2003/1

PIF 2

NOTICE OF INTENTION TO PARALLEL IMPORT A MEDICINE UNDER PATENT

DETAILS PARALLEL IMPORTATION PERMIT HOLDER:	**Name:**_____ **Business address:**_____ _____ **Permit Number:**_____
DETAILS OF MEDICINE REGISTERED IN SOUTH AFRICA:	**Proprietary name:** _____ **Registration No.** _____
DETAILS OF MEDICINE TO BE PARALLEL IMPORTED:	**Proprietary name:**_____ **PIM Registration No:**_____ **Country of origin:** _____ **Manufacturer:** _____ **Price of medicine:** **R**_____**per**_____
INTENTION TO PARALLEL IMPORT THE ABOVE MEDICINE	**Approximate date of importation:** _____
DETAILS OF PATENT HOLDER:	**Name:** _____ **Business address:** _____ _____
SIGNATURE OF PERMIT HOLDER:	
DATE:	
A copy of the completed form must be sent to the Medicines Control Council	

Version MCC2003/1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON GENERIC SUBSTITUTION

This document has been prepared to serve as a recommendation to authorised health practitioners involved in the dispensing and administration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. The MCC is committed to ensure that all medicines in use will be of the required quality, safety and efficacy. It is important for all who deal with medicines to adhere to the administrative and technical requirements to avoid unwanted or adverse events that may compromise the health of the population. This guideline must be read in conjunction with the definition of "interchangeable multi source medicine" in the Act and Regulation 2 of the Medicines and Related Substances Act No. 101 of 1965, as amended.

This guideline will be updated on a regular basis as new information becomes available.

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

GUIDELINE ON NON-SUBSTITUTABLE MEDICINES

1. **This guideline replaces Circular 16 of 1994. LIST OF NON-SUBSTITUTABLE MEDICINES. This list will be updated as new information on generic substitution becomes available. The absence of substance from this list must not be construed to mean that such a substance will be substitutable. The attention of all health practitioners who dispense or administer medicines is drawn to this list to assist in taking decisions where one or more alternatives are available.**

2. **The interchangeable use of different brands of chemically equivalent medications (i.e. those which contain the same active ingredients, the same quantities thereof, in the same pharmaceutical dosage form, or as more commonly named, "generics") could under certain circumstances compromise therapeutic response and safety of the patient.**

3. **The Medicines Control Council, having studied the matter in depth on both a local and international level, recommends that substitution should not occur when prescribing and dispensing "generic" medicines which:**

   i) have a narrow therapeutic range;
   ii) have been known to show erratic intra- and interpatient responses;
   iii) are contained in dosage forms that are likely to give rise to clinically significant bio-availability problems, e.g. extended or delayed release preparations, as well as those known to be super bioavailable*;
   iv) are intended for the critically ill and/or geriatric and paediatric patient.

4. **In terms of the afore-mentioned factors, the following list of medicines have on occasion, been known to present bio-equivalence problems and should ideally not be interchanged with other "generics" unless adequate provision is made for monitoring the patient during the transition period.**

Alendronate tablets or capsules
Atenolol tablets or capsules
Carbamazepine tablets or capsules
Chlorpromazine tablets or capsules
Dexamethasone tablets or capsules
Diethylstilboestrol tablets or capsules
Digoxin tablets or capsules
Disulfiram tablets or capsules
Ethinyl Oestradiol tablets or capsules
Fluoxymesterone tablets or capsules
Furosemide tablets or capsules
Glibenclamide tablets or capsules
Hydralazine, Hydrochlorothiazide and Reserpine combination tablets or capsules
Hydralazine and Hydrochlorothiazide combination tablets or capsules

