* Biological Medicines, only

3. PREPARING AND SUBMITTING AN APPLICATION FOR REGISTRATION OF A NEW MEDICINE

3.1 Applications for registration of a medicine must be submitted on the MEDICINE REGISTRATION FORM (MRF 1) obtainable from office of the Registrar of Medicines.

3.2 Each page of the application must be numbered and the printing must be clearly legible.
Index according to the MRF 1, e.g. 2B-1 (referring to PART 2B, first page).
Double-sided copies are allowed except for package inserts.

3.3 The application for registration dossier must be properly indexed by the use of clearly labeled tabs to indicate each PART of the dossier.

3.4 Each PART must contain a complete index to that specific PART.

3.5 The application for registration must be properly bound on the left side as this allows for easy update/addition of pages. Binding is left to the discretion of the applicant, however, the use of lever-arch files is not accepted.

3.6 The application/covering letter must be bound to the application dossier.

3.7 The cheque must be attached to the covering letter. Proof of electronic payment and copies of deposit slips must be submitted with the application forms

3.8 The requirements with regard to metrication in accordance with the Trade Metrology Act must be applied.

3.9 The boxes in which documentation are submitted to the MCC must be clearly labeled. The following details should appear clearly on each box:

- Applicant name
- Name of the product
- The contents of the box e.g. File numbers, Parts, Sample, Cover letter, Cheque etc.
- Product identification code for each application (e.g. NCE-04NOV01)
- Number of boxes e.g. 1 of 10
- Type of application e.g. expedited registration, AMRP
- Colour stickers indicating screening copy (red) or post-screening copies (green)

In the case of expedited registration, approval letters must be attached. Applicants are advised to consult the relevant schedule of fees.

3.10 A duly completed pre-screening checklist and screening form, a product sample and the non- refundable prescribed screening fee that is attached to the cover letter, must accompany each application.

3.11 On receipt at the MCC, all applications for registration will be subject to a pre-screening according to a checklist (see attachment A).

3.12 Upon successful pre-screening, the application will be logged onto the system, allocated an application number and a letter acknowledging receipt of the application and the screening fee will be issued to the applicant.

3.13 If the pre-screening is unsuccessful, the applicant will be notified via e-mail or fax to collect the application within a certain period of time or the application will be submitted to council for a decision.

3.14 After successful pre-screening the application will be subjected to technical screening according to the screening form (MRF 2).

3.15 The HOLD and RETURN AS INCOMPLETE screening outcomes will be communicated to the applicant together with the reasons. Time frames for the applicant to submit outstanding information or to collect the application will also be communicated to the applicant. The outcome of the screening and the submitted screening documentation will be tabled at the next Council meeting for a decision.

3.16 The ACCEPTED screening outcome, the application fee, the number of copies and the time frame for these copies to be submitted will be communicated to the applicant. Where an expedited registration has been approved the application will be so marked. Any future correspondence regarding an expedited registration application shall be accompanied by a reference number and a copy of the approval letter.

3.17 The correct number of copies of applications and additional documents required for the evaluation of the application must be submitted in the format detailed in section 4 below.

4. PRESENTATION OF SCREENING AND POST SCREENING COPIES

In order to facilitate processing of the application for registration it is required that certain Parts of the application for registration be duplicated and submitted as prescribed in the screening approval letter together with the application fee. All documentation must be in English or the original document must be accompanied by a translation into English.

No additional documentation other than that which has been clearly stipulated below may be bound in any of the files identified below.
Where applicants have submitted electronic applications, there must be prior arrangements with the registrar for such applications, which will be submitted in the prescribed format.

4.1 Screening submission:

Covering letter
Screening fee
Completed pre-screening checklist

Completed screening form
One complete application for registration dossier
'File 1' below

(i) File 1 (with original submission for screening)

Copy of the latest Inspection Report (not older than 2 years) from the Medicines Control Council and/or foreign regulatory body recognized by the Council for the manufacturer of imported medicinal products and medicines Inspection flow diagram (what about locally manufactured medicines
GMP/WHO certificate
Certificate of analysis for the sample submitted
One sample of smallest pack size
Batch manufacturing documents for the sample submitted or available for inspection
License for Manufacturer, Packer, Laboratory
Proof of registration of the Company and the authorised person as a pharmacist.

4.2 Full submission:

Covering letter and application fees, plus the number of copies requested by MCC post screening.

