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

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GOVERNMENT NOTICE

DEPARTMENT OF HEALTH

No. 757 **6 June 2003**

MEDICINES CONTROL COUNCIL

MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965)

GUIDEINES WITH RESPECT TO THE MEDICINES AND RELATED SUBSTANCES ACT (ACT 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 four weeks from the date of publication this notice:

VETERINARY MEDICINES	
1	Application And Information Requirements
2	Guideline For Clinical Trials On Veterinary Medicines
3	Bioavailability And Bioequivalence For Veterinary Medicines
4	Guideline On Preclinical Safety Studies For Veterinary Medicines
5	Guideline On Efficacy For Veterinary Biological Medicines
6	Guideline On Safety Of Veterinary Biological Medicines
7	VMRF 1 Form for Application for Registration of Veterinary Medicines
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8	Guideline for Applications to Amend the Registration Dossier of a Medicine
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Ms M.P. MATSOSO
Registrar of Medicines

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON APPLICATION AND INFORMATION REQUIREMENTS - 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 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 medicines. 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. 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: 30-05-2003

Version MCC2003/1

CONTENTS:

1. GENERAL INFORMATION

The Medicines and Related Substances Control Act, No 101 (Act No. 101 of 1965) requires that a application for registration of medicines including Veterinary Medicines must be submitted in prescribed format. These guidelines are for veterinary medicines and must be read in conjunction with th general guidelines for the application for registration of medicines.

A pre-screening process must be completed and the necessary form MRF 2.0 together with the pre screening fee must be submitted.

Once the pre-screening is complete the full application in the required format must be submitted.

2. STRUCTURE OF THE APPLICATION

The structure of the application should be as follows:

1. Cover/title page
2. Declaration by Applicant
3. Table of Contents
4. Summary
5. Body of Application
6. Other Relevant Information
7. Bibliography
8. Copies of referenced material
9. Appendices if required

3. NUMBER OF COPIES REQUIRED

Applicants must provide:

i. Four copies of the full application.

ii Fifteen copies of the Summary Basis of Registration Application of Veterinary Medicine (SBRAV) of the main application findings, abstracts of reference materials and ful bibliography/reference lists for distribution to committee members.

4. INFORMATION REQUIREMENTS AND APPLICATION FORMAT

4.1 COVER/TITLE PAGE

The cover / title page should indicate:

i. The subject of the application.
ii. The name and address of the applicant.
iii. The name of a contact person.
iv. The date on which the application was submitted.

4.2 DECLARATION BY APPLICANT

Applications for a rescheduling decision must contain a declaration by the applicant certifying that to th best of the applicant's knowledge all information relevant to the application has been submitted and i true and accurate.

4.3 TABLE OF CONTENTS

The table of contents should tabulate and correlate the titles of each section and major subsections of the application with their appropriate page numbers.

4.4 Summary Basis of Registration Application of Veterinary Medicines (SBRAV)

(i) The SBRAV is intended to be a very brief and concise document containing the core data on th basis of which the applicant intends to obtain registration for the veterinary product. It is to b presented as a summary only: therefore no articles, reports etc. are to be incorporated into th SBRAV nor should such papers be attached to it either, as these belong with the full submission.

(ii) Applicants must ensure that the general quality of the studies , proper cross referencing to th data, explanatory notes and the quality of photocopying and binding are of an appropriat standard. The SBRAV must be cross -- referenced with the documentation submitted to th Medicines Control Council.

(iii) SBRAV format

Refer to the format below for details.

5. BODY OF THE APPLICATION

The body of the application should communicate the aims and justification of the proposal in a concise clear and logical manner. Appropriate data and information must be supplied to demonstrate that th substance or product will be safe for the public when supplied and used in the proposed manner. Whilst th format of each application may vary the Committee recommends the use of a standard framewor consisting of the following:

5.1 Purpose of the Application

A general statement of the purpose of the application (new, amendment, change in indications etc.) must be made.

5.2 General Background

5.2.1 Current Regulatory Status

Reference should be made to the current local regulatory status of the product or substance in terms of dosage forms registered, scheduling status and approved indications. If applicable, the registration number must be indicated.

5.2.2 International Regulatory Status:

Classification/ scheduling status in other countries where the drug is registered, including information of the approved indications and dosage forms. The availability status should be clearly indicated in terms of prescription only, pharmacy only, general sales outlets, etc. (The term OTC should distinguish between general sale and pharmacy, if relevant). It should be noted that recognized regulatory authorities include those in the USA, EU, Australia and Canada.

5.3 Technical Information

Additional information on the active ingredient that was not submitted during the registration of the original product. Data that was submitted during the registration process may be summarized.

.5.3.1. Physico-Chemical Properties of the Active Ingredient

i. Structural formula or any available information on the structure of the substance.
ii. All relevant chemical and physical properties.

5.3.2 Pharmacology

i. Any known information relating to the structural and pharmacological relationship to other drugs or chemicals
ii. The pharmacodynamic and pharmacokinetic profile
iii. Interactions, incompatibilities, side effects or adverse reactions
iv. Any recognized standard such as a pharmacopoeia monograph.

5.3.3 Clinical Data

i. Post-marketing reports
ii. Additional clinical reports
iii. Adverse drug reaction reports
iv. Epidemiology reports
v. Poisoning reports

5.3.4 Toxicology

i. Summary of the known toxicology of the product.
ii. Summary of the known metabolism of the product.
iii. Relevant details of any published or unpublished toxicological investigations of the product / substance

5.3.5 Safety Reports:

i. A summary of animal studies that show low general toxicity and no relevant reproductive toxicity, genotoxic, or carcinogenic properties relevant to the experience/ exposure of the product.
ii. Information from post-marketing surveillance studies, clinical trials and published literatur presenting the issue of drug safety. For OTC's: Considerable experience of patient exposure including at least 2 years of use in the relevant or similar population.
iii. Information on adverse drug reactions. In the case of OTC medication the information shoul include experience without medical supervision in other countries. Variables such as number of patients treated, demographic details, indications for use and dose should be provided an taken into account in providing and interpreting the data;
iv. Drug interactions with food or commonly prescribed drugs.
v. Consideration of the consequences concerning misuse.

5.3.6 Occupational Health and Safety Information: (If applicable)

A summary of occupational health and safety aspects.

5.3.7 Pharmaceutical Aspects:

Any intended change in formulation, pack size, packaging, etc should be indicated. However pharmaceutical data such as stability need not be included, this data must be evaluated as part of registration application or amendment to the registration application.

6. **Package Insert**

The under-mentioned information with regard to this medicine shall appear on the scientific packag insert. The information shall be presented in the format stipulated: Provided that the Council ma authorise any deviation from such information or such format. (Ref. Regulation 40)

1. Scheduling status.
2. Proprietary name
3. Dosage form
4. Composition.
5. Pharmacological classification
6. Pharmacological action. Pharmacokinetics
7. Indications.
8. Contra-indications.
9. Warnings.
10. Dosage and directions for use.
11. Side effects and special precautions
12. Interactions
13. Known signs of over dosage and particulars of its treatment.
14. Identification.
15. Presentation.
16. Storage instructions.
17. Registration number (or reference number).
18. Name and Business Address of the Holder of the certificate of registration.
19. Date of notification of approval of the scientific package insert.

7. SUMMARY BASIS FOR REGISTRATION APPLICATION OF VETERINARY MEDICINES (SBRAV)

1. THIS APPLICATION INVOLVES : a new application

2. DATE OF THIS SBRAV :

2.1 Submitted
2.2 Discussed(official use)
2.3 to applicant (official use)

3. PRODUCT DETAILS

Active ingredient(s) and quantity thereof
Proprietary name
Applicant :
Application / Registration No:
Pharmacological classification
Dosage form

4. **NAME(S)** of Registration Person and/or Medical Adviser responsible for compilation of this application, and telephone number where responsible individual may be contacted during office hours:

Name	Position	Qualifications	Tel. No.

5. **PROVEN (ESTABLISHED) PHARMACOLOGICAL ACTION:**

(Only information concerning the clinical issues and indications claimed are relevant).
(MAXIMUM 100 WORDS).
(At least two key references in support, preferably published – see 13 below).

6. **EVIDENCE OF EFFICACY IN TARGET SPECIES:**

(Data should be summarized in tabulated format, preferably under the following headings, as applicable:

- Key trial(s) reference number: as listed under item 13 of SBRAV
- Trial design : indicate with abbreviations/symbols, e.g.
- 0 = open
- X = cross-over
- P = parallel groups
- R = randomised
- C = controlled
- PC = placebo-controlled
- MC = multi-centre
- LS = Latin square

- Indications/Diagnosis.

- Number of patients treated with each drug.

- Dosage range used.

- Duration of treatment.

- Reference/comparative drug(s).

- Parameters evaluated/findings.

- Statistical data

(Please indicate separately, the total (overall) number of patients treated with the product)

Indicate clearly which trials were done/not done with the formulation and dosage form, for which registration is being applied.

(Free comment, if required, MAXIMUM 200 WORDS, excluding tabulated data).

7. **MAIN SAFETY ISSUES AND TOXICOLOGY:**

(a) Target species studies:

i) (List side effects/adverse reactions/toxicological profile, with incidence figures and key references).
ii) Pre-clinical studies: (Animal and in vitro toxicology data)

(Free comment, if required: MAXIMUM 200 WORDS, excluding tabulated data).

8. EVIDENCE OF LONG TERM SAFETY/EFFICACY

Tabulate key long-term studies, their duration, indications, findings, tolerability, etc.; with references, where applicable).

(Free comment, if required: MAXIMUM 100 WORDS).

9. EVIDENCE OF BIOAVAILABILITY AND PHARMACOKINETICS OF THE ACTIVE COMPONENT (S):

Methods used and number of subjects studied to be clearly specified, where applicable. Pharmacokinetic data summarized in tabular or graphical form is essential. (MAXIMUM 100 WORDS).

For medicines containing more than one active component, provide a summary of evidence (with key references), that each contributes materially to the efficacy of the product. (MAXIMUM 100 WORDS).

10. REGISTRATION STATUS IN OTHER COUNTRIES:

Country	Date of registration

11. PROPOSED SCHEDULING STATUS:

(Provide reasons briefly, and illustrate structural formula)

12. LIST OF KEY REFERENCES:

(MAXIMUM 25)

(Directly applicable publications in referred scientific journals are preferred. Where suitable published scientific documentation is lacking, selected unpublished key scientific reports or in-house documents may be quoted, provided these are clearly indicated as such.

The "Vancouver Style" of setting out published references, entails the following*:

Author(s), title of article, names of journal (abbreviated according to Index Medicus), journal particulars (year, volume, page no.).

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR CLINICAL TRIALS ON VETERINARY MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for the conduct of clinical trials for 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 the conduct of clinical trials for veterinary medicines. 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: 30-05-2003

INDEX:

1. SCOPE OF THE GUIDELINE

This document is intended to provide guidance for the conduct of clinical trials on veterinary medicinal products. It is intended to ensure that those trials are conducted and documented in according to International Guidelines.

2. INTRODUCTION

The objective of this document is to provide guidance for practice on the conduct of clinical trials on veterinary medicinal products. It is directed to all those involved in the conduct of such trials and is intended to ensure that those trials are conducted and documented in accordance with International Standards.

Pre-established systematic written operating procedures for the organisation, conduct, data collection, documentation and verification of clinical trials are necessary to establish the validity of data and to improve the ethical, scientific and technical quality of trials.

The welfare of the trial animals is ultimately the responsibility of the investigator for all matters relating to the trial. All investigators must demonstrate the highest possible degree of professionalism in the observation of animals in the trials and the reporting of such observations. Independent assurance that the trial animals and the human food chain are protected should be provided by the authorisation procedure of the competent authority and the procedure for informed consent of the owner of the animals. The approval of a competent Ethical Committee must be obtained. In certain basic trials this requirement may be waived. The authority should be consulted as to which trials are exempt from this requirement.

Safety and pre-clinical trials, including pharmacokinetic studies, are not included in the scope of this document since there are already such guidelines. Data derived from such trials must be submitted to the authority in order that the clinical trial or series of trials may be properly authorised prior to commencement.

In conducting clinical trials, due regard must be taken of the possible effects of the product on the environment, on residues in the produce of treated animals, and the eventual fate of animals used for food consumption.

3. RESPONSIBILITIES

Sponsor

1. Each Sponsor will confirm detailed Standard Operating Procedures (SOP) for the elements contained in the protocol.
2. With regard to trial protocols the recommendations contained in Chapter 2 of this guideline will be carefully followed during their construction.
3. Both the Sponsor and Investigator/Study director will sign the protocol as an agreement of the details of the clinical trial. Any amendments to the protocol must have the signed agreement of both Sponsor and Investigator/Study director.
4. All studies started after 2 May 2003 shall be carried out in accordance with this note for guidance
5. Furthermore, the Sponsor will:
   a) select the Investigator/Study director, and assure his/her qualifications, assure his/her availability for the entire duration of the study, ensure that he/she agrees to undertake the

study as laid down in the protocol according to this note for guidance of practice, including the acceptance of verification procedures; and

b) inform the Investigator/Study director of the relevant chemical, pharmaceutical, toxicological and clinical details as a prerequisite in planning the trial; and
c) submit notification/application to the relevant authorities where required; and
d) provide the investigational medicinal product(s) in suitable packaging and labelling, in conformity with the principles of GMP, and in such a way that any blinding procedure is not invalidated. The labelling should include the words
"For Veterinary Clinical Trial Only";
- A sample of each batch should be kept for reference for one year after the end of shelf life.
- Records of the quantities of medicinal product(s) supplied should be maintained with batch/serial numbers and Certificates of Analysis. Certificates of delivery of the medicinal product(s) signed by the investigator must detail the method and place of storage to identify the exclusive use of the product(s) in the trial. It will subsequently be used to account for unused supplies.
- Appropriate recommendations for disposal of unused test product/s should be given.

e) appoint appropriately qualified and trained Monitor(s); and
f) report all suspected Adverse Drug Reactions (ADR) in accordance with relevant requirements; and
g) inform the Investigator/Study director of any critical information that becomes available during a trial and ensure that when required the relevant authority is notified; and
h) ensure that a final trial report is prepared whether or not the trial has been completed; and
i) provide adequate indemnity for the Monitor and Investigator/Study director and compensation for animal owners in the event of injury or death of the animal or loss of productivity related to the trial.
j) ensure that an appropriate independent Ethical Committee approval is obtained prior to the commencement of the trial.

Monitor

The Monitor will be the principal communication link between the Sponsor and the Study director/Investigator and will:

1. help the Sponsor to select the Study director/Investigator; and
2. work according to predetermined SOPs, visit the Investigator\Study director at critical time points during the trial to control adherence to the protocol and ensure that all data are correctly and completely recorded and reported and that informed consent is being obtained and recorded from the owner(s) of trial animals prior to including his/her animals; and
3. ensure that the trial site has adequate space, facilities, equipment, staff, and that an adequate number of trial animals is likely to be available for the duration of the trial; and
4. ensure that trial staff have been adequately informed about the details of the trial; and
5. be reasonably available to the Investigator/Study director for consultation, in person or via telephone, facsimile machine, telex, electronic mail etc.; and
6. check that the storage, dispensing and documentation for the supply of investigational medicinal product(s) are safe and appropriate, and ensure that any unused medication is returned by the owner(s) to the Sponsor or to an approved site; and
7. submit a written report to the Sponsor at agreed regular intervals to include the reporting of all telephone calls, visits, letters and other contacts with the Investigator/Study director (audit paper trail concept). These reports will form part of the trial documentation.

Investigator/Study director

The Investigator/Study director will:

1. agree the protocol with the Sponsor via the Monitor and confirm in writing that he/she will work according to the protocol, and adhere to this note for guidance; and
2. submit an up-to-date curriculum vitae in MCC format and other credentials to the Sponsor; and
3. obtain informed consent from the owners of trial animals where applicable. The animal owner must receive written information from the Investigator/Study director in advance; and
4. provide all relevant information to all staff members involved with the trial or with other elements of the management of the trial animals. This should include the local veterinarian that normally attends the animals; and
5. ensure that the investigational medicinal product(s) are correctly stored and safely handled. Ensure investigational medicinal products are dispensed to trial subjects in accordance with the protocol and to maintain a full inventory of receipt, usage and remaining stocks. At the end of the trial it must be possible to reconcile delivery records with those of usage and returns including accounting for any discrepancies; and
6. manage any code procedure and documentation (e.g. randomisation envelopes), with due professional care, and ensure that any treatment code is only broken in accordance with the protocol and with the Sponsor's/Monitor's knowledge and consent; and
7. collect and record data in accordance with protocol requirements; and
8. in the case of ADRs immediately notify the Sponsor and Monitor and, where required, relevant authorities; and
9. make all data available to the Sponsor/Monitor for the purposes of validation;
10. ensure the accuracy of any report drafted for him/her; and
11. forward signed Record Sheets to the Monitor. Collaborative Investigators and those responsible for the analyses (including statistical analyses) and the interpretation of the results should also sign the relevant Record Sheets. Where appropriate, all practice records will be clearly marked that the animal(s)/owner is participating in a clinical trial; and
12. observe the following points particularly related to animal care:
    a) the Investigator/Study director will be expected to give assurance that he/she has sufficient time to devote to the study, access to adequate staff and facilities for the conduct of the study, and that suitable equipment is immediately available in case of emergency;
    b) the Investigator/Study director is responsible for animals under his/her care for the purpose of the trial and, where the Investigator/Study director is not a veterinarian, will ensure that their care is maintained during and after the trial. The local veterinarian should be kept informed.
    c) the Investigator/Study director shall ensure the correct disposal of study animals at the completion of the trials. This should include compliance with appropriate withdrawal periods for animals that could enter the food chain as stipulated by the appropriate authority.

4. GUIDE FOR THE CONDUCT OF CLINICAL TRIALS

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/Study director 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.

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.
3. Summary of the preclinical and relevant pharmaceutical data for NCE's.

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/safety

1. Definition of the effects to be achieved before efficacy/safety 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 (for blinded studies) 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.

5. DATA HANDLING

General

1. The person recording an observation will sign and date 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 the Investigator/Study director considers additional observations necessary 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. The Investigator must certify values outside an accepted reference range. 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 printout. In this case the electronic record or the printout 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 printout that 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.

6. STATISTICS

1. Access to bio-statistical 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.

7. 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 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.

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DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

BIOAVAILABILITY AND BIOEQUIVALENCE FOR VETERINARY MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of efficacy for veterinary medicines using bioavailablity/ bioequivalence studies. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach. Alternative approaches may be used but must be scientifically 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 medicines.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
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1. INTRODUCTION

Adequate evidence/proof of efficacy and safety for all multisource products in the form of appropriate *in vivo* bioequivalence studies must be submitted with each application for the registration of a veterinary medicine.

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

Comparison of therapeutic performances of two pharmaceutical products containing the same active substance is a critical means of assessing the possibility of using either the innovator or a multi-source (generic) pharmaceutical product. Assuming that in the same subject a similar plasma drug concentration time course will result in similar drug concentrations at the site of action and thus in a similar effect, pharmacokinetic data instead of therapeutic results may be used to establish bioequivalence.

The objectives of this guideline are to:

i. Define when bioavailability or bioequivalence data will be required in order to prove safety and efficacy.

ii. Provide guidance on the design and conduct of studies and the evaluation of data.

iii. Provide guidance when *in vitro* instead of *in vivo* data may be used.

iv. Provide guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.

For pharmaceutical products where the active ingredient is not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied. Under these conditions availability (local) may be assessed by quantitative measurements which appropriately reflect the presence of the active ingredient at the site of action.

2 DEFINITIONS

2.1 Active Pharmaceutical Ingredient (API)

A substance or compound used or intended to be used in the manufacture of a pharmaceutical product and which is expected to have a medicinal or pharmacological effect when administered.

2.2 Pharmaceutical Product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

2.3 Pharmaceutical Equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in the product performance.

2.4 Therapeutic Equivalence

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

2.5 Bioavailability

Bioavailability refers to the rate and extent to which the active pharmaceutical ingredient, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

2.6 Bioequivalence

Bioequivalence is defined as the absence of a significant difference in the bioavailability between two pharmaceutically equivalent products under similar conditions in an appropriately designed study.

Comparative studies using clinical or pharmacodynamic end points may be used to demonstrate bioequivalence.

2.7 Pharmaceutical Dosage Form

A pharmaceutical dosage form is a pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution etc.) suitable for administration to human and animal subjects.

2.8 Multi-Source (Generic) Pharmaceutical Product

Multi-source pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

2.9 Proportionally Similar Dosage Forms/Products

Pharmaceutical products are considered proportionally similar in the following cases:

i. When all active pharmaceutical ingredients and inactive components are in exactly the same proportion between different strengths (e.g. a 100mg strength tablet has all active and inactive pharmaceutical ingredients exactly half of a 200mg strength tablet and twice that of a 50mg strength tablet).

ii. When the active and inactive ingredients are not in exactly the same proportion but the ratios of inactive pharmaceutical ingredients to the total weight of the dosage form are within the limits defined by the Guideline for Major and Minor Amendments.

iii. When the pharmaceutical products contain high potency active pharmaceutical ingredients and these products are of different strengths but are of similar weight.

The difference in API content between strengths may be compensated for by weight changes in one or more of the inactive pharmaceutical excipients provided that the total weight of the pharmaceutical product remains within 10% of the weight of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same inactive pharmaceutical excipients must be used for all strengths, provided that the changes remain within the limits defined by the Guideline for Major and Minor Amendments.

Exceptions to the above definitions may be considered provided justification is submitted.

3. DESIGN AND CONDUCT OF STUDIES FOR ORALLY ADMINISTERED PHARMACEUTICAL PRODUCTS

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound alternatively well-established designs such as parallel designs for very long half-life substances could be considered.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required and must be justified.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of Cmax and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80% is covered before 72 hours.

3.2 Trial Animals

3.2.1 Number of Animals

It is recommended that the number of subjects should be justified on the basis of providing at least 80% power of meeting the acceptance criteria.

The minimum number of animals should not be less than 8. If 8 animals do not provide 80% power more subjects should be included.

A minimum of 12 animals is required for modified release oral dosage forms.

The number of animals required to provide an 80% power of meeting and passing the acceptance criteria for the 0,8 - 1,25 acceptable interval can be determined from Table 1 below (Reference 1).

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Table 1 Sample sizes to attain a power of 70%, 80% and 90% in the case of the multiplicative model: $\alpha = 5\ \%$, $\theta_1=0.8$, $\theta_2=1.25$ and various CVs.

CV	Power	μ_T/μ_R							
(%)	(%)	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	70	10	6	4	4	4	4	6	16
7.5		16	6	6	4	6	6	10	34
10.		28	10	6	6	6	8	16	58
0		42	14	8	8	8	12	24	90
12.		60	18	10	10	10	16	32	128
5		80	22	12	12	12	20	44	172
15.		102	30	16	14	16	26	56	224
0		128	36	20	16	20	30	70	282
17.		158	44	24	20	22	38	84	344
5		190	52	28	24	26	44	102	414
20.		224	60	32	28	32	52	120	490
0									
22.									
5									
25.									
0									
27.									
5									
30.									
0									
5.0	80	12	6	4	4	4	6	8	22
7.5		22	8	6	6	6	8	12	44
10.		36	12	8	6	8	10	20	76
0		54	16	10	8	10	14	30	118
12.		78	22	12	10	12	20	42	168
5		104	30	16	14	16	26	56	226
15.		134	38	20	16	18	32	72	294
0		168	46	24	20	24	40	90	368
17.		206	56	28	24	28	48	110	452
5		248	68	34	28	34	58	132	544
20.		292	80	40	32	38	68	156	642
0									
22.									
5									
25.									
0									
27.									
5									
30.									
0									
5.0	90	14	6	4	4	4	6	8	28
7.5		28	10	6	6	6	8	16	60
10.		48	14	8	8	8	14	26	104
0		74	22	12	10	12	18	40	162
12.		106	30	16	12	16	26	58	232
5		142	40	20	16	20	34	76	312
15.		186	50	26	20	24	44	100	406
0		232	64	32	24	30	54	124	510
17.		284	78	38	28	36	66	152	626
5		342	92	44	34	44	78	182	752
20.		404	108	52	40	52	92	214	888
0									
22.									
5									
25.									
0									
27.									
5									
30.									
0									

Note: Less than 8 subjects should not be used even if the above table indicates that a power of 80% can be attained with less than 12 subjects.

