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Primary stability studies are intended to show that the active substance will remain within specification during the retest period if stored under recommended storage conditions.

1.1.1.iv Selection of Batches

Stability information from accelerated and long-term testing is to be provided on at least three batches. The long-term testing should cover a minimum of 12 months duration on at least three batches at the time of submission of the application for registration.

The batches manufactured to a minimum of pilot plant scale should be by the same synthesis route and use a method of manufacture and procedure that simulates the final process to be used on a manufacturing scale.

The overall quality of the batches of active substance placed on stability should be representative of both the quality of the material used in pre-clinical and clinical studies and the quality of material to be made on a manufacturing scale.

In the event of more than one manufacturer being used it must be confirmed that the same method of synthesis is used or extensive comparative data submitted including all aspects of quality, safety and efficacy.

Supporting information may be provided using stability data on batches of active substance made on a laboratory scale.

The first three production batches of active substance manufactured post approval, if not submitted in the original application for registration, should be placed on long-term stability studies using the same stability protocol as in the approved application for registration.

1.1.1.v Test Procedure and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical and microbiological test characteristics. Validated stability-indicating testing methods must be applied. The need for the extent of replication will depend on the results of validation studies.

1.1.1.vi Specifications

Limits of acceptability should be derived from the profile of the material as used in the preclinical and clinical batches. It will need to include individual and total upper limits for impurities and degradation products, the justification for which should be influenced by the levels observed in material used in preclinical studies and clinical trials.

1.1.1.vii Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Application of the same storage conditions as applied to the drug product will facilitate comparative review and assessment. Other storage conditions are allowable if justified. In particular, temperature sensitive active substances should be stored under an alternative, lower temperature condition which will then become the designated long-term testing storage temperature. The six months accelerated testing should then be carried out at a temperature at least 15 °C above this designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature). The designated long-term testing conditions will be reflected in the labelling and retest date.

STABILITY

	Conditions	Minimum time period at submission
Long-term testing	25 +- 2 °C/60 +- 5%RH	12 months
Accelerated	40 +- 2 °C/75 +- 5%RH	6 months

Where "significant change" occurs during six months storage under conditions of accelerated testing at 40 °C +- 2 °C/75%RH +- 5%, additional testing at an intermediate condition (such as 30 ° C +- 2 ° C/65% +- 5%RH) should be conducted for active substances to be used in dosage forms tested long term at 25 °C/60%RH and this information included in the application for registration. The initial application should include minimum of 6 months' data from a 12month study.

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"Significant change" at 40 °C/75%RH or 30 °C/60%RH, is defined as failure to meet the specification.

The long-term testing will be continued for a sufficient period of time beyond 12 months to cover all appropriate retest periods, and the further accumulated data can be submitted to the Council during the assessment period of the application. The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short-term excursions outside the label storage conditions such as may occur during shipping.

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

1.1.1.viii Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the active substance. Testing under the defined long-term conditions will normally be every three months over the first year, every six months over the second year and then annually.

1.1.1.ix Packaging/Containers

The containers to be used in the long-term, real-time stability evaluation should be the same as or simulate the actual packaging used for storage and distribution.

1.1.1.x Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the active substance and evaluating the stability information (covering as necessary the physical, chemical, and microbiological test characteristics), a retest period applicable to all future batches of the bulk active substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the retest date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate, and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0,25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of any degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under the circumstances, it is normally

unnecessary to go through the formal statistical analysis but merely to provide a full justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend the retest period at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanism of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should cover not only the assay but the levels of degradation products and other appropriate attributes.

When degradation products are identified in significant amounts or suspected of toxicity, a concerned effort has to be made to collect the following additional information about the substance concerned:

- chemical structure
- cross-reference to any available information about biological effect and significance at the concentrations likely to be encountered
- procedure for isolation and purification
- mechanism of formation, including order of reaction
- physical and chemical properties
- specifications and directions for testing their presence at the levels of concentrations expected to be present, and
- indication of pharmacological activity, or inactivity or toxicity profile.

Where the route of degradation is not known, suitable screening chromatographic or other tests may be required.

Official compendia or other tests designed to identify impurities in the active substance used in the formulation may not necessarily be suitable for investigation into degradation products.

When it has been considered necessary to perform toxicity studies these results should be presented.

Consideration should be given to the stereo-chemical and polymorphic integrity of active substances.

Stability information gained should enable the applicant to institute a routine system whereby re-analysis to validate the conformance to specification of the active substance is done in order that the stability of the dosage form concerned is assured.

1.1.1.xi Statements/Labelling

A storage temperature should be based on the stability evaluation of the active substance. Where applicable, specific requirements should be stated, particularly for active substances that cannot tolerate freezing. The use of terms such as "ambient conditions" or "room temperature" is unacceptable.

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A retest period should be derived from the stability information.

1.1.2 Well-known Chemical Entities (established active substances)

Literature data on decomposition process and degradability are generally available and must be included in the submission.

If degradation pathways/products are unknown, references to support such conclusions must be included or experimental data submitted. Reference to pharmacopoeias will not satisfy this requirement.

1.2 DOSAGE FORMS

1.2.1 Products containing New Chemical Entities

1.2.1.i General

The design of the stability program for the finished product should be based on the knowledge of the behaviour and properties of the active substance and the experience gained from clinical trial formulation studies and from stability studies on the active substance. The likely changes on storage and the rationale for the selection of product variables to include in the testing program should be stated.

1.2.1.ii Selection of Batches

Stability information from accelerated and long-term testing is to be provided on three batches of the same formulation and dosage form in the containers and closure proposed for marketing. Two of the three batches should be at least pilot scale. The third batch may be smaller (e.g., 25 000 to 50 000 tablets or capsules for solid oral dosage forms).

The long-term testing should cover at least 12 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large- scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification as to be applied to release of material. Where possible, batches of the finished product should be manufactured using identifiably different batches of active substance.

Where an application includes different sources of active substances that are not physically and/or chemically equivalent and/or where the difference in physical and/or chemical specifications may adversely affect the stability of the product, stability studies should be performed on the final product manufactured from each active substance.

Data on laboratory scale batches is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supportive information, provided that the difference in the formulations is clearly stated. The first three production batches manufactured post approval, if not submitted in the original application for registration should be

placed on accelerated and long-term stability studies using the same stability protocols as in the approved application for registration.

1.2.1.iii Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated, and assays should be stability-indicating. .

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Where the "in-use" form of the product differs markedly from the manufactured and packaged form (for example, where the product is required to be reconstituted, diluted or mixed prior to use), data to establish the stability of the "in-use" form of the product should be supplied. "In-use" stability studies may also be required for certain sensitive products where the opening and closing of the containers may have an effect. This also applies to "in-use" multidose vials.

Where the manufacturer claims the product may be diluted with a range of solutions prior to use, for example, products that require dilution prior to parenteral infusion, stability data to establish compatibility with and stability in each solution should be submitted. Data on compatibility with the range of materials, such as are used for the intravenous infusion containers and the administration sets recommended for use should be submitted.

Where the dosage form is to be reconstituted at the time of dispensing, its labelling should bear supportive expiration information and storage conditions for both the reconstituted and unreconstituted dosage forms.

The range of testing should cover not only chemical and biological stability but also loss of preservative (where relevant), physical properties and characteristics, organoleptic properties and, where required, microbiological attributes.

Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives.

Stability should be established for the whole period of intended use under the conditions reflected in the printed packaging components (Annexure 1).

1.2.1.iv Specifications

The stability studies must include testing of those attributes of the product that are susceptible to change during storage and that are likely to influence quality, safety and efficacy.

Limits of acceptance should relate to the release limits (where applicable), to be derived from consideration of all the available stability information. The shelf life specification could allow acceptable and justifiable deviations from the release specification based on the stability evaluation and the changes observed on storage. It will need to include specific upper limits for degradation products, the justification for which should be influenced by the levels observed in material used in pre-clinical studies and clinical trials. The justification for limits proposed for certain other tests such as particle size and/or dissolution rate will require inference to the results observed for batch(es) used in bioavailability and/or clinical studies. Any differences between the

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release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing.

1.2.1.v Storage Test Conditions

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labelling).

See table below for accelerated and long-term storage conditions and minimum times. An assurance that long-term testing will continue to cover the expected shelf-life should be provided. Other storage conditions are allowable if justified. Heat sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature. Special consideration may have to be given to products that change physically or even chemically at lower storage conditions, e.g. suspensions or emulsions which may sediment or cream, oils and semi-solid preparations, which may show an increased viscosity.

The clarity of solutions and the physical stability of semi-solid preparations and emulsions should be determined over a wide temperature range. Where a lower temperature condition is used, the six months accelerated testing should be carried out at a temperature at least 15 ° C above its designated storage temperature (together with appropriate relative humidity conditions for that temperature). For example, for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25 +- 2 °C/60%RH +- 5%RH. The designated long-term testing conditions will be reflected in the labelling and expiration date.

Storage under conditions of high relative humidities applies particularly to solid dosage forms. For products such as solutions, suspensions, etc., contained in packs designed to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary, but the same range of temperatures should be applied. Low relative humidity (e.g., 10 - 20% RH) can adversely affect products packed in semi-permeable containers (e.g., solutions in plastic bags, nose drops in small plastic containers, etc.,) and consideration should be given to appropriate testing under such conditions.

For solutions with a high sugar content (greater than 60 %) or where the solubility of the active is low (less than 5 mg per 100 ml) or its content is close to saturation, stability data at low temperatures (2 to 8 ° C) must be conducted for at least 14 days.

	Conditions	Minimum time period at submission
Long-term testing	25 +- 2 °C / 60 +- 5%RH	12 months
Accelerated	40 +- 2 °C / 75 +- 5%RH	6 months

Where "significant change" occurs due to accelerated testing additional testing at an intermediate condition, e.g., 30°C +- 2 °C / 65%RH +- 5%RH should be conducted. "Significant change" at accelerated condition is defined as:
- A 5% potency loss from the initial assay value of a batch;
- Any specified degradant exceeding its specification limit;
- The product exceeding its pH limits;

- Dissolution exceeding the specification limits for 12 capsules or tablets;
- Failure to meet specifications for appearance and physical properties, e.g., colour, phase separation, resuspendability, delivery per actuation, caking, hardness, etc.

Should significant change occur at 40 °C/75%RH then the initial application for registration should include a minimum of 6 months' data from an ongoing one-year study at 30°C/65%RH, the same significant change criteria shall apply.

The long-term testing will be continued for a sufficient time beyond 12 months to cover shelf-life at appropriate test periods.

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

1.2.1.vi Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the drug product. Testing will normally be every three months over the first year, every six months over the second year, and then annually throughout the proposed shelf-life.

The use of matrixing or bracketing can be applied if justified (See Glossary).

1.2.1.vii Packaging Material

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected drug product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive packs).

Where package container sealant integrity is to be assessed, higher than 75% relative humidity may be appropriate to stress its adhesive properties at 30 to 40°C e.g., blister units and strip packages. Alternatively, sealant integrity can be performed through physical testing of the pack itself

The loss of moisture can be important for liquid formulations, semisolid and certain solid dosage forms packed in moisture permeable containers and studies at low relative humidity and high temperature for a limited period of time may be appropriate for these products.

For most dosage forms stability data need only be obtained for the container-closure system to be marketed, provided that all container-closure systems are of identical composition and seal integrity and a brief justification is included stating the reasons for the container size chosen e.g. larger air volume, or largest surface contact etc.

If the product is to be marketed in more than one type of container and the applicant proves that resistance to variables such as moisture permeation, oxygen permeation, light diffusion etc., is demonstrated to be equal to or better than existing container closure systems, additional stability testing would usually not be required for solid dosage forms before such changes in packaging can be supplemented.

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Physician's samples should be included in the stability studies if their container-closure system is different from the marketing container unless equivalence or superiority of the packaging material can be demonstrated.

In instances where the product will be marketed packaged in a "moisture permeable" material (e.g., polyethylene, polypropylene, polyvinyl chloride, etc.), the stability of the product should be determined under conditions of high humidity and elevated temperature.

Stability may be conducted in the least protective container-closure system if the superiority of the other containers can be proven. These data must be included in Part G .

The time that the product is stored in the bulk container, prior to packing into the final immediate container, constitutes part of the approved shelf-life, that is, the date of expiry remains a function of the date of manufacture, not the date of packaging. Stability data must be submitted for bulk products that are stored for a period of time prior to packaging into the final immediate containers e.g., for 25% or more of the approved shelf-life.

1.2.1.viii Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover as necessary physical, chemical, biological and microbiological quality characteristics, including particular properties of the dosage form (for example dissolution rate for oral solid dosage forms).

The design of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf-life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the expiration date.

An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate, and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0,25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Where the data shows so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission.

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Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated data supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data, and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

Any evaluation should consider not only the assay, but the levels of degradation products and appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance, different stability, and degradation performance.

The stability of the drug products after reconstituting or diluting according to labelling, should be addressed to provide appropriate and supportive information.

In the case of reconstituted products for oral use, the reconstituted product must be tested for at least the recommended storage period at 25 °C even if the recommended storage temperature is 2-8 °C.

1.2.1.ix Statements/Labelling

The storage temperature should be based on the stability evaluation of the drug product. Where applicable, specific requirements should be stated particularly for drug products that cannot tolerate freezing.

The use of terms such as "ambient conditions" or 'room temperature" is unacceptable.

There should be a direct linkage between the label statement and the demonstrated stability characteristics of the drug product.

The use of a temperature range, for example 15 - 25 °C, is not acceptable, unless adequate motivation for the lower temperature is submitted. The recommendation, "Store below 25 °C. Do not refrigerate" could be considered.

1.2.2 PRODUCTS CONTAINING WELL-KNOWN CHEMICAL ENTITIES (GENERICS)

1.2.2.i Selection of Batches

Stability information from accelerated and long-term testing is to be provided on at least two batches of the same formulation and dosage form in the containers and closure proposed for marketing. One of the two batches should be at least pilot scale. The second batch may be smaller (e.g.,
25 000 to 50 000 tablets or capsules for solid oral dosage forms). The long-term testing should cover at least 9 months duration at the time of submission. The manufacturing process to be used should meaningfully simulate that which would be applied to large scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specification as to be applied to release of material.

1.2.2.ii Storage Test Conditions

STABILITY

	Conditions	Minimum time period at Submission
Long-term testing	25 +- 2°C / 60 +- 5%RH	9 months
Accelerated	40 +- 2°C / 75 +- 5%RH	3 months

The above criteria will be used for allocation of a tentative shelf-life of 24 months.
Stability data over the full shelf-life period must submitted for confirmation. 3 to confirm the tentative ~~At least 9 months' data must be submitted before a shelf-life can be considered.~~

Long-term stability studies can also be performed at 30°C/65% RH, but then there are no intermediate conditions (Zone IV)

The first two production batches manufactured post approval, if not submitted in the original application for registration, should be placed on long-term stability using the same stability protocols as in the approved application for registration.

If the accelerated data submitted in the original application were derived from batches other than production batches, accelerated data on at least one production batch must be generated.

Heat-sensitive drug products should be stored under an alternative lower temperature condition which will eventually become the designated long-term storage temperature. Where a lower temperature condition is used, the 3 months accelerated testing should be carried out at a temperature at least 15 °C above its designated long-term storage temperature (together with appropriate relative humidity conditions for that temperature).

Note:
Other general points discussed under "Products containing new chemical entities" are also relevant to generics.

2. PRESENTATION OF STABILITY DATA

a) The criteria for acceptance of each parameter (minimum and maximum values) relating to stability must be stated.
b) Overages in the formulation of batches included in the stability investigation should be clearly stated.
c) The actual analytical results obtained at the commencement (zero time) and at nominated time intervals throughout the trial (for example 0, 3, 6, 9, 12, 18, 24, 30, 36 months which can if necessary be adapted to suit the product) must be provided in a tabulated form. For products predicted to degrade rapidly more frequent sampling is necessary.
d).The container-closure system used must be clearly indicated, e.g., the type, nature, grade and colour of the material of the container and closure must be stated, composition of strip packaging, blister packaging and liners and size of the container(s) or pack-size must be clearly stated.
e) Storage conditions must be clearly defined in respect of temperature, light, humidity, opening and closing of container, whether stored upright or inverted, whether a desiccant is included in the container and presence of foam/cotton wool.

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f) The name and strength of product, dosage form, batch size, batch number, name of manufacturer, source of active substance, dates of manufacture and initial testing must be stated.
g) If more than one assay result is available for any particular time interval, all results should be quoted including the Mean and Standard Deviation (where possible).
h) The actual result obtained for an assay at the beginning of the stability trial should be recorded and compared with subsequent values.
i) Initial assay results should be expressed as the quantity of active substance per unit dosage form in terms of micrograms, milligrams or grams. Assay results for subsequent checkpoints should be given in the same way and in terms of percentage of initial assay.
j) Quantitative results must be reflected wherever relevant in which case the expression "complies" does not suffice.
k) All results obtained should be discussed and conclusions drawn from the stability studies be given. A shelf-life must be concluded from the results. Explanations should be given where necessary e.g., anomalous or unusual results, change in assay method. Results should be processed utilizing current statistical methods and any assumption made should be statistically tested at the 90 - 95 % confidence level.
l) Stability-indicating method refers to the specific analytical method and does not absolve the applicant from submitting reasons why the assay methods are assumed to be stability-indicating.
m) An assurance that long-term testing will continue to cover the shelf-life period must be given in Part 2G (written undertaking at the time of submission of the application). Applicants are reminded of the recommendation under Testing frequency that products should be tested at least annually after the second year.

3. PREDICTION OF SHELF-LIFE FROM STABILITY DATA

a) At least nine months' data derived from the product stored at the maximum recommended storage conditions and three months under conditions of stress for generic products must be available at the time of submission , for consideration of a tentative shelf-life of 24 months. For products containing new entities, the data accumulated over a sufficient period of time, beyond the initial 12 months, to cover appropriate retest periods must be available.
b) Generally a tentative shelf-life shall only be assigned provided that the stability investigation of the product as above has been satisfactorily completed.
c) Applicants are reminded that a tentative shelf-life is often established on condition that the applicant has committed himself by an undertaking to continue and complete the required studies and to submit the results as they become available.

4. FOLLOW-UP STABILITY DATA

a) The tentative shelf-life must be substantiated by stability data derived from at least two production batches, stored at the maximum recommended storage conditions for the full period of shelf-life for generics. If the accelerated data submitted previously were derived from batches other than production batches, three months' accelerated data on at least one of the production batches are required.
b) For products containing new entities, the tentative shelf-life must be substantiated by stability data derived from at least three production batches. If the accelerated data submitted previously were derived from batches other than production batches, six months' accelerated data on the three production batches are required.
c) The maximum recommended storage conditions, integrity of container used and formulation will determine the temperatures and humidity conditions to be included in the stress-testing program.

d) Stability trials involving the product stored at the maximum recommended temperature must be continued for the full period to validate the tentative shelf-life.
e) An approved shelf-life may be extended through submission of additional data accumulated on production batches covering the full period applied for. Applicants should note, however, that the shelf-life may not be extended until the data have been evaluated and approved.

5. CALCULATION OF EXPIRY DATE

The expiry date is calculated from the date of manufacture. If the production batch contains reprocessed material the expiry date is calculated from the date of manufacture of the oldest reprocessed batch and it should be verified that the batch will meet the final product specification for the full period of the shelf-life allocated.

6. STORAGE IN BULK

The applicant must consider the suitability of the container used for in-process storage and transportation of bulk product in terms of compatibility, moisture permeation and closure seal ability.

7. EXTENSION OF SHELF-LIFE

For an extension of shelf-life real time data obtained according to the program on at least two production batches for the full period required must be submitted for generics and on at least three batches for new entities.

Note:
In order to facilitate evaluation, the application for an extension of shelf-life should include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches).
Reference only to previously submitted data is not acceptable.

8. STABILITY REQUIREMENTS FOR POST REGISTRATION AMENDMENTS

Procedures and submission of data relating to changes in formulation, site and method of manufacture and packaging, that may influence the shelf-life quality of a product are outlined in the Guideline for Minor and Major Amendments.

APPENDIX I

GLOSSARY AND INFORMATION

The following terms have been in general use, and the following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

STABILITY

Studies designed to increase the rate of chemical degradation or physical change of an active substance or product by using exaggerated storage conditions as part of the formal, definitive, storage program. These data, in addition to long-term stability studies, may also be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Active substance; Active Pharmaceutical Ingredient; Drug Substance; Medicinal Substance

The unformulated active substance which may be subsequently formulated with excipients to produce the product.

Bracketing

The design of a stability schedule so that at any time point only the samples on the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that the stability of the intermediate condition samples are represented by those at the extremes. Where a range of dosage strengths is to be tested, bracketing designs may be particularly applicable if the strengths are very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Where a range of sizes of immediate containers is to be evaluated, bracketing designs may be applicable if the material of composition of the container and the type of closure are the same throughout the range.