Hydrocortisone tablets or capsules
Hydrocortisone Acetate injection
Isoproterenol Metered Dose inhaler
Isoethrane Metered Dose inhaler
Isosorbide Dinitrate sustained release tablets and capsules
Itraconazole tablets or capsules
Levodopa tablets and capsules
Nifedipine: all extended/delayed release formulations
Oestrogens, Conjugated tablets or capsules
Oestrogens, Esterified tablets or capsules
Penicillin G Benzathine injection
Phenytoin tablets and capsules
Phytomenadione injection
Prazosin Hydrochloride tablets 5mg*
Prednisolone tablets or capsules
Prednisolone Acetate injection
Prednisolone Tebutate injection
Prednisone tablets or capsules
Promethazine tablets
Propylthiouracil tablets
Reserpine tablets
Reserpine and Chlorothiazide combination tablets
Reserpine and Trichloromethiazide combination tablets
Tamoxifen tablets or capsules
Theophylline controlled release tablets or capsules
Triamcinolone tablets or capsules
Trichloromethiazide tablets or capsules
Warfarin Sodium tablets or capsules

The list is subject to periodic review and alteration at the discretion and recommendation of the Medicines Control Council.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR PREPARATION OF SITE MASTER FILE

This document has been prepared as a guide to assist applicants to comply with the requirements for Site Master Files with regard to all sites for pharmaceutical business. The MCC is committed to ensure that all sites where medicines are manufactured, stored or tested are of an acceptable standard and that all premises where pharmaceutical business is conducted comply with statutory requirements. Applicants must endure that all administrative requirements are adhered to.

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

INDEX

1. INTRODUCTION

The Site Master File is prepared by the manufacturer and contains specific information about the quality assurance, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a
pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc.

When submitted to a regulatory authority, the Site Master File provides information on the manufacturer's operations and procedures that can be useful in the efficient planning and undertaking of a GMP inspection.

These guidance notes have been set out in such a manner that each chapter and the paragraphs noted under "REQUIREMENT" is followed by "GUIDANCE" to provide details of how the requirements should be interpreted.

A Site Master File should be succinct and, as far as possible, not exceed approximately twenty-five to thirty A4 pages.

The Site Master File should have an edition number and an effective date.

Wherever possible, simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans *etc.* should fit on A4 sheets of paper. A deliberate limit has been set on the length of the narrative. If more detailed information is required, then this will be taken up by the Inspector in his/her part of the report.

2. PURPOSE

The aim of these Explanatory Notes is to guide the manufacturer of medicinal products in the preparation of a Site Master File that can be useful to the regulatory authority in planning and conducting GMP inspections.

3. SCOPE

These Explanatory Notes apply to the preparation of the Site Master File. Refer to national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File.

4. SITE MASTER FILE

Refer to Annex for the format to be used.

5. PREPARATION OF SITE MASTER FILE

REQUIREMENT

C.1. GENERAL INFORMATION

C.1.1. Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understand the manufacturing operations.

GUIDANCE

C.1.1. In not more than 250 words (one A4 page) outline the firm's activities, other sites, in addition to the site which is the subject of this report.

REQUIREMENT

C.1.2 . Pharmaceutical manufacturing activities as licensed or approved by the Competent Authorities.

GUIDANCE

C.1.2.Quote the relevant document as issued by the Competent Authority. State period of validity of licence document (if the validity of the document is given in the country concerned). Any conditions and/or restrictions should be stated.

REQUIREMENT

C.1.3. Any other manufacturing activities carried out on the site.

GUIDANCE

C.1.3. This covers both pharmaceutical and non-pharmaceutical activities. NB: See para C.1.6

REQUIREMENT

C.1.4. Name and exact address of the site, including telephone, fax and 24 hrs telephone numbers.

GUIDANCE

C.1.4. Name and Address of Site
C.1.4.1. Name of Company (and trading style if different). Postal Address including. Code (street address if different).
C.1.4.2. Telephone No. of contact person.
C.1.4.3. Fax No. of contact person.

C.1.4.4. hour contact Telephone No.

REQUIREMENT

C.1.5. Type of actual products manufactured on the site (see list at Appendix), and information about specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).

GUIDANCE

C.1.5. Type of Actual Products Manufactured

C.1.5.1. Quote the type of actual products as described at Appendix.
C.1.5.2. Note any toxic or hazardous substances handled e.g. antibiotics, hormones, cytostatics. Note whether the products are manufactured in a dedicated facility or on a campaign basis.
C.1.5.3. Mention if human and veterinary products are both prepared on the site.

REQUIREMENT

C.1.6. Short description of the site (size. location and immediate environment and other manufacturing activities on the site).