To determine the number of animals required, proceed as follows:

i. Determine the CV% of the appropriate BA/BE parameter for the drug under investigation from published literature or an appropriate pilot study.

ii. Choose an appropriate mean test/ reference ratio that is envisaged for the BA/BE parameter (μ_T / μ_R). Ideally this value will be 1.00, however, in practice this is seldom the case so the choice of this ratio is at the discretion of the Sponsor/Applicant.

iii. Determine from the table the number of animals required for the appropriate CV%, Power and μ_T / μ_R.

For example, if the drug under investigation has an AUC CV of 20% and if a μ_T/μ_R of 0.95 or 1.05 is selected, then a minimum of 20 and 18 animals respectively will be required for a power of 80%.

Alternatively, the sample size can be calculated using appropriate power equations, which must be presented in the protocol.

Add-ons will be permitted but the number of animals in the add-on should not excee d the initial number of animals in the study, unless fully justified. The applicant must show that the data are homogeneous using appropriate statistical tests. The provision for add-ons must be made in the protocol *a priori*.

3.2.2 Selection of Animals

The animal population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy animals.

The inclusion/exclusion criteria should be clearly stated in the protocol.

3.3 Standardisation of the Study Conditions

The test conditions should be standardised in order to minimise the variability of all factors involved, except that of the products being tested. Therefore standardisation of the diet, fluid intake and exercise is recommended.

3.4 Sample Collection and Sampling Times

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the drug. In most cases the drug may be measured in serum or plasma, however, in some cases, whole blood may be more appropriate for analysis.

When blood is collected:

i. The duration of blood sampling in a study should be sufficient to account for at least 80% of the known AUC to infinity (AUC_∞). This period is approximately three terminal half-lives of the

drug.

ii. For most drugs 12 including a pre-dose sample should be collected per animals per dose.

iii. Sample collection should be spaced such that the maximum concentration of drug in blood (C_{max}) and the terminal elimination rate constant (K_{el}) can be estimated.

iv. At least three to four samples should be obtained during the terminal log-linear phase to estimate K_{el} by linear regression analysis.

v. The actual clock time when samples are collected as well as the elapsed time relative to drug administration should be recorded.

If drug concentrations in blood are too low to be detected and a substantial amount (> 40%) of the drug is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

When urine is collected:

i. The volume of each sample must be measured immediately after collection and included in the report.

ii. Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life so that the amount excreted to infinity (Ae_{∞}) can be estimated.

iii. Sufficient samples must be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours are usually appropriate.

3.5 Characteristics to be Investigated

3.5.1 Blood/Plasma/Serum Concentration *versus* Time Profiles

In most cases evaluation of bioavailability and bioequivalence will be based upon measured concentrations of the parent compound (i.e. the API) where the shape of and the area under the plasma concentration *versus* time curves are generally used to assess the rate and extent of absorption.

In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound.

i. If the concentration of the active substance is too low to be accurately measured in the biological matrix.

ii. If there is a major difficulty with the analytical method.

iii. If the parent compound is unstable in the biological matrix.

iv. If the half-life of the parent compound is too short thus giving rise to significant variability.

Justification for not measuring the parent compound must be submitted by the applicant and

bioequivalence determinations based on metabolites should be justified in each case.

Sampling points should be chosen so that the plasma concentration *versus* time profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. AUC_t, AUC_∞, C_{max}, t_{max} for plasma concentration *versus* time profiles.

ii. AUC_τ, C_{max}, C_{min}, fluctuation (%PTF) and swing (%Swing) for studies conducted at steady state.

iii. Any other justifiable characteristics (cf. Appendix I).

iv. The method of estimating AUC-values should be specified.

3.5.2 Urinary Excretion Profiles

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug input. However, justification must also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. Ae_t, Ae_∞ as appropriate for urinary excretion studies.

ii. Any other justifiable characteristics (cf. Appendix I).

iii. The method of estimating AUC-values should be specified.

3.5.3 Pharmacodynamic Studies

If pharmacodynamic parameters/effects are used as bioequivalence criteria, justification for their use must be submitted by the applicant. Bioequivalence determinations based on these measurements should be justified in each case. In addition:

i. A dose response relationship should be demonstrated.

ii. Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.

iii. The complete effect curve should remain below the maximum physiological response.

iv. All pharmacodynamic measurements/methods must be validated with respect to specificity, accuracy and reproducibility.

3.6 Chemical Analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and cGMP.

Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix. Validation should therefore address the following characteristics of the assay (Reference 2):

i. Stability of stock solutions.

ii. Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

iii. Specificity.

iv. Accuracy.

v. Precision.

vi. Limits of detection and quantitation.

vii. Response function.

viii. Robustness and ruggedness.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run.

A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).

All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed.

Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation and all modifications should be reported and the scope of revalidation justified.

3.7 Reference Product

N.B. Products that are not registered in South Africa cannot be used as reference products in bioequivalence studies submitted in support of an application e.g. a product approved for marketing in another country(s) but not approved for marketing in South Africa cannot be used as a reference product.

3.7.1 Reference Products Registered and Marketed in South Africa

The reference product must be an innovator product registered with the Medicines Control Council (MCC) and must be procured in South Africa except that an "OLD MEDICINE" may be used as a reference product when no other such product has been registered and provided that it is available on the South African market. If more than one such product is available, then the product that is the market leader in South Africa should be used as the reference.

3.7.2 Reference Products Registered but not Procured inside South Africa.

1. A foreign reference product can be used provided that the following evidence is submitted:

   i. The reference product has an identical formulation (the same in all respects) as the innovator product marketed in South Africa.

   ii. The reference product is manufactured by the same method as the innovator product marketed in South Africa.

   iii. The reference product is manufactured at the same site as the innovator product marketed in South Africa.

   The intention of the above clause is to provide for the use of a reference product where that innovator product has been imported for use in South Africa.

2. As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in SA and must meet the f_2 requirements when tested in dissolution media of pH 1.2, 4.5 and 6.8, using an appropriate dissolution apparatus (see Guideline for Dissolution Testing).

   The intention of the above clause is to make provision for dossiers submitted prior to the implementation of this guideline.

3.7.3 Reference Products Registered in South Africa but not Marketed (Available) in South Africa

If a reference product is registered in SA but cannot be procured (i.e. is not available) in South Africa, then the reference product used can be obtained from outside South Africa provided that the product meets the following criteria:

i. The reference product must be a conventional, immediate-release oral dosage form.

ii. There is no documented evidence of bioavailability problems related to the active pharmaceutical ingredient(s) or the pharmaceutical product, or ingredients or products of similar chemical structure or formulations.

iii. It must be documented that the pharmaceutical product is authorised for marketing by the health authority of a country with drug registration requirements acceptable to the MCC. In such instances the registration requirements of the country where the reference product was approved must be submitted.

iv. It must be documented that the pharmaceutical product is marketed in the country of origin by the same innovator company or corporate entity which currently markets the same active pharmaceutical ingredient in the same dosage form in South Africa; or, that it is marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity which currently markets the product in South Africa. The country of manufacture must be stated.

v. Copies of the labelling for the reference as well as the innovator product marketed in South Africa, together with Certificates of Analysis for both products, analysed using the specifications for description, assay, content uniformity and dissolution proposed in the submission for the multi-source product, must be provided.

vi. The active pharmaceutical ingredient is uncomplicated i.e. it does not exhibit any of the following:

- A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
- A steep dose / response relationship.
- A risk of serious undesired effects.
- Complicated or variable pharmacokinetics e.g.:
  - non linear pharmacokinetics
  - variable or incomplete absorption
  - an absorption window, i.e. site specific absorption
  - substantial first-pass metabolism (>40%)
  - an elimination half life of 24 hours or more

vii. The active pharmaceutical ingredient must not be a pro-drug.

viii. The dosage form:

- Contains a single API.
- Contains the same quantity of medicinal ingredient as the innovator product registered in South Africa.
- Is the same as the dosage form registered in South Africa with respect to colour, shape, size, weight, type of coating and other relevant attributes.

3.7.4 Reference Products for Combination Products

Combination products should in general, be assessed with respect to bioavailability and bioequivalence of individual active substances:

i. Either individually (in the case of a new combinations), or

ii. Using an existing combination as the reference.

iii. In the former instance, immediate release oral dosage forms containing a single API can be used as the reference. These reference products may include "OLD MEDICINES".

Bioequivalence testing of such products will be permitted only for those products approved by the MCC.

3.8 Study Products and Batch Size

3.8.1 Study Products

The following information on test and reference products must be submitted:

i. Assay of test and reference product.

ii. Comparative dissolution profiles of the test and the reference product.

iii. A CoA of the API used in the test product bio-batch as well as quality control data demonstrating compliance with the specifications.

In addition, the test and reference products must conform to the following:

i. Test and the reference product should not differ by more than 5% in assay.

ii. A sufficient number of retention samples of both test and reference products used in the bioequivalence study must be kept by the study sponsor for one year in excess of the accepted shelf life or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by the MCC.

iii. A complete audit trail of procurement, storage, transport and other use of both the test and reference products must be recorded.

3.8.2 Batch Size

The bio-batch used in the bioequivalence study must satisfy the following requirements:

i. The bio-batch must be a minimum of 10 000 units or at least 10% of the production batch which ever is greater.

If the bio-batch is less than 10 000 the applicant must motivate and justify the use of a smaller batch.

ii. If the production batch is smaller than 10 000 units, a full production batch will be required.

iii. A high level of assurance must be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale -up, this should be validated appropriately.

3.9 Data Analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the test and reference products and to demonstrate that any clinically important difference is unlikely.

3.9.1 Statistical Analysis

The statistical method for testing relative bioavailability (i.e average bioequivalence) is based upon the 90% confidence interval for the ratio of the population means (Test/Reference) on the log-transformed scale, for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t, AUC_∞, C_{max} should be analysed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation.

If appropriate to the evaluation, the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data.

In addition to the appropriate 90% confidence intervals, summary statistics such as geometric and arithmetic means, SD and %RSD as well as ranges for pharmacokinetic parameters (minimum and maximum) should be provided.

3.9.2 Acceptance Range for Pharmacokinetic Parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

3.9.2.1 Single-Dose Studies

In single-dose studies designed to determine average bioequivalence, acceptance criteria for the main bioequivalence parameters are as follows:

i. AUC_t - ratio

The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

In certain cases an alternative approach may be acceptable.

Justification for the use of alternative methods e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs has been described in the literature (Reference 2 and 3). Use of alternative methods MUST be stated *a priori* in the protocol and cannot be added retrospectively.

ii. C_{max} - ratio

The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133% calculated using log transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125% will apply.

In certain cases e.g. in the case of highly variable API's, a wider interval or other appropriate measures may be acceptable but must be stated *a priori* and justified in the protocol (See references 3 and 4).

3.9.2.2 Steady-State Studies

i. Immediate Release Dosage Forms

The acceptance criteria are the same as for single dose studies but using AUC_τ instead of AUC_t

ii. Controlled/Modified Release Dosage Forms

The acceptance criteria are as follows:

- AUC_τ - ratio

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

- $C_{max\,(ss)}$ and $C_{min\,(ss)}$

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.75-1.33 (75 – 133%) calculated using log transformed data.

- %Swing and %PTF

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

3.10 Reporting of Results

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP, GLP and cGMP.

3.10.1 Clinical Report

In addition to the protocol etc., the clinical section of the bioequivalence study report should include the following:

i. A statement indicating the independence of the ethics committee.

ii. Documented proof of ethical approval of the study.

iii. A complete list of the members of the ethics committee, their qualifications and affiliations.

iv. An independent monitor's report on the study.

v. Names and affiliations of the all investigator(s), the site of the study and the period of its execution.

vi. The names and batch numbers of the products being tested.

vii. The manufacturing sites (address of the manufacturer of both the reference and the test product).

viii. Expiry date of the reference product and the date of manufacture of the test product used in the study.

ix. Assay and comparative dissolution profiles for test and reference products.

x. CoA of the API used in the test product bio-batch.

xi. A signed statement confirming that the test product used in the bio-study is the same as the one that is submitted for registration.

xii. A summary of adverse events which must be accompanied by a discussion on the influence of these events on the outcome of the study.

xiii. A summary of protocol deviations (sampling and non-sampling) which must be accompanied by a discussion on the influence of these adverse events on the outcome of the study.

xiv. Animals who are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

3.10.2 Analytical Report

The analytical section of the bioequivalence report should include the following which must be clearly presented:

i. The full analytical validation report.

ii. All individual subject concentration data.

iii. All individual plasma concentration *versus* time profiles presented on a linear/linear as well as log/linear scale (or, if appropriate, cumulative urinary excretion data presented on a linear/linear scale).

iv. Calibration data i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters for the entire study.

v. Quality control samples for the entire study.

vi. Chromatograms from analytical runs for 20% of all subjects (or a minimum of 4 subjects) including chromatograms for the associated standards and quality control samples.

vii. Analytical data from subjects who dropped out of the study due to an adverse drug event should also be presented.

viii. A summary of protocol deviations which must be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations must be justified.

3.10.3 Pharmacokinetic and Statistical Report

The pharmacokinetic and statistical section of the bioequivalence report should include the following, which must be clearly presented:

i. All drug concentration *versus* time data from the bio-study. This data must be submitted in hard copy and also formatted on a diskette in a format compatible for processing by SAS software. Individual subject data should be in rows and arranged in columns which reflect the subject number, phase number, sequence, formulation and sample concentration *versus* time data (Appendix 2).

ii. The method(s) and programs used to derive the pharmacokinetic parameters from the raw data.

iii. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.

iv. Tabulated summaries of pharmacokinetic and statistical data.

v. The statistical report should contain sufficient detail to enable the statistical analysis to be repeated, e.g. individual demographic data, randomisation scheme, individual subject concentration vs. time data, values of pharmacokinetic parameters for each subject, descriptive statistics of pharmacokinetic parameters for each formulation and period.

vi. Drug concentration data of any subject withdrawn from the study due to an adverse drug event should also be submitted, but should not be included in the statistical analysis.

3.10.4 Quality Assurance

i. The study report should be accompanied by a signed QA statement confirming release of the document.

ii. A declaration must be made by the applicant to indicate whether the site(s) (clinical and analytical) where the study was performed was subjected to a pre-study audit to ascertain the status of GCP and GLP &/or cGMP conditions at the site(s). All audit certificates should clearly indicate the date of audit and the name(s), address(es) and qualifications of the auditor(s).

iii. The applicant should submit an independent monitor's report on the clinical portion o f the study.

This report should clearly indicate the date of monitoring and the name, address and qualifications of the monitor and should be included in the study report.

3.11 Expiry Dates of Biostudies

The bioavailability/ bioequivalence study must have been completed not longer than three years prior to the date of submission.

4 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4.1 Orally Administered Drug Products Intended for Systemic Action

4.1.1 Solutions

A bioequivalence waiver may be granted for oral solutions, elixirs, syrups or other solubilized forms containing the same active pharmaceutical ingredient(s) in the same concentration(s) as the South African reference product and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).

4.1.2 Suspensions

Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

4.1.3 Immediate Release Products – Tablets and Capsules

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vivo* dissolution profiles on all strengths of each product. Waivers for *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on comparative dissolution studies may be acceptable (see Guideline for Dissolution Testing).

4.1.4 Modified Release Products

Modified release products include delayed release products and extended (controlled) release products. In general bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

4.1.5 Miscellaneous Oral Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE. Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because they might be swallowed by an animal without proper chewing. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same active ingredient/moiety.

4.2 Orally Administered Drugs Intended for Local Action

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required.

4.3 Parenteral Solutions

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently approved product.

In the case of other parenteral routes other than i/v., e.g. intramuscular or subcutaneous, if the test product is of the same type of solution (aqueous) as the reference product, contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required provided that the formulation does not contain an excipient(s) known to significantly affect absorption of the active ingredient(s).

For all other parenterals bioequivalence studies are required.

For intramuscular dosage forms monitoring is required until at least 80% of the AUC_{∞} has been covered.

4.4 Topically Administered Products

4.4.1 Locally Acting

Topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test) is recommended to prove bioequivalence. Validated visual and/or chromometer data will be necessary.

Topical formulations, other than a simple solution, with bacteriostatic, bactericidal, antiseptic and/or antifungal claims, clinical data (comparative clinical efficacy) will be required. Microbial growth inhibition zones will not be acceptable as proof of efficacy. Simple solutions however, may qualify for a waiver based on appropriate *in vitro* test methods.

Proof of release by membrane diffusion will not be accepted as proof of efficacy unless there has been data to show the correlation between release through a membrane and clinical efficacy data.

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

4.4.2 Systemically Acting

For locally applied products with systemic action e.g. transdermal products, a bioequivalence study is always required.

4.5 Products Intended for Other Routes of Administration

Products for local use (oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration.) intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. However, pharmacokinetic studies may be required as measures of safety.

4.6 Variations or Post Registration Amendments

For all post registration changes that require proof of efficacy the requirements of this guideline will be applicable.

5. WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

Bio-waivers will be considered under the circumstances detailed below.

5.1 Immediate Release Products

5.1.1 Class 1 Drug Substances

When the drug product contains a Class 1 drug substance(s) (based on the Biopharmaceutics Classification System, BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients a bio-waiver may be acceptable.

The drug substances must be highly soluble, highly permeable and the dosage form rapidly dissolving (see Guideline for Dissolution Testing).

The applicant must provide relevant information to prove that the drug substance falls within the Class 1 classification (Reference 5).

5.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (See Section 2.9) in its active and inactive ingredients, a bio-waiver may be acceptable.

In such cases the demonstration of bioequivalence *in vivo* of one or more of the lower strength/s may be waived based on dissolution tests (see Guideline for Dissolution Testing) and an *in vivo* study on

the highest strength.

1. **For Multi-source pharmaceutical products**, conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength when an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

   i. Linear elimination kinetics has been shown over the therapeutic dose range.

   ii. The higher strength is proportionally similar to the lower strength.

2. **For New Chemical Entities** with questions on toxicity, bio-wavers for a higher strength will be determined to be appropriate based on:

   i. Clinical safety and/or efficacy studies including dose desirability of the higher strength, and

   ii. Linear elimination kinetics over the therapeutic dose range, and

   iii. The higher strength being proportionally similar to the lower strength, and

   iv. The same dissolution procedures being used for both strengths and similar dissolution results obtained.

Dissolution profiles are required for all strengths. The f_2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f_2 value <50, it may be necessary to conduct an *in vivo* study. The difference factor, f_1, must also be submitted but will not be used as an acceptance criterion (Reference 6).

Note: Details on the performance of dissolution studies are described in the Guideline for Dissolution Testing and not in the BA-BE guideline.

5.2 Modified Release Products

5.2.1 Beaded Capsules - Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A bio-waiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a bio-waiver should be generated for each strength using the recommended dissolution test methods described in the Guideline for Dissolution Testing.

5.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

i. In the same dosage form but in a different strength, and

ii. Is proportionally similar in its active and inactive ingredients, and

iii. Has the same drug release mechanism,

an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

For Section 5.2.1 and 5.2.2 above, the f_2 factor should be used to compare profiles from the different strengths of the product. An f_2 value of ≥ 50 can be used to confirm that further *in vivo* studies are not needed (see Guideline for Dissolution Testing).

6 References

1. Sample size determination for bioequivalence assessment by means of confidence intervals. International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29 No. 1 (1991) 1-8, E. Diletti, D. Hauschke and V.W. Steinijans.

2. Workshop Report: Shah, V.P. et al., *Pharmaceutical Research*: 2000; 17:1551-1557.

3. Evaluation of the Bioequivalence of Highly-Variable Drugs and Drug Products. Pharm. Res. 18:6 (2001) 728-733, L. Tothfalusi, L. Endrenyi, K.K. Midha, M. J. Rawson and J.W. Hubbard.

4. Limits for the Scaled Average Bioequivalence of Highly-Variable Drugs and Drug Products. Pharm. Res. 20:3 (2003) 382-389, L. Tothfalusi and L. Endrenyi.

5. Guidance for Industry. Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

6. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

APPENDIX 1 - Abbreviations and Symbols.

C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
$C_{max\,(ss)}$	maximum plasma concentration at steady-state
$C_{min\,(ss)}$	minimum plasma concentration at steady-state
C_{av}	average plasma concentration
t_{max}	time to C_{max}
AUC_t	area under the plasma/serum/blood concentration-time curve from time zero to time t where t is the last time point with measurable concentration.
AUC_∞	area under the plasma/serum/blood concentration-time curve from time zero to time infinity
AUC_τ	AUC during a dosage interval at steady state
MRT	mean residence time
Ae_t	cumulative urinary excretion from drug administration until time t
Ae_∞	Amount of unchanged drug excreted in the urine at infinite time (7 -10 half lives).
$t_{1/2}$	elimination half-life
%PTF	$(C_{max\,(ss)} - C_{min\,(ss)}) / C_{av}.100$
%Swing	$(C_{max\,(ss)} - C_{min\,(ss)}) / C_{min}.100$

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GUIDELINE ON PRECLINCAL SAFETY STUDIES FOR VETERINARY MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data for preclinical studies. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach and does not bind the MCC nor confirm any rights for or on any person. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all studies are conducted in line with good practice guidelines. The MCC make amendments in keeping with the knowledge which is current at the time of consideration of safety data

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1. PRECLINICAL STUDIES

The safety documentation of the dossier shall show:

- the potential toxicity of the veterinary medicine and any dangerous effects which may occur under the proposed conditions of use in animals. These should be evaluated in relation to the severity of the pathological condition concerned;
- the potential harmful effects to man of residues of the veterinary medicine or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuff;
- the potential risks which may result from the exposure of human beings to the medicinal product, for example during manufacture, in feed mixing of or on administration to the animal;
- the potential risks for the environment resulting from the use of the medicinal product.

All results shall be reliable and valid generally. Where ever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results. Additionally, clinicians shall be given information about the therapeutic potential of the product and about the hazards concerned with its use.

The following preclinical information must be submitted

i. Pharmacology
ii. Pharmacodynamics
iii. Pharmacokinetics
   a Kinetic and metabolism in rats
   b Kinetic and metabolism in primates)

1.1 Toxicity

The study procedures, as found in the latest published guidelines of the following authorities, are acceptable for Preclinical Studies to be performed:
OECD Guidelines for Testing of Chemicals and/or
EEC Directives, Methods for the Determination of Toxicity, and/or
US EPA Pesticide Assessment Guidelines, and/or
JAPAN/MAFF: Testing Guidelines For Toxicity Studies

1.2 Acute toxicity

1.3 LD_{50}

Single-dose toxicity studies can be used to:

- predict the possible effects of acute overdosing in the target species;
- predict the possible effects of accidental administration to humans;
- predict the doses which may usefully be employed in the repeat dose studies;
- assess the relative toxicity of the compound.

Single dose toxicity studies should reveal the acute toxic effects of the substances and the time course for their onset and remission.

These studies should normally be carried out in both sexes of at least two mammalian species. One species may be replaced, if appropriate, by an animal species for which the medicinal product is intended. Preferably two different routes of administration

should be studied. The route selected should be the same as that proposed for the target species. If substantial exposure of the user of the medicinal product is anticipated, for example for inhalation or dermal contact, these routes should be studied.

The LD50 studies need not be performed if sufficient data is generated by other methods to satisfy the requirements of the medicines authority.

1.4 Approximate LD

In order to reduce the number and suffering of the animals involved, new protocols for single dose toxicity testing are continually being developed. Studies carried out in accordance with these new procedures when properly validated will be accepted, as well as studies carried out in accordance with established internationally recognized guidelines. The "fixed dose procedure" proposed by the British Toxicological Society could be followed (e.g. Van den Heuvel *et al.* 1990. *Fd. Chem. Toxic.* Vol 28, 469-482).

All studies must be done on the active ingredient. If acute toxicity studies with the formulation are available these should also be submitted.

1.5 Subacute toxicity

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of substances or medicinal products intended solely for use in animals that do not produce food for human consumption, a repeat-dose toxicity study in one species of experimental animal will normally be sufficient. This study may be replaced by a study conducted in the target species. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or medicinal products intended for use in food producing animals, the studies should be conducted in at least two species, one of which should be a non-rodent. The investigator shall give reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The duration of some of the studies shall be at least 90 days. The investigator shall clearly state and give reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

In the case of new combinations of known substances which have been investigated in accordance with the provisions of this Directive, the repeated-dose tests may,

except where toxicity test have demonstrated potentiation or novel toxic effects, be suitably modified by the investigator, who shall submit his reasons for such modifications.