Climatic Zones

The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions. Fluctuations in climatic conditions throughout South Africa prohibit the characterization of this country by any one of the four identified zones and the conditions of storage likely to be encountered in South Africa must be considered in designing the stability trial.

Dosage Form; Preparation

A pharmaceutical product type, for example tablet, capsule, solution, cream, etc. that contains an active ingredient generally, but not necessarily, in association with excipients.

Product; Finished Product
The dosage form in the final immediate packaging intended for marketing.

Excipient

Anything other than the active substance in the dosage form.

Expiry/Expiration Date

The date placed on the container/labels of a product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it must not be used.

Formal (Systematic) Studies

Formal studies are those undertaken according to a pre-approval stability protocol which embraces the principles of these guidelines.

Long-Term (Real Time) Testing

Stability evaluation of the physical, chemical, biological, and microbiological characteristics of a product and an active substance, covering the expected duration of the shelf life and retest period, that are claimed in the application for registration and will appear on the labelling.

Mass Balance; Material Balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 per cent of the initial value, with due consideration of the margin of analytical precision. This concept is a useful scientific guide for evaluating data, but it is not achievable in all circumstances. The focus may instead be on assuring the specificity of the assay, the completeness of the investigation of routes of degradation, and the use, if necessary, of identified degradants as indicators of the extent of degradation via particular mechanisms.

Matrixing

The statistical design of a stability schedule so that only a fraction of the total number of samples is tested at any specified sampling point. At a subsequent sampling point, different sets of samples of the total number would be tested. The design assumes that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same product should be identified as, for example, covering different batches, different strengths, different sizes of the same container and closure and possibly, in some cases, different container/closure systems.
Matrixing can cover reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors needing to be covered and evaluated. This potential complexity precludes inclusion of specific details and examples, and it may be desirable to discuss design in advance with the Council, where it is possible. In every case it is essential that all batches are tested initially and at the end of the long-term testing.

Mean Kinetic Temperature

When establishing the mean value of the temperature, the formula of J D Haynes* can be used to calculate the mean kinetic temperature. It is higher than the arithmetic mean temperature and takes into account the Arrhenius equation from which Haynes* derived his formula. *. Pharm. Sci. J 60, 927-929, 1971.

New Chemical Entity; New Molecular Entity; New Active Substance

A substance that has not previously been registered as a new active substance with the Council.

Pilot Plant Scale

STABILITY

The manufacture of either active substance or product by a procedure fully representative of and simulating that to be used on a full manufacturing scale. For oral solid dosage forms this is generally taken to be at a minimum scale of one-tenth that of full production or 100 000 tablets or capsules, whichever is the larger.

Primary Stability Data

Data on the active substance stored in the proposed packaging under storage conditions that support the proposed retest date. Data on the product stored in the proposed container-closure for marketing under storage conditions that support the proposed shelf-life.

Retest Date

The date when samples of the active substance should be re-examined to ensure that material is still suitable for use.

Retest Period

The period of time during which the active substance can be considered to remain within the specification and therefore acceptable for use in the manufacture of a given drug product, provided that it has been stored under the defined conditions after this period, the batch should be retested for compliance to its specification and then used immediately.

Shelf-life; Expiration Dating Period

The time interval that a product is expected to remain within the approved shelf-life specifications provided that it is stored under the conditions defined on the label in the proposed containers and closure.

The shelf-life is used to establish the expiry date of individual batches. It is the length of time required for:

a) the least stable active ingredient to degrade to the specified, motivated and approved or proposed fraction of the labeled quantity
b) some element of pharmaceutical elegance to drop to an unacceptable level, or
c) an arbitrary minimum of 2 years, unless otherwise determined by Council.
The shelf-life could also reflect the length of time required for:
d) a measurable increase in toxicity as shown by either animal experiments or clinical adverse reaction reports, or,
e). a measurable loss in reported clinical effectivenessteven though analytical methods show little or no reduction in apparent concentration).

– Release Specification

The combination of physical, chemical, biological, and microbiological test requirements that determine a product is suitable for release at the time of its manufacture.

- Shelf Life Specification

STABILITY

The combination of physical, chemical, biological and microbiological test requirements that an active substance must meet up to at its retest date or a product must meet throughout its shelflife.

Stability-Indicating Assay Methodology

Analytical method(s) that will quantitatively differentiate between the active ingredient and all known degradation products and/or related impurities.

Stability

The capacity of an active ingredient or dosage form to remain within specifications established to assure its identity, purity, strength and critical physico-chemical characteristics.

Storage Conditions

An acceptable variation in temperature and relative humidity of storage facilities. The equipment must be capable of controlling temperature to a range of +- 2 °C and Relative Humidity to +- 5%RH. The real temperatures and humidities should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable.
The effect of variations during equipment failure should be addressed by the applicant and reported if judged to impact stability results. Exceptions that exceed these ranges (i.e., 2 °C and/or 5%RH) for more than 24 hours should be described in the study report and their impact assessed.

Strength

A quantitative measure of active ingredient, as well as other ingredients requiring quantitation.

Stress Testing (Active Pharmaceutical Ingredient)

These studies are undertaken to elucidate intrinsic stability characteristics of the API. Such testing is part of the development strategy which is normally carried out under more severe conditions than that used for accelerated tests. Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the active substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the active substance. These studies should establish the inherent stability characteristics of the molecule, such as the degradation pathways, and lead to identification of degradation products and hence support the suitability of the proposed analytical procedures. The detailed nature of the studies will depend on the individual active substance and type of drug product.

This testing is likely to be carried out on a single batch of material and to include the effect of temperature in
10 °C increments above the accelerated temperature test condition (e.g., 50°C, 60°C, etc.) humidity where appropriate (e.g., 75% or greater); oxidation and photolysis on the
active substance plus its susceptibility to hydrolysis across a wide range of pH values when in solution and suspension. Results from these studies will form an integral part of the information provided to the Council.

Photostability testing should be an integral part of stress testing.

It is recognized that some degradation pathways can be complex and that under forced conditions decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing. This information may be useful in developing and validating suitable analytical methods, but it may not always be necessary to examine specifically for all degradation products, if it has been demonstrated that in practice these are not formed.

Stress Testing (Finished Product)

Studies undertaken to assess the effect of severe conditions on a product.

Light testing should be an integral part of stress testing (see above).

Special test conditions for specific products (e.g., metered dose inhalations and creams and emulsions) may require additional stress studies.

Supporting Stability Data

Data other that primary stability data, such as stability data on early synthetic route batches of active substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closures other than those proposed for marketing, information regarding test results on containers, and other scientific rationale that support the analytical procedures, the proposed retest period or shelf life and storage conditions.

Tentative Shelf-life

A provisional shelf-life determined by projecting results from less than full term data (such as "accelerated studies") and storage under maximum recommended conditions for a period motivated by the applicant using the dosage form to be marketed in the proposed container-closure system.

APPENDIX 2

APROPRIATE TESTS

Both physical and chemical characteristics of the product should be monitored during storage. The possibility of interaction between the components of a fixed-combination product should be considered. Where a pharmaceutical interaction appears possible, the applicant should either submit data to establish that an interaction does not occur, or that it is clearly recognized and defined. Where significant interaction with the pack is likely, the effects on the product and on the pack (e.g., due to leaching of extractables, or due to absorption of constituents), should be evaluated and the results reported. The following tests must always be included for all dosage forms:

- Appearance
- Assay of all actives
- Degradation, if relevant

Assay

Detailed records of all analytical methods used in the stability studies should be kept along with validation data.

STABILITY

Published methods of analysis for which validations are also published as well as compendia methods of analysis should be kept, with partial validation data only demonstrating suitability of the in-house equipment and personnel. If a change in procedure is necessary during the stability trial, data should be generated and kept and processed in such a way as to prove that no statistically significant difference exists between the results of the older method versus the newer method.

The stability-indicating methodology should be validated by the applicant (and the accuracy, precision and reproducibility established) and analytical procedures described in sufficient detail to permit validation.

Degradation products

Chromatographic or other analytical methods designed to determine the content of degradation products should be submitted with the assay results even where an assay procedure specific for the active ingredient has been used.

Physical properties

In addition to assay for content of active ingredient and degradation products, it is necessary to ensure that physical properties of the product are unimpaired after storage. Consideration should be given to the stereo-chemical integrity of the product. The additional tests will vary with the formulation in question, but important attributes of various dosage forms may include the following:

a) Tablets
Disintegration time, dissolution rate (multi-point profiles for each active if it is a multi component product), moisture content, appearance, hardness, friability, colour and odour.

Solubility time and appearance of solution for soluble tablets, dispersion time, fineness of dispersion, dissolution rate (unless the active ingredient is in solution after dispersion) for dispersible tablets.

b) Capsules
Moisture content, colour and appearance (capsule shell and contents), brittleness, disintegration time (when dissolution rate is not applicable) and dissolution rate (multipoint profile).

In conducting stability trials for solid dosage forms and other products with compendia dissolution requirements, and which have a history of bioavailability problems, dissolution rates should be determined and multi-point profiles presented in tabulated form as a function of percentage of labelled claim dissolved to time.

c) Emulsions and suspensions
Appearance (such as colour and phase separation), odour, pH and viscosity,
resuspendability, particle size, sterility for ophthalmic preparations, preserving ability, preservative content.

d) Solutions
Appearance, pH, viscosity and density, (where relevant), solubility time (reconstitution and appearance thereof), and sterility preserving ability and preservative content (where relevant).

STABILITY

Tests should be performed to ensure compatibility between the container-closure system and the product and the results included in the submission.

Test methods to determine particle size should not employ extensive dilution of particles or any other manipulation which could affect the real particle size existing in the dosage form. The applicability of the particle size dependent variable, such as sedimentation should also be considered.

After storage, samples of suspensions should be prepared for assay in accordance with the recommended labelling under "Directions for use".

e) Powders, granules (including those for reconstitution)
Moisture, resuspendability/reconstitution time and appearance of reconstituted product, microbial limits. The reconstituted product must be tested according to a solution or suspension.

f) Metered Dose Inhalation aerosols
Uniformity of delivered dose, number of metered doses, particle size (suspensions), spray pattern, microbial limits, deposition of emitted dose.

