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

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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.

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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.

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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.

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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

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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.*

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.

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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.*

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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.

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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.

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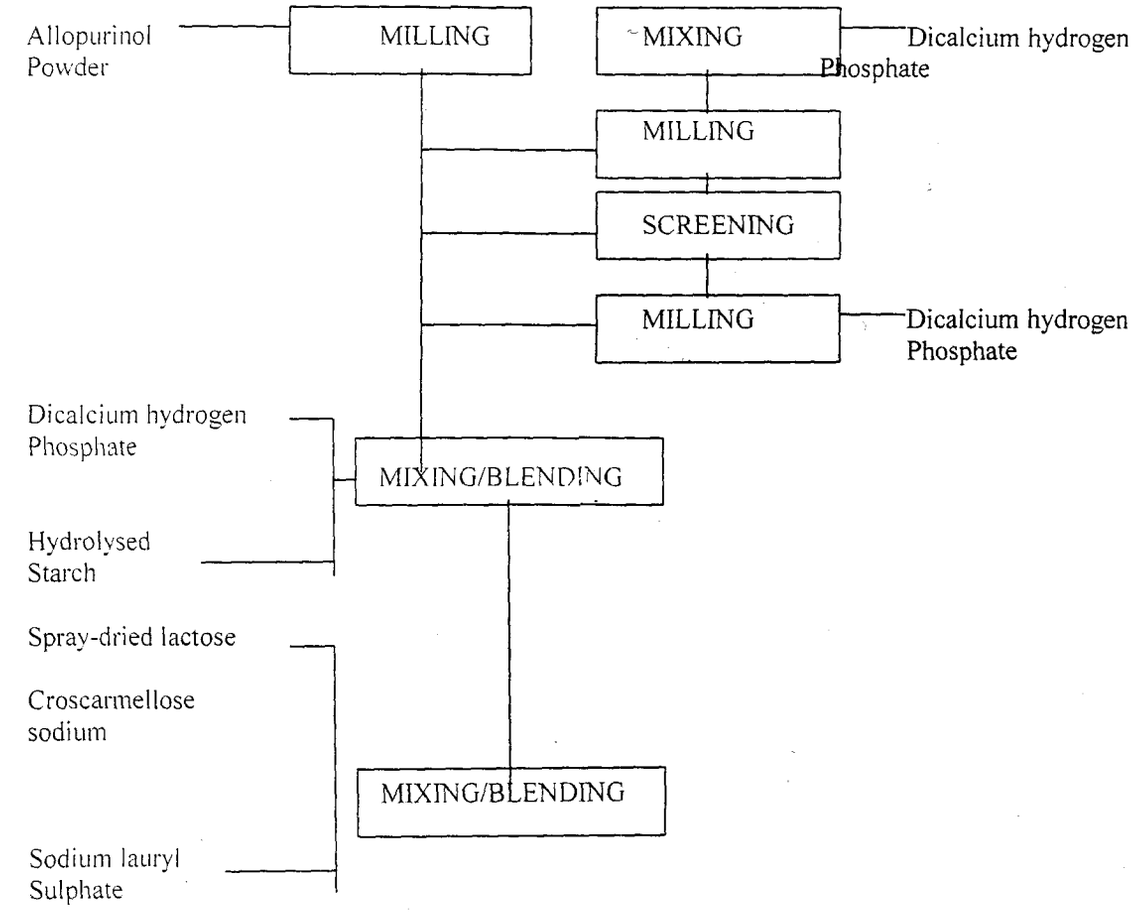
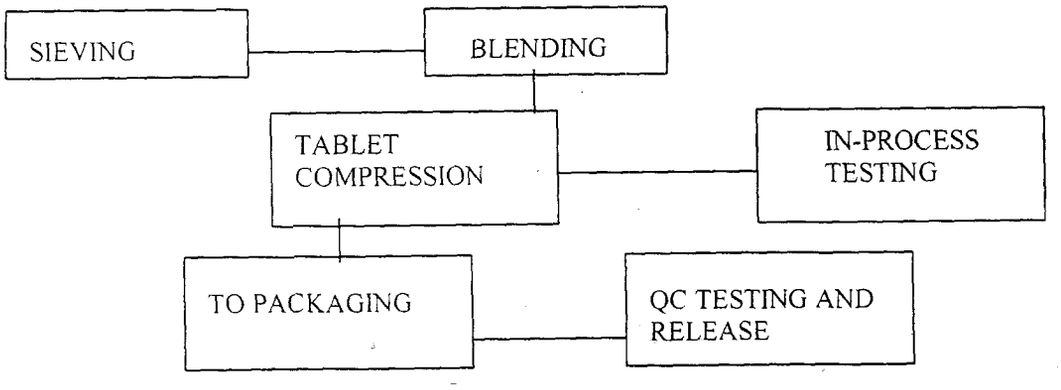
MANUFACTURING PROCESS FLOW DIAGRAM