1.6 Chronic toxicity and carcinogenicity studies

Where applicable long-term toxicity determinations i.e. one year chronic study in dogs or a lifetime chronic study in rats, may be required.

Long-term animal carcinogenicity studies will usually be required for substances to:

- which human beings will be exposed,
- which have a close chemical analogy with known carcinogens,
- which during mutagenicity testing produced results indicate a possibility of carcinogenic effects
- which gave rise to suspect signs during toxicity testing.

1.7 Mutagenicity/Clastogenicity

Mutagenicity tests are intended to assess the potential of substances to cause transmissible changes in the genetic material of cells. If there is any indication of mutagenicity, carcinogenicity studies will be required.

Any new substances intended for use in veterinary medicinal products must be assessed for mutagenic properties.

The number and types of tests and the criteria for the evaluation of the results shall depend on the state of scientific knowledge when the application is submitted.

1.8 Reproductive toxicity

Reproductive studies will be required if there is any indication of adverse effects on potential reproduction in the preceding preclinical studies.

The purpose of such studies is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the medicinal products or substance under investigation.

In the case of substances or medicinal products intended for use in food-producing animals, the study of the effects on reproduction shall be carried out in the form of a two-generation study on at least one species, usually a rodent. The substances or product under investigation shall be administered to males and females from an appropriate time prior to mating. Administration should continue until the weaning of the F2 generation. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Evaluation of the effects on reproduction shall be based upon fertility, pregnancy and maternal behaviour; suckling growth and development of the F1 offspring from conception to maturity and the development of the F2 offspring to weaning.

1.9 Study of embryotoxic/foetotoxic effects including teratogenicity

Embryotoxic/foetotoxic, including teratogenicity studies will be required :

- In the case of substances or medicinal products intended for use in food-producing animals, studies of embryotoxic/foetotoxic effects, including teratogenicity, shall be carried out. These studies shall be carried out in at least two mammalian species, usually a rodent and the rabbit. The details of the test (number of animals, doses, time at which administered and criteria for the evaluation of results) shall depend on the state of scientific knowledge at the time the application is lodged and the level of statistical significance that the results should attain. The rodent study may be combined with the study of effects on reproductive function.

- In the case of substances or medicinal products which are not intended for use in food-producing animals, to animals which might be used for breeding, a study of embryotoxic/foetotoxic effects, including teratogenicity, shall be required in at least one species, which may be the target species.

1.10 Neurotoxicity

Neurotoxicity studies will be required if there is any indication of such effects in the preceding preclinical studies or if the product is chemically related to a group with such potential.

1.11 Other requirements

1.11.1 Immunotoxicity

Where the effects observed during repeated dose studies in animals reveal specific changes in lymphoid organ weights and/or histology and/or changes in the cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, the investigator shall consider the need for additional studies of the effects of the product on the immune system.

The state of scientific knowledge at the time the application to be is submitted shall be taken into account when designing such studies and evaluating their results.

1.11.2 Microbiological properties of residues

1.11.2a Potential effects on the human gut flora

The microbiological risk presented by residues of anti-microbial compounds for the human intestinal flora shall be investigated in accordance with the state of scientific knowledge at the time the application is submitted.

1.11.2b Potential effects on the microorganisms used for industrial food processing

In certain cases, it may be necessary to carry out tests to determine whether residues cause difficulties affecting technological processes in industrial foodstuff processing *e.g.* cheese production..

1.11.3 Observations in humans

Information shall be provided showing whether the constituents of the veterinary medicinal product are used as medicinal products in human therapy. If this is so, a report should be compiled on all the effects observed (including side-effects) in humans. This may be important for assessment of the veterinary medicinal product. When constituents of the veterinary medicinal products are no longer used as medicinal products in human therapy, the reasons should be stated.

Where a medicinal product is intended for topical use, systemic absorption shall be investigated in the target species of animal. If it is proved that systemic absorption is negligible, the repeated dose toxicity tests, the tests for reproductive toxicity and the carcinogenicity tests may be omitted, unless:

- under the conditions of use laid down, oral ingestion of the medicinal products by the animal is to be expected, or
- the medicinal particular may enter foodstuffs obtained from the treated animal (intra-mammary preparations).

2 SAFETY STUDIES IN TARGET SPECIES

2.1 Tolerance studies

In accordance with the guidelines (Evaluation of the safety of veterinary medicinal products for the target animals) provided in terms of Directive 81/851/EEC as amended should be followed. Details should be provided of any signs of intolerance which have been observed during studies conducted in the target species. The studies concerned, the dosages at which the intolerance occurred and the species and breeds concerned should be specified. Details of any unexpected physiological changes should also be provided.

To assess the safety of the compound being applied for the formulation should be tested at multiples of the recommended dose/concentration until signs of intoxication is induced in at least one animal of each sex. A ten fold overdose need not be exceeded. If applicable, the degree of irritation that the formulation causes following administration should also simultaneously be assessed.

2.2 Reproductive safety studies

Reproductive safety studies in the target species will be required if there is any indication of adverse effects on potential reproduction in the preceding trials.

2.3 Field safety studies

In food-producing animals the safety of the formulation should be extensively tested under a wide variety of local field conditions at least double the recommended dose/concentration.

3 ENVIRONMENTAL SAFETY STUDIES

.3.1 Ecotoxicity

The purpose of the study of the ecotoxicity of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks.

An assessment of ecotoxicity shall be compulsory for any application for marketing authorization for a veterinary medicinal product other than applications submitted in accordance with point 10 of Article 5, second paragraph, of Directive 81/851/EEC.

This assessment shall normally be conducted in two phases.

PRECLINICAL SAFETY STUDIES

- In the first phase, the investigator shall assess the potential extent of exposure to the environment of the product, its active ingredients or relevant metabolites, taking into account:
- the target species, and the proposed pattern of use (for example, mass-medication or individual animal medication),
- the method of administration, in particular the likely extent to which the product will enter directly into environmental systems.
- the possible excretion of the product, its active ingredients or relevant metabolites into the environment by treated animals and in particular persistence in such excreta,
- the disposal of unused or waste product.

- In a second phase, having regard to the extent of exposure of the product to the environment and the available information about the physical/chemical, pharmacological and/or toxicological properties of the compound which has been obtained during the conduct of the other tests and trials required by this Directive, the investigator shall consider whether further specific investigation of the effects of the product on particular eco-systems is necessary.

If appropriate, further investigation may be required of:

- fate and behaviour in soil,
- fate and behaviour in water and air and
- effects on aquatic organisms,

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GUIDELINE ON EFFICACY OF VETERINARY BIOLOGICAL MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of efficacy for veterinary biological medicines. It represents the Medicines Control Council's current thinking on this topic. It is not intended as an exclusive approach and does not bind the MCC nor confirm any rights for or on any person. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy.

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PURPOSE

(1) Guidelines are to be re-evaluated from time to time and amended if necessary.

(2) Deviations from these guidelines may be acceptable, provided that they are scientifically justified.

(3) The Regulatory Authority will, in the case of a biological destined for use in production animals, evaluate the proposed administration of the product to ensure that it is in line with local husbandry practices.
An evaluation of efficacy will also be done in light of the specific strains of local organism(s) that are present.

(4) Purpose:

The purpose of efficacy data to be submitted for the registration of veterinary biologicals is to prove that the use of the product according to the label claims (as far as recommended age, route of administration and type of species are concerned), should have the desired effect as claimed on the label.

I. GENERAL DATA:

The efficacy of the product is firstly dependent on the quality of the product. This is determined by the nature and quality of the starting materials and the manufacturing process. Quality control procedures employed during the production process and quality control tests that are carried out on the starting materials and the final product will ensure the quality of the biological. The efficacy of the administration of the product is subsequently proved in the target species, according to the directions for use on the label/package insert.

The following information is required:

(1) Basic information on the product:

(a) Strain(s) present in the product

(b) History of strain

(c) Manipulation of strain (number of passages)

(d) Composition of final product:

(i) Each component:
- description
- function
- reference

(ii) Percentage moisture in the case of live vaccines

(iii) Percentage inactivant in the case of inactivated vaccines

(9) Autogenous biologicals:

(a) Data to be submitted on the efficacy of autogenous vaccines may consist of:
(i) laboratory trial data obtained by the applicant
(ii) information obtained from the literature

If it is impractical to obtain laboratory data prior to the application and if information is not available from the literature, the applicant should submit a suitable motivation for exemption from the submission of efficacy data as mentioned in point 9 (a)(i), and (ii).

Efficacy data will be obtained through the application of the biological and needs to be submitted at the end of 12 months. No challenge work is required, but the veterinarian under whose supervision the biological is used, has to monitor the situation and keep records.

III. ADDITIONAL EFFICACY DATA

1. Interference tests:
(a) If the product contains two or more antigenic components, the absence of interference between the two components (decrease in the protective immunological response to one of the components) should be proved.

(b) If an inactivated liquid product is used as a diluent for a desiccated live vaccine, proof must be submitted that there is no bactericidal or virucidal activity due to residual inactivating agent in the inactivated liquid product.

(c) The absence of possible interference between two different vaccines from the same manufacturer that are recommended to be given to the same animal within a 2-week period also has to be proved.

IV. REFERENCES:

1. United States Department of Agriculture (USDA) (1999). Code of Federal Regulations, Title 9, Parts 1-199. US Government Printing Office, Washington D.C., USA.

2. Office International des Epizooties (OIE) (2000) Manual of Standards for Diagnostic Tests and Vaccines.

3. European Agency for the Evaluation of Medicinal Products (EMEA) (2002) 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK.

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Republic of South Africa

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SAFETY OF VETERINARY BIOLOGICAL MEDICINES

This guideline has been prepared to serve as a recommendation to applicants wishing to submit data as evidence of safety for veterinary biological medicines. It represents the Medicines Control Council's current thinking on this topic. Alternative approaches may be used but must be scientifically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy.

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GUIDELINES

General:

(1) Guidelines are to be re-evaluated from time to time and amended if necessary.

(2) Deviations from these guidelines may be acceptable, provided that they are scientifically justified.

(3) The feasibility of the registration of a biological will be evaluated by the Regulatory Authority to ensure that the use of the product will not introduce an unwanted foreign organism into the country (live vaccine) or cause sero-conversion in animals that will have a negative impact on serological surveys or animal disease control programmes (inactivated vaccines).

(4) Purpose of submission of safety data:

The purpose of safety data to be submitted for the registration of veterinary biologicals is to prove that the use of the product according to the labels claims (as far as recommended age, route of administration and type of species are concerned), does not pose any danger to the life, general well-being or production potential of the animal to be vaccinated.
The evaluation of the safety of the use of the product is also of prime importance to human health to ensure that no harmful residues are present in animals that are destined for human consumption.

I GENERAL DATA:

The safety of the product is firstly dependent on the quality of the product. This is determined by the nature and quality of the starting materials and the manufacturing process. Quality control procedures employedduring the production process and quality control tests that are carried out on the starting materials and the final product will determine the absence of extraneous agents (viruses, bacteria, fungi etc) that could influence the safety of the product. The safety of the administration of the product is subsequently proved in the target species, according to the directions for use on the label/package insert.

The following information is required:

1) Basic information on the product:
   (a) Strain(s) present in the product

   (b) History of strain

   (c) Manipulation of strain (number of passages)

(d) Composition of final product:

(i) Each component:
- description
- function
- reference

(ii) Percentage moisture in the case of live vaccines
(iii) Percentage inactivant in the case of inactivated vaccines

(2) Manufacture:
(a) Outline of Production:

(b) Starting materials (reference or proof of quality):
(i) Starting materials listed in a pharmacopoeia
(ii) Materials of biological origin:
(i) Specific pathogen free eggs
-Flock tests (type of test, sampling frequency)

(ii) Other
- primary cells
- cell lines
- Specific products of animal origin (body fluids, secretions)
- Evaluation of risk of transmission of TSE (transmissible Spongiform Encephalopathy agents)

(iii) Starting materials of non-biological origin, not listed in a pharmacopoeia

(iv) In-house preparation of media

(3) Quality assurance during production:
(a) Quality control procedures:
- Flow chart of production and quality control procedures
- Description of tests:
- Results of 3 consecutive production runs

(4) Control tests on finished product:
(a) Description of tests
(b) Results of tests on 3 consecutive batches

(5) Stability/shelf life:
(a) Storage conditions
(b) Proposed shelf life
(c) Justification of proposed shelf life of:
(i) Finished product:
- data required for at least three batches
- data included for at least three months after the proposed expiry date
(ii) Reconstituted product (if applicable)

II SPECIFIC SAFETY DATA:

The following data are required:

(1) Biological properties of the organism(s) used in the vaccine.

(2) Proof of the safety of the product with the exact composition as stated in I(1)(d). This would include the specific strain of virus or bacterium, at the passage level as stated, with the exact same type and volume of excipients in the final product. These would be inclusive of (but not exclusively) any stabilizer, traces of cell culture medium etc

(3) Proof of the safety of the exact product to be registered for the minimum recommended age of administration. *

(4) Proof of the safety of the exact product to be registered for each species on the label. *

(5) Proof of the safety of the exact product to be registered for each route of administration as mentioned on the label in each of the species mentioned.
Note: Different intramuscular injection sites require separate safety data*

(6) Safety data should include the following:*
- (a) Safety data for the administration of a single dose
- (b) Safety data for the administration of an overdose (x10 for live and x2 for inactivated products)
- (c) Revaccination:
  If revaccination is recommended on the label, proof of the safety of a repeated administration has to be submitted.
  Note: This requirement is not applicable if a single administration is recommended only.

* Note: If a test in a laboratory animal (e.g. guinea pig or mouse) is used, proof of validation of the test for this purpose has to be supplied.

Mouse safety tests are applicable to bacterins, toxoids, bacterin-toxoids and bacterial extracts, unless the product is inherently lethal to mice, in which case a guinea pig safety test is used. If the product is recommended for use in poultry, safety tests are carried out in poultry. Products that are recommended for use in fish, other aquatic species or reptiles are tested for safety in the target species.

Inactivated virus vaccines are either safety tested in the host animal, or a mouse or guinea pig safety test is used. Inactivated vaccines for use in poultry are always safety tested in poultry.

(7) Field safety tests:
All veterinary biological products destined for use in production animals should be tested for safety in the field. Field safety studies are destined to detect unexpected reactions, including mortality that may not have been observed during the development of the product. The tests should be done in the target species, preferably at a variety of geographical locations, using a sufficient number of susceptible animals. The test animals should represent all the ages and husbandry practices for which the product is indicated. A protocol should be developed indicating the observation and recording methods.
Field safety tests could be combined with field efficacy tests.

(8) Safety data for a multi-component biological may be used to prove the safety of a biological that only contains one or more of the components, provided that the composition of the biologicals apart from the active ingredient(s) are identical.

(9) All trial data should consist of:

(a) Properly documented scientific trial data.
An indication should be supplied of the person responsible for the trial (designation), the trial site as well as the trial date.

(b) Exact trial procedure:
(i) Numbers used
(ii) Exact dosages/titres
(iii) Details of route of administration

(c) Results:
(i) Should be supplied in detail
(ii) Abbreviations in tables, graphs should be explained
(iii) A statistical analysis of the results should be included

(10) Autogenous biologicals:

(a) Autogenous vaccines may only consist of micro-organisms either proven to be safe or rendered safe by inactivation.

(b) The safety of an autogenous vaccine should be satisfactorily proven prior to authorisation for use in the case of poultry vaccines or where possible. In the case of a vaccine for use in large animals if testing in the applicable species is not practical prior to authorisation, the lack of safety testing should be indicated on the label and the user advised. The user should also be advised that the vaccine is to be initially administered to five animals on the farm and these animals monitored for adverse reactions.

III ADDITIONAL SAFETY DATA:

(1) Examination of reproductive functions particularly in the case of modified live biologicals:
Safety data are not required if the product is not indicated for use in animals of a reproductive age

(2) Examination of immunological functions:
Safety data are not required if:
(i) The product is an inactivated vaccine
(ii) The active ingredient is not immunosuppressive
(iii) The active ingredient in its natural form does not affect organs of the immune system

(3) Spread of the vaccine strain:
Data have to be submitted to prove the safety of the product as far as the excretion by and the spread of the vaccine strain by the most sensitive category of the target species.

(4) Data have to be submitted to prove the safety of the unintended spread of the vaccine strain to susceptible animals of a non-target species that is also susceptible to infection by the organism(s) in the vaccine

(5) Dissemination in the vaccinated animal:

Data have to be submitted for the most sensitive category of the target species

(6) Reversion to virulence:

In the case of a virus vaccine:
Data have to be submitted to compare the virulence of the vaccine virus after 10 *in vivo* back passages (in the case of poultry vaccines) or 5 *in vivo* back passages (in the case of vaccines other than for use in poultry) of the vaccine virus with the parental wild type virus in the most sensitive category of the target species.

(7) Recombination or genomic re-assortment:

An evaluation of the possibility of recombination or genomic re-assortment should be submitted.

(8) Residues:

Data on the presence and safety of residues in the target species should be submitted.
In the case of an inactivated vaccine (adjuvants) or a live vaccine (preservatives), residues could either pose a human health hazard or lead to aesthetically unacceptable lesions at the injection site that could lead to condemnation at the abattoir in the case of animals destined for human consumption.

(9) Interactions:

Data are required to prove the safety of the biological product if used in combination with other products.

(10) Ecotoxicity:

An assessment of the risk to the environment of the use of the product has to be submitted.

The risk assessment should include:

1. Hazard identification
   (a) Capacity of the live organism to transmit to non-target species
   (b) Shedding of live product organisms (route, numbers, duration)
   (c) Capacity to survive, establish and disseminate
   (d) Pathogenicity to other organisms
   (e) Potential for other effects of the live product organism

(f) Toxic effects of the product components

(g) Toxic effects of excreted metabolites

2. Assessment of likelihood of a hazard occurring

3. Assessment of the consequences of a hazard occurring

4. Assessment of level of risk.

(11) Safety of biotechnology-derived vaccines:
Biotechnology-derived products do not differ fundamentally from conventional products and the existing guidelines would apply to these products as well.
It should be ensured that the use of these products does not pose a threat to either public health or the environment.

These products can be divided into three categories, based on their biological properties and on the safety concerns that they represent:

Category I:
Non-viable or killed products that pose no risk to the environment and present no new or unusual safety concerns. Such products include inactivated micro-organisms, either whole or as sub-units, created by using rDNA.

Category II:
Products that contain live micro-organisms modified by adding or deleting one or more genes. Added genes may code for marker antigens, enzymes or other biochemical by-products. Deleted genes may code for virulence, oncogenicity, marker antigens, enzymes or other biochemical by-products.
The application must include a characterisation of the DNA segments added or deleted, as well as a phenotypic characterisation of the altered organism. The genetic modification must not result in any increase in virulence, pathogenicity or survivability in the altered organism in comparison with the wild-type form. It is important that the genetic modification does not cause deterioration in the safety characteristics of the organism.

Category III:
These products make use of live vectors to carry recombinant-derived foreign genes that code for immunising antigens. Live vectors may carry one or more foreign genes that have been shown to be effective for immunising target host animals.

IV. REFERENCES:

1. United States Department of Agriculture (USDA) (1999). Code of Federal Regulations, Title 9, Parts 1-199. US Government Printing Office, Washington D.C., USA.

2. Office International des Epizooties (OIE) (2000) Manual of Standards for Diagnostic Tests and Vaccines.

3. European Agency for the Evaluation of Medicinal Products (EMEA) (2002) 7 Westferry Circus, Canary Wharf, London, E14 4HB, UK.

VMRF 1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FOR REGISTRATION OF A VETERINARY MEDICINE

ADMINISTRATIVE DATA

APPLICATION NUMBER

A. PARTICULARS OF PROSPECTIVE HOLDER OF THE CERTIFICATE OF REGISTRATION

Name: ----------
Business address: ----------
Postal address: ----------
Telephone No: ----------
Fax No: ----------
E-Mail address: ----------
Site Master File Number: ----------

Authorised person/applicant to communicate with regulatory authority on behalf of the holder of the certificate of registration

Name: ----------
Business address: ----------

Telephone no: ----------
Fax No.: ----------
E-mail: ----------

(Attach letter of authorisation signed by the Managing Director)

VMRF 1

B. PARTICULARS OF VETERINARY MEDICINE

Proprietary name: ----------

Pharmacological Classification: ----------

Dosage form:----------

Dosage unit:----------

Active pharmaceutical ingredient(s) and strength(s) per dosage unit:

Descriptive name of veterinary biological:----------

Indicate with an X in the appropriate block if the application is for a

☐ New product with new active ☐ new product with existing active

☐ Amendment to existing product. Registration no. ☐☐☐☐☐☐☐

☐ Parallel product ☐ daughter product ☐ multi – source product

Route of administration: ----------

Pharmacological classification:----------

Manufacturer:----------

Business address:----------

Site Master File reference number: ----------

Packer: ----------

Business address:----------

Site Master File reference number: ----------

Final product release control (FPRC):----------

Business address:----------

Site Master File reference number: ----------

Final product release responsibility (FPRR):----------

Business address: ----------

Site Master File number: ----------

The undersigned hereby declares that all the information herein and in the PARTS hereto are correct and true and are relevant to this particular medicine.

.....

Signature of Managing Director/Authorised person

....

Name in block letters Date of application

....

Designation Date of current amendment **(Post-registration only)**

VMRF 1

C. UPDATE HISTORY (**For Post-registration only**)

LETTER DATE OF APPLICATION FOR AMENDMENT	SUMMARISED DETAILS OF AMENDMENT	DATE OF APPROVAL BY COUNCIL

Guideline references:

VMRF 1

TECHNICAL DATA

PART 1 A

PARTICULARS OF THE VETERINARY MEDICINE SCIENTIFIC PACKAGE INSERT

The under-mentioned information with regard to this medicine shall appear on the scientific package insert. The information shall be presented in the format stipulated: Provided that the Council may authorise any deviation from such information or such format (refer to Regulation 40).

1. The words "**Veterinary Medicine**"
2. Scheduling status
3. Proprietary name and dosage form
4. Scheduling status
5. Dosage form
6. Composition
7. Pharmacological classification
8. Pharmacological action
   Pharmacokinetics and pharmacodynamics
9. Indications per species.
10. Contra-indications
11. Warnings or withdrawal period in the case of food-producing animals
    Safety in pregnancy and lactation
12. Dosage and directions for use including age and species dosage
13. Side effects and special precautions for use per species. Interactions
14. Known signs of overdosage and particulars of its treatment per species
15. Conditions of registration
16. Identification
17. Presentation
18. Storage instructions
19. Registration number
20. Name and business address of the holder of the certificate of registration
21. Date of publication of the package insert

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PART 1 B SPECIMEN OF THE LABEL

A specimen of the immediate container label and, if applicable, the outer label shall be included here. This shall conform to Regulation 48.

VMRF 1

PART 1 C FOREIGN REGISTRATION

a) A list of countries in which an application has been lodged and the status of these applications shall be furnished, detailing approvals, deferrals, withdrawals and rejections.

b) If the veterinary medicine has been registered in another country, the conditions of registration and proof thereof shall be furnished. If registered in the European Union commission (including countries employing the mutual recognition system), Australia, United Kingdom, United States of America, Canada, The Netherlands, Sweden and Japan, the approved package insert (data sheet) shall be provided (All documents must be submitted in English).

c) Name and business address of the manufacturer, packer and testing laboratory, where applicable.

d) Details of any negative decision by any recognised Medicines Regulatory Authority shall be Provided.

VMRF 1

PART 2

QUALITY CONTROL

PART 2A (i) VETERINARY MEDICINES OTHER THAN BIOLOGICALS

ACTIVE PHARMACEUTICAL INGREDIENT REQUIREMENT (DEVELOPMENT CHEMISTRY AND CHARACTERISATION)

a) The name(s), structural formulae, empirical formulae, molecular mass, solubility and storage requirements are as follows:

International Nonproprietary Name (INN) or approved name and chemical name	Structural formula, empirical formula, molecular mass	Solubility	Storage requirements	Shelf-life (and re-test period)

b) The active pharmaceutical ingredients are obtained from the following sources:
Name and business address of the manufacturer(s)

c) Active Pharmaceutical Ingredient File (APIF) or DMF (open part) or certificate of suitability (CEP)

d) Certificate of analysis of two batches

e) Proof of physical and chemical equivalence (more than one manufacturer)

f) Stability data and shelf-life of active pharmaceutical ingredient

VMRF 1

PART 2A (ii) PRIMARY PRODUCTION LOT/BATCH (BIOLOGICAL VETERINARY MEDICINES)

1. DESCRIPTION OF THE PREPARATION AND PRODUCTION OF THE PRIMARY PRODUCTION LOT.

a) Name and address of the manufacturing facility in which production of the primary production lot takes place.

b) Master seed Identification , description and control

c) The complete description of the preparation and manufacturing process of the primary production or bulk lot, the tests carried out on the product and the stages at which such tests are carried out to confirm the integrity of the product must be submitted.