GUIDANCE

C.1.6. A Short Description of the Site (not more than 250 words/one A4 page)

C.1.6.1. The location and immediate environment.
C.1.6.2. The size of the site, types of buildings and their ages.
C.1.6.3. Other manufacturing activities on the site.

REQUIREMENT

C.1.7. Number of employees engaged in the quality assurance, production, quality control, storage and distribution.

GUIDANCE

C.1.7. (Note: Include employees working only part-time on full-time equivalent basis. Give the rate of the academic and non-academic persons.)

C.1.7.1. Quality Assurance
C.1.7.2. Production
C.1.7.3. Quality Control
C.1.7.4. Storage and distribution
C.1.7.5. Technical & Engineering Support Services
C.1.7.6. Total of the above

REQUIREMENT

C.1.8. Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.

GUIDANCE
C.1.8. For each outside contractor give:
C.1.8.1. Name and address of the company.
C.1.8.. Telephone No.
C.1.8.3. Fax No.
C.1.8.4. Brief outline of the activity being undertaken in not more than 100 words (half an A4 page).

REQUIREMENT

C.1.9. Short description of the quality management system of the firm responsible for manufacture.

GUIDANCE

C.1.9. (Not more than 750 words or three A4 pages)

C.1.9.1. State the firm's Quality Policy.
C.1.9.2. Define the responsibility of the Quality Assurance function.
C.1.9.3. Describe the elements of the QA system e.g. organisational structure, responsibilities, procedures, processes;
C.1.9.4.Describe the audit programmes (self inspection or audits by external organisations undertaken).
C.1.9.5. Describe how the results are reviewed to demonstrate the adequacy of the quality system in relation to the objective i.e. quality efficacy and safety of the product. See also paragraph 6.1.2
C.1.9.6. Record if standards such as ISO 9001-9004 are used by the company to assess its suppliers.
C.1.9.7. When suppliers of critical starting materials and packing materials - actives, excipients, containers and closures and printed materials are assessed, give details of how this is done.
C.1.9.8. Describe the release for sale procedure for finished products.

REQUIREMENT

C.2. PERSONNEL

C.2.1. Organisation chart showing the arrangements for quality assurance, including production and quality control. (see also C.1.9.3)
C.2.2. Qualifications, experience and responsibilities of key personnel.
C.2.3. Outline of arrangements for basic and in-service training and how records are maintained.

C.2.4. Health requirements for personnel engaged in production.
C.2.5. Personnel hygiene requirements, including clothing.

GUIDANCE

C.2. PERSONNEL (500 words/two A4 pages)

C.2.1. Organisation chart

C.2.1.1. Organogram for quality assurance including production and quality control. Record senior managers and supervisors only.

C.2.2. Qualifications, Experience and Responsibilities of Key Personnel.

C.2.2.1. Brief details of academic qualifications and work related qualifications and years relevant experience since qualifying.

C.2.3. Outline of Arrangements for Basic and In-service Training and how Records are maintained

Give brief details of the training programme and include induction and continuous training, as follows:

C.2.3.1. Describe how training needs are identified and by whom.
C.2.3.2. Give details of training relative to GMP requirements.
C.2.3.3. State the form of training e.g. in-house, external, and how practical experience is gained and which staff are involved.
C.2.3.4. Explain how the efficacy of the training is assessed e.g. by questionnaires.
C.2.3.5. Explain how retraining needs are identified.
C.2.3.6. Give brief details of records kept.

C.2.4. Health Requirements for Personnel Engaged in Production

C.2.4.1. Who is responsible for checking health of employees?
C.2.4.2. Is there a pre-employment medical examination?
C.2.4.3. Are employees routinely checked from time to time depending on nature of their work?
C.2.4.4. Is there a system for reporting sickness or contact with sick people before working in a critical area?
C.2.4.5. Is there a system of reporting back after illness?
C.2.4.6. Are those who work in clean areas (grade A-D) subject to additional monitoring?

C.2.5. Personnel Hygiene Requirements Including Clothing

C.2.5.1. Are there suitable washing, changing and rest areas?
C.2.5.2. Is the clothing suitable for the activity undertaken? Briefly describe

the clothing.
C.2.5.3. Are there clear instructions on how protective clothing should be used and when it should be changed? Detailed procedures are not needed. Is in house or external laundry used?

