

MEDICINES CONTROL COUNCIL



GENERAL INFORMATION

This guideline is intended to provide recommendations to applicants wishing to submit applications for the 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 any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

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

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**REGISTRAR OF MEDICINES
MS M HELA**

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GUIDELINES FOR THE REGISTRATION OF MEDICINES

GENERAL INFORMATION

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 Act, 1965 (Act 101 of 1965), and the Regulations to this Act.

1 INTRODUCTION

The registration of medicine in South Africa is governed by the provisions and requirements of the Medicines and Related Substances Control Act No. 101 of 1965, (hereafter 'the Act') and the Regulations and Guidelines published in terms thereof.

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

The aim of these Guidelines is to assist applicants in the preparation of documentation for the registration of medicines for human use. The types of medicine include a new medicine for a new chemical entity (NCE), a multisource (generic) product, a product line extension, and a biological medicine.

It is a legal requirement that data submitted for evaluation should substantiate all claims and should meet technical requirements of **quality, safety** and **efficacy** of the 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, however, that in some instances scientific developments may dictate alternative approaches. When a deviation from a guideline is decided on, a detailed motivation giving the reason(s) for the deviation and justification for the alternative approach should be included in the expert report 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; refer to the website for contact details. Applicants should always refer to the **current** version of the relevant **Guidelines for the Registration of Medicines** and the Addenda thereto before completing the application form.

Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of regional and international regulatory authorities. The MCC (Council) 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

Legislation requires that the Council shall register every medicine before it may be sold/marketed.

An application for the registration of a medicine should therefore be submitted for evaluation and approval.

These guidelines are relevant only to human medicines including biological and complementary medicines. Separate guidelines apply to the registration of veterinary medicines and medical devices.

2.2 APPLICANT/PROPOSED HOLDER OF THE CERTIFICATE OF REGISTRATION (PHCR)

2.2.1 Eligibility to apply for registration of a medicine is governed by Regulation 22 of the Act. An application may be made by any of the following:

- a) a person, body corporate/juristic person, company, residing and doing business in South Africa;
- b) a close corporation incorporated in South Africa; or
- c) a company in South Africa with at least
 - a responsible delegated person residing in South Africa and
 - an authorised person residing in South Africa who must be a person with appropriate knowledge of all aspects of the medicine and who shall be responsible for communication with Council.

2.2.2 If the applicant is not a registered pharmacist or pharmacy the application should be co-signed by a registered pharmacist, as defined in the Pharmacy Act (Pharmacy Act 53 of 1974 as amended). This may be the Responsible Pharmacist or another registered pharmacist responsible for regulatory affairs and with appropriate knowledge of all aspects of the medicine. This person should be in the full-time employ of the company. Proof of registration (copy of certificate) of the pharmacist who signed the dossier, and the Responsible Pharmacist, in terms of Act 53 must be included.

2.2.3 An Applicant/PHCR should submit a Site Master File (SMF) in accordance with the SMF guideline. For subsequent applications reference to the allocated SMF number will suffice.

2.3 CONFIDENTIALITY/SECREC Y

The confidentiality of information submitted to the MCC is governed by Section 34 of the Act. The MCC, committee members or staff of the Medicines Regulatory Affairs (MRA), may NOT

- disclose to any person, any information acquired in the exercise of powers or performance of functions under the Act and relating to the business affairs of any person, 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, or
- use such information for self-gain or for the benefit of his employer.

The MCC may insist on written confirmation of the identity and affiliation of an individual inquiring telephonically, or in person, about a medicine. No information shall be disclosed telephonically unless the Medicines Control Officer knows the enquirer is entitled to receive the information.

2.4 LANGUAGE

In terms of Regulation 22(4) of the Act, all applications and supporting data submitted to the MCC should be presented in English (British). Original documents not in English should be accompanied by an English translation.

2.5 WHERE TO SUBMIT APPLICATIONS

Applications should be posted to Private Bag X 828, Pretoria, 0001 or preferably be delivered by the applicant, rather than a courier, to Room 214, Hallmark Building, 237 Proes Street, Pretoria, where they will be logged and acknowledged. All correspondence should be addressed to the Registrar of Medicines and should be clearly coded as indicated in section 13 of this guideline.

The MCC will not take responsibility for documents posted or delivered to any other place or in any other manner.

2.6 WHEN A PRODUCT SHOULD BE REGISTERED

A product is liable for registration with the Medicines Control Council if any of the following apply.

- i) Any of the ingredients of a product is listed in one of the Schedules to the Act;
- ii) The product is a medicine by virtue of the definition of a medicine in the Act.

The Act 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;

- (a) the diagnosis, treatment, mitigation 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 function in man;
- and includes any veterinary medicine."

- iii) If the product falls under any of the pharmacological classifications as specified in Regulation 25 of the Act.
- iv) The intended use of a product and the text/words used in promoting the product, even if no claims are reflected on the label, render the product registerable. A substance not ordinarily eaten or drunk by man cannot be considered a foodstuff just because no apparent medicinal claims are made for it.

The relevant provisions and guidelines shall apply to a medicine called up as a complementary medicine.

2.7 TYPES OF APPLICATIONS

Medicine applications for registration for humans are divided into the following types for the determination of fees and allocation to reviewers for evaluation:

- 2.7.1 New chemical entity applications that include **pre-clinical** and **clinical** information in support of the efficacy and safety of the formulation/dosage form, indication/s and dosage regimen.
- 2.7.2 Multisource/generic applications and innovator product line extension applications that include clinical information in support of efficacy and safety of the formulation/dosage form, or indication/s or dosage regimen.
- 2.7.3 Multisource/generic applications and innovator line extension applications that include comparative bio-availability/bioequivalence studies as proof of efficacy.
- 2.7.4 Multisource/generic applications and innovator line extension applications
 - that include comparative dissolution studies as proof of efficacy
 - that include any other comparative studies as proof of efficacy
 - others, not mentioned above e.g. liquids/solutions.
- 2.7.5 Biological medicines: Biopharmaceuticals and Biosimilars

Biological medicine: A medicine where the active ingredient and/or key excipients have been derived from living organisms or tissues, or manufactured using a biological process. Biological medicines can be defined largely by reference to their method of manufacture (the biological process). These include *inter alia* medicines prepared from the following substrates:

- (i) Microbial cultures (fermentation);
- (ii) Plant or Animal Cell cultures (including those resulting from recombinant DNA or hybridoma techniques);
- (iii) Extraction from biological tissues; and
- (iv) Propagation of live agents in embryos or animals.

2.7.5 Types of applications - Biological medicines continued

The living substrate may be genetically modified in a number of ways to provide the required active ingredient, including recombinant DNA technology or hybridoma techniques.

Biological Medicines include, but may not be limited to the following:

- (i) Plasma-derived products, e.g. Clotting factors, Immunosera, etc;
- (ii) Vaccines;
- (iii) Biotechnology-derived medicinal products (rDNA products) e.g. rHu-antihemophilic factors, Hormones, Cytokines, Enzymes, Monoclonal antibodies, erythropoietins;
- (iv) Human Gene therapy.

It has been the practice, in South Africa, that Council will decide that certain well-characterised low-molecular weight medicinal biological compounds, such as antibiotics, insulin etc be excluded from biological medicine status, and they are therefore not reviewed by the Biological Medicines Committee.

Biopharmaceutical: Patented biological medicine.

Biosimilar: A biological medicinal product referring to an existing biological medicinal product for which registration has been applied for.

2.8 EVALUATION PROCEDURES

Routine	
Expedited	refer point 6
AMRP	refer point 7

2.9 FEES

The following non-refundable fees are relevant:

- 2.9.1 A non-refundable screening fee payable with the screening submission.
- 2.9.2 An application fee payable with the full submission of the application for registration.
- 2.9.3 A registration fee, payable when the application complies with all the requirements for registration, and which is payable before a registration certificate is issued.
- 2.9.4 An annual retention fee to maintain registration.
- 2.9.5 A fee to cover any amendments to the dossier or certificate.
- 2.9.6 A fee to cover any inspection of any manufacturing site.
- 2.9.7 A fee to cover authorization of the use of an unregistered medicine.
- 2.9.8 The fees are published in the Government Gazette and are also available on the website.
- 2.9.9 Methods of payment: By cheque or electronic payment / direct transfer.
Also refer to the Bank Detail guideline for electronic payment / direct transfer.
Cheques should be made out to "Medicines Control Council". Only bank guaranteed cheques will be accepted and are to be submitted in a separate envelope attached to a **copy** of the covering letter of the relevant submission(s).
Direct electronic payment should include a clear reference, e.g. the product application number or purpose of the payment. Proof of electronic payment / direct transfer must be submitted in a separate envelope attached to a **copy** of the covering letter of the relevant submission(s).
Refer to 4.7 below for payment submitted with new applications.
- 2.9.10 To ensure evaluation of the relevant submission(s) (2.9.3 to 2.9.7 above) a **copy** of proof of payment / cheque must also be attached to the *original* covering letter of the relevant submission.

2.10 SAME OR SEPARATE APPLICATIONS

For the purpose of registration the following products will be regarded as either being the same product or separate product applications:

TYPE OF APPLICATIONS	Application	
	Same	Separate
2.10.1 Each individual dosage form of a particular medicine		X
2.10.2 Variations of the active pharmaceutical ingredient (API) of a product		X
2.10.3 Tablets/Capsules/Suppositories/Lozenges		
a) Different pack-sizes of exactly the same strength and formulation.	X	
b) Different strengths and formulations.		X
c) Uncoated and coated tablets of the same strength and formulation.		X
2.10.4 Syrups/Liquids/Solutions(excluding parenterals) /Creams/Ointments		
a) Different container sizes of the same strength and formulation.	X	
b) The same container size of different strengths and formulations.		X
2.10.5 Ampoules and Vials and Large Volume Parenterals		
a) Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e. resulting in different total doses).		X
b) Ampoules containing solutions of different strengths.		X
c) Ampoules and single dose vials containing e.g. dry powder, crystals of different mass.		X
d) Ampoules and single dose vials containing the same respective masses of e.g. dry powder, crystals.	X	
e) 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	
f) Dental cartridges containing different volumes of fluids of the same strength (provided the dose remains constant).	X	
g) Ampoules containing "water for injection", but of different volumes.	X	
h) Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection if water for injections is fully described in dossier.	X	
i) Ampoules containing identical solutions of different volumes used only as diluent in the reconstitution of a preparation for parenteral use.	X	
j) Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	X	
k) Multidose vials and a single dose ampoule of the same formulation if the single-dose ampoule corresponds to the dose indicated for the multidose vial.	X	
l) Multidose vials containing dry powder of different mass of the same formulation, and the same concentration when reconstituted.	X	
m) An ampoule of diluent packed together with any preparation including biological medicines if diluent is fully described in dossier.	X	

2.10.5 Ampoules and Vials and Large Volume Parenterals - continued	Same	Separate
n) Infusion solutions of the 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	
o) Infusion solutions of the same formulation and of the same or different volume which are packed in containers made of different types of materials.	X	
p) A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.	X	
q) Products with the same strength and formulation but with different colours and/or flavours.		X
r) Applications containing the same API(s) applying for additional indications which render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		X
s) Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		X
2.10.6 Same formulation with different proprietary names whether of the same or different applicants		X

2.11 TRANSITIONAL CONVERSION TABLE

The Medicines Registration Form (MRF1) replaces the MBR1 form for the application for registration of a medicine prescribed by the Act. Biological medicines no longer have a separate form.