2. SPECIFICATIONS OF RAW MATERIALS USED IN THE PRIMARY PRODUCTION LOT.

The following are the specifications that apply to the raw materials used in the primary production or bulk lot of a veterinary biological medicine, including the titles of the tests and the limits and criteria of acceptance of each parameter contained in the specification. (Where the test mentioned corresponds to a recognised pharmacopoeia, the source shall be mentioned):

3. TESTS CARRIED OUT ON RAW MATERIALS IN THE PRIMARY PRODUCTION LOT AND THE LABORATORIES

The following is a complete description of the tests carried out on all the raw materials used in the primary production or bulk lot, specifying the name and address of the laboratory(ies) in which such tests are carried out.

VMRF 1

PART 2 B (i) FORMULATION

FORMULATION OF THE FINAL DOSAGE FORM

a) Below is a schedule of the names and quantities of each active and inactive ingredient contained in a dosage unit. Where no dosage unit exists, other suitable unit of mass or volume of the veterinary medicine may be used and these shall conform to the relevant particulars in the package insert and on the label with regard to the active pharmaceutical ingredients.

b) The purpose(s) of each inactive ingredient in the formulation shall be specified, including that of raw materials used in manufacturing, but which are not present in the final product.

Approved name	Quantity per dosage unit*	Active or inactive	Purpose of inactive

*mg per tab/cap/loz/supp or mg or ml per specified volume or mass of product

c) Potency calculations. A statement to the effect that the actual quantity of the active pharmaceutical ingredient will depend on the potency shall be included.

d) Composition of inactive ingredients in combination, mixtures, etc.

e) Overages and justification for their inclusion.

f) Toxicity level per dosage unit must be indicated for all solvents and for other ingredients when required by Council. Levels must be indicated as per "USP DI" or "Martindale", or "The Complete Drug Reference", or other specified reference.

VMRF 1

PART 2 B (ii) FORMULATION OF THE FINAL FILLING LOT FOR VETERINARY BIOLOGICALS

a) Below is a schedule of the names and the strength or concentration of each active and inactive in the veterinary biological veterinary medicine and with regard to the active ingredients , conform to the relevant particulars in the package insert and on the label .

b) The purpose of each ingredient in the formulation shall be specified, and raw materials used, even if not present in the final dosage form but used during manufacture , shall be mentioned.

Approved name or chemical name of constituent	Quantity per unit *	Purpose	Purpose of inactive

*%m/m,m/v,v/v

VMRF 1

SECTION3B(iii) FORMULATION OF THE RECONSTITUTING LIQUID FOR THE FINAL FILLING LOT FOR BIOLOGICAL VETERINARYMEDICINES

(a) Below is a schedule of the names and quantities of each ingredient contained in the diluent.

(b) The purpose of each ingredient in the formulation shall be specified , and raw materials used , even if not present in the final diluent shall also be given .

Approved name or chemical name of constituent	Quantity	Purpose

VMRF 1

PART 2C SPECIFICATIONS AND CONTROL PROCEDURES FOR RAW MATERIALS USED IN THE MANUFACTURE OF THE FINAL PRODUCT (VETERINARY MEDICINES) OR FINAL FILLING LOT AND DILUENTS (BIOLOGICALS)

a) Pharmacopoeial ingredients.

Raw Material		Specifications and Pharmacopoeial reference*	Limits	Additional Tests (e.g. particle size)
Active				
Inactive				

*The latest edition of the pharmacopoeia is implied, unless otherwise specified and justified.

(b) Non-pharmacopoeial ingredients. In – house specifications and control procedures for these ingredients should be included .

Raw Material		Specifications	Limits	In-house control procedures
Active				
Inactive				

c) The applicant must comply with and confirm the following requirements in the application:

(i) Identification and assay of the active raw material, irrespective of the possession of a certificate of analysis from the supplier.

(ii) Identification of the inactive raw material, irrespective of the possession of a certificate of analysis from the supplier.

(iii) Perform any other tests not included in a valid certificate of analysis.

d) The frequency of testing of water, where applicable, must be included

VMRF 1

PART 2 D CONTAINER AND PACKAGING MATERIAL

a) **DESCRIPTION OF CONTAINERS**

(i) Immediate container, including any patient-ready packs, closure, wadding, desiccant (type of material and dimensions, including sketches).

(ii) Outer container (type of material of container).

(iii) Bulk container (type of material of container).

(iv) Application and administrative sets (type of material and dimensions including sketches).

b) **SPECIFICATIONS AND LIMITS FOR PACKAGING MATERIALS**

The following must be completed :

Specification	Limit	Name of manufacturer/packer of the final product

Indicate those tests performed by the supplier of the packaging material.

c) **DESCRIPTION OF CONTROL PROCEDURES PERFORMED BY MANUFACTURER/PACKER OF FINAL PRODUCT**

d) **PACK SIZES**

VMRF 1

PART 2 E MANUFACTURING PROCEDURES

MANUFACTURING PROCEDURES OF FINAL PRODUCT (VETERINARY MEDICINES)

FINAL FILLING LOT AND DILUENT (BIOLOGICAL VETERINARY MEDICINES)

a) INSPECTION FLOW DIAGRAM:

b) MANUFACTURING PROCEDURES:

(i) Batch Manufacturing Formula(s) and Batch Size(s)

(ii) Copy of the Batch/Master Manufacturing document for a real batch. A comprehensive flow diagram or a description of the manufacturing procedures detailing the various stages of manufacturing. Indicate the type of equipment, sieve sizes (µm), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm), etc. The frequency of all in-process control tests (analytical, microbiological, and physical) shall be shown in the flow diagram or specified in the description.

c) PACKAGING PROCEDURES:

Copy of the Batch/Master Packaging document or a comprehensive flow diagram or a description of the packaging procedures detailing the various stages of packaging and labeling. Indicate the type of equipment used in the packaging process. The in-process tests, the frequency of testing and control procedures carried out during the packaging process shall be included.

d) MANUFACTURING PROCESS VALIDATION PROTOCOL:

The process validation protocol is as follows:

VMRF 1

PART 2 F FINISHED PRODUCT (VETERINARY PHARMACEUTICAL)

FINAL FILLING LOT & DILUENT (VETERINARY BIOLOGICAL)

a) **SPECIFICATIONS AND LIMITS**

The following tables include the specifications , limits criteria for acceptance of all physical , chemical and , where applicable , microbiological parameters and the responsible laboratories for :

(i) in - process control

Specification	Limits	Responsible Laboratory (ies)

(ii) Final product control

Specification	Limits	Responsible Laboratory (ies)

(iii) Stability studies

Specification	Limits	Responsible Laboratory (ies)

(iv) Manipulated final product

Specification	Limits	Responsible Laboratory (ies)

Final product specifications , for imported products upon local receipt the product must be re – identified and assayed , unless a supplier / transport validation has been submitted to and approved by Council. In all cases a valid Certificate of Analysis which shows all the tests described in the final product specification must accompany the shipment . Should any of the required tests be omitted from the CoA , then these tests must be re – done locally prior to the release.

b) **TABLE OF TESTS TO BE PERFORMED**

	TITLE OF SPECIFICATION
FPRC	
FPRC responsible for tests after importation	Identification Assay

VMRF 1

FPRR	Appearance of dosage form Container Package insert Label Batch No. Expiry date. Certificate of Analysis Batch release documents

c) **CONTROL PROCEDURES**

Description of the control procedures for all the specifications in section (a) must be included

d) **CERTIFICATE OF ANALYSIS OF THE FINAL PRODUCT**

e) **VALIDATION**

Validation data for all quantitative assay methods must be included.

It must be demonstrated that the assay method is stability indicating , i.e. will distinguish between the active ingredient and the degradation product (s). If the assay method is not stability indicating the validation data of the procedures used to determine the assay and that used to determine the degradation product must be submitted separately.

VMRF 1

PART 2 G STABILITY DATA FOR THE FINISHED PRODUCT

a) **STABILITY PROGRAMME**

Describe the stability programme to be followed and include, the following:

(i) Conditions (temperature, humidity)

(ii) Time points of determination, e.g. 0, 3, 6, 9 months, etc.

(ii) Specifications to be determined

(iii) Frequency of stability testing on future batches (Refer to WHO and cGMP stability testing guidelines.)

(iv) Stability test control procedures

b) **PRESENTATION OF STABILITY DATA**

Product Name: Batch No.: Batch Size: Date of Manufacture:		Packaging (material and pack sizes): Storage conditions: Name of manufacturer: Source of active pharmaceutical ingredient:					
Date of commencement of stability study:							
		Time intervals (Months)					
Specification	Limit	0	3	6	9	12	24

c) **DISCUSSION AND CONCLUSION OF SHELF-LIFE FOR EACH TYPE OF CONTAINER**

VMRF 1

PART 2 H PHARMACEUTICAL DEVELOPMENT

a) Highlight and motivate any differences in formulation and/or method of manufacturing of the different batches used in stability, bioequivalence and clinical studies.

b) Pharmaceutical Expert Report

i) Active Pharmaceutical Ingredient(s):

ii) Formulation:

iii) Production/Manufacture:

iv) Stability:

v) Conclusion of Expert Report:

vi) Name, signature and date of the responsible person:

vii) Reference list used in the compilation of the report:

VMRF 1

PART 2 I EXPERTISE AND PREMISES USED FOR MANUFACTURING OF VETERINARY BIOLOGICALS

1. DETAILS RELATING TO THE PREMISES WHERE PRIMARY PRODUCTION IS UNDERTAKEN AND THE STAFF INVOLVED IN THE PRODUCTION AND TESTING OF VETERINARY BIOLOGICALS.

a) Description of the premises where all procedures involved in the preparation of the primary production or bulk batch is carried out. (A floor plan must be included):

b) Details of other purposes for which the premises are used:

c) Names, qualifications and field and duration of experience of the persons responsible for the manufacture, testing and release of the veterinary biological medicine, in the form of the primary production or bulk lot and the final containers ready for sale:

2. NAME AND ADDRESS OF FACILITY WHERE THE IMPORTED FINAL FILLING LOT IS STORED

VMRF 1

PART 3 BIOEQUIVALENCE AND BIOAVAILABILTY

a) **STATE THE PURPOSE OF THE STUDY**

(i) As comparison of formulation to be marketed versus formulation used in clinical trials, or
(ii) As proof of efficacy for a multi - source application, or
(iii) As proof of efficacy of new formulation (formulation change)

(b) **REFERENCE PRODUCT USED**

(i) Clinical trial formulation
(ii) Innovator product
(iii) Current formulation (for change of formulation)

The following must be indicated:

	Reference product	Formulation applied for
Name of product		
Batch no		
Holder of certificate of registration		
Country where purchased		
Assay results		
Source of API		

(c) **METHOD USED**

Describe the method in full, e.g. bioavailability, dissolution, etc.

(d) **VALIDATION**

Validation data for all quantitative assay methods shall be included.

(e) **STUDIES**

Include protocol , final report , assay validation report , pharmacokinetic report (including individual animal data) and statistical report.

(f) **DISCUSSION AND CONCLUSION**

Attach documents (where applicable)

VMRF 1

PART 4 PRE-CLINICAL STUDIES

a) Pre-clinical Expert Report

b) The following are Parts obtained and conclusions drawn from tests performed pre-clinically to demonstrate all aspects of the toxicity of the medicine, and to prove the safety of its use, with special reference to -

(i) acute toxicity,
(ii) subacute toxicity studies;
(iii) chronic toxicity studies;
(iv) reproduction toxicity and teratogenicity studies;
(v) carcinogenicity studies;
(vi) mutagenicity studies; or
(vii) environmental impact studies for veterinary medicines
(viii) pharmacokinetics studies:
(ix) neurological studies
(x) other tests to substantiate the safety of the veterinary medicine;

c) The following are Parts obtained and conclusions drawn from tests performed pre – clinically to demonstrate all aspects of the efficacy of the veterinary medicine , with special reference to ;

(i) The methods and experimental results of and the conclusions drawn from tests performed pre-clinically with reference to the efficacy of the veterinary medicine;
(ii) the relationship between the tests performed and the purpose for which the veterinary medicine is or will be used, or for which it will be propagated, and
(iii) the dosage and method of administration of the veterinary medicine, are as follows:

In cases of multi – source products, the MCC may grant exemption from the submission of some or all of the above information.

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PART 5 SAFETY AND EFFICACY

a) Expert Report

b) The field trials performed on target species with regard to the safety of the use of the veterinary medicine, with special reference to the particular dosage, routes of administration used and the side-effects observed,

c) Particulars of clinical or field trials conducted to establish the efficacy of the use of the veterinary medicine ,

d) Experimental details and results of the studies performed to establish the correlation between the applicable blood and other suitable physiological concentrations and the pharmacological action claimed for the veterinary medicine are as follows:

e) Veterinary medicines for food – producing animals : Residue depletion studies and recommended withdrawal periods

In cases of multi – source products , the Council may grant exemption from the submission of some or all of the above information as laid down in the guidelines for the registration of these products.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR APPLICATIONS TO AMEND THE REGISTRATION DOSSIER OF A MEDICINE

This document has been prepared to serve as a recommendation to the holder of a certificate of registrations wishing to submit applications for amendment of registration dossiers of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. Applicants should note that there are major changes in the mannerin which amendments will be handled in future as described in this document.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

TABLE OF CONTENTS

AMENDMENTS

1. INTRODUCTION

This document has been prepared to guide holder of a certificate of registration when making amendments to registered medicines. It is acknowledged that the holder of a certificate of registration may make amendments from time to time with the aim to improve safety, quality and efficacy of a medicine or to improve product information. It is, therefore, the objective of the MCC to process the amendments as quickly as possible, hence, this policy document has been prepared to be used as a tool to address all matters concerning amendments

Amendments to the registration dossier are necessary to maintain the safety, quality and efficacy of a medicine and to ensure compliance with current technical requirements and to adhere to administrative aspects, and to keep abreast of scientific progress, or to reflect new therapeutic indications.

This document is intended to changes in facilities (including change in the holder of certificate of registration), pharmaceutical and analytical aspects of the medicine. It is the responsibility of the holder of the certificate of registration to provide comprehensive documentation to support the amendment application and to comply with the conditions determined by Council.

2. APPLICATION FOR THE AMENDMENT TO A REGISTRATION DOSSIER OF A MEDICINE

2.1 Applications for amendments to existing dossiers must be submitted on the appropriate application form (MRF 3A or MRF 3B) and accompanied by a cover letter detailing the type of amendment required as described below.

2.2 **Incomplete submissions or submissions which do not comply with the requirements as described will not be evaluated. These must be collected within 14 working days, failing which such applications will be confiscated.**

2.3 An amendment application may not address more than one product unless the products constitute a range for which a single application for registration dossier was submitted at the time of application for registration. Further, unless it is an application for change of name or address of the holder of certificate of registration only, in which case details for a group of products may be submitted. However, each registration dossier must be updated in accordance with the change

2.4 All applications for amendments must be properly bound on the left side as this allows for easy update and addition of pages to the dossier. It is preferred that documents be bound with plastic ring binding or punched (2-hole) and secured. The use of lever-arch files and any kind of paper clip is not recommended.

2.5 The date of the covering letter must be reflected on every page of the submission letter in black.

2.6 All pages must be paginated and the document indexed according to the existing MRF 1 Parts (e.g. page 2B-1 referring to PART 2B, first page).

2.7 Include dividers or tabs where applicable for ease of locating sections in the document.

2.8 Submit the front page of the amended MRF 1 Parts and the amended pages only when amendments are made which involve updating of a limited number of pages.

2.9 When extensive updating of the dossier is done, **a completely updated dossier** must be submitted and the amended sections clearly indicated. It is not acceptable to submit selected pages only when a full update is submitted. Such full updates must preferably be bound with plastic ring binding or punched (2-hole) and secured. The use of lever-arch files or any kind of paper clip is not recommended.

2.10 All documents in a foreign language must be translated into English and certified or verified.

2.11 When an application for amendment is submitted, the ADMINISTRATIVE DATA of the MRF1 form must be updated with regard to C. UPDATE HISTORY. The date of application of each amendment (previous and current) for the last three amendments, summarised details of the amendment/s, and date of approval by the Medicines Control Council must be provided in tabulated format.

2.12 Amendments to applications for registration before registration are not permitted, unless advised by or negotiated with Council.

3. APPLICATION TO AMEND THE PARTICULARS REGARDING PROPRIETARY NAME, HOLDER OF CERTIFICATE OF REGISTRATION, MANUFACTURER, PACKER, FINAL PRODUCT RELEASE CONTROL AND FINAL PRODUCT RELEASE RESPONSIBILITY

3.1 GENERAL INFORMATION

3.1.1 Applications pertaining to the above must be submitted under cover of form MRF 3A.

3.1.2 Amendments must be accompanied by the appropriate amendment fee. If a cheque is submitted to cover the amendment fees for more that one product, a list of the products involved with the reference numbers and date of requesting the specific amendment for each product must be supplied. A copy of this letter as well as a copy of the cheque must be included in the application for each individual product.

3.1.3 Amendments to registered products must be accompanied by the original registration certificate. A copy of the registration certificate will not be accepted as the original must be replaced. Where the original certificate has already been submitted to Council, this must be indicated on the MRF 3A form. **(Original certificate already submitted with application dated ....., reference no. .....)**

3.1.4 All amendments must be accompanied by updated administrative details (front page) of the MRF 1 front page.

3.1.5 As the processing of these amendments results in the updating of the database and the issue of amended registration certificates, the holder of the certificate of registration must ensure that details with regard to previously approved facilities are updated to reflect

name and address changes of companies through the years. Changes must be detailed, and the appropriately amended Parts included in the submission.

3.1.6 Should there be a discrepancy between the administrative data submitted with the amendment request and the relevant Parts, the data in the Registration Dossier on file will be reflected on the registration certificate.

3.1.7 It is the responsibility of the holder of the certificate of registration to ensure that details with regard to the facilities / laboratories applied for are correctly reflected on the front page, and to check registration certificates for correctness and communicate discrepancies to Council within 30 days of receipt thereof.

3.1.8 If the holder of the certificate of registration is of the opinion that the information reflected on the registration certificate is incorrect, the holder of certificate of registration must provide the correct approved **information together with the letter(s) of approval by the Council**. An amended registration certificate will be issued free of charge should the error have occurred at this office.

3.1.9 A change can only be considered final once the holder of the certificate of registration has been supplied with the new registration certificate for registered medicines, or a final letter of approval of the amendment from the Council in the case of an old medicine.

3.1.10 Updating of dossier: If the dossier has not been updated during the previous 5 years, or an application for a major change is lodged, a fully updated dossier must accompany an application for transfer of the certificate of registration or change in manufacturer.

3.1.11 All relevant documentation must be submitted as one document and different Parts should not be submitted separately. Duplicate documents may not be submitted to different sections.

3.1.12 The processing of the request is not a mere formality. Each application has to be evaluated on an individual basis before such a request may be approved. The authorisation for change is dependent on various aspects including the proposed new holder of certificate of registration / manufacturer / packer / laboratory's infrastructure and its compliance with Good Manufacturing Practice in terms of the guidelines as recommended by the World Health Organisation and SA Guide to GMP.

3.1.13 In order to assess the suitability of the proposed holder of certificate of registration, manufacturer, packer or laboratory, an inspection by Council Inspectors may have to be performed prior to the authorisation of the change requested.

3.1.14 Please, note that once a change in HCR /manufacturer/packer/FPRC/FPRR has been approved, the updated pages to the Parts are placed on file. Subsequent updates of the dossier should not again indicate an application for change in these aspects.

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3.2 CHANGE OF PROPRIETARY NAME

3.2.1 Application to change the proprietary name of a product must be submitted on an official letterhead of the HCR and the reason for the amendment must be clearly stated.

3.2.2 Changing of the proprietary name during the evaluation and registration phase will only be permitted if the Council has not accepted the name originally proposed by the applicant.

3.2.3 The HCR must be accompanied by an amended Administrative Section of MRF 1, Part 2B (Formulation) and the professional package insert and patient information leaflet.

3.2.4 The policy on change of proprietary names is detailed in the Guidelines for Registration of Medicines – General Information.

3.3 CHANGE OF HOLDER OF CERTIFICATE OF REGISTRATION

3.3.1 The proposed HCR must have submitted a Holder of the Certificate of Registration Master File HCRMF) prior to any application for transfer of a medicine registration certificate.

3.3.2 An application for a change of HCR must be submitted on a company letterhead under cover of MRF 3A together with the following documentation:

3.3.2.1 Details of the current holder of the certificate of registration
3.3.2.2 Details of all other companies involved in the manufacturing of this product.
3.3.2.3 Statement by holder of certificate of registration to confirm possession of master documents, existence of contracts, commitment to updating dossiers and detailing changes in the manufacturing process
3.3.2.4 Signed letter of cession by the current HCR on an official letterhead
3.3.2.5 Signed letter of acceptance by the proposed HCR on an official letterhead
3.3.2.6 The original registration certificate (registered products
3.3.2.7 The amendment fee
3.3.2.8 Updated administrative data (MRF 1 front page cover)
3.3.2.9 Inspection flow diagram for the product
3.3.2.10 Organogram of proposed HCR (including the names of key personnel with specific reference to production and quality assurance)

3.3.3 The letter of cession from the current legal HCR must confirm that the full application dossier (MFR 1) and product history have been transferred to the proposed HCR.

3.3.4 It should be noted that the final product release responsibility (FPRR) often changes when a registration certificate is transferred. The application for registration dossier must be appropriately updated to reflect this change. (Front page cover). This change must be clearly indicated.

3.3.5 The Registration dossier must be fully updated to the current statutory format and current scientific standards within 12 months after transfer of the registration certificate. In the case of mergers the HCR must adhere to the programme of updating of dossiers as approved by the Council. The date by which the dossier will be fully updated must be clearly reflected in the covering letter.

AMENDMENTS

However, if the dossier had not been updated during the previous 5-year period, a fully updated dossier must accompany the application for transfer of the registration certificate.

3.3.6 The proposed HCR must ensure that the registration dossier presented to them has been fully updated recently (at least during the last 5 years) and that the full product history is provided by the current HCR.

3.3.7 An holder of certificate of registration must be in possession of all specifications relevant to a product

3.3.8 The current HCR remains legally responsible and liable until transfer of the registration certificate has been confirmed in writing.

3.4 CHANGE OF / ADDITIONAL: MANUFACTURER, PACKER/ FPRC/FPRR

3.4.1 An application for change of manufacturer/packer/FPRC/FPRR must be submitted on an official company letter head under cover of form MRF 3A

3.4.2The following documentation must be included:

3.4.2.1 Details of holder of certificate of registration

3.4.2.2 Details of all other companies involved in manufacturing of the product

3.4.2.3 Statement by holder of certificate of registration confirming possession of master documents, existence of contracts, committing to updating of dossiers and detailing changes in the manufacturing process

3.4.2.4 Inspection flow diagram for the product

3.4.2.5 The original registration certificate (registered products)

3.4.2.6 The amendment fee

3.4.2.7 Updated administrative data MRF 3

3.4.3 The following data pertaining to manufacturing/packing/laboratory sites (local and overseas) will be required.

- Site Master File if not previously submitted
- Organogram listing all the key personnel

3.4.4 For manufacturers/packers outside the borders of South Africa the following additional information will be required:

3.4.4.1Copy of the latest inspection report-

3.4.4.2 For a recognised country with a competent regulatory authority, a GMP certificate of compliance in terms of WHO Certification Scheme or a GMP certificate issued by a competent authority for the manufacturing site or copy of the manufacturing licence (not older than 2 years) will be sufficient.

3.4.4.3 For manufacturers in "non-recognised" countries, that haven not been inspected by a recognised authority, an inspection report from a recognised authority will be required.

OR

3.4.4.4 For manufacturers in "non-recognised" countries that have not been inspected by a recognised authority, an inspection by Council Inspectors may be required.

