GENERAL INFORMATION

		(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	C, 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)

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 immed ately

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

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

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)**

MRF 1

C. UPDATE HISTORY (For Post-registration only)

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

Guideline references:

MRF 1

TECHNICAL DATA

PART 1 A (i) SCIENTIFIC PACKAGE INSERT (HUMAN MEDICINES)

The under-mentioned information with regard to this medicine shall appear on the scientific package insert. The information shall be presented in the format stipulated: Provided that the Council may authorise any deviation from such information or such format (refer to Regulation 9).

1. Scheduling status
2. Proprietary name and dosage form
3. Composition
4. Pharmacological classification
5. Pharmacological action
(Pharmacokinetics, pharmacodynamics and summary of clinical studies, where applicable)
6. Indications
7. Contra-indications
8. Warnings
9. Interactions
10. Pregnancy and lactation
11. Dosage and directions for use
12. Side effects and special precautions
13. Known symptoms of overdosage anc particulars of its treatment
14. Identification
15. Presentation
16. Storage instructions
17. Registration number
18. Name and business address of the holder of the certificate of registration
19. Date of publication of the package insert

MRF 1

PART 1 A (ii) SCIENTIFIC PACKAGE INSERT (VETERINARY MEDICINES)

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

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

MRF 1

PART 1 B PATIENT INFORMATION LEAFLET

The under-mentioned information with regard to this medicine shall appear on the patient information leaflet. The information shall be presented in the format stipulated, provided that the Council may authorise any deviation from such information or such format (refer to Regulation 10)

1. Scheduling Status
2. Proprietary name and dosage form
3. Composition of the medicine, that is, what this medicine contains
4. Approved indication and use, that is, what this medicine is used for
5. Instruction before taking the medicine (refer to the Guidelines)
6. Instructions on how to take the medicine (refer to the Guidelines)
7. Side effects (refer to the Guidelines)
8. Storage and disposal information (refer to the Guidelines)
9. Presentation
10. Identification
11. Registration number
12. Name and business address of the holder of the certificate of registration
13. Date of publication of the Patient Information Leaflet

MRF 1

PART 1 C SPECIMEN OF THE LABEL

A specimen of the immediate container label and, if applicable, the outer label shall be included here. This shall conform to Regulation 8 in the case of human medicine, or Regulation 48 in the case of veterinary medicine.

MRF 1

PART 1 D FOREIGN REGISTRATION

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

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

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

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

MRF 1

PART 2A (i) ACTIVE PHARMACEUTICAL INGREDIENT (DEVELOPMENT CHEMISTRY AND CHARACTERISATION)

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

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

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

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

d) Certificate of analysis of two batches

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

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

MRF 1

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

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

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

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

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

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

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

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

MRF 1

PART 2 B (i) FORMULATION

FORMULATION OF THE FINAL DOSAGE FORM FOR PHARMACEUTICAL MEDICINES
FORMULATION OF THE FINAL FILLING LOT/BATCH FOR BIOLOGICAL MEDICINES

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

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

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

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

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

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

e) Overages and justification for their inclusion.

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

MRF 1

PART 2 B (ii) FORMULATION OF THE RECONSTITUTING LIQUID FOR THE FINAL FILLING LOT FOR BIOLOGICAL MEDICINES

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

b) The purpose of each ingredient in the formulation shall be specified, including that of raw materials used in the composition, but which are not present in the diluent.

Approved name or chemical name of constituent	Quantity	Purpose

MRF 1

PART 2C SPECIFICATIONS AND CONTROL PROCEDURES FOR RAW MATERIALS

a) Pharmacopoeial ingredients.

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

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

(b) Non-pharmacopoeial ingredients.

Raw Material		Specifications	Limits	In-house control procedures
Active				
Inactive				

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

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

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

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

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

MRF 1

PART 2 D CONTAINER AND PACKAGING MATERIAL

a) DESCRIPTION OF CONTAINERS

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

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

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

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

b) SPECIFICATIONS AND LIMITS FOR PACKAGING MATERIALS

Specification	Limit	Name of manufacturer/packer of the final product

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

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

d) PACK SIZES

MRF 1

PART 2 E MANUFACTURING PROCEDURES

MANUFACTURING PROCEDURES OF FINAL PRODUCT (PHARMACEUTICAL MEDICINES)

FINAL FILLING LOT AND DILUENT (BIOLOGICAL MEDICINES)

a) INSPECTION FLOW DIAGRAM:

b) MANUFACTURING PROCEDURES:

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

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

c) PACKAGING PROCEDURES:

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

d) MANUFACTURING PROCESS VALIDATION PROTOCOL:

The process validation protocol is as follows:

MRF 1

PART 2 F FINISHED PRODUCT (PHARMACEUTICAL) FINAL FILLING LOT & DILUENT (BIOLOGICAL)

a) SPECIFICATIONS AND LIMITS

List specifications and limits for the following, if applicable:

(i) In-process control

(ii) Final product control

(iii) Stability tests

(ii) Manipulated final product

Specifications	Limits

(See guideline on **Stability** for specifications to be considered for each dosage form).

b) TABLE OF TESTS TO BE PERFORMED

	TITLE OF SPECIFICATION
FPRC	
FPRC responsible for tests after importation	Identification Assay
FPRR	Appearance of dosage form Container Package insert Label Batch No. Expiry date. Certificate of Analysis Batch release documents

c) CONTROL PROCEDURES

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

d) CERTIFICATE OF ANALYSIS OF THE FINAL PRODUCT

e) VALIDATION

Validation data for all quantitative assay methods must be included.

MRF 1

PART 2 G STABILITY DATA FOR THE FINISHED PRODUCT

a) STABILITY PROGRAMME

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

(i) Conditions (temperature, humidity)

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

(iii) Specifications to be determined

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

(v) Stability test control procedures

b) PRESENTATION OF STABILITY DATA

Product Name:	Packaging (material and pack sizes):
Batch No.:	Storage conditions:
Batch Size:	Name of manufacturer:
Date of Manufacture:	Source of active pharmaceutical ingredient:
Date of commencement of stability study:	

		Time intervals (Months)					
Specification	Limit	0	3	6	9	12	24

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

MRF 1

PART 2 H PHARMACEUTICAL DEVELOPMENT

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

b) Pharmaceutical Expert Report

i) Active Pharmaceutical Ingredient(s):

ii) Formulation:

iii) Production/Manufacture:

iv) Stability:

v) Conclusion of Expert Report:

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

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

MRF 1

PART 2 I EXPERTISE AND PREMISES USED FOR MANUFACTURING OF BIOLOGICAL MEDICINES

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

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

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

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

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

MRF 1

PART 3 BIOEQUIVALENCE STUDIES FOR PROOF OF EFFICACY

a) STATE THE PURPOSE OF THE STUDY

(i) As comparison of formulation to be marketed versus formulation used in clinical trials, or

(ii) As proof of efficacy for a generic application, or

(iii) As proof of efficacy of new formulation (formulation change)

(b) REFERENCE PRODUCT USED

(i) Clinical trial formulation

(ii) Innovator product

(iii) Current formulation (for change of formulation)

The following must be indicated:

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

(c) METHOD USED

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

(d) VALIDATION

Validation data for all quantitative assay methods shall be included.

(e) DATA

(f) DISCUSSION AND CONCLUSION

Attach documents (where applicable)

MRF 1

PART 4 PRE-CLINICAL STUDIES

a) Pre-clinical Expert Report

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

(i) acute toxicity,
(ii) subacute toxicity studies;
(iii) chronic toxicity studies;
(iv) reproduction toxicity and teratogenicity studies;
(v) carcinogenicity studies;
(vi) mutagenicity studies; or
(vii) other tests to substantiate the safety of the medicine;
(viii) pharmacokinetics studies;

c) The methods and experimental results of and the conclusions drawn from tests performed pre-clinically with reference to the efficacy of the medicine, with special emphasis on the relationship between the tests performed and the purpose for which the medicine is or will be used, or for which it will be propagated, and further with regard to the dosage and method of administration of the medicine, are as follows:

In cases where well-known active pharmaceutical ingredients are concerned, the Council may grant exemption from the submission of some or all of the above information.

PART 5 CLINICAL STUDIES

a) Clinical Expert Report

b) The clinical trials performed on human volunteers and patients (target species for veterinary medicines) with regard to the safety of the use of the medicine, with special reference to the particular dosage, routes of administration used and the side-effects observed, are as follows:

c) Particulars of clinical trials conducted to establish the efficacy of the use of the medicine are as follows:

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

e) Periodic Safety Update Report for medicines for human use

f) Veterinary medicines: Residue studies and withdrawal period

In cases where well-known active pharmaceutical ingredients are concerned, the Council may grant exemption from the submission of some or all of the above information.

Guide to complete clinical trials application.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDE TO COMPLETE CLINICAL TRIALS APPLICATION FORMS.

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for the conduct of clinical trials. 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

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

Version: MCC2003/1

TO ALL APPLICANTS

GUIDE TO COMPLETING CLINICAL TRIALS APPLICATION FORMS.

The following attached documents should be used to assist you in completing clinical trials application forms.

1.	A	Guide to completing clinical trials application (CTA).
2.	B	Declaration by Principal Investigator.
3.	C	Provisional Declaration by Co-and or Sub-Investigators and other staff involved in a clinical trial.
4.	D	Declaration by Regional Monitor
5.	E	Joint Declaration by Sponsor (or representative) and Principal Investigator (or National Principal Investigator) concerning sufficient funds to complete study.
6.	F	Standardized wording to be added to PILs
7.	G	MCC Format for CVs of Individuals Participating in the Conduct of Clinical Trials in South Africa.

A. SOUTH AFRICA: CLINICAL TRIALS APPLICATION

Guide to completing Clinical Trials Application (CTA)
[Version MCC/2003/1]

The purpose of the CTA is to assist members of the Clinical Trials Committee to determine the answers to the following questions:

- Does this proposed trial contribute to new knowledge in a scientific way?
- Are all aspects of this proposed trial ethical?
- Can patient safety be assured?
- Should this trial be done in SA?

The application is divided into three sections.

Section 1: A checklist of required documentation. (If the documentation is incomplete, the application will not be further processed.)
Section 2: Administrative and Supplementary Details.
Section 3: Applicant's Report / Presentation

Section 1: Use the checklist to ensure that all the necessary documentation has been collated.