Circulars issued before and during the transformation process made reference to the Annexures of the previous MBR1 application forms. For ease of reference the following conversion table is included.

MBR1	Biol*	MRF1	SUBJECT
Annexures		PART	<i>* biological</i>
Front page		1A	Administrative Data
1	15	1C	PI / PIL / Label
2	6	3B	Formulation / final filling lot formulation*
2	10	3B	Formulation diluent if applicable/ final filling lot reconstituting liquid/diluent*
3	-	3A	Active Pharmaceutical Ingredient (API)
-	4	3Aa)	Primary lot preparation and production and control tests*
-	2	3Ab)	Primary lot pharmaceutical ingredient specifications*
-	3	3Ac)	Primary lot pharmaceutical ingredient control procedures and laboratories*
4	-	3C	API and inactive pharmaceutical ingredient (IPI) specifications
5	5	3C	Pharm ingredient control procedures / primary lot control tests and laboratory*
6	3/5	3C	Pharmaceutical ingredient release laboratories
7	-	3F	Final product specifications and control
-	8	3F	Final filling lot and diluent analytical and other control tests*

MBR1	Biol*	MRF1	SUBJECT
Annexures	PART		* <i>biological</i>
8	9	3D	Containers and packaging materials / immediate container and laboratory*
9A	-	3F	Finished product (release criteria and laboratories)
9B	-	3D	Container and packaging material (release criteria and laboratories)
-	10	3F	Diluent / reconstituting fluid specifications, tests*
10	11	3G	Stability programme and data (also diluent if applicable)
11	7/10	3E	Manufacturing procedure / final filling lot and diluent production*
12	14	1D	Foreign registration
13	-	2	<i>In vivo</i> and/or <i>in vitro</i> equivalence studies as proof of efficacy
14	13	4	Pre-clinical studies / Clinical evidence of safety*
15	12	5	Clinical studies / Clinical evidence of efficacy*
16	-	3H	Pharmaceutical development
-	1	3I	Expertise and premises used for manufacturing of biological medicines*

2.12 CANCELLATION OR WITHDRAWAL OF APPLICATIONS

HCRs of medicines and applicants should, before applying to the Registrar, carefully consider any decision to cancel or withdraw, as the case may be, a registration or application for registration, as Council after consideration of all issues involved has resolved the following with immediate effect.

2.12.1 Any medicine

- of which the registration has been cancelled, or any “old medicine” of which the application for registration has been withdrawn by notice in the Government Gazette, and
- for which a written application or request to the Registrar of Medicines has been submitted by the holder of a certificate of registration or by the applicant,

will under no circumstances be re-instated.

2.12.2 Should the HCR or the applicant desire to re-register such medicine, a new application for registration of a medicine must be submitted in accordance with the requirements of the Act and the relevant Regulations.

2.12.3 An application for registration of a medicine may at whatever stage of processing be withdrawn by written application to the Registrar of Medicines. The withdrawal shall under no circumstances be reversed once such an application is approved and the approval confirmed in writing. A new application for registration must be submitted should the applicant wish to proceed with registration thereafter.

3 REQUIREMENTS OF AN APPLICATION

3.1 PART 1 ADMINISTRATIVE INFORMATION

3.1.1 PART 1A Administrative Particulars

The details as per the application form should be completed.

- a) applicant/prospective holder of the certificate of registration (refer to this guideline section 2.2).

3.1.1 PART 1A Administrative Particulars continued

- b) "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.
- c) Person authorised to communicate with Council. Refer to Regulation 22(2) of the Act.
- d) Category. Refer to Regulation 25 of the Act.
- e) "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) of the Act in respect of such medicine. (Refer to section 8 of this guideline).

Medicines which are not identical in composition or strength are not regarded as the same medicine and should be submitted separately. (Refer to this guideline section 2.9).

- f) Pharmacological classification. Refer to Regulation 25 of the Act.
- g) 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 medicine registration certificate. For the purpose of the package insert, application may be made to give a more detailed description of the dosage form, e.g. chew tablet, slow release tablet.

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

- h) 'Approved name' in relation to a medicine means the internationally recognised name of such medicine, or such other name as the Council may determine, not being a brand name or trade name registered in terms of the Trade Marks Act, 1963 (Act 62 of 1963). (Defined in Section 1 of the Act.)
- i) The API and strength per dosage unit applies only in the case of a dosage form with a single API.
- j) The 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 Council.

3.1.1 PART 1A Administrative Particulars continued

- k) The country of origin, i.e. the country where the original development was done. If development took place in more than one country all the countries should be specified.
- l) The name and complete physical address including the country, of all the manufacturing and packer facilities/sites for the medicine should be given. The site performing each stage of manufacturing and packaging where these do not all occur at the same site, should be clearly indicated. The various stages of manufacturing and packing reflected should correspond with those submitted in PART 3E.
- The name and complete *physical* address including the country, of the final product testing laboratory/ies (FPRC) and final product release responsibility (FPRR) should be given. If applicable the details of both the pre- and post- importation FPRC and FPRR should be given. This information may be submitted on the next page as a separate appendix if necessary.
- m) The following are required for all the manufacturing, packaging, FPRC and FPRR sites:
- i) Site (Plant) Master File (SMF)
 - ii) - Confirmation of a Technical agreement between the parties, and
- a schedule of the limits of responsibilities accepted by each of the parties as specified in a Technical agreement or addendum to the contract should be included
 - iii) From the country of manufacture, if not South Africa:
 - A copy of manufacturing licence or a statement by the competent medicine regulatory authority that the manufacturing facility complies with GMP and
 - A copy of the Certificate of GMP compliance in terms of the WHO Certification Scheme.
 - Confirmation that the manufacturing site is inspected at regular intervals and a copy of the latest written inspection report (not older than 3 years), from a Medicine Regulatory Authority of the country of origin is available for inspection.
 - A copy of the registration or marketing authorisation certificate.
 - A Certificate of a Pharmaceutical Product in terms of the WHO certification scheme (Free Sales Certificate)
- n) FPRR should be vested in a person who has appropriate knowledge of the relevant aspects of the medicine and who is either the holder of the certificate of registration or is in the employment of the holder of such a certificate.
- o) For subsequent post registration amendments to the dossier PART 1Ac) Amendment history, of the MRF1 should be completed in accordance with the Post-registration amendment guideline.

3.1.2 PART 1B Table of contents

A comprehensive Table of Contents of the dossier including the SUB-PARTs of the different PARTs should be included.

Each heading and sub-heading of the MRF1 should be identified by a page number or tab and should be tabbed accordingly. Should the heading not apply an explanation as to why the heading does not apply should be supplied on the relevant numbered page or cover page of the relevant tab.

3.1.3 PART 1C Labelling

Refer also to the guideline "Package insert amendments concerning urgent safety restrictions: Urgent safety restriction notice (USRN)"

- a) PART 1Ca) Package inserts (Regulation 9 of the Act)
- b) Headings and particulars in a package insert (Regulation 9 of the Act)

Refer to Attachment B, to be superseded by the Package Inserts for Human Medicines Guideline on 1 August 2008.

c) PART 1Cb) Patient information leaflet (PIL) (Regulation 10 of the Act)

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

PILs should be typed in double-spaced text and should be in English (British) and at least one other official language.

The printing quality of the package insert should be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process. The spelling and grammar in the package insert text should be checked thoroughly before submission of the application.

Reference to the package insert for each statement should be included in a broad margin left on the right hand side of each page of the patient information leaflet for this purpose. The exact page/s should be stated. No references should however be included in the finalised printed PIL.

An electronic copy (Word document) on diskette or CD of the package insert should be included.

Headings and particulars in a patient information leaflet (PIL)

In addition to the requirements of Regulation 10 the following should also be included under the relevant headings.

The sub headings listed below are recommended:

Scheduling status

The scheduling status of the medicine as in the package insert.

Proprietary name and dosage form

Should be in accordance with PART 1 of the MRF1 as in the package insert.

What This Medicine Contains Regulation 10 which refers to Regulation 9 (1)(c) of the Act.

The composition of the medicine in accordance with the package insert.

What this medicine is used for

The registered indications for use of the medicine, as accepted by Council, in the package insert.

Before taking this medicine

The following information should be included:

- Contra-indications
- precautions
- warnings, e.g. warnings concerning sedative properties of the medicine; warnings concerning the risks involved with sudden withdrawal of the medicine, should be included
- interactions
- When umbrella/brand names are used, precautionary statements of the simultaneous usage of these products, so as to inform patients of their correct use, and potential safety concerns should be included. For example, if a range of products under the same umbrella name contains paracetamol, a product should not be used in conjunction with another product in the range that also contains paracetamol.

General statements to be included in this section: Regulation 10(1)(e)(v) of the Act.

“If you are taking medicines on a regular basis, concomitant use of the medicine may cause undesirable interactions. Please consult your doctor, pharmacist or other health care professional, for advice.”

c) *Headings and particulars in a PIL – continued*

“If you are pregnant or breast feeding your baby while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.”

(THESE STATEMENTS SHOULD BE BOXED AND BOLDFACED)

How to take this medicine

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

Information on what to do in specific circumstances, for example, in the case of a missed dose, an unexpected reaction or in the case of an overdose, should be included.

“Do not share medicines prescribed for you with others.” should be stated, as well as,

“In the event of overdosage, consult your doctor or pharmacist. If neither is available, rush the patient to the nearest hospital or poison control centre”.

Side effects

General statement to be included: Regulation 10(1)(g)

"Not all side-effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.

Storage and disposal information

Should contain information in accordance with MRF1 PART 3G on how to store the medicine properly, and how to dispose of unused medicine, such as by returning the medicines to the pharmacy.

The following statement should be stated:

“Keep all medicines out of the reach of children.”

Presentation

In accordance with MRF1 PART 3D as in the package insert.

Identification of the medicine

In accordance with MRF1 PART 3F as in the package insert.

Registration number/reference number

As allocated by the Registrar in accordance with Section 15 of the Act and in the package insert.

The name and the business address of the holder of the certificate

In accordance with MRF1 PART 1A as in the package insert.

The date of publication of the patient information leaflet

Date of the council resolution as in the package insert.

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

d) PART 1Cc) Label (Regulation 8)

An example or a facsimile of the label should be included. Requirements, e.g. font size, as stipulated in the Regulation 8 of the Act, should be adhered to.

The following inclusions are permitted:

“For state use only – Not for sale” – for tender items

Note: Any deviation from the requirements described in these guidelines will require approval by Council in terms of Section 18(4) or Section 36 of the Act, prior to implementation.

Sugar quantity contained in medicines for oral or parenteral administration Regulation (8)

3.1.4 PART 1D FOREIGN REGISTRATION

A list of countries, including SADC countries in which an application has been lodged, and the status thereof, should be furnished. Approvals (with indications), deferrals, withdrawals and rejections, should be stated.