3.4.4.5 For change in manufacturer:

3.4.4.5.1 Where the manufacturing procedure (including equipment) is identical to the manufacturing procedure currently used, the following mustbe submitted:

i) a statement signed by the managing director (or in the case of an overseas country the head of the production plant or chief technical

officer) that the manufacturing procedures and equipment are the same as that currently used;

ii) updated Front Page

iii) *However, if the dossier had not been updated during the previous 5-year period a fully updated dossier must accompany the application for change of, or for an additional, manufacturer.*

3.4.4.5.2 Where the manufacturing procedure (including equipment) differs, but falls within the minor Type A of Type B amendments, the following must be submitted:

i) a statement signed by the managing director (or in case of an overseas country, the head of the production plant or chief technical officer) that the changes to the manufacturing procedures fall within the Type A ot Type B amendments;

ii) updated Parts according to the prescribed format. The changes in the manufacturing process must be clearly stated to facilitate evaluation
PART 2E
PART 2C where relevant.
- Other amendments falling within the Type A or Type B changes.

iii) *However, if the dossier had not been updated during the previous 5-year period, a fully updated dossier must accompany the application for change of, or additional, manufacturer.*

3.4.4.5.3 For an alternative or additional manufacturer where the manufacturing procedure (or equipment) is different from the manufacturing procedure (or equipment) currently on file falling out of the Type A or Type B amendments, the following must be submitted:

i) Changes to PARTS in prescribed format. The changes in the manufacturing process must be detailed to facilitate evaluation

ii) A fully updated dossier.

iii) details of the proposed validation programme to be followed for at least the first three production batches.

iv) stabililty data and comparative efficacy data as required for Type C amendments

AMENDMENTS

Note: Major deviations: sale of product may only commence after written approval had been granted by the Council. When such batches are manufactured, all documents and bulk and/ or intermediate stock should be clearly marked as being "validation batches".

3.4.4.6 Change in packer

- Statement confirming that the packing process is unchanged

or

- Updated PART 2E and Part 2D (where relevant) in prescribed format. The changes in the packing process must be detailed to facilitate evaluation.

3.4.4.7 Change of final product release laboratory of final product release responsibility

- Updated Administration Front Page.

3.4.4.8 Holder of certificate of registrations should study the requirements in the SA Guide to GMP.

Attention is particularly invited to the following from the GMP Guide:
12.2.1 A Contract Giver should assure himself that the Contract Acceptor has adequate premises, equipment, and staff with sufficient knowledge and experience, to carry out satisfactorily the work placed with him. In order to do this, the Contract Giver should audit the Contractor Acceptor's premises, equipment and systems both before the contract is given and at regular intervals thereafter. Audit reports should be issued and kept on record. A Contract Giver may only use the contract manufacturer or packer as approved in the registration dossier.

5.4.4.9 The HCR is advised to discuss the latest Council inspection report of the proposed contract giver with the contract acceptor prior to entering into an agreement with the contract giver.

3.4.4.10 In the case of contract packaging by a third party, the relevant cGMP requirements should be adhered to.

3.5 CHANGE OF NAME OF HOLDER OF CERTIFICATE OF REGISTRATION ONLY

3.5.1 In this case application to change the name of the holder of certificate of registration may be submitted for a whole range of products. Old medicines and registered products must be dealt with under separate cover.

3.5.2 The application for change of name of holder of certificate of registration must be submitted on an official letter head under cover of MRF 3A

3.5.3 The updated HCRMF, updated organogram of the proposed HCR, copies of the registration certificates (IPCSA and Registrar of Companies) as well as copies of the old and new company letterheads must be submitted.

3.5.4 In alpha-numerical order according to application number of the product:

3.5.4.1 The registration certificate of each product (for registered products)
3.5.4.2 Updated front page
3.5.4.3 Updated front page to reflect the name change only of the FPRR, if the holder of certificate of registration is also the FPRR.
3.5.4.4 Amendment fee

3.6 CHANGE OF ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION

3.6.1 In the case of a change in address of a HCR, the HCRMF has to be updated.

3.6.2 The front page of the Registration dossier for each product must be updated during the first subsequent update of the dossier.

3.6.3 A separate letter addressed to DATA CONTROL section must be submitted reflecting details of the change of the HCR's address to ensure the updating of all lists.

3.6.4 However, if the HCR is also the FPRR, the requirement for change of holder of certificate of registration will apply as this will result in a changed in the registration certificate.

3.7 CHANGE OF ADDRESS OF HOLDER OF CERTIFICATE OF REGISTRATION / MANUFACTURER / PACKER / LABORATORY

3.7.1 In the case of any of the above, the following has to be provided:

3.7.1.1 Updated SMF
3.7.1.2 Organogram of the proposed holder of certificate of registration (including the names of key personnel with specific reference to production and quality assurance departments)
3.7.1.3 The relevant amendment fee
3.7.1.4 The original registration certificate
3.7.1.5 An updated front page reflecting the name and address of manufacturer(s), packer(s), FPRC and FPRR
3.7.1.6 Updated Parts, as relevant, in the prescribed format

4 AMENDMENTS TO THE PHARMACEUTICAL AND ANALYTICAL ASPECTS OF REGISTERED MEDICINES

4.1 INTRODUCTION

This information is for amendment of a registration dossier already lodged with the medicines control council, pertaining to parts 2 (Part 2A through to Part 2I) of the application registration dossier (The active ingredient, formulation, active and inactive pharmaceutical ingredients, specifications and procedures; manufacturing and packaging procedures; in-process and final

AMENDMENTS

The holder of certificate of registration must undertake to ensure that the stability of the relevant product is established and that validation and qualification procedures are instituted in order to ensure that the quality, safety and efficacy of the original product has not been affected by these amendments.

The holder of certificate of registration must ensure that, in the case of solid oral dosage forms, the acceptance criteria for dissolution rate on release characteristics comply with the current specification for the product. These studies must be performed in accordance with current guidelines wherever required prior to implementation of changes.

Data to demonstrate efficacy and or stability must be derived from batches of at least 100 000 tablets or capsules. For semi-solid dosage forms batch sizes greater than 100 kg are to be used.

NB: Only relevant data in support of the proposed changes/amendments should be submitted together with the reasons for submitting such data

4.4.1 Type A - Amendments that do not require prior approval and that can be implemented without involvement of the MCC

The holder of certificate of registration should have a standard operating procedure whereby amendments are recorded and available for inspection by the MCC. At any point where amendments are submitted to MCC – all Type A amendments should be included in the MFR 1 - Administration Data - section C. (Update History). For Type A amendments see Table 1 below.

4.4.1.1 The following general conditions should be complied with whenever Type A and/or Type B amendments are made:

Type B should not made with amendments that require prior approval

4.4.1.1.1 Amendments can only be made to registered products or "Old medicines"

4.4.1.1.2 Date of implementation of Type B amendment should be indicated

4.4.1.1.3 If the M.C.C request copies of experimental validation data, these should be supplied within 30 days of the request and they are made available during GMP inspections

4.4.1.1.4 Specific conditions relating to the amendment are complied with.

4.4.1.1.5 All M.C.C standards are complied with.

4.4.1.1.6 Type B amendments are always accompanied by a statement that no amendments have been made to the product other than those specified in the notification.

4.4.2 Type B – Amendments that require only notification.

The appropriately amended Annexures affected by the change must **be submitted** and be **accompanied or followed by** stability data as indicated in the attached table. Written notification of the type of amendment must **then** be forwarded to this office **30 days** prior to **implementation**. The notification must be clearly marked "Type B amendment" (see Table 1 below) **and must outline (a) the nature of the change with the relevant code, (b) the category number of the applicable item in the table below, (c) the affected and amended Parts / Annexures of the MRF1 / MBR1 dossier, (d) any supportive information and/or data, and (e) any applicable documentation included in the above-mentioned submission.**

Where a site change for manufacturing or packaging is concerned, confirmation of the positive GMP status of the new site must be obtained in writing from the inspectorate before implementation.

4.4.3 Type C - Amendments that require prior approval:

The appropriately amended Annexures / Parts affected by the change must be submitted together with the relevant data/documentation. The submission must be clearly marked: "Type C amendment" (see Table 3). Written approval from the MCC must be obtained before the change may be implemented.

4.4.4 Type D- Amendments that should be considered to be new applications

4.4.4.1 Change in the active pharmaceutical ingredient (API) to a different API

4.4.4.2 Inclusion of an additional API, or removal of one API from multi-component product

4.4.4.3 Change in the dose of one or more of the API

4.4.4.4 Change in the dosage including: change from an immediate –release product to modified-release dosage form or vice versa and change form liquid to powder for reconstitution, or vice versa

4.4.4.5 A change in the route of administration

NB: For amendments not covered by this document and/or where the specified conditions are not complied with, the normal data requirements apply and prior approval must be obtained.

TABLE 1. TYPE A - Amendments that (i) do not require prior approval; (ii) do not require notification, before implementation; (iii) must be recorded and made available for inspection; (iv) must be reflected under "Update History" in the MBR1 or MRF 1 form {(a)-(j) under column 'CONDITION' refers to stability requirements in section 4.5}.

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	Notification
1	Deletion of colour/flavour/fragrance (including capsules shells) **Removal of** printing ink on the dosage form	Package insert, formulation, raw material specifications and control procedures, final product specifications and control procedures, manufacturing procedures	Validation/(J)	-
2	Replacement or addition of colorant/ flavourant/ fragrance (final product **specifications or** description remains the same)	Package insert, formulation, raw material specifications and control procedures, manufacturing procedures	Comply with Foodstuffs, Disinfectants and Cosmetics Act 54 of 1972 or FDA purity standards or EU Commission Directives/validation/ (b)	-
3	Change in excipient range: - Immediate release solid oral dosage form. - Modified release solid oral dosage form (but restricted to non-release controlling excipients) Excipient % excipient (m/m) per total target dosage form mass Filler ≤ 5% Disintegrant: Starch ≤ 3% Other ≤ 1% Binder ≤ 0,5% Lubricant	Formulation, final product specifications and control procedures, manufacturing procedures	Validation/(b)	-

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	Notification
	Ca/Mg stearate ≤ 0,25% Other ≤ 1% Glidant: Talc ≤ 1% Other ≤ 0,1% Filmcoat ≤ 1% The total effect of all excipients changes should not be more than 5% m/m relative to the total dosage mass Calculation example Active 500mg Excipient 100mg Total dosage mass 600mg Lactose: change from 30 to 45mg (+15/600) = +2,5% Cellulose: change from 50 to 35mg (- 15/600) = - 2,5% Absolute total change = 5%			
4	Granulating solution ≤ 20% of the original stated granulating solution	Formulation, manufacturing procedures	-	-
5	Film coating change from organic solution to aqueous solution (**Qualitative** composition of components, excluding change in sealant if used e.g. modified release)	Formulation, raw material specifications and control procedures, manufacturing procedures	Validation/(a)	-
6	Change in the quantity of sugar coating material only: no change in final product specification except mass	Formulation, manufacturing procedures	Validation/no API in the coating/(j)	-
7	Change in composition of the sugar coating material: no change in final product specifications except mass (either qualitative, or qualitative and quantitative, excluding change in sealant)	Formulation, raw material specifications and control procedures, manufacturing procedures	(a)	-
8	Change in mass of empty capsule shell (size)	Formulation, final product specifications	Validation	-

TABLE 2: TYPE B- Amendments that (i) do not require prior approval; (ii) require notification only, before implementation; (iii) must be recorded and made available for inspection; (iv) must be reflected under "Update History" in the MBR1 or MRF 1 form. {(a)-(j) under column 'CONDITION' refers to stability requirements in section 4.5}.

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	NOTIFICATION
1 (including parenterals)	Change/additional source of active material (method of synthesis the same)	Name and address of source, Active Ingredient File (AIF), (if not previously included), CoA, (See Guidelines on Active Raw Material Requirements)	Validation/Comparative data has been generated.	X
2	Packaging material (excluding labeling): • Changes in composition of the immediate container (at least equivalent in protection of light and moisture permeability to that of the existing container) * • Composition not equivalent, but provide better protection to the product • Changes to colour, at least equivalent in protection (light sensitive products) • Changes to closures in contact with product in compliance • with the USP permeation test • *To prove equivalence use USP criteria for containers	Package insert (if relevant), container specifications and control procedures, manufacturing procedures (if relevant)	Excluding labelling/(a)	X
3 (including parenterals)	Storage conditions	Package insert and label, stability data and batch information	(g)	X
4 (including parenterals)	**Site change with** same: • Equipment • SOPs • Environmental conditions (e.g. temp and RH) and controls	Front page, manufacturing procedures, affidavit confirming same as previous, site master file	Validation/(a)/ The positive GMP status of the new site must be confirmed by the Inspectorate in	X

	• Personnel competency Common master manufacturing, packaging or testing procedures		Inspectorate in writing prior to implementation)	
5	• Change to shape of tablet – where the surface area is different	Package insert, raw material specifications and control procedures, final product specification, manufacturing procedures	Validation/comparative dissolution profiles have been generated	X
6	Change in: • Equipment or process machinery but with same processing principles e.g. low energy/low energy • Process timing and/or operating speed, but same final product specifications and content uniformity • Process temperature and/or environmental humidity, but same final product specifications	Front page, manufacturing procedures, affidavit confirming same as previous, site master file	Validation/ product not modified rot slow release (a).	X
7 (including parenterals)	Scale-up to and including ten times the batch used to support stability and efficacy or the approved or validated batch, using the same: • Formulation • Equipment design and operating principles • Controls • SOPs	Manufacturing procedures	Validation (a)	X
8	Replacement of an excipient with a comparable* excipient with no change in dissolution profile for solid dosage forms provided that it has functional characteristics. The final product specifications should remain unchanged.	Formulation, raw material specifications and control procedures	Validation/(b)	X

	*in terms of chemical and physical forms that have the same pharmaceutical effect.			
9 (for parenterals)	Quantity of ingredient change (overages): • Overage of active change: ≤ 10% of active • Overage of water soluble vitamins ≤ 50% of vitamin **content** • Preservative* (semi-solid dosage form) ≤ 10% of preservative • Preservative* (other dosage forms) ≤ 20% of preservative * **specifically refers to antimicrobial preservatives**	Formulation, raw material specifications and control procedures, manufacturing procedures	Validation/(j)	X
10	Shelf-life extension	Stability data to cover the extension period (see Addendum 4)	(f)	

TABLE 3. Type C Amendments (including parenterals) that (i) require prior approval before implementation; (ii) must be reflected under "Update History" in the MBR1 or MRF 1 form. The following are examples:
If an amendment is not listed as a Type A or Type B, it will by default be a Type C or Type D amendment.
{(a)-(j) under column 'CONDITION' refers to stability requirements in section 4.5}.

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	EFFICACY
1	Excipient: • Addition of one or more excipient • Ranges more than allowed for Type A or B changes for immediate release solid oral dosage forms and for modified release solid oral dosage forms (non-release controlling ingredient). • Addition or removal or increasing or decreasing any release controlling ingredient. • Changes in technical grade i.e. Avicel PH102 to Avicel PH200 • Replacement of more than one excipient.	Formulation, raw material specifications and control procedures, final product specification, manufacturing procedures, batch information of stability data	(c)	Proof of efficacy **(See current guidance on proof of efficacy)**
2	Sugarcoat: Changes in composition (qualitative and/or quantitative), which result in a change in final product specification.	Package insert (if relevant), formulation, raw material specifications and control procedures, final product specifications, manufacturing procedures, batch information of stability data	(c)	Proof of efficacy **(See current guidance on proof of efficacy)**
3	Overage greater than the overages allowed for in Type A or B changes. • Wide therapeutic effect • No increase in the severity of known side effects • No additional side effects	Formulation, final product specifications, manufacturing procedures, batch information of stability data	(c)	Proof of efficacy **(See current guidance on proof of efficacy)**
4	Analytical methodology: Raw material specifications • Less stringent requirement	 Raw material specifications and control procedures	(c)	-

STAATSKOERANT, 6 JUNIE 2003 No. 25054 117

5. AMENDMENTS TO THE PACKAGE INSERT

Amendments to the clinical aspects of the package insert for human orthodox medicines must be submitted under cover of MRF 4

LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
FPRC	Final Product Release Control
FPRR	Final Product Release Responsibility
HCR	Holder of the Certificate of Registration
HCRMF	Holder of the certificate of registration Master File

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

AMENDMENT APPLICATION FORM FOR CHANGE OF HOLDER OF THE CERTIFICATE OF REGISTRATION, MANUFACTURER, PACKER AND TESTING LABORATORIES

This form should be read with the "Guideline for Application to Amend the Registration Dossier of a Medicine".

MRF 3A

AMENDMENT APPLICATION

APPLICATION TO AMEND THE PARTICULARS REGARDING PROPRIETARY NAME, HOLDER OF THE CERTIFICATE OF REGISTRATION, MANUFACTURER, PACKER, FPRC OR FPRR IN A MEDICINE DOSSIER ALREADY REGISTERED BY THE COUNCIL

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

Tick the appropriate box with √ to indicate all issues relevant to this application. Section A must be complete for all applications. Indicate all amendments in Section B	Tick (√) in each appropriate box to indicate the documentation submitted to facilitate this amendment.
SECTION A	
❑ - **Registered product** ❑ -- **Old medicine** *** Changes not permitted to pending applications.**	❑ - **Original registration certificate** ❑ - **Amendment fee** ❑ - **Fee for amended certificate** ❑ - **Already Submitted with Application dated.....Reference No.....**
SECTION B	
❑ - **Proprietary name change**	❑ - **Letter detailing request** ❑ - **Amended front page to Registration dossier** ❑ - **Amended package insert, label, patient information leaflet** ❑ - **PART 2 B (or Annexure 2)**
❑ - **Transfer of registration certificate**	❑ **Application to change in accordance with format prescribed in guidelines (Appendix A1)** ❑ - **Letter of cession & Letter of acceptance.** ❑ - **Statement regarding master documentation (Appendix A 2)** ❑ - **Amended front page to Registration dossier**

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MRF 3A

Tick the appropriate box with √ to indicate all issues relevant to this application. Section A must be complete for all applications. Indicate all amendments in Section B	Tick (√) in each appropriate box to indicate the documentation submitted to facilitate this amendment.
	❑ - **Due date of update of dossier stipulated** ❑ - **New holder of the certificate of registration information** (Master File, date of last inspection, organogram)

MRF 3A

APPENDIX A1

1. PRODUCT TO WHICH THIS APPLICATION REFERS

Proprietary name of product	Registration/Reference number	Registered medicine (R) Old Medicine (OM)

2. BUSINESS DETAILS

Information	Current	Proposed
Proprietary Name		
Applicant Name and Address		
MCC Licence No.		
SMF Reference No		
Contact person: Name Designation Telephone no		
Manufacturer Name and Address		
MCC Licence No.		
SMF Reference No.		
Packer Name and Address		
MCC Licence No.		
SMF Reference No		
FPRC Name and Address		
MCC Licence No.		
SMF Reference No		
FPRR Name and Address MCC Licence No SMF Reference No		

MRF 3A

APPENDIX A2

STATEMENT BY THE APPLICANT (On company letterhead)
(In the case of transfer of the certificate of registration, this must be done by the proposed HCR)

I, ...(insert full name and surname) Managing Director/responsible pharmacist of
..... (insert Company name), confirm that:

a) I am in possession of the master documentation pertaining to the above-mentioned medicine,

b) this master documentation is the same as that which was in existence when the medicine was initially registered or which has been updated in accordance with amendments of the medicine registration form (MRF 1) in accordance with the provisions of the regulations under the Medicines and Related Substances Act No. 101 1965.

c) the master documentation conforms with the Registration dossier;

d) the master documentation is properly authorised i.e. signed and dated by at least the managing director/responsible pharmacist, and the quality assurance or production manager;

e) The master documentation has been supplied to the new manufacturer/packer or laboratory (state company and role) and that applicable control records have been compiled. I confirm further that I have signed these to indicate my approval that they contain all the requirements listed in the relevant master documents; namely

formula and method of manufacture and packaging
in process control procedures
specifications for raw materials
specifications for the final product
specifications for the packaging material
specifications for the label
specifications for the package insert
testing procedures for the raw materials
testing procedures for the final product
testing procedures for the packaging materials.

f) I confirm that a technical agreement and signed contract(s) exist(s) with all third party manufacturer(s)/packer(s)/laboratory(ies) involved in manufacturing of this product

g) For an alternative/additional manufacturer:
I confirm that the manufacturing procedure (including equipment) is identical to the manufacturing procedure currently used

or

MRF 3A

I confirm that the manufacturing procedure (including equipment) differs, but falls within the permitted amendments

or

I confirm that the manufacturing procedure (or equipment) is different from the manufacturing procedure (or equipment) currently on file outside of the permitted amendments and that comparative data (efficacy) stability data and a validation protocol for the first three production batches are submitted.

h) I confirm that the package insert will be updated to reflect the new applicant details and will submit the amended package insert with the first update of the dossier after authorisation of this amendment.*(for certificate transfer only).*

i) I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards within 12 months of transfer of the certificate of registration, or approval of additional, or change of manufacturer. *(Not applicable for Type C changes)*

or

I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards by (stipulate date) in accordance with the programme as approved by the Inspectorate. *(Not applicable for Type C changes)*

_____

Signature, Date

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

AMENDMENTS APPLICATION FORM – PHARMACEUTICAL AND ANALYTICAL CHANGES

This form must be read with the "Guideline for Application to Amend the Registration Dossier of a Medicine"

MRF 3B

APPLICATION TO AMEND THE PARTICULARS REGARDING

(1) THE ACTIVE INGREDIENT;

(2) THE FORMULATION;

(3) SPECIFICATIONS AND PROCEDURES FOR THE ACTIVE AND INACTIVE INGREDIENTS;

(4) THE MANUFACTURING AND PACKAGING PROCEDURES;

(5) THE IN-PROCESS AND FINAL PRODUCT SPECIFICATIONS AND CONTROL PROCEDURES;

(6) THE CONTAINER AND LABEL SPECIFICATIONS AND CONTROL METHODS;

(7) THE STABILITY AND SHELF-LIFE OF THE PRODUCT;

IN A REGISTRATION DOSSIER ALREADY LODGED WITH THE MCC

MRF 3B

HOLDER OF THE CERTIFICATE OF REGISTRATION: ----------

.....

BUSINESS ADDRESS: ----------

DETAILS OF PRODUCT:

PROPRIETARY NAME: .....
APPLICATION OR REGISTRATION NUMBER: .....

NOTE: INCOMPLETE APPLICATIONS FOR AMENDMENTS AND DISCREPANCIES WITH REGARD TO DETAILS AND REQUIREMENTS WILL RESULT IN REJECTION OF AN APPLICATION FOR AMENDMENT. A FURTHER AMENDMENT FEE WILL BE PAYABLE FOR A RE-SUBMISSION.

Tick the appropriate box with √ to indicate all issues relevant to this application. Section A must be completed for all applications. Indicate all amendments in Section B.	**Tick √ in each appropriate box to indicate the documentation/data submitted to facilitate or support this amendment.**
SECTION A	
GENERAL ☐ **Registered product** ☐ **Reply to Council Resolution** ☐ **1st** ☐ **2nd** ☐ **Old Medicine**	....

MRF 3B

SECTION B	
Tick the appropriate box with √ to indicate all issues relevant to this application. Section A must be completed for all applications. Indicate all amendments in Section B.	**Tick √ in each appropriate box to indicate the documentation submitted to facilitate or support this amendment.**
ACTIVE PHARMACEUTICAL INGREDIENT ☐ **Change of approved name** ☐ **Change of method of synthesis** ☐ **Change of source (manufacturer)** ☐ **Other (Specify).....**	☐ **APIF** ☐ **Certificate of Analysis** ☐ **Physical/ Chemical equivalence** ☐ **Other (Specify).....**
FORMULATION ☐ **Change of quantity of API** ☐ **Change of quantity of inactive ingredient(s)** ☐ **Addition of inactive ingredient(s)** ☐ **Deletion of inactive ingredient(s)** ☐ **Substitution of inactive ingredient(s)**	☐ **Updated final product specifications** ☐ **Updated formula** ☐ **Update of ingredient specifications and control methods** ☐ **Stability data** ☐ **Efficacy data**
SPECIFICATIONS AND CONTROL PROCEDURES FOR ACTIVE AND INACTIVE INGREDIENTS ☐ **Change of specifications** ☐ **Change of control procedures**	☐ **Updated specifications** ☐ **Update of control procedures**
CONTAINER SPECIFICATIONS AND CONTROL PROCEDURES ☐ **Change of container material** ☐ **Change of container specifications** ☐ **Change of container control procedures** ☐ **Alternative container**	☐ **Stability data** ☐ **Updated specifications** ☐ **Updated Control Procedures** ☐ **Equivalency of containers** ☐ **Package Insert**

MRF 3B

MANUFACTURING PROCEDURE ☐ **Change/addition of batch size** ☐ **Change of equipment** ☐ **Change of process** ☐ **Change of process conditions** ☐ **Change of in-process controls** ☐ **Change of packaging process**	☐ **Updated Manufacturing procedures** ☐ **Update packaging procedures** ☐ **Validation protocol** ☐ **Stability data** ☐ **Efficacy data**
FINAL PRODUCT SPECIFICATIONS AND CONTROL PROCEDURES ☐ **Change of product specifications** ☐ **Change of control procedures** ☐ **Change of Assay procedure** ☐ **Other procedures**	☐ **Updated specification** ☐ **Updated control procedure** ☐ **Validation data**
☐ **SHELF-LIFE EXTENSION** ☐ **SHELF-LIFE CONFIRMATION** ☐ **BATCH-SPECIFIC SHELF-LIFE EXTENSION**	☐ **Stability data**

DECLARATION

I declare that the application has been checked and that the information supplied herewith is accurate.
I further declare that the information on the updated front page concurs with the approved application for registration dossier and amendments detailed above, with regard to all details.

