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

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

4.12 Council may in writing withdraw any such authorisation.

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

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

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

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

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

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

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

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

4.18 Copy of Authorisation Form

1. APPLICANT DETAILS

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

2. PATIENT DETAILS

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

3. DRUG / PRODUCT INFORMATION

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

4. MOTIVATION FOR THE USE OF UNAUTHORISED MEDICINE

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

---

6. PATIENT / GUARDIAN'S INFORMED CONSENT AND PROCEDURE

7. AUTHORISED BY:

8. AUTHORISATION NUMBER:

4.18 COPY OF AUTHORISATION FORM

Medicines Control Council

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

A. APPLICANT DETAILS

1) Name:.....

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

.....

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

4) Fax number : .....

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

6) Qualification : .....

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

B. OWNER AND PATIENT DETAILS

1) Name of owner:.....

2) Physical address.....

.....

3) Patient data:

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

.....

i) species:.....

ii) breed:.....

iii) sex and age : .....

4.) Diagnosis / purpose.....

.....

.....

5.) Current treatment : .....

.....

.....

C. UNREGISTERED DRUG/PRODUCT INFORMATION

1) Generic name : .....

2) Trade name : .....

3) Quantity required: .....

4) Indication:.....

.....

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

.....

6.) Concomitant medication:.....

.....

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

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

.....

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

.....

D. MOTIVATION FOR THE USE OF UNAUTHORISED MEDICINE:

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VETERINARY SECTION 21 APPLICATION

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

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.....

F. OWNERS CONSENT (YES/NO)

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

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

If "NO" above , motivate

:.....

.....

.....

.....

.....

.....

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

Annexure 1

GUIDELINES FOR SECTION 21 APPLICATIONS FOR VETERINARY MEDICINES

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

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

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

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

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

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

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

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

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

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

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

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

CONTACT DETAILS FOR THE VETERINARY CLINICAL COMMITTEE SECRETARIAT:

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

Telephone: 012 312 0301
Fax : 012 312 3106

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR PREPARATION OF SITE MASTER FILE

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

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

INDEX

1. INTRODUCTION

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

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

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

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

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

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

2. PURPOSE

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

3. SCOPE

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

4. SITE MASTER FILE

Refer to Annex for the format to be used.

5. PREPARATION OF SITE MASTER FILE

REQUIREMENT

C.1. GENERAL INFORMATION

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

GUIDANCE

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

REQUIREMENT

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

GUIDANCE

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

REQUIREMENT

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

GUIDANCE

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

REQUIREMENT

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

GUIDANCE

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

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

REQUIREMENT

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

GUIDANCE

C.1.5. Type of Actual Products Manufactured

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

REQUIREMENT

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

GUIDANCE

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

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

REQUIREMENT

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

GUIDANCE

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

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

SITE MASTER FILE

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

REQUIREMENT

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

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

REQUIREMENT

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

GUIDANCE

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

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

SITE MASTER FILE

REQUIREMENT

C.2. PERSONNEL

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

GUIDANCE

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

C.2.1. Organisation chart

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

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

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

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

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

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

C.2.4. Health Requirements for Personnel Engaged in Production

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

SITE MASTER FILE

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

C.2.5. Personnel Hygiene Requirements Including Clothing

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

REQUIREMENT

C.3. PREMISES AND EQUIPMENT

Premises

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

C.3.2. Nature of construction and finishes.

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

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

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

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

Equipment

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

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

SITE MASTER FILE

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

Sanitation

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

GUIDANCE

C.3. PREMISES AND EQUIPMENT

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

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

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

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

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

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

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

C.3.2.3. A narrative format is preferred.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Equipment (250 words/one A4 page)

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

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

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

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

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

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

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

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

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

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

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

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

REQUIREMENT
C.4. DOCUMENTATION

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

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

GUIDANCE

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

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

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

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

SITE MASTER FILE

6. Analytical methods
7. QA release procedures.

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

C.4.2. Other Documentation related to Product Quality

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

REQUIREMENT

C.5. PRODUCTION

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

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

C.5.3. Arrangements for reprocessing or rework.

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

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

GUIDANCE .

C.5.PRODUCTION

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

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

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

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

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

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

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

Sampling plans.