The Council aligns itself with

- the following regulatory authorities: USA (FDA), UK (MHRA), Sweden (MPA,) Australia (TGA), Canada (Health Canada), European Union (EMA) and Japan (MWH).
- members of the PIC/S (Pharmaceutical Inspection Co-operation Scheme) for quality matters relating to GMP

If the medicine has already been registered in any of the countries mentioned above,

- a copy of the registration certificate and the
- approved package insert (data sheet), as well as
- the conditions of registration, should be provided.
- For rejections or withdrawals relating to safety matters the details for each case should be provided.
- It should be stated whether data packages submitted in these countries, including the proposed indications, are essentially similar to those submitted to Council.

If not registered and/or applied for registration in the country of origin the reason should be given.

3.2 PART 2 BASIS FOR REGISTRATION AND OVERVIEW OF APPLICATION

PART 2 addresses the basis for registration and makes provision for an overview of the application and consists of the following Sub-PARTs:

3.2.1 PART 2A Pharmaceutical and biological availability

Refer to the Pharmaceutical and Analytical guideline.

3.2.2 PART 2B Summary basis for registration application (SBRA)

If clinical/pre-clinical data are submitted without pre-clinical and clinical expert reports, a Summary Basis for Registration Application (SBRA), should be included in the application for registration to expedite the review process of the safety and efficacy of the medicine. (Refer to Clinical guideline)

3.2.3 PART 2C Pharmaceutical Expert Report (PER)/Quality Overall Summary (QOS)

Refer to Pharmaceutical and Analytical guideline

3.2.4 PART 2D Pre-clinical expert report

Refer to section 8 of this guideline

3.2.5 PART 2E Clinical expert report

Refer to section 8 of this guideline.

3.3 PART 3 PHARMACEUTICAL AND ANALYTICAL

Refer to the pharmaceutical and analytical guideline.

3.4 PART 4 PRE-CLINICAL STUDIES

Refer to the Clinical guideline.

3.5 PART 5 CLINICAL STUDIES

Refer to the Clinical guideline.

4 PREPARATION AND SUBMISSION OF AN APPLICATION

Note: The official headings, text and footer of the current version of the MRF1 may not be changed.

4.1 Applications for registration of a medicine should be submitted on the MEDICINE REGISTRATION FORM (MRF1) obtainable from the Registrar of Medicines or from the MCC website www.mccza.com

4.2 Each page of the application should

- be numbered and the printing should be in a font size with a legibility equivalent to at least Arial 10 point black on white and the copies including figures, tables, photo's should be clearly legible. Shading and/or coloured filling/background and/or print, e.g. in tables, should be avoided.
- have a header reflecting the HCR, product name, dosage form and strength.

The pages should be numbered according to the MRF1, e.g. 3B.1 (referring to PART 3B, first page). Double-sided copies are allowed except for those of the package insert and patient information leaflet.

4.3 The application for registration of a dossier should have clearly labelled tabs to indicate each PART of the dossier.

4.4 Each PART or Sub-PART should contain a Table of Contents.

4.5 The application for registration should be properly bound on the left side as this allows for easy update/addition of pages. The left margin of documents should be wide enough to allow for legibility after copying and binding. Binding is left to the discretion of the applicant; however, the use of lever-arch files and ring binders is not accepted. The binding should enable the easy handling and evaluation of documents without it coming apart. The dossier should, therefore, be bound in units not exceeding 4 cm, also depending on the binder used.

4.6 Copies of both screening and final submission covering letters in addition to all screening outcome letters should be bound to the application dossier as indicated in the section 5 PRESENTATION OF SCREENING AND POST-SCREENING COPIES of this guideline.

4.7 Cheques or proof of payment should be submitted in a separate envelope attached to the original covering letter. No other documents should be attached.

4.8 The requirements with regard to metrication in accordance with the Trade Metrology Act should be applied.

4.9 The boxes in which documentation is submitted to the MCC should be clearly labelled. The following details should appear clearly on each box:

- a) Applicant name
- b) Name of the product (at applicant's discretion) or the applicant's product identification code for each application (e.g. NCE-04NOV01)
- c) The contents of the box, e.g. File numbers, PARTs, Sample, Covering letter, Cheque.

4 Preparation and submission of an application - continued

- d) Number of boxes, e.g. 1 of 10
 - e) Type of application, e.g. routine, expedited review (fast track), or AMRP.
 - f) Colour stickers indicating screening (red) or post-screening (green).
- 4.10 In the case of expedited review (fast track), a copy of the approval letter should be attached in the front of each volume.
- 4.11 On receipt at the MCC, all applications for registration will be subject to pre-screening according to the checklist, attachment A, also completed by the applicant.
- 4.12 Upon successful pre-screening, the application will be logged onto the system and allocated a screening number. A letter acknowledging receipt of the application and receipt of the screening fee will be issued to the Applicant.
- 4.13 If the applicant does not comply with the pre-screening requirements the application will be returned to the Applicant as incomplete.
- 4.14 After successful pre-screening the application will be subjected to screening according to the screening form MRF2. The screening process endeavours to confirm that all the data required have been included and does not involve evaluation of either the data or any motivation for omission of data. Except for the Inspectorate requirements referred to, the MRF2 headings are in accordance with those of the MRF1 and the questions under each heading are in accordance with the relevant guidelines. Reference to the relevant guidelines should therefore be made if the meaning of any particular question is not clear. Motivation for the omission of data is required.
- 4.15 The screening outcomes i.e. HOLD or RETURN AS INCOMPLETE will be communicated to the applicant together with reasons. Time frames for the applicant to submit outstanding information, or to collect the application, will also be communicated to the applicant. In the event of a dispute regarding outstanding information or time frames, the application will be tabled at the next Council meeting for a formal decision.
- 4.16 The ACCEPTED screening outcome, the required application fee, and the number of copies will be communicated to the applicant. At this point the application number will also be allocated. Applications for which an expedited review (fast-track) has been approved should be clearly marked. The allocated reference number and a copy of the approval letter should be included and also accompany any subsequent correspondence regarding an expedited review application.
- 4.17 The correct number of copies of application and additional documents required for the evaluation of the application, should be submitted in the format detailed in the section 5 PRESENTATION OF SCREENING AND POST-SCREENING COPIES of this guideline. **This date will be regarded as the date of submission of the application for registration.**

5 PRESENTATION OF SCREENING AND POST-SCREENING COPIES

Certain PARTs of the application for registration should be duplicated and submitted as prescribed in the screening approval letter together with the application fee. Cheques or proof of payment should be submitted in a separate envelope attached to the original covering letter. No other documents should be attached.

No additional documentation, other than that which has been clearly stipulated below, may be bound in any of the sets identified below. Applicants who wish to submit applications in electronic format should make prior arrangements with the Registrar.

5.1 SCREENING SUBMISSION SET 1

- Covering letter in the front of each volume
- Screening fee (please do not include the application fee with the screening fee)

5.1 Screening submission Set 1 - continued

- Completed pre-screening checklist (Attachment A)
- Completed MRF2 (screening form)
- One complete application for registration dossier (MRF1) and the following:
 - Copy of the latest Inspection Report (not older than 3 years) from the Medicines Control Council and/or foreign regulatory body recognised by the Council for the manufacturer of imported medicinal products and medicines
 - GMP/WHO certificate
 - Certificate of analysis for the sample submitted
 - One sample of smallest pack size
 - Batch manufacturing documents for the sample should be submitted or available for inspection
 - Licence for Manufacturer, Packer, Laboratory
 - Proof of registration of the Company and the authorised person.

5.2 FULL SUBMISSION

Covering letter for final submission (this date becomes the date of submission) and application fee, all screening outcome letters, plus the number of copies of the sets requested by MCC post screening (the amendments in response to the screening outcome must be included in the sets copied). Only the information indicated should be included in each set.

5.2.1 SET 2 (P + A)

- Covering letter in each volume
- Completed MRF2 (screening form)
- All screening outcome letters and amendments if relevant incorporated into the submission
- PARTs 1A to D, 2A (only if not a biostudy), 2C if applicable, 3A to I

5.2.2 SET 3 (NAMES and SCHEDULING)

- Covering letter in each volume
- PARTs 1A, C, and 3B

5.2.3 SET 4 (MEDICINE REGISTER)

- Covering letter in each volume
- PARTs 1A, C, 3B,
- PART 3E front page with manufacturing sites *only* if more than one site is involved where sites are linked to specific processes and 3Fb) if more than one site is involved and sites are linked to specific processes i.e. is more detailed than in PART 1Ab)

5.2.4 SET 5 (SCHEDULING NCE)

- Covering letter in each volume
- PARTs 1A, C, and 3B
- PARTs 2B, 2D and 2E

5.2.5 SET 6 (CLINICAL AMRP)

- Covering letter
- PARTs 1A to D, and 2B or 2D and 2E, as applicable

5.2.6 SET 7 (CLINICAL)

- Covering letter in each volume
- PARTs 1A to D, 2B, or 2D and 2E, 3B, 4 and 5.

5.2.7 SET 8 (BIOSTUDY or OTHER)

- Covering letter in each volume
- Completed MRF2 (screening form)
- All screening outcome letters and amendments if relevant incorporated into the submission
- PARTs 1A to D, 2A, 2C if applicable, 3A to I, 4 and 5.

5.2.8 Summary table of the sets generally required for applications

	Screening	P+A	Names Scheduling	Register Medicine	Scheduling	Clinical AMRP	Clinical	BA BE or Other
SET	1	2	3	4	5	6	7	8
New Chemical Entity medicines Biological medicines	1	3 5	5	1	1	-	1 3	-
Medicines with Pre-clinical & Clinical data Biological medicines	1	3 5	5	1	-	-	1 3	-
AMRP	1	3	5	1	-	1	-	-
AMRP if NCE	1	3	5	1	1	1	-	-
Medicines with dissolution or other data (including solutions and injections)	1	-	5	1	-	-	-	3
Medicines with biostudy(ies)	1	2	5	1	-	-	-	2

5.3 Acknowledgement of receipt

An acknowledgement letter will be sent to the applicant and evaluation of the application will proceed on receipt of the additional copies.

5.4 Communication

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

6 EXPEDITED REVIEW PROCESS (FAST-TRACK)

The 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 further information refer to Regulation 5 of the Act.

6 Expedited review process - continued

The applicant should submit an expedited review request to the Minister of Health and a copy thereof for the attention of the Registrar of Medicines, before submitting the full application. Products that will be considered for expedited review are:

- Medicines on the Essential Drugs List (EDL)
- New Chemical Entities that are considered essential for national health but do not appear on the Essential Drugs List.

6.1 MEDICINES ON THE EDL

A declaration from the applicant that such a medicine appears on the EDL is required.

6.2 NEW CHEMICAL ENTITIES

The following should be submitted with the application:

- A written notification from the Minister to the effect that the medicine is considered essential to national health;
- an expert report (which is not more than 2 (two) years old and which is written by an independent expert),
- a package insert (where the product has been approved) and
- a summary basis for the registration (SBRA) (refer to Clinical guideline for details of an SBRA).

The Registrar shall notify the applicant within 30 days of the date of receipt of the application whether or not the application is to be subjected to the expedited registration process as stipulated in Regulation 5 of the Act.

The Council may request any information with respect to an application under consideration and the information should be submitted by the applicant within a period indicated by Council, failing which the Council may reject an application.

The Council shall, within 9 months from the date of receipt of the application by the Registrar, make a decision with regard to the application and inform the applicant of such decision.

