POST-IMPORTATION ID/TESTING

**N.B.** The Medicines Control Council reserves the right to withdraw the exemption, should the applicant give cause.
Applicants who have obtained permission for exemption previously from the MCC for their products must re-apply for exemption.

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

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

POST-IMPORTATION ID/TESTING

**MASTER RELEASE DOCUMENT**

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

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

| |
|---|
| Position/ Function |

| | |
|---|---|
| Signature | Date |

# MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

## ADDENDUM 2

# VALIDATION PROTOCOLS AND VALIDATION REPORTS

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

**Guidelines and application forms are available from the office of the Registrar of Medicines.**

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

## VALIDATION PROTOCOLS AND VALIDATION REPORTS

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

### 1 IMPORTANT REFERENCES:

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

### 2 GENERAL COUNCIL POLICY:

The standard to be used to assess compliance with current Good Manufacturing Practice, would be the South African Guide to Good Manufacturing Practice (SAGMP) (latest edition).

"that the Guide to Good Pharmaceutical Manufacturing Practice as amended, which was prepared jointly by the secretariat and the PMA, be considered as the standard determined by Council as referred to in the specific condition for registration of a medicine, namely that the applicant shall ensure that the medicine is manufactured and controlled in accordance with Good Manufacturing Practice as determined by Council."

### 3 WHAT VALIDATION IS:

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

**"VALIDATE...**

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

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

3.3 There should be levels where validation and qualification should be performed, and the level should determine the intensity of these products. It should be least for liquid preparations (solutions) and most for parenteral medicines. For solid

dosage forms, it should depend on the criticality of the product as far as the patient is concerned.

## 4 WHEN VALIDATION SHOULD BE DONE:

4.1 Validation should be considered in the following situations:

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

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

4.3 In this phase the extent to which deviations from the chosen processing parameters can influence product quality should also be evaluated. In general the final batch size should not be more than ten times the batch size of the representative development batches.

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

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

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

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

## 5 WHAT VALIDATION INVOLVES:

VALIDATION PROTOCOLS/REPORTS

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

## 6 THE VALIDATION PROTOCOL (VP)

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

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

## 7 THE VALIDATION REPORT (VR)

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

7.2 The report should include at least:

- the title and objective of the study,
- refer to the protocol,
- detail of material,
- equipment,
- programmes and cycles used
- details of procedures and test methods
- results (compared with the acceptance criteria).

- recommendations on the limits and criteria to be applied to all future production batches (which could form part of the basis of a batch manufacturing document).

## 8 RE-VALIDATION:

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

- change of formulae, procedures or quality of raw materials
- change of equipment, installation of new equipment, major revisions to machinery or apparatus and breakdowns
- major changes to process parameters
- changes to facilities and installations which influence the process
- on appearance of negative quality trends
- on appearance of new findings based on current knowledge, e.g. sterilisation where

the frequency of checking is dependent on sophistication of in-process methodology

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

## 9 GENERAL NOTES

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

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

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

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

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

## 10 REQUIREMENTS

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

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

10.3 There should be a Validation Report (VR) following the completed validation.

10.4 Validation Protocols and Validation Reports should be available for inspection purposes by the inspectorate.

The following is applicable:

10.4.1 New Applications for registration:
A VP must be included in Part 2E. (The VR should only be submitted when requested by the inspectorate).

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

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

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

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

# MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

## ADDENDUM 1

## ALCOHOL CONTENT

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

**Guidelines and application forms are available from the office of the Registrar of Medicines.**

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

**ALCOHOL CONTENT FOR MEDICINES INTENEDED FOR ORAL ADMINISTRATION**

a)The following maximum concentration limits will be allowed for ethyl alcohol as inactive ingredient:

0,5 % (v/v) ethyl alcohol for children under 6 years of age
5,0 % (v/v) ethyl alcohol for children 6-12 years of age
10,0 % (v/v) ethyl alcohol for adults and adolescents over 12 years of age.

b) Minute dose preparations are exempted from this requirement.

c) For products where higher concentration of alcohol are required, (e.g. plant extracts or where solubility or preservation might be problematic), exemption from ethanol concentration limits will be considered individually, provided that justification and motivation is submitted together with proof that the proposed dosage will not result in blood alcohol levels of 25 mg/dl or higher. (Table 1 is attached for reference purposes only).

d) In all instances, the alcohol content of a mixture must be stated prominently on the immediate container label, the outer label (carton), as well as in the package insert and patient information leaflet.

e) All medicines (registered products, "Old medicines" and new applications) must comply with the alcohol levels stated in this policy.