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

C.5.2.1. Control of Bulk Manufacture

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

C.2.2. Packing

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

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

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

C.5.3. Arrangements for Reprocessing or Rework

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

C.5.4. Arrangements for Handling Reject Materials and Products

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

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

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

REQUIREMENT

C.6. QUALITY CONTROL

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

GUIDANCE

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

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

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

REQUIREMENT

C.7. CONTRACT MANUFACTURE AND ANALYSIS

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

GUIDANCE

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

REQUIREMENT

C.8. DISTRIBUTION, COMPLAINTS AND PRODUCT RECALL

C.8.1. Arrangements and recording system for distribution.

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

GUIDANCE

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

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

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

Complaints

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

SITE MASTER FILE

3. Investigating complaints.

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

C.8.2.2. Product Recalls

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

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

REQUIREMENT

C.9. SELF INSPECTION

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

GUIDANCE

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

6. APPENDIX

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

A. Sterile products

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

A.1.1 Aseptically prepared

A.1.2 Terminally sterilized A.2

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

A.2.1 Aseptically prepared

A.2.2 Terminally sterilized

A.3 Semi-solid dosage forms

A4 Solid dosage form

A.4.1 Solid fill

A.4.2 Freeze-dried

B. Non-sterile products

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

C. Biological products

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

D. Specifically toxic and hazardous substances

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

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

E. Packaging only

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

F. Contract manufacturing (kind of products)

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

G. Contract analysis

Firm reported upon is:

F.1. Acceptor
F.2. Giver

H. Drugs for clinical trials

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

7. REFERENCES

Circular 34/93
PIC/S guide

8. CONTACT DETAILS

1. Ms J. Gouws
Director: Inspectorate and Law Enforcement Directorate
Tel: 012 312 0230/47
Fax: 012 312 3114

2. Mr. .K Mofokeng
Deputy Director: Inspectorate and Law Enforcement Directorate
Tel: 012 312 0259

SITE MASTER FILE

Fax: 012 312 3114

3. Mr P. Seleka
Principal Medicines Control Officer
Tel: 012 312 0252
Fax: 012 312 3114

4. Ms P. Matsoso
Registrar of Medicines
Tel: 012 312 0285
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9. GUIDELINE UPDATE HISTORY

Date	Reason for update	Version
April 2003	New	MCC2003/1

MRF 4

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FORM FOR AMENDMENTS TO APPROVED PACKAGE INSERTS

Version MCC2003/1

MRF 4

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

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

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

The submission should be presented as follows:

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

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

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

Note:

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

MRF 4

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

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

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

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE FOR PARALLEL IMPORTATION OF MEDICINES IN SOUTH AFRICA

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

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

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

Version MCC2003/1

TABLE OF CONTENTS

1. INTRODUCTION

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

2. BACKGROUND

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

3. LEGISLATIVE PROVISIONS

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

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

Parallel importation is defines in the Regulations as

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

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

4. CONDITIONS FOR PARALLEL IMPORTATION OF A MEDICINE

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

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

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

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

4.5 The parallel importer shall be liable for destruction of any expired, parallel imported medicines still remaining on stock after the expiry date, whether during the duration of the permit or after the parallel importation permit has expired.

5. PROCEDURE FOR OBTAINING A PERMIT TO PARALLEL IMPORT MEDICINES

5.1 The application for a permit to parallel import a medicine must be submitted to the office of the Minister of Health. The application must be accompanied by the following:

i) Written confirmation of the lowest price at which the medicine is currently sold by the holder of the certificate of registration in South Africa dated not more than one month before the date of submission of the application for a parallel import permit;

ii) The price at which the parallel imported medicine will be sold in South Africa by the importer;

iii) A declaration by the importer that the medicine to be imported is a medicine under patent in South Africa;

iv) The prescribed application fee;

v) A certified copy of his or her identity document, or in the case of a juristic person, a certificate of registration as such in the Republic;

vi) A certified copy of his, her or its registration in terms of the Pharmacy Act, 1974, where applicable;

vii) A certified copy of the licence in respect of the premises in terms of: -

a) Section 19 of the Customs and Excise Act, 1964 (Act No. 91 of 1964); and

b) Section 22 of the Pharmacy Act, 1974;

viii) An undertaking that he, she or it will ensure the continued safety, efficacy and quality of the medicine; and

ix) Any other information the Minister may require.