(ii) File 2
Covering letter
Application for registration MRF 1 front page
Copy of screening form (MRF 2, completed in full)
Parts 1 A, 1B, 1C, 1D, 2A, 2B, 2C, 2D, 2E, 2F, 2G and 2H

(iii) File 3
Covering letter
Application for registration MRF 1 front page
Parts 1A, 1B, and 2B

(iv) File 4
Covering letter
Application for registration MRF 1 front page
Parts 1A, 1B, 1C, 2B, 2E, and 2F

(v) File 5
Covering letter
PART 2A

(vi) File 6
Covering letter
SBRA / Clinical Expert Report, if applicable

(vii) File 7

Covering letter
Application for registration MRF 1 front page
Parts 1 A, 1C, and 1D.
Approved foreign package insert/s
Clinical and Toxicological Expert reports

(viii) File 8

Covering letter
Application for registration MRF 1 front page
Copy of screening form (MRF 2, completed in full)
Parts 1A, 1B, 1C, 1D, 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 3, 4 and 5

4.3 Once the applicant has submitted additional copies, an acknowledgement letter will be sent to the applicant and the application will proceed with the evaluation process.

4.4 The applicant will not be permitted to communicate directly with the evaluator. All queries and concerns must be communicated through the secretariat.

5. Summary Basis of Registration Application (SBRA)

a) General

To expedite the review process of the safety and efficacy of medicines it is required that an Summary Basis for Registration Application (SBRA) accompany each application for registration where a clinical and pre-clinical expert report is not presented and clinical/pre-clinical data is submitted in support of the application.

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

Applicants must ensure that the general quality of the studies, proper cross-referencing to the data, explanatory notes and the quality of photocopying and binding are of an appropriate standard. SBRA must be cross-referenced with the documentation submitted to the Medicine Control Council.

Adaptation to the format prescribed in b) below, to suit each individual product/dosage form at the discretion of the applicant, where specific items are not applicable, may be necessary. Applicants are kindly requested to leave a wide left-hand margin (of at least 5 cm), for office use.

b) SBRA format

Refer to format below for details and a completed hypothetical example.

GENERAL INFORMATION

SUMMARY BASIS FOR REGISTRATION APPLICATION (SBRA)

1. **THIS APPLICATION INVOLVES:**

a new application
or
a resubmission
or
a package insert amendment

2. **DATE OF THIS SBRA:**

2.1 submitted:
2.2 discussed (office use):
2.3 comment to applicant (office use):

3. **PRODUCT DETAILS:**

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

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

Name	Position	Qualifications	Tel. No.

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

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

6. **EVIDENCE OF EFFICACY IN HUMANS:**

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

- Key trial(s) reference number: as listed under item 13 of SBRA
- Trial design : indicate with abbreviations/symbols, e.g.
  - DNB = double-blind
  - SB = single-blind
  - 0 = open
  - X = cross-over
  - P = parallel groups
  - R = randomized

- C = controlled
- PC = placebo-controlled
- MC = multicenter
- LS = Latin square

- Indications/Diagnosis.
- Number of patients treated with each drug.
- Dosage range used.
- Duration of treatment.
- Reference/comparative drug(s).
- Parameters evaluated/findings.
- Statistical data

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

Indicate clearly which trials were done/not done with the formulation and dosage form, for which registration is being applied (as reflected in Part 2B of MRF).

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

7. MAIN SAFETY ISSUES AND TOXICOLOGY:

7.1 Human studies:

(List side effects/adverse reactions/toxicological profile, with incidence figures and key references).

7.2 Pre-clinical studies:

(Animal and in vitro toxicology data)

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

8. EVIDENCE OF LONG TERM SAFETY/EFFICACY

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

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

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

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

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

11. REGISTRATION STATUS IN OTHER COUNTRIES:

Country	Date of registration

12. PROPOSED SCHEDULING STATUS:

(Provide reasons briefly, and illustrate structural formula)

13. LIST OF KEY REFERENCES:

(MAXIMUM 25)

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

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

Author(s), title of article, name4 of journal (abbreviated according to Index Medicus), journal particulars (year, volume, page no.).

Eg.:

1. Smith J treatment of mild hypertension. Br Med J. 1981; 283:628.

*Please refer to. "Uniform requirements for manuscripts submitted to biomedical Journals". S Afr Med J. 1981;60:263-268).