**TABLE 1.#**

Volume (Millilietres) of Ethanol Preparation Predicted to Produce a Blood Ethanol Concentration of 25mg/100ml* (100ml=1dl)

| **% Ethanol (v/v) in Product** | **Age (Weight)** | | | | | |
|---|---|---|---|---|---|---|
| | 2yr (12kg) | 4yr (16kg) | 6yr (21kg) | 8yr (27kg) | 10yr (32kg) | 12yr (38kg) |
| 2,5 | 91 | 122 | 160 | 205 | 243 | 289 |
| 5,0 | 46 | 61 | 80 | 103 | 122 | 144 |
| 7,5 | 30 | 41 | 53 | 68 | 81 | 96 |
| 10,0 | 23 | 30 | 40 | 51 | 61 | 72 |
| 12,5 | 18 | 24 | 32 | 41 | 49 | 58 |
| 20,0 | 11 | 15 | 20 | 26 | 30 | 36 |
| 25,0 | 9 | 12 | 16 | 21 | 24 | 29 |

ALCOHOL CONTENT

* Values were calculated from data contained in McCoy et al, 1979, by use of the formula: dose (in milligrams) = plasma concentration (Cp) x volume distributed (Vd) and assuming that absorption is complete. For example, the calculation to obtain the value of 40 ml for a 6-year-old ingesting a product containing 10% alcohol would be made as follows: Cp = 250 mg/L and Vd = 0.6 L/kg x 21 kg; therefore, dose = 250 mg/L x (0.6L/kg x 21kg) = 3.150 mg. Because for absolute ethanol (specific gravity 0.789), 1 g = 1.27 ml, 31.5 g = 40 ml; thus, for 10% ethanol, the calculated volume is 40 ml.

# TABLE 1 is an abstract from an article on "Ethanol in Liquid preparations intended for Children", by the American Academy of Pediatrics, published in PEDIATRICS, Vol. 73 no.3 March 1984, page 406.

# MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

# CLINICAL REQUIREMENTS

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

**These guidelines should be read in conjunction with Regulations 5, 22, 24, 25, 42 and 43 of the Medicines and Related Substances Act No. 101 of 1965.**

**Guidelines and application forms are available from the office of the Registrar of Medicines.**

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003
Version MCC2003/1

CLINICAL REQUIREMENTS

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CLINICAL REQUIREMENTS

## 1. INTRODUCTION

This guideline serves to help applicants with the correct way of presenting a package insert for evaluation on application for registration of a medicine. Applicants are requested to follow the format stipulated in the guideline, in conjunction with provisions set out under Regulation 9 of the Act 90 of 1997 (hereafter referred to as the Act).

The professional package insert is regarded as the document that ensures the safe and effective use of the medicine under most circumstances. It presents a scientific, objective account of the medicines' uses and limitation as established by the supporting evidence. Ensure that all statements are adequately cross-referenced (See **Addendum I**). No promotional material may be included. Promotional statements and comparisons to other agents, indicative of any potential advantage over competitors will not be allowed.

After registration, the professional package insert may not be altered without the approval of the Medicines Control Council. In the case of safety-related matters the Council should be informed immediately, with submission of an approved professional package insert, a proposed amended package insert and the evidence/motivation for the change. (refer to PART 5.3 – Application for the Amendment to a package insert).

## 2. GENERAL:

2.1 Package inserts must be typed in a double-spaced text with a minimum legibility of 6-point Helvetica typeface in black ink on white cartridge paper or the equivalent thereof. The package insert text must be in at least English (British English) and any other official language.

2.2 Cross-referencing of the package insert shall be by leaving a broad margin on the right hand side of the page where every statement is clearly referenced.

2.3 Every statement shall be verified by a reference for purposes of evaluation. The exact page/s shall be stated and, if possible, the column and line number. Note, however, that no references shall appear on the finalized printed package insert. If an entire section is quoted from one source, it will be acceptable to indicate the one reference at the end of the relevant section.