7 ABBREVIATED MEDICINE REVIEW PROCESS (AMRP)

The AMRP is a system initiated by Council to limit the evaluation time of pharmaceutical products that are registered in countries with which the Council aligns itself, if the evaluation report is readily available.

The abbreviated medicine review process is based mainly on the expert reports of the pharmacotoxicological and clinical data. It should be noted that the AMRP is an abbreviated **evaluation** process and not an abbreviated **application**.

- 7.1 Only new chemical entities registered with one or more of the authorities with which the Council aligns itself will qualify for AMRP. (Refer to section 3.1.4 of this guideline).
- 7.2 The applicant should obtain the Expert Reviewers' reports on safety, quality and efficacy from the relevant medicines regulatory authority.
- 7.3 The certificate of approval of registration of the new chemical entity by one of the recognised registering authorities should be included. (Refer to section 3.1.4 of this guideline).
- 7.4 Written confirmation that the proposed package insert is based on the package insert and the complete dossier of the licensing country is required.

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 also be submitted.

7 Abbreviated medicine review process - continued

- 7.5 Written confirmation that the data submitted to the MCC are identical to that submitted to the authority which has granted approval should be given. Raw data of experimental and clinical studies should be excluded. A letter authorising the MCC to contact the relevant MRA for an evaluator's report or assessor's report should be included.
- 7.6 Expert reports on chemical-pharmaceutical, pharmaco-toxicological and clinical documentation should be included.
- 7.7 Relevant correspondence between the applicant and the registering authority including the negative (e.g. queries, non-acceptance of certain claims/statements) as well as the positive correspondence should be included.
- 7.8 Written confirmation that the formulation applied for is identical to that approved by the registering authority should be given.
- 7.9 Applications for AMRP can only be accepted if the product has been approved by the said authorities within the last three years of the licence in the licensing country.

8 EXPERT REPORTS MRF1 PARTs 2C to E

- 8.1 *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.
- 8.2 *Expert reviewer's report*: the report of the regulatory reviewer, after evaluation of the data submitted in support of approval for licensing.
- 8.3 All issues and properties of the product in the submission should be clearly identified and critically discussed in the Expert Reports in light of current scientific knowledge.
- 8.4 The Expert Report should address all the aspects in the package insert.
- 8.5 A list of the key references used in compiling the Expert Report should be attached.
- 8.6 The *curriculum vitae* of the expert should be included.
- 8.7 If the application for 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 Reports only. Furthermore, written confirmation that the AMRP-SBRA was compiled from the Expert Report only, should accompany the AMRP-SBRA submission.

9 PROPRIETARY NAME POLICY [Section 15 (3) of the Act]

The term "PROPRIETARY NAME" is defined in the Regulations pertaining to the Act 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 should 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. Mistaking one drug for another because of similar proprietary names can have serious consequences.

9 Proprietary name policy - continued

Since many medication errors are caused by look-alike and sound-alike medication names, it is evident that public health considerations should 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.

9.1 SAFETY CONCERNS

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 guidelines bearing in mind the paramount criterion of "potential safety risk".

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

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.

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

9.1.2 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.

9.1.3 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.

9.1.4 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. It is the responsibility of applicants to include precautionary statements of usage of these brands, simultaneously, so as to inform patients of their correct use.

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

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

9.1.7 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.

9.1.8 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 responsibility of applicants, not the Medicines Control Council. If however, valid safety concerns are identified, the applicant will be advised accordingly.

9.1.9 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.

9 Proprietary Name Policy – Safety Concerns - continued

9.1.10 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.

9.2 INTERNATIONAL NON-PROPRIETARY NAMES' (INN) CONCERNS

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").

- 9.2.1 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. Using a common stem indicates the relationship of pharmacologically related substances, 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 the MCC, and are taken into consideration when considering proprietary names.
- 9.2.2 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 API, 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.
- 9.2.3 A proprietary name commencing with, or containing "ac" in another position within the name could, however, be considered.
- 9.2.4 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 if the product contains another loperamide-type compound.
- 9.2.5 If a proprietary name is derived from a generic name, it should not be similar to the generic name, since it can lead 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 cotrimoxazole, even though the name does not contain an INN-stem for any of these groups.
- 9.2.6 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.
- 9.2.7 Exceptions may be considered for the anti-retrovirals if these have been previously approved by a recognised Regulatory Authority and are accompanied by a motivation.

9.3 OTHER CONCERNS

- 9.3.1 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.

9.3 Proprietary Names - Other Concerns - continued

- 9.3.2. 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).
- 9.3.3. 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.
- 9.3.4 A proprietary name should not convey any promotional message with respect to the use of the product.
- 9.3.5 Use of capitals in proprietary names should reflect the proposed/approved trademark registration.
- 9.3.6 A different proprietary name is required for a medicinal product containing a pro-drug of another product containing the parent active substance. (An umbrella name is not acceptable).
- 9.3.7 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 de-scheduled product.
- 9.3.8 Any phrase that implies superiority, including use of animal species associated with speed or strength, or implies superiority over other products, is not allowed.
- 9.3.9 The meaning of abbreviations, symbols, numerals and names, which are in a language other than English, should 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.
- 9.3.10 Proprietary names will only be evaluated as part of a new application for registration or application for change. Requests for evaluation of acceptability of possible proprietary names prior to submitting a formal application will not be processed.
- 9.3.11 Proprietary names cannot be reserved for applications that have not yet been submitted.
- 9.3.12 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.
- 9.3.13 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 API(s), are included on this list.
- 9.3.14 As stated above, 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 The Complete Drug Reference/other reference book for a product not containing the same ingredient(s) and which may be on the market elsewhere.
- 9.3.15 As with all registration matters, applicants always have the opportunity to submit comments in the event of a difference in opinion. Such comments will be forwarded to Council for consideration.

10 MANUFACTURING REQUIREMENTS

Only medicines manufactured, packed and quality controlled at sites compliant with the current principles of Good Manufacturing Practice (GMP) as prescribed by the Medicines Control Council will be considered for registration.

Council's general policy is that the standard to be used to assess compliance with current Good Manufacturing Practice (cGMP), is the South African Guide to Good Manufacturing Practice (SA guide to GMP) (latest edition) as minuted:

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

Under Section 22C of the Act, all South African manufacturers should be licensed (effective 2 May 2004).

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.

The Act requires that overseas manufacturers of medicine supplied to South Africa should comply with the same or equivalent manufacturing standards as expected of South African manufacturers.

Evidence in relation to compliance with Good Manufacturing Practices of the overseas manufacturer is required for applications for registration of imported medicines. When acceptable evidence of GMP compliance is not available, overseas manufacturers are inspected by the GMP Inspectorate before registration of the medicine is approved.

11 SAMPLES

All medicine applications for registration must include a sample of a unit pack, Section 15(1) of the Act.

12 STANDARDISED PACKAGE INSERT WARNINGS AND INFORMATION

In addition to the warnings required by Regulations 8, 9 and 10 of the Act, the following warnings should be included in the package insert, unless the applicant can provide convincing evidence to the contrary. The wording need not be identical.

12.1 ANTIHISTAMINES (OLD GENERATION) GENERAL DROWSINESS WARNING

"This medicine may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be advised, particularly at the initiation of therapy, against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration could lead to accidents."

12.2 ANTIHISTAMINES (NEW GENERATION) GENERAL DROWSINESS WARNING

"This medicine lacks significant sedative effects."

12.3 NON-CONTENT CLAIM: "CONTAINS NO ASPIRIN"

The use of the words "Contains no Aspirin" may not appear on the package insert or in the advertising of non-aspirin containing medicines. In terms of regulation 8(3), the wording may still appear on the immediate label of the medicine, provided that the type (or font) size is not bigger than the type size in which the APIs appear.

12.4 DEPENDENCE PRODUCING POTENTIAL OF MEDICINES

Warnings concerning the dependence-producing potential of certain substances may be made known to the professionals.

12.5 MALARIA PROPHYLAXIS IMPORTANT PATIENT INFORMATION

The following patient warnings should be included in all package inserts of products intended for malaria prophylaxis:

"Because no form of prophylaxis is fully effective, the prevention of mosquito bites should form the mainstay of malaria prophylaxis. The following preventative measures to prevent mosquito bites should be taken:

- a) Endemic areas should preferably be visited during the dry season or in years when rainfall is low.
- b) High-risk patients should avoid malaria areas altogether.

High-risk persons include:

- babies and young children less than 5 years of age;
- pregnant women;
- immuno-compromised individuals such as those on long-term steroids, cancer patients and those on chemotherapy, AIDS patients and those who have had their spleens removed.

- c) Refrain from going outside between dusk and dawn when mosquitoes are most active.
- d) Apply insect repellent to exposed skin and clothing.
- e) Wear long sleeves and trousers at night.
- f) Use mosquito nets, screens, coils or pads."

"Should the patient develop flu-like symptoms, the patient should inform the doctor that he has been to a malaria endemic area."

12.6 USE OF MEDICINES DURING PREGNANCY AND LACTATION

In cases where the safety of a medicine, with regard to its use in pregnancy and lactation, has not been established, the following warning should be included in the package inserts for those medicines.

"The safety of this preparation in pregnancy and lactation has not been established."

12.7 PACKAGE INSERTS/SLOGANS

Advertising (slogans), in package inserts, is not permissible.

12.8 WATER FOR INJECTION

General exemption from package insert requirements, in respect of sales packs of water for injection, will be considered provided that the following warning appears on at least the outer label in prominent type:

"Water for injection must not be administered on its own"

12.9 ACE-INHIBITORS

The following boxed warnings should be included:

“Should a woman become pregnant while receiving an ACE-inhibitor, the treatment should be stopped promptly and switched to a different medicine.”

“Should a woman contemplate pregnancy, the doctor should consider alternative medication.”

The following warnings should be included:

“ACE-inhibitors pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of ACE-inhibitors in the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur.”

12.10 ANTIBIOTICS FOR THE TREATMENT OF BETA-HAEMOLYTIC STREPTOCOCCAL INFECTIONS

The following statement should be included under the heading, “DOSAGE AND DIRECTIONS FOR USE:”

“In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.”

12.11 REYE'S SYNDROME WARNING FOR MEDICINES CONTAINING ASPIRIN

The following warning should be included in all package inserts for aspirin containing products:

“Warning: Aspirin has been implicated in Reye's syndrome, a rare but serious illness in children and teenagers with chickenpox and influenza. A doctor should be consulted before aspirin is used in such patients.”

12.12 BENZALKONIUM CHLORIDE-PRESERVED OPHTHALMOLOGICAL PREPARATIONS

The concentration of benzalkonium chloride should not exceed 0,01 % and should not be used in preparations intended for soft contact lens solutions.

The following warnings should be included in the package insert:

“As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.”

12.13 BENZODIAZEPINE

Unless the applicant can provide convincing evidence to the contrary, package inserts for benzodiazepine should contain the following, although the wording need not be identical:

Side-effects and special precautions:

“The side-effects most frequently encountered are drowsiness and over-sedation. Drowsiness is more common in elderly and debilitated patients, and in those receiving high doses. Less common are depression of mood and affect, disorientation or confusion, lethargy, ataxia, constipation, nausea, diarrhoea and changes in libido.”

