MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH
Republic of South Africa

MEDICINES CONTROL COUNCIL

STABILITY

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

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

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REGISTRAR OF MEDICINES
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STABILITY TESTING

The Tripartite guideline, which has been developed within the Expert Working Group (Quality) of the International Conference on Harmonisation (ICH), provides a general indication of the requirements for stability testing. It primarily addresses the information required in applications for registration for new chemical entities and associated medicinal products. This guideline is adopted with only minor modifications. It contains aspects relating to testing conditions, numbers of batches to be tested and the requirements regarding follow-up stability data.

The Tripartite guideline latest additions/ updates appear on the ICH, FDA and EMEA websites. Other relevant guidelines on the websites should also be referred to.

World Health Organization has recently published revised guidelines on stability testing (Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, Technical Report Series 953, Annex 2). These guidelines make provision for the following long-term storage conditions for stability testing:

Climatic zone	**Definition**	**Criteria** Mean annual temperature measured in the open air/ Mean annual partial water vapour pressure	**Long-term Testing Conditions**
I	Temperate climate	≤ 15 °C / ≤ 11 hPa	21 °C / 45 % RH
II	Subtropical & Mediterranean climate	> 15 to 22 °C / > 11 to 18 hPa	25 °C / 60 % RH
III	Hot and dry climate	> 22 °C / ≤ 15 hPa	30 °C / 35 % RH
IVA	Hot and humid climate	> 22 °C / > 15 to 27 hPa	30 °C / 65 % RH
IVB	Hot and very humid climate	> 22 °C / > 27 hPa	30 °C / 75 % RH

South Africa is classified in CZ II. In Table 2 of the WHO guideline the long-term stability conditions for WHO Member States by Region are listed, with South Africa indicated as zone IVA. Long-term stability studies conducted at zone IVA and IVB conditions, instead of or in addition to zone II will also be acceptable.

1 STABILITY TRIAL DESIGN

There should be a written testing programme designed to assess stability characteristics of dosage forms. The results of such stability testing should be used in determining appropriate storage conditions and retest or expiry dates.

The design of the study should consider the methodology for determining the stability of the active pharmaceutical ingredient (API) and dosage forms. The following factors should be considered in designing a stability trial:

1.1 ACTIVE PHARMACEUTICAL INGREDIENT (API)

1.1.1 New Chemical Entity

a) General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation.

The actual studies to be carried out will depend on the nature of the API, but may include the effect of elevated temperatures or low temperatures, susceptibility to moisture, oxidation and the effect of light. The effect of pH and high oxygen atmosphere may be important for aqueous solutions or suspensions of the API.

b) Stress Testing

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products, and to validate the stability indicating power of the analytical procedures used.

c) Formal Studies

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

d) 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 produced by the same synthesis route, and with a method of manufacture and procedure, which simulates the final process to be used on a manufacturing scale.

The overall quality of the batches of API 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 should be confirmed that the same method of synthesis is used by all manufacturers, or extensive comparative data should be submitted, which include all aspects of quality, safety and efficacy.

Supporting information may be provided in the form of stability data on batches of API that were produced on a laboratory scale.

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

e) Test Procedures and Test Criteria

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

f) Specifications

Limits of acceptability should be derived from the profile of the material, which was used in the pre-clinical 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 pre-clinical studies and clinical trials. . Normally, impurities and degradation products in concentrations higher than 0,1 % should be identified.

g) Storage Conditions

The length of the studies and the storage conditions should be sufficient to cover the periods of storage, shipment, and subsequent use. Application of the same storage conditions as applied to the FPP will facilitate comparative review and assessment. Other storage conditions are allowed if they can be fully justified by the applicant. In particular, temperature sensitive APIs 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.

	Storage conditions	Minimum time period at submission
Long-term testing	25 ± 2 ^{o}C/60 ± 5 % RH	12 months
Accelerated testing	40 ± 2 ^{o}C/75 ± 5 % RH	6 months

Where “significant change” occurs during six months of storage under conditions of accelerated testing (40 ^{o}C ± 2 ^{o}C/75 % RH ± 5 %), additional testing at an intermediate storage condition (such as 30 ^{o}C ± 2 ^{o}C/65 % ± 5 % RH), should be conducted. This applies to APIs that will be used in dosage forms which will be subjected to long-term testing at 25 ^{o}C/60 % RH. This information should also be included in the application for registration. The initial application should include a minimum of 6 months’ data from a 12-month study.

"Significant change" at 40 ^{o}C/75 % RH or 30 ^{o}C/65 % RH, is defined as failure to meet the specified requirements.

The long-term testing will be continued for a sufficient period of time beyond 12 months to cover all appropriate retest periods. The additional 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 ^{o}C/65 % RH, in which case additional data at intermediate conditions are not required. (Zones III & IV)

h) Testing Frequency

Frequency of testing should be sufficient to establish the stability characteristics of the API. 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 once annually.

i) Packaging/Containers

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

j) Evaluation

The design of the stability study is to establish, based on testing a minimum of three batches of the API 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 API manufactured under similar conditions. The degree of variability of individual batches affects the likelihood that a future production batch will remain within specifications 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. This can be done by 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.

Should the data show that minimum degradation and variability of the API occurred during stability testing, it may be inferred that the requested retest period will be granted. Under these circumstances, it would normally not be necessary to go through the formal statistical analysis. A full justification for the omission will suffice.

Limited extrapolation of the real time data, beyond the observed range, to extend the retest period at approval time, particularly where the accelerated data support this, may be done. However, this assumes that the same degradation relationship will continue to apply beyond the observed data. The use of extrapolation should, therefore, 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 not only cover the assay of the API, but also the levels of degradation products and other appropriate attributes.

When degradation products are identified in significant quantities (0,1 % or more) or suspected of toxicity, a concerted effort has to be made to collect the following additional information about the API 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 concentration levels expected, 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.

The results of any toxicity studies, which may have been conducted, should be reported.

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

Stability information gained, should enable the applicant to institute a routine system whereby re-analysis to validate conformance to specifications of the API, is conducted to assure the stability of a particular dosage form.

k) Statements/Labelling

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

1.1.2 Well-known Chemical Entities (established APIs)

Information on the stability of the active pharmaceutical ingredient is an integral part of the systematic approach to stability evaluation.

The re-test period or shelf-life assigned to the API should be derived from stability testing data.

a) Active pharmaceutical ingredients not described in official pharmacopoeia

Stability studies are required for APIs not described in an official pharmacopoeial monograph (European Pharmacopoeia, the United States Pharmacopoeia of British Pharmacopoeia).

b) Active pharmaceutical ingredients described in official pharmacopoeia

API monographs that include degradation products and limits thereof.

Two options are acceptable for API described in an official pharmacopoeial monograph (European Pharmacopoeia, the United States Pharmacopoeia or British Pharmacopoeia), which *covers the degradation products and for which suitable limits have been set* but a re-test period is not defined:

i) The applicant should specify in Section 1.7.4.1 that the API complies with the pharmacopoeial monograph immediately prior to manufacture of the finished product.

In this case no stability studies are required on condition that the suitability of the pharmacopoeial monograph has been demonstrated for the particular named source;

ii) A re-test period based on the results of long term testing, taking the results of testing under accelerated or, where applicable, intermediate storage conditions, into consideration (see Storage Conditions) should be allocated/proposed.

API monographs that do not include degradation products and limits thereof

When degradation products and suitable limits are not described in the accepted pharmacopoeia, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways.

c) Stress Testing

Stress testing of the API can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used.

For an API the following approaches may be used:

i) When an API is described in an official pharmacopoeial monograph (European Pharmacopoeia, the Unites States Pharmacopoeia of British Pharmacopoeia) and fully meets its requirements no data are required on the degradation products if they are named under the headings “purity test” and / or “section on impurities”.

ii) For API not described in an official pharmacopoeial monograph, there are two options:

- When available, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways;
- When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided in the application.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperatures (in 10 °C increments (e.g., 50 °C, 60 °C, etc.) above that for accelerated testing), humidity (e.g., 75 % RH or greater) where appropriate, oxidation, and photolysis on the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a wide range of pH values when in solution or suspension.

Assessing the necessity for Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B Photostability Testing of New Active Substances and Medicinal Products.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term conditions.

d) Selection of Batches

Stability information from accelerated and long term testing is to be provided on at least two batches of at least pilot scale manufactured by the same manufacturing (synthetic) route and procedure described in part 3.2.S.2 of the application.

e) Change in the manufacturing process of the active pharmaceutical ingredient

In case of amendment to the manufacturing process of the API, the following approaches may be considered as acceptable:

If the quality characteristics (e.g. physical characteristics, impurity profile) of the API are changed in such a way that stability may be compromised, comparative stability data are required in accelerated and long term testing conditions, on the API before and after the change:

- for API known to be stable: three months on one batch of at least pilot scale. An API is considered as stable if it is within the initial specifications when stored at 25 °C/ 60 % RH or 30 °C/65% RH, respectively, (2 years) and 40 °C/75 %RH (3 months).
- for API known to be unstable: six and three months long term and accelerated respectively on two batches of at least pilot scale.

e) Change in the manufacturing process of the active pharmaceutical ingredient - continued

If the quality characteristics of the API are changed in such a way that it may impact the stability of the finished product, additional stability data on the finished product, in accelerated and long term testing conditions, three months on one batch of at least pilot scale, may be required.

Storage conditions:

	Storage conditions	Minimum time period at submission
Long-term testing	25 ± 2 ^{o}C / 60 ± 5 % RH	6 months
Accelerated	40 ± 2 ^{o}C / 75 ± 5 % RH	3 months

Stability data over the full shelf-life period should be submitted for confirmation of the provisional retest period.

1.2 DOSAGE FORMS

1.2.1 General requirements for finished pharmaceutical products (FPPs) containing New Chemical Entities and finished pharmaceutical products (FPPs) containing well-known entities

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

a) 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 of the FPP. Analytical test procedures should be fully validated and assay methods should be stability-indicating.

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 on the integrity of the product. 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 a 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 un-reconstituted, dosage forms.

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

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

Stability should be established for the whole period of intended use under the intended storage conditions and reflected in the printed packaging components in PART 1 / Section 1.3.

b) Specifications

Stability studies should 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 for acceptable and justifiable deviations from the release specification based on the stability evaluation and the changes observed on storage. It should 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.

Any differences between the release and shelf-life specifications for antimicrobial preservatives, should be supported by preservative efