CLINICAL REQUIREMENTS

- The Act
- Application form - PART 4
- Regulations

8.3 *For Biological Medicines the applicant must include details (published or unpublished) of the results of any trials or experiments carried out in man or in the animal target species, or carried out in other animals, that establish and confirm the safety of the medicine, with particular reference to the dosage and directions for use.*

8.4 For medicines other than biological medicines

In PART 4 the applicant needs to address the Pharmacology and Toxicology of the medicine:

8.4.1 Pharmacology:

8.4.1.1 Pharmacodynamics:

i) The primary effects of the medicine, with results in different animal species (ED_{50} values if possible) must be addressed.

ii) Comparison of the effects of the product with that of reference products is valuable information.

iii) Where relevant, the pharmacology of significant metabolites must be investigated.

iv) Other pharmacodynamic effects, especially those that might be of significance for adverse effects of the medicine, should be studied and described.

v) Interaction studies, where relevant, should be included.

8.4.1.2 Pharmacokinetics:

i) To assist in the interpretation of toxicological studies, it is important to compare the exposure of the animals used in the toxicity testing with that anticipated in patients given the proposed therapeutic dose regimen.

ii) PART 4 should, therefore, include comparative pharmacokinetics data, which includes C_{max} (after a single dose and at steady state) and AUC data for the parent drug and major/active metabolite(s), where relevant, in human and all species used in the toxicity, carcinogenicity and reproduction studies.

iii) These data should preferably be obtained from the toxicity studies.

iv) Other information (for example, $t_{½}$ and clearance), may be of value where important differences have been shown between animals and man.

8.4.2 Toxicology:

i) A summary or expert report must be submitted for each animal species studied, including sex, number of animals, dosage, route of administration, duration of study and toxic manifestations.

ii) Important points pertaining to preclinical toxicity to consider and address are:

- Dose-response relationship
- Time-response relationship
- Species specificity
- Target organ specificity
- Reversibility / irreversibility of toxic effects.

iii) Medicines that show specific toxicological effects, such as immunotoxicity, hepatotoxicity or neurotoxicity, should be investigated further, taking into account the points under ii)

iv) New medicines, which belong to classes that are known to produce a particular toxic effect, should be tested appropriately.

v) The possible mechanism(s) underlying the changes observed in toxicity studies need to be investigated and addressed.

vi) Due to the local climatic conditions the phototoxic potential of a medicine should be considered.

vii) The points to address in the reproduction studies are: fertility, embryonal toxicity, teratogenicity, peri- and postnatal effects.

8.5 The details of results from tests shall depend on the state of scientific knowledge at the time when the application is lodged. Any interim and final results of ongoing studies must be submitted as soon as these data become available.

8.6 A new route of administration or an increased daily dose of known excipients may result in the need for additional pharmaco-toxicological data.

9. PART 5 - CLINICAL STUDIES

9.1 Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities (USA, UK, Sweden, EU, Canada, Netherlands, Australia). The Medicines Control Council endeavors to keep abreast of such developments and keep its application requirements and evaluation policies in line with "best international practice" as per introduction. Please refer the Medicines Control Council Clinical trials guidelines.

9.2 Legislation to be read in conjunction with these guidelines are:

- Act
- Application form - PART 5.
- Regulation.

9.3 The clinical data must be presented in such manner that allows for easy cross-referencing to the index, other studies and the professional package insert. [Applicants wishing to submit data in electronic form should discuss the requirements with the Registrar of the Medicines Control Council].

9.4 Data presented in support of the safety and efficacy of the medicine must be derived from clinical trials conducted in compliance with

internationally accepted GCP guidelines. The studies must be properly designed and conducted and must be of acceptable statistical power. Where relevant, results published in peer reviewed scientific journals should be submitted.

9.5 Clinical trials should be conducted with the formula as applied for. Where studies have been conducted with different formulations, comparative equivalence studies need to be submitted to enable extrapolation to the formula intended for the market.

9.6 Normally individual patient data from clinical trials need not be included in an application dossier (except in the case of bioequivalence studies where the individual plasma/serum concentrations and derived pharmacokinetic data are to be supplied). Tabulated individual patient data may be included in the application if the applicant considers it appropriate.