Because the container contents are under pressure, filled containers must be checked for loss in mass over the expiration dating period. For suspensions, aggregate (or solvate) formation may lead to clogged valves, or the delivery of a pharmacologically inactive dose. Corrosion of the metering valve or deterioration may adversely affect the delivery of the correct amount of active ingredient.

g) Ointments and creams
Homogeneity, pH, rheological properties, particle size and mass loss (plastic containers). Preserving ability if preservative present. Preserving ability for all topical preparations containing corticosteroids.

h) Parenterals
Small volume parenterals include an extremely wide range of preparations and container-closure types. Each should be included in the stability study. Evaluation of these products should include at least the following: pH particulate matter, pyrogens (containers larger than 15 ml), syringeability of non-aqueous products.

If a validated system exists, sterility will generally not be required to be included in the stability program. Initial sterility should be recorded on stability reports.

Tests should be performed to ensure the compatibility between the container-closure and the product and the results submitted. Aspects to be investigated on the closure include possible pigmentation, resealing following multiple penetration and force for needle to penetrate.
For Large Volume Parenterals the smallest container-closure size should be studied, provided that all container-closure systems are identical in composition and seal integrity.

A brief justification should be included stating the reasons for the container size chosen e.g., largest air volume or largest surface contact etc. Additional tests - globule size (where applicable), volume(plastic containers), moisture permeability (where applicable) and extractables (plastic containers). Tests should be performed to ensure the compatibility between the container-closure and the product. These data must be submitted.

STABILITY

i) Suppositories
Melting range point, breaking strength and disintegration. The effect of aging may also be observed from hardening of the suppository base, therefore, control and stability testing should include disintegration time at 37 degrees C. Accelerated studies should be conducted at 2 - 3 degrees C below the melting point of the suppositories. In such cases, the product labelled to be administered by addition to another product (e.g., parenterals, aerosols) should be studied for stability and compatibility in admixture.

j) Admixtures
For any product intended for use as an additive to another product, the possibility of incompatibilities exists.

A suggested protocol should provide for tests to be conducted at zero-, 6-, 8-, 24- hour intervals. These should include:
- Assay of active ingredient and any other ingredient for which a limit is set in the final product specification;
- pH (especially for unbuffered LVPs), colour, clarity (particulate matter);
- interaction with the container;
- identification of precipitant/sediment (although the presence of any precipitant is already non-conforming)

k) Intra-uterine Devices (IUD)
Tensile strength of the withdrawal string and integrity of the package, i.e., seal strength of the pouch, sterility of the device. If the device contains a reservoir from which active ingredient diffuses through a controlled release membrane, it should be tested for total active content, degradation products and in vitro release rate of the active ingredient in
addition to the above tests. Vaginal devices such as doughnut shaped silastic or other polymeric matrix containing an active ingredient uniformly dispersed throughout the matrix must be checked for in vitro release rate of the active ingredient and extraneous extractable substances to establish stability and compatibility of the active with the matrix.

l) Tran dermal patches
Release rate, seal integrity, mass variation, adhesive properties.

Content of Antimicrobial Preservatives

Dosage forms containing preservatives to control microbial contamination should have the preservative content monitored initially (zero time) and at reasonable intervals throughout the projected expiration dating period of the product. This may be accomplished by performing microbial challenge tests (e.g., Antimicrobial Preservative Effectiveness Test of the USP or BP which is applicable to unopened containers) and by performing chemical assays for the preservative. When the minimum quantity of preservative to achieve effective microbial control has been determined for solutions, chemical assays for the full period of the shelf-life may be adequate, provided that the results of tests demonstrating the preservative effectiveness are submitted for evaluation. It is particularly important to consider the adequacy of the preservative system under conditions of use for multidose vials. When less than full term data are submitted for registration purposes, or for a major change in formulation, preliminary results for preservative effectiveness are a minimum storage period of nine months should be included for

those products for which the effect of aging on preservative effectiveness needs to be demonstrated e.g., suspensions, creams etc.

Those products requiring control of the microbial quality that do not contain preservatives, should be tested initially (at zero time) and at the termination of study or at the end of the projected expiration dating period according to the final product specification (Part 2F), for bio burden (e.g., Microbial limits Tests of the USP or BP, which includes a limit for total microbial count and for absence of Staphylococcus aureus, Escerichia coli, Pseudomonas aeruginosa and Salmonella species. In addition, it is recommended that topical preparations be controlled for the absence of
Pseudomonas cepacia, Aspergillus niger and Candida albicans as well as any other topical pathogens that may be identified as potentially harmful. Simulated use tests on topical preparations packed in jars and on ophthalmics are desirable.

Effects of Opening and Closing Containers

Investigation into "in-use" stability may be important for certain sensitive products. Where applicable, the opening and closing of containers may follow a recommended dosage direction included in Part 1A to the MRF application form.

Desiccants

Duration of satisfactory performance of desiccants should be related to the shelf-life/expiry date.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

ADDENDUM 3

POST-IMPORTATION IDENTIFICATION AND TESTING OF MEDICINES

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

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

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

POST-IMPORTATION IDENTIFICATION AND TESTING OF MEDICINES

1. Imported medicines must be identified chemically, assayed through a stability-indicating method, and other relevant tests as may be required, conducted before release, to prove that the product integrity has not been prejudiced during transport from sources in other countries.

(a) Exemption from these requirements will be considered in the following circumstances:

(b) When very small quantities are imported for "selected" patients, or groups of patients.

(c) If the identification and assay cannot be performed in South Africa the applicant must submit full justification and motivation, as the return of samples to overseas testing laboratories or manufacturers is not acceptable. The MCC may direct that a laboratory recommended by it perform the tests.

(d) Any other reason deemed by the applicant as being of such nature as to qualify for consideration for this exemption.

2. Any exemption approved will be valid for three years, provided that all the requirements are complied with during the period of validity. Initially, post importation testing must be done and subsequently at specific intervals.

3. When requesting exemption the following must be submitted:

ii. A suitable motivation for the request, that is, a suitable projection as to the annual usage of the relevant project, and/or detail of the identification and assay method which cannot be performed locally.

iii. Validation of transport, that is, evidence that the conditions during transport are continuously monitored by temperature and, where relevant, humidity recorders.

A tabulated summary indicating the method of transport utilized and the conditions during transport as indicated below must be submitted. A minimum of five printouts are required, giving an account of the same product or, five different products, provided that the products require the same storage conditions, and provided that the products are dispatched from the same site but by different shipments.

iv. A copy of the accelerated stability data of the formulation being applied for, packed in the final container as specified in Part 2D (to determine if the humidity must be monitored).

v. A copy of Part 2B as per the MRF 1 Form.

POST-IMPORTATION ID/TESTING

vi. An indication as to whether the request is for bulk products or for the product packed in the final container.

vii. A certificate of GMP compliance not older than 2 years, issued by competent regulatory authority or in terms of the WHO certification scheme.

viii. A copy of the proposed master release document in accordance with Part 2F reflecting the specifications pertaining to the product in question (example attached).

- The type of recorder used in transit
- Specify that the received certificate of analysis is valid, is complete (reflects the actual results of the tests performed) and reflects compliance with the registration requirements.
- Visual identification of the product and dosage form
- A consignment reference e.g. GRN (goods received notice) or invoice, etc. (Batch numbers on the invoice must concur with the batch numbers of the products).
- Confirmation of the integrity of the containers, seals, and labels. Each aspect must be specified and controlled to ensure that no damaged articles are accepted.

4. Furthermore, the following must be ensured:
   a) The transport conditions (temperature and humidity, where relevant) of each shipment are recorded by a suitable device which provides a printout that will form a permanent record of the specific shipment and is filed with the batch release documents
   b) An SOP, specifying the details of inclusion of the recorders, must be available for inspection. The procedure must include amongst others, the number of recorders, position of placement, date of activation and inactivation (on leaving the place of dispatch i.e. factory, and on receipt by the applicant i.e. warehouse) and evaluation of the printout with the reference to the stability data.
   c) The monitor must be validated and the validation data must be available for inspection.
   d) Please note that exemption is applicable only if each future shipment is monitored and subsequently evaluated for compliance with the stability profile.
   e) The submission must include the necessary supportive stability data. If previously submitted, a statement to this effect will suffice.
   f) The transport monitoring method, or transport conditions must be specified in the master release document. Applicants should note that any shipment received, not complying with these transport specifications, does not qualify for the exemption. These shipments must be assayed and identified as if exemption was not granted in the first instance.

POST-IMPORTATION ID/TESTING

N.B. The Medicines Control Council reserves the right to withdraw the exemption, should the applicant give cause.
Applicants who have obtained permission for exemption previously from the MCC for their products must re-apply for exemption.

NAME OF PRODUCT:
REGISTRATION NUMBER:
DOSAGE FORM:
APPROVED STORAGE CONDITION:
QC FUNCTION TO BE AUTHORISED (point (v) below):
ASSURANCE: TEMPERATURE RECORDED IN EACH SHIPMENT

Name of Product	Batch Number	Maximum and minimum temperature recorded	Maximum humidity recorded (Where relevant)	Duration of transport (Date commenced and date terminated)	Mode of Transport	Signature of MD/responsible pharmacist who verified the printouts

POST-IMPORTATION ID/TESTING

MASTER RELEASE DOCUMENT

Product name and code	
Batch number	
Approved storage conditions	
Final product specification reference number	
Receiving notice number (GRN)	
Date of dispatch and of receipt	
Quantity dispatched	
Number of containers received	

Test	Specification	Result	Signature
Temperature printout (storage conditions)	Present, attached, conforms to stability profile submitted		
Certificate of Analysis	Present, valid (batch specific), conforms to MBR1, complete		
Visual Identification	e.g. Product description, labelling, container, batch number, expiry date		
Shipping containers' condition	Clean, undamaged	Number approved, Number rejected	
Shipping container label	Untampered		
Shipping container seal	Present, intact		

Position/ Function

Signature	Date

MEDICINES CONTROL COUNCIL

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ADDENDUM 2

VALIDATION PROTOCOLS AND VALIDATION REPORTS

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

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

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

VALIDATION PROTOCOLS AND VALIDATION REPORTS

This guideline intends to communicate to Industry, the policy and requirements in respect of validation protocols and validation reports to be submitted to the Medicines Control Council.

1 IMPORTANT REFERENCES:

Chapter 9 of the SA Guide to Good Manufacturing Practice (1996 edition)
Circulars
United States Pharmacopoeia (USP)
British Pharmaceutical Codex (BPC)
FDA Guidelines on Validation

2 GENERAL COUNCIL POLICY:

The standard to be used to assess compliance with current Good Manufacturing Practice, would be the South African Guide to Good Manufacturing Practice (SAGMP) (latest edition).

"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."