PRODUCT NAME: ALLOPURINOL TABLETS (EXAMPLE)



Purified Talc



PACKAGING PROCESS FLOW DIAGRAM

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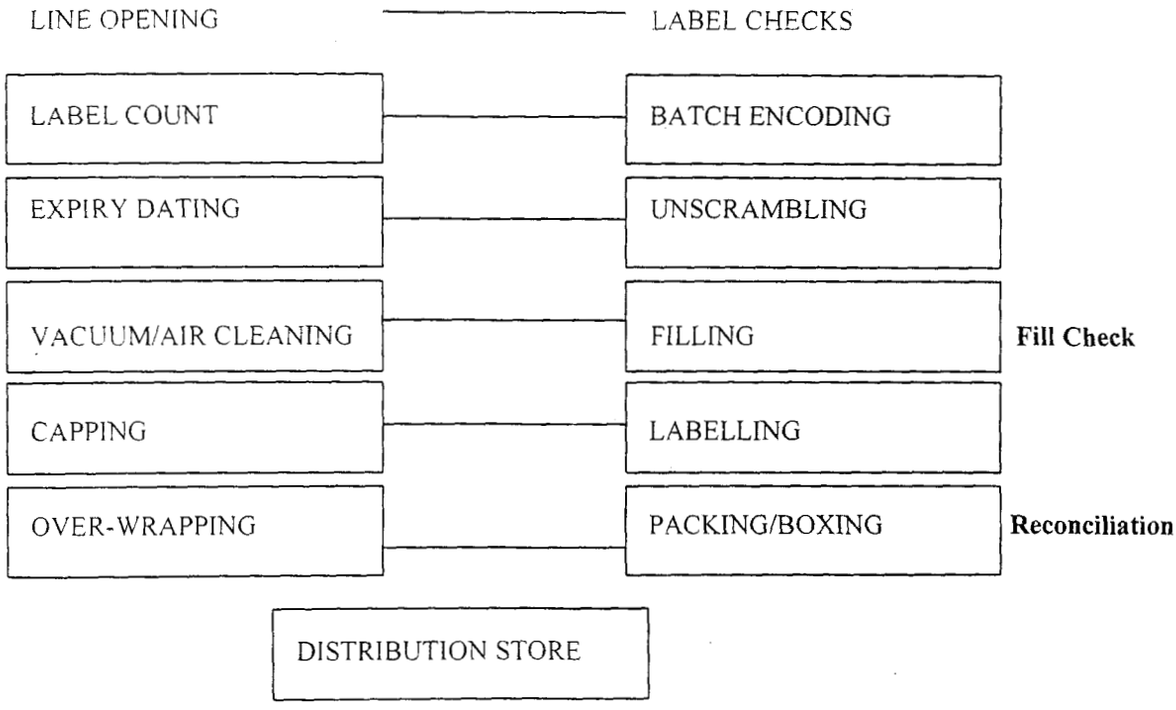

NB: Details of equipment and process conditions may be added in or next to each stage (box) or separately in an itemized paragraph.

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.

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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.

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.

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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, of 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

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

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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.