9.7 Studies designed to demonstrate the pharmacodynamics of a medicine should address the effect of the medicine, duration of effect, dose-response and tolerance. Additional action on the central nervous system, respiration, circulation, blood chemistry, liver and kidney function, etc., should be considered at the proposed therapeutic dose(s).

9.8 Pharmacokinetics studies should be conducted with the formula as applied for. All relevant pharmacokinetics data shall be given, such as amount and rate of absorption after various routes of administration, plasma concentration, half-lives, drug clearance, drug metabolism as well as the routes and rates of excretion.

The pharmacokinetics studies are to be carried out with both single dose and multiple doses to steady state within the recommended dosage range.

Where applicable the plasma concentration(s) producing pharmacological and/or therapeutic effects, as well as adverse effects should be presented.

Possible dose-dependent pharmacokinetics needs to be addressed.

9.9 The trial design of the relevant clinical studies should be such that the safety and efficacy of the medicine can be established in comparison to either placebo and/or a registered medicine in UK, USA, Sweden, Netherlands, Canada, Australia and EU. The description of the studies must include patient population size and diagnosis, in- and exclusion criteria, test and comparator drug dosage regimens and duration of therapy, parameters assessed for efficacy and safety, including results of special investigations. Detailed statistical results must be presented. It should be noted that the randomised, double blind, placebo and/or active controlled trial design remains the gold standard for establishing the efficacy and safety of medicines.

9.10 The dosage of the active comparator (refer to Section 4.10 Bio-equivalence of a new multi-source medicines) must be in line with that approved for the specific indication.

9.11 The patient drop-outs must be addressed, including the time of and reason(s) for withdrawal.

9.12 To enable evaluation of safety of the medicine it should be noted that the long-term safety, particularly for medicines proposed for chronic use, needs to be addressed.

9.13 While a product is being evaluated, applicants should notify MCC of:

i) any approvals, rejections or withdrawals of applications in other countries and

ii) any serious adverse effects observed for the first time, or at a frequency, which has become a concern.

9.14 During the evaluation period, if new significant data becomes available that is contrary to the use of the medicines, applicants must notify Council. With this notification the applicant should state it's intention.

10. STANDARD PACKAGE INSERT INFROMATION FOR CERTAIN CATEGORIES/INGREDIENTS:

Unless the applicant can provide convincing evidence to the contrary, package inserts should contain the following, although the wording need not be identical. Standard information to be included in the professional package insert:

10.1 GENERAL DROWSINESS WARNING FOR ANTIHISTAMINES (OLD GENERATION)

This medicine may lead to drowsiness and impaired concentration that may be aggravated by simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned against taking care of vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.

10.2 GENERAL DROWSINESS WARNING FOR ANTIHISTAMINES (NEW GENERATION)

This medicine lacks significant sedative effects.

10.3 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 9(3) the wording may still appear on the immediate label of the medicine provided that the type size is not bigger than the type size in which the active ingredients appear.

10.4 DEPENDENCE PRODUCING POTENTIAL OF MEDICINES

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

10.5 IMPORTANT PATIENT INFORMATION TO BE INCLUDED IN ALL PACKAGE INSERTS OF MEDICINES INTENDED FOR MALARIA PROPHYLAXIS

The following patient warnings must 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:

i) endemic areas should preferably be visited during the dry season or in years when rainfall is low;
ii) 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;
iii) not going outside between dusk and dawn, when mosquitoes are most active;
iv) applying insect repellant to exposed skin and clothing;
v) wearing long sleeves and trousers at night;
vi) using mosquito nets, screens, coils or pads

A warning that should flu-like symptoms present the patient must inform the doctor that he has been to a malarious area.

10.6 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 must be included in the package inserts for those medicines
"The safety of this preparation in pregnant women has not been established."

10.7 PACKAGE INSERTS / SLOGANS

Advertising (slogans) in package inserts is not permissible.

10.8 PACKAGE INSERT REQUIREMENTS : 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 alone"

10.9 PRODUCTS CONTAINING ACE-INHIBITORS

The following boxed warnings must be included:

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

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

The following warnings must 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."