NAME IN BLOCK LETTERS _____ **SIGNATURE** _____

DESIGNATION _____ **DATE OF APPLICATION FOR AMENDMENT** _____

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR COMPLETION OF ANNUAL RETURNS FORM

This document has been prepared to serve as a recommendation to applicants wishing to complete and submit forms for annual returns and it is in line with the International Narcotics Control Board requirements and the provisions of the Medicines and Related Substances Act.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

GUIDELINES FOR COMPLETION OF THE ANNUAL RETURNS FORM

1. EXPLAINING THE COLUMNS OF THE ANNUAL RETURNS FORM/ TABLES:

Before reading this page, please first refer to the two tables for narcotic and psychotropic substances on the next two pages. Descriptive notes are supplied in each column to explain the specific information required in the column.

NOTES:

* Unless otherwise specified, "Quantity of substances" or "Quantity" means the total quantity of the active narcotic\psychotropic substances, expressed **as a base,** in both raw material form and contained in preparations/finished products. These preparations or finished products **do not include Schedule III preparations** (see definition of Schedule III products on page 5) of a particular narcotic substance. Schedule III preparations are not regarded as controlled substances anymore. (Calculations of the pure base content is explained in the section on statistics).

1. Please make sure that the figure supplied by you for stock held at 31 December 1997 (the previous year) and the stocks held at 1 January 1998 correspond.
2. The tables do not require all the information regarding stocks of drugs which you would normally have in a schedule 6 and 7 register, eg. Quantity of narcotic preparation manufacturer or sold locally or Quantity destroyed, etc. The tables should therefore not be seen as a register and the figures will not always "balance". The information supplied by you will not be used for "checking up" or querying your activities. However, every figure required on the forms is to be used in further calculations and we rely on your accurate reporting. Please do not hesitate to contact us if you need more information.
3. Where the substance has been purchased locally as a raw material, please indicate the quantity as well as the name of the local supplier.
4. Where stocks are held or manufacture has been undertaken on behalf of another applicant, this fact should be indicated.

2. DEFINITIONS:

2.1. **Manufacturer:** means all processes, other than production, by which drugs may be obtained and includes refining as well as transformation of drugs into other drugs, eg. transformation of Morphine into Apomorphine. (For the purpose of the annual returns "Production" means the separation of opium, coca leaves, cannabis and cannabis resin from the plants which they are obtained).

2.2 **Narcotic Substances**: means any substances included in Schedule I and II of the Single Convention on Narcotic drugs, 1961. (See the attached list of substances under international control).

2.3. **Psychotropic Substance:** means any of the substances included in Schedule I, II, III and IV of the 1971 Convention on Psychotropic Substances. (See attached list of substances under international control).

2.4. **Preparations:** means a mixture, solid or liquid containing a narcotic or psychotropic substance.

ANNUAL RETURNS FOR NARCOTIC SUBSTANCES FOR 1998

NARCOTIC SUBSTANCE (BASE)	Quantity held in stock at 1 January 1998 (Substance as a raw material and in preparations).		Quantity Imported (Substance as a raw material and in preparations).		Quantity of raw material manufactured locally		Quantity of raw material purchased locally (Please name local supplier)		Quantity Exported (Substance as a raw material and in preparations)		Quantity used in the manufacture of :				Quantity held in stock at 31 December 1998	
											Other narcotic substances		Schedule III prepara-tions	Uncontrolled substances		
	kg	g	kg	g	kg	g	kg	g	kg	g	kg	g	kg	kg	g	kg	g
name of the substance controlled internationally as a base eg: Morphine (not morphine sulphate)	See * on page 2.		See * on page 2. Only specify quantities of raw material/ products imported by yourself. Do not include imported goods purchased from a local supplier.		This column is only for the few companies who manufacture the chemical raw material locally				See * on page 2.		The amount of narcotic substance (raw material) transferred into a totally different narcotic substance which is controlled internationally. For example: Morphine transformed into Codeine.		See page 5 for definition of schedule II products. This is not Schedule 3 in terms of Act 101, but Schedule III in terms of the International Conventions.	Transformation of a narcotic substance into a chemical substance which is not controlled internationally. For example: morphine to apomorphine.		See * on page 2.	

ANNUAL RETURNS FOR PSYCHOTROPIC SUBSTANCES FOR 1998

PSYCHOTROPIC SUBSTANCE (BASE)	Quantity held in stock at 1 January 1998 (Substance as a raw material and in preparations)		Quantity Imported (Substance as a raw material and in preparations).		Quantity of raw material manufactured locally		Quantity of raw material purchased locally (Please name local supplier)		Quantity Exported (Substance as a raw material and in preparations)		Quantity of the raw material transformed into a different chemical substance		Quantity held in stock at 31 December 1998	
	kg	g	kg	g	kg	g	kg	g	kg	g	kg	g	kg	g
Name of the substance controlled internationally as a base eg: phendimetrazine (not phendimetrazine bitartrate)	See * on page 2.		See * on page 2. Only specify quantities of raw material/ products imported by yourself. Do not include imported goods purchased from a local supplier.		This column is only for the few companies who manufacture the chemical raw material locally				See * on page 2.		The amount of the psychotropic substance transformed into a totally different psychotropic or into an uncontrolled substance.		See * on page 2.	

2.5. **Schedule III preparations:** Schedule III of the 1961 Convention consist of list of preparations being exempted from certain international control measures. Most of these preparations contains a schedule 7 (in terms of Act 101, 1965) narcotic substance in such a low concentration that it is excluded from schedule 7 and falls in a lower schedule eg. Schedule 2 of Act 101, 1965. Take note that not all preparations excluded from Schedule 7 of Act 101, 1965 fall into schedule III of the 1961 Convention, but only those specifically listed as schedule III. (See list of substances under international control, provided). For the purpose of the annual returns, schedule III preparations are not regarded as narcotic preparations anymore and the stocks held at 31 December must not include schedule III finished products.

2.6. **Uncontrolled substances**: any narcotic or psychotropic substance which is not controlled internationally. In other words, any substance which is not included in the attached list of substances under the control of the Single Convention of Narcotic Drugs, 1961 and the 1971 Convention on Psychotropic Substances.

3. STATISTICS AND CALCULATIONS

3.1 Units of mass

Full quantities of substances and preparations of such substances must be expressed in **kilograms and grams, as percentage pure anhydrous base** of the relevant substances.

Fractions of gram must be rounded off to the next higher gram. When dealing with minute quantities of raw material consisting only of a fraction of a gram, it should be rounded off to the third decimal. Example: 7.2365 kg is rounded off to 7.237 kg and the reported as 7 kg and 237 g in the two separate columns provided in the table for kilograms and grams.

3.2 Percentage pure anhydrous base content and calculations thereof:

For the purpose of statistics, the different forms of a substance, e.g. morphine sulphate and morphine HCl, must be reduced to a common denominator, which is in most cases the equivalent in anhydrous base expressed in grams. Please refer to tables for conversion of Narcotic and Psychotropic Substances in base form into their approximate equivalent in pure anhydrous base. (Substances not listed = 100 %).

3.3 Examples of calculations of the pure anhydrous drug content:

3.3.1. A narcotic raw material in basic form or as a salt

Example: Calculate the pure anhydrous drug content of 20 kilograms of Codeine Phosphate B.P. with half a molecule of water of crystallization:

Refer to the tables of percentage pure anhydrous drug content for narcotics. Codeine (1/2 H2O)Phosphate contains 74 per cent pure anhydrous Codeine base.

20 kg x 74% = 14 kg 800 g Codeine = figure to be reported on the annual returns form.

3.3.2. Preparation in tablet form

Example: A proprietary preparation contains Amfepramone (=diethylpropion) in the form of tablets, each containing 75 milligram of Amfepramone Hydrochloride:

In terms of pure drug content this salt contains 86 per cent pure anhydrous Amfepramone base; therefore the content in anhydrous Amfepramone base of thirty tablets are:

$30 \times 75 \text{ mg} \times 85\% \times 10^{-3} = 1{,}9125$ grams Amfepramone

= 2 grams (rounded off)

3.3.3. Preparations in the form of ampoules

When an injectable ampoule contains a single dosage unit, its real volume exceeds its nominal volume by a percentage which may vary depending on the nominal volume and mobility of the liquid. The quantity to be reported to the Medicines Control Council must take of the real volume of the preparation and not the nominal volume. **The real volume equals nominal volume plus recommended excess volume.**

The table below indicates the standard excess volumes used for injectable preparations depending on the volume and viscosity of the preparation.

Nominal Volume (Labelled Size)	Recommended Excess Volume:	
	For Mobile liquids	For Viscous liquids
0.5 ml	0.10 ml	0.12 ml
1.0 ml	0.10 ml	0.15 ml
2.0 ml	0.15 ml	0.25 ml
5.0 ml	0.30 ml	0.50 ml
10.0 ml	0.50 ml	0.70 ml
20.0 ml	0.60 ml	0.90 ml
30.0 ml	0.80 ml	1.20 ml
50.0 ml or more	2%	3%

(a)Example: Calculate: 10 000 ampoules of Pethidine hydrochloride 50mg per 1ml. The nominal volume is 1,0 ml and therefore real volume is 1,10 ml. This salt of Pethidine contains the equivalent of 87 per cent pure anhydrous base (refer to conversion tables):

The contents in anhydrous Pethidine base of ten thousand ampoules is:

$10\,000 \times 1{,}1 \times 50 \text{ mg} \times 87\ \% \times 10^{-3}$ (mg to g) = 478,5 grams Pethidine

= 479 grams Pethidine (rounded off)

(b)10 000 Pethidine hydrochloride ampoules containing 100 mg per 2 ml (nominal volume):
10 000 x 2,15 (real volume) x **50 mg (mg/ml)** x 87% x 10^{-3}
= 935 grams Pethidine base (rounded off)

3.3.4. Opium preparations

A. Preparations made direct from opium:

Opium preparations (including "medicinal opium"), extracts and tinctures of opium, must not be expressed in terms of the opium base, but in terms of **opium containing 10% morphine**.

Therefore an amount of opium preparations, extracts or tinctures, containing 1kg of morphine base is equivalent to 10 kg of opium; in other words the morphine content preparations, extracts and tinctures should be multiplied by 10 in order to calculate the amount of opium with a 10% morphine content.

EXAMPLE: 25 kg Extract of Opium for tincture B.P., containing 11,8% anhydrous morphine:
-to calculate the morphine content: 25 kg x 11,8 % = 2,95 kg morphine
-convert to Opium with a 10% morphine content:2.95 kg x 10
= 29,5 kg Opium, 10 % morphine content
Therefore 25 kg Extract of Opium (11,8 morphine content) =
29.5 kg Opium (10% morphine content), to be reported on the forms.

B. Preparations which are not made from opium itself, but are obtained by a mixture of opium alkaloids (as is the case of example with omnopon and papaveretum) they should be considered as morphine and expressed as such. In other words Total Extracts of Opium must be given in their morphine equivalent, which is 50%. A quantity of 1 kg of Omnopon is equivalent to 500 grams of morphine.

Example: calculate the base drug in: 100 x 1ml ampoules of Total Extract of Opium (e.g. Omnopon, Pantopon and Papaveretum) 20mg/ml. Each ampoule has a nominal volume of 1,0 ml and a real volume of 1,1 ml:

In terms of pure drug content it contains 50 per cent anhydrous Morphine base.
The contents in anhydrous Morphine of one hundred ampoules is:
100 x 1,1 x 20 mg x 50% x 10^{-3}
= 11 grams Morphine

4. COMMON ERRORS FOUND ON THE COMPLETED FORMS:

It might be helpful to draw your attention to the most common errors found in the annual returns forms of previous years:

1. Substances, preparations, etc. are not expressed in terms of the pure anhydrous base content.
2. Stocks held at 1 January do not correspond to stocks held at 31 December of the preceding year as reported on the annual returns the year before.
3. Quantities of imported substances purchased locally are indicated as imports. Only the actual importer himself should indicate this.

ANNUAL RETURNS

4. Preparations defined as schedule III products are regarded as controlled substances.
5. Forms not returned by 28 February.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GOOD WHOLESALING PRACTICE FOR WHOLESALERS, DISTRIBUTORS and BONDEDWAREHOUSES

This document has been prepared to serve as a recommendation to applicants wishing to conduct business as medicine wholesalers, distributors and those who wish to operate bonded warehouses. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. This guide must read together with the SA Guide to Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

INDEX

1. INTRODUCTION

Wholesaler distribution forms part of the supply chain of medicine manufactured. Wholesalers/ Distributors are responsible for the effective, efficient and safe handling, storage and distribution of such products. This Code of Practice sets out appropriate steps for meeting this responsibility. Further does this code also apply to the storage of medicine in a Bonded Warehouse.

Except for a brief mention under "storage", the Code does not deal with either common or statute law requirements such as the obligations of contractors, Occupational Health and Safety, Customs and Excise, Narcotics, Dangerous Goods, or the many legal requirements surrounding building construction. These must be understood by and met by the wholesaler/ distributor.

2. INTERPRETATION

In this Code, the word "should" indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

3. BUILDINGS

Warehousing of medicines should be carried out in buildings or parts of buildings that have been built for, or adapted to, this purpose.

The grounds should be established and maintained so as to minimise ingress into the buildings of dust, soil, or other contaminants and should be maintained in an orderly condition. They should be free of accumulated waste, dirt and debris. Waste should be collected in designated closed containers and disposed of at frequent intervals.

Buildings should be kept free of rodents, vermin, birds, pets and pests.

Buildings should provide protection for the goods from contamination and deterioration, including protection from excessive local heating or undue exposure to direct sunlight. The goods received or dispatched at receiving or dispatch bays, docks, platforms or areas should also be protected from dust, dirt and rain.

Buildings should have sufficient security to prevent misappropriation of the goods.

Sufficient space should be provided for the orderly receipt, warehousing and dispatch of goods and, in particular, a quarantine area for isolation of goods when necessary, including isolation of faulty packs and recalled goods.

Buildings and fixtures should be kept clean and well maintained. Cleaning equipment should be stored in hygienic conditions.

4. FACILITIES

Storage facilities should protect goods from deterioration. The conditions of storage for the goods should be compatible with the storage conditions specified on their labels.

Controlled storage environments, e.g. deep freeze, refrigeration, should be monitored, using suitable temperature recording devices and the records reviewed and filed. Refrigerated and freezing storage environments should be fitted with both an alarm and a visual signal to indicate that refrigeration has failed. The signal should permit resetting only by an authorised person.

Temperatures in other areas where goods requiring specific storage conditions are held should be monitored and the results tabulated and analysed so as to demonstrate the suitability of these areas for their purposes.

If any temperature is found to have deviated outside the relevant recommended conditions for an extended time, the manufacturer of the goods should be contacted and the suitability of the product for use resolved.

Instruments or equipment used for monitoring temperature should be calibrated on a regular basis to ensure their accuracy.

Special storage facilities should be provided for poisons, narcotics and psychotropic products as provided for by the Medicines and Related Substances Control Act under Schedule 6 and Specified Schedule 5 substances.

Incompatible activities such as manufacture (including repackaging) or the handling of toxic chemicals should be avoided in areas in which medicine are handled by wholesale.

5. PERSONNEL

Key personnel bearing the responsibility for ensuring that products/materials are correctly handled, stored and distributed, should have the education, training, experience or combination of these elements that will allow then to effectively discharge this responsibility.

Operating personnel should be trained to perform assigned duties and functions at an acceptable level.

Procedures and conditions of work for employees and other persons having access to the products must be designed and administered to minimise the possibility of drugs coming into unauthorised possession.

6. Stock Handling and Stock Control

General

Handling and storage of medicine should be in accordance with established procedures designed to prevent contamination or deterioration of the goods, damage to packs or confusion of products. Particular care should be given to maintaining the integrity of seals on packs of sterile goods. Attention should be paid to any special instructions from the manufacturer relating to handling or storage of the goods.

Importers should take all reasonable measures to ensure that goods are not mishandled or exposed to adverse storage conditions at wharves or airports.

Storage, supply, distribution and recording of Specified Schedule 5 and Schedule 6 medicines must be in accordance with the provisions of the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965).

Storage areas should be adequate and organised to permit segregation and identification of the various materials and products stored and should enable stored goods to be easily maintained in a clean, dry and orderly condition. Particular care should be taken to avoid mould growth in refrigerated rooms or cabinets.

There should be a system to ensure stock rotation, with frequent regular checks that the system is operating correctly.

Spilled substances should be cleaned up promptly and rendered safe as quickly as practicable and under the supervision of a responsible person. A written procedure for dealing with spillage of items of special hazard, such as cytotoxic drugs, should be available.

Measures should be taken to demonstrate that restricted goodsare not misappropriated.

Goods bearing an expiry date must not be received or supplied after their expiry date or so close to their expiry date that this date is likely to occur before the goods are used by the consumer. Such goods must be withdrawn from sale and quarantined pending disposal in accordance with agreements between wholesaler and supplier.

Receiving of Goods

Stock should be received and examined for correctness against an order, for expiry date and for absence of damage.

There should be a system for the recognition and prompt handling of Specified Schedule 5 and Schedule 6 medicines, of those products requiring specific temperature storage, of products that have a short shelf life and of any other products that require special care.

Goods from suppliers rejected by the wholesaler because of error, breakage, leaking containers or other faults should be placed in quarantine until the matter is resolved with the supplier.

Damaged Goods From Stock

Stock which has been damaged or withheld from sale and which is not immediately destroyed should be placed in quarantine until disposal so that it cannot be sold in error or, in the case of liquid leakage, cause contamination of other goods.

Stocks of products with broken seals, damaged packaging or suspected of possible contamination must not be sold or supplied. Special attention should be given to the integrity of packages containing sterile medical devices.

Returned Goods from Customer

Goods which have left the care of the wholesaler should only be returned to saleable stock if:

a) they are in their original unopened containers, in good condition and bear a valid expiry date;
b) it is not evident that they have been subject to adverse conditions;
c) they are packed separately from other goods and accompanied by a separate Returns Note; and
d) they have been examined and assessed by a person authorised to do so. Such assessment should take into account the nature of the goods, and any special storage conditions they may require. If necessary, advice should be sought from the person responsible for the quality assurance of the manufactured product.

Reconditioning or repackaging (including relabelling) of medicines must not be carried out by wholesalers unless such activity is specifically exempted from the requirement to hold a manufacturers licence.

Returned Goods - from Recall

There should be a written procedure detailing the action to be taken in recalling goods on behalf of their manufacturer or sponsor, subject to any amendment necessaryin specific circumstances. This procedure should be consistent with the "Guidelines on Recalls of Medicines" issued by the Department of Health. The wholesaler should be able to

facilitate a recall procedure relative to the area to which goods have been supplied. Recalls carried out should be documented and records of all recalled goods received into the warehouse should be kept.

7. TRANSPORT

Containers for delivery of goods should be clean and provide adequate protection for the goods delivered.

Goods labelled to require refrigerated storage should, where appropriate, be transported in insulating containers with ice or other cooling agent. The agent should not cause freezing of goods marked 'Refrigerate - do not freeze'. Goods labelled to require frozen storage should be transported in such away that they remain frozen. Where appropriate, the transport packaging should be fitted with devices to detect exposure to conditions outside specific limits.

Delivery of other goods requiring controlled temperatures should be carried out by the fastest practical means. However, in assessing suitable conditions for delivery in any particular case, due account should be taken of the time required for delivery, prevailing or likely weather conditions and the nature of the goods and their labelled storage requirements. Special procedures should be established for goods likely to be exposed to unfavourable environments over holiday periods or during transport to far destinations.

8. COMPLAINTS

Complaints regarding the product or its packaging, as distinct from those relating solely to matters within the wholesalers control, must be notified promptly to the manufacturer of the goods. Complaints relating to the wholesalers' own activity should be evaluated and measures taken, where appropriate, to prevent their recurrence.

9. RECORDS

Invoices or packing slips should be issued for each delivery and accompany the goods.

Clear and readily available records should be maintained showing the receipt and disposal of all products purchased and sold. Such records should be kept in an accessible form and place for the period in force under the Medicines and Related Substances Control Act, 1965 (Act 101 of 1965).

10. CONTACT DETAILS

The Registrar of Medicines
Private Bag X828

PRETORIA
0001

IMPORTATION AND EXPORTATION

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR THE IMPORTATION AND EXPORTATION OF MEDICINE

This guideline has been prepared to serve as a recommendation to those who import and export medicines. The MCC is committed to ensure that all medicines gaining market approval locally and abroad will be of the required quality, safety and efficacy.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 30/5/2003

IMPORTATION AND EXPORTATION
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1. INTRODUCTION

The importation and exportation of Medicines and Scheduled substances are subject to control in terms of the provisions of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended. South Africa is also a signatory to three International Drug Conventions, namely:

- The Single Convention on Narcotic Drugs, 1961;
  [The Medicines Control Council is responsible for implementing the measures required by the said convention]

- The Convention on Psychotropic Substances, 1971; and
  [The Medicines Control Council is responsible for implementing the measures required by the said convention]

- The United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988.
  [The Department of Trade and Industry is responsible for implementing the measures required by the said convention]

As South-Africa is signatory to these conventions, the control measures contained in Act 101 were based directly on the controls required by these conventions. The obligation of South-Africa and therefore the policy of the Department of Health is thus to keep national legislation in line with these conventions.

2.0 LEGAL REQUIREMENTS FOR THE IMPORTATION OR EXPORTATION OF MEDICINES OR SCHEDULED SUBSTANCES

2.1 ORDERING MEDICINES FROM ABROAD

No person shall order any medicine from abroad for personal use unless the Medicines Control Council has granted the said person an authorization in terms of section 21 of the Act to import during a specified period a specified quantity of the particular medicine, which is not registered with Council.

Purchasing a medication from an illegal Website or supplier puts you at risk. You may receive a contaminated, counterfeit or substandard product. Taking an unsafe or inappropriate medication puts you at risk for dangerous drug interactions and other serious health consequences.

2.2 PERSONS ENTERING OR DEPARTING FROM THE REPUBLIC

Regulation 16(1) of the Act stipulates that:

IMPORTATION AND EXPORTATION

(1) any person entering or departing from the Republic of South Africa may be in possession, for personal medicinal use, of a quantity of a Schedule 3, Schedule 4, Schedule 5 or 6 substance which shall not exceed a quantity required for use for a period of one month; and

(2) the said person must have-
(a) a valid prescription for such Scheduled substance or medicine;
(b) a certificate to the effect that the Scheduled substance or medicine concerned including its quantity was prescribed for the person including the name and address of such authorised presrciber; and
(c) his or her particulars of residence in the Republic, in the case of the person entering the Republic, recorded at the port of entry.

2.3 AUTHORIZATION IN TERMS OF SECTION 21

In terms of section 14(1) of the Act, no person shall import and supply any medicine, which is subject to registration by virtue of a resolution published in terms of section 14(2) unless it registered with Council.

However, in terms of section 21 of the Act, Council may in writing authorize any person to import and sell during a specified period to any specified person or institution a specified quantity of any particular medicine, which is not registered. This permission is however subjected to confirmation from a medical professional that the product is needed and that no similar product is available in the country. Council will evaluate the requests and may grant the authorization which will be issued by the Registrar in the prescribed manner and subject to such conditions as Council deems fit.