2.4 The printing quality of the package insert must be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process. The spelling and grammar in the package insert text, and typographical errors must be checked by the applicant before submission to the Medicines Control Council. Failure to do so shall result in a delay of the registration process.

2.5 Electronic submissions will be preferred.

CLINICAL REQUIREMENTS

## 3. PART 1A – PROFESSIONAL PACKAGE INSERT MULTI-SOURCE MEDICINES

### 3.1 HEADINGS AND PARTICULARS IN A PACKAGE INSERT

Applicants shall take note of which sources to be used as a reference for the different headings specified in Regulation 9 of Act 90 of 1997. Applicants also to note that in-house package insert templates shall be used as a reference during the evaluation process of therapeutically equivalent, interchangeable multi-source medicines. (Schedule of definitions (2) of Regulation 9 of Act 90 of 1997), and as contemplated under sub-regulation 1 (s)(iv) of Act 90.

### 3.2 SCHEDULING STATUS

Applicants shall note the scheduling status of medicines as determined from time to time by the Minister, and as published in the Government Gazette. The correct term for unscheduled medicines is "Not Scheduled".

### 3.3 PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of the MRF 1.

### 3.4 COMPOSITION

An approved name of all active ingredients in accordance with Part 2 shall be listed.
The quantity thereof per dosage unit. per suitable mass, per volume, or per unit of the medicine shall be indicated.
The approved name and quantity of any preservative shall be listed and expressed as a percentage. The content of ethyl alcohol, where such quantity exceeds 2% shall be indicated.

Any ingredient which may cause an allergic reaction, or which may be harmful to certain individuals e.g. tartrazine, must be indicated as such, in accordance with Regulation 9 of the Act.

### 3.5 PHARMACOLOGICAL CLASSIFICATION

Shall be in accordance with Regulation 25 of the Act.

### 3.6 PHARMACOLOGICAL ACTION INCLUDING PHARMACOKINETICS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

CLINICAL REQUIREMENTS

## 3.7 INDICATIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.8 CONTRA-INDICATIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.9 WARNINGS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.10. INTERACTIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.11 PREGNANCY AND LACTATION

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.12. DOSAGE AND DIRECTIONS FOR USE

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.13. SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

## 3.14. KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data

### 3.15. IDENTIFICATION

In accordance with Part 2F.

### 3.16. PRESENTATION

In accordance with Part 2D.

### 3.17. STORAGE INSTRUCTIONS

In accordance with Part 2G.

The statement "Store all medicines out of reach of children." must be stated.

### 3.18. REGISTRATION NUMBER

Allocated by the Medicines Control Council.

### 3.19. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the package insert.

### 3.20. DATE OF PUBLICATION OF THE PACKAGE INSERT

This date shall be the date of the Medicines Control Council Resolution. The date shall only change when the package insert is amended extensively and is re-evaluated by Council.

**Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.**

## 4. PART 1A - PROFESSIONAL PACKAGE INSERT NEW CHEMICAL ENTITIES

### 4.1 HEADINGS AND PARTICULARS IN A PACKAGE INSERT

The package insert shall follow the same format as laid out in the guidelines for interchangeable multi-source medicines above, in conjunction with Regulation 9 of the Act. The difference being that the primary source of reference for headings 5 to 13 below shall be the clinical study data in the SBRA, or the AMRP, whichever is applicable to that particular application.

## 4.2. SCHEDULING STATUS

Applicants to note that the scheduling status of medicines shall be determined from time to time by the Minister.

## 4.3. PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of the MRF 1.

## 4.4. COMPOSITION

An approved name of all active ingredients in accordance with Part 2B(i) shall be listed.
The quantity thereof per dosage unit, per suitable mass, per volume, or per unit of the medicine shall be indicated.
The approved name and quantity of any preservative shall be listed and expressed as a percentage. The content of ethyl alcohol, where such quantity exceeds 2% shall be indicated.
Any ingredient which may cause an allergic reaction, or which may be harmful to certain individuals e.g. tartrazine, must be indicated as such, in accordance with Regulation 9 of the Act.

