c) Particulars must be given of the other biological source material from which a biological medicine (e.g. blood fractions) is extracted, including the origin of culture or blood.

d) Specifications must be at the level of the latest editions of recognised pharmacopoeial reference books and any deviations must be disclosed and fully substantiated.

e) Reference only to the recognized pharmacopoeial reference books shall be acceptable where the specifications correspond to the reference.

2.1.11 For biological medicines full details of tests carried out on the raw materials must be provided. (Refer to WHO guidelines on Biologicals).

2.2 PART 2B - FORMULATION

2.2.1 The formula must show the INN or approved names and/or chemical names of all APIs and approved names of excipients (inactive ingredients) including those that do not remain in the final product after manufacturing.

2.2.2 The name and the amount of the API must correspond to the name and quantity stated under Composition in the package insert.

2.2.3 A product may contain more than one API provided that

a) each API makes a contribution to the claimed indications;

b) the effect of combining the APIs in one product does not decrease the safety, stability or efficacy of the product; and

c) the product provides rational concurrent therapy for a significant proportion of the target population. e.g. tuberculostatic combinations.

2.2.4 Each raw material must be listed together with its quantity per dosage unit. This would include the vehicle(s), solvent(s) or base(s). In the absence of an approved name (INN) or chemical name, a chemical description or characterization of the substance must be given. Special technical characteristics of the excipient, where applicable, must be indicated. The technical grade of excipients, where relevant, must be indicated.

2.2.5 The purpose of each inactive ingredient or excipient must be stated briefly. If the excipient is used for multiple purposes in the formulation, each purpose must be mentioned.

2.2.6 For inactive ingredients, such as coating formulations, or excipients that are chemically modified, the chemical composition and the quantity of each component must be specified.

2.2.7 Any overages for the API must be stated separately and the justification for them must be given. The label claim quantity must be stated and the excess quantity indicated as the actual quantity or as a percentage. For example, 500 mg + 5 mg (=1%) overage*

*Use the asterisk to indicate the justification for the overage.

2.2.8 Where a potency adjustment for the API has to be made, a statement to the effect that the actual quantity of the active will depend on the potency, and the excipient(s) that will be used to adjust the bulk quantity must be identified, as well as the manner in which the

adjustment will be made. Potency calculations and formulae, where applicable, must be included and must also be shown in PART 2E **(Manufacturing Procedures)**.

2.2.9 Permitted flavouring and colouring agents (that comply with the **The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972**), because of their complexity in many instances, may be described in terms of their main constituents only, provided that appropriate chemical identification and characterisation for them is given in the relevant section. The Colour Index Numbers (Foodstuffs, cosmetics and disinfectants Act, 1972 Reg. Food Colourants) of colourants must be included in the formula. The use of dyes, printing ink, coating materials, flavourants and organic solvents is subject to the same safety and quality requirements that apply to medicinal substances.

2.2.10 The content of alcohol, if included in medicines for oral administration, must comply with the requirements of Supplementary Guideline SG 1.

2.2.11 Where the vehicle is added up to the required volume or mass of the product, the actual or estimate quantity of that vehicle may be stated. However, expressions such as "add up to" and "q.s." are acceptable. Solutions added to adjust the pH must be described in terms of composition and strength (normality, molarity, etc.), but it is not necessary to state the actual quantity added as none may be added or only minute quantities may be needed.

2.2.12 For capsules, the fill mass, as well as the capsules size, composition and mass must be indicated.

2.2.13 In the case of coated dosage forms, the theoretical mass of the core, coating material, as well as the total mass of the dosage form/unit must be indicated

2.2.14 For biological medicines the details of any solution supplied by the manufacturer for the reconstitution before use of a dried biological medicine that is offered for sale in a dried form shall be supplied

2.2.15 oxicity levels 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, etc.

2.3 PART 2 C - SPECIFICATIONS AND CONTROL PROCEDURES FOR ACTIVE AND INACTIVE INGREDIENTS

2.3.1 Specifications and the limits of all active and inactive ingredients must be listed and adherence to pharmacopoeial requirements (BP, USP and EP), where applicable, is recommended. Any deviation from such specifications and limits must be fully substantiated. Use of any other pharmacopoeia must be justified and acceptable to the Council. In the latter case, copies of the relevant monographs must be included. More than one pharmacopoeia may be used for the active or inactive ingredients provided that each individual reference is used fully and not partially or selectively. For example, USP may be used for starch, and BP for lactose.

2.3.2 Any in-house specifications that are at a lower quality standard than that of an approved pharmacopoeia must be fully motivated, subject to approval by the Council.

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

2.3.3 Additional specifications for isomers, polymorphs, as well as impurities, particle size distribution, residual solvents, etc., where relevant, must be submitted for all APIs

2.3.4 Control procedures for all active and inactive ingredients must be fully described. When pharmacopoeial methods are used, copies of those procedures must be submitted.

2.3.5 Specification limits and the control procedures for particle size of APIs which have a solubility of less than 1 part in 200 parts water, and for those which the Council may request, must be submitted. Particle size must be stated in SI units (μm). Exemption from this requirement may be granted if the API is administered as, a clear solution.

2.3.6 Colourants and flavourants must comply with either one of the following:

a) at least a specification limit and control procedure regarding chemical identification and a statement that the flavourants comply with the general requirements and that the colourants comply with the purity criteria of Act 54 of 1972 **(The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972)**.

b) at least a specification limit and control procedure regarding chemical identification and a statement that it complies with the directives of the EU or the register of the FDA.

2.3.7 The following minimum requirement must be confirmed:

a) Identification and assay of the API will be performed irrespective of the possession of a certificate of analysis from the manufacturer.

b) Identification of the inactive ingredient will be performed irrespective of the possession of a certificate of analysis from the supplier; and that

c) Any tests not included in a valid* certificate of analysis will be performed.

*valid as defined by c GMP

2.3.8 Inactive ingredients for which a conclusive identification test is not described, all those parameters which are specific to the identification of those raw materials must be listed and the tests performed irrespective of the possession of a Certificate of Analysis from the supplier.

2.3.9 Microbial limits and control procedures for all natural raw materials of organic origin, must be included.

2.3.10 Frequency of testing of water, if applicable, shall be included. Water must be tested at least once a week for microbiological contaminants, and daily or just before use for conductivity, pH and total organic carbon if applicable.

2.3.11 All raw material of bovine origin must be certified BSE/TSE free and talc, asbestos-free

2.3.12 *For biological medicines:*

a) Specifications for the primary production lot used in the manufacture of the final filling lot of a biological medicine and specifications for all raw materials for the diluent must be listed.

b) Tests of a biological source material must include tests to confirm the identification, safety and potency of the primary production or bulk lot used in the manufacture of the final filling lot.

c) Parameters and criteria of acceptance to confirm the identification, safety and potency of the product must be provided.

2.4 PART 2D - CONTAINERS AND PACKAGING MATERIALS

2.4.1 Full details of the immediate container specifications and limits, including the nature of material, dimensions and sketches where applicable, as well as those of applicators and administration sets, the closure system, wadding and any other component in direct contact with the product, where applicable, and a description of the control procedures must be supplied.

2.4.2 A brief description of the outer container, if any, must also be given. At least the nature of the material must be mentioned e.g. Outer cardboard carton.

2.4.3 The type of container described here must correspond to that described in the package insert under "Presentation" and in the stability studies.

2.4.4 If the product is packed in bulk containers, the type of material of the container must be stated

2.4.5 All pack sizes must be described in the submission.

2.5 PART 2E - MANUFACTURING PROCEDURES

2.5.1 An Inspection Flow Diagram must be included.

2.5.2 The batch manufacturing formula and the batch size(s) must be included. Where more than one batch size is indicated, the batch formula of all batch sizes must be given.

2.5.3 A copy of Batch/Master manufacturing document for a real batch must be submitted. In addition, either a comprehensive flow diagram or a description of the manufacturing procedures detailing the various stages of manufacturing must be submitted. Indicate the type and size of equipment (including sieve sizes in µm), duration of treatment, temperature, light and humidity conditions, machine settings (e.g. rotation speed or rpm) etc. The frequency of all inprocess control tests (analytical, microbiological, and physical) must be shown in the flow diagram or specified in the description.

2.5.4 A copy of the Batch/Master Packaging document or a comprehensive description of the packaging procedures, detailing the various stages of packaging and labeling must be submitted. The type of equipment used in the packaging process must be indicated. The in-process tests and control procedures carried out during the packaging process must be included.

2.5.5 A process validation protocol must be submitted and, subsequent to this, a validation report when available (see Addendum 2: Validation Protocols and Validation Reports)

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

2.6 PART 2F – FINISHED PRODUCT

2.6.1 Final product specifications and limits must be listed for in-process controls, final product controls (batch release), stability controls and the manipulated final product (if applicable).

2.6.2 The description of the final product must correlate with the description given under "Identification" in the package insert.

2.6.3 Content uniformity must be specified and a control procedure must be submitted if the quantity of the API is less than 2 mg or less than 2% mass per mass of the total mass of the dosage unit (e.g. tablet, capsule, suspensions, etc.), unless otherwise requested by Council. The active content assay need not be performed separately in the case where Uniformity of Content has already been performed for batch release purposes.

2.6.4 For quality control and batch release purposes, final product specifications for all solid oral dosage forms and suspensions shall include a requirement for dissolution of API(s) unless otherwise requested by Council.

2.6.5 Disintegration time, where relevant, for example for chew tablets, matrix tablets and soft gelatin capsules will be determined as a lot release requirement on all batches on which dissolution is not determined as a criterion for lot release as well as for stability. Disintegration time can be used as a lot release requirement for preparations containing multivitamins and minerals, unless a dissolution requirement for a specific product is included in the USP, in which case dissolution must be done as a lot release requirement.

2.6.6 See Appendix 2 of Stability guideline (Addendum 4, for minimum suggested specifications required for each dosage form.

2.6.7 For imported products, at least the identification and assay of the API content must be performed by an approved laboratory (FPRC) after importation. This is intended to verify that the product has not been affected adversely during the transfer process. Exemption from this requirement may be applied for according to the Guide on Post-importation Identification and Testing of Medicines (See Addendum 3).

2.6.8 The final non-analytical release criteria must include the verification of the appearance of the dosage form, the container, the package insert, the label, the batch number, the expiry date of the product, the certificate of analysis and the batch release documents (Final Product Release Responsibility or FPRR functions).

2.6.9 All control procedures other than those from a recognized pharmacopoeia must be described in full. Copies of pharmacopoeial procedures, when referenced, must also be submitted.

2.6.10 A complete analysis report or certificate of analysis for one batch (pilot or production not older than 2 years) of the finished product must be submitted with the application.

2.6.11 The full validation data of the assay method of the API related to batch release must be submitted. Chromatograms confirming the separation of the active from the degradation products, if relevant, must be included (See Addendum 4: Stability studies).

It must be demonstrated that the assay method is stability indicating, i.e. it must distinguish between the APIs and the degradation products.

If the assay method used to determine the API content is not stability indicating, then it cannot be used for assaying after importation.

If the assay method (chromatographic) is taken from one of the latest recognized pharmacopoeias, then other partial validation data, e.g. system suitability and specificity must be submitted.

If different assay method/s are used for stability testing, then a full description of the method and the validation thereof must be submitted.

Supportive Chromatograms for the validation must be submitted.

2.6.12 All other quantitative assay methods (for preservatives, degradation products, antioxidants, dissolution assay, etc) must be validated and the validation data included.

2.6.13 For a product from a non-biological origin which has endotoxin levels, the validation data as required by the USP / BP/ EP must be submitted.

2.6.14 If the endotoxin levels are not determined according to the method in a recognised pharmacopoeia, the validation data must be submitted for evaluation.

2.6.15 For medicines imported into the country see Addendum 3.

2.7 PART 2G – STABILITY DATA: FINISHED PRODUCT

2.7.1 All applications for registration of a medicine must be submitted with stability data in accordance with the minimum requirements stated in Addendum 4: Stability studies.

2.7.2 The stability program must be described in detail and must include the following information:

(a) Conditions (temperature, humidity)

(b) Time points for testing e.g. 3 months, 6 months etc.

(c) Specifications to be determined

(d) How often the stability testing will be performed on future batches (should be in accordance with cGMP guidelines.)

2.7.3 Stability data must be presented in a tabulated format and must include the following:

i. Batch No. (Confirm that the formula is the same as the one applied for)

ii. Date of manufacture.

iii. Date of commencement of stability study

iv. Name of manufacturer.

v. Source of API (manufacturer not the supplier).

vi. Indicate whether production/pilot/experimental batch.