The ethics approval can be submitted later – but a copy of the letter of application for an ethics committee to assess the proposed clinical trial must be included.

If the insurance certificate is not specific to the particular protocol, ensure that there is an accompanying letter stating that the insurance does cover this particular protocol.

TO ALL APPLICANTS

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If the insurance certificate is not specific to the particular protocol, ensure that there is an accompanying letter stating that the insurance does cover this particular protocol.

List the files submitted electronically and their format(s). Ensure that all required documentation is available electronically. This does not include electronic copies of insurance certificate, CVs, declarations, certificates of analysis, ethics approval, recruitment advertisements, etc. Ensure that it is possible for the reviewer to 'copy and paste' from the electronic documents should this be necessary. [Note: If complete information is provided in Section 3 without any inconsistencies or discrepancies between it and the information in the protocol, the investigator's brochure or other documentation, this should not be necessary.]

Section 2: Should be self-explanatory.

Section 3: Applicants are advised to complete this as a report / presentation as if they were reviewing the proposed trial. Apart from the required information about the trial itself, the question 'why' should be asked constantly and the answers provided in the form of a rationale or justification. The reviewers will read all the documentation provided, will double-check the accuracy of the information provided in this section, and will raise unsatisfactorily addressed issues or unanswered questions. Their recommendation to the CTC / MCC will be based on their ability to answer the four questions above after reading all the documentation and the applicant's report / presentation.

Item 1. Check that the title is accurate and specific (e.g. if a drug being tested is actually an adjuctive treatment, this should be stated in the title). Make sure that no component is left out of the title – e.g. 'phase'.

Item 3. Make sure that the rationale for doing the study is clear. It could be the next logical component in a series of studies (e.g. phase III following phase I or II trial). It could be to test different delivery mechanisms. It could be a 'marketing study'. Try to make sure the answer to the question 'Why should this study be done at all?' is clear and logical.

Item 4. Should be self-explanatory – the important thing is to be brief without losing essential data.

Item 5. State objectives and give rationale for each of them. Ensure that these are scientifically credible. Double check that each objective will in fact be 'analysed' in the statistics section – or else questions must be asked of sponsor / other about why the objective is included without analysis.

Item 6. Summarise study design in one (to two) sentences then justify each component. Show that this study design is the correct scientific one to answer the stated objectives.

Item 7. Provide details of numbers of participants required and why. Justify, using data from section 2, the ability to recruit the required numbers within a certain time period.

Item 8. List the inclusion and exclusion criteria – and justify each of them in a sentence or a half sentence. Pay particular attention to how these criteria may or may not confound or invalidate the objectives of the trial. Ensure that no discrimination against certain groups takes place – or that particular criteria are well justified. (E.g. HIV patients who have developed resistance to all available treatments.)

Item 9. A brief summary of the actual administration of medications. If participants take certain medications at home, or use a patient-diary, ensure that these are described and are not confusing. Ensure that dosage regimens are consistent with recommendations in the investigator's brochure – e.g. dose modifications in cytotoxic therapy.

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Item 9. A brief summary of the actual administration of medications. If participants take certain medications at home, or use a patient-diary, ensure that these are described and are not confusing. Ensure that dosage regimens are consistent with recommendations in the investigator's brochure – e.g. dose modifications in cytotoxic therapy.

Item 10. Clear descriptions of outcome measures. If surrogate markers are being used when the drug is intended to decrease mortality, etc., they should be justified. Ensure that all intended measurements necessary. Ensure that no intended measurements are likely to be of more risk to participants, than they are likely to provide useful information.

Item 11. Indicate how known or likely adverse events will be dealt with. Clearly describe components requested in Section 3.

Item 12. Ensure that all components are adequately addressed. Answer the question, 'Is this the best statistical approach / method for the outcome measures / objectives?' Clearly indicate reasons for doing an interim analysis or for not doing one.

Item 13. Comment on the adequacy of each of the ethics components requested in terms of the proposed trial. Pay special attention to the Patient Information Leaflet and the Informed Consent process / form. Have they been properly modified for SA? Ensure that if any blood specimens are to be archived or kept for genetics research, that this is appropriately addressed in a separate consent form, and that it makes the various ethical aspects of this clear.

Item 14. Any other comments on the proposed trial – including the quality of the protocol, (e.g. well or poorly written / structured; or does it look like it was simply downloaded from a website?); the extent to which the four questions (which the reviewer must answer) can be satisfactorily answered; any other relevant information which the reviewer could take into account in making a recommendation to the CTC / MCC.

B. DECLARATION BY PRINCIPAL INVESTIGATORS

Name:

Title of Trial:

Protocol:

Site:

1. I have read and understood Item 1.5.5 on page 5 and Section 3 (pages 14 – 20) 'Responsibility of The Principal Investigator (PI) and Participating Investigators' of the *Clinical Trials Guidelines of the Department of Health:2000.*

2. I have notified the South African regulatory authority of any aspects of the above guidelines with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)

3. I have thoroughly read, understood, and critically analysed (in terms of the South African context) the protocol and all applicable accompanying documentation, including the investigator's brochure, patient information leaflet(s) and informed consent form(s).

4. I will conduct the trial as specified in the protocol.

5. To the best of my knowledge, I have the potential at the site(s) I am responsible for, to recruit the required number of suitable participants within the stipulated time period.

6. I will not commence with the trial before written authorisations from the relevant ethics committee(s) as well as the South African Medicines Control Council (MCC) have been obtained.

7. I will obtain informed consent from all participants or if they are not legally competent, from their legal representatives.

8. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.

9. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.

[*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*

*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)

10. I have* / have not (delete as applicable) previously been the principal investigator at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)

11. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)

12. I will submit all required reports within the stipulated time-frames.

Signature: Date:

Witness: Date:

C. PROVISIONAL DECLARATION BY CO- AND SUB-INVESTIGATORS AND OTHER STAFF INVOLVED IN A CLINICAL TRIAL

Name:

Title of Trial:

Protocol:

Principal Investigator's Name:

Site:

Designation:

13. I will carry out my role in the trial as specified in the protocol.

14. I will not commence with my role in the trial before written authorisations from the relevant ethics committee(s) as well as the South African Medicines Control Council (MCC) have been obtained.

15. If applicable to my role in the trial, I will ensure that informed consent has been obtained from all participants or if they are not legally competent, from their legal representatives.

16. I will ensure that every participant (or other involved persons, such as relatives), shall at all times be treated in a dignified manner and with respect.

17. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.

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18. I have not previously been involved in a trial which has been closed due to failure to comply with Good Clinical Practice.

19. I will submit all required reports within the stipulated time-frames.

Signature: Date:

Witness: Date:

D. DECLARATION BY REGIONAL MONITOR

Name:

Title of Trial:

Protocol:

Site:

20. I have read and understood Item 1.5.7 (p5) and Section 5.1 (p30-33) 'The Monitor' of the *Clinical Trials Guidelines of the Department of Health:2000.*

21. I have notified the South African regulatory authority of any aspects of the above guidelines with which I do not / am unable to, comply. (If applicable, this may be attached to this declaration.)

22. I will carry out my responsibilities as specified in the trial protocol and according to the *Clinical Trials Guidelines of the Department of Health:2000.*

23. Using the broad definition of conflict of interest below, I declare that I have no financial or personal relationship(s) which may inappropriately influence me in carrying out this clinical trial.

[*Conflict of interest exists when an investigator (or the investigator's institution), has financial or personal relationships with other persons or organizations that inappropriately influence (bias) his or her actions.*]*
*Modified from: Davidoff F, et al. Sponsorship, Authorship, and Accountability. (Editorial) JAMA Volume 286 number 10 (September 12, 2001)

24. I have* / have not (delete as applicable) previously been the monitor at a site which has been closed due to failure to comply with Good Clinical Practice. (*Attach details.)

25. I have* / have not (delete as applicable) previously been involved in a trial which has been closed as a result of unethical practices. (*Attach details)

26. I will submit all required reports within the stipulated time-frames.

Signature: Date:

Witness: Date

E. JOINT DECLARATION BY SPONSOR (OR REPRESENTATIVE) AND PRINCIPAL INVESTIGATOR (OR NATIONAL PRINCIPAL INVESTIGATOR) CONCERNING SUFFICIENT FUNDS TO COMPLETE STUDY*

Title:

Protocol:

I, <full name>, representing <sponsor or representative)

And

I, <full name>, Principal Investigator/National Principal Investigator

Hereby declare that sufficient funds have been made available to complete the above-identified study.

Signed Date

SPONSOR (or alternative)
Name
Address
Contact details

Signed Date

PRINCIPAL INVESTIGATOR (or National PI)
Name
Address
Contact details

*Section 4.13, page 26: Clinical Trials Guidelines 2000, Department of Health, South Africa.

F. STANDARDISED WORDING TO BE ADDED TO PATIENT INFORMATION LEAFLET. (PILS)

(Approved by Clinical Trials Committee on 15/07/2002)

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar
SA Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 323-4474

e-mail: labusa@health.gov.za

G. MCC FORMAT FOR CVS OF INDIVIDUALS PARTICIPATING IN THE CONDUCT OF CLINICAL TRIALS IN SOUTH AFRICA.

Trial:

Protocol:

Designation: (e.g. National Principal Investigator, Investigator (Principal, Co- or sub-), Study Co-ordinator, Regional Monitor, Local Monitor, Contract Research Affiliate)

1. Personal Details
   Name:
   Work Address:
   Telephone Number:
   Fax Number:
   Cell-phone Number:
   e-mail address:

2. Academic and Professional Qualifications
3. Health Professions Council of South Africa (HPCSA) registration number if applicable (or other health professions body registration particulars if applicable – e.g. Nursing Council)
4. Current personal medical malpractice insurance details [medical and dental practitioners]
5. Relevant related work experience (brief) and current position
6. Participation in clinical trials research in the last three years (title, protocol number, designation) [If multiple trials, only list those with relevance to this application, or in the last year.]
7. Peer-reviewed publications in the past 3 years
8. Date of last GCP training (as a participant or presenter)
9. Any additional relevant information supporting abilities to participate in conducting this trial. [briefly]

Signature: Date:

MRF 2

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

SCREENING FORM FOR APPLICATION FOR REGISTRATION OF A MEDICINE

Where appropriate, abbreviations **Y, N, or N/A** must be used in filling out this form. The comment section may be used for any additional information or explanation.