10.10 ANTIBIOTICS INDICATED FOR THE TREATMENT OF BETA-HAEMOLYTIC STREPTOCOCCAL INFECTIONS

The following statement must be included under the heading DOSAGE AND DIRECTIONS FOR USE:

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

10.11 REYE'S SYNDROME WARNING FOR MEDICINES CONTAINING ASPIRIN

The following warning 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."

10.12 BENZALKONIUMCHLORIDE-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 op 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."

10.13 PACKAGE INSERTS FOR 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:

Under "Side-effects and special precautions"

CLINICAL REQUIREMENTS

The side-effects most commonly encountered are drowsiness and over sedation. Drowsiness is more common in elderly and debilitated patients and in patients receiving high doses. Less common are depression of mood and affect, disorientation or confusion, lethargy and ataxia.

Paradoxical reactions such as acute hyper excitable states with rage may occur. If these occur, the medicine should be discontinued.

There is a potential for abuse. Withdrawal symptoms (including convulsions) have occurred following abrupt cessation especially in patients receiving 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);

- patients with pulmonary disease and limited pulmonary reserve;
- patients suffering from impairment or 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. Given 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, climb dangerous heights or operate dangerous machinery. In these situations, impaired decision making could lead to accidents.

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

10.14 BENZODIAZEPINE OR BENZODIAZEPINE-LIKE COMPOUNDS

Product name to be inserted in [ ]

Indications

CLINICAL REQUIREMENTS

[ ] is only indicated when the disorder is severe, disabling or subjecting the individual 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 reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom-free. The overall duration of treatment generally should not be more than 8-12 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.

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

Duration of treatment
The duration of treatment should be as short as possible (see Dosage), but should not exceed 4 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 situation. 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 be 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 must be adapted according to approved indications for each individual product.

10.15 BETA-2 AGONISTS

INDICATION

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

Under "SIDE EFFECTS AND SPECIAL PRECAUTIONS"

Hypokalaemia may occur.
Overdosage may cause cardiac effects.
High dosages may increase the risk of serious side-effects, including cardiac dysrhythmias. This risk is further aggravated if 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.

Under "DOSAGE AND DIRECTIONS FOR USE":

Do not exceed the recommended dose.

10.16 STANDARDIZED PACKAGE INSERTS FOR 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:

Under "Side-effects and special precautions"

a) Bronchoconstriction may occur in patients suffering from asthma, bronchitis and other chronic pulmonary diseases
b) Congestive cardiac failure and marked bradycardia may occur
c) A variety of neuropsychiatric disorders may occur, ranging from vague fatigue and nightmares to overt psychosis
d) 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 gastrio-intestinal disturbances. Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

CLINICAL REQUIREMENTS

e) Adverse reactions are more common in patients with renal decompensation, and in patients who receive the drug intravenously.
f) It is dangerous to administer this medicine concomitantly with the following medicines: hypoglycaemic agents, phenothiazines and various antiarrhythmic gents.

NB: - 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 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.

g) 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.
h) Administration to pregnant mothers shortly before giving birth, or during labour may result in the newborn infants being born hypotonic, collapsed and hypoglycaemic.
i) Patients with phaeochromocytoma usually require treatment with an alpha-adrenergic blocker.

Under "Contra-Indications":

a) 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.
b) The normal dose should be reduced in elderly patients, or in patients suffering from renal dysfunction.
c) In the perioperative 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.

Under "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 4 hours, as apnoea and cardiovascular collapse may appear suddenly.

Gastric lavage should be performed within 4 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 give intravenously. Alternatively, dobutamine or isoprenaline may be required to reverse beta-blockade.

CLINICAL REQUIREMENTS

Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled or IV beta-agonist eg. salbutamol.

10.17 WARNINGS FOR INCLUSION IN BETA-BLOCKER AND CLONIDINE PACKAGE INSERTS

The following warnings must 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".

10.18 BETA-LACTAM ANTIBIOTICS

The following statement must be included in the package inserts of all beta-lactam and fluoroquinolone antibiotics containing an indication or claim for Pseudomonas aeruginosa under the heading

INDICATIONS:

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

10.19 BISMUTH CONTAINING MEDICINES

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

10.20 PACKAGE INSERTS FOR CLOFIBRATE CONTAINING

Package inserts for all clofibrate-containing medicines must reflect:

Under "Indications"

Before starting treatment with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control over diabetes mellitus, etc.