“Paradoxical reactions such as acute hyper-excitability with rage may occur. If these occur, the medicine should be discontinued.”

12.13 *Benzodiazepine - continued*

“There is a potential for abuse. Withdrawal symptoms (including convulsions) have occurred following abrupt cessation, especially in patients who have received large doses for prolonged periods.”

“*Injections:* Respiratory depression due to a depressant effect on the respiratory centre and cardiovascular collapse may occur following intravenous and intramuscular administration.”

Special Precautions: “Particular caution should be exercised with the elderly and debilitated - who are at particular risk of over-sedation, respiratory depression and ataxia. (The initial oral dosage should be reduced in these patients).”

“Caution should be exercised in the following patients:

- patients suffering from impairment of renal or hepatic function;
- patients suffering from anxiety accompanied by an underlying depressive disorder;
- patients receiving barbiturates or other central nervous system depressants. There is an additive risk of central nervous system depression when these medicines are taken together;
- patients should be cautioned regarding the additive effect of alcohol.”

“The medicine should be used judiciously during pregnancy and preferably avoided. During labour it crosses the placenta and may cause the “floppy-infant” syndrome characterised by central respiratory depression, hypothermia and poor sucking. It should not be administered to lactating mothers.”

“Patients should be advised, particularly at the initiation of therapy, not to drive a motor vehicle or operate dangerous machinery or perform potentially hazardous tasks where impaired decision making could lead to accidents.”

Overdosage: “Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension.”

12.14 **BENZODIAZEPINE OR BENZODIAZEPINE-LIKE COMPOUNDS**

Product name to be inserted in []

Indications:

“[] is only indicated when the disorder is severe, disabling or when the individual is subject to extreme stress.”

Dosage and directions for use:

“Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.”

For products with anxiety approved as indication:

“Treatment should be as short as possible. The patient should be assessed regularly and the need for continued treatment should be re-evaluated especially when the patient is symptom-free. The overall duration of treatment, generally, should not be more than 8 to 12 weeks, including a tapering off process. In certain cases extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient’s status.”

For products with insomnia approved as an indication:

“Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks, with a maximum of four weeks including the tapering-off process. In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient’s status.”

Side effects and special precautions:

“[] is not recommended for the primary treatment of psychotic illness. [] should not be used alone to treat depression, or anxiety with depression, as suicide may be precipitated in such patients. [] should be used with extreme caution in patients with a history of alcohol or drug abuse.”

12.14 Benzodiazepine or Benzodiazepine-Like Compounds –continued*Dependence:*

“There is a potential for abuse and the development of physical and psychological dependence, especially with prolonged use and high doses. The risk of dependence is also greater in patients with a history of alcohol or drug abuse. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.”

“In severe cases, the following symptoms may occur: de-realisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.”

Rebound effects:

“A transient syndrome, which may occur in withdrawal of treatment, whereby the symptoms that led to treatment with [] recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal or rebound phenomena, is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.”

Duration of treatment:

“The duration of treatment should be as short as possible (see Dosage), but should not exceed four weeks for insomnia and eight to twelve weeks in case of anxiety, (**) including the tapering-off process.

Extension beyond these periods should not take place without re-evaluation of the patient. It may be useful to inform the patient, when treatment is started, that it will be of limited duration, and to explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient is aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the product is being discontinued.”

“(**) Note that the duration should be adapted according to approved indications for each individual product.”

12.15 BETA-2 AGONISTS**Indications:**

“Treatment of reversible airway obstruction in asthma, chronic bronchitis and emphysema, and prevention of bronchospasm in exercised-induced asthma.”

Side effects and special precautions:

“Hypokalaemia may occur. Overdosage may cause cardiac effects. High doses may increase the risk of serious side effects, including cardiac dysrhythmias. This risk is further aggravated if the drug is administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias, or in the presence of hypoxia and acidosis. The maximum dose should not be exceeded.”

Dosage and directions for use:

“Do not exceed the recommended dose.”

12.16 BETA-BLOCKING AGENTS

Unless the applicant can provide convincing evidence to the contrary, package inserts for beta-blocking agents should contain the following, although the wording need not be identical:

Side effects and special precautions:

“Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases. Congestive cardiac failure and marked bradycardia may also manifest. A variety of neuropsychiatric disorders, ranging from vague fatigue and nightmares to overt psychosis, have been observed.”

12.16 Beta-Blocking Agents - continued

“The following may occur: exacerbation of peripheral vascular disease, or the development of Raynaud's phenomenon (due to unopposed arteriolar alpha-sympathetic activation), sexual impotence, hypoglycaemia, skeletal muscle weakness and gastro-intestinal disturbances. Severe peripheral vascular disease and even peripheral gangrene may be precipitated. Adverse reactions are more common in patients with renal decompensation, and in patients who receive the drug intravenously.”

“It is dangerous to administer this medicine concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and various antiarrhythmic agents. Such drug-drug interactions can have life-threatening consequences.”

“SPECIAL NOTE: - digitalisation of patients receiving long-term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.”

“Abrupt discontinuation of therapy may cause exacerbation of angina pectoris in patients suffering from ischaemic heart disease. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.”

“Administration to pregnant mothers shortly before giving birth or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.”

“Patients with pheochromocytoma usually require treatment with an alpha-adrenergic blocker.”

Contra-Indications:

“Particular caution should be exercised with patients suffering from the following: asthma, bronchitis, chronic respiratory diseases, second and third degree heart block and bradycardia (less than 50 beats per minute), peripheral vascular diseases and Raynaud's phenomenon. The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction. In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardic response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.”

Known symptoms of overdosage and particulars of its treatment:

“Overdosage may produce bradycardia and severe hypotension. Bronchospasm and heart failure may be produced in certain individuals. Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly. Gastric lavage should be performed within four hours of suspected overdose. Repeated activated charcoal is necessary in severe overdose.”

“Atropine may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine or isoprenaline, may be required to reverse beta-blockade. Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled, or IV beta-agonist, e.g. salbutamol.”

12.17 BETA-BLOCKER AND CLONIDINE

The following warnings should be included in all beta-blocker and clonidine package inserts.

“Caution should be exercised when transferring a patient from clonidine. The withdrawal of clonidine may result in the release of large amounts of catecholamines that may give rise to a hypertensive crisis. If beta-blockers are administered in these circumstances, the unopposed alpha receptor stimulation may potentiate this effect.”

“If a beta-blocker and clonidine are given concurrently, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker, as severe rebound hypertension may occur.”

12.18 BETA-LACTAM ANTIBIOTICS

The following statement should be included in the package inserts of all beta-lactam and fluoroquinolone antibiotics containing an indication or claim for *Pseudomonas aeruginosa* infections.

Indications:

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly."

12.19 BISMUTH-CONTAINING MEDICINES

The package inserts for bismuth-containing preparations should include a warning regarding the possibility of neurotoxicity with prolonged or excessive use.

12.20 CLOFIBRATE

Package inserts for all clofibrate-containing medicines should reflect the following statement:

Indications:

"Before starting treatment with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, e.g. weight loss in obese patients, control over diabetes mellitus. If, after considering the possible benefits in relation to the risks, it is decided to institute clofibrate therapy, then it should be indicated in the treatment of types II(B), III, IV and V hyperlipoproteinaemias (Frederickson and Levy Classification)."

FREDERICKSON TYPE	LIPOPROTEIN ELEVATION	MAJOR LIPID ELEVATION
I (very rare)	chylomicra	Triglycerides
II (a)	LDL	Cholesterol
II (b)	pre- (VLDL & LDL)	Cholesterol & Triglycerides
III (rare)	Abnormal (LDL)	Cholesterol & Triglycerides
IV	Pre (VLDL)	Cholesterol & Triglycerides
V (rare)	Chylomicra & pre (VLDL)	Cholesterol & Triglycerides

"It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has detrimental, beneficial or no effects, on morbidity or mortality, due to atherosclerosis or coronary heart disease. Clofibrate therapy should be discontinued if a significant lowering in serum lipids is not obtained."

Side effects and special precautions:

"Due to its action on cholesterol metabolism, clofibrate may increase the lithogenicity of bile and, thereby, cause an increased frequency of gallstones. A possible association between treatment with clofibrate and gastro-intestinal malignancies exists."

12.21 CONTRAST MEDIA - WATER SOLUBLE - BOXED WARNING

"Fatal reactions have been associated with the administration of water-soluble contrast media. It is, therefore, of utmost importance that a course of action is carefully planned, in advance, for the immediate treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of a severe reaction. Patients should be observed for a possible severe reaction, during, and for at least 30 to 60 minutes after, administration of [proprietary name]. Patients with known or suspected hypersensitivity to iodated contrast media should be closely observed."

12.22 CONTACT LENS SOLUTIONS EXEMPTION

THIS EXEMPTION SPECIFICALLY DOES NOT APPLY TO ARTIFICIAL TEAR SOLUTIONS.

Contact lens solutions are exempted from package insert requirements, provided that:

- a) the relevant immediate container labels and cartons (if any) contain the necessary information that would normally be required on the package insert;
- b) such labels are fully bilingual;
- c) no advertising matter of reference to other products be included on such labels; and
- d) the draft labels be submitted to this office for prior approval.

12.23 POTENT TOPICAL CORTICOSTEROID

The following warning should be included in all potent topical corticosteroid package inserts:

“Potent topical corticosteroid preparations, such as (name), should not be applied to any skin crease areas.”

12.24 CORTICOSTEROIDS PRODUCTS FOR TOPICAL USE

Package insert for all topical corticosteroid should reflect the following:

Contra-indications:

“Corticosteroids have been shown to be teratogenic in animals following dermal application. As these agents are absorbed percutaneously, teratogenicity following topical application, cannot be excluded. Therefore, (name of product) should not be used during pregnancy.”

12.25 CO-TRIMOXAZOLE

All package inserts of products containing co-trimoxazole, or long-acting sulphonamides, should include a warning with regard to the occurrence of erythema multiforme, toxic dermal necrolysis and allergic vasculitis.

12.26 DICYCLOMINE IN INFANTS

The indication “infantile colic” and dosage schedule for children younger than six months of age, should not be included. A warning against its use in “infantile colic” should be included.

Applicants to submit evidence of, as well as a motivation for, the dosage, dosage intervals, efficacy and safety of administration to children older than six months.

12.27 DISOPYRAMIDE**Side-effects and special precautions:**

“The administrations of disopyramide may precipitate cardiac failure when administered to patients with congestive failure who have been stabilised.”

Contra-indications:

“The administration of disopyramide is contra-indicated in patients with congestive cardiac failure, irrespective of whether the patient is digitalised, or not.”

12.28 FLUOROQUINOLONE ANTIBIOTICS

Refer to Beta-lactam antibiotics

12.29 GLIBENCLAMIDE AND GLICLAZIDE: BOXED WARNING

“A reduction in dosage may be necessary in patients with renal dysfunction.”

12.30 IODINE AND IODIDE-CONTAINING MEDICINES

Synthetic thyroid hormone preparations are exempted from the following requirements.

The following warning should appear on the LABELS as well as IN the package inserts of all medicines containing more than 0,60 mg iodine/ionic iodide per daily dose:

“Not to be used during pregnancy or lactation.”

On the package inserts of ALL iodine-containing preparations, there should be a warning:

“Not to be used by persons who are allergic to iodine.”