Note: Applicants must ensure that the application is completed fully and accurately, presented in the prescribed format and that all required documentation is included. Each item must be referenced to the relevant page number of the application, where applicable

Applications that are incomplete or are non-compliant in any way will be returned as non-compliant.

Prospective Holder of the Certificate of Registration:			
Product Name:			
Date of Submission:			
	Y, N or N/A	**Page No.**	**MRA use**
FRONT PAGE GENERAL INFORMATION:			
1. Are full particulars of the prospective holder of the certificate of registration included on the application Front Page? (i.e., name, business and postal addresses, telephone, fax, e-mail, etc)			
2 Is the application signed by the Managing Director or authorised person?			
3. Is the letter of authorisation for communication on behalf of the prospective holder of the certificate of registration included in the application?			

MRF 2

• PRODUCT INFORMATION/DOCUMENTATION

3. Please indicate the type of application using a check mark (✓) or a cross (×)

_____ Human Medicine
_____ Veterinary Medicine
_____ Biological Medicine

_____ AMRP
_____ New Chemical Entity
_____ New Indication
_____ New Dosage Form
_____ Multi-source (Generic) Medicine:
Immediate release
Controlled release
_____ Fast Track Application

• A. TECHNICAL INFORMATION: CLINICAL

4. New Chemical Entities and other applications with clinical data:

4.1 Is the product registered in any other country?			
4.2 Has proof of registration of the product in other countries been submitted in PART 1D?			
4.3 Has a copy (or copies) of the latest version of the approved package insert been included from regulatory authorities with which the product is registered in PART 1D?			
4.4 Was the product rejected for registration by any regulatory authority?			
4.5 If yes above, was rejection due to (i) safety (ii) efficacy (ii) safety and efficacy (iii) other reason (specify):.....			
4.6 Is the proposed package insert included in PART 1A?			
4.7 Has an electronic copy of the package insert also been submitted?			
4.8 Is information in the package insert cross-referenced to supporting evidence in PART 5 and/or the latest edition of the standard reference books?			
4.9 Is the package insert typed in double spacing?			
4.10 Does the package insert comply with Regulation 9 or 40?			
4.11 Is the proposed patient information leaflet (PIL) included in PART 1B?			
4.12 Has an electronic copy of the PIL also been submitted?			
4.13 Is information in the PIL cross-referenced to supporting evidence in PART 5 and/or the latest edition of the standard reference books?			
4.14 Is the PIL typed in double spacing?			
4.15 Does the PIL comply with Regulation 10?			
4.16 Have pre-clinical data been submitted in PART 4?			
4.17 Have clinical data been submitted in PART 5?			
4.18 Has residue depletion data and withdrawal time for veterinary medicines in food-producing animals been submitted in PART 5?			
4.19 Have the Clinical studies been indexed and numbered?			
4.20 Have all irrelevant raw data (individual patient data) been removed?			
4.21 Has either a Clinical Expert Report (CER) or an SBRA* report been			

MRF 2

submitted?			
4.22 Are the tables and graphs in the CER cross-referenced to the documentation submitted?			
4.23 Have all the references referred to in the package insert been included?			
*Summary basis for registration application			
5 Generic Applications			
5.1 Have all the references referred to in the package insert been included?			
5.2 Is the proposed package insert included in Part 1A?			
5.3 Has the electronic copy of the package insert also been submitted?			
5.4 Is information in the package insert cross-referenced to the latest editions of the standard reference books and the latest version of the innovator package insert?			
5.5 Is the package insert typed in double spacing and in black print?			
5.6 Does the package insert comply with Regulation 9 or 40?			
• B. TECHNICAL INFORMATION: INSPECTORATE			
6. Does the label information comply with Regulation 8 or 48?			
7. Is a copy of the latest inspection report (not older than 2 years) from the Medicine Regulatory Authority of country of origin for the manufacturer of imported products available for inspection?			
8. Is a copy of the latest GMP certificate or copy of the appropriate manufacturing license, attached (not older than two years)?			
9. Date of submission and number of prospective holder of certificate of registration Site Master File:			
10. Provide license number and date of issue for holder of the certificate of registration:			
11. Is proof of registration of the Company as a pharmacy included (include copy of certificate)?			
12. Is proof of registration of the Responsible person as a pharmacist included (include copy of certificate)?			
10. Is the batch manufacturing record of the sample included in Part 2E?			
11. Is the CoA for the sample included?			
12. Is a permit to manufacture specified Schedule 5, Schedule 6 or Schedule 7 products included?			
13. Is Master documentation for PART 2E available for inspection?			

14. MANUFACTURING, TESTING AND PACKAGING FACILITIES

Please provide details by completing the following:

	License number and date of issue	Date of submission of SMF & number	Date of last inspection	Local or Foreign?	GMP Status	Is contract with HCR* in place?
Manufacturer 1 2.						
Packer 1 2						

MRF 2

Testing Lab 1 2						
*Holder of certificate of registration						
• C. TECHNICAL INFORMATION: PHARMACEUTICAL & ANALYTICAL						
16. General Administrative information						
16.1 If Fast Tracking has been applied for, is a copy of the approval letter attached to the screening form?						
16.2. Has the application been submitted in the format prescribed by MRF 1?						
16.3 If the application is submitted in the EU format, has a separate document cross referencing the MRF 1 format to the EU format been submitted?						
17. Technical requirements						
17.1 Is a motivation for exemption included for PARTS not being addressed?						
17.2 Is the appearance of the sample comparable to the description given under identification in the package insert?						
17.3 Is a specimen of the label included in PART 1C?						
17.4 Has the solubility of the API(s) in water and in the solvent of choice been quantified in PART 2A?						
17.5 Has a recent (not older than 2 years) Certificate(s) of Analysis (CoA) for the API(s) been included in PART 2A?						
17.6 Has the method(s) of synthesis of the API(s) been submitted?						
17.7 Are stability data submitted in PART 2A for the API(s) in compliance with the guideline? Environmental test conditions (Temperature and humidity) ❖ Real time conditions ❖ Accelerated conditions Stability data submitted ❖ Real time data (months /years) ❖ Accelerated data (months) Stability Batches Number and types/sizes (production, pilot or experimental) of batches						
17.8 Where more than one manufacturer of the API is used, have comparative chemical and physical data in tabular format been submitted to demonstrate equivalence?						
17.9 Has the comparative chemical and physical data been generated from the same testing laboratory under the same conditions?						
17.10 Do all ingredients in the unit formula in PART 2B correspond with those in the batch formula in PART 2E?						
17.11 Have reasons been stated for overages in the quantity of the active pharmaceutical ingredient(s) (APIs) and /or other ingredients in PART 2B?						
17.12 Has the potency calculation been included for the API(s) in PART 2B?						
17.13 Has the composition and, where possible, quantities, of all auxiliary components (to facilitate manufacturing and processing of the final product), such as pH adjusters, etc. been stated separately?						

MRF 2

17.14 Have specifications and control procedures for all ingredients listed in PART 2B been submitted in PART 2C?			
17.15 Has the frequency of testing of water been stated in PART 2C?			
17.16 Have container specifications and control procedures been submitted in PART 2D?			
17.17 Are test results taken from the supplier's CoA clearly indicated?			
17.18 Is the batch manufacturing formulas and batch sizes included in PART 2E?			
17.19 Is a copy of the batch documentation for a real batch included in PART 2E?			
17.20 Is a comprehensive flow diagram or a description of the manufacturing process, detailing the various production stages, equipment types and sizes, sieve sizes, machine settings, duration of treatment, temperature, humidity, light, etc. included?			
17.21 Is documentation detailing the Packaging of product (procedures, packaging stages, equipment types, and conditions of temperature, humidity, light, etc.) included in PART 2E?			
17.22 Has a flow diagram for the Packaging procedures been included?			
17.23 Has a manufacturing validation protocol been included in PART 2E?			
17.24 Have specifications and control procedures for final product been submitted in PART 2F?			
17.25 Has assay method validation data been submitted in PART 2F?			
17.26 Are all the analytical and non-analytical release criteria and tests indicated in PART 2F?			
17.27 Are stability data submitted in PART 2G in compliance with the guideline? Environmental test conditions (Temperature and humidity) ❖ Real time conditions ❖ Accelerated conditions Stability data submitted ❖ Real time data (months /years) ❖ Accelerated data (months) Stability Batches ❖ Number and types/sizes (production, pilot or experimental) of batches			
17.28 Have details of the container, batch number, batch size, date of manufacture of the batch and storage conditions been reflected on the data sheet?			
17.29 Have all the stability specification parameters listed in PART 2F been included in the stability data presented in PART 2G?			
17.30 (a). Have stability data been derived with API sourced from the manufacturer identified in PART 2A?	a.		
(b). If not, have additional stability data derived from the source being applied for been submitted?	b.		
17.31 (a). Have stability data been derived from the product packed in packaging material detailed in PART 2D?	a.		
(b). If not, have additional stability data derived from the product packed in containers being applied for been submitted?	b.		

MRF 2

17.32. Has validation data for the assay method (pharmacopoeial and or different to that in PART 2F) used in the stability testing been submitted			
17.33 Have complete pharmaceutical development data been submitted in PART 2H?			
17.34 Has an expert pharmaceutical report been submitted in PART 2H?			
17.35 Have details of expertise and the premises used in Part 2I been included?			
18. Generic Medicines: Proof of efficacy (PART 3)			
18.1 Is proof of safety and efficacy based on a bioequivalence study (*in vivo*) or are claims made on the basis of *in vitro* data only?			
18.2 Have all the components of the biostaudy been submitted including: a. Date and place of study: b. The Protocol c. Evidence of ethical approval d. Assay data validation plus representative chromatograms e. Investigator credentials f. Monitor's report g. Auditor's report?	a. b. c. d. e. f. g.	a. b. c. d. e. f. g.	a. b. c. d. e. f. g.
18.3 Was the biostudy performed using the innovator product currently registered and procured in South Africa?			
18.4 If not, (a) has comparative data to demonstrate equivalence of the reference product to the S.A. registered innovator product been submitted? (b) has the origin of the reference product and name of manufacturer together with the address of the manufacturing site been stated?.	a. b.		
18.5 If a biowaiver is requested, have motivation and justification with supporting data been included, i.e. comparative *in vitro* dissolution data comparing the test and reference products in three dissolution media, pH's 1.2, 4.5 and 6.8?			
18.6 If a biowaiver is requested for different strengths of the product, are the different strengths proportionally formulated?			
18.7 Have full details of each formulation strength been included with this application?			
18.8 Were the different strengths manufactured by the same manufacturer, at the same site, from API(s) sourced from the same manufacturer?			
18.9 Does your product meet the acceptance criteria for Cmax and AUC as prescribed in the Guidelines?			
18.10 Have appropriate quantitative methods been used to confirm *in vitro* similarity/differences and are the appropriate data included with this application? (i.e. similarity (f_2) and difference (f_1) factors)?			
18.11 Have full details of each formulation strength been included with this application?			