3 WHAT VALIDATION IS:

3.1 The SA Guide to GMP defines "validate" as follows:

"VALIDATE...

To provide documented evidence that an item of equipment, process, system or method is in a state of control (i.e. that all assignable causes of variation have been eliminated) and is able to consistently deliver specified results."

3.2 Validation is an integral part of current good manufacturing practice; it is, therefore, also an element of the quality assurance programme associated with a particular product or process.

3.3 There should be levels where validation and qualification should be performed, and the level should determine the intensity of these products. It should be least for liquid preparations (solutions) and most for parenteral medicines. For solid

dosage forms, it should depend on the criticality of the product as far as the patient is concerned.

4 WHEN VALIDATION SHOULD BE DONE:

4.1 Validation should be considered in the following situations:

- totally new processes
- new equipment
- processes and equipment which have been altered to suit changing priorities
- processes where the end product test if poor and an unreliable indicator of product quality

4.2 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to consistently yield a product of the required quality.

4.3 In this phase the extent to which deviations from the chosen processing parameters can influence product quality should also be evaluated. In general the final batch size should not be more than ten times the batch size of the representative development batches.

4.4 The validation in the production unit mainly comprises the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.

4.5 At least three batches (including at least two production batches in the final batch size) should be validated, to show consistency. Worst case situations should be considered.

4.6 When certain processes or products have been validated during the development stage, it is not always necessary to re-validate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process control and final product specifications.

4.7 There should be a clear distinction between in-process controls and validation. In-process tests are performed each time on a batch-to-batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously.

5 WHAT VALIDATION INVOLVES:

VALIDATION PROTOCOLS/REPORTS

Validation involves the accumulation of documentary evidence relating to a process, item of equipment, or facility. This is achieved by means of validation protocol which should exist for every product and which details the tests to be carried out, the frequency of testing, and the results anticipated (acceptance criteria).

6 THE VALIDATION PROTOCOL (VP)

The Validation protocol should clearly describe the procedure to be followed for performing validation. The protocol should include at least:

- the objectives of validation and qualification study,
- site of the study,
- the responsible personnel,
- description of equipment to be used (including calibration before and after validation),
- SOP's to be followed,
- standards and criteria for the relevant products and processes,
- the type of validation,
- time/frequency should be stipulated,
- processes and/or parameters to be validated (e.g. mixing times, drying temperatures, particle size, drying times, physical characteristics, content uniformity etc.) should be clearly identified.

7 THE VALIDATION REPORT (VR)

7.1 A written report should be available after completion of the validation. The results should be evaluated, analysed and compared with acceptance criteria. All results should meet the criteria of acceptance and satisfy the stated objective. If necessary, further studies should be performed. If found acceptable, the report should be approved and authorised (signed and dated).

7.2 The report should include at least:

- the title and objective of the study,
- refer to the protocol,
- detail of material,
- equipment,
- programmes and cycles used
- details of procedures and test methods
- results (compared with the acceptance criteria).

- recommendations on the limits and criteria to be applied to all future production batches (which could form part of the basis of a batch manufacturing document).

8 RE-VALIDATION:

a). As a rule re-validation is required under the following circumstances:

- change of formulae, procedures or quality of raw materials
- change of equipment, installation of new equipment, major revisions to machinery or apparatus and breakdowns
- major changes to process parameters
- changes to facilities and installations which influence the process
- on appearance of negative quality trends
- on appearance of new findings based on current knowledge, e.g. sterilisation where

the frequency of checking is dependent on sophistication of in-process methodology

NOTE: The extent of re-validation will depend on the nature and significance of the changes.

9 GENERAL NOTES

9.1 The following aspects could be considered during the validation of specific dosage forms.

9.2 Validation of tableting: In the case of an oral tablet manufactured by granulation and compression, the critical process parameters may include (but not be limited to):

- blending time for the powder
- particle size distribution of the active
- granulating time and speed
- amount of granulating fluid-binder concentration
- drying time - final moisture content
- granule particle size distribution
- granule active content and homogeneity
- blending time of external phase
- tablet hardness with respect to water content, friability, disintegration, and dissolution
- lubrication level with respect tablet hardness, disintegration, dissolution and die-ejection force
- tablet mass and thickness control uniformity of content

If the tablet is film coated, the following additional parameters may require validation:

- spray rate of coating solution
- inlet and outlet air temperatures
- coating mass of polymer with respect to table appearance, friability, disintegration, and dissolution

10 REQUIREMENTS

10.1 Each applicant should have a Validation Master Plan (VMP) (See SA Guide to GMP, Chapter 9)

10.2 Each product must have a Validation Protocol (VP), (where validation is required, i.e. for *inter alia* solid dosage forms, certain suspensions, sterile products etc or where major changes in formulation or manufacturing method is envisaged).

10.3 There should be a Validation Report (VR) following the completed validation.

10.4 Validation Protocols and Validation Reports should be available for inspection purposes by the inspectorate.

The following is applicable:

10.4.1 New Applications for registration:
A VP must be included in Part 2E. (The VR should only be submitted when requested by the inspectorate).

10.4.2 Applications for change in applicant/manufacturer/packer/laboratory
A VP must be submitted with each application for a change in manufacturer or laboratory, or change in applicant where it also involves a change in manufacturer.

[If the validation had already been done, it should be indicated as such in the application. A VR should only be submitted when requested by the inspectorate.]

10.5 Applications will not be accepted if the Validation Protocol should be found to be incomplete.

10.6 Applicants should note that the submission of the VP or VR does not imply that the VP or VR had been approved by the council or secretariat.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

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ADDENDUM 1

ALCOHOL CONTENT

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

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

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

ALCOHOL CONTENT FOR MEDICINES INTENEDED FOR ORAL ADMINISTRATION

a)The following maximum concentration limits will be allowed for ethyl alcohol as inactive ingredient:

0,5 % (v/v) ethyl alcohol for children under 6 years of age
5.0 % (v/v) ethyl alcohol for children 6-12 years of age
10,0 % (v/v) ethyl alcohol for adults and adolescents over 12 years of age.

b) Minute dose preparations are exempted from this requirement.

c) For products where higher concentration of alcohol are required, (e.g. plant extracts or where solubility or preservation might be problematic), exemption from ethanol concentration limits will be considered individually, provided that justification and motivation is submitted together with proof that the proposed dosage will not result in blood alcohol levels of 25 mg/dl or higher. (Table 1 is attached for reference purposes only).

d) In all instances, the alcohol content of a mixture must be stated prominently on the immediate container label, the outer label (carton), as well as in the package insert and patient information leaflet.

e) All medicines (registered products, "Old medicines" and new applications) must comply with the alcohol levels stated in this policy.

TABLE 1.#

Volume (Millilietres) of Ethanol Preparation Predicted to Produce a Blood Ethanol Concentration of 25mg/100ml* (100ml=1dl)

% Ethanol (v/v) in Product	**Age (Weight)**					
	2yr (12kg)	4yr (16kg)	6yr (21kg)	8yr (27kg)	10yr (32kg)	12yr (38kg)
2,5	91	122	160	205	243	289
5,0	46	61	80	103	122	144
7,5	30	41	53	68	81	96
10,0	23	30	40	51	61	72
12,5	18	24	32	41	49	58
20,0	11	15	20	26	30	36
25,0	9	12	16	21	24	29

ALCOHOL CONTENT

* Values were calculated from data contained in McCoy et al, 1979, by use of the formula: dose (in milligrams) = plasma concentration (Cp) x volume distributed (Vd) and assuming that absorption is complete. For example, the calculation to obtain the value of 40 ml for a 6-year-old ingesting a product containing 10% alcohol would be made as follows: Cp = 250 mg/L and Vd = 0.6 L/kg x 21 kg; therefore, dose = 250 mg/L x (0.6L/kg x 21kg) = 3.150 mg. Because for absolute ethanol (specific gravity 0.789), 1 g = 1.27 ml, 31.5 g = 40 ml; thus, for 10% ethanol, the calculated volume is 40 ml.

TABLE 1 is an abstract from an article on "Ethanol in Liquid preparations intended for Children", by the American Academy of Pediatrics, published in PEDIATRICS, Vol. 73 no.3 March 1984, page 406.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

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

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

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

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003
Version MCC2003(1)

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CLINICAL REQUIREMENTS

1. INTRODUCTION

This guideline serves to help applicants with the correct way of presenting a package insert 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 9 of the Act 90 of 1997 (hereafter referred to as the Act).

The professional 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 medicines' uses and limitation as established by the supporting evidence. Ensure that all statements are adequately cross-referenced (See **Addendum** I). No promotional material may be included. Promotional statements and comparisons to other agents, indicative of any potential advantage over competitors will not be allowed.

After registration, the professional package insert may not be altered without the approval of the Medicines Control Council. In the case of safety-related matters the Council should be informed immediately, with submission of an approved professional package insert, a proposed amended package insert and the evidence/motivation for the change. (refer to PART 5.3 – Application for the Amendment to a package insert).

2. GENERAL:

2.1 Package inserts must be typed in a double-spaced text with a minimum legibility of 6-point Helvetica typeface in black ink on white cartridge paper or the equivalent thereof. The package insert text must be in at least English (British English) and any other official language.

2.2 Cross-referencing of the package insert shall be by leaving a broad margin on the right hand side of the page where every statement is clearly referenced.

2.3 Every statement shall be verified by a reference for purposes of evaluation. The exact page/s shall be stated and, if possible, the column and line number. Note, however, that no references shall appear on the finalized printed package insert. If an entire section is quoted from one source, it will be acceptable to indicate the one reference at the end of the relevant section.

2.4 The printing quality of the package insert must 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, and typographical errors must be checked by the applicant before submission to the Medicines Control Council. Failure to do so shall result in a delay of the registration process.

2.5 Electronic submissions will be preferred.

CLINICAL REQUIREMENTS

3. PART 1A – PROFESSIONAL PACKAGE INSERT MULTI-SOURCE MEDICINES

3.1 HEADINGS AND PARTICULARS IN A PACKAGE INSERT

Applicants shall take note of which sources to be used as a reference for the different headings specified in Regulation 9 of Act 90 of 1997. Applicants also to note that in-house package insert templates shall be used as a reference during the evaluation process of therapeutically equivalent, interchangeable multi-source medicines. (Schedule of definitions (2) of Regulation 9 of Act 90 of 1997), and as contemplated under sub-regulation 1 (s)(iv) of Act 90.

3.2 SCHEDULING STATUS

Applicants shall note the scheduling status of medicines as determined from time to time by the Minister, and as published in the Government Gazette. The correct term for unscheduled medicines is "Not Scheduled".