5.2 The Minister may, upon consideration, approve with or without conditions, or reject, such an application.

5.3 If a permit is issued, it shall be valid for a period of 24 months.

5.4 The permit holder must, at least three months before the expiry date, apply to the Minister for its renewal in accordance with the procedure prescribed by the Minister.

5.5 The Minister may, at any time and on good cause shown, cancel the permit to import any medicine.

6. PROCEDURE FOR OBTAINING REGISTRATION OF A MEDICINE THAT IS TO BE PARALLEL IMPORTED

6.1 After being issued with a permit to import a medicine, the importer must apply to Council for: -

i) Authorisation to import a sample of the medicine to be submitted together with the application for registration of the medicine; and

ii) Registration of the medicine, using Form MRF 1 (provided by the Registrar of Medicines).

6.2 An application for the registration of a parallel-imported medicine must be accompanied by the following:

i) Copies of the package insert and patient information leaflet, where available, which must be translated into English and verified;

ii) An appropriately labelled sample of the medicine in accordance with the requirements of Regulation 8 or Regulation 48;

iii) Information on the exporter, stating whether it is a manufacturer, packer, re-packer, wholesaler or broker;

iv) A cGMP Certificate from a recognised authority, which must be specific for the manufacturer, packer, re-packer, laboratory, distributor, wholesaler or broker of the imported medicine;

v) Real-time stability data for the duration of shelf-life using a stability-indicating method for the active pharmaceutical ingredient, according to the requirements of the Guideline for Stability Studies – Addendum 4;

vi) Comparative dissolution data against the MCC-approved product (same formulation, same name, same dosage form, etc.) that has been procured in South Africa, in terms of the requirements for proof of efficacy (Also Refer to the Guidelines on Dissolution Testing) and using f_2 values.

6.3 The following is the minimum information required for the registration of a parallel imported medicine:

i) Administrative Data (section A and B).

ii) Parts 1A, 1B and 1C.

iii) Part 2B.

iv) Part 2D for repackaged medicines and if the packaging material is different from that used by the patent holder.

v) Part 2E (b) (i) and (c); for repackaged medicines only.

vi) Part 2F (a), (b), (d) and (e).

vii) Part 2G for repackaged medicines only.

6.4 Council will only consider approval of registration of the medicine if the importer has: -

i) been issued with a permit to parallel import the medicine;

ii) a registered office in South Africa;

iii) a storage facility approved by Council for such medicine;

iv) a responsible pharmacist as required in terms of the Pharmacy Act, 1974 (Act No. 54 of 1974);

v) undertaken to be responsible for ensuring that such medicine meets the safety, quality and efficacy standards as determined by Council and accepts liability for any consequences arising from the distribution and use of the medicine;

vi) in place recall procedures as determined by Council,

vii) complied with any other conditions as Council may determine; and

viii) an MCC-approved manufacturing site in the case where the imported medicine is to be repackaged.

6.5 The parallel importer may proceed with the sale of the medicine only after the medicine has been registered.

7. REGISTRATION OF MEDICINES TO BE PARALLEL IMPORTED

7.1 The evaluation and registration of medicines intended for importation will follow the same procedure as provided for in Section 15 of the Act and as prescribed in the regulations, except as specified under item 6.3 above.

7.2 Council may impose any conditions necessary for the registration of the medicine.

7.3 The Registrar shall keep a separate register for parallel imported medicines.

8. CANCELLATION OF REGISTRATION OF PARALLEL IMPORTED MEDICINES

Council may, on good cause shown and in consultation with the Minister, cancel the registration of any parallel imported medicine.

9. INFORMATION TO BE PROVIDED TO THE PATENT HOLDER OR HOLDER OR THE CERTIFICATE OF REGISTRATION

The importer must, within 30 days after registration of the medicine, inform the patent holder or the holder of the certificate of registration in South Africa, of this fact and submit a copy of the letter to the Registrar.

10. IMPORTATION OF MEDICINES

10.1 The parallel importer must inform the holder of the certificate of registration at least four weeks prior to importation, on a form determined by Council, of his or her intention to parallel-import the medicine. The requirements for post-importation identification and testing of medicines, as described in Addendum 2 of the *Guidelines for the Registration of Medicines in South Africa,* will apply.

10.2 The parallel importer may not manufacture or re-export any medicine registered in South Africa as a parallel imported medicine.

11. REPACKAGING AND RELABELING OF PARALLEL-IMPORTED MEDICINES

11.1 Where the medicine is to be repackaged in South Africa after importation, this must be done at a site approved and licensed by the Council for this purpose.

11.2 The medicine must be labelled, packaged and have a package insert and patient information leaflet as prescribed in terms of regulations 8, 9 and 10.

11.3 The parallel importer may use the proprietary name approved in South Africa as well as any trade marks applicable to the medicine in order to ensure the public health interests.

11.4 The words "Parallel imported medicine" or the abbreviation "PIM" must be included on the label of each distribution pack.

11.5 The batch numbers of repackaged medicines must be identical to those of the original medicines and all original packaging material must be destroyed.

12 INFORMATION TO BE PROVIDED TO THE MEDICINES CONTROL COUNCIL

The following information must be supplied to Council by the parallel importer:

12.1 Any change in the conditions under which the medicine was registered;

12.2 Any adverse drug reactions or events arising from the use of the medicine;

12.3 Any report of risks associated with the medicine that may affect its quality, safety or efficacy.

13. TRANSFER OF CERTIFICATE OF REGISTRATION

A certificate of registration for an imported medicine may only be transferred to another person or company with the approval of the Minister.

14. AMENDMENTS TO THE DETAILS OF A PARALLEL IMPORTED MEDICINE

The importer must apply to Council on form PIF 1, available from the office of the Registrar, for approval of any change in the conditions of registration of an imported medicine or change in the storage conditions or change in any of the particulars of the medicine.

15. FEES PAYABLE

An applicant for the registration of a medicine to be parallel imported shall pay an application fee and a registration fee as determined by Council.

16. FORMS TO BE COMPLETED

The following forms, obtainable from the office of the Registrar, must be completed in respect of an application for amendment to the details of a parallel imported medicine and for informing the patent holder of the intention of the parallel importer to import a medicine, respectively: PIF 1 and PIF 2.

PIF 1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION TO AMENDMENT THE DETAILS OF A PARALLEL IMPORTED MEDICINE

PIF 1

1. Details of the importer

Name:

Business Address:

Postal Address:

Tel:

Fax:

Wholesale Distribution License Number:
(Issued in terms of Regulation 19)

Responsible Pharmacist (To be contacted in case of safety and quality problems of the medicine):

Name:

Address:

Registration number (in terms of Act No. 54 of 1974):

Cell phone number:

Fax:

E-mail:

2. Details of the medicine

Proprietary Name:

INN or Approved name:

Strength:

Pharmaceutical Dosage Form:

Pack size(s):

Registration number:

Date of MCC notice submitted:

3. Scope of the change(s)

☐ Change(s) resulting from amendments to the MCC Decision

☐ Change(s) proposed by the importer not related to the MCC Decision

Provide details of change and Parts of dossier affected:

_____

_____

_____

_____

_____

_____

_____

_____

☐ It is certified that the original condition of the product has not beendirectly or indirectly affected by the proposed change (Submit transport validation data where applicable).

5. Submission of copies of inner and outer labels and package insert

Copies of the amended outer and/or inner package labels and/or package insert of the medicine must be enclosed where applicable together with an electronic version in Microsoft Word (on diskette or by E-mail).

	YES	NO remains unchanged
Copy of the amended outer package label enclosed	☐	☐
Copy of the amended inner package label enclosed	☐	☐
Copy of the amended package insert enclosed	☐	☐

_____ _____

Signature Place

_____ _____

Name Date

_____

Designation

Note: Please return the form and its required annexes to:

The Registrar of Medicines
Medicines Control Council
Private Bag X828
Pretoria 0001

PIF 2

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

NOTIFICATION FORM – PARALLEL IMPORTED MEDICENES

Version MCC2003/1

PIF 2

NOTICE OF INTENTION TO PARALLEL IMPORT A MEDICINE UNDER PATENT

DETAILS PARALLEL IMPORTATION PERMIT HOLDER:	**Name:**_____ **Business address:**_____ _____ **Permit Number:**_____
DETAILS OF MEDICINE REGISTERED IN SOUTH AFRICA:	**Proprietary name:** _____ **Registration No.** _____
DETAILS OF MEDICINE TO BE PARALLEL IMPORTED:	**Proprietary name:**_____ **PIM Registration No:**_____ **Country of origin:** _____ **Manufacturer:** _____ **Price of medicine:** **R**_____**per**_____
INTENTION TO PARALLEL IMPORT THE ABOVE MEDICINE	**Approximate date of importation:** _____
DETAILS OF PATENT HOLDER:	**Name:** _____ **Business address:** _____ _____
SIGNATURE OF PERMIT HOLDER:	
DATE:	
A copy of the completed form must be sent to the Medicines Control Council	