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

GUIDELINES FOR THE DESTRUCTION OF SCHEDULE 5 MEDICINES AND SUBSTANCES

This document has been prepared to serve as a recommendation to applicants wishing to destroy any Schedule 5 medicines and/ or substances. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safe destruction of any Schedule 5 medicine and / or substances.

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

Version 2003/1

INDEX

1 SCOPE OF THE GUIDELINES

These guidelines should be read in conjunction with the Medicines and Related Substances Control Act (Act 101 of 1965), and its supporting Regulations.

As these guidelines are constantly evolving due to harmonisation initiatives as well as due to new scientific developments, applicants are advised to always consult the latest information available. The Medicines Control Council endeavours to keep abreast of such developments and to keep its application requirements and evaluation procedures and policies in line with "best international practice".

The destruction of Schedule 5 medicines and substances may only take place in accordance with the Medicines and Related Substances Control Act (Act 101 of 1965)

2 DESTRUCTION AUTHORISED BY AN INSPECTOR

The destruction of Schedule 5 medicines and substances that have been entered into a register, may take place under the supervision of an inspector designated in terms of Section 40(1) of the Act, an officer of the SAPS or other person authorised in terms of the legislation to supervise this action.

2.1 All destruction must take place in accordance with local municipal regulations regarding the disposal of chemical or medicinal waste. The applicant (person requesting destruction) may be requested to prove that the method of destruction is in accordance with such regulations.

2.2 All medicines or substances must be destroyed in such a manner that does not allow recovery.

2.3 The inspector must, on behalf of the Medicines Regulatory Authority (MRA), provide a certificate of destruction and in the case of an officer of the SAPS, a case number must be provided which must be kept with the register for a period of 5 years.

2.4 All quantities destroyed must be indicated in the relevant register on the date of destruction and signed by the applicant, indicating the reference to the destruction certificate or case number.

3 PROCEDURE FOR WRITTEN AUTHORISATION OF DESTRUCTION FROM THE MEDICINES REGULATORY AUTHORITY:

The MRA may authorise the destruction of Schedule 5 medicines or substances in writing, without the presence of an inspector, if a pharmaceutical company or other institution in question, has sufficient personnel, procedures and capacity to follow the procedure described below.

4. APPLICATION FOR AUTHORISED DESTRUCTION

4.1 The Applicant must request permission for destruction of specific quantities of the medicines or substances in question in writing.

4.2 The request will indicate -

- the name of each medicine or substance to be destroyed,
- the exact quantities and batch numbers (if applicable) of the medicines or substances to be destroyed,
- the reason for the destruction and
- the names of the two pharmacists who will witness the destruction as required by the procedure. The MRA may consider a deviation from the requirement of two pharmacists in exceptional cases only. This will depend on the motivation supplied and on alternative arrangements to obtain sufficient control.

4.3 The MRA will authorise the destruction of the medicines or substances in question in writing, specifying the quantities indicated in the request, provided that the following procedure be followed:

5 GENERAL

5.1 Destruction may only take place after the written authorisation from the MRA has been received.

5.2 All destruction must take place in accordance with the local municipal regulations regarding the disposal of chemical or medicinal waste. The applicant may be requested to prove that the method of destruction is in accordance with such regulations.

5.3 All medicines and substances must be destroyed in such a manner that prevents their recovery.

5.4 The destruction must be properly documented:

- All quantities destroyed must be indicated in the relevant registers and signed by the witnesses required in the procedure. (See registers below)
- Destruction certificates (where applicable) and the letter of authorisation must be referenced in, or attached to the relevant Schedule 5 register and retained for the same period of time as the register itself. (5 years)

6. METHOD OF DESTRUCTION

6.1 Potent or large quantities of medicines and substances

6.1.1 Depending on the municipal regulations regarding the disposal of chemical or

medicinal waste, the applicant may choose an appropriate method of destruction such as incineration or destruction by a reliable contractor who specialises in waste disposal.

6.1.2 If a contractor is not used (eg. incineration), **two pharmacists** employed by the applicant must witness the **removal and destruction** of the correct quantities of the medicines or substances authorised for destruction, regardless of the where destruction will take place.

6.1.3 In the case of a contractor, where destruction does not take place at the premises of the applicant, and a certificate of destruction will be provided, **two** pharmacists employed by the applicant must witness the **removal from the stock** of the correct quantities of the medicines or substances authorised for destruction and at least **one** of the **pharmacist** should accompany the goods to the place of **destruction**, to witness that these have actually been destroyed or disposed of in such a manner that precludes their recovery.

6.1.4 In the case of a contractor, a valid certificate of destruction must be obtained.

6.2 Small quantities

6.2.1 Small amounts of medicines or substances may be destroyed on the premises where these are kept. Appropriate methods must be used which are unlikely to cause any adverse health or environmental consequences, must be in accordance with local municipal regulatons and will not allow the drugs to be readily recovered. Two pharmacists employed by the company must witness the removal from stock and the destruction of the correct quantities of each medicine or substance.

7 SCHEDULE 5 REGISTER

7.1 The quantities of any medicines or substances destroyed must be entered into the register on the date of destruction.

7.2 The inscription in the register must be signed by the two pharmacists employed by the company, who witnessed their removal from stock destruction. The Managing Director must co-sign, unless the Managing Director was one of the pharmacists involved with the removal and destruction.

7.3 The letter of authorisation and the destruction certificate (if applicable) must be referenced in or attached to the schedule 5 register and retained for a period of 5 years.

8 LEGAL REPORTING REQUIREMENTS

8.1 If the amount of substance destroyed according to any method above, is more than :

- 1 milligram for potent narcotic drugs (fentanyl, sufentanil, alfentanil, etc.).
- more than 1 gram for all other narcotic drugs or
- more than 1 kilogram for any psychotropic substance,

the base amount of each substance destroyed must be indicated on the annual returns of specified Schedule 5 substances in terms of Regulation 29 of the Medicines and Related Substances Control Act (Act 101 of 1965), relating to the year in which the destruction took place.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

GUIDELINES FOR THE DESTRUCTION OF SCHEDULE 6 MEDICINES AND SUBSTANCES

This document has been prepared to serve as a recommendation to applicants wishing to destroy any Schedule 6 medicines and/ or substances. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safe destruction of any Schedule 6 medicine and / or substances.

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

Version 2003/1

INDEX

1 SCOPE OF THE GUIDELINES

These guidelines should be read in conjunction with the Medicines and Related Substances Control Act (Act 101 of 1965), and its supporting Regulations.

As these guidelines are constantly evolving due to harmonisation initiatives as well as due to new scientific developments, applicants are advised to always consult the latest information available. The Medicines Control Council endeavours to keep abreast of such developments and to keep its application requirements and evaluation procedures and policies in line with "best international practice".

The destruction of Schedule 6 medicines and substances may only take place in accordance with the Medicines and Related Substances Control Act (Act 101 of 1965)

2 DESTRUCTION AUTHORISED BY AN INSPECTOR

The destruction of Schedule 6 medicines and substances that have been entered into a register, may take place under the supervision of an inspector designated in terms of Section 40(1) of the Act, an officer of the SAPS or other person authorised in terms of the legislation to supervise this action.

2.1 All destruction must take place in accordance with local municipal regulations regarding the disposal of chemical or medicinal waste. The applicant (person requesting destruction) may be requested to prove that the method of destruction is in accordance with such regulations.

2.2 All medicines or substances must be destroyed in such a manner that does not allow recovery.

2.3 The inspector must, on behalf of the Medicines Regulatory Authority (MRA), provide a certificate of destruction and in the case of an officer of the SAPS, a case number must be provided which must be kept with the register for a period of 5 years.

2.4 All quantities destroyed must be indicated in the relevant register on the date of destruction and signed by the applicant, indicating the reference to the destruction certificate or case number.

3 PROCEDURE FOR WRITTEN AUTHORISATION OF DESTRUCTION FROM THE MEDICINES REGULATORY AUTHORITY:

The MRA may authorise the destruction of Schedule 6medicines or substances in writing, without the presence of an inspector, if a pharmaceutical company or other institution in question, has sufficient personnel, procedures and capacity to follow the procedure described below.

4. APPLICATION FOR AUTHORISED DESTRUCTION

4.1 The Applicant must request permission for destruction of specific quantities of the medicines or substances in question in writing.

4.2 The request will indicate -

- the name of each medicine or substance to be destroyed,
- the exact quantities and batch numbers (if applicable) of the medicines or substances to be destroyed,
- the reason for the destruction and
- the names of the two pharmacists who will witness the destruction as required by the procedure. The MRA may consider a deviation from the requirement of two pharmacists in exceptional cases only. This will depend on the motivation supplied and on alternative arrangements to obtain sufficient control.

4.3 The MRA will authorise the destruction of the medicines or substances in question in writing, specifying the quantities indicated in the request, provided that the following procedure be followed:

5 GENERAL

5.1 Destruction may only take place after the written authorisation from the MRA has been received.

5.2 All destruction must take place in accordance with the local municipal regulations regarding the disposal of chemical or medicinal waste. The applicant may be requested to prove that the method of destruction is in accordance with such regulations.

5.3 All medicines and substances must be destroyed in such a manner that prevents their recovery.

5.4 The destruction must be properly documented:

- All quantities destroyed must be indicated in the relevant registers and signed by the witnesses required in the procedure. (See registers below)
- Destruction certificates (where applicable) and the letter of authorisation must be referenced in, or attached to the relevant Schedule6 register and retained for the same period of time as the register itself. (5 years)

6. METHOD OF DESTRUCTION

6.1 Potent or large quantities of medicines and substances

6.1.1 Depending on the municipal regulations regarding the disposal of chemical or

medicinal waste, the applicant may choose an appropriate method of destruction such as incineration or destruction by a reliable contractor who specialises in waste disposal.