12.31 METOCLOPRAMIDE

This warning should appear on ALL package inserts:

“The use of metoclopramide during pregnancy is considered unsafe as teratogenicity has been demonstrated in animal studies.”

12.32 METRONIDAZOLE

The following warning should be included in the package inserts of all products containing metronidazole:

“Pseudomembranous colitis has been reported following the use of metronidazole.”

12.33 NON STEROIDAL ANTI-INFLAMMATORY AGENTS

The following warning, regarding the use of non-steroidal anti-inflammatory drugs in pregnancy, should be included in all package inserts of non-steroidal anti-inflammatory agents:

“Regular use of non-steroidal anti-inflammatory drugs during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.”

In addition to the above, the following special precaution should be included: “In view of the product’s inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.”

12.34 OESTROGEN-CONTAINING PRODUCTS

With the exclusion of oestrogen-containing oral contraceptives, all other oestrogen-containing medicines shall have package inserts bearing the following warnings:

“Not for use during pregnancy. Vaginal adenosis, and vaginal and cervical adenocarcinoma, has been noted in post-pubertal girls whose mothers were treated for threatened abortion with large doses of stilboestrol, or related oestrogenic substances, during their pregnancies.”

12.34 Oestrogen-containing products - continued

“An increased incidence of endometrial uterine carcinoma, related to the continuous use of oestrogens in the post-menopausal period, has been reported.”

Products intended solely for post-menopausal use may have in their package inserts, instead of the aforementioned warning, the warning:

“Not for use during pregnancy.”

All combination oral contraceptive products containing oestrogen shall have package inserts reflecting:

Side effects and special precautions:

“Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days thereafter. Those on long-term antibiotic therapy need only take extra precautions for the first two weeks of antibiotic therapy. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.”

12.35 PHENYLBUTAZONE AND OXYPHENBUTAZONE

The indications and period of use for phenylbutazone and oxyphenbutazone preparations should be restricted to “acute exacerbations of ankylosing spondylitis” and a maximum period of use of 7 days.

Warnings (to be in prominent type and boxed) - the following should be included:

“Because of potentially serious and occasionally fatal adverse effects, use should be restricted to a maximum of 7 days and the maximum recommended dosage should not be exceeded. Caution against repeated short-term use is advised due to the possible danger of sensitisation. Haematological disorders are potentially fatal. For parenteral dosage forms, the dosage should be limited to a maximum of 600 mg per day. Combination products, containing phenylbutazone and oxyphenbutazone, are not allowed.”

12.36 POTASSIUM SUPPLEMENTATION

The following statement should be included in package inserts of medicines containing potassium for the purpose of potassium supplementation (under “pharmacological action”):

“This medicine contains potassium (salt to be named). It has not been proven that this dosage will necessarily prevent a significant potassium loss or correct an existing deficiency of potassium.”

12.37 LONG-ACTING SULPHONAMIDES

Refer to co-trimoxazole.

12.38 TAMOXIFEN

The following safety information (warning) should be included in the package inserts of all tamoxifen-containing products:

“An increased incidence of endometrial changes, including hyperplasia, polyps and cancer, have been reported in association with tamoxifen treatment. Any patients receiving, or who have previously received, tamoxifen and who report vaginal bleeding, should be promptly investigated.”

12.38 Tamoxifen - continued**Side effects and special precautions:**

"Tamoxifen was shown to be genotoxic in some *in vivo* genotoxicity tests in rodents. Gonadal tumours in mice, and liver tumours in rats receiving tamoxifen, were reported in long-term studies. The clinical relevance of these findings has not been established."

12.39 TARTRAZINE (FD & C yellow no 5)

The following warning should be included (under the heading of "WARNING") in the package insert of medicines which contain tartrazine:

"This product contains FD & C Yellow No 5 (Tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of Tartrazine sensitivity in the general population is currently thought to be low, it is frequently seen in patients who also have aspirin sensitivity."

12.40 TOPICAL TRETINOINS - statement on pregnancy and lactation

"Oral tretinoin has been shown to be teratogenic in a variety of animal species. Limited animal data urge caution in the use of preparations containing tretinoin during the first trimester of pregnancy."

"Topical tretinoin should be used during pregnancy only if the potential benefits outweigh the potential risks. In the case of an eventual pregnancy, the patient should inform her doctor."

"It is not known whether tretinoin is excreted in animal or human milk. However, because many medicines are excreted in human milk, caution should be exercised when applying topical tretinoin to nursing women. In this event, the product should not be used on the chest."

12.41 TRICYCLIC ANTIDEPRESSANTS: Acceptable claims

Serious depressive conditions such as major depressive illness, reactive depression and secondary depression. The following reflects what is defined under the various disorders:

Major depressive illness:

- Endogenous depression, unipolar depression, bipolar depression (manic-depressive psychosis), masked depression;

Reactive depression:

- neurotic depression;

Secondary depression:

- Depression associated with alcoholism, schizophrenia, and Parkinsonism depression associated with personality disorder, depression caused by medicines and senility with depression.

The claims for enuresis and other states, such as phobic anxiety disturbances, obsessive compulsive disturbances and chronic pain, which may benefit from the administration of tricyclic antidepressants, may be considered but will require the submission of substantiating data.

12.42 TRICYCLIC ANTIDEPRESSANTS standardised package inserts

Unless the applicant can provide convincing evidence to the contrary, package inserts for tricyclic antidepressants should contain the following, although the wording need not be identical:

12.42 Tricyclic antidepressants standardised package insert - continued

Side-effects and special precautions:

“Peripheral anticholinergic side effects, notably dry mouth, constipation, urinary retention and pupillary dilatation with blurred vision and changes in visual accommodation. When anticholinergic effects are severe, the medicine should be discontinued or reduced.”

“Drowsiness or excessive sedation may be caused in certain patients. On the other hand, disorientation and agitation, insomnia and restlessness can also occur with normal doses. The risks of central nervous system depression are greater when administered together with other central nervous system depressants, e.g. alcohol, barbiturates.”

“NOTE: Elderly patients are more prone to all these effects, and therapy should be initiated at lower than standard doses in the elderly.”

Special Precautions:

“At the time of initiation of therapy, patients should be advised not to drive a motor vehicle, climb dangerous heights or operate dangerous machinery for at least several days. In these situations, impaired decision making could lead to accidents.”

“Caution should be exercised with patients suffering from a depressive phase of manic depressive psychosis, as occasionally hypomania or mania can be precipitated in such patients. Withdraw the drug if the depression turns into a manic phase.”

“In elderly male patients suffering from prostatism, urinary retention may be precipitated.”

“In patients suffering from cardiac disease, special caution should be observed because of the occasional problems of tachycardia, dysrhythmias orthostatic hypotension and other unwanted effects on blood pressure, aggravation of conduction disturbances and electrocardiographic abnormalities. Regular cardiological and electrocardiographic examination is advised.”

“Epilepsy may be aggravated.”

“The medicine should not usually be given to patients receiving other central nervous system depressants, for e.g. barbiturates, and to patients receiving monoamine oxidase inhibitors - only after a suitable interval has elapsed (the drugs may be given together if the dosages are carefully controlled, preferably in hospital). The pressor effects of the direct-acting sympathomimetic agents, adrenaline and noradrenaline, are enhanced, and the use of local anaesthetics containing these vasoconstrictors should be avoided as hypertensive reactions may occur. The simultaneous administration of anticholinergic agents may be dangerous. The hypotensive effect of certain antihypertensive agents may be reduced.”

“Narrow-angle glaucoma may be aggravated.”

“Withdraw the drug if allergic skin reactions appear.”

Contra-Indications:

“The acute-phase of myocardial infarction. Administration is not advised during the first trimester of pregnancy, unless there are compelling reasons for its use.”

Overdosage:

“Overdosage and poisoning may be characterised by central nervous system depression or excitation, severe anticholinergic effects and cardiotoxicity. The following symptoms and signs are characteristic of acute overdosage: drowsiness, restlessness, ataxia, stupor, coma, pyrexia, palpitations, tachycardia, cardiac arrhythmias, hypotension, and in severe cases, respiratory depression. Epileptiform seizures may occur. Mixed poisoning with other central nervous system depressants is not uncommon.”

Special warning:

“This medicine should at all times be kept out of the reach of children, as even small doses may be fatal to them.”

12.43 L-TRYPTOPHAN CONTAINING PRODUCTS: Statement on eosinophilia myalgia syndrome

The following statement should be included under “WARNINGS” in the package inserts of products containing L-Tryptophan:

“In the USA the Eosinophilia Myalgia Syndrome has been associated with the intake of L-Tryptophan.”

12.44 CODEINE WARNING

The following warning should appear on the immediate container label, the outer label (if applicable) and the package insert of all CODEINE-containing products.

“Exceeding the prescribed dose, together with prolonged and continuous use of this medication, may lead to dependency and addiction.”

13 CODING OF SUBMISSIONS

Coding of applications/submissions/correspondence facilitates distribution, processing and tracking. The coding of uncoded items occurs after receipt at Registry on the second floor, Hallmark Building, Room 214, (see 2.5) where documents are logged into the internal mail/post system.

The following codes, placed on the **first page of each cover letter in bold lettering**, should be used for submissions to the MCC to reduce the possibility of misdirection.

Each code consists of three letters. The first letter represents the Section or Unit where the responsibility or function resides. The last two letters indicate the type of application or nature of the request. It should correspond with the specific request(s) stated in the covering letter.

When more than one code is applicable, each should be indicated, for example, VMC/VPC/VLC. A separate application should be submitted per Unit.

13.1 PRE-REGISTRATION (PHARMACEUTICAL AND ANALYTICAL)

The Pre-registration Unit is responsible for pre-registration applications and responses to resolutions and matters pertaining to a medicine during review for registration.