3.3 PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of the MRF 1.

3.4 COMPOSITION

An approved name of all active ingredients in accordance with Part 2 shall be listed.
The quantity thereof per dosage unit, per suitable mass, per volume, or per unit of the medicine shall be indicated.
The approved name and quantity of any preservative shall be listed and expressed as a percentage. The content of ethyl alcohol, where such quantity exceeds 2% shall be indicated.

Any ingredient which may cause an allergic reaction, or which may be harmful to certain individuals e.g. tartrazine, must be indicated as such, in accordance with Regulation 9 of the Act.

3.5 PHARMACOLOGICAL CLASSIFICATION

Shall be in accordance with Regulation 25 of the Act.

3.6 PHARMACOLOGICAL ACTION INCLUDING PHARMACOKINETICS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

CLINICAL REQUIREMENTS

3.7 INDICATIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data

3.8 CONTRA-INDICATIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.9 WARNINGS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.10. INTERACTIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.11 PREGNANCY AND LACTATION

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.12. DOSAGE AND DIRECTIONS FOR USE

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.13. SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data.

3.14. KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Shall be in line with the relevant package insert template as determined by the Council. Any additional information as required by the applicant must be submitted with relevant clinical data

3.15. IDENTIFICATION

In accordance with Part 2F.

3.16. PRESENTATION

In accordance with Part 2D.

3.17. STORAGE INSTRUCTIONS

In accordance with Part 2G.

The statement "Store all medicines out of reach of children." must be stated.

3.18. REGISTRATION NUMBER

Allocated by the Medicines Control Council.

3.19. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the package insert.

3.20. DATE OF PUBLICATION OF THE PACKAGE INSERT

This date shall be the date of the Medicines Control Council Resolution. The date shall only change when the package insert is amended extensively and is re-evaluated by Council.

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

4. PART 1A - PROFESSIONAL PACKAGE INSERT NEW CHEMICAL ENTITIES

4.1 HEADINGS AND PARTICULARS IN A PACKAGE INSERT

The package insert shall follow the same format as laid out in the guidelines for interchangeable multi-source medicines above, in conjunction with Regulation 9 of the Act. The difference being that the primary source of reference for headings 5 to 13 below shall be the clinical study data in the SBRA, or the AMRP, whichever is applicable to that particular application.

CLINICAL REQUIREMENTS

4.2. SCHEDULING STATUS

Applicants to note that the scheduling status of medicines shall be determined from time to time by the Minister.

4.3. PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of the MRF 1.

4.4. COMPOSITION

An approved name of all active ingredients in accordance with Part 2B(i) shall be listed.
The quantity thereof per dosage unit, per suitable mass, per volume, or per unit of the medicine shall be indicated.
The approved name and quantity of any preservative shall be listed and expressed as a percentage. The content of ethyl alcohol, where such quantity exceeds 2% shall be indicated.
Any ingredient which may cause an allergic reaction, or which may be harmful to certain individuals e.g. tartrazine, must be indicated as such, in accordance with Regulation 9 of the Act.

4.5. PHARMACOLOGICAL CLASSIFICATION

Shall be in accordance with Regulation 25 of the Act.

4.6. PHARMACOLOGICAL ACTION

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.7. INDICATIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.8. CONTRA-INDICATIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.9. WARNINGS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.10. INTERACTIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.11. PREGNANCY AND LACTATION

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.12. DOSAGE AND DIRECTIONS FOR USE

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

4.13. SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

The side effects that belong together shall be grouped together either in one paragraph or under one sub-heading, e.g. gastro-intestinal, skin, hematological etc., as per the System Organ Class Classification System of either WHOART or MeDRA.
Side effects that occur more frequently as well as the more serious type of side effects shall be listed at the beginning of the paragraph. The terms "more frequent" or "less frequent" may be used.

In the case of multi-component formulations, the side effects shall be listed separately for each active ingredient

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

4.14. KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Source of particulars shall be the clinical data in the SBRA (Summary Basis for Registration Application), or the AMRP (Abbreviated Medicines Registration Procedure) documents, whichever applies.

For treatment of over-dosage it is usually acceptable to state, "Treatment is symptomatic and supportive". There are exceptions where a standard text is required e.g. paracetamol, codeine, beta-blockers. Applicants should update themselves with the relevant Circulars on a regular basis.

4.15. IDENTIFICATION

In accordance with Part 2F.

4.16. PRESENTATION

In accordance with Part 2D.

4.17. STORAGE INSTRUCTIONS

In accordance with Part 2G.

The statement "Store all medicines out of reach of children." must be stated.

4.18. REGISTRATION NUMBER

Allocated by the Medicines Control Council.

4.19. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTFICATE

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the package insert.

4.20. DATE OF PUBLICATION OF THE PACKAGE INSERT

This date shall be the date of the Council Resolution. The date shall only change when the package insert is amended extensively and is re-evaluated by Council.
Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

5. PART I B -PATIENT INFORMATION LEAFLET

5.1 INTRODUCTION:

This guideline serves to help applicants with the correct way of presenting a patient information leaflet 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 90 of 1997 (hereafter referred to as the Act).

5.2 GENERAL:

5.2.1 Patient information leaflet shall be typed in a double-spaced text with a minimum legibility of 6-point Helvetica typeface in black ink on white cartridge paper or the equivalent thereof. The package insert text must be in at least English (British English) and any other official language.

5.2.2 Cross-referencing of the patient information leaflet shall be by leaving a broad margin on the right hand side of the page where every statement is clearly referenced.

5.2.3 Every statement shall be verified by a reference for purposes of evaluation. The exact page/s shall be stated and, if possible, the column and line number. Note, however, that no references shall appear on the finalized printed patient information leaflet. If an entire section is quoted from one source, it will be acceptable to indicate the one reference at the end of the relevant section.

5.2.4 The printing quality of the patient information leaflet must be clear to enable duplication, for inclusion into various documents, during the evaluation and registration process. The spelling and grammar in the patient information leaflet text, and typographical errors must be checked by the applicant before submission to the Medicines Control Council. Failure to do so shall result in a delay of the registration process.

5.2.5 Electronic submissions will be preferred.

5.3 HEADINGS AND PARTICULARS IN A PATIENT INFORMATION LEAFLET

The patient information leaflet must be written in easily understandable English, be consistent with the professional package insert and in accordance with the regulation 10, in terms of the legibility, language and format. (Refer to Addendum I for Lay terms).

Each immediate container should have a patient information leaflet and should reflect the following:

5.3.1 SCHEDULING STATUS

That is the scheduling status of the medicine as in the professional package insert.

5.3.2 PROPRIETARY NAME AND DOSAGE FORM

Shall be in accordance with the first page of MRF I. When umbrella / brand" names are used, the applicants would be responsible to include precautionary statements of usage of these products simultaneously so as to inform patients of the correct usage and potential safety concerns. Example, if a range of products under the same umbrella name contains

paracetamol; it should not be used in conjunction with another products in the range also containing paracetamol.

6 WHAT THIS MEDICINE CONTAINS

The composition of the medicine, that is -

(i) the approved name of each active ingredient and the quantity thereof contained in a dosage unit or per suitable mass or volume or unit of the medicine;

(ii) all inactive ingredients must be listed qualitatively;

7 WHAT THIS MEDICINE IS USED FOR

The registered indications for use of the medicine as accepted by the Council in the professional package insert;

(e) **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 etc must be included here
- interactions
- General statement to be included in this section:

  "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."

  "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."

  (THIS STATEMENT SHOULD BE BOXED AND BOLDED)

(f) **HOW TO TAKE THIS MEDICINE**

The recommended dosage must 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.**" must be stated. As well as, **"In the event of over-dosage, consult your doctor or pharmacist. If neither is available, rush the patient to the nearest hospital or poison control centre".**

(g) **SIDE-EFFECTS**

(i) This section should be in layman's terms for the consumer to understand -

CLINICAL REQUIREMENTS

(a) Side-effects associated with the use of the particular medicine – listing the more frequent side-effects first.

(b) Side-effects that can be easily recognised by the patient.

(ii) The following general statement should be stated:
"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."

(h) **STORAGE AND DISPOSAL INFORMATION -**

Should contain information on how to store the medicine properly and how to dispose of unused medicine, such as by returning such medicines to the pharmacy. The following statement must be stated:
"Store all medicines out of reach of children."

(i) **PRESENTATION**

The number, volume or mass per package unit must be mentioned. A description of the packaging material (i.e. bottle, blister, etc.) should be included.

(j) **IDENTIFICATION OF THE MEDICINE**

A complete description of the physical appearance of the medicine.

(k) **REGISTRATION NUMBER/ REFERENCE NUMBER**

The number as allocated by the Medicines Control Council.
This date shall be the date of the Council Resolution. The date shall only change when the patient

(l) **THE NAME AND THE BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE**

The name and business address of the holder of the certificate of registration, or the holder of the parallel importer license, whichever is applicable, shall be listed under this section of the patient information leaflet.

(m) **THE DATE OF PUBLICATION OF THE PATIENT INFORMATION LEAFLET**

The information leaflet is amended extensively and is re-evaluated by Council.

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council prior to implementation.

CLINICAL REQUIREMENTS

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

6. PART 1 C- LABEL

An example of the facsimile of the label must be included here. Requirements e.g. font size as stipulated in the Regulations should be adhered to.

The following inclusions are permitted:

"For state use only – Not for sale" – for tender items

"Professional sample" - samples for professionals

Note: Any deviations from the requirements as described in these guidelines will require approval by the Council in terms of Section 36 of the Act, prior to implementation.

7. PART 1 D - FOREIGN REGISTRATION

7.1 A list of countries including SADC countries in which an application has been lodged and the status of such applications shall be furnished. Countries that are members of the PER Scheme, other EU countries and the USA should specifically be identified. Approvals (with indications), deferrals, withdrawals and rejections should be stated. 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.

7.2 It should be stated whether data packages submitted in the countries in 7.1 are essentially similar to those submitted to the Medicines Control Council, including the proposed indications.

7.3 The Medicines Control Council should also be notified of any rejections, withdrawals or approvals of applications in the EU commission (mutual recognition process), Australia Canada, the Netherlands, Sweden, UK and USA during the evaluation period. Where the rejections or withdrawals relate to safety matters details in each case should be provided.

8. PART 4 - PRE-CLINICAL STUDIES

8.1 Guidelines are constantly evolving as a result of scientific developments and harmonisation of the requirements of the major overseas regulatory authorities. 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".