6.1.2 If a contractor is not used (eg. incineration), **two pharmacists** employed by the applicant must witness the **removal and destruction** of the correct quantities of the medicines or substances authorised for destruction, regardless of the where destruction will take place.

6.1.3 In the case of a contractor, where destruction does not take place at the premises of the applicant, and a certificate of destruction will beprovided, **two** pharmacists employed by the applicant must witness the **removal from the stock** of the correct quantities of the medicines or substances authorised for destruction and at least **one** of the **pharmacist** should accompany the goods to the place of **destruction**, to witness that these have actually been destroyed or disposed of in such a manner that precludes their recovery.

6.1.4 In the case of a contractor, a valid certificate of destruction must be obtained.

6.2 Small quantities

6.2.1 Small amounts of medicines or substances may be destroyed on the premises where these are kept. Appropriate methods must be used which are unlikely to cause any adverse health or environmental consequences, must be in accordance with local municipal regulatons and will not allow the drugs to be readily recovered. Two pharmacists employed by the company must witness the removal from stock and the destruction of the correct quantities of each medicine or substance.

7 SCHEDULE 6 REGISTER

7.1 The quantities of any medicines or substances destroyed must be entered into the register on the date of destruction.

7.2 The inscription in the register must be signed by the two pharmacists employed by the company, who witnessed their removal from stock destruction. The Managing Director must co-sign, unless the Managing Director was one of the pharmacists involved with the removal and destruction.

7.3 The letter of authorisation and the destruction certificate (if applicable) must be referenced in or attached to the schedule 6 register and retained for a period of 5 years.

8 LEGAL REPORTING REQUIREMENTS

8.1 If the amount of substance destroyed according to any method above, is more than :

- 1 milligram for potent narcotic drugs (fentanyl, sufentanil, alfentanil, etc.),
- more than 1 gram for all other narcotic drugs or
- more than 1 kilogram for any psychotropic substance,

the base amount of each substance destroyed must be indicated on the annual returns of Schedule 6 substances in terms of Regulation 29 of the Medicines and Related Substances Control Act (Act 101 of 1965), relating to the year in which the destruction took place.

CTF 1

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION TO CONDUCT CLINICAL TRIALS

TO ALL APPLICANTS

APPLICATION TO CONDUCT A CLINICAL TRIAL

The following are the requirements when submitting a clinical trial application.

1. Covering letter.
2. Cover sheet.
3. Checklist.
4. Completed Application form.
5. All documents to be submitted in duplicate with two electronic copies.
6. Additional 25 copies of the application form itself must be submitted.
7. Protocol
8. Patient Information leaflet and Informed consent form
9. Standardized MCC contact details/wording to be added to PILs.
10. Investigators Brochure/Package insert.
11. Signed investigator(s) CV(s) in MCC CVs format.
12. Signed Declaration by Principal investigator(s).
13. Signed joint declaration by Sponsor/National Principal investigator.
14. Signed Provisional declaration by Co- or Sub-investigators
15. Signed Declaration by regional monitor
16. Indemnity and Insurance Certificate and/or
17. Proof of Malpractice insurance of trialist(s).
18. Ethics committee(s) approval or
19. Copy of letter submitted to Ethics committee(s).
20. Diskettes to be submitted in word.
21. Financial declaration

SOUTH AFRICA : CLINICAL TRIAL APPLICATION

SECTION 1 – CHECK-LIST OF REQUIRED DOCUMENTATION

To be completed by Applicants for all Clinical Trials

COVER SHEET

Study Title:

Protocol No:

Version No: Date of Protocol:

Study Drug:

MCC Ref number (if applicable):

MCC Ref number(s) of comparator drug(s) (if applicable):

MCC Ref number(s) of concomitant drug(s) (if applicable):

Date(s) MCC approval of previous protocol(s):

Sponsor:

Applicant:

Contact Person:
Address:
Telephone Number: Fax Number:
Cell Number:
E-mail address:

To be completed by MCC

Date original application received:

Tracking No:

Proposed Clinical Trials Committee Meeting Date if applicable:

Signature: Date:

ACKNOWLEDGEMENT OF RECEIPT OF CTA (Contact details to be completed by the applicant). Whole cover sheet to be faxed to applicant once details in block above are completed.

Contact Details: Name : Fax No.:

Receipt of new application is hereby acknowledged. Date:

Signature (of MCC recipient): Name:

CHECKLIST

Applicant's check list		MCC double-check
☐	COVERING LETTER	☐
☐	FULLY COMPLETED APPLICATION (SECTIONS 1–3)	☐
☐	PROTOCOL (INCLUDING RELEVANT QUESTIONNAIRES ETC.)	☐
☐	PATIENT INFORMATION LEAFLET(S) AND INFORMED CONSENT(S)	☐
☐	INVESTIGATORS BROCHURE AND / OR ALL PACKAGE INSERT(s)	☐
☐	INVESTIGATOR'S CV(s) IN MCC FORMAT	☐
☐	SIGNED DECLARATION(s) BY INVESTIGATOR(s)	☐
☐	REGIONAL MONITOR'S CV AND DECLARATION	☐
☐	CERTIFICATE(S) OF ANALYSIS (May be submitted with ethics approval letter)	☐
☐	INSURANCE CERTIFICATE	☐
AND IF NECESSARY:		
☐	LETTER ENDORSING GENERIC INSURANCE CERTIFICATE	☐
☐	ETHICS APPROVAL	☐
OR		
☐	COPY OF LETTER APPLYING FOR ETHICS COMMITTEE APPROVAL	
☐	COPY/IES OF RECRUITMENT ADVERTISMENT(s) (IF APPLICABLE)	☐
☐	FINANCIAL DECLARATION (SPONSOR AND NATIONAL PI)	☐

Electronic versions of the application form (Sections 1 –3), the protocol, the investigator's brochure and/or other relevant documents:

☐ LABELLED DISKETTE/CD-ROM (MSWORD OR RICH TEXT FORMAT) ☐

List of files submitted on diskette/CD-ROM:

NB: DO NOT SUBMIT THE APPLICATION IF DOCUMENTATION IS INCOMPLETE: IT WILL NOT BE PROCESSED

Declaration by applicant:

We, the undersigned have submitted all requested and required documentation, and have disclosed all information which may influence the approval of this application.

We, the undersigned, agree to ensure that if the above-said clinical trial is approved, it will be conducted according to the submitted protocol and South African legal, ethical and regulatory requirements.

Applicant (local contact)	Date
National Principal Investigator / National Co-ordinator / Other (state designation)	Date

SECTION 2 – ADMINISTRATIVE AND SUPPLEMENTARY DETAILS

Title:

Protocol Number/identification:

Date of protocol (initial/final):

Part 1: CONTACT DETAILS (NAME/ADDRESS/TEL/CELL/FAX/E-MAIL)

1.1 Applicant: (as in Section 1)

1.2 Sponsor: (as in Section 1)

1.3 If no sponsor – person or organisation initiating, managing, and / or funding the clinical trial:

1.4 Local Contact Person for correspondence:

1.5 National Principal Investigator/Coordinator: (or equivalent person)

1.6 International Principal Investigator: (if applicable)

1.7 Regional Monitor: (as in Section 1)

Part 2: DETAILS OF INVESTIGATIONAL PRODUCT(s)

2.1 Name(s) and details of investigational product(s) to be used in trial: [Formulation(s) and strength(s) (e.g. 10 mg/ml–10ml amp.)] Include MCC registration number and date of registration if applicable.

2.2 Name(s) and details (as above) of comparator product(s) and MCC registration number(s) and date(s) of registration if applicable: [Ensure package inserts or complete pharmacological information been included (Section 1).]

2.3 Name(s) and details (as above) of concomitant medication(s) including rescue medications which are required in the protocol, and MCC registration number(s) if applicable: [Ensure package inserts or complete pharmacological information has been included with application (Section 1).]

2.4 Estimated Quantity of Trial Material (each drug detailed separately) for which exemption will be required:

2.5 If any of the above drugs are available in South Africa, give an explanation for not using what is available in South Africa:

2.6 Details of receiving of drugs from supplier, storage, dispensing, packaging of drugs:

2.7 Date MCC registration applied for – or envisaged date of application for trial medication. Explain if registration is **not** envisaged:

2.8 Registration status of entity, for the indication to be tested in this trial, in other countries: (i.e. Country: date registered / date applied for / date registration refused / date registration withdrawn by applicant / date registration cancelled by regulatory authority) [Attach as an appendix if necessary.]

Part 3: DETAILS OF TRIALIST(s) AND SITE(s)

3.1 Details of Investigator(s): [designation, title: (i.e. principal investigators / investigators) Include Name/Address/Tel/Cell/Fax/E-Mail]

3.2 Current work-load of Investigator(s): (Number of studies currently undertaken by trialist(s) as principal and/or co- or sub-investigator, and the total number of patients represented by these studies. Time-commitments of researcher(s) in relation to clinical trial work *and* non-trial work.)

Recommended format for response:

Investigator (Name and designation):			
Total number of current studies (all stages) on specified date	Number	Date	
Total number of patients / participants for which responsible on specified date	Number	Date	
ESTIMATED TIME PER WEEK [168 hours denominator]		**Hours**	**%**
Clinical trials	Clinical work (patient contact)		
	Administrative work		
Organisation (Practice / university / employer)	Clinical work		
	Administrative work		
Teaching	Preparation / evaluation		
	Lectures / tutorials		
Writing up work for publication / presentation			
Reading / sourcing information (e.g. internet searches)			
Other (specify)			

3.3 Details of Site(s) (Name of site, physical address, contact details, contact person, etc.)

3.4 Capacity of Site(s): (Number of staff, names, qualifications, experience -- including study co-ordinators, site facilities, emergency facilities, other relevant infrastructure)

Part 4: PARTICIPANTS (SUBJECTS)

4.1 Number of participants in South Africa:

4.2 Total worldwide:

4.3 Total enrollment in each SA centre: (if competitive enrollment, state minimum and maximum number per site.)

4.4 Volunteer base from which South African participants will be drawn:

4.5 Retrospective data indicating potential of each site to recruit required number of patients within envisaged duration of trial. (SA Guidelines 2000, Item 3.3, p15) [May be attached. Label clearly as 'Section 2 Item 4.5']

Part 5: OTHER DETAILS

5.1 If the trial is to be conducted in SA and not in the host country of the applicant / sponsor, provide an explanation:

5.2 Estimated duration of trial:

5.3 Name other Regulatory Authorities to which applications to do this trial have been submitted, but approval has not yet been granted. Include date(s) of application:

5.4 Name other Regulatory Authorities which have approved this trial, date(s) of approval and number of sites per country:

5.5 If applicable, name other Regulatory Authorities or Ethics Committees which have rejected this trial and give reasons for rejection:

5.6 If applicable, details of and reasons for this trial having been halted at any stage by other Regulatory Authorities:

5.7 Details if this trial is being undertaken in SADC, any other country in Africa, or any country where there is no regulatory control of clinical trials:

5.8 Previous studies using this agent which have been approved by MCC:

MCC approval number:
Study title:
Protocol number:
Date of approval:
National PI / Principal Investigator:
Date(s) Progress report(s):
Date Final report:

5.9 If any substudies are proposed as part of this protocol, indicate whether or not they will also be done in South Africa. If not, please explain.