GENERAL INFORMATION

HYPOTHETICAL EXAMPLE: SUMMARY BASIS FOR REGISTRATION APPLICATION (SBRA)

1. **THIS APPLICATION INVOLVES:**

A new application

2. **DATE OF THIS SBRA:**

2.1 submitted: 01-10-1986

2.2 discussed:

2.3 comment to applicant:

3. **PRODUCT DETAILS:**

Active ingredient(s) and Quantity thereof	:	rosalone 10 mg
Proprietary name	:	ROZIN
Applicant	:	ROSEPHARM Laboratories
Application/Registration No.	:	
Pharmacological classification	:	6.1 Cardiac stimulants
Dosage form	:	film-coated tablets

4. **NAME(S) of registration Person and/or Medical Adviser responsible for compilation of this application:**

Name	Position	Qualifications	Tel. No.
Mr J Smith	Registration Manager	B.Sc (Pharm)	011-9628413
Dr P Jones	Medical Director	M.B., Ch.B.	012-488327

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

Rosalone is a positive inotropic agent, with direct vasodilator activity, different in structure and mode of action from either digitalis glycosides or catecholamines. Rosalone produces clinically and statistically significant improvements in haemodynamic indices of congestive heart failure, without significant increases in heart rate or myocardial oxygen consumption. Haemodynamic improvements are both dose

and plasma level-related. In addition to increases in contractility, rosalone improves diastolic function as evidenced by improvements in left ventricular diastolic relaxation.

(References: 1, 2 and 6)

6. EVIDENCE OF EFFICACY IN HUMANS:

Key Ref No.	Design: O=Open DB=Double-blind R=Randomized X=Crossover P=Parallel Groups PC=Placebo controlled MC-Multi-center	Indication	No. of patients entered and (completed)	Statistical data	Dosage, dosage form and (formulation)	Reference Drug and dosage	Duration of treatment	Parameters evaluated/ Findings
3	O, MCDB, R, X, PC	Congestive cardiac failure	92 (80)	P<0,01 for all para= meters, except (c)	10 mg/day *(f.a.a.f.)	Placebo	6 weeks	a) .... b) ....
5	O, X	"	55 (51)	Not done	20 mg/day (capsule)	Digoxin (0,25 mg/day)	4 weeks	c) .... d) ....
8	O, MC	"	214 (189)	.....	10 mg/day *f.a.a.f.)	-	14 weeks	.....
12	DB, R, P, PC	"	20 (16)	.. . .	20 mg/day *(f.a.a.f.)	Placebo	2 weeks	.....
15	DB, R, P	"	76 (63)	.....	10 mg/day *(f.a.a.f.)	Digoxin (0,25 mg/day)	8 weeks	....

TOTAL NUMBER OF PATIENTS TREATED IN ALL CLINICAL TRIALS, WITH ROSALONE: 618 (562 COMPLETED THERAPY)

See also item 8.

All studies (listed under items 6 and 8), except ref. 5, were done with dosage form and formulation that registration is being applied for; (*=formulation as applied for).

7. MAIN SAFETY ISSUES AND TOXICOLOGY:

7.1 Human studies:

Effect	Incidence	Key ref.
Ventricular arrhythmias	12,6%	13
Supraventricular arrhythmias	3,6%	13,3
Hypotension	3,1%	13
Angina/Chest pain	1,4%	5
Headaches	4,4%	4, 12, 13
Hypokalaemia	0,7%	15

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Tremor	0,5%	8
Thrombocytopenia	5%	13
Alkaline phosphatase	9%	8, 13, 15

Allergic reactions occurred in +1,4% of patients.

Dermatological reactions (rash, pruritus, etc) were reported in + 20% of patients. Despite this, patient acceptance and compliance was very good.