If after considering the possible benefits in relation to the risks, it is decided to use clofibrate it is indicated in types II(B), III, IV and V hyperlipoproteinaemias (Frederickson and Levy Classification)

FREDERICKSON TYPE	CLINICAL REQUIREMENTS LIPOPROTEIN ELEVATION	MAJOR LIPID ELEVATION
I (very rare)	chylomicra	Triglycerides
II (a)	(LDL)	Cholesterol
II (b)	pre - + (VLDL + RDL)	Cholesterol + Triglycerides
III (rare)	abnormal (LDL)	Cholesterol + Triglycerides
IV	pre (VLDL)	Triglycerides
V (rare)	chylomicra + pre (VLDL)	Triglycerides + cholesterol

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.

Under "Side-effects and special precautions"
Due to its action on cholesterol metabolism, clofibrate may increase the lithogenicity of bile and there is an increased frequency of gallstones.

A possible association between treatment with clofibrate and gastro-intestinal malignancies exists.

10.21 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 be 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 - 60 minutes after administration of [proprietary name]. Patients with known or suspected hypersensitivity to iodated contrast media must be closely observed.

10.22 EXEMPTION FROM PACKAGE INSERT REQUIREMENTS IN RESPECT OF CONTACT LENS SOLUTIONS.

THIS EXEMPTION SPECIFICALLY DOES NOT APPLY TO ARTIFICIAL TEAR SOLUTION.

CLINICAL REQUIREMENTS

Contact lens solutions are exempted from package insert requirements in respect of contact lens solutions provided that: -

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

10.23 WARNING FOR INCLUSION IN POTENT TOPICAL CORTICOSTEROID PACKAGE INSERTS

The following warning must be included in all potent topical corticosteroid package inserts:
"Potent topical corticosteroid preparations (name) should not be applied to any skin crease areas"

10.24 PRODUCTS FOR TOPICAL USE CONTAINING CORTICOSTEROIDS

Package insert for all topical corticosteroid must reflect the following:

Under "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."

10.25 CO-TRIMOXAZOLE

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

10.26 DICYCLOMINE IN INFANTS

The indication "infantile colic" and dosage schedule for children under six months of age be not included and a warning against its use in "infantile colic" be included.

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

10.27 PACKAGE INSERTS FOR DISOPYRAMIDE PREPARATIONS

Under "Side-effects and Special Precautions"

CLINICAL REQUIREMENTS

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

Under "Contra-indications"

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

10.28 FLUOROQUINOLONE ANTIBIOTICS

Refer to Beta-lactam antibiotics

10.29 BOXED WARNING FOR GLIBENCLAMIDE & GLICLAZIDE

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

10.30 IODINE AND IODIDE CONTAINING MEDICINES

Synthetic thyroid hormone preparations are exempted from the following requirements.

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

" NOT TO BE USED DURING PREGNANCY OR BY LACTATING MOTHERS"

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

" NOT TO BE USED BY PERSONS WHO ARE ALLERGIC TO IODINE"

10.31 PACKAGE INSERTS FOR METOCLOPRAMIDE PREPARATIONS

Kindly note that this warning must appear on ALL package inserts

"WARNING

The use of metoclopramide throughout the duration of pregnancy is considered unsafe as teratogenicity has been demonstrated in animal studies."

10.32 WARNING TO BE INCLUDED IN THE PACKAGE INSERTS OF ALL PRODUCTS CONTAINING METRONIDAZOLE

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

"Pseudomembranous colitis has been reported following the use of metronidazole".

10.33 NON STEROIDAL ANTI-INFLAMMATORY AGENTS

The following warning regarding the use of non-steroidal anti-inflammatory agents in pregnancy must be included in all package insert of non-steroidal anti-inflammatory agents:

"Regular use of NSAIDs 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 newborn. 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."

10.34 PACKAGE INSERT WARNING FOR 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."

"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:

Under "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 afterwards. 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.