Vii. Container (Confirm that the container is the same as the one applied for).

viii. Storage conditions (must be controlled according to guidelines).

ix. Specifications and limits.

x. Stability results.

xi. Discussion and conclusion of shelf life for each type of container must be provided.

2.8 PART 2H - PHARMACEUTICAL DEVELOPMENT

2.8.1 Any change or differences in the formulation during the development history must be indicated clearly.

2.8.2 A separate Pharmaceutical Expert Report (of not be more than 25 pages of A4 paper) must be submitted with each application and must include at least the following:

a) **Active Pharmaceutical Ingredient(s):**

- Comment on the synthesis of the API(s);
- Discuss all physico-chemical properties, e.g. solubility, water content, particle size, crystal properties, polymorphs, chirality, stability etc. Reference may be made to the APIF.

b) **Formulation:**

- Motivate and explain the function of the inactive ingredients;
- Indicate the safety/toxicity profile of the inactive ingredients;
- State any interactions likely to occur or that may occur under given circumstances;
- Motivate/explain all overages;
- Discuss relevant physico-chemical parameters separately, e.g., dissolution and choice of medium, pH. etc.
- Include pre-formulation studies and motivate.
- Novel formulations and excipients must be discussed /explained.

c) **Production/Manufacture:**

- Describe how the manufacturing method was derived;
- Describe how in-process controls and validation plans were developed.

d) **Stability:**

- Discuss the stability of the final product formulation and the parameters used during stability and to confirm quality for lot release;
- Discuss the containers used during stability studies;
- Discuss dissolution;
- Conclusion on stability and shelf-life allocation.

e) **Conclusion in Expert Report**

f) **Name, signature, date of signature and CV of responsible person.**

a) A reference list used in the compilation of the report.

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

2.9 PART 2I – EXPERTISE AND PREMISES USED FOR BIOLOGICAL MEDICINES - DETAILS RELATING TO THE PREMISES ON WHICH PRIMARY PRODUCTION OF BIOLOGICAL MEDICINES IS UNDERTAKEN AND TO THE STAFF INVOLVED IN THE PRODUCTION AND TESTING OF THE PRODUCT

2.9.1 A description of the premises where preparation of the primary production or bulk batch are carried out, names, qualifications, field and experience of the persons involved in preparation of the primary production and the final lot and details of the facility where the imported final filling lot is stored must be recorded.

2.9.2 A floor plan of the premises must be included.

2.9.3 If the premises are used for other purposes such details must be supplied.

2.9.4 Conditions under which the product is stored must be described.

3. PART 3 - BIOEQUIVALENCE STUDIES AS PROOF OF EFFICACY

3.1 Where clinical evidence in support of efficacy has not been submitted, studies and data to demonstrate the pharmaceutical and/or biological availability of the product must be included.

3.2 The applicant may request partial or total exemption from these requirements if efficacy and safety are intended to be established by means of clinical data (or for other reasons determined by the Council): Provided that clinical trials have been conducted with the same formulation as the one being applied for.

3.3 For details on requirements for bioequivalence refer to Addendum 5: Bioequivalence Studies as Proof of Efficacy as well as Addendum 6: Dissolution Studies.

3.4 The following must be included:

a) The purpose of the study must be stated.

b) Full details of the reference products used as the standard for reference purposes (including the applicant, proprietary name, lot number, expiry date, etc.) must be supplied. The reference products used must be motivated and will be subject to approval by the Council.

c) Details of the method used must be given.

d) Full data must be submitted. (including all individual patient data)

e) A discussion and the conclusion drawn from the data must be submitted

f) If pharmaceutical availability or equivalence data is submitted, the studies must be carried out according to the guidelines determined by the Council, and the data must be submitted in the format determined by the Council.

g) The applicant must state whether there are any *in vivo-in vitro* correlation from the data obtained by the method used.

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

h) The applicant must confirm that the data submitted have been obtained with the formulation being applied for.

i) Bioequivalence studies must be carried out for all antibiotics and bioavailability for antimicrobial preparations (such as for tuberculosis) unless otherwise determined by the Council.

j) The applicant must motivate and justify why the study and the results obtained should be acceptable.

k) When bio-equivalence studies are submitted in support of efficacy of the formulation. the Application control document for bioequivalence studies included under FORMS must accompany the data.