7.2 Pre-clinical Studies

			NINCIDENCE	KEY REF.
A Acute Toxicity Studies:	(i)	LD50: Rabbit (i.v.) 16 mg/kg Mouse (s.c.) 140 mg/kg Dog (p.o.) 400 mg/kg		11
	(ii)	Dog p.c. LD50: severe emesis.		(11)
B Subacute Toxicity Studies (4 weeks)	(i)	Marked increase in Heinz inclusion bodies at 300 mg/kg p.o (Rat)	25%	(11)
	(ii)	Elevated reticulocyte count in males given 80 mg/kg i.p., coupled with polychromasia (Rat)	1/10 3/10	(11)
	(iii)	Plasma urea 48% higher (80 mg/kg) (Rat) i.p.	2/5	(11)
	(iv)	Crystal-like structures detectable in some tubuli of high dose male rats.	30/40	(11)
	(v)	Allergenic reaction 40 mg – 80 mg/kg p.o. in 3 dogs at beginning of study.	3/12	(9)
	(vi)	Evidence of functional and morphological kidney damage in monkeys 40 and 30 mg/kg i.v. Serum urea and creatinine increased.	12%	(9)
	(vii)	Evidence of functional and morphological kidney Damage observed in 2/4 monkeys at 30 mg/kg. Crystalline precipitates observed	2/4	(9)
C Subchronic Toxicity Studies	(i)	Reduced erythrocyte counts and reduced haemoglobin and haematocrit values – high dose monkeys (18 mg/kg i.v.) Crystalloid substances in distal tubles of 2 high- dose monkeys	8/20 2/15 7/10 high dose rats 3/10	(7) (7) (7) (7)
	(ii)	Crystals in urine sediment (rats)		
	(iii)	Death of 3 high dose rats (500 mg/kg).		
D Chronic Toxicity: (Six months)	(i)	Crystals observed in urine sediment of 2 males and 2 females from high dose group (500 mg/kg p.o.) (Rats)	4/20 2/10	(7)
	(ii)	Histopathological examination revealed mild to moderate foreign body reaction in kidneys of 2 monkeys receiving 90 mg/kg. Kidney changes were associated with intratubular crystallization, but no indication of functional impairment.		(7)
Oculotoxicity:		(Rhesus monkeys) No oculotoxicity observed	32/32	(7)
Arthropathy:		Articular cartilage damage (juvenile rats) Lesions in articular cartilage (dogs)	11/20 12/12	(7) (7)
Fertility:	(i)	Slight decrease in implantations (no statistically significant) at 100 mg/kg dose (rat).		(7)
	(ii)	No untoward effect on fertility or reproductive performance		

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		(Rabbit)		(7)
Reproduction:	(i)	Maternal Toxicity but no teratogenicity (rabbits)		(7)
	(ii)	No maternal toxicity (rabbit)		(7)
	(iii)	No maternal toxicity/embryotoxicity/teratogenicity (mouse)		(7)
	(iv)	No maternal toxicity/embryotoxicity/teratogenicity (Rat)		(7)
Mutagenicity/Oncogenicity		None observed (in vitro; as well as in rats)		(11)

8 EVIDENCE OF LONG TERM SAFETY/EFFICACY

Key Ref No	Design: O=Open DB=Double blind R=Randomized P=Parallel Groups MC=Multicenter	Indications	No. of patients Entered and (completed)	Statistical data	Dosage, dosage form and (formulation)	Reference Drug and dosage	Duration of treatment	Parameters evaluated/Findings
4	O, MCDB, R, P	Congestive cardiac failure	112 (91)	.....	10 mg/day (f.a.a.p.)	Digoxin (0,25 mg/day)	30 weeks	.....
*8			214 (189)	.....	10 mg/day (f.a.a.p.)		14 weeks	.....

(* Also included under item 6) (f.a.a.p. = formulation as applied for)

N.B: No tolerance developed during any of the clinical studies.

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

PHARMACOKINETIC PARAMETERS FOR ROSALONE (n=24)

Parameter	Units	Mean	S.E.M.	Range
Cmax	ug/ml	120.1	4.25	97.3-154.0
Serum-protein binding	percent %	50.4	2.65	27.1-59.9
AUC 0-24 hr (trapezoidal)	ug.hr/ml	231.8	9.18	178.8-285.8
t½	hr	0.15	0.02	0.04-0.33
t½	hr	10.06	0.86	8.68-12.35
Tmax	hr	0.75	0.06	0.42-1.17
24 hour urinary excretion	% of dose	63.1	1.84	51.9-73.5
Serum clearance	ml/min/kg	0.94	0.07	0.66-1.60
Bioavailability	%	56		39-67

(References: 10, 14)

GENERAL INFORMATION

10. **NOT APPLICABLE TO THIS PRODUCT.**

11. **REGISTRATION STATUS IN OTHER COUNTRIES:**

Country	Date of registration
U.S.A.	25-07-1986
U.K.	10-05-1985
Australia	04-02-1985

GENERAL INFORMATION

12. PROPOSED SCHEDULING STATUS:

S4

(Similar compounds have been allocated to S$ by Council, in the past).

13. LIST OF KEY REFERENCES

1) James X. Pharmacology of rosalone. Br Med J 1984; 91:640-645

2) Etc.

3) Etc.

4) Scott et al. Rosalone in congestive heart failure: a double blind trial vs. digoxin. S Afr Med J 1985: 68: 201-205

13) "Side effects and ADR's of rosalone" – Rosepharm Labs, Report R+d 534, 1984

14) Etc.

Etc.

.....