10.35 PHENYLBUTAZONE & OXYPHENBUTAZONE

The indications and period of use for phenylbutazone and oxyphenbutazone preparations must 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 must 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 be limited to a maximum 600 mg per day:
Combination products containing phenylbutazone and oxyphenbutazone is not allowed

10.36 POTASSIUM SUPPLEMENTATION

The following statement must be included in package inserts of medicines containing potassium for the purpose of potassium supplementation (under the heading 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".

10.37 LONG-ACTING SULPHONAMIDES

Refer to co-trimoxazole

10.38 TAMOXIFEN

The following safety information must be included in the package inserts of all tamoxifen containing products:

WARNINGS:
"Endometrial changes
An increased incidence of endometrial changes, including hyperplasia, polyps and cancer has been reported in association with tamoxifen treatment. Any patients receiving or having previously received tamoxifen, who report vaginal bleeding should be promptly investigated".

CLINICAL REQUIREMENTS

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.

10.39 TARTRAZINE (FD & C YELLOW NO 5) – WARNING IN THE PACKAGE INSERT

It is required that the following warning 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."

10.40 TOPICAL TRETINOINS - STATEMENT ON PREGNANCY AND LACTATION.

Oral tretinoin has been shown to be teratogenic in a wide variety of animals.

Limited animal data urge caution in the use of preparations containing tretinoin during the first trimester of pregnancy.

In the case of eventual pregnancy the patient should inform her doctor.
Therefore, it may be concluded that cutaneous administration of tretinoin to pregnant women should not pose a significant hazard, although, as with all medicines, its use should be avoided during pregnancy unless the benefits outweigh any potential risk to the foetus.

It is not known whether tretinoin is excreted in animal or human milk. 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.

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

10.42 STANDARDIZED PACKAGE INSERTS FOR TRICYCLIC ANTIDEPRESSANTS

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:

Under "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 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:

a) 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.

b) Caution should be observed 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.

c) In elderly male patients suffering from prostatism urinary retention may be precipitated.

d) 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 electrocardiagraphic examination is advised.

CLINICAL REQUIREMENTS

e) Epilepsy may be aggravated.

f) The medicine should not usually be given to patients receiving other central nervous system depressants, e.g. barbiturates, and to patients receiving monoamine oxidase inhibitors only after a suitable interval (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.

g) Narrow-angle glaucoma may be aggravated.

h) Withdraw the drug if allergic skin reactions appear.

Under "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.

Under "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.

10.43 STATEMENT ON EOSINOPHILIA MYALGIA SYNDROME TO BE INCLUDED IN PACKAGE INSERTS OF L-TRYPTOPHAN CONTAINING PRODUCTS

The following statement must be included under the heading "WARNINGS" in the package inserts of the products containing L-Tryptophan.

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

10.44 CODEINE WARNING

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

CLINICAL REQUIREMENTS

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

PHARMACEUTICA & ANALYTICAL REQUIREMENTS

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

PHARMACEUTICAL AND ANALYTICAL REQUIREMENTS

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

These guidelines should be read in conjunction with Regulations 2, 8, 9, 22, 24, 42, 43, 44 and 48.

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

Version MCC2003/1

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

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PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

1. INTRODUCTION

The technical requirements for pharmaceutical and analytical information are divided into ten parts in the application form. The parts are as follows:

Part 2A – Active Pharmaceutical Ingredient.

Part 2B – Formulation.

Part 2C – Specifications and control procedures for active and inactive ingredients.

Part 2D – Containers and Packaging materials.

Part 2E – Manufacturing procedure.

Part 2F – Finished Product Pharmaceutical medicines.
Final filling lot and diluent Biological medicines

Part 2G – Stability studies.

Part 2H – Pharmaceutical Development.

Part 2I – Expertise and premises used for manufacture of biological medicines.

Part 3 – Bioequivalence studies as proof of efficacy.

The above Parts must be read together with the following documents:

ADDENDA TO THE GUIDELINES

ADDENDUM 1: Alcohol Content
ADDENDUM 2: Validation Protocols and Validation Reports
ADDENDUM 3: Post-importation Identification and Testing of medicines
ADDENDUM 4: Stability Studies
ADDENDUM 5: Bioequivalence Studies as Proof of Efficacy
ADDENDUM 6: Dissolution Studies

2. PHARMACEUTICAL AND ANALYTICAL REQUIREMENTS

2.1 PART 2A - ACTIVE PHARMACEUTICAL INGREDIENT

2.1.1 The International Nonproprietary Name (INN), or approved name, or chemical description of the active pharmaceutical ingredient(s) must be stated including the structural formula, the empirical formula and the molecular mass.