## 4.5. PHARMACOLOGICAL CLASSIFICATION

Shall be in accordance with Regulation 25 of the Act.

## 4.6. PHARMACOLOGICAL ACTION

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.7. INDICATIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.8. CONTRA-INDICATIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.9. WARNINGS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.10. INTERACTIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.11. PREGNANCY AND LACTATION

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.12. DOSAGE AND DIRECTIONS FOR USE

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

## 4.13. SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

The side effects that belong together shall be grouped together either in one paragraph or under one sub-heading, e.g. gastro-intestinal, skin, hematological etc., as per the System Organ Class Classification System of either WHOART or MeDRA.
Side effects that occur more frequently as well as the more serious type of side effects shall be listed at the beginning of the paragraph. The terms "more frequent" or "less frequent" may be used.

In the case of multi-component formulations, the side effects shall be listed separately for each active ingredient.

Special precautions shall be grouped together in a separate sub-section or paragraph. They should also be listed in order of importance.

## 4.14. KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

For treatment of over-dosage it is usually acceptable to state, "Treatment is symptomatic and supportive". There are exceptions where a standard text is required e.g. paracetamol, codeine, beta-blockers. Applicants should update themselves with the relevant Circulars on a regular basis.

### 4.15. IDENTIFICATION

In accordance with Part 2F.

### 4.16. PRESENTATION

In accordance with Part 2D.

### 4.17. STORAGE INSTRUCTIONS

In accordance with Part 2G.

The statement "Store all medicines out of reach of children." must be stated.

### 4.18. REGISTRATION NUMBER

Allocated by the Medicines Control Council.

### 4.19. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTFICATE

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the package insert.

### 4.20. DATE OF PUBLICATION OF THE PACKAGE INSERT

**This date shall be the date of the Council Resolution. The date shall only change when the package insert is amended extensively and is re-evaluated by Council.**
**Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.**

## 5. PART 1 B -PATIENT INFORMATION LEAFLET

### 5.1 INTRODUCTION:

This guideline serves to help applicants with the correct way of presenting a patient information leaflet for evaluation on application for registration of a medicine. Applicants are requested to follow the format stipulated in the guideline. in conjunction with provisions set out under Regulation 10 of the Act 90 of 1997 (hereafter referred to as the Act).

### 5.2 GENERAL:

5.2.1 Patient information leaflet shall be typed in a double-spaced text with a minimum legibility of 6-point Helvetica typeface in black ink on white cartridge paper or the equivalent thereof. The package insert text must be in at least English (British English) and any other official language.

5.2.2 Cross-referencing of the patient information leaflet shall be by leaving a broad margin on the right hand side of the page where every statement is clearly referenced.

5.2.3 Every statement shall be verified by a reference for purposes of evaluation. The exact page/s shall be stated and, if possible, the column and line number. Note, however, that no references shall appear on the finalized printed patient information leaflet. If an entire section is quoted from one source, it will be acceptable to indicate the one reference at the end of the relevant section.

5.2.4 The printing quality of the patient information leaflet must be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process. The spelling and grammar in the patient information leaflet text, and typographical errors must be checked by the applicant before submission to the Medicines Control Council. Failure to do so shall result in a delay of the registration process.

5.2.5 Electronic submissions will be preferred.

## 5.3 HEADINGS AND PARTICULARS IN A PATIENT INFORMATION LEAFLET

The patient information leaflet must be written in easily understandable English, be consistent with the professional package insert and in accordance with the regulation 10, in terms of the legibility, language and format. (Refer to Addendum 1 for Lay terms).

Each immediate container should have a patient information leaflet and should reflect the following:

### 5.3.1 SCHEDULING STATUS

That is the scheduling status of the medicine as in the professional package insert.

### 5.3.2 PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of MRF 1. When umbrella / brand" names are used, the applicants would be responsible to include precautionary statements of usage of these products simultaneously so as to inform patients of the correct usage and potential safety concerns. Example, if a range of products under the same umbrella name contains

paracetamol; it should not be used in conjunction with another products in the range also containing paracetamol.

