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 mass — % excipient (m/m) per total target dosage form 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	-

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	Notification
9	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)	
10 (including parenterals)	Change to container dimensions, same content size Change of presentation size **(addition or removal)**, same container and closure system.			
11 (including parenterals)	Analytical methodology: Raw material specifications • More stringent • Additional • Upgrading to latest pharmacopoeia Final product specifications • More stringent • Additional • Upgrading to latest pharmacopoeia (BP; USP; Ph. Eu.)	 Raw material specifications and control procedures Final product specifications and control procedures	Validation/changes do not reflect a change in processing e.g. fine to microfine particle size	-
12	Change to appearance/description / shape (excluding scoring for dosage claim) restricted to: • Shape (providing the surface area remains unchanged – otherwise it is Type B) • Imprinting/embossing	Package insert, raw material specifications and control procedures, final product specification, manufacturing procedures	Validation/ Comply with Foodstuffs, Disinfectants and Cosmetics Act 54 of 1972 or FDA purity	

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	Notification
	• printing		standards or EU Commission Directives	
13	Change to dimensions of tablet or capsule, without any other change to the final product specifications	Package insert, final product specification and control procedures, manufacturing procedures	Validation	-
14 (including parenterals)	Change of name of active or other ingredient to an INN or approved name			
15	Change in: • process timing and/or operating speeds(if validated), but same final product specifications and content uniformity • process temperature and/or humidity(within validation range), but same final product specifications and content uniformity • order of addition of raw material with same processing principles and same final product specifications	Manufacturing procedures and validation protocol of critical steps	Validation/(a)/product not modified rot slow release	

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)	-

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CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	EFFICACY
	• Deletion of specification • Not in accordance with latest pharmacopoeia (full motivation) Final product specifications • Less stringent • Deletion (excluding particle size) • Not in accordance with the latest pharmacopoeia (full motivation)	Final product specifications and control procedures		
5	Active ingredient (suspension dosage form): Change in crystalline or polymorphic form	Chemical details, raw material specifications and control procedures, final product specifications and control procedure	(c)	Supportive literature on efficacy of relevant polymorphic form
6	Change to scoring of tablet (change in dosage regimen)	Package insert, final product specifications, manufacturing procedures	(c)	-
7	Packaging material: • Changes in composition of the immediate container affecting stability • Changes to less protective colour (light sensitive products) • Changes to closures in contact with product not in compliance with the USP permeation test	Package insert (if relevant), container specifications and control procedures, manufacturing procedures (if relevant)	(c)	-
8	Additional source/change in active raw material source (route of synthesis not the same), or change in method of synthesis	From each source: • Method of synthesis (AIF) • COA (See Guidelines on Active Raw Material Requirements) Demonstration of equivalence between material from each source by common laboratory, Verification of compliance to	-	-

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	EFFICACY
		Guidelines on Active Raw Material Requirements in tabulated form		
9	Change in: • type of process used in the manufacturing of the product outside validation (i.e. completely different method of processing) e.g. change from dry to wet granulation	Formulation (if relevant), raw material specifications and control procedures (if relevant), manufacturing procedures and validation protocol	(d)	Proof of efficacy
10	Different equipment/process machinery with different processing principles (Note: if change occurs, current manufacturer, if retained, must follow same manufacturing procedures unless product integrity can be maintained by both processes)	Front Page, formulation, raw material specifications and control procedures, final product specifications, manufacturing procedures, site master file, validation protocol	(d)	Proof of efficacy
11	Change in process of combining phases in the production of semi-solid dosage topical dosage form	Manufacturing procedures	(c)	-
12	Change in sterilisation process and method (e.g. from filtration sterilisation to autoclaving)	Manufacturing procedures	(c)	-
13	Scale-up to more than ten times the size of the batch used to support stability and efficacy, using the same: • Formulation • Equipment design and operating principles • Controls • SOPs	Manufacturing procedures, batch information of stability data	(i)	Proof of efficacy
14	Scale-up to more than ten times the batch size of the approved and validated batch	Manufacturing procedures, batch information of stability data	(i)	Proof of efficacy

CATEGORY	DESCRIPTION	DOCUMENTS OF DOSSIER WHICH MAY BE AFFECTED	CONDITION	EFFICACY
15 (only parenterals)	• Change from a glass ampoule to a glass vial with an elastomeric closure • A change to a prefilled dosage form from another container system • A change that add or delete silicone treatment to container closure system • Changes in the size and / or shape of a container for a sterile drug product where the head space changes. • A change to a flexible container system bag) from another container system	Package insert (if relevant), container specifications and control procedures, manufacturing procedures (if relevant)	(d)	
16	Batch-specific shelf-life extension		(h)	
17	Once-off formula or manufacturing procedure change	Batch manufacturing record	(j)	

4.5 Legends for stability data required.

(a) The results of an ongoing long-term study derived from the first production batch, stored at 25°C/60% RH, must be submitted as soon as 12 months data are available. The approved shelf-life is retained. The study must continue till the approved shelf-life has been substantiated

(b) The results of an ongoing long-term study derived from the first production batch, stored at 25°C/60%RH, must be submitted as soon as 12 months data are available, plus 3 months' data, storage at 40°C/75%RH. The approved shelf-life is retained. The long-term study must continue till the approved shelf-life has been substantiated.

(c) Three months stability data derived from at least one pilot batch, stored at 25°C/60%RH, plus three months' data, storage at 40°C/75%RH, must be submitted at the time of submission to obtain a tentative shelf-life of 24 months. This shelf-life must be substantiated on the first two production batches.

(d) Nine months stability data derived from at least one pilot batch, stored at 25°C/60%RH, plus three months' data, storage at 40°C/75%RH, must be submitted at the time of submission to obtain a tentative shelf-life of 24 months. This shelf-life must be substantiated on the first two production batches.

(e) Three months stability data derived from the product, stored at 25°C/60% RH, plus three months' data, storage at 40°C/75%RH, must be submitted at the time of submission to obtain a tentative shelf-life of 24 months. This shelf-life must be substantiated by submission of the results of the long-term study at 24 months. **(NB. This set of data would apply specifically to new applications for registration of medicines)**

(f) Stability data derived from three production batches (products containing new chemical entities) or two production batches (products containing well established entities – generics) stored at 25°C/60% RH, for the full period of the requested shelf-life, and three months' data, storage at 40°C/75%RH, complying with all specifications, must be submitted. (Stability guidelines to be followed)

(g) Stability data derived from three production batches (new chemical entities) or two production batches (generics) stored at the maximum requested recommended storage conditions for the full period of the shelf-life, plus three months' data at least 15°C higher than the recommended storage conditions, complying with all specifications must be submitted.

(h) Follow-up stability data derived from the specific batch of the product stored at the maximum recommended storage conditions must be submitted every three months, till the end of the extended shelf-life.

(i) Three months stability data derived from the product stored at 25°C/60% RH, plus 3 months' data, storage at 40°C/75%RH, must be submitted at the time of submission. The approved shelf-life is retained. The long-term study must continue till the approved shelf-life has been substantiated.

(j) Follow the stability schedule and place the batch as per schedule onto stability. The data must be submitted as soon as the 12 months data is available. The study must continue till the approved shelf-life has been substantiated

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

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Republic of South Africa

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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

Version MCC2003/1

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

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

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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 _____

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DEPARTMENT OF HEALTH
Republic of South Africa

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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

ANNUAL RETURNS

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.

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

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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 necessary in 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

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IMPORTATION AND EXPORTATION

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 presriber; 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