REQUIREMENT

C.3. PREMISES AND EQUIPMENT

Premises

C.3.1. Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required).

C.3.2. Nature of construction and finishes.

C.3.3. Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for manufacture of sterile products should be mentioned.

C.3.4. Special areas for the handling of highly toxic, hazardous and sensitising materials.

C.3.5. Brief description of water systems (schematic drawings of the systems are desirable) including sanitation

C.3.6. Maintenance(description of planned preventive maintenance programmes and recording system).

Equipment

C.3.7. Brief description of major production and control laboratories equipment (a list of equipment is not required).

C.3.8. Maintenance (description of planned preventative maintenance programmes and recording system).

C.3.9. Qualification and calibration, including recording system. Arrangements for computerized systems validation.

Sanitation

C.3.10. Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

GUIDANCE

C.3. PREMISES AND EQUIPMENT

C.3.1.Premises
C.3.1.1. Provide a site plan highlighting production areas.

C.3.1.2. Provide a simple plan of each production area with indication of scale. Label areas and annotate plan with names.

C.3.1..3. Plans should be legible and on A4 sheets of paper. Plans could be on A3 sheets of paper if considered necessary.

C.3.1.4. For sterile product areas indicate room and area classification and pressure differentials between adjoining areas of different classifications.

C.3.2. Nature of Construction and Finishes (500 words/two A4 pages)

C.3.2.1. To reduce narrative for a large complex plant, the details should be limited to critical areas.

C.3.2.2. These areas must include all processing and packaging and critical storage areas.

C.3.2.3. A narrative format is preferred.

C.3.3. Brief Description of Ventilation Systems etc. (500 words/two A4 pages)

Note 1: More details should be given for critical areas with potential risks of airborne contamination. This will include sterile product areas as well as areas for processing powders, granulation and tabletting. For sterile product areas a summary of the results of the most recent qualification/requalification should be given.

Note 2: To reduce the narrative, schematic drawings should be used.
The following data should be given: -

C.3.3.1. Design criteria e.g.
- Specification of the air supply
- Pressure differentials and air change rate
- Simple pass or recirculation (%)
-Temperature
- Humidity

C.3.3.2. Filter design and efficiency e.g.
- Bag 99% eff.
- Hepa 99.997% eff.
Details of any alarms on the ventilation system should be given.

C.3.3.3. The limits for changing the filters should be given.
C.3.3.4. If DOP (dioctyl-phthalate) is introduced, the point must be shown.
C.3.3.5. Give the frequency of revalidation of the system.

C.3.4. Special Areas for the Handling of Highly Toxic Hazardous and Sensitising Materials
C.3.4.1. Follow the same layout as 3.1 above.

C.3.5. Brief Description of Water Systems, including sanitation (500 words / two A4 pages)

Schematic drawings of the systems are preferred. The following information must appear:

C.3.5.1. The schematic must go back to the city supply system.
C.3.5.2. The capacity of the system (maximum quantity produced per hour).
C.3.5.3. Construction materials of the vessels and pipework.
C.3.5.4. Specification of any filters in the system must be given.
C.3.5.5. If water is stored and circulated, what is the temperature at the point of return.
C.3.5.6. The specification of the water produced
a) chemical
b) conductivity
c) microbiological
The sampling points and frequency testing.
The procedure and frequency for sanitation.

C.3.6.Maintenance (250 words/one A4 page)

Note: For the purpose of this guide "Maintenance" is carried out by the manufacturer and "servicing" by an outside contractor.

C.3.6.1. Describe the planned preventative maintenance programme.
C.3.6.2. Are there written procedures and suitable reporting forms for maintenance and servicing? Do the documents record type frequency of services/checks, details of service, repairs and modifications?
C.3.6.3. Are the maintenance routines that could affect product quality clearly identified?
C.3.6.4. Are the reports made known to the users?

Equipment (250 words/one A4 page)

C.3.7. Brief Description of Major Production and Control Laboratory Equipment

Note: Makes and model numbers equipment are not required. However the following points should be addressed:

C.3.7.1. Is the equipment designed with ease of cleaning in mind?