8.2 Legislation to be read in conjunction with these guidelines is:

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, $t_{\frac{1}{2}}$ 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.

CLINICAL REQUIREMENTS

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 othe. 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

CLINICAL REQUIREMENTS

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 patents 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	LIPOPROTEIN ELEVATION	CLINICAL REQUIREMENTS 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.

CLINICAL REQUIREMENTS

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

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 represent 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

TABLE OF CONTENTS

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.

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

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

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

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

2.2 PART 2B - FORMULATION

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

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

2.2.3 A product may contain more than one API provided that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2.15 *oxicity levels per dosage unit must be indicated for all solvents and for other ingredients when required by Council. Levels must be indicated as per USP DI or Martindale, or The Complete Drug Reference, etc*

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

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

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

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

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

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

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

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

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

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

2.3.7 The following minimum requirement must be confirmed:

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

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

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

*valid as defined by c GMP

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

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

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

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

2.3.12 *For biological medicines.*

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

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

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

2.4 PART 2D - CONTAINERS AND PACKAGING MATERIALS

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

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

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

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

2.4.5 All pack sizes must be described in the submission.

2.5 PART 2E - MANUFACTURING PROCEDURES

2.5.1 An Inspection Flow Diagram must be included.

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

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

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

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

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

2.6 PART 2F – FINISHED PRODUCT

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Supportive Chromatograms for the validation must be submitted.

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

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

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

2.6.15 For medicines imported into the country see Addendum 3.

2.7 PART 2G – STABILITY DATA: FINISHED PRODUCT

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

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

(a) Conditions (temperature, humidity)

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

(c) Specifications to be determined

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

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

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

ii. Date of manufacture.

iii. Date of commencement of stability study

iv. Name of manufacturer.

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

vi. Indicate whether production/pilot/experimental batch.

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

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

ix. Specifications and limits.

x. Stability results.

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

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

2.8 PART 2H - PHARMACEUTICAL DEVELOPMENT

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

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

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

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

b) **Formulation:**

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

c) **Production/Manufacture:**

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

d) **Stability:**

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

e) **Conclusion in Expert Report**

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

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

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

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

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

2.9.2 A floor plan of the premises must be included.

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

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

3. PART 3 - BIOEQUIVALENCE STUDIES AS PROOF OF EFFICACY

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

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

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

3.4 The following must be included:

a) The purpose of the study must be stated.

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

c) Details of the method used must be given.

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

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

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

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

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

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

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

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

REFERENCES

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

2. **WHO Guidelins on biologicals**

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

4. **Photostability Testing (Q1B)**

LIST OF ABBREVIATIONS

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

PHARMACEUTICAL & ANALYTICAL REQUIREMENTS

TERMINOLOGY

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

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

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

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

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

Medicinal product
See pharmaceutical product

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

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PART 2 OF 2

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

GUIDELINES FOR REGISTRATION OF MEDICINES IN SOUTH AFRICA

GENERAL INFORMATION

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

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

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

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

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GENERAL INFORMATION

MEDICINES CONTROL COUNCIL

GUIDELINES FOR THE REGISTRATION OF MEDICINES

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

1. INTRODUCTION

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

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

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

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

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

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

2. GENERAL

2.1 SCOPE OF THESE GUIDELINES

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

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

2.2 ELIGIBILITY

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

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

2.3 CONFIDENTIALITY

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

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

2.4 LANGUAGE

GENERAL INFORMATION

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

2.5 WHERE TO SEND APPLICATIONS

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

2.6 WHEN IS A PRODUCT REGISTERABLE?

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

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

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

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

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

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

e. If it is a complementary medicine.

2.7 TYPES OF APPLICATIONS

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

2.7.1 New chemical entities (NCEs)

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

- efficacy and safety of the formulation

- safety and efficacy of a new indication

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

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

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

2.7.5 Biological medicines

2.8 FEES

For medicine registration the following fees are relevant:

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

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

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

2.9.1 Tablets/Capsules/Suppositories/Lozenges

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

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

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

2.9.3 Ampoules, Vials and Large Volume Parenterals

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

a) characteristics of the rubber stopper;
b) specifications for the glass;
c) a comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used;
d) data on particulate matter (contamination);

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

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

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

2.9.4 Different applicants/proprietary names for same formula

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

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TABLE FOR SAME/SEPARATE APPLICATIONS

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

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

2.10 TRANSITIONAL CONVERSION TABLE

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

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

For ease of reference the following conversion table is included.

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

* Biological Medicines, only

3. PREPARING AND SUBMITTING AN APPLICATION FOR REGISTRATION OF A NEW MEDICINE

3.1 Applications for registration of a medicine must be submitted on the MEDICINE REGISTRATION FORM (MRF 1) obtainable from office of the Registrar of Medicines.

3.2 Each page of the application must be numbered and the printing must be clearly legible.
Index according to the MRF 1, e.g. 2B-1 (referring to PART 2B, first page).
Double-sided copies are allowed except for package inserts.

3.3 The application for registration dossier must be properly indexed by the use of clearly labeled tabs to indicate each PART of the dossier.

3.4 Each PART must contain a complete index to that specific PART.

3.5 The application for registration must be properly bound on the left side as this allows for easy update/addition of pages. Binding is left to the discretion of the applicant, however, the use of lever-arch files is not accepted.

3.6 The application/covering letter must be bound to the application dossier.

3.7 The cheque must be attached to the covering letter. Proof of electronic payment and copies of deposit slips must be submitted with the application forms

3.8 The requirements with regard to metrication in accordance with the Trade Metrology Act must be applied.

3.9 The boxes in which documentation are submitted to the MCC must be clearly labeled. The following details should appear clearly on each box:

- Applicant name
- Name of the product
- The contents of the box e.g. File numbers, Parts, Sample, Cover letter, Cheque etc.
- Product identification code for each application (e.g. NCE-04NOV01)
- Number of boxes e.g. 1 of 10
- Type of application e.g. expedited registration, AMRP
- Colour stickers indicating screening copy (red) or post-screening copies (green)

In the case of expedited registration, approval letters must be attached. Applicants are advised to consult the relevant schedule of fees.

3.10 A duly completed pre-screening checklist and screening form, a product sample and the non- refundable prescribed screening fee that is attached to the cover letter, must accompany each application.

3.11 On receipt at the MCC, all applications for registration will be subject to a pre-screening according to a checklist (see attachment A).

3.12 Upon successful pre-screening, the application will be logged onto the system, allocated an application number and a letter acknowledging receipt of the application and the screening fee will be issued to the applicant.

3.13 If the pre-screening is unsuccessful, the applicant will be notified via e-mail or fax to collect the application within a certain period of time or the application will be submitted to council for a decision.

3.14 After successful pre-screening the application will be subjected to technical screening according to the screening form (MRF 2).

3.15 The HOLD and RETURN AS INCOMPLETE screening outcomes will be communicated to the applicant together with the reasons. Time frames for the applicant to submit outstanding information or to collect the application will also be communicated to the applicant. The outcome of the screening and the submitted screening documentation will be tabled at the next Council meeting for a decision.

3.16 The ACCEPTED screening outcome, the application fee, the number of copies and the time frame for these copies to be submitted will be communicated to the applicant. Where an expedited registration has been approved the application will be so marked. Any future correspondence regarding an expedited registration application shall be accompanied by a reference number and a copy of the approval letter.

3.17 The correct number of copies of applications and additional documents required for the evaluation of the application must be submitted in the format detailed in section 4 below.

4. PRESENTATION OF SCREENING AND POST SCREENING COPIES

In order to facilitate processing of the application for registration it is required that certain Parts of the application for registration be duplicated and submitted as prescribed in the screening approval letter together with the application fee. All documentation must be in English or the original document must be accompanied by a translation into English.

No additional documentation other than that which has been clearly stipulated below may be bound in any of the files identified below.
Where applicants have submitted electronic applications, there must be prior arrangements with the registrar for such applications, which will be submitted in the prescribed format.

4.1 Screening submission:
Covering letter
Screening fee
Completed pre-screening checklist

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Completed screening form
One complete application for registration dossier
'File 1' below

(i) File 1 (with original submission for screening)

Copy of the latest Inspection Report (not older than 2 years) from the Medicines Control Council and or foreign regulatory body recognized by the Council for the manufacturer of imported medicinal products and medicines Inspection flow diagram (what about locally manufactured medicines
GMP WHO certificate
Certificate of analysis for the sample submitted
One sample of smallest pack size
Batch manufacturing documents for the sample submitted or available for inspection
License for Manufacturer, Packer, Laboratory
Proof of registration of the Company and the authorised person as a pharmacist.

4.2 Full submission:

Covering letter and application fees, plus the number of copies requested by MCC post screening.

(ii) File 2
Covering letter
Application for registration MRF 1 front page
Copy of screening form (MRF 2, completed in full)
Parts 1A, 1B, 1C, 1D, 2A, 2B, 2C, 2D, 2E, 2F, 2G and 2H

(iii) File 3
Covering letter
Application for registration MRF 1 front page
Parts 1A, 1B, and 2B

(iv) File 4
Covering letter
Application for registration MRF 1 front page
Parts 1A, 1B, 1C, 2B, 2E, and 2F

(v) File 5
Covering letter
PART 2A

(vi) File 6
Covering letter
SBRA Clinical Expert Report, if applicable

(vii) File 7

Covering letter
Application for registration MRF 1 front page
Parts 1 A, 1C, and 1D.
Approved foreign package inserts
Clinical and Toxicological Expert reports

(viii) File 8

Covering letter
Application for registration MRF 1 front page
Copy of screening form (MRF 2, completed in full)
Parts 1A, 1B, 1C, 1D, 2A, 2B, 2C, 2D, 2E, 2F, 2G, 2H, 3, 4 and 5

4.3 Once the applicant has submitted additional copies, an acknowledgement letter will be sent to the applicant and the application will proceed with the evaluation process.

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

5. Summary Basis of Registration Application (SBRA)

a) General

To expedite the review process of the safety and efficacy of medicines it is required that an Summary Basis for Registration Application (SBRA) accompany each application for registration where a clinical and pre-clinical expert report is not presented and clinical/pre-clinical data is submitted in support of the application.

The SBRA is intended to be a very brief and concise document containing the core data on the basis of which the applicant intends to obtain registration for the product. It is to be presented as a summary only; therefore no articles, reports etc. are to be incorporated into the SBRA nor should such papers be attached to it either, as these belong with the full submission.

Applicants must ensure that the general quality of the studies, proper cross-referencing to the data, explanatory notes and the quality of photocopying and binding are of an appropriate standard. SBRA must be cross-referenced with the documentation submitted to the Medicine Control Council.