REFERENCES

1. **ICH Guidelines (Q1A, Q1B and Q1F)**

2. **WHO Guidelins on biologicals**

3. **Stability Data Package for Registration in Climatic Zones III and IV (Q1F)**

4. **Photostability Testing (Q1B)**

LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
APIF	Active Pharmaceutical Ingredient File
BSE	Bovine Spongiform Encephalitis
BP	British Pharmacopoeia
CGMP	Current Good Manufacturing Practices
CoA	Certificate of Analysis
CV	Curriculum Vitae
DMF	Drug Master File
EP	European Pharmacopoeia
EU	European Union
FDA	Food and Drug Administration (USA)
FPRC	Final Product Release Control
FPRR	Final Product Release Responsibility
GMP	Good Manufacturing Practices
INN	International Nonproprietary Name
MCC	Medicines Control Council
NCE	New Chemical Entity
NTI	Narrow Therapeutic Index
TSE	Transmissable Spongiform Envcephalopathy
USP	United States Pharmacopoeia
USP DI	United Stated Pharmacopoeia Drug Index
WHO	World Health Organisation

TERMINOLOGY

Active pharmaceutical ingredient
A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient

Finished product
A product that has undergone all stages of production, including packaging in its final container and labelling

Inactive ingredient
A substance or compound that is used in the manufacture of a pharmaceutical product and does not contribute to the therapeutic effect of the product, but is intended to enhance the consistency, appearance, integrity, stability, release characteristics, or other features of the product.

Manufacture (manufacturing)
All operations of purchase of materials and products, production, quality control, release, storage, shipment of finished product and related controls

Medicine
As defined in section 1 of the Medicines and Related Substances Act 1965, (Act No. 101 of 1965)

Medicinal product
See pharmaceutical product

Pharmaceutical product
Any preparation for human or veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient

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Government Gazette

REPUBLIC OF SOUTH AFRICA

Regulation Gazette No. 7659

Vol. 455 Pretoria 2 May 2003 **No. 24785**

PART 2 OF 2

AIDS HELPLINE: 0800-0123-22 Prevention is the cure

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

GUIDELINES FOR REGISTRATION OF MEDICINES IN SOUTH AFRICA

GENERAL INFORMATION

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

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

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

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

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GENERAL INFORMATION

MEDICINES CONTROL COUNCIL

GUIDELINES FOR THE REGISTRATION OF MEDICINES

NOTE: These guidelines outline the format and data requirements for preparation and submission of an application for registration of medicines, and should be read in conjunction with the Medicines and Related Substances Control Act (Act 101 of 1965, and the Regulations to this Act.

1. INTRODUCTION

The registration of medicines in South Africa is governed by the provisions and requirements of the Medicines and Related Substances Control Act No. 101 of 1965, and the Regulations and Guidelines published in terms thereof. The relevant sections of the Act and Regulations that apply to these guidelines are: Regulation 2, Regulation 5, Regulations 8, 9, and 10, Regulation 22, Regulation 24 and Regulation 25.

These Guidelines describe the information required with the application form for registration of "medicines" and for application to amend a registered medicine. The information submitted will be evaluated in terms of the Act.

The aim of these Guidelines is to assist applicants in the preparation of documentation of applications for the registration of medicines for animal and human use, namely a new medicine (for a new chemical entity [NCE]), a multi-source (generic) product, a product line extension, or a biological medicine.

It is a legal requirement that data submitted for evaluation must satisfactorily substantiate claims for cure and must meet technical requirements of **quality, safety** and **efficacy** of the medicinal product for the purposes for which it is intended. The Guidelines are meant to guide the applicant in meeting the requirements of the Act. It is acknowledged that in some instances scientific developments may dictate alternative approaches. Hence, where the applicant chooses to deviate from a guideline, a motivation for such deviation must be submitted, the decision must be fully explained, motivated and justified in the expert reports submitted with the application.

Whenever there is doubt, applicants are advised to consult the Medicines Control Council (MCC) for confirmation and/or clarification before completing and submitting the application form. Applicants must always refer to the **current** version of the relevant **Guidelines for the Registration of Medicines in South Africa** and the Addendums thereto before completing the application form.

Guidelines are dynamic and constantly evolving as a result of scientific developments and harmonisation of the requirements with regional and international regulatory authorities. The MCC endeavours to regularly update the guidelines to reflect current thinking and keep its technical requirements and evaluation policies in line with "best international medicines regulatory practice".

2. GENERAL

2.1 SCOPE OF THESE GUIDELINES

The MCC requires that an application be submitted for registration of medicines for purposes of sale and marketing in South Africa.

These guidelines are relevant only to human and veterinary medicines. Separate guidelines that apply to the registration of complementary medicines and medical devices should be referred to and are obtainable from the office of the registrar.

2.2 ELIGIBILITY

Eligibility to apply for registration of a medicine is governed by Regulation 22 of the Act.

An application may be made by any person residing and doing business in South Africa, by a closed corporation incorporated in South Africa, or by a company with at least a responsible delegated person residing in South Africa.
An Applicant Master File must have been submitted previously to MCC and a satisfactory Applicant Inspection performed If the applicant is not a registered pharmacist or registered veterinarian, the application must be co-signed by a Responsible Pharmacist as defined in the Pharmacy Act (Pharmacy Act No. 53 0f 1974 as amended, Section 1) or a registered veterinarian who may sign applications for registration of veterinary products, or the applicant must be a person with appropriate knowledge of all aspects of the medicine and who shall be responsible for communication with Council.

2.3 CONFIDENTIALITY

The confidentiality of information submitted to the Medicines Control Council is provided for by the Act (Act No. 101 of 1965, Section 34). A member of the MCC, a Committee member or a staff member may **NOT** disclose to any person any information in relation to the acquisition, supply, marketing, importation, export, development, manufacture or research in connection with any medicine, veterinary medicine or any other matter related thereto, except for the purpose of exercising his/her powers or for the performance of his/her functions under the Act or when required to do so by any competent court or under any law, or with the written authority of the Director-General. Certain conditions may apply regarding the Access to Information Act, and an officer designated as the Chief Information Officer shall be responsible for disclosure of such information.

The MCC may insist on written confirmation of the identification and affiliation of an individual inquiring telephonically or in person about a medicine. No information shall be disclosed telephonically.

2.4 LANGUAGE

In terms of Regulation 22 of the Act, all applications and supporting data submitted to the Medicines Control Council must be presented in English. Any documents in languages other than English must be accompanied by an English translation (see regulations).

2.5 WHERE TO SEND APPLICATIONS

Applications should be posted or delivered to the Directorate: Operations and Administration in Room 204, Hallmark Building, 237 Proes Street, Pretoria, where they will be logged and acknowledged. All correspondence should be addressed to the Registrar of Medicines.
The MCC will not take responsibility for documents posted or delivered to any place or in any manner other than as described.

2.6 WHEN IS A PRODUCT REGISTERABLE?

A product is liable for registration with the Medicines Control Council if:

a. Any of the ingredients of a product is listed in one of the Schedules to the Act

b. The product is a medicine by virtue of the definition of a medicine in the Act. The Medicines and Related Substances Control Act, 1965 (Act 101 of 1965) defines a medicine as:

> "any substance or mixture of substances used or purported to be suitable for use or manufactured or sold for use in:
>
> (1) the diagnosis, treatment, mitigation or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or
> (2) restoring, correcting or modifying any somatic or psychic function in man; and includes any veterinary medicine.

c. If the product falls under any of the pharmacological classifications as specified in Regulation 25 of the Act.

d. In addition, the intended use of a product and the text/words use in promoting the product, even if no claims are reflected on the label, may still render a product registerable. If a substance is not ordinarily eaten or drunk by man, it cannot be considered a foodstuff only because there are no apparent claims. Legislation requires that every medicine shall be registered by the Council before it may be sold or marketed. Where a medicine has been called up as a complementary medicine, the relevant provisions and guidelines shall apply.

e. If it is a complementary medicine.

2.7 TYPES OF APPLICATIONS

Medicines for human and animal use are divided into the following types for purposes of ease for evaluation and determination of fees:

2.7.1 New chemical entities (NCEs)

2.7.2 Multi-source/generic applications (including line extensions) where clinical information is presented to support:

- efficacy and safety of the formulation

- safety and efficacy of a new indication

2.7.3 Multi-source/generic (including line extensions) applications with:

- dissolution studies as evidence in support of comparative efficacy
- bioavailability studies as evidence in support of comparative efficacy
- other availability data as evidence in support of comparative efficacy

2.7.4 Other multi-source/generic (including line extensions) applications e.g. liquids/solutions not mentioned under 2.7.3 above.