C.3.7.2. Only a general description is required e.g. a rotary tablet press etc. If the equipment has additional devices, these should be recorded e.g. automatic weighing machines with

printer; a labeller incorporating a bar code reader for the label; a lot number and expiry date over printer; a freeze drier equipped with a steam sterilisation facility.
C.3.7.3. In the quality control laboratory only general descriptions such as pH meters, chromatographic equipment GLC (gas-liquid chromatography), HPLC (high performance liquid chromatography) with computer systems, particle size analysers.
C.3.7.4. Is the machinery constructed of appropriate material (e.g. AISI grade 316 stainless steel for product contact equipment?)*
C.3.7.5. Have other materials been suitably validated e.g. polypropylene, chrome-plated brass, PVC (poly vinyl chloride), non-reactive plastic materials?
C.3.7.6. In microbiology use general descriptions such as incubators (temperature ranges) facilities for LAL (limulus amebocyte lysate) testing, membrane filtration sterility testing, antibiotic assay, etc.
C.3.7.7. In particular give brief information on the use of computers, microprocesors etc. in the factory.

C.3.8. Maintenance (250 words/one A4 page)

C.3.8.1. Who is responsible for maintenance and servicing?
C.3.8.2. Are there written procedures and contractual details for outside work?
C.3.8.3. Are maintenance routines which could affect product quality clearly identified?
C.3.8.4. Are records kept of:
1 .type and frequency of service/check;
2. details of service repairs and modifications?

C.3.8.5. Are reports made known to the users?

C.3.9. Qualification, validation and Calibration (750 words/three A4 pages)

C.3.9.1. Briefly describe the Company's general policy and protocols for qualification and validation (prospective and retrospective).
C.3.9.2. Is there regular revalidation of critical equipment?
C.3.9.3. Describe equipment calibration policy and records kept. (
C.3.9.4. An outline of process validation may be given here or cross-referenced to production para 5.4
C.3.9.5. What are the arrangements for computer validation, including software validation?
C.3.9.6. Describe the system for the release for sale or supply of development and validation batches.

C.3.10. Sanitation
Cleaning procedures for manufacturing areas and equipment (250 words/one A4 page)

C.3.10.1. Are there written specifications and procedures for cleaning, cleaning agents and their concentration for the method of cleaning and the frequency?
C.3.10.2. Are cleaning agents changed from time to time?
C.3.10.3. Have the cleaning procedures been validated and what was the method of evaluating the effectiveness of cleaning?

C.3.10.4. Are cleaning methods monitored routinely by chemical and/or microbiological methods?
C.3.10.5. What are the cleaning methods (and their frequency) for the water supply system, air handling system and dust extraction system?

REQUIREMENT
C.4. DOCUMENTATION

C.4.1. Arrangements for the preparation, revision and distribution of necessary documentation for manufacture.

C.4.2. Any other documentation related to product quality which is not mentioned elsewhere (e.g. microbiological controls on air and water).

GUIDANCE

C.4. DOCUMENTATION (500 words/two A-4 pages)

Note: This section refers to all documentation used in manufacture. Manufacture involves all activities relating to the production and control of pharmaceutical products.

C.4.1. Arrangements for the Preparation and Revision and Distribution of Documentation

C.4.1.1. Is there a description of the documentation system?
C.4.1.2. Who is responsible for the preparation revision and distribution of documents?
C.4.1.3. Where are the master documents stored?
C.4.1.4. Is there a standard format and instruction of how documents are to be prepared?
Are there documents for:
1. Product/process specification
2. Raw material specifications
3. Packaging component specifications
4. Standard process instructions including packaging
5. Batch records including packaging
1. Product/Process Specifications
6. Analytical methods
7. QA release procedures.

C.4.1.5. How is the documentation controlled?
C.4.1.6. For how long are documents kept after release of the batch?
C.4.1.7. Detail any arrangements for electronic or microfilmed records.

C.4.2. Other Documentation related to Product Quality

Are the following documents available and in use?
C.4.2.1. Specifications for disposables i.e. cleaning materials.
C.4.2.2. Standard operating procedures.