2.1.2 The solubility of each active pharmaceutical ingredient must be stated in terms of a unit part of the substance per number of parts of the solvent, or in unit mass of substance in a given volume of solvent, at a specific temperature. The solvents must include water and the solvent(s) relevant to the formulation.

2.1.3 The storage requirements for the active pharmaceutical ingredient and the retesting period must be stated

2.1.4 The name and physical address of each manufacturer of the API being applied for must be stated. No API from any source other than the approved source(s) may be used.

2.1.5 The Active Pharmaceutical Ingredient File (APIF) or open part of the DMF must be submitted and should include the following information:

- The name and physical address of the manufacturer (including any intermediate manufacturer)
- The INN or approved name of the relevant API
- The chemical name and chemical structure of the API
- A description of the pathway of synthesis using a flow chart which includes the starting materials, reagents, solvents, conditions, processes, duration of treatments, intermediates formed and any other relevant aspects. Note that specifications and control procedures for substances used in this process are not generally required. (The specific processes under any intermediate manufacturer must be identified)
- Evidence of occurrence of isomers and polymorphism, where applicable
- Structure elucidation for NCEs
- A description of impurities and a clear distinction between actual and possible impurities
- A description of possible degradation products
- The physical and chemical properties of the API
- The detailed methods used for identification and assay, including chromatograms wherever relevant
- CoA results relating to at least two full-scale batches manufactured not more than 2 years prior to date of submission
- Results of stability studies performed on the API obtained by the above method of synthesis. The conditions under which degradation products are formed. A validated stability-indicating assay method must be used in these studies, and must be described in full. Supporting chromatograms wherever relevant must be included.

2.1.6 Alternatively, if available, an EU certificate of suitability (CEP) can be submitted. Ensure that the CEP is accompanied by report A and any appendices mentioned in the CEP. If a CEP is submitted, detailed methods for the identification and assay of the API is not required in the APIF, and only an outline of the method of synthesis will suffice. Impurities and residual solvents listed in the CEP must be included in the API specifications (Part 2C).

2.1.7 Certificates of analyses (CoAs)

Valid CoAs* of two batches of the API, purchased and received by the manufacturer of the final product must be submitted. Any test not included in the valid CoA as specified in Part 2C must be performed by or on behalf of the manufacturer of the final product. A valid CoA must be on the letterhead of the manufacturer of the API.

2.1.8 When more than one manufacturer is being applied for or when different methods of synthesis are used in the manufacture of API, the following must be submitted:

a) An Active Pharmaceutical Ingredient File (APIF) for each manufacturer Note that if an identical method of synthesis is used by each manufacturer, or by each site of the same parent company, a statement to this effect will suffice.

b) Communication pointing out the differences in the methods used, where applicable, and the differences with regard to the impurity profiles and residual solvents. The specifications for the API must make provision for these impurities and residual solvents

c) Valid CoAs* issued by each manufacturer or site and the analytical reports issued by or on behalf of the manufacturer of the final product. For new sources the valid CoA* is required.

d) Comparative critical tests e.g. identification, assay, solubility and/or dissolution, particle size distribution, polymorphism, optical rotation, residual solvents and impurity profiles, performed on samples from each source to demonstrate physical and chemical equivalence, must be performed by the same laboratory (either the laboratory of the manufacturer or an independent laboratory). The same analytical methods and equipment must be used for these tests. These results must be presented in tabulated format.

*Valid as defined in the cGMP

2.1.9 Stability data on new chemical entity APIs must be generated according to the stability guidelines.

2.1.10 For biological medicines, specifications of raw materials used in the primary production lot are required:

a) In the case of a biological medicine of microbial origin, history and preparation of the seed lot must be described with specific reference to the tests that are carried out on such a seed lot to establish and maintain the integrity thereof.

b) Particulars of the composition of all culture media used in the preparation and testing of a biological medicine must be given.