The following codes are recommended for applications and correspondence for the Pre-registration Unit:

CODE	SUBJECT	SUPPORTIVE DOCUMENTATION
PGC	Enquiries that are not technical or are not product-specific	Application letter and supporting information / motivation
PBE	Bioequivalence protocol	Cover letter, protocol, application form and any additional data
PBV	Bioequivalence protocol amendments (variations)	Cover letter, variations
PPI	Package insert: involving Composition, Identification, Presentation, and Storage conditions	Annexure 1 PART 1C
PFA	Formulation change: Additions, deletions, reduction or increase in API or IPI, overages, potency calculations and other formulation changes.	Annexure 2 PART 3B
PPR	Responses to P&A Committee recommendations	Copy of recommendation, data, amendment schedule – see Post-registration Amendment guideline

Pre-registration (pharmaceutical and analytical issues) continued

PRS	Source of API(s), Method of synthesis, Proof of equivalence (physical and chemical), Certificate of Analysis (CoA) for the API, Drug Master File.	Annexure 3 PART 3A
PRM	Specifications and control procedures for APIs and IPIs, release criteria and laboratories including frequency of testing	Annexures 4, 5 and 6 PART 3C
PPF	Specifications and control procedures for the final product	Annexure 7A and 7B PART 3F
PVA	Manufacturing and analytical process validation protocol and report	Annexures 7B and 11 PARTs 3E and 3F
PCA	Specifications and control procedures for Containers.	Annexures 8A and 8B PART 3D
PSE	Stability data, shelf-life confirmation and extension, Preservative efficacy and effect on ageing	Annexure 10 PART 3G
PMP	Manufacturing and packaging process change and in-process control changes	Annexure 11 PART 3E
PFR	Foreign registration, authorisation and package inserts (English translations)	Annexure 12 PART 1D
PEF	Efficacy, Bioavailability, Bioequivalence, Proof of efficacy: acid neutralisation, inhibition zones, skin blanching, and membrane permeability.	Annexure 13 PART 3
PPD	Pharmaceutical development: batch numbers and sizes, source of product and of API, dates of manufacture.	Annexures 16 cross-referenced to Annexures 7, 10, 11 and 13 PART 3H xref to 2, 3E, 3F, + 3G

13.2 POST-REGISTRATION AMENDMENTS (PHARMACEUTICAL AND ANALYTICAL)

The Post-registration Unit is responsible for

- a) applicant transfers and applicant name and address changes ;
- b) changes of the manufacturer, packer and testing laboratories (FPRC and FPRR);
- c) proprietary name changes in consultation with the Names Committee;
- d) pharmaceutical changes or amendments to the registration dossier; and
- e) cancellations of registered medicines and withdrawal of applications for the registration of medicines

The following codes are recommended for applications and correspondence for the Post-registration Unit:
(Refer to the Post-registration amendment guideline for the required documentation)

CODE	SUBJECT
VGC	General correspondence involving enquiries on policy issues and changes that are not product-specific
VAC*	Applicant transfer, name and address change of the applicant
VAA	Address only change for the HCR only
VMC*	Change of manufacturer or site of manufacture, name and address change of manufacturer
VPC*	Change of packer, name and address change of packer

Post-registration amendments (pharmaceutical and analytical) continued

VLC*	Change of laboratory, name and address change of laboratory (FPRC or FPRR)
VNC*	Updates following a proprietary name change approval
VPI	Package insert changers involving the Composition, Identification, Presentation and Storage conditions only.
VFA	Formulation change: Additions, deletions, quantity reduction or increase in API or IPI, overages, potency calculations and other formulation changes.
VRS	Change in source of API or method of synthesis
VRM	Specifications and control procedures for APIs and IPIs, release criteria and laboratories including frequency of testing
VFP	Specifications and control procedures for the final product
VVA	Manufacturing and analytical process validation protocol and report
VCA	Specifications and control procedures for Containers
VSE	Request for shelf-life, shelf-life confirmation; extension and reduction; Preservative efficacy and effect on ageing
VMP	Manufacturing and packaging process changes and in-process control changes
VFR	Foreign registration; notification of foreign submissions, approval or outcome
VEF	Proof of efficacy
VPD	Pharmaceutical development
VUR	Full Update for registered medicines including those with a change in the proprietary name, manufacturer, packer and/or testing laboratories
VUO	Full Update for "Old Medicines" including those with a change in the proprietary name, manufacturer, packer and/or testing laboratories
VCR	Cancellation of registered medicine
VCO	Withdrawal of an application for registration of a medicine
VIA	Applications for exemption from post importation testing of medicines
VRR	Response to query or recommendation from the unit
VSB Urgent	Submission of data/information on request by the Unit with a specific deadline. These will be transferred to the Unit immediately after log-in for finalisation of applications. Failure to supply the required information within the specified period will result in relegation of the application to the end of the queue.

*The applications are first evaluated by the Inspectorate – see code BNC

13.3 INSPECTION AND LAW ENFORCEMENT

The Inspection and Law Enforcement Unit is responsible for

- a) inspection and evaluation of sites for the manufacturing, packing, and testing of medicines nationally and internationally, as well as inspection and evaluation of all storage and distribution sites for medicines;
- b) investigation of complaints regarding registered and unregistered medicines;
- c) monitoring compliance to the Act and prosecution in case of non-compliance;
- d) monitoring the importation and exportation of medicines in consultation with customs authorities;
- e) evaluation of proprietary names and changes thereto.

Inspection and law enforcement continued

The following codes should be used for applications and correspondence for the Inspection and Law Enforcement Unit: (Any supporting documentation should be included with the cover letter.)

CODE	SUBJECT
BGC	General correspondence involving enquiries on policy and administrative issues
BAI	Advertising enquiries
BCA	Advertising complaints - legal
BCM	Complaints - manufacturing
BCQ	Complaints - quality
BEP	Export permits
BEQ	Exemption from any provision of Act 101 in terms of section 36
BFG	Site master file
BFP	Inspection follow-up
BFS	WHO free sale certificate
BII	Request for inspections
BIP	Import permit/MBR 20 Bill of Entry
BIR	Response to inspection reports
BLA	Applications for licensing of manufacturer, wholesaler or distributor (Section 22C of the Act)
BLE	Law enforcement – complaints/theft of medicines
BLV	Application for amendment to a licence
BLM	Labelling matters
BNC	Application for proprietary name change
BOA	Request for once-off approval
BPP	Request for/inquiry on repackaging
BSR	Request for scheduling/Scheduled substances

13.4 CLINICAL EVALUATION

The Clinical Evaluation Unit is responsible for

- a) evaluation of clinical and pre-clinical data
- b) evaluation of clinical aspects of the package insert and relevant changes to package insert;

The following codes should be used for applications and correspondence for the Clinical Evaluation Unit: (Any supporting documentation should be included with the cover letter.)

CODE	SUBJECT
CGC	General correspondence
CDR	Clinical data in support of registration

Clinical evaluation - continued

CDP	New indication/dosage schedule, other major changes for registered /old medicines
CPR	Package insert registration
CPA	Package insert amendments for clinical aspects of registered/ old medicines
CIS	PIL submissions for clinical aspects of registered / old medicines
CIA	PIL amendments for clinical aspects of registered / old medicines
CFT	Fast track requests
CSU	Periodic safety update reports
CUSRN	Urgent Safety Restriction Notice

13.5 CLINICAL TRIALS

The Clinical Trials Unit is responsible for the evaluation of

- a) clinical trial applications and clinical trial amendments;
- b) reports of adverse events arising from a clinical trial;
- c) applications for named patient use of unregistered medicines;
- d) applications for the use of unregistered medicines for clinical trial purposes.

The following codes should be used for applications and correspondence for the Clinical Trials Unit: (Any supporting documentation should be included with the cover letter.)

CODE	SUBJECT
TGC	General correspondence
TCA	Application to conduct a clinical trial
TCV	Amendment of an existing clinical trial
TCR	Response to CTC resolution
TAE	Report of adverse drug events arising from a clinical trial
TUM	Applications in terms of Section 21 of the Act (unregistered human medicines)

13.6 COMPLEMENTARY MEDICINES

The Complementary Medicines Unit is responsible for

- a) evaluation and review of applications for the registration of Complementary Medicines;
- b) receiving and collating initial and subsequent responses to the call-up notice as published in Government Gazette Number 23128 (22 February 2002);
- c) evaluation and review of applications for the amendment of the register for Complementary Medicines;
- d) issue of temporary permits for the manufacture, distribution and dispensing of Complementary Medicines.

N.B. Where applicable, the first code should be used for applications for registration of medicines. The second code should be used for amendments and other enquiries regarding registered medicines.

Complementary medicines continued

Supportive documentation for applications

Cover letter, Front Page & Annexures 1, 2 and 12 / Cover letter PARTs 1A, 1C 1D, 3B

CODE not registered	CODE registered	SUBJECT
MAR	MAX	Anthroposophical Medicines
MBR	MBX	Aromatherapeutic substances/ medicines
MCR	MCX	Ayurvedic Medicines
MDR	MDX	Chinese Traditional Medicines
MER	MEX	Energy substances
MFR	MFX	Homoeopathic Medicines
MGR	MGX	Nutritional substances with medicinal claims
MHR	MHX	Western Herbal Medicines
MIR	MIX	Unani-Tibb Medicines
MJR	MJX	Combination Homoeopathic/Flower Essence
MKR	MKX	Combination Complementary Medicines
MLR	MLX	Other Complementary Medicines
MGC		General correspondence not product-related

13.7 BIOLOGICALS

The Biologicals Sub-Unit is responsible for

- biological pre-registration applications and responses to resolutions, and matters pertaining to biological medicines during review for registration
- evaluation of technical changes to registered biological medicines and "old" biological medicines
- evaluation of clinical aspects of the package insert and relevant changes to package insert for biological medicines
- technical support to other units with respect to biological matters.

The following codes should be used for applications for the Biologicals Evaluation Sub-Unit:
(Any supporting documentation should be included with the cover letter.)

CODE	SUBJECT
QGC	General correspondence
QDR	Clinical data in support of registration
QDP	New indication/dosage schedule, and other major changes to the package insert of registered / old biological medicines (excluding the Composition, Presentation, Identification, and Storage Conditions)
QPI	Package insert for registration of biological medicines
QPA	Package insert amendments for clinical aspects of registered / old biological medicines
QSU	Periodic safety update reports for biological medicines
QSV	Annual strain update

Note: For biologicals:

- for any other activities not described above, the applications and/or queries should be directed to and properly coded for the relevant Units.
- relevant supportive documentation should be attached as per the Annexures described in the MBR1 form for biological medicines/ or as described in the MRF1 PARTs.

13.9 OPERATIONS AND ADMINISTRATION

The Operations and Administration Directorate is responsible for the following:

- a) receiving and acknowledging applications for registration of medicines and for amendment of registration dossiers;
- b) receiving correspondence dealing with administrative processes, registration and other application forms, and registration policy information documents and guidelines;
- c) receiving fees payable to the Registrar;
- d) co-ordination of Council and Committee reports on the evaluation of medicines;
- e) preparation and distribution of Council and Committee documents;
- f) handling personnel matters; and
- g) processing of Council and Committee claims.

The following codes should be used for applications for the Operations and Administration Directorate:

CODE	SUBJECT
AGC	General correspondence: Routine enquiries, Registration policy and Registration queries
AFR	Application for registration fees
AFJ	Retention fees
ACC	Committee and Council claims
ACR	Evaluators and Chairperson reports
ACM	Council Documentation
AHR	Human Resources issues
AIM	Information Management matters
ANA	Submission of new applications and post-screening copies

ATTACHMENT A

PRE-SCREENING CHECK LIST

PRODUCT NAME:

COMPANY:

COMPLIANCE WITH ADMINISTRATIVE CRITERIA	*	OFFICIAL USE	
		YES	NO
Box size (A4 box)			
Number of boxes			
Are the boxes clearly labelled on the side to specify the number and content of each box, e.g. set numbers, PARTs, sample, covering letter, cheque or proof of payment and product identification code? Does a colour sticker indicate the screening phase? (red = screening; green = post-screening)			
Is the dossier correctly bound? (No lever arch files, no ring binders, 4 cm thick but not over-full for the binder used)			
Is each PART of the dossier properly marked with tabs according to the cover letter?			
Does each PART of the dossier have a Table of Contents?			
Is each page of the dossier numbered?			
Is a sample included in an envelope? (screening copy)			
Is the cheque or proof of payment for the screening fee or application fee, as applicable, submitted in a separate envelope, with the covering letter, but no other documents attached?			
Is the type of application indicated? (section 2.7.1 to 2.7.5 of this guideline) Is an approval letter regarding "fast track" status included if relevant?			
Is the completed screening form MRF2 included? (screening and post-screening copies)			

* to be completed by the applicant

Name and signature of applicant: _____ **Date:** _____

If there is a "NO" answer to any question above, immediately return the dossier to the applicant as incomplete

Outcome: Accept _____ Hold _____ Return as Incomplete _____

Name and signature of MCC official: _____

Date: _____

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ATTACHMENT B

PART 1Ca) and b) to be superseded by the Package Inserts for Human Medicines guideline on 1 August 2008.