C.4.2.3. Equipment specifications.
C.4.2.4. Quality Control Procedures.
C.4.2.5. Training procedures.
C.4.2.6. Computer program specifications.
C.4.2.7. Documentation control of process deviations.
C.4.2.8. Calibration and test documents (see para 3.9.5)
C.4.2.9. Validation documents (see paras 3.9 and 5.4)
C.4.2.10. Reconciliation of batches of raw materials, major packing components i.e. product-contact and printed materials.
C.4.2.11. List and briefly explain the use of any additional standard documentation used routinely.

REQUIREMENT

C.5. PRODUCTION

C.5.1. Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters (see at Appendix the list of products manufactured).

C.5.2. Arrangements for the handling of starting materials. packaging materials, bulk and finished products, including sampling quarantine, release and storage.

C.5.3. Arrangements for reprocessing or rework.

C.5.4. Arrangements for the handling of rejected materials and products.

C.5.5. Brief description of general policy for process validation.

GUIDANCE .

C.5.PRODUCTION

This narrative should be kept to a minimum and generalized schematic layouts used where possible. The following points should be addressed:

C.5.1. Describe the operations capable of being carried out at the site with the existing facilities and specify the types of pharmaceutical products. (See para 1.5.1 and the Appendix for types of products manufactured).

When packaging only is undertaken, give a brief description only, e.g. labelling, filling etc, and the nature of containers used e.g. sachets, tamper evident glass containers.

If cytotoxic or radio-active substances are handled give details of the products.
Describe the production operations using flow charts if possible. Technical details are not required.

Describe how products are identified during production and how in-process storage is organized.

C.5.2. Arrangements for handling Starting Materials, Packing Materials, Bulk and Finished Products including Sampling Quarantine Release and Storage

Identification of suppliers lot number with the company's lot number. Status labelling e.g. by using labels or by computer. Issue of materials to manufacture and package. The control of weighing.

Sampling plans.

How are materials being used for manufacture identified and released?
Checking methods

C.5.2.1. Control of Bulk Manufacture

Checks on key parameters during manufacture e.g. blend times, filter integrity tests. Records of key parameters.
Records of in-process checks.
Compliance with the Marketing Authorisation.
In-process checks.

C.2.2. Packing

Release of bulk, semi-finished products, packing materials;
Confirmation of identity and line clearance checks;
In-process checks.

C.5.2.3. Quarantine and release of finished products; compliance with the Marketing Authorisation.

C.5.2.4. Explain the role of the Authorized Person(s).

C.5.3. Arrangements for Reprocessing or Rework

C.5.3.1. What arrangements are in place for reprocessing or reworking batches of products?

C.5.4. Arrangements for Handling Reject Materials and Products

C.5.4.1. Are reject materials and products clearly labelled? Are they stored separately in restricted areas?
C.5.4.2. Describe arrangements for sentencing the materials and disposal. Is destruction recorded?

C.5.5. Brief Description of the General Policy for Process Validation

An outline of process validation protocol only is required. (See para 3.9.3)

REQUIREMENT

C.6. QUALITY CONTROL

C.6.1. Description of the Quality Control system and of the activities of the Quality Control Department Procedures for the release of finished products.

GUIDANCE

C.6. QUALITY CONTROL
C.6.1. Activities of the Quality Control Department

C.6.1.1. (a) Describe the elements of the QC system e.g. specifications, test methods, and other quality related data collection.
(b) Briefly describe the activities of analytical testing, packaging, component testing, biological and microbiological testing.

C.6.1.2. If the review of batch documentation and release of final documentation takes place in this department, give details. (See also para 1.9.5)
C.6.1.3. Outline the involvement in the arrangements for the preparation, revision and distribution of documents in particular those for specification test methods and release criteria if not mentioned elsewhere. (See also para 1.9 and , Documentation)

REQUIREMENT

C.7. CONTRACT MANUFACTURE AND ANALYSIS

C.7.1. Description of the way in which the GMP compliance of the contract acceptor is assessed.

GUIDANCE

C.7. CONTRACT MANUFACTURE AND ANALYSIS
C.7.1. Describe briefly the details of the technical contract between the contract giver and acceptor and the way in which the GMP compliance is assessed to ensure product compliance with the Marketing Authorization.