Part 6: ETHICS

6.1 Ethics Committee responsible for each site, date of approval or date of application:

6.2 Attach copy of response(s) made by, and/or conditions required by ethics committee(s) if available. Ensure that date of EC response is legible.

6.3 State which Good Clinical Practice (GCP) guidelines are being followed. (Particular reference to the South African guidelines required):

6.4 Details of capacity building component of the trial, if any:

6.5 Details of the training of investigators, monitors, study co-ordinators in terms of carrying out this trial and in terms of GCP:

6.6 Detailed safety and monitoring plan for each site: [May be attached. Label as 'Section 2 Item 6.6']

6.7 Details of trial insurance certificate: (e.g. title, protocol, dates, policy #, amount)

6.8 Details of possible conflict of interest of any person(s)/organisation(s) who/which will be involved in the trial:

6.9 Remuneration to be received in SA Rands: (Investigators) (Trial participants) (Others) Indicate broad breakdown of costs to be covered by this amount – if applicable. [Note: the CTC recommends a minimum compensation of R50.00 per visit for participants travel and incidental expenses.]

Reviewer's comments on Section 2:

SECTION 3 – APPLICANT'S REPORT / PRESENTATION
[Please use Black 12 point Arial Font, using MSWord or rich text format (rtf) for electronic version]

1. Title:

CTC Reviewer's comment:

2. Protocol Number/identification:

3. Rationale for study summarised: (Why should this trial be done at all?) Include statement about South African contribution, if any, to the development of this protocol.

CTC Reviewer's comment:

4. Background information (**summarised** – **essential** points that apply to this trial) [1-2 sentences max for each point]:
Disease / problem
South African context (e.g. local epidemiology)
Properties of Drug / Entity; hypotheses about mechanism of action, etc.
Pre-clinical findings: (e.g. laboratory / animal / toxicity / mutagenicity)
Clinical findings (e.g. phases: PK; PD; dose-finding; ADRs, NNT/NNH, other)
Systematic review(s) and/or citations per year-group on a Medline search

CTC Reviewer's comment:

5. Objectives of study (clearly listed and justified)

CTC Reviewer's comment:

6. Study design (clearly described and each component justified)
[includes phase, use of placebo, dosages, randomisation, blinding, duration, etc.]

CTC Reviewer's comment:

7. Participants: (number of participants; ability to enroll required number within stated time)

CTC Reviewer's comment:

8. Eligibility and enrollment: (Inclusion and exclusion criteria listed and justified)

CTC Reviewer's comment:

9. Treatment modalities and regimens, drug accountability [clearly explained and justified for all participant groups/arms e.g. in terms of route of administration, dose, etc. Drug accountability clearly described.]

CTC Reviewer's comment:

10. Outcome measurements/variables (each clearly stated and justified)

CTC Reviewer's comment:

11. Adverse events (prevention, definitions – including causality assignment, recording, reporting, time-lines, action to be taken, all clearly described)

CTC Reviewer's comment:

12. Statistical measures:
Determination of sample size correct, clear and justified (with and/or without stratification)
Statistical method(s) and analysis of quantitative measures appropriate, clear and justified
Statistical method(s) and analysis of qualitative measures appropriate, clear and justified
Data processing (how, where, when, who) clearly described and justified. If a SA person will be involved in data processing, please identify that person
Interim analysis envisaged or not (justify) and stopping rules if applicable (explain)

CTC Reviewer's comment:

13. Ethical Issues: justification of 'Section 2 part 6' including:

- Explanation of which GCP guidelines are or are not being followed – with particular reference to the South African guidelines
- Comment on choice of investigators (refer to point C of Introduction, page 2 SA Clinical Trials Guidelines 2000)
- Comment on need for, appropriateness of, and relevance of GCP training / updating / for staff involved in this trial
- Comment on capacity building element of trial
- Comment on resources of sites and sponsor
- Comment on monitors and monitoring plan
- Indicate how additional staff (monitors, pharmacists, nursing staff, etc.) will maintain patient confidentiality, follow the protocol, and abide by ethical and regulatory requirements
- Comment on insurance and indemnity measures
- Comment on Patient Information Leaflet and Informed Consent (NB: inclusion of ABPI guidelines; appropriate level of education/English; possible benefits / risks clear; ensuring patient rights; contact names and numbers, as well as MCC details, included)
- Comment on availability and completeness of separate PILs and informed consent forms for any proposed archiving of blood specimens for later research or for genetics research.
- Comment on ethics of the publication policy
- Comment on treatment and/or management of participants and their disease condition(s) after completion of trial
- Comment on ethics committee capacity to monitor site if not a local ethics committee
- Provide an explanation if minimum recommended compensation for participants is not being provided.

CTC Reviewer's comment:

14. Other relevant information not included above
E.g. Are references adequate and dates of references current?
Are there discrepancies between protocol and IB or package inserts? Are there specific explanation(s) for these discrepancies?
Are the explanations for not following the SA 'GCP guidelines' acceptable?
Other comments on this trial.

CTC Reviewer's comment:

For office use:

CTC Reviewer's questions and concerns to be considered and/or forwarded to applicant:

CTC Reviewer's recommendation:

Declaration of conflict of interests by CTC reviewer:

CTC recommendation (date): 1A, 1B, 2, 3, 4, 5

MCC decision (date):

RECALLS

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

GUIDELINES FOR RECALL OF MEDICINES

This document has been prepared to serve as a recommendation to applicants regarding the recalls of medicines, and the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. 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 which has been submitted regarding any recalls. The MCC is committed to ensure that all medicines that are registered are of the required quality, safety and efficacy. It is important for applicants to adhere to these requirements.

REGISTRAR OF MEDICINES
MS. M.P. MATSOSO
DATE: 29/04/2003

Version 2003MCC/1

INDEX

GUIDELINES FOR RECALL/WITHDRAWAL OF MEDICINES

1. INTRODUCTION

The guidelines for recall/withdrawal of medicines is the result of an agreement between the holder of the certificate of registration/parallel importer of the medicine and the Department of Health: (Medicines Control Council) (MCC) in South Africa. Its purpose is to define the action to be taken by the Cluster: Medicines Regulatory Affairs: Directorate: Inspectorate and Law Enforcement and the holder of the certificate of registration /parallel importer of the medicine, when medicines for reasons relating to their safety, quality and efficacy are to be removed from the market.

The Registrar of Medicines, the Director and Deputy Director: Inspectorate ad Law Enforcement and the Medicines Control Officer(s) are responsible for recall/ withdrawal, and will monitor closely the effectiveness of the holder of the registration certificate/parallel importer's recall actions and provide a scientific, technical and operational advice.

Each holder of a certificate of registration certificate(HCR)/parallel importer should advice the Medicines Regulatory Affairs (MCC) of the names, after hours and telephone numbers of two persons who have authority to discuss and, if necessary, implement a recall.

These guidelines serve to remind the holder of a certificate of registration/parallel importer that the Medicines Control Council expects them to take full responsibility for medicines recalls, including follow-up checks to ensure that the recalls are successful.

Most recalls are conducted on voluntary basis. The MCC can recall medicines when registration thereof has been cancelled, or when medicines are sold illegally in South Africa. If the recalling performance is deemed inadequate the MCC is prepared to take appropriate actions to remove the product from sale or use.

2. DEFINITIONS

Recall-means the removal of a specific batch/batches of a medicinal product from the market for reasons relating to deficiencies in the quality, safety or efficacy.

Withdrawal-means the total withdrawal of a medicinal product from the market

Medicine-means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in-

(a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man: or

(b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine

Parallel importation- means the importation into the Republic of a medicine protected under patent and/or registered in the Republic that has been put onto the market outside the Republic by or with the consent of such patent holder.

Parallel importer- means a person who parallel imports a medicine into the Republic on authority of a permit issued in terms of regulation 7(3) of the Medicines and Related Substances Control Act, 101 of 1965.

Holder of a certificate of registration-means a person in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality and safety and compliance with conditions of registration

Stock recovery-means a firm's removal or correction of a product that has been released for sale and has not yet been despatched or has not left the direct control of the holder of a certificate of registration/parallel importer (Refer regulation 43(1) of the Medicines and Related Substances Control Act, Act 101 of 1965)

3. PROVISIONS OF THE ACT

3.1 Section 19 (1) of the Medicines and Related Substances Control Act, Act 101 of 1965. Act 101 of 1965 –*No person shall sell any medicine unless it complies with the prescribed requirements. Any person who contravenes provision of this sub-section shall be guilty of an offence.*

3.2 Regulation 43(1)-Every medicine shall comply with the standards and specifications which were furnished to the Council on the form prescribed by regulation 22 and which have been accepted by the Council with regard to such medicine.

4. NOTIFICATION/INITIATION OF THE RECALL

The recall of a medicine can be initiated as a result of reports referred to the holder of a certificate of registration/parallel importer or Medicines Regulatory Affairs (MRA)(MCC) from various sources, e.g. manufacturers, wholesalers, retail and hospital pharmacists, doctors, etc. A report of an adverse drug reaction to a particular batch(es), product quality deficiency, technical complaints experienced with regard to the printed packaging material, contamination, mislabelling, counterfeit including adulterated medicines.

When initiating a recall the holder of a certificate of registration should take the following aspects into consideration: the extent of public warnings and the successfulness of the recall.