6. EXPEDITED REVIEW PROCESS

INTRODUCTION

Medicines Control Council may, under certain circumstances, (as in most other national drug regulatory authorities) speed up the registration process for specific medicines that have important therapeutic benefit and which are required urgently to deal with key health problems. In such cases, an accelerated review system is applied. For detailed information refer to Regulation 5 of the Act and Guideline on Expedited Review Process.

7. ABBREVIATED MEDICINE REVIEW PROCESS (AMRP)

7.1 INTRODUCTION

The AMRP is a system initiated by Council to limit the evaluation time of pharmaceutical products registered in countries with which the Council aligns itself, and where the evaluation report is readily available. The abbreviated medicine review process is then based mainly on the expert reports on the pharmaco-toxicological and clinical data. It should be noted that the AMRP is an abbreviated **evaluation** process and not an abbreviated **application**.

7.2 TERMINOLOGY

7.2.1 Expert report: an independent, objective and encompassing report on all the relevant aspects in the specific field of expertise of the reporter who is familiar/acquainted with the development of the product.

7.2.2 Expert reviewer's report: the report of the regulatory reviewer, after evaluation of the data submitted in support of approval for licensing.

7.3 REQUIREMENTS FOR AMRP

7.3.1 Only new chemical entities registered in one or more of the following authorities with which the Council aligns itself will qualify for AMRP. The countries (and their authorities) are: USA (FDA), UK (MCA), Sweden (MPA), Australia (TGA) and Canada (Health Canada), European Union (EMEA), and Japan.

7.3.2 The applicant must obtain the Expert Reviewers' reports (which are not more than two years old) on safety, quality and efficacy, from an approved medicines regulatory authority; or request the secretariat to obtain such reports from the regulatory authorities where agreements have been signed; or from PICS member states and where the mutual recognition agreements or memoranda of understanding on exchange of evaluation reports on pharmaceutical products, where such medicines regulatory authority from a participating nation has approved the medicine.

7.3.3 The certificate of approval of registration of the new entity by one of the following registering authorities: FDA, MCA, Swedish MPA, Canada, Australian TGA or EMEA.

7.3.4 Submit written confirmation that the proposed package insert is based on the package insert and the complete dossier of the licensing country.

Apart from the approved package insert on which the submission is based, the package insert of the other countries where registration has been approved should be submitted.

7.3.5 Written confirmation that the data submitted to the Medicines Control Council is identical to that submitted to the authority that has granted approval. Raw data of experimental and clinical studies should be excluded. Letter authorising MCC to contact the relevant MRA for an evaluator's report or assessor's report.

7.3.6 Expert reports on chemical-pharmaceutical, pharmaco-toxicological and clinical documentation.

7.3.7 Relevant correspondence between the applicant and the registering authority concerning the registration of the product. The negative (queries, non acceptance of certain claims/statements etc) as well as positive correspondence.

7.3.8 Written confirmation that the formulation applied for is identical to that approved by the registering authority.

7.3.9 Applications for AMRP can only be accepted if the product has been approved by the said authorities, within the last three years of their licence in the licensing country.

7.4 REQUIREMENTS IN RELATION TO THE EXPERT REPORTS:

7.4.1 All problems in the submission should be clearly identified and addressed in the Expert report.

7.4.2 The Expert report should address all the aspects in the package insert.

7.4.3 A list of the key references used in compiling the Expert Report should be attached.

7.4.4 The curriculum vitae of the Expert should be included.

7.4.5 If the application for the registration complies with the requirements for the AMRP system, it should be further determined whether the Expert report reveals all the necessary information for Council to make a considered decision on registration. For this purpose an AMRP-SBRA should be drafted. An AMRP-SBRA should be based on the information in the Expert report only. Furthermore, written confirmation that the AMRP-SBRA was compiled from the Expert report only, should accompany the AMRP-SBRA submission.

8. PROPRIETARY NAME POLICY.

In terms of section 15 (3) of the medicines act

The term "PROPRIETARY NAME" is defined in the Regulations pertaining to The Medicines and Related Substances Control Act, 1965 as follows:

"PROPRIETARY NAME, in relation to a medicine, veterinary or complementary medicine and medical device, means a name -

a) that is unique to a particular medicine, veterinary, or complementary medicine and medical device;

b) that is generally identifiable; and approved in respect of that specific medicine, veterinary, or complementary medicine and medical device in terms of the Act. The Act states that a medicine, complementary medicine, veterinary medicine or device must be registered under such name as the Council may approve.

In evaluating the safety of a medicinal product during the registration process, the Medicines Control Council is obliged to consider whether the proposed proprietary name of such a product could potentially pose public health and safety concerns or if it may be misleading. The possibility of mistaking one drug for another because of similar proprietary names can have serious consequences. Since many medication errors are caused by look-alike and sound-alike medication names, it is evident that

public health considerations must be paramount in determining whether a particular proprietary name may be used for a medicinal product.

In order to enable applicants to propose acceptable proprietary names for medicinal products, it is essential that:

a) consistent, non-arbitrary criteria are applied when reviewing the acceptability of proposed proprietary names;

b) a transparent procedure is in place for evaluating the acceptability of proposed names.
The MCC has adopted the WHO naming policy with adaptations

8.1 SAFETY CONCERNS REGARDING PROPRIETARY NAMES

In assessing the merits of a proposed proprietary name, the first and foremost issue considered is that of patient safety. Applicants are advised to consider the following guidance bearing in mind the paramount criterion of "potential safety risk"

8.1.1 The proposed proprietary name should not convey misleading therapeutic or pharmaceutical connotations.

8.1.1.1 An example may be the use of the name "SEDINAX" for a product intended to treat pain and fever containing only an analgesic or the name "PAINKID" for a product not indicated for paediatric use.

8.1.2 Similarly, the name "CARDIODORON" should only be used for medicinal products for the treatment of cardiovascular diseases

8.1.3 A proprietary name may include a pharmacological/therapeutic connotation, provided that it is in line with the indications in the package insert. Each application, however, will be evaluated on merit.

8.1.4 It is important to bear in mind the claims made in the package insert in relation to the proposed name of the product, when considering the acceptability of names, hence the requirement of submission of package inserts in all instances.

8.1.5 The use of "umbrella/brand types" of names across products in associated therapeutic categories generally may not pose a problem. However, when such names are used for products in different commodity categories, the misrepresentation of non-medicines as medicines and vice versa would be considered unacceptable. Applicants would be responsible to include precautionary statements of usage of these brands simultaneously so as to inform patients of their correct use.

8.1.6 The proposed proprietary name should not be misleading with respect to the composition of the product.

8.1.7 The proposed proprietary name should not be liable to cause confusion in print, handwriting or speech with the proprietary name of another.

8.1.8 For example, the names "AMYTAL" (barbiturate) and "AMITOL" (multivitamin) could have serious safety implications if a barbiturate is supplied to a patient instead of a vitamin.

8.1.9 When the name being applied for is identical/too similar to a name already approved for another product, applicants will be advised that the proposed name is too close to an existing name. Only if the existing product is registered will the name be disclosed. Disputes regarding similarity of names not identified by the Medicines Control Council at the time of registration/ change are the concern of applicants, not the Medicines Control Council. If however, valid safety concerns are identified, the applicant will be advised accordingly.

8.1.10 Names which are identical to, or which are similar to, the names of products previously marketed will generally not be favourably considered regardless of whether such products are dormant or not.

8.1.11 If an objection is raised on the basis of similarity between the proposed proprietary name and an existing name or name raising a risk of confusion in print, handwriting or speech, the objection will be evaluated taking into account other potentially distinguishing factors, such as:

- The pharmaceutical form
- The route of administration
- The indication and legal status/condition of supply

After assessing these factors as a whole, a decision on whether the proposed proprietary name poses a potential safety risk will be made.

8.2 ADDRESSING INTERNATIONAL NONPROPRIETARY NAMES' (INN) CONCERNS IN PROPOSING PROPRIETARY NAMES

The Medicines Control Council subscribes to the WHO guideline in respect of the protection of INN-stems and encourages the pharmaceutical industry to be continually aware of this issue (Document No. "WHO/EDM/QSM/99.6").

8.2.1 A proprietary name should not contain an INN-stem (as published by the WHO). The WHO stresses the importance of the need to protect INN-stems. The relationship of pharmacologically related substances is indicated by using a common stem, which in turn forms part of the INN Name. The orderly development of generic nomenclature could be hindered if these stems are not protected. The sentiments of the WHO in this regard are shared by MCC, and are taken into consideration when considering proprietary names.

8.2.1 For example, "-ac" is an INN-stem for anti-inflammatory agents of the ibufenac group, and a proprietary name ending with "ac" would not be acceptable regardless of the active ingredient, which it contains. The reasons are protection of the stem and confusion, which could arise if the product does not contain an anti-inflammatory agent of the ibufenac group

8.2.2 A proprietary name commencing with, or containing "ac" in another position within the name could, however, be considered.

8.2.3 The derivation of proprietary names from INN Names, i.e., generic names is discouraged, as this practice could lead to confusion. For example, the choice of the name "METAPERAMIDE" for a product containing loperamide, could cause confusion that the product contains another loperamide-type compound.

8.2.4 If a proprietary name is derived from a generic name, it should not be similar to the generic name, thereby leading to confusion. For example, the name "TRIMAZOLE" could be interpreted as being an antiprotozoal of the metronidazole group, an antifungal of the miconazole group or a brand of co-

trimoxazole even though the name does not contain an INN-stem for any of these groups.

8.2.5 In the case of single component generic medicines, applicants are encouraged to market their products under the complete generic name followed or preceded by their company name, acronym or other distinguishing feature.

8.2.6 Exceptions may be considered for the antiretrovirals if these have been previously approved by a recognized Regulatory Authority and are accompanied by a motivation.

8.3 OTHER CONCERNS REGARDING PROPRIETARY NAMES

8.3.1 The issue of whether a particular proprietary name may constitute an infringement of another entity's intellectual property rights cannot be one of the Medicines Control Council's concerns and is therefore not taken into account during consideration of the acceptability of a proposed proprietary name.

8.3.2 The proprietary name should preferably consist of only one word and should avoid qualification by letters or numbers. The use of short qualifications/ abbreviations that do not carry an established and relevant meaning is unacceptable. Promotional qualifications/abbreviations/ manufacturer's codes are also unacceptable. However, if other qualifications/ abbreviations are to be included, appropriate justification should be provided (e.g. For insulin mixtures the proprietary name could be followed by a number or letter representing the fast-acting component of the mixture).

8.3.3 The use of descriptive abbreviations may also be acceptable if there is a need to distinguish different routes of administration for the same medicinal product: e.g. IV: intravenous, IM: intramuscular, SC: subcutaneous.

8.3.4 A proprietary name should not convey any promotional message with respect to the use of the product.

8.3.5 Use of capitals in proprietary names should reflect the proposed/approved trademark registration.

8.3.6 For a medicinal product containing a prodrug, a different proprietary name to that containing the parent active substance is required.

8.3.7 In the case of a switch from "prescription" to "non-prescription" status for limited indications only, a new proprietary name should be chosen for the descheduled product.

8.3.8 Any phrase that implies superiority, including use of animal species associated with speed or strength, or implies superiority over other products is not allowed.

8.3.9 The meaning of abbreviations, symbols, numerals and names, which are in a language other than English must be explained in the covering letter

accompanying an application. With regard to phrases which occur in the proprietary names of products, and which are not English, applicants are requested to submit to the Medicines Control Council, reputable interpretations/translations/explanations of the phrases in question, in relation to the claims made for the product: i.e. the intended use thereof.

8.3.10 Proprietary names will only be evaluated as part of a new application for registration or application for change. Request for evaluation of acceptability of possible proprietary names prior to submitting a formal application will not be processed.

8.3.11 Proprietary names cannot be reserved for applications that have not yet been submitted.

8.3.12 Current policy will not be applicable to line extensions of older products unless a valid safety aspect has come to the fore, in which case the applicant will be advised accordingly.

8.3.13 A list of names that are regarded as potentially misleading is available on request. Names which may lead to self-diagnosis in conditions requiring professional diagnosis or names implying efficacy that cannot be substantiated for the active ingredient(s) are included on this list.

8.3.14 Legislation determines that the name under which a medicine is registered shall be unique. The importance of this requirement cannot be over-emphasised, particularly when developing a range of products. Each strength and/or dosage form requires a unique name. Applicants should examine all available resources to establish that names are unique. Motivations should accompany applications where relevant e.g. to justify the use of an identical or very similar name which appears in Martindale/other reference book for a product not containing the same ingredient(s) and which may be on the market elsewhere.

8.3.15 As with all registration matters, applicants always have the opportunity to submit comments in the event of a difference in opinion. Such comment will be forwarded to Council for consideration.

9. MANUFACTURING REQUIREMENTS

Only medicines manufactured, packed and quality controlled at sites compliant with the principles of GMP (Good Manufacturing Practice) will be considered for registration. With the amendment to the Medicines Act (effective 2 May 2003), all South African manufacturers must be licensed under Section 22C of the Medicines and Related Substances Control Act, 1965.

The aim of these licensing requirements and standards is to protect public health by ensuring that medicines meet defined standards of quality and are manufactured in conditions that are clean and free of contaminants.

10. SAMPLES

The Medicines and Related Substances Control Act, 1965 require that all medicine applications for registration include a sample of a unit pack proposed for use in South Africa.