Adaptation to the format prescribed in b) below, to suit each individual product-dosage form at the discretion of the applicant, where specific items are not applicable, may be necessary. Applicants are kindly requested to leave a wide left-hand margin (of at least 5 cm), for office use.

b) SBRA format

Refer to format below for details and a completed hypothetical example.

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SUMMARY BASIS FOR REGISTRATION APPLICATION (SBRA)

1. **THIS APPLICATION INVOLVES:**

a new application
or
a resubmission
or
a package insert amendment

2. **DATE OF THIS SBRA:**

2.1 submitted:
2.2 discussed (office use):
2.3 comment to applicant (office use):

3. **PRODUCT DETAILS:**

Active ingredients(s) and quantity thereof:
Proprietary name
Applicant:
Application/Registration No.:
Pharmacological classification:
Dosage form:

4. **NAME(S)** of Registration Person and/or Medical Adviser responsible for compilation of this application, and telephone number where responsible individual may be contacted during office hours:

Name	Position	Qualifications	Tel. No.

5. **PROVEN (ESTABLISHED) PHARMACOLOGICAL ACTION:**

(Only information concerning the clinical issues and indications claimed are relevant). (MAXIMUM 100 WORDS).
(At least two key references in support, preferably published – see 13 below).

6. **EVIDENCE OF EFFICACY IN HUMANS:**

(Data should be summarized in tabulated format, preferably under the following headings, as applicable:

- Key trial(s) reference number: as listed under item 13 of SBRA
- Trial design : indicate with abbreviations/symbols, e.g.
  - DNB = double-blind
  - SB = single-blind
  - O = open
  - X = cross-over
  - P = parallel groups
  - R = randomized

- C = controlled
- PC = placebo-controlled
- MC = multicenter
- LS = Latin square

- Indications/Diagnosis.
- Number of patients treated with each drug.
- Dosage range used.
- Duration of treatment.
- Reference/comparative drug(s).
- Parameters evaluated/findings.
- Statistical data

(Please indicate separately, the total (overall) number of patients treated with the product)

Indicate clearly which trials were done/not done with the formulation and dosage form, for which registration is being applied (as reflected in Part 2B of MRF).

(Free comment, if required. MAXIMUM 200 WORDS, excluding tabulated data).

7. MAIN SAFETY ISSUES AND TOXICOLOGY:

7.1 Human studies:

(List side effects/adverse reactions/toxicological profile, with incidence figures and key references).

7.2 Pre-clinical studies:

(Animal and in vitro toxicology data)

(Free comment, if required: MAXIMUM 200 WORDS, excluding tabulated data).

8. EVIDENCE OF LONG TERM SAFETY/EFFICACY

Tabulate key long-term studies, their duration, indications, findings, tolerability, etc.; with references, where applicable).

(Free comment, if required: MAXIMUM 100 WORDS).

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9. **EVIDENCE OF BIOAVAILABILITY AND PHARMACOKINETICS OF THE ACTIVE COMPONENT(S):**

(Methods used and number of subjects studied to be clearly specified, where applicable. Pharmacokinetic data summarized in tabular or graphical form is essential).
(MAXIMUM 100 WORDS).

10. For medicines containing more than one active component, provide a summary of evidence (with key references), that each contributes materially to the efficacy of the product.
(MAXIMUM 100 WORDS).

11. **REGISTRATION STATUS IN OTHER COUNTRIES:**

Country	Date of registration

12. **PROPOSED SCHEDULING STATUS:**

(Provide reasons briefly, and illustrate structural formula)

13. **LIST OF KEY REFERENCES:**

(MAXIMUM 25)

(Directly applicable publications in referred scientific journals are preferred. Where suitable published scientific documentation is lacking, selected unpublished key scientific reports or in-house documents may be quoted, provided these are clearly indicated as such.

The "Vancouver Style" of setting out published references, entails the following*:

Author(s), title of article, name4 of journal (abbreviated according to Index Medicus), journal particulars (year, volume, page no.).

Eg.:

1. Smith J treatment of mild hypertension. Br Med J. 1981: 283:628.

*Please refer to: "Uniform requirements for manuscripts submitted to biomedical Journals". S Afr Med J. 1981:60:263-268).

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HYPOTHETICAL EXAMPLE: SUMMARY BASIS FOR REGISTRATION APPLICATION (SBRA)

1. **THIS APPLICATION INVOLVES:**

A new application

2. **DATE OF THIS SBRA:**

2.1 submitted: 01-10-1986

2.2 discussed:

2.3 comment to applicant:

3. **PRODUCT DETAILS:**

Active ingredient(s) and Quantity thereof	:	rosalone 10 mg
Proprietary name	:	ROZIN
Applicant	:	ROSEPHARM Laboratories
Application/Registration No.	:	
Pharmacological classification	:	6.1 Cardiac stimulants
Dosage form	:	film-coated tablets

4. **NAME(S) of registration Person and/or Medical Adviser responsible for compilation of this application:**

Name	Position	Qualifications	Tel. No.
Mr J Smith	Registration Manager	B.Sc (Pharm)	011-9628413
Dr P Jones	Medical Director	M.B., Ch.B.	012-488327

5. **PROVEN (ESTABLISHED) PHARMACOLOGICAL ACTION:**

Rosalone is a positive inotropic agent, with direct vasodilator activity, different in structure and mode of action from either digitalis glycosides or catecholamines. Rosalone produces clinically and statistically significant improvements in haemodynamic indices of congestive heart failure, without significant increases in heart rate or myocardial oxygen consumption. Haemodynamic improvements are both dose

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and plasma level-related. In addition to increases in contractility, rosalone improves diastolic function as evidenced by improvements in left ventricular diastolic relaxation.

(References: 1, 2 and 6)

6. EVIDENCE OF EFFICACY IN HUMANS:

Key Ref No.	Design: O=Open DB=Double-blind R=Randomized X=Crossover P=Parallel Groups PC=Placebo controlled MC=Multi-center	Indication	No. of patients entered and (completed)	Statistical data	Dosage, dosage form and (formulation)	Reference Drug and dosage	Duration of treatment	Parameters evaluated/ Findings
3	O, MCCB, R, X, PC	Congestive cardiac failure	92 (80)	P<0,01 for all para-meters, except (c)	10 mg/day *(f.a.a.f.)	Placebo	6 weeks	a) ..... b) ..... c) ..... d) .....
5	O, X	"	55 (51)	Not done	20 mg/day (capsule)	Digoxin (0.25 mg/day)	4 weeks	
8	O, MC	"	214 (189)	.....	10 mg/day *f.a.a.f.)	-	14 weeks	.....
12	DB, R, P, PC	"	20 (16)	.....	20 mg/day *(f.a.a.f.)	Placebo	2 weeks	.....
15	DB, R, P	"	76 (63)	.....	10 mg/day *(f.a.a.f.)	Digoxin (0.25 mg/day)	8 weeks	.....

TOTAL NUMBER OF PATIENTS TREATED IN ALL CLINICAL TRIALS, WITH ROSALONE: 618 (562 COMPLETED THERAPY)

See also item 8.

All studies (listed under items 6 and 8), except ref. 5, were done with dosage form and formulation that registration is being applied for; (*=formulation as applied for).

7. MAIN SAFETY ISSUES AND TOXICOLOGY:

7.1 Human studies:

Effect	Incidence	Key ref.
Ventricular arrhythmias	12,6%	13
Supraventricular arrhythmias	3,6%	13,3
Hypotension	3,1%	13
Angina/Chest pain	1,4%	5
Headaches	4,4%	4, 12, 13
Hypokalaemia	0,7%	15

Tremor	0,5%	8
Thrombocytopenia	5%	13
Alkaline phosphatase	9%	8, 13, 15

Allergic reactions occurred in +1.4% of patients.

Dermatological reactions (rash, pruritus, etc) were reported in + 20% of patients. Despite this, patient acceptance and compliance was very good.

7.2 Pre-clinical Studies

			INCIDENCE	KEY REF
A Acute Toxicity Studies:	(i)	LD50: Rabbit (i.v.) 16 mg/kg Mouse (s.c.) 140 mg/kg Dog (p.o.) 400 mg/kg		(1)
	(ii)	Dog p.o. LD50: severe emesis.		(11)
B Subacute Toxicity Studies (4 weeks)	(i)	Marked increase in Heinz inclusion bodies at 300 mg/kg p.o (Rat)	25% 1/10	(11)
	(ii)	Elevated reticulocyte count in males given 30 mg/kg i.p., coupled with polychromasia (Rat)	3/10	(11)
	(iii)	Plasma urea 48% higher (80 mg/kg) (Rat) i.p.	2/5	(11)
	(iv)	Crystal-like structures detectable in some tubuli of high dose male rats.	30/40	(11)
	(v)	Allergenic reaction 40 mg – 80 mg/kg p.o. in 3 dogs at beginning of study.	3/12	(9)
	(vi)	Evidence of functional and morphological kidney damage in monkeys 40 and 90 mg/kg i.v. Serum urea and creatinine increased.	12%	(9)
	(vii)	Evidence of functional and morphological kidney damage observed in 2/4 monkeys at 30 mg/kg. Crystalline precipitates observed	2/4	(9)
C Subchronic Toxicity Studies	(i)	Reduced erythrocyte counts and reduced haemoglobin and haematocrit values – high dose monkeys (18 mg/kg i.v.) Crystalloid substances in distal tubles of 2 high- dose monkeys	3/20 2/15 7/10 high dose rats 3/10	(7) (7) (7) (7)
	(ii)	Crystals in urine sediment (rats)		
	(iii)	Death of 3 high dose rats (500 mg/kg).		
D Chronic Toxicity (Six months)	(i)	Crystals observed in urine sediment of 2 males and 2 females from high dose group (500 mg/kg p.o.)	4/20	(7)
	(Rats)		2/10	
	(i)	Histopathological examination revealed mild to moderate foreign body reaction in kidneys of 2 monkeys receiving 90 mg/kg. Kidney changes were associated with intratubular crystallization, but no indication of functional impairment.		(7)
Oculotoxicity:		(Rhesus monkeys) No oculotoxicity observed	32/32	(7)
Arthropathy.		Articular cartilage damage (juvenile rats) Lesions in articular cartilage (dogs)	11/20 12/12	(7) (7)
Fertility:	(i)	Slight decrease in implantations (no statistically significant) at 100 mg/kg dose (rat).		(7)
	(ii)	No untoward effect on fertility or reproductive performance		