2.7.5 Biological medicines

2.8 FEES

For medicine registration the following fees are relevant:

i) A non-refundable pre-screening fee, accompanying the screening submission
ii) An application fee, accompanying the application for registration;
iii) A registration fee, payable when the application complies to all requirements for registration, and is payable before a registration certificate is issued;
iv) An annual retention fee to maintain registration.
v) A fee to cover any amendments to the dossier or certificate.
vi) A fee to cover any inspection of any manufacturing site.

The fees are determined according to the type of application and will be published in the Government Gazette.

2.9 GUIDELINES ON SAME OR SEPARATE APPLICATIONS FOR THE PURPOSE OF REGISTRATION (For easy reference see table below):

2.9.1 Tablets/Capsules/Suppositories/Lozenges

i) An application with different pack-sizes of the same strength and formulation will be considered as the same application
ii) Applications with different strengths and/or formulations will be considered as separate applications.
iii) Uncoated and coated tablets of the same strength and formulation will be considered as separate applications.

2.9.2 Syrups/Liquids/Solutions (excluding parenterals)/Creams/Ointments

i) Applications with different container sizes of the same strength and formulation will be considered as the same application.
ii) Applications with the same container size of different strengths and/or formulations will be considered as separate applications.

2.9.3 Ampoules, Vials and Large Volume Parenterals

i) Applications with ampoules containing identical solutions of the same strength but of different volumes will be considered as separate applications;

ii) Applications with ampoules containing solutions of different strengths will be considered as separate applications;

iii) Applications with ampoules and/or single dose vials containing dry powder, crystals etc, of different mass will be considered as separate applications;

iv) Applications with ampoules and single dose vials containing the same respective masses of dry powder, crystals etc, will be considered as separate applications;

v) Applications with ampoules, single dose vials, as well as disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid will be considered as the same application

vi) Applications with dental cartridges containing fluids of different volumes will be considered as the same application;

vii) Applications with ampoules containing "water for injection", but of different volume will be considered as the same application;

viii) Special ampoules of dry powder and "water for injections contained in the same unit, but intended for mixing at the time of injection, may be considered as the same application provided that the "water for injections" is fully described in the dossier;

ix) Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, may be considered as the same application, depending on the relevant information being submitted;

x) Multi-dose vials of the same strength and formulation in different volumes may be considered as the same application, depending on the relevant information submitted (administered according to the same dosage schedule);

xi) Multi-dose vials and a single dose ampoule of the same formulation will be considered as the same application provided that the single-dose ampoule corresponds to the dose indicated for the multi-dose vial;

xii) Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted may be considered as the same application;

xiii) A container of diluent to be used with any preparation in (iii), (iv) or (xii) including a biological medicine will be considered as a the same application provided that the diluent is also fully described in the dossier together with the medicinal product;

xiv) Infusion solutions of the same or different volumes and of the same formulation which are packed in containers of exactly the same type of material, may be treated as the same application, depending on the relevant information submitted;

xv) Infusion solutions of the same or different volumes and of the same formulation which are packed in containers made of different types of materials shall be considered as separate applications;

xvi) Should a preparation, packed in plastic containers, be intended to be marketed in glass containers containing the same volume and the same formulation, it may be considered as the same application provided the following data are submitted: -

a) characteristics of the rubber stopper;

b) specifications for the glass;

c) a comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used;

d) data on particulate matter (contamination);

e) stability data with reference to the effect of the pH of the solution.

xvii) Products with the same strength and formulation but with different colours and/or flavours will be considered as separate applications;

xiii) Applications containing the same active pharmaceutical ingredient(s), and where additional indications are sought, where such new indications render the product in a different scheduling status, or different pharmacological classification or have any other restrictions imposed other than the original application, will require a separate registration.

2.9.4 Different applicants/proprietary names for same formula

Same formulation applied for under different proprietary names or by different applicants will be considered separate applications.

