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 and 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		

(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

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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

GUIDE TO COMPLETING CLINICAL TRIALS APPLICATION FORMS.

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A. SOUTH AFRICA: CLINICAL TRIALS APPLICATION

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[Version MCC/2003/1]

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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.

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.]

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