2.4 AUTHORIZATION TO IMPORT A SAMPLE FOR REGISTRATION PURPOSES

Council may in writing authorise any person to import a sample for registration purposes as contemplated in section 15(1) of the Act. An application shall contain at least the following information:
(a) name and address (both physical and postal) of the applicant;
(b) telephone and fax number of the applicant;
(c) licence number of the applicant as contemplated in section 22(1)(b) of the Act;
(d) purpose for which the application is made;
(e) proprietary name, dosage form, batch number, expiry date and quantity of the sample to be imported; and
(f) port of entry.

IMPORTATION AND EXPORTATION

2.5 LICENCE TO IMPORT OR EXPORT MEDICINES OR SCHEDULED SUBSTANCES

In terms of section 22C(1)(b) of the Act, Council may, on application in the prescribed manner and on payment of the prescribed fee, issue to a manufacturer, wholesaler or distributor of a medicine a licence to import or export, upon such conditions as to the application of such acceptable quality assurance principles and good manufacturing and distribution practices as the Council may determine.

Section 22C(6) of the Act stipulates that no manufacturer, wholesaler or distributor shall import or export any medicine unless he or she is the holder of a licence as contemplated in section 22C(1)(b) of the Act.

Regulation 19(1)(a)(i) stipulates that a person referred to in section 22(1)(b) of the Act must apply to the Council for a licence to import or export medicines or Scheduled substances. The person must submit to the Registrar an application for a licence, on a form approved and provided by the Council.

Regulation 20(1) of the Act stipulates that a licence issued in terms of regulation 19 shall be valid for a period of 5 years from the date of issue.

Every application for a licence by a manufacturer, wholesaler or distributor of a medicine, must have a responsible pharmacist with the knowledge and responsibility to ensure that the correct procedures are followed during distribution. The owner of the manufacturer, wholesaler or distributor of a medicine, must provide and maintain such staff, premises, equipment and facilities to enable the responsible pharmacist to carry out the said functions.

The Medicines Control Council upon issuing a licence and/or reviewing a licence holder will review the following aspects and conditions:

- The manufacturer, wholesaler or distributor of a medicine applying for a licence must be registered with the Department of Health relating to the ownership of the manufacturer, wholesaler or distributor;
- The manufacturer, wholesaler or distributor of a medicine applying for a licence must be registered with the Medicines Control Council relating to the Good Manufacturing Practises, and Good Wholesaling/ Distribution Practises entertained at the manufacturer, wholesaler or distributor.
- The review will address Good Manufacturing, Wholesaler and Distribution Practices.

In order to comply with the above aspects and conditions the following should be covered and implemented:

- A Quality System addressing all aspects of quality assurance must be in place, covering Contracts (Agreements); Purchasing; Final Product handling, storage; facility installation, servicing, cleanliness;

documentation controls and records; international regulatory control; internal and external audits; training; complaint handling; emergency plan and recalls; quality assurance and management review; distribution (transport, delivery, temperature control); counterfeit medicines; theft of product; export documentation (proof of export);

- If any of the Quality System aspects are delegated to a competent third party it should be done in a written formal agreement

Issuing of Certificates by the Medicines Control Council:

- GMP certificates and Certificates of Pharmaceutical Products (WHO-type) needs to be applied for in the prescribed manner at the office of the Registrar of Medicines;
- GMP certificates will be issued subject to the status of the current Medicines Control Council endorsed audit report pertaining to the relevant facility;
- Certificates of Pharmaceutical Products (WHO-type) will be issued to medicines registered by the Medicines Control Council in accordance with the current legal registration dossier;
- Inclusion of additional information on the Certificate of Pharmaceutical Product (WHO-type) will be evaluated per application and could be considered in cases as i.e. additional, MCC GMP-approved packaging facility capable of the process involved according to the current MCC audit report of the facility in accordance with the international registered information.

Compliance to International Registration requirements:

- It is the responsibility of the licensed Exporter and Registration Holder of the importing country to comply with the legal registration information approved by the relevant Ministry of Health;
- If it entails deviation from the registered medicine registration information as approved by the Medicines Control Council, any manipulation i.e. manufacture, packaging, labelling, final pack size or container when performed in South Africa needs to take place according to current GMP in an MCC approved GMP facility;
- Medicines registered by another Health Authority however not registered by the Medicines Control Council of South Africa and not intended for sale or distribution in South Africa however manipulated i.e. manufactured, packed, labelled, stored in South Africa prior to export to the importing country will be subject to GMP, GWP and GDP. Meaning any manipulation that takes place need to be performed in a MCC GMP-approved facility according to the standard of current GMP, GWP and GDP guidelines of the Medicines Control Council.;

2.6 PERMIT TO EXPORT SCHEDULED SUBSTANCES FOR ANALYTICAL PURPOSES, MANUFACTURE OF FOODS, COSMETICS, EDUCATIONAL OR SCIENTIFIC PURPOSES

Section 22A(7)(a) of the Act determines that no person other than a pharmacist, pharmacist intern or pharmacist's assistant acting under the personal supervision of a pharmacist shall export a Schedule 1, Schedule 2, Schedule 3, Schedule 4, Schedule 5 or Schedule 6 substance for analytical purposes, manufacture of foods, cosmetics, educational or scientific purposes, unless a permit, issued in accordance with the prescribed conditions has, subject to paragraph (b), been obtained from the Director-General for such purpose.

The applicant shall use the official form GW 12/44 to apply for an export permit.

The export of specified Schedule 5 and Schedule 6 substances are under international control. Regulation 15(4) of the Act stipulates that the applicant must submit with the application a certified copy of the permit for importation issued by the country to which the substance is to be exported.

2.7 PERMIT TO IMPORT OR EXPORT SPECIFIED SCHEDULE 5, SCHEDULE 6, SCHEDULE 7 OR SCHEDULE 8 SUBSTANCES

In terms of section 22A(11)(a) of the Act, no person shall import or export any specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substance or medicine prescribed for that purpose unless a permit has been issued to him or her by the Director-General in the prescribed manner and subject to such conditions as may be determined by the Director-General.

Regulation 15(1) of the Act stipulates that any person desiring to import or export specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substances shall apply to the Director-General for a permit to import or export such substances.

The applicant shall use the official form GW 12/10 to apply for an import permit and form GW 12/44 to apply for an export permit

Regulation 15(4) of the Act stipulates that the applicant must submit with the application a certified copy of the permit for importation issued by the country to which the substance is to be exported.

In terms of the provisions of section 22A(11)(c) of the Act, the issue of the

permit may be refused if-

(i) the Director-General is not convinced that the applicant is capable of keeping or storing the substance or medicine in a satisfactory manner in order to prevent the loss thereof;

(ii) the use of such substance or medicine has not been authorised in terms of the Act;

(iii) the Director-General is of the opinion that the annual importation quota for such substance has been exceeded or will be exceeded;

(iv) the Director-General is of the opinion that such substance or medicine, of an acceptable quality, is already available in the Republic; or

(v) the applicant did not comply with the conditions under which a previous permit was issued to him or her.

Regulation 15(4) of the Act stipulates that the applicant must submit with the application a certified copy of the permit for importation issued by the country to which the substance is to be exported.

Any permit issued under section 22A(11)(a) of the Act, shall be subject-

(a) to the applicant's furnishing the Registrar annually with the prescribed information (see Annual Returns);

(b) to the requirement that there shall be no deviation from the particulars reflected on the permit: Provided that if the quantity of such substance or medicine to be imported is less than that provided for in the permit, the Director-General shall be informed in writing thereof within 10 days after the importation of such substance or medicine; and

(c) to the conditions, as detailed on the permit, having been complied with, the triplicate copy of the permit having been certified by a customs officer or an employee of the S.A. Post Office Limited.

In terms of section 22A(11)(e) of the Act, an import or export permit shall be valid for a period of six months from the date of issue thereof.

2.8 PERMIT FOR PARALLEL IMPORTATION OF MEDICINES

Regulation 7(1)(c) stipulates that any person desiring to import a medicine referred to in section 15C(b) of the Act, shall be in possession of a permit issued by the Minister.

The applicant shall submit to the Minister an application form in the prescribed manner and subject to such conditions as determined by the Minister.

The permit shall be valid for a period of two years.

2.9 PORTS OF ENTRY

Regulation 12(1) of the Act states that no person shall import any medicine or Scheduled substance, including medicines imported in terms of section 15C of the Act, read together with regulation 7, into the Republic except through one of the following ports of entry:

(a) Cape Town Airport or harbour;
(b) Port Elizabeth Airport or harbour;
(c) Durban Airport or harbour;
(d) Johannesburg International Airport

2.10 FEES

Fees payable to the Registrar as contemplated in regulation 35 of the Regulations, shall be levied in respect of all permits and authorizations issued for the importation or exportation of medicines and / or Scheduled substances.

3.0 MBR 20 DOCUMENT

For each consignment of medicines and / or specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substances, the importer shall complete and personally sign the MBR 20 document (GW 12/11).

The importer shall attached the following documentation to the MBR 20 document and submit it to the customs officer at the port of entry:

(a) Copy of the invoice for the medicines and / or Scheduled substances which have been imported; and
(b) Copy of the licence to import medicines as contemplated in section 22C(1)(b) of the Act; and
(c) Copy of the import permit for specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 medicines and / or substances as contemplated in section 22(11)(a) of the Act; or
(d) Copy of the import authorization to import samples for registration purposes as contemplated in section 15(2)(a) of the Act; or
(e) Copy of the import authorization to import unregistered medicines as contemplated in section 21 of the Act

The importer shall retain a copy of this document at his business address for inspection purposes.

The customs officer shall be responsible to post the MBR 20 document and its ttachments immediately to the office of the Registrar of Medicines

4.0 WHERE TO SEND APPLICATIONS

Applications should be delivered to Room 204, Hallmark Building, 237 Proes Street, Pretoria or send to:

The Registrar of Medicines
Department of Health
Private Bag X 828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

AEROSOL MANUFACTURING

This document has been prepared to serve as a recommendation to manufacture aerosol-based medicines. It represents the Medicines Control Council's current thinking on the manufacture of aerosol-based medicines.
These guidelines should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

1 AEROSOL MANUFACTURING

INDEX

1. INTRODUCTION

The manufacture of pressurized aerosol products for inhalation with metering valves requires special consideration because of the particular nature of this form of product. It should be done under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

2. GENERAL

2.1 There are presently two common manufacturing and filling methods as follows:

2.1.1 Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is put into the container, the valve crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

2.1.2 One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature, or both. The suspension is then filled directly into the container in one shot.

3. PREMISES AND EQUIPMENT

3.1 Manufacture and filling should be carried out as far as possible in a closed system.

3.2 Where products or clean components are exposed, the area should be fed with treated filtered air, and should be entered through airlocks.

3.3 Suitable systems should exist to determine required environment conditions and to monitor and control these conditions, e.g. temperature controls and propellant loss.

4. PRODUCTION AND QUALITY CONTROL

4.1 Metering valves for aerosols are more complex pieces of engineering than most items used in pharmaceutical production. Their specifications, sampling and testing should recognise this. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

4.2 All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.
4.3 Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. Containers should be fed to the filling line in a clean condition or cleaned on line immediately before filling.

4.4 Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout

the filling process.

4.5 When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition.

4.6 Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

5.CONTACT DETAILS

The Registrar of Medicines
Private bag X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

CEPHALOSPORIN MANUFACTURING

This guideline has been prepared to serve as a recommendation to manufacturers of cephalosporins. This guideline must be read together with the SA Guide to Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

CEPHALOSPORIN MANUFACTURING

INDEX

1. INTRODUCTION

These standards do not have direct statutory force , but will be used by the inspectors of the MEDICINES CONTROL COUNCIL, in order to evaluate the suitability of a pharmaceutical plant to manufacture cephalosporin products and to evaluate whether non-cephalosporin products are free and likely to remain free from cephalosporin contamination

These standards will therefore be one of the criteria used by the Council, to decide on the registration and the continued registration of pharmaceutical products

These standards do not replace any of the generally accepted G.M.P. standards, but must be seen as an addition to them, the main focus being on the specific problem of cross-

contamination

2. GLOSSARY

For the purpose of these standards, cephalosporins include cephalosporin P, cephalosporin N, cephalosporin C, semithynthetic compounds derived from 7 aminocephalosporanic acid as well as the cephamycins. This definition includes both Category A and B substances of Act 101 of 1965

3. PREMISES

3.1 Cephalosporin products should only be manufactured in separate, dedicated self contained areas with separate air handling facilities dedicated to these products and on a different site to that of the manufacture of non-cephalosporin products

This means complete separation of:

3.1.1 Active raw material storage

3.1.2 weighing

3.1.3 mixing

3.1.4 processing

3.1.5 filling
3.1.6 packaging

3.1.7 any other associated processes

3.2 Entry into and exit from the cephalosporin area should only be through a properly constructed air-lock

3.3 Change rooms should be provided for the personnel to shed their street clothes and put on their protective clothing for the cephalosporin area

3.4 Adequate shower facilities should be available for the personnel to shower when they leave the cephalosporin area

4. SECONDARY PACKAGING

Secondary packaging i.e. labelling and cartoning of the finished cephalosporin products may be done in a general packaging area, provided that the operation is separated from the general area in such a way as to contain any spillage of
cephalosporin

5. AIR HANDLING SYSTEMS

5.1 Separation

Completely separate air supply systems must be provided for cephalosporin and non-cephalosporin products

5.2 Air pressure Differentials

5.2.1 Air pressure differentials must be adjusted to provide a NEGATIVE PRESSURE in relation to the outside air in the cephalosporin area. The air must enter the area and be vented from the area in such a way as to ensure that no cephalosporin contaminated air enters the atmosphere

5.2.2 Air pressure differentials should be adjusted to be the greatest in the areas where the most dust is generated and cascade down to those areas where the least dust is generated

5.2.3 For sterile products positive air pressure differentials are required initially: however, the air pressure differentials in the area immediately adjacent to the non-cephalosporin area must be negative The same precautions for the contamination of the atmosphere are applicable

5.2.4 The air handling system must be validated at regular intervals

6. EQUIPMENT

6.1 Equipment should be dedicated to the cephalosporin manufacturing area only

6.2 Any maintenance of the equipment should be done in the cephalosporin area. If the equipment needs removal from the cephalosporin area proper validated decontamination procedures should be available and should be followed

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

ISOLATOR TECHNOLOGY

This document has been prepared to serve as a recommendation for work on isolator technology. It represents the Medicines Control Council's current thinking on this subject. These guidelines should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

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ISOLATOR TECHNOLOGY

1 PRINCIPLES

1.1 Isolator technology is now widely used and accepted for the aseptic processing of pharmaceuticals. The use of barrier systems offers improvements in the handling of pharmaceutical products in circumstances where product protection and the maintenance of asepsis, and/or operator protection and the control of hazardous substances are critical requirements. Isolators have several advantages over conventional clean rooms and laminar flow cabinets for aseptic preparation and dispensing of injections. Isolators provide an acceptable level of sterility assurance for aseptic operations. Isolators cannot be regarded as totally sealed units since access to the controlled workspace must be open when materials are transferred into and out of this area and the workspace is continuously supplied with HEPA filtered air. Other than this air supply, the controlled workspace of the isolator will, when in use, be sealed from its background environment.

1.2 Critical SOP's include those detailing sanitisation, introduction of material, withdrawal of material, and training of personnel.

2 DEFINITION OF TERMS

2.1 Isolator

A containment device which utilises barrier technology for the enclosure of a controlled workspace.

2.2 Type 1 Isolator

An isolator primarily designed to protect the product from process-generated and external factors that would compromise its quality.

2.3 Type 2 Isolator

An isolator designed to protect the product from process-generated and external factors that would compromise its quality and to protect the operator from[n hazards associated with the product during operation and in the event of failure.

2.4 Air lock

An enclosed space with two or more doors and which is interposed between the controlled workspace and the background environment of the isolator, for the purpose of controlling air flow between them and to facilitate the transfer of materials between them.

2.5 Alarm

An audible and/or visible signaling system which warns of a fault condition. It must incorporate a device to ensure that it cannot be cancelled until corrective action is taken.

ISOLATOR

2.6 Background Environment

The environment in which the isolator is sited. Background environments are categorised in table 3.

2.7 Controlled Work Space

An enclosed space constructed and operated in such a manner and equipped with appropriate air handling and filtration systems to reduce to a pre-defined level the introduction, generation and retention of contaminants within it.

2.8 Critical Zone

That part of the controlled workspace where containers are opened and product is exposed. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use.

2.9 Decontamination

A process which reduces contaminating substances to a de-defined acceptance level.

2.9.1 Sanitisation

That part of decontamination which reduces viable micro-organisms.

2.9.2 Particulate Decontamination

That part of decontamination which reduces visible and sub-visible levels to a defined acceptable level.

2.9.3 Chemical Decontamination

That part of decontamination which reduces chemical contamination to a defined acceptance level.

2.10 Docking Device

A sealable chamber which can be (completely removed from or locked onto an isolator and then opened without contamination passing into, or out of, the controlled workspace or the chamber.

2.11 Exhaust Filter

A filter through which the exit stream of air from an isolator

2.12 HEPA (High Efficiency Particulate Air) Filter

Filters with no greater than 0,003 % penetration of 0,5 um particles when tested according to BS 3928.

2.13 Laminar Flow

Airflow in which the entire body of air within a confined area moves with uniform velocity along parallel flow lines.

Note: May also be referred to as "unidirectional flow'.

2.14 Sterilisation

The process applied to a specified field which inactivates viable micro-organisms and thereby transforms the non-sterile field into a sterile one.

2.15 Transfer Chamber

A device which facilitates the transfer of goods into or out of the controlled workspace whilst minimising the transfer of contaminants.

2.16 Transfer Hatch

See Transfer Chamber.

2.17 Transfer Isolator

A separate isolator which can be fixed or removable and which is attached to the main operational unit, acting as a complete transfer device.

2.18 Transfer Device

A device, which can be fixed or removable, which allows materials to be transferred into or out of the controlled

2 19 Transfer Port

See transfer chamber.

2.20 Transfer System

The process of transfer of materials into and out of the isolator through a transfer device.

2.21 Turbulent Flow

A flow of air which is non-laminar.

3 ISOLATOR DESIGN PRINCIPLES

Although the specifications should not be restrictive, there are basic design parameters to which isolators should conform.

3.1 Air input may be laminar flow, turbulent flow, or a combination of the two.

3.2 The critical zone of the controlled workspace should be equivalent to the EC Grade A, but the airflow in the critical zone need not be laminar flow (see 23.3.3).

3.3 If the isolator is not supplied with a laminar air flow system, tests should be performed so as to confirm that only air complying with the requirements of EC Grade A is applied to the critical zone. Air should be effectively swept from the controlled workspace and startling vortices. Stagnant areas should not exist.

3.4 Type 2 isolators should operate under negative pressure.

3.5 Type 2 isolators for use with radiopharmaceuticals should incorporate an appropriate radiation protective system against ionising radiations.

3.6 For operator protection, in the event of a breach in type 2 isolators a minimum breach velocity of O,7m sec- should be maintained.

3.7 The transfer of materials into and out of the controlled workspace is a critical factor of the isolator's operation. The transfer device separates the background environment from the Grade A controlled workspace. It should be designed such that it does not compromise the Grade A controlled environment. To this end an interlocked device will provide greater security. The size of the transfer device should be sufficient to allow all necessary materials and equipment to be passed through

Note: Commissioning studies should include tests to confirm that contaminants will not pass from the transfer device into the controlled work area. A fully validated transfer procedure should be in place.

3.8 All internal surfaces (including seals, holes, screws) should be accessible to the operator for cleaning and disinfection purposes without compromising the isolator's integrity. They should be resistance to corrosion by cleansing and disinfecting agents and should be capable of withstanding gaseous disinfection or sterilisation.

3.9 The pressure differential between the Grade A controlled workspace and the background environment should be continuously monitored.

3.10 All filters in isolators in which hazardous substances are handled must have a safe change facility. Both the manufacturer and the user should be made aware of the risks associated with changing filters.

3.11 All exhaust (or re-circulated) air should pass through one or more HEPA filters.

Extract air from type 2 isolators should normally be ducted to the outside through one or more HEPA filters and another necessary absorption media (eg. carbon). Where isolators are used infrequently or low levels of hazardous materials are handled, then the exhaust air may be re-circulated into the background environment through two HEPA filters in series provided the risk has been assessed and has been shown to be low risk. (For further details of exhaust filters see also appendix 5.)

3.12 When designing isolators, consideration should be given to optical clarity, lighting, noise levels, humidity, electrical safety, temperature, vibration, ergonomics and the comfort of the operator (s),

3.13 Pressure differentials and the direction of air flow should be such that when the access between the transfer system and the controlled workspace is open, contaminants will not pass into the controlled workspace and, additionally in type 2 isolators, operator protection is also maintained.

3.14 If a fixed transfer device has its own air supply it should be HEPA filtered.

3.15 The air change rates in all parts of the isolator system should be sufficient to maintain the defined grade of environment

Note: The air change rate will be such that any unfiltered air that enters the isolator or transfer device will be purged from the system within 5 minutes.

3.16 The fan should not be capable of damaging the filters in their maximum loaded state.

3.17 Isolators should have the facility to enable routine leak testing and particle counts to be carried out in the isolator itself and in its transfer devices. Where access points are provided for test equipment they should be labelled.

3.18 The isolator should be designed so that the HEPA filters can be integrity tested in situ.

4 THE SITING OF ISOLATORS

4.1 Isolator(s) should be sited in a dedicated rooms(s) used only for the isolator and its ancillary equipment and related activities. The interior surfaces of the rooms (walls, floots, ceiling) should be smooth, free from cracks and open joints. They should not shed particulate matter and should allow easy and effective cleaning and sanitisation.

4.2 The classification of the background environment in which the isolator is located will depend upon the design and, operational characteristics of the isolator, but should be at least grade D. When deciding on the siting of isolators, consideration should be given to the following:
The type of isolator - type l/type 2.
The transfer system - see appendix 1.
The level and frequency of use i.e. dispensing/ preparation/manufacture.

In order to address these variables, isolators have been classified according to the transfer system.

Details of the different transfer systems and the corresponding transfer devices are shown in appendix 1. The background environment for the isolator can then be categorised as I, II, III, IV, V or EC Grade A-D depending upon the transfer system and the use to which the isolator will be put (tables 1 and 2).

4.3 The definitions of air quality categories I-V are given in table 3. The categories have been defined according to their permitted levels of viable and non viable particles. For comparative purposes, the requirements of the different environmental classifications from commonly quoted standards documents are also included in the table.

It should be noted that the levels of viable micro-organisms for categories II-IV of the background environment are more stringent than then nearest grade of air quality specified in the EC GMP.

4.4 For pharmaceutical applications the major criterion upon which the background environment is categorised should be the risk of microbiological contamination of the product. For this reason the environment has been classified in this document according to the number of viable organisms that can be detected.

It is recognised however that environmental testing is not a guarantee that environmental quality is maintained.
Procedures and quality systems should be used to provide the necessary level of quality assurance.

5 FACTORY ACCEPTANCE TEST (FAT)

5.1 A factory acceptance test (FAT) should be performed. The report should cover at least a check against Customer Order for completeness, visual check for appearance and identification, the record of serial numbers of filters, dimensional check, electrical installation and safety check, functional check, including operation of interlocks and alarms and documentation dossier.

6 INSTALLATION QUALIFICATION (IQ)

6.1 Qualification data (records) of the isolator should at least cover installation qualification (IQ), i.e. integrity and leakage test, filter integrity test, filter mounting integrity test, instrument check and calibration as well as functional check of all operating systems.

7 OPERATIONAL QUALIFICATION (OQ)

7.1 Operational qualification (OQ) should be performed.

7.2 Records should cover checks on air flow rates, pressures controlled within specified

limits, air flow patterns, temperature and humidity patterns, particle counts as well as noise and light levels.

7.3 Testing of filters and filter housings should be done at regular intervals.

7.4 The vibration effects of HVAC fans and filling equipment on joints and particularly on hepa filter clamping systems should be tested. Maximum limits for vibration should be set, monitored and controlled.

7.5 The ventilation/filtration system should be appropriate for functions performed in the isolator and should be validated.

7.6 Leak tests of the Isolator should be performed on a regular basis, including the glove/sleeve system.

8 PERFORMANCE QUALIFICATION (PQ)

8.1 Performance qualification (PQ) should be performed.

8.2 Sterilisation cycles with standard loadings should be developed and validated.

23.8.3 There should be relevant SOP's with respect to operations being performed.

2 3.9 MICROBIOLOGICAL MONITORING

9.1 General

Viable particle monitoring for micro-organisms and non-visible particle monitors should be performed at regular intervals.