## 6 WHAT THIS MEDICINE CONTAINS

The composition of the medicine, that is -

(i) the approved name of each active ingredient and the quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine:

(ii) all inactive ingredients must be listed qualitatively;

## 7 WHAT THIS MEDICINE IS USED FOR

The registered indications for use of the medicine as accepted by the Council in the professional package insert;

(e) **BEFORE TAKING THIS MEDICINE** – the following information should be included

- contra-indications
- precautions
- warnings e.g. warnings concerning sedative properties of the medicine, warnings concerning the risks involved with sudden withdrawal of the medicine etc must be included here
- interactions
- General statement to be included in this section:
  **"If you are taking medicines on a regular basis, concomitant use of the medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional for advice."**
  **"If you are pregnant or breast feeding your baby while taking this medicine please consult your doctor, pharmacist or other health care professional for advice."**
  *(THIS STATEMENT SHOULD BE BOXED AND BOLDED)*

(f) **HOW TO TAKE THIS MEDICINE**

The recommended dosage must be included here. (Any special information, which the patient may require for the proper and safe use of the medicine, should be provided)

Information on what to do in specific circumstances, for example in the case of a missed dose, an unexpected reaction or in the case of an overdose should be included. "**Do not share medicines prescribed for you with others.**" must be stated. As well as, **"In the event of over-dosage, consult your doctor or pharmacist. If neither is available, rush the patient to the nearest hospital or poison control centre".**

(g) **SIDE-EFFECTS**

(i) This section should be in layman's terms for the consumer to understand -

CLINICAL REQUIREMENTS

(a) Side-effects associated with the use of the particular medicine – listing the more frequent side-effects first.

(b) Side-effects that can be easily recognised by the patient.

(ii) The following general statement should be stated:
"Not all side-effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice."

(h) **STORAGE AND DISPOSAL INFORMATION -**

Should contain information on how to store the medicine properly and how to dispose of unused medicine, such as by returning such medicines to the pharmacy. The following statement must be stated:
"Store all medicines out of reach of children."

(i) **PRESENTATION**

The number, volume or mass per package unit must be mentioned. A description of the packaging material (i.e. bottle, blister, etc.) should be included.

(j) **IDENTIFICATION OF THE MEDICINE**

A complete description of the physical appearance of the medicine.

(k) **REGISTRATION NUMBER/ REFERENCE NUMBER**

The number as allocated by the Medicines Control Council.
This date shall be the date of the Council Resolution. The date shall only change when the patient

(l) **THE NAME AND THE BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE**

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the patient information leaflet.

(m) **THE DATE OF PUBLICATION OF THE PATIENT INFORMATION LEAFLET**

The information leaflet is amended extensively and is re-evaluated by Council.

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

Note:
The responsibility for ensuring that the patient information leaflet is in line with the regulations, including assurance that the patient information leaflet corresponds with the information in the professional package insert will essentially rest with the applicant.

## 6. PART 1 C- LABEL

An example of the facsimile of the label must be included here. Requirements e.g. font size as stipulated in the Regulations should be adhered to.

The following inclusions are permitted:

"For state use only – Not for sale" – for tender items

"Professional sample" – samples for professionals

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council in terms of Section 36 of the Act, prior to implementation.

## 7. PART 1 D - FOREIGN REGISTRATION

7.1 A list of countries including SADC countries in which an application has been lodged and the status of such applications shall be furnished. Countries that are members of the PER Scheme, other EU countries and the USA should specifically be identified. Approvals (with indications), deferrals, withdrawals and rejections should be stated. If the medicine has already been registered in any of the countries mentioned above, a copy of the registration certificate and the approved package insert (data sheet) as well as the conditions of registration, should be provided.

7.2 It should be stated whether data packages submitted in the countries in 7.1 are essentially similar to those submitted to the Medicines Control Council, including the proposed indications.

7.3 The Medicines Control Council should also be notified of any rejections, withdrawals or approvals of applications in the EU commission (mutual recognition process), Australia Canada, the Netherlands, Sweden, UK and USA during the evaluation period. Where the rejections or withdrawals relate to safety matters details in each case should be provided.

## 8. PART 4 - PRE-CLINICAL STUDIES

8.1 Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities. The Medicines Control Council endeavors to keep abreast of such developments and keep its application requirements and evaluation policies in line with "best international practice".

8.2 Legislation to be read in conjunction with these guidelines is: