STABILITY

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.

STABILITY

"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.

STABILITY

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

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.

STABILITY

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.

STABILITY

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.

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 1

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 effectiveness(even 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.

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 sheif-life/expiry date.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

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.

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.