11. GUIDELINES FOR GOOD MANUFACTURING PRACTICE

Certification in relation to the Good Manufacturing Practice of the overseas manufacturer is required for applications for registration of imported medicines. However, the Medicines Control Council can request that the overseas sites of manufacture be inspected for compliance with GMP before registration of the medicine is approved.
Applications for registration of medicines manufactured in South Africa must meet the requirements that are set out in the guide: **Good Manufacturing Practice for Medicines in South Africa.**

12. REQUIREMENTS FOR COMPLETION OF AN APPLICATION FOR REGISTRATION DOSSIER.

Administrative Data (MRF 1 front page)

Details as per application form must be completed.

i) "Business address" in relation to a business that is carried on in the Republic of South Africa, means the full physical address of the premises where such business is conducted.

ii) "Proprietary name" means the name that is unique to a particular medicine and by which it is generally identified and which, in the case of a registered medicine, is the name approved in terms of section 24 (8) in respect of such medicine. (Refer to section 4.8 of these guidelines.) It should be noted that medicines which are not identical in composition or strength are not regarded as the same medicine (refer to guidelines section 3.4)

iii) Dosage form: Select the most appropriate dosage form from this list, when completing the administrative data. This dosage form will also be reflected on the registration certificate. For the purpose of the package insert application may be made to give more detailed description of the dosage form e.g. chew tablet, slow release tablet etc.

GENERAL INFORMATION

Blood bag	Globule	Pessaries
Bone cement	Granules	Plaster
Beads	Gum	Pods
Capsules	Implant	Powder
Cleansing bar	Infusion (parenteral)	Shampoo
Combination of dosage forms	Inhaler	Soap
Cone	Injection	Solution
Cord	Insert	Sponge
Cream	Intra-uterine device	Spray
Cardioplegic solution	Jam	Stent
Chip (dental)	Leaves	Stick
Decoction	Liquid	Suppository
Dialysate	Lotion	Suspension
Diluent for injection	Lozenge	Swab
Dental material	Lump	Syrup
Dressing	Mouthwash	Tablet
Drops	Nasal inhaler	Tampon
Elixir	Nasal spray	Tincture
Emulsion	Oil	Toothpaste
Enema	Ointment	Towelette
Foam	Ovule	Transdermal therapeutic system
Gas	Paste	Vaginal ring
Gel	Pellet	Wafer

iv) Descriptive name of biological medicine e.g. viral vaccine, viral antiserum, bacterial vaccine, bacterial antiserum, allergen, immunoglobulin or blood product, as given in a recognised pharmacopoeia or where such name does not exist, a name determined by the MCC.

v) The name and full physical address, including the country, of the manufacturer/s, packer/s, final product testing laboratory/ies (FPRC) and final product release responsibility (FPRR).

vi) Pharmacological classification. Refer to Act 101 amended, Reg.

vii) The applicant must fill Section C of the front page of the MRF 1 when an application for registration of a medicine has already been submitted.

viii) The responsible person filling in the form should provide his/her e-mail address and/or a central company e-mail address (if available).

ix) FPRR should be the holder of the certificate of registration or the person (a pharmacist) with appropriate knowledge of all aspects of the medicine and in full time employment of the holder of the certificate.

GENERAL INFORMATION

ATTACHMENT A

Pre-Screening check list

Product name:_____ Company_____

Compliance to admin criteria	YES	NO
Box size (A4 box)		
Number of boxes received		
Is the box clearly labeled, on the side, to specify the content with a colour sticker, indicating route? (red = screening green = post screening)		
Is the dossier correctly bound? (No arc lever files, no ring binders)		
Is each Part of the dossier properly indicated by tabbing according to the cover letter ?		
Is each Part of the dossier properly indexed ?		
Is each page of the dossier numbered ?		
Is sample present in an envelope?		
Is a BMF (batch manufacturing file) document included ?		
Is the Cheque for the screening fee submitted in a separate envelope?		
Is the approval letter regarding the "fast track" status included?		
Is the completed screening form included?		

If any NO's return as incomplete immediately

Signature: _____ **Date:** _____ **Official Stamp**_____

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FOR REGISTRATION OF A MEDICINE

ADMINISTRATIVE DATA

APPLICATION NUMBER

A. PARTICULARS OF PROSPECTIVE HOLDER OF THE CERTIFICATE OF REGISTRATION

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

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

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

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

(Attach letter of authorisation signed by the Managing Director)

B. PARTICULARS OF MEDICINE

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

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

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

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

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

Descriptive name of Biological medicine:----------

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

.....

Signature of Managing Director/Authorised person

....

Name in block letters Date of application

....

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