5. INFORMATION REQUIRED FOR THE ASSESSMENT OF A RECALL

Recall information	**Information by the HCR/Parallel importer**	**Comments by MRA(MCC))** *(for official use only)*
Origin of report		
1. Name of person/organisation reporting the problem		
2. Company		
3. Physical address		
4. Telephone number		
5. Facsimile number		
6. E-mail address		
7. Date of report		
8. Name of recipient at the MRA		
Product(medicine) details		
1. Name of product affected		
2. Registration number		
3. Dosage form		
4. Strength		
5. Pack size/type		
6. Batch number and expiry date		
7. Manufacturer/holder of the certificate of registration, address and contact details		
8. Date manufactured		
9. Date released		
10. Total quantity prior to distribution		
11. Quantity released for distribution prior to the recall		
13. Date of distribution		
14. Local distribution (*give full details and quantity)*		
15. Overseas distribution (*give full details and quantity)*		
Nature of defect		
1. Source of problem (e.g. patient/hospital/pharmacy/manufacturer, etc)		
2. Details of problem		
3. Number of complaints received		
4. Name and address of any Medicines Regulatory Affairs notified of the problem		
5. Action taken so far (if any)/ Proposed		

action and its urgency		
6. Type of hazard/health risk and assessment of risk to the user		
7. Proposed recall classification and type		
8. Other relevant information		

The above information could be provided verbally but should be confirmed in writing within **3 working days**

For office use only Decision on next action

6. CLASSIFICATION OF RECALLS

Recalls are classified into both the **class** according to the level of health hazard involved (risk to the patient) and **type** which denotes the depth or extent to which the product should be recalled from the distribution chain, e.g. Class I, Type C recall, etc.

Class I
Class I is for defective/dangerous/potentially life-threatening medicines that predictably or probably could result into serious health risk/adverse events or even death.

Class II
Class II is for medicines that possibly could cause temporary or medically reversible adverse health problem or mistreatment.

Class III
Class III is medicines that are defective and are likely to cause any adverse health reaction or which do not comply with the requirements of Act 101 of 1965 in terms of the requirements of printed packaging material, product specification, labelling, etc.

Type A

A type A recall is designed to reach all suppliers of medicines (all distribution points) i.e. Wholesalers throughout the country, directors of hospital services (private as well as state hospitals), retail outlets, doctors, nurses, pharmacists, authorised prescribers and dispensers and individual customers or patients through media release (radio, television, regional and national press).

Action: Recall letter to all distribution points plus media release.

Type B

A type B recall is designed to reach wholesalers throughout the country, directors of hospital services (private as well as state hospitals), retail outlets, doctors, nurses, pharmacists, authorised prescribers and dispensers.

Action: Recall letter to all distribution points.

Type C

A type C recall is designed to reach wholesale level and other distribution points (e.g. pharmacies, doctors, hospitals) this can be achieved by means of a representatives calling on wholesalers and/or retail outlets. If it is known where the product in question had been distributed to, specific telephone calls or recalls letters to arrange for the return of the product could be made.

Action: Specific telephone calls, recall letters to/representatives calling at distribution points if known where the medicines have been distributed.

NOTE: Decisions on the class and type of a recall to be initiated are a matter of the Medicines Control Council and Medicines Regulatory Affairs in consultation with a holder of the registration certificate and shall be based on the evidence and/or expert opinion of the MCC and HCR. In the event of greater urgency e.g. after hours or over weekends, the decision to recall can be initiated by HCR.

7. RECALL LETTER CONTENTS

Recall communication from holder of the registration certificate to the distribution chain should be written in accordance with the following directive:

1. Shall be on the company's letterhead and signed by the Managing Director or any authorised person/responsible pharmacist .
2. The heading should indicate that it is an "Urgent Medicine Recall"
3. Name of product, dosage form, strength, registration number, pack size, batch number(s), expiry date and any other relevant information necessary to allow absolute identification

4. Nature of the defect (be brief to the point)
5. Urgency of the action
6. Reason for the action (reason for recall)
7. Indication of a health risk (this should also state exactly what the product may do if taken, i.e., side effects)
8. Provide specific information on what should be done in respect of the recalled medicine. Method of recovery or product correction, which will be used.
9. Where necessary a follow-up communication shall be sent to those who filed to respond to the initial recall communication.
10. A request to retain the letter in a prominent position for one month in case stock is in transit (*where applicable*).
11. Where recalled stock has been distributed to a limited number of hospitals and the recall letter is not to be sent to all hospitals in the province, the letter should include the following:

    " *If any of the recalled stock could have been transferred from your hospital to another, please let that hospital know or alternatively inform our company so that we can make contact with the hospital supplied from your hospital*".

NB: The recall communication shall not contain any material that can be viewed as promotional in nature.

8. MEDIA RELEASE

In a case of a recall where media release is indicated, the holder of a certificate of registration and the MRA makes the text of the media release jointly Expert advice may also be required.

The media release should contain sufficient information to describe the product and a clear outline of the problem (without causing unnecessary alarm) and must state the appropriate response by the consumer/client.

A 24-hour access telephone number of the holder of the registration certificate should be given for further information. The media release will be issued by the holder of the registration certificate. In the event that the holder of the registration certificate refuses to do a media release the Medicines Control Council will do the release via the Cluster: Communication of the Department of Health.

9. POST RECALL PROCEDURES

The Medicines Control Council shall be furnished within **30 days** of the recall having been instituted with a final reconciliation report. The report shall contain the following information:

NOTE: An interim report may be requested even before the 30 days have elapsed.

Post recall information	**Information by the HCR /Parallel importer**	**Comments by MRA/MCC** *(for official use only)*
1. Name of product		
2. Registration number		
3. Dosage form		
4. Strength of product		
5. Pack size/type		
6. Batch number and expiry date		
7.Nature of defect		
8. Action taken (taking into account the area of distribution of recalled medicine), if exported confirmation from the Regulatory Authority and the holder of the registration certificate in the country of origin		
9. Urgency of the action taken		
10. Reason for the action		
11. Indication of the health risk and the reported clinical problems		
12. Steps taken to prevent re-occurrence of the problem		
13. Fate of the recalled product (including the decision taken)		
14. The result of the recall-quantity of stock returned, corrected, outstanding, etc		
15. Confirmation that		

customers have received the recall letter		
16. Copies of all recall correspondence including previous correspondences to Council regarding this recall.		

For official use only Comments on the success of the recall.

10. REFERENCES

1. Circular 9/98 from the Medicines Control Council.
2. Uniform Recall Procedure for the Therapeutic Goods.

11. CONTACT DETAILS

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

2. Mr. .K Mofokeng
Deputy Director: Inspectorate and Law Enforcement Directorate
Tel: 012 312 0259
Fax: 012 312 3114

3. Ms H. Moropyane
Principal Medicines Control Officer
Tel: 012 312 0243
Fax: 012 312 3114

4. Ms P. Matsoso
Registrar of Medicines
Tel: 012 312 0285
Fax: 012 312 3105

12. UPDATE HISTORY

Date	Reason for update	Version
April 2003	New	2003/1

CTF 2

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FOR PROTOCOL AMENDMENT

Version MCC/2003/1

MCC CLINICAL TRIALS SECTION TRACKING NUMBER FOR THIS CORRESPONDENCE:

REGISTRAR OF MEDICINES
APPLICATION FOR APPROVAL OF:

☐ **PROTOCOL AMENDMENT**
☐ **INCREASE IN NUMBER OF PATIENTS PARTICIPATING**
☐ **CHANGES IN DOSE / REGIMENT OF STUDY DRUG**

Protocol number, title and date

1. **APPLICANT**

1.1 Name/address/tel/fax number of Applicant wishing to conduct trial

1.2 Name/address/tel/fax number of CRO representing sponsor as Applicant or Local Sponsor Company details (if applicable)

1.3 Name, designation and qualifications of person representing the Applicant (***Local Contact Person for all further correspondence***)

1.4 National Coordinator name, address, tel/fax number

1.5 International Principal Investigator name, address, tel/fax number

1.6 Name of sponsor

2. **TRIAL PARTICULARS (original application)**

2.1 MCC Approval Number:

2.2 Date of Approval of original protocol:

2.3 Number of Investigators in South Africa already approved for this trial:

2.4 Number of sites in South Africa already approved for this trial:

2.5 Number of patients in South Africa already approved for this trial:

3. AMENDMENT PARTICULARS

(Please list requests for approval)

Does the applicant wish to increase the number of patients participating in this trial in South Africa?

Yes ☐
No ☐

If "Yes" please submit a letter requesting amendment together with this application?

Does the applicant wish to change the dose / regimen of the study drug?

Yes ☐
No ☐

If "Yes" please submit a letter requesting amendment together with this application?

Does this amendment request require a new consent form from the participant?

Yes ☐
No ☐

If "Yes" please submit new PIL together with this application.

3.1 Amendment Number:

3.2 Version Number and Date of Amendment (for each document submitted):

3.3 **General motivation for the proposed Amendment: List all the issues included in the amendment and give a rationale for each point being changed)**

3.4 Details of the proposed Amendment. For each point or section give a brief motivation and clearly **highlight changes**; this can be done either as **"old text"** replaced with **"new text"** or with the **old text deleted** with a line through it and the **new text in Bold and underlined**:

3.5 Brief description and purpose of the trial (do not repeat title) and motivation for amendment:

3.6 Will this Amendment apply to all approved South African investigators/sites:

YES ☐ **NO** ☐

If NO: Specify the South African investigator(s) / site(s) for which the Amendment will apply:

4. ETHICS COMMITTEE APPROVAL

4.1 Have the Ethics Committee(s) responsible for each centre to which this amendment applies been notified?

4.2 List Ethics Committees

4.3 Date of application to Ethics Committee

4.4 Date of approval by Ethics Committee

I, the undersigned, agree to conduct / manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility to sign this form).