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINE ON GENERIC SUBSTITUTION

This document has been prepared to serve as a recommendation to authorised health practitioners involved in the dispensing and administration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. The MCC is committed to ensure that all medicines in use will be of the required quality, safety and efficacy. It is important for all who deal with medicines to adhere to the administrative and technical requirements to avoid unwanted or adverse events that may compromise the health of the population. This guideline must be read in conjunction with the definition of "interchangeable multi source medicine" in the Act and Regulation 2 of the Medicines and Related Substances Act No. 101 of 1965, as amended.

This guideline will be updated on a regular basis as new information becomes available.

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

GUIDELINE ON NON-SUBSTITUTABLE MEDICINES

1. This guideline replaces Circular 16 of 1994. LIST OF NON-SUBSTITUTABLE MEDICINES. This list will be updated as new information on generic substitution becomes available. The absence of substance from this list must not be construed to mean that such a substance will be substitutable. The attention of all health practitioners who dispense or administer medicines is drawn to this list to assist in taking decisions where one or more alternatives are available.

2. The interchangeable use of different brands of chemically equivalent medications (i.e. those which contain the same active ingredients, the same quantities thereof, in the same pharmaceutical dosage form, or as more commonly named, "generics") could under certain circumstances compromise therapeutic response and safety of the patient.

3. The Medicines Control Council, having studied the matter in depth on both a local and international level, recommends that substitution should not occur when prescribing and dispensing "generic" medicines which:

   i) have a narrow therapeutic range;
   ii) have been known to show erratic intra- and interpatient responses;
   iii) are contained in dosage forms that are likely to give rise to clinically significant bio-availability problems, e.g. extended or delayed release preparations, as well as those known to be super bioavailable*;
   iv) are intended for the critically ill and/or geriatric and paediatric patient.

4. In terms of the afore-mentioned factors, the following list of medicines have on occasion, been known to present bio-equivalence problems and should ideally not be interchanged with other "generics" unless adequate provision is made for monitoring the patient during the transition period.

Alendronate tablets or capsules
Atenolol tablets or capsules
Carbamazepine tablets or capsules
Chlorpromazine tablets or capsules
Dexamethasone tablets or capsules
Diethylstilboestrol tablets or capsules
Digoxin tablets or capsules
Disulfiram tablets or capsules
Ethinyl Oestradiol tablets or capsules
Fluoxymesterone tablets or capsules
Furosemide tablets or capsules
Glibenclamide tablets or capsules
Hydralazine, Hydrochlorothiazide and Reserpine combination tablets or capsules
Hydralazine and Hydrochlorothiazide combination tablets or capsules

GENERIC SUBSTITUTION

Hydrocortisone tablets or capsules
Hydrocortisone Acetate injection
Isoproterenol Metered Dose inhaler
Isoethrane Metered Dose inhaler
Isosorbide Dinitrate sustained release tablets and capsules
Itraconazole tablets or capsules
Levodopa tablets and capsules
Nifedipine: all extended/delayed release formulations
Oestrogens, Conjugated tablets or capsules
Oestrogens, Esterified tablets or capsules
Penicillin G Benzathine injection
Phenytoin tablets and capsules
Phytomenadione injection
Prazosin Hydrochloride tablets 5mg*
Prednisolone tablets or capsules
Prednisolone Acetate injection
Prednisolone Tebutate injection
Prednisone tablets or capsules
Promethazine tablets
Propylthiouracil tablets
Reserpine tablets
Reserpine and Chlorothiazide combination tablets
Reserpine and Trichloromethiazide combination tablets
Tamoxifen tablets or capsules
Theophylline controlled release tablets or capsules
Triamcinolone tablets or capsules
Trichloromethiazide tablets or capsules
Warfarin Sodium tablets or capsules

The list is subject to periodic review and alteration at the discretion and recommendation of the Medicines Control Council.

Version MCC2003/1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR PREPARATION OF SITE MASTER FILE

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

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

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