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3.1.3 PART 1C Labelling

Refer also to the guideline "Package insert amendments concerning urgent safety restrictions: Urgent safety restriction notice (USRN)"

a) PART 1Ca) Package inserts (Regulation 9 of the Act)

This guideline serves to help applicants with the correct way of presenting a package insert for evaluation. Applicants are requested to follow the format stipulated in the guideline in conjunction with provisions set out under Regulation 9 of the Act.

The package insert is regarded as the document that ensures the safe and effective use of the medicine under most circumstances. It presents a scientific, objective account of the medicine's use and limitation as established by the supporting evidence. All statements should be adequately cross-referenced and referenced. No promotional material may be included. Promotional statements and comparisons to other agents, suggestive of any potential advantage over competitors, will not be allowed.

After registration, the package insert may not be altered without the approval of the MCC. In the case of safety-related matters the Council should be informed immediately. The approved package insert, a proposed amended package insert and the evidence/motivation for the change should be submitted together with the notification MRF4 Package insert amendment form.

Package inserts should be typed in double-spaced text in black print and should be in English (British) and at least one other official language. The spelling and grammar in the package insert text should be checked thoroughly before submission of the application. The date of the package insert should be included as a footer, i.e. on each page.

The printing quality of the package insert should be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process.

References for each statement should be included in a broad margin on the right hand side of each page of the package insert. Alternatively the reference numbers may be included in the text as in scientific publications. Every statement should be verified by a reference. The exact page/s should be stated and if possible, the column and line number. If an entire section is quoted from one source, the reference may be listed at the end of the relevant section. No references should however be included in the finalised printed package insert.

An electronic copy (Word document) on diskette or CD of the package insert should be included.

b) Headings and particulars in a package insert (Regulation 9 of the Act)

Multisource medicine (MSM) New Chemical Entity (NCE)

In-house package insert templates if available, should be used as reference for the compilation of MSM package inserts. The templates will also be used for the subsequent evaluation of therapeutically equivalent, interchangeable, multisource medicines. Reference to the following standard references if applicable, are generally acceptable if templates are not available.

Pharmacological actions	Goodman and Gilman, The Pharmacological Basis of Therapeutics
Safety matters	Martindale, The Complete Drug Reference
General	USP DI

Scheduling status

Applicants to note that the scheduling status of medicines shall be determined from time to time by the Minister and shall be published in the Government Gazette. Medicines are scheduled from S0 to S6.

Proprietary name and dosage form

In accordance with the MRF1 PART 1.

Composition

In accordance with Regulation 9 of the Act.

Pharmacological classification

In accordance with Regulation 25 of the Act.

Pharmacological action

MSM Should be in line with the relevant package insert template if available, or if not available should be referenced to the latest edition of Goodman and Gilman, The Pharmacological Basis of Therapeutics. Any additional information as required by the applicant should be submitted with relevant clinical data.

NCE Source of particulars should be the clinical data and other references submitted.

Indications

MSM Should be in line with the relevant package insert template if available, or if not available in line with the innovator package insert. Any additional information as required by the applicant should be submitted with relevant clinical data.

NCE Source of particulars should be the clinical data and other references submitted. Where appropriate the following should be addressed: the maximum recommended single, daily and/or total dose, the need for dose titration, the normal duration of used and any restrictions on duration and the need for tapering off the dose.

Contra-Indications

Situations where the medicinal product must not be given for safety reasons, i.e. absolute contraindications, are the subjects of this section. Such circumstances could include particular clinical diagnosis, concomitant diseases, demographic factors (e.g. gender, age) or pre-dispositions (e.g. metabolic or immunological factors, prior adverse reactions to the medicine or class of medicines). The situations must be unambiguously, comprehensively and clearly outlined.

Other medicines or classes of medicine which should be specifically avoided (i.e. contraindicated) for concomitant or consecutive use should be stated. Also, where there are strong theoretical reasons (for example, on grounds of pharmacokinetics, pharmacodynamics, or common state of knowledge in medicine) for not using the combination, these should be stated.

Hypersensitivity to any of the pharmaceutical ingredients or residues from the manufacturing process should be included, as well as any contraindication arising from the presence of certain pharmaceutical ingredients.

Warnings

This section should be reserved for pertinent safety issues or any precautions that need the specific attention of the prescriber or the user.

MSM Should be in line with the relevant package insert template if available, or if not available referenced to the latest edition of Martindale, The Complete Drug Reference. The USP DI may also be used as reference. The safety profile should at least however be in line with that of the innovator package insert. Any additional information as required by the applicant should be submitted with relevant clinical data.

NCE Source of particulars should be the clinical data and other references submitted.

Standard package insert information for certain categories/ingredients

MSM In addition to the warnings required by Regulations 8, 9 and 10 of the Act, certain warnings should be included in the package insert, unless convincing evidence to the contrary can be provided. The wording need not be identical. Refer to section 12 of this guideline.

NCE Source of particulars should be the clinical data and other references submitted.

Interactions

Include known clinically relevant interactions and other potentially serious interactions based on the pharmacology of the medicine. It is useful to group interactions according to outcome e.g. potentiation or reduction in effect and to explain the mechanism of the interaction if it is known.

MSM Should be in line with the relevant package insert template if available, or if not available referenced to the latest edition of Martindale, The Complete Drug Reference. The USP DI may also be used as reference. The safety profile should at least however be in line with that of the innovator package insert. Any additional information as required by the applicant should be submitted with relevant clinical data.

NCE Source of particulars should be the clinical data and other references submitted.

Pregnancy and lactation

It should be clearly indicated whether pregnancy and lactation are contra-indicated or whether limited or no information in pregnancy and lactation is available.

In the case of a medicine where the safety of a medicine with regard to its use in pregnancy has not been established, the following statement must be included: "The safety of this medicine in pregnant and lactating woman has not been established." While applicants may reformulate this statement to suit their own style, deviation of the essentials of this message will not be acceptable.

MSM Should be in line with the relevant package insert template if available, or if not available referenced to the latest edition of Martindale, The Complete Drug Reference. The USP DI may also be used as reference. The safety profile should at least however be in line with that of the innovator package insert. Any additional information as required by the applicant should be submitted with relevant clinical data.

NCE Source of particulars should be the clinical data and other references submitted.

Dosage and directions for use

MSM Should be in line with the relevant package insert template if available, or if not available in line with the innovator package insert. Any additional information as required by the applicant should be submitted with relevant clinical data.

NCE Source of particulars should be the clinical data and other references submitted. Where appropriate the following should be addressed: the maximum recommended single, daily and/or total dose, the need for dose titration, the normal duration of used and any restrictions on duration and the need for tapering off the dose.

Side effects and special precautions

MSM Should be in line with the relevant package insert template if available. Any additional information as required by the applicant should be submitted with relevant clinical data or references and/or references to the latest editions of the standard reference books.

NCE The side effects that belong together should be grouped together, either in one paragraph or under one sub-heading, e.g. gastrointestinal, skin, haematological, as per Organ Class Classification System of either WHOART or MeDRA, for example:

- Infections and infestations
- Neoplasms benign and malignant (including cysts and polyps)

b) *Headings and particulars in a package insert - Side effects and special precautions continued*

- Blood and the lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders
- Nervous system disorders
- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders
- Hepato-biliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal, connective tissue and bone disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital and familial/genetic disorders
- General disorders and administration site conditions
- Investigations
- Injury and poisoning
- Surgical and medical procedures
- Social circumstances

If a term or the spelling of a term is included in either of these internationally recognised terminologies, such spelling or term is allowed in package inserts.

Side effects should be ranked according to frequency within each System Organ Class using the following convention:

Very common ($>1/10$); common ($>1/100 \leq 1/10$); uncommon ($>1/1\ 000 \leq 1/100$);
rare ($> 1/10\ 000 \leq 1/1\ 000$); very rare ($\leq 1/10\ 000$), including "isolated reports".

The terms "more frequent" or "less frequent" may be used.

The CIOMS definitions of frequency based on incidence rates for Clinical trial ADRs and on reporting rates for post-marketing ADRs should be used. (In clinical trials the number of patients treated and the number of these patients with an ADRs are known whereas for post-marketing ADRs the actual numbers of patients treated and with ADRs are not known and it is therefore not possible to calculate the incidence rates for post-marketing ADRs. Reporting rates calculated by using distribution data and the number of reports for a specific ADR in a post-marketing database, can be used to estimate frequencies of post-marketing ADRs.)

In the case of multicomponent formulations, the side effects should be listed separately for each active pharmaceutical ingredient (API).

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

The following should be described if appropriate:

- the conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled (for example, relative contraindications).
- special patient groups likely to experience product or class related adverse reactions (ADRs) occurring under normal conditions of use e.g. specified age groups, patients with renal, hepatic impairment (including the degree of impairment, such as mild, moderate or severe) or cardiac failure (including the NYHA classification).
- circumstances where all patients are at risk of a specified adverse reaction, but the incidence or severity of the reaction differs in particular populations.

b) Headings and particulars in a package insert - Side effects and special precautions continued

- serious adverse reactions to which the prescriber needs to be alerted, the situations in which these may occur and the action that may be required, e.g. emergency resuscitation.
- when the outcome of an adverse reaction is frequently serious, this could be emphasised by presenting the statement at the top of this section, in bold type, within a box.
- if there are particular risks associated with starting the medicinal product (e.g. first dose effects) or stopping it (e.g. rebound, withdrawal effects), these should be mentioned in this section, together with the action required for prevention.
- any measures which can be taken to identify patients at risk and prevent the occurrence, or detect early the onset or worsening, of noxious conditions. If there is a need for awareness of symptoms or signs representing early warning of a serious ADR, a statement should be included. Any need for specific clinical or laboratory monitoring should be stated.
- clinically relevant interactions where in general the use of the combination should be avoided (relative contraindication) should be mentioned here.

Known symptoms of overdose and particulars of its treatment

MSM Should be in line with the relevant package insert template if available. Any additional information as required by the applicant should be submitted with relevant clinical data or references and/or references to the latest editions of the standard reference books.

Standard text is required for e.g. paracetamol, codeine and beta-blockers.

NCE For treatment of overdose it is usually acceptable to state, "Treatment is symptomatic and supportive". Specific text could however be required.

Identification

In accordance with PART 3F.

Presentation

In accordance with PART 3D.

Storage instructions

In accordance with PART 3G.

Registration number

Allocated by the Registrar in accordance with Section 15 of the Act.

Name and business address of the holder of the certificate

In accordance with MRF1 PART 1A.

Date of publication of the package insert

This date should be the date of the Medicines Control Council resolution. The date should only change when the package insert is re-evaluated by Council.

Note: Any deviation from the prescribed requirements of Regulation 9 of the Act should be in compliance with Regulation 9(s)(i), (ii), (iii) and (iv).