_____ _____

Applicant (local contact) Date

CTF 3

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

APPLICATION FOR ADDITIONAL INVESTIGATOR(S) OR CHANGE OF INVESTIGATOR(S) AND APPLICATION FOR ADDITIONAL SITES

MCC CLINICAL TRIALS SECTION TRACKING NUMBER FOR THIS CORRESPONDENCE:

REGISTRAR OF MEDICINES
APPLICATION FOR APPROVAL OF:

☐ **CHANGES IN INVESTIGATOR (S) AT APPROVED SITE (includes additional investigators)**
☐ **ADDITIONAL SITE (S)**

Protocol number, title and date

1. APPLICANT

1.1 Name/address/tel/fax number of Applicant wishing to conduct trial

1.2 Name/address/tel/fax number of CRO representing sponsor as Applicant or Local Sponsor Company details (if applicable)

1.3 Name, designation and qualifications of person representing the Applicant (***Local Contact Person for all further correspondence***)

1.4 National Coordinator name, address, tel/fax number

1.5 International Principal Investigator name, address, tel/fax number

1.6 Name of sponsor

2. TRIAL PARTICULARS **(original application)**

2.1 MCC Approval Number:

2.2 Date of Approval of original protocol:

2.3 Number of Investigators in South Africa already approved for this trial:

2.4 Number of sites in South Africa already approved for this trial:

2.5 Number of patients in South Africa already approved for this trial:

3. INVESTIGATOR DETAILS

3.1 Name and address of additional Investigator(s) / Changes to Investigators

3.2 For Investigators who have not previously been in clinical trials, proof of adequate training and experience to properly conduct the study must be provided.

3.3 Summarise other ongoing/planned studies at this site involving this investigator *(give details of indication, phase, study status, number of patients intended, number of patients already enrolled, whether the investigator is involved in research in a full-time or part-time capacity, and any other detail that may effect the capacity of the site at any one time)*

3.4 Details of Ethics Committee(s) who will approve investigator(s)

3.5 Date of application to Ethics Committee

3.6 Date of approval by Ethics Committee

3.7 Is CV for additional Investigator(s) attached (list)
YES ☐

3.8 Is the Declaration of Intent attached (list)
YES ☐

4. CAPACITY OF THE SITE

4.1 Describe how the site is structured so as to be able to take on the work for which this application is being made. (Give details of support staff, facilities, back up and any other relevant infrastructure)

5. RATIONALE FOR APPLICATION

5.1 Briefly explain the reason for the new investigator/s

I, the undersigned, agree to conduct / manage the above-mentioned trial under the conditions as stated in this application. (The person(s) undertaking legal responsibility to sign this form).

Applicant (local contact) Date

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

MEDICINE DONATIONS TO SOUTH AFRICA

This document has been prepared to serve as a guideline to applicants wishing to submit applications for the donation of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for the donation of medicines. The MCC is committed to ensure that all medicines available that are donated will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

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

INDEX

MEDICINE DONATIONS TO SOUTH AFRICA

1. INTRODUCTION

These guidelines aim to improve the quality of donations, not to hinder them. They are intended to serve as a base for national guidelines, to be reviewed, adapted and implemented by the government and organizations dealing with drug donations.

There are many different scenarios for medicines donations. They may take place in acute emergencies or as part of development aid in non-emergency situations. They may be corporate donations (i.e. direct or through private voluntary organisations), aid by governments, or donations aimed directly at single health facilities. Therefore, these guidelines aim to describe this common core of " Good Donations Practise."

Four core principles interlay the guidelines:

1. A drug donation should benefit the recipient to the maximum extent possible.

2. A donation should be given with full respect for the wishes and authority of the recipient and are supportive of existing government policies and administrative arrangements.

3. There should be no double standards in quality; if the quality of an item is unacceptable in the donor country, it is also unacceptable as a donation.

4. There should be effective communication between the donor and the recipient; donations should be based on an expressed need and should not be sent unannounced.

2. BACKGROUND

Over the last three or four decades in particular, there has been an enormous increase in our scientific knowledge about the mode of action, effects, and side effects of medicines. Medicines are not automatically beneficial, that they have to be used carefully and appropriately, and that some can do more harm than good, as a result more cautious and critical attitude towards medicines have been developed.

Subsequently, South African government or/and the Department of Health in particular recognises the need of appropriate curative services, hence it has developed essential drug list based on the health needs of the majority of the population and used as a foundation for medicine donations.

It suffice to say that the goal of the National Drug Policy is to ensure an adequate and reliable supply of safe, cost effective medicines of acceptable quality to all the citizens of South Africa and the national use of medicines by prescribers, dispensers and consumers.

3. THE LEGAL SITUATION

MEDICINE DONATIONS TO SOUTH AFRICA

In the Medicines and Related Substances Control Act, No 101 of 1965, South Africa has sophisticated legislation, which prohibits the use, sale, or supply of any medicine unless it has been evaluated in terms of its safety, quality and efficacy and has thereafter been registered.

Section 21 of the legislation does allow the Medicines Control Council to permit the use of unregistered medicines (which what donated medicines are) subject to such conditions as the Council may determine. As a consequence no donated medicines may be used unless the Council has specifically authorized its use. Application for the donation of medicine must be made to the Registrar of Medicines. In submitting an application the following information must be supplied: name, expiry date, batch number, package, site of manufacture, package insert, quantity, intended for and local recipient.

4. SELECTION OF MEDICINES

4.1 All medicine donations should be based on the health needs and disease pattern of the Republic of South Africa. Drugs should not be sent without prior consent by the recipient.

The purpose of this guideline is to stress the point that it is the prime responsibility of the recipient to specify their needs. It is intended to prevent unsolicited donations, and donations which arrive unannounced and unwanted. It also empowers the recipients to refuse unwanted gifts.

4.2 Donated medicines should not be sent without prior consent of the Medicines Control Council.

4.3 Donated medicines must appear on the Essential Drug List and must be compatible with overall Government Policy. Exception may be made on recommendation by the Medicines Control Council (MCC).

It further intends to ensure that medicine donations comply with the South African National Drug Policy and essential drugs programme. It aims at maximizing the positive impact of the donation, and prevents the donation of medicines, which are unnecessary and/or unknown in the recipient country.

Possible exceptions

An exception could be made for medicines needed in sudden outbreaks of uncommon or newly emerging diseases, since such medicines may not be approved for use in South Africa. Exceptions could also be made on the basis of a specific request by the Government of South Africa.

4.4 The presentation, strength and formulation should be similar to those used in South Africa.

Quality assurance and shelf life.

4.5 All donated medicines have to originate from a reliable source and comply with the

requirements in terms of quality standards, safety and efficacy, in both the donor and South Africa. All donated drugs must be accompanied by the relevant documentation that include a summarised application in terms of Regulation 15 (excluding the annexures as approved by the MCC), Registration certificate from the country of origin and a WHO GMP Certificate. All application for donated medicines must be reviewed by the MCC (through the MCC fast track procedure) before they can be released for distribution. The approval granted by the MCC for distribution will only be valid for a specific consignment applied for. ***(It should be re-iterated that the approval should NOT be regarded as a blank approval for additional importation / distribution of the same product).***

This provision prevents double standards: medicines of unacceptable quality in the donor country should not be donated to other countries. Donated medicines should be authorised for sale in the country of origin, and manufactured in accordance with International standards of Good Manufacturing Practice (GMP).

4.6 Medicines that had been issued to patients and then returned to a pharmacy or elsewhere, or were given to health professionals as free samples shall not be accepted as donated medicines.

In South Africa re-issue of returned medicines is not permitted because their quality cannot be guaranteed. For that reason returned medicines should not be donated. In addition to quality issues, returned medicines are very difficult to manage at receiving end because of broken packages and small quantities involved.

4.7 All donated medicines should have a remaining shelf life of at least 12 months after arrival in South Africa.

Due to logistical problems limiting immediate distribution through different storage levels (e.g. central store, provincial store, district hospital) may take six to nine months. This provision prevents the donation of medicines near their expiry date that could reach the patients after expiry.

Possible exceptions

Possible exception is those drugs that because of their physical properties are manufactured with a short shelf life of less than two years. Vaccine requires stringent conditions during storage and distribution. They should only be donated in close collaboration with the Directorate of Administration of Medicines- Department of Health.

Presentation, Packing and Labelling

4.8 All donated medicines must be labelled in at least English, and the label should contain at least the International Non-proprietary Name (INN, or generic name), batch number, expiry date, dosage form, strength, name and address of the manufacturer, quantity and storage conditions.

All donated medicines, including those under brand name should also be labelled with their International Non-proprietary Name. Training programmes in South Africa are based on the use of generic names. Receiving medicines under different and often unknown brand names and without the generic name can confuse health workers and constitutes a risk in therapeutic practice. In case of injections, the route of administration should be indicated.

4.9 Donated medicines should be presented in large quantity packaging units and hospital packs as used in South Africa.

Large quantity packs (e.g. containers of 1,000 tablets) are cheaper, and easier to transport. This provision prevents the donation of medicines in sample packages, which are not practical to manage.

4.10 Donated medicines must be packed in containers that comply with international shipping regulations and accompanied by a detailed packing list. Medicines should not be mixed with other supplies in the same carton. Transport conditions should be in accordance with the storage condition of the medicines.

This provision is intended to facilitate the administration, storage and distribution of donations in emergency situations, as the identification and management of unmarked boxes with mixed medicines is very time and labour intensive. This provision specifically discourages donations of small quantities of mixed medicines.

4.11 Different medicines should not be packed together in one carton and medicines should not be mixed with other supplies.

Information and Management

4.12 The government of South Africa through the Directorate of Administration of Medicines (Department of Health) should be informed of all medicine donations that are considered, prepared or actually underway. Prior approval for the donation should be obtained from the Directorate Medicine Administration to avoid unnecessary delays at the port of entry. The information should extend to delivery dates, possible delays, port of entry, method of transport, and information as required in ports.

Detailed advance information on all medicine donations is essential to enable South Africa to plan for the receipt of the donation and to coordinate the donation with other sources of supply. The information should at least include: the type and quantities of donated medicines including their generic name, strength, dosage form, and the identity and contact address of the donor.

4.13 The declared value to South Africa of a medicine donation should be based upon the wholesale world- market price for its generic equivalent.

This provision is needed in South Africa to prevent medicine donations being priced

according to the retail price of the product in the donor country, which may lead to elevated overhead cost for import tax, clearance, and handling in South Africa. It may also result in a corresponding decrease in the public sector drug budget in South Africa. All costs of international and local transport, warehousing, port clearance, quality testing and appropriate storage and handling should be paid by the donor, unless specifically agreed otherwise with the South African Government in advance. Similarly, the cost of disposing of a medicine donation adjudged to be unsuitable should be borne by the donor.

These incidental costs can be quite prohibitive and erode the Department of Administration of Medicines (Department of Health) budget. On the other hand, if the donor makes the provisions for these costs, the benefits of the donation will be maximised.

5. CONTACT DETAILS:

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6. UPDATE HISTORY

Date	Reason for update	Version
February 1996	New	1996/1