GENERAL INFORMATION

TABLE FOR SAME/SEPARATE APPLICATIONS

Type of applications	Same application	Separate applications required
Each individual dosage form of a particular medicine		X
Deviations or variances of the active ingredient of a product		X
Tablets/Capsules/Suppositories/Lozenges		
1. Different pack-sizes of exactly the same strength and formulation	X	
2. Different strengths and formulations		X
3. Uncoated and coated tablets of the same strength and formulation		X
Syrups/Liquids/Solutions (excluding parenterals) /Creams/Ointments		
1. Different container sizes of the same strength and formulation	X	
2. The same container size of different strengths and formulations		X
Ampoules, Vials and Large Volume Parenterals		
1. Ampoules containing identical solutions of the same strength (provided the dose remains constant) but of different volumes		X
2. Ampoules containing solutions of different strengths		X
3. Ampoules, single dose vials containing masses of dry powder, crystals etc. of different mass		X
4. Ampoules, single dose vials containing the same respective masses of dry powder, crystals etc.	X	
5. Ampoules, single dose vials, as well as pre-filled disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid	X	
6. Dental cartridges containing fluids of the same strength (provided the dose remains constant) but different volumes	X	
7. Ampoules containing "water for injection", but of different volumes	X	
8. Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection	X	
9. Ampoules containing identical solutions of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, pending relevant information	X	
10. Multi-dose vials of the same strength and formulation in different volumes, same dosage schedule	X	
11. Multi-dose vials and a single dose ampoule of the same formulation if the single-dose ampoule corresponds to the dose indicated for the multi-dose vial;	X	
12. Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted	X	
13. A container of diluent packed together with any preparation described in 3., 4. and 12. including biological medicines	X	
14. Infusion solutions of the same or different volumes and of the same formulation which are packed in containers of exactly the same type of material depending on the relevant information submitted	X	
15. Infusion solutions of the same or different volumes and of the same formulation which are packed in containers made of different types of materials		X
16. A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation provided the following data are submitted: - - characteristics of the rubber stopper; - specifications for the glass; - a comprehensive manufacturing process with particular reference to the washing and sterilizing cycles and apparatus used; - data on particulate matter (contamination); - stability data with reference to the effect of the pH of the solution.	X	
Products with the same strength and formulation but with different colours and/or		

Type of applications	Same application	Separate application s required
flavours		X
Applications containing the same active pharmaceutical ingredient(s), and **where additional indications** are sought, where such new indications render the product in a **different scheduling status**, or **different pharmacological classification** or **WITH AN ADDITIONAL PROPRIETARY NAME** or have **any other restrictions** imposed other than the original application		X
Different applicants/proprietary names for same formula Same formulation applied for under different proprietary names or by different applicants.		X

2.10 TRANSITIONAL CONVERSION TABLE

The MBR1form for application for registration prescribed by Act 101 of 1965 is replaced by the Medicines Registration Form (MRF 1). There will no longer be a separate form for biological medicines.

Circulars issued before and during the transformation process made reference to the Annexures of the previous MBR1 application form. These Guidelines will be continuously updated to reflect policies developed by the Council.

For ease of reference the following conversion table is included.

MBR1 FORM	MRF 1	SUBJECT
Cover page	Cover page	Administrative Data
Annexure 1	Part A, B, C	PI / PIL / Label
Annexure 2	Part 2B i	Formulation
	Part 2B ii	Formulation for reconstitution liquid for final filling lot*
Annexure 3	Part 2A i	Active Pharmaceutical Ingredient
	Part 2A ii	Primary production lot*
Annexure 4	Part 2C	Raw materials (specifications)
Annexure 5	Part 2C	Raw materials (control procedures)
Annexure 6	Part 2C	Raw materials (release laboratories)
Annexure 7	Part 2F	Finished product
Annexure 8	Part 2D	Container and packaging material
Annexure 9A	Part 2F	Finished product (release criteria and labs)
Annexure 9B	Part 2D	Container and packaging material (release criteria and laboratories)
Annexure 10	Part 2G	Stability program and data
Annexure 11	Part 2E	Manufacturing procedures
Annexure 12	Part 1D	Foreign registration
Annexure 13	Part 3	*In vivo and/or in vitro* equivalence studies as proof of efficacy
Annexure 14	Part 4	Pre-clinical studies
Annexure 15	Part 5	Clinical studies
Annexure 16	Part 2H	Pharmaceutical development
Annexure 1 of Old Biological Form	Part 2I	Expertise and premises used for manufacturing of biological medicines*