A plan of the isolator should be prepared with coded positions for settle plate, swabbing and air sampling sites. The following methods may be employed:

9.2 Settle Plates
Coded and dated, sterile, tryptone soya agar plates should be exposed for two hours at all test sites within the isolator.

These should be incubated in accordance with a written SOP at the appropriate temperature for up to five days, or as otherwise chosen by the microbiologist.

9.3 Surface Samples
Surface samples at coded sites using sterile contact plates or sterile moistened swabs should be taken

Note: Each sample site should be sanitized to remove any material transferred to it during the sampling process.

9.4 Active Air Sampling

Samples should be taken at the coded sites.

Where the test utilises standard plates or strips, these should be incubated at the appropriate temperature for up to five days.

The point during the production process that finger dabs should be carried out should be defined eg. at a break time or end of a day's work, in accordance with a written SOP

9.6 Broth, or Media Fills (Media Process Simulation)

The broth fill is a validation procedure that challenges both operator and facilities. The purpose of broth fills is to simulate routine aseptic operations in such a way as to produce broth filled units that can be tested for microbiological contamination.

The number of units filled should represent a normal batch size.

Incubate at the designated temperature for up to 14 days. If the final container is part filled to ensure all surfaces are in contact with broth at some stage during incubation.

A procedure should define actions following positive results and should focus initially on whether the facility/equipment or operator practices are failing.

Note: The type of broth used is often sterile tryptone soya broth that may be presented in double strength to allow for dilution with buffer, saline, or water to simulate the process.

Any suitable liquid culture medium may however be used but the ability of the broth to support growth should be demonstrated.

10 SANITISATION OF MATERIALS

This section addresses disinfection procedures using chemical agents during which fluids are applied to surfaces with the intention of reducing the count of micro-organisms inside the controlled workspace of an isolator.

10.1 Introduction

Most isolator systems will require two different procedures:

- A procedure for treatment of the impervious internal surfaces of the isolator and external surfaces of the resident equipment.

- A second procedure for treating surfaces of transient components which will be present in the isolator for a particular procedure.

The cleaning down of equipment and related treatments can employ a wide range of agents. Components and other aids to production should usually be treated with alcohol-based preparations, which enable rapid evaporation of the solvent of such disinfectant agents and therefore facilitates a smooth, responsive work flow during production.

10.2 Methods for Treating Resident Surfaces

Transient material should be removed from the controlled workspace. Internal surfaces should be cleaned with a non-corrosive and low residue detergent. There should be no evidence of corrosion due to incompatibility with disinfection regimes.

10.3 Methods for Treating Transient Surfaces

The surfaces of components and aids to preparation (syringes etc.) should be treated by using rapid drying agents, such as aspectically filtered alcohol (70% w/v ethanol or isopropanol).

10.4 Disinfectants should not penetrate outer packaging and thus contaminate the contents.

11 GAS STERILISATION OF ISOLATOR SYSTEMS

11.1 Introduction

Alcohol-based solutions are routinely used to sanitise equipment and component surfaces during aseptic processing. The major disadvantage of this technique is that alcoholic agents process negligible activity against bacterial endospores. Control measures can minimise the incidence of spores on the surfaces of vials; syringe wraps etc; but their absence is not assured. A properly designed and validated gas treatment of isolator systems can reduce the probability of spores surviving and increase the sterility assurance of the product.

Gaseous agents may be introduced into the controlled workspace of the isolator system to sterilise the entire space, integral surfaces and transient or resident components inside. It reduces the numbers of viable micro-organisms to a predetermined and acceptable level.

11.2 Objectives of Gas Sterilization

Various gaseous agents can be used within suitably-designed isolators to achieve sterilisation of working and component surfaces, thereby significantly reducing the overall probability of sterility failure in the final product.

Note: This process does not guarantee product sterility, but merely eliminates one of the factors which can result in product contamination during aseptic processing.

11.3 Choice of Agent

The ideal sterilant would have the following properties:

rapidly lethal against all micro-organisms, highly penetrative, non-aggressive to metals or polymers, rapid elimination of residues and harmless to humans.

A sterility assurance level of 10^6 of better should be achieveable. A variety of methods are available and include the use of ethylene oxide, formaldehyde, paracetic acid, hydrogen peroxide or chlorine dioxide.

The agent of choice will be determined by a number of and equipment-related factors. For pharmaceutical applications in isolators the sterilants in most general use are peracetic acid and hydrogen peroxide.

11.4 Gas Contact

To ensure their effectiveness, the sterilant vapours must be in contact with all contaminated surfaces. The following points should be considered:

* Equipment should be raised appreciably above worktops, and efforts made to provide point contact of supports.

* Components should not be laid on worktops or other solid surfaces. Wire baskets or racking can be utilised to approximate point contact support. Wherever possible, containers and components should be suspended farce point contacts (eg. wire hooks), to allow free circulation of sterilant around all items. If necessary components should be rotated or repositioned during processing to ensure all surfaces are exposed to the gaseous sterilant.

* Glove/gauntlet fingers should be fully extended, and supported well clear of the worktop in such a way that the glove/sleeve materials are not unduly folded.

Critical validation issues associated with the sterilisation process should include the concentration of the sterilent, uniform distribution of sterilent, contact times, temperature aeration post sterilisation, condensate remonvals and residue as well as the frequency of sterilisation.

11.5 Microbiological Validation

Biological indicators (BI) can be used to confirm the effectiveness of the selected conditions and standard patterns. The test organisms should be selected to represent a known challenge to the process. In practice Bacillus subtilis (var niger) is frequently used, at a concentration of 10^6 - 10^7 spores per strip.

Initial tests should concentrate on establishing approximate death curves for the test organism, and/or progressively increasing sterilant contact time until the target lethality is achieved. The process contact time and sterilant vapour concentration should then be selected to include an acceptable safety margin, which makes allowance also for the compatibility of equipment and with the sterilant. Once process conditions have been established, the cycle/loading pattern should be validated by performing replicate cycles, again using BI's in worst case positions. Positive controls should be performed and the

recovery conditions verified. When some degree of occlusion is unavoidable such that the diffusion path of gas is greater than 1 or 2 ram, the actual lethality delivered can be investigated by direct inoculation of the surfaces and estimation of survivors. Positive controls should be used for other techniques and recovery conditions verified as being effective.

11.6 Routine Cycle Monitoring

The correct loading of the isolator prior to gassing should be the subject of properly documented control, and it is good practice for isolator access doors to be locked once correct loading has been checked. The gas generator's airflow and sterilant dispenser flow are often pre-set by the manufacturer, but if this is not the case their correct adjustment should also be formally documented. The generator should ideally allow these parameters, as well as sterilant injection time, to be recorded for each cycle, as happens with steam sterilisers. If the generator does not feature computer or chart recording of data, the parameters should be manually recorded at regular intervals, and documented for each cycle.

12. CONTACT DETAILS

The Registrar of Medicines
Private Bag X828
PRETORIA
0001

13. TABLE 3

DEFINITION OF AIR QUALITY CATEGORIES 1-V.
COMPARISON WITH EQUIVALENT INTERNATIONAL STANDARDS

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

PENICILLIN MANUFACTURING

This document has been prepared to serve as a recommendation for penicillin manufacturing. It represents the Medicines Control Council's current thinking on this subject.
This guideline should be read in conjunction with the SA Guidelines for Good Manufacturing Practices.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

PENICILLIN MANUFACTURING

INDEX

PENICILLIN MANUFACTURING

1. INTRODUCTION

These standards do not have direct statutory force, but will be used by the inspectors of the MEDICINES CONTROL COUNCIL, in order to evaluate the suitability of a pharmaceutical plant to manufacture penicillin products and to evaluate whether non-penicillin products are free and likely to remain free from penicillin contamination.

These standards will therefor one of the criteria used by the Council ,to decide on the registration and the continued registration of pharmaceutical products.

These standards do not replace any of the generally accepted G.M.P. standards, but must be seen as an addition to them , the main focus being on the specific problem of cross-

contamination

2. GLOSSARY

For the purpose of these standards , penicillin includes all forms of penicillin i.e. all naturally produced penicillin, all synthetic and semi-synthetic preparations as compounds derived from 6-amino-penicillanic acid. This definition includes both Category A and B substances in terms of Act 101 of 1965

3. PREMISES

3.1 Penicillin products should only be manufactured in separate, dedicated self contained areas with separate air handling facilities dedicated to these products and on a different site to that of the manufacture of non-penicillin products.

This means complete separation of:
3.1.1 Active raw material storage

3.1.2 weighing

3.1.3 mixing

3.1.4 processing

3.1.5 filling

3.1.6 packaging

3.1.7 any other associated processes.

3.2 Entry into and exit from the penicillin area should only be through a properly constructed

air-lock

3.3 Change rooms should be provided for the personnel to shed their street clothes and put on their protective clothing for the penicillin area

3.4 Adequate shower facilities should be available for the personnel to shower when they leave the penicillin area.

4. SECONDARY PACKAGING

Secondary packaging i.e. labelling and cartoning of the finished penicillin products may be done in a general packaging area, provided that the operation is separated from the general area in such a way as to contain any spillage of penicillin

5. AIR HANDLING SYSTEMS

5.1 Separation

Completely separate air supply systems must be provided for penicillin and non-penicillin products

5.2 Air pressure Differentials

5.2.1 Air pressure differentials must be adjusted to provide a NEGATIVE PRESSURE in relation to the outside air in the penicillin area. The air must enter the area and be vented from the area in such a way as to ensure that no penicillin contaminated air enters the atmosphere.

5.2.2 Air pressure differentials should be adjusted to be the greatest in the areas where the most dust is generated and cascade down from this area to those areas where the least dust is generated.

5.3 For sterile products positive air pressure differentials are required initially: however the area immediately adjacent to the non-penicillin area must be

negative.
The same precautions for the contamination of the atmosphere is applicable

5.4 The air handling system must be validated and re-validated at suitable intervals

6. EQUIPMENT

6.1 Equipment should be dedicated to the penicillin manufacturing area only.

6.2 Any maintenance of the equipment should be done in the penicillin area. If the equipment needs removal from the penicillin area proper validated decontamination procedures should

be available and should be followed

7. PERSONNEL

7.1 Clothing

7.1.1 Overalls, shoe covers, head gear, mask and gloves to be used for penicillin manufacture only, must be provided.

7.1.2 All clothing used in the penicillin manufacturing area must be properly decontaminated according to a validated procedure before being removed from the area for laundering

7.2 Procedures

Written procedures with respect to dress, movement into and out of the area and all other special precautions must be compiled and available at the point of implementation

7.3 Training
Training with respect to the special problems of penicillin manufacture must be provided in addition to normal G.M.P. training

7.4 Health checks

Health checks with respect to penicillin sensitivity must be done on a regular basis

8. MONITORING

Air quality outside the penicillin area must be monitored on a regular basis to detect any penicillin contamination

9. DECONTAMINATION

Validated decontamination procedures must be compiled and implemented where necessary

10. TESTING OF NON-PENICILLIN PRODUCTS

No detectable levels of contamination should be allowed, employing a test method acceptable to Council

The accuracy of the method should be such as to detect quantities of not less than 0,05 units of penicillin

11. VALIDATION

All methods and processes should be validated and re-validated at suitable intervals.

Equipment should be qualified at regular intervals.

12. CONTACT DETAILS

The Registrar of Medicines
Private Bag X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

RADIOPHARMACEUTICAL MANUFACTURING

This document has been prepared to serve as a recommendation for manufacture of radiopharmaceuticals. It represents the Medicines Control Council's current thinking on the subject.
This guideline should be read in conjunction with the SA Guidelines for Good Manufacturing Practices..

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

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RADIOPHARMACEUTICALS

1. Introduction:

Radio pharmaceutical products should be manufactured in accordance with the Good Manufacturing Practices, described in the current South African Guide to Good Manufacturing Practices, this guidance document and the supplementary guidelines such as those for sterile preparations where appropriate. Some points are nevertheless specific to the handling of radioactive products and are modified by or detailed in these supplementary guidelines.

2. General:

2.1 Radio pharmaceutical preparations are preparations containing one or more radionuclides. They may be formulated in any of the pharmaceutical formulations covered in this guide and the general and specific guidance should be followed at all times, but considerations must be given to the special requirements of radiation work.

2.2 The manufacturing and handling of RADIO PHARMACEUTICALS is potentially hazardous. The level of risk depends in particular on the types of radiation emitted and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants and to waste disposal. Special consideration may be necessary with reference to small batch sizes made frequently for many RADIO PHARMACEUTICALS. Due to their short half-life, some RADIO PHARMACEUTICALS are released before completion of certain Quality Control tests. In this case, the continuous assessment of the effectiveness of the Quality Assurance system becomes very important.

3. Registration Requirements:

3.1 Care should be taken to comply with national and local regulations concerning production, supply, storage, use and disposal of radioactive products.

3.2 Premises in which radioactive work is conducted must be licensed by the Department of Health.

3.3 RADIO PHARMACEUTICALS, produced by a nuclear reactor or cyclotron, may only be used by physicians who are qualified by specific training in the safe use and handling of radioisotopes, and whose experience and training have been approved by an appropriate governmental agency authorised to licence the use of radionuclides.

3.4 All people engaged in radioactive work are required by law to be registered as radiation workers. Maximum permitted radiation doses for radiation workers are prescribed by the International Atomic Energy Agency and are monitored by film badges and pocket dosimeters or TLD. At all times the ALARA principle (i.e. as low as reasonably attainable dose) applies to any person working with radioactivity.

4. Personnel:

4.1 All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

5. Premises and Equipment:

5.1 Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. The equipment used for manufacturing operations should be reserved exclusively for RADIO PHARMACEUTICALS.

5.2 In order to contain the radioactive particles, it may be necessary for the air pressure to be lower where products are exposed than in the surrounding areas. However, it is still necessary to protect the product from environmental contamination.

5.3 For sterile products, the working zone where products or containers may be exposed should comply with the environmental requirements described for Sterile Products. This may be achieved by the provision within the work station of a laminar flow of HEPA-filtered air and by fitting air-locks to entry ports. Total containment work stations may provide these requirements. They should be in an environment conforming to at least a grade D.

5.4 Air extracted from areas where radioactive products are handled should not be recirculated; air outlets should be designed to avoid possible environmental contamination by radioactive particles and gases.

5.5 There should be a system to prevent air entering the clean area through extraction ducts e.g. when the extraction fan is operating.

6. Production and Handling of Radioactive preparations:

6.1 Each isotope should be worked in a separate specially shielded, contained work station to prevent cross-contamination of the radionuclide. Production of different radioactive producers in the same workstations and at the same should be avoided in order to minimize the risk of cross-contamination or mix-up. The operator must be shielded from the radiation which must be contained in the work station.

6.2 Radioactive materials should be handled in a contained work station operated at an air-pressure below that of the room in which it is sited. Air admitted to the work station should still have passed through terminal filters of appropriate porosity so that the required class conditions are maintained at the point of greatest risk, where

products are exposed.

6.3 All operations should be carried out in such a manner as to minimize the risk of microbial or particulate contamination.

6.4 All sterile products are terminally sterilised before despatch either by autoclave or filtration.

NOTE: The radiation in the Radio pharmaceutical is not sufficient to effect sterilisation.

6.5 Process validation, in-process controls and monitoring or process parameters and environment assume particular importance in cases where it is necessary to take the decision to release or reject a batch or a product before all the tests are completed.

7. Quality Control:

7.1 When products have to be dispatched before all the tests are completed, this does not obviate the need for a formal recorded decision to be taken by the Qualified Person on the conformity of the batch. In this case there should be a written procedure detailing all production and Quality Control data which would be considered before the batch is dispatched. A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results are obtained after dispatch.

7.2 Unless otherwise specified in the marketing authorization, reference samples of each batch should be retained.

8. Packaging of RADIO PHARMACEUTICALS:

8.1 Due to the short half-life of certain RADIO PHARMACEUTICALS it may be necessary to despatch the products before all the tests are completed. This does not reduce the need for a formal recorded decision to be taken by an authorized person as to whether or not the product should be released based on the production and quality control data available at the time. Specifications should define at which stage of testing a decision on release may be taken.

8.2 All containers must be checked by a Health Physicist for radioactive contamination before packaging and the radiation levels emanating from the package monitored by a Health Physicist.

8.3 IAEA transport regulations prescribe the maximum acceptable levels of radiation measured at the surface of the package and one metre from the package permitted on road and air transport. The conditions under which the packages may be transported are also prescribed.

9. Non-Radioactive Kits:

9.1 Non-radioactive chemicals are supplied as kits to be reconstituted with the radioactive eluate from a radionuclide generator such as a Molybdenum-99 / Technetium-99m generator at the hospital. These kits must conform to the requirements of pharmaceuticals as listed in the chapter on guidelines for small volume parenterals.

9.2 The preparation of these RADIO PHARMACEUTICALS at the hospital must be carried out using aseptic technique. It may be acceptable to carry out this work under environmental conditions of a lower grade than those prescribed for aseptic work when the following situation pertains:

- the preparation is done entirely by transference of materials between closed containers, for example by use of syringe and hypodermic needle penetrating a rubber closure (so-called 'closed procedures')
- manipulations are performed within a contained work station which, whilst giving the required degree of operator protection, also maintains the critical working zone at the standard of Class 1
- the product is administered within a few hours of preparation.

10. Distribution and Recalls:

10.1 Detailed distribution records should be maintained and there should be procedures which describe the measures to be taken for stopping the use of defective RADIO PHARMACEUTICALS. Recall procedures should be shown to be operable within a very short time.

11. Contact Details:

The Registrar of Medicines
Private Bag X828
PRETORIA
0001

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR ELECTRONIC SUBMISSION OF APPLICATIONS TO REGISTER MEDICINES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines in electronic format. Comments on this document will be appreciated before 30 June 2003.

REGISTRAR OF MEDICINES
MS M. P. MATSOSO
DATE: 30-05-2003

ELECTRONIC SUBMISSION PROJECT

GUIDELINES FOR AN E-SUBMISSIONS PILOT OF MEDICINES REGISTRATION APPLICATIONS

1. General

- The applicant is to supply a comprehensively completed hard copy application of the medicine they wish to get registered.
- The applicant must make sure that the electronic submission of the application being submitted is an exact replica of the hard copy version.
- A windows-based notebook to be submitted with the following minimum specifications.
    - Pentium III or higher, 128MB RAM, 20GB HDD and DVDROM drive
    - Adobe Acrobat 5.0 (or later)
    - Microsoft Word 2000 (or later)
- When submitting an electronic version of the dossier, the following recommendations will help the applicant create PDF files that the MRA can evaluate and archive accordingly.

2. Version

The MRA will use version 4.0 (or higher) of Acrobat Reader with the search plug in. This allows for ease of document navigation and access.

3. Fonts

We believe that Times New Roman, 12-point font is adequate in size for reading narrative text. In tables and charts, fonts smaller than 12 points should be avoided whenever possible.

The applicant is to make sure that the font used in the PDF file can be relayed (copied) into the MRA's preferred word processor (MS WORD 2000), for evaluation and report writing purposes.

We recommend the use of a black font colour, with a blue font used for hypertext links. If font colors other than black are used, avoid light coloured fonts.

4. Page Orientation

Pages should be properly oriented. For example, the applicant should set the page orientation of landscape pages to landscape prior to saving the PDF document in final form to ensure correct page presentation.

5. Page Size and Margins

The print area for pages should fit on a sheet of paper that is 21cm X 29.7cm (A4). The applicant should allow a margin of at least 1.6 centimeters on all sides to avoid obscuring information if the pages are subsequently printed and bound.

6. Source of Electronic Document

PDF documents produced by scanning paper documents are usually inferior to those produced from an electronic source document. Scanned documents are more difficult to read and do not allow us to search or copy and paste text for editing. They should be avoided if at all possible. If the applicant uses optical character recognition software, the applicant should verify that all imaged text converted by the software is accurate.

Due to the integrity of electronic documents and regulation standards, an original hard copy of any the source documents can be requested at any given time.

7. Methods for Creating PDF Documents and Images

Choose a method for creating PDF documents that produces the best replication of a paper document. The applicant should ensure that the paper and PDF version of the document are the same by printing the document from the PDF version. This will be evident when submitting the hard copy version of the submission.

Documents that are available only in paper should be scanned at resolutions that will ensure the pages are legible both on the computer screen and when printed.

We recommend scanning at a resolution of 300 dots per inch (dpi) to balance legibility and file size. This also applies to paper documents containing handwritten notes. These should be written in black ink for clarity after scanning.

For photographs, the image should be obtained with a resolution of 600 dpi. If black and white photos are submitted, consider 8-bit gray scale images. If color photos are submitted, consider 24bit RGB images.

Plotter output graphics should be scanned or captured digitally at 300 dpi.

8. Hypertext Linking and Bookmarks

Hypertext links and bookmarks are techniques used to improve navigation through PDF documents. Hypertext links can be designated by the use of blue text. The applicant can use invisible rectangles for hypertext links in a table of contents to avoid obscuring text. In general, for documents with a table of contents, provide bookmarks and hypertext links for each item listed in the table of contents including all tables, figures, publications, other references, and appendices. These bookmarks and hypertext links are essential for the efficient navigation through documents.

Make the bookmark hierarchy identical to the table of contents. Each additional level increases the need for space to read the bookmarks. We recommend using no more than 4 levels in the hierarchy where possible.

Hypertext links throughout the body of the document to supporting annotations, related sections, references, appendices, tables, or figures that are not located on the same page are helpful and improve navigation efficiency. Absolute links that reference specific drives and root directories will no longer work once the submission is loaded onto our network servers.

When creating bookmarks and hyperlinks, choose the magnification setting*Inherit Zoom* so that the destination page displays at the same magnification level that the evaluator is using for the rest of the document.

9. Page Numbering

Submission are divided into categories i.e. one document per category, include page numbers to these documents.

10. Open Dialog Box

The open dialog box sets the document view when the file is opened. The initial view of the PDF files should be set as *Bookmarks* and *Page*. Set the *Magnification* and *Page* to default. This will help he evaluator have a sense of uniformity.

11. Naming PDF Files

The applicant can use file names up to 32 characters in length with a 3-character extension. Avoid using punctuation, spaces, or other non-alphanumeric symbols in file names.

For is ease of file navigation, the suggested format is a follows:
(pt#)_(first six letters of the heading)_(month and year)
e.g. pt3_2a_pharma_0303.pdf

12. Security

The applicant may include security settings or password protection for PDF files as follows. A password can be set when opening a CD or document, with the passwords delivered to the MRA on paper. Allow printing, selecting text and graphics and adding or changing notes and form fields. Our internal security and archival processes will maintain the integrity of the submitted files. A read-only copy of the files, generated from the submitted files, will be provided to the evaluator.

Equivalent (or superior) measures to ensure confidentiality of the information submitted to the MCC is in accordance with the prescribed "Guidelines for the registration of medicines in South Africa: General Information".

13. Indexing PDF Documents

We use full text indexes to help find specific documents and/or search for text within documents. When a document or group of documents is indexed, all words and numbers in the file and all information stored in the Document Information fields are stored in special index files that are functionally accessible using the search tools available in Acrobat. Portions of a document that are imaged are not indexed. Even if the document only contains images, the text in the Document Information fields of the file will be indexed.
These full text indexes should not be confused with a table of contents. Adobe Acrobat Catalog is one example of a tool that can be used to index PDF documents. Indexes should not require extensions or additions to off-the-shelf Acrobat programs.

With many submissions, we ask that the applicant associate the table of contents file for a section with the corresponding full text index file. By associate, we mean that when the table of contents file is opened, the index file is automatically added to the available index list and is ready to be used.

14. Plug Ins

It is acceptable to use plug-ins to assist in the creation of a submission. However, the evaluation of the submission should not require the use of any plug-ins, in addition to those provided with Acrobat Reader 4 (or higher) because we are not prepared to archive additional plug-in functionality.

15. Electronic Signatures

The Managing Director of the company should account for all electronic signatures on the application:

- A list of electronic signatures in the dossier should be provided and numbered
- Details of person who signed, date and place are requirements.

16. Method of Packaging

Each documented category from the application should be on a separate CD-R or DVD-R disk. For a category that spans multiple disks, a hyperlinked table of contents should be present for every disk presented. The CD-R or DVD-R should be well labelled and reflective of the contents.

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