REQUIREMENT

C.8. DISTRIBUTION, COMPLAINTS AND PRODUCT RECALL

C.8.1. Arrangements and recording system for distribution.

C.8.2. Arrangements for the handling of complaints and product recalls.

GUIDANCE

C.8. DISTRIBUTION
C.8.1. A Description of Storage and Distribution Practices

C.8.1.1. Is the warehouse secure?
C.8.1.2. Is it environmentally controlled?
C.8.1.3. Is there refrigerated storage?
C.8.1.4. How are the materials stored e.g. pallet racking?
C.8.1.5. How is the status of products controlled e.g. by computer, by label?
C.8.1.6. What are the methods of distribution to customers?
C.8.1.7. Does the despatch order ensure first in/first out and identify the lot number?

C.8.2. Records of Distribution
Do the retained records permit full batch traceability from the factory to the customer, in terms of the date of sale, customer details and quantity despatched?

Complaints

C.8.2.1.1. Is there a written complaints procedure?
C.8.2.1.2. Who is responsible for:
1. Logging;
2. Classifying;
3. Investigating complaints.

C.8.2.1.3. Are written reports prepared?
C.8.2.1.4. Who reviews these reports?
C.8.2.1.5. For how long are complaints records kept?

C.8.2.2. Product Recalls

C.8.2.2.1. Is there a written procedure which describes the sequence of actions to be followed including:
1. Retrieval of distribution data;
2. Notification of customers;
3. Receipt/segregation/inspection of returned product;
4. Investigation/reporting of cause;
5. Reporting corrective action.

C.8.2.2. Who is responsible for coordinating product recalls?
C.8.2.3. Who notifies the Competent Authority of complaints and recalls.
C.8.2.4. Is the Competent Authority involved in complaints and the decision to recall?
C.8.2.5. Can recalls be effected below wholesale level?

REQUIREMENT

C.9. SELF INSPECTION

C.9.1. Short description of the self inspection system See also para 1.9.4.).

GUIDANCE

C.9.1.1. Describe how the self inspection system verifies that those activities that have a bearing on quality comply with the planned arrangement.
C.9.1.2. Are the quality systems effective?
C.9.1.3. Are there documented procedures for the self inspection system and for the follow-up actions?
C.9.1.4. Are the results of the self inspection system documented, brought to the attention of the personnel having responsibility for the area and activities inspected?
C.9.1.5. Does the system ensure that those responsible for the area or activity take timely corrective action on the deficiencies found?

APPENDIX

TYPE OF PRODUCTS MANUFACTURED (referred to in paragraph C.1.5)

A. Sterile products

A.1 Liquid dosage forms (large volume solutions, including LVP and rinsing solutions)

A.1.1 Aseptically prepared

A.1.2 Terminally sterilized A.2

A.2. Liquid dosage forms (small volume solutions, including SVP and eye drops)

A.2.1 Aseptically prepared

A.2.2 Terminally sterilized

A.3 Semi-solid dosage forms

A4 Solid dosage form

A.4.1 Solid fill

A.4.2 Freeze-dried

B. Non-sterile products

B.1 Liquid dosage forms
B.2. Semi-solid dosage forms
B.3. Solid dosage forms
B.4. Unit dose form (tablet, capsules, suppositories, pessaries)
B.5 Multi dose form (powder, granules)

C. Biological products

C.1. Vaccines C.
C.2 Sera C.
C.3 Blood products
C.4 Others (describe)

D. Specifically toxic and hazardous substances

D.1 Penicillins
D.2 Cephalosporins
D.3. Hormones
D.4. Cytostatics

D.5. Others (describe)

E. Packaging only

E.1 Liquid dosage forms
E.2 Semi-solid dosage forms
E.2 Solid dosage forms

F. Contract manufacturing (kind of products)

F.1. Firm reported upon is:
F.2. Acceptor .
F.3. Giver

G. Contract analysis

Firm reported upon is:

F.1. Acceptor
F.2. Giver

H. Drugs for clinical trials

I. Others
(e.g. veterinary products, cosmetics, etc)

9. REFERENCES

Circular 34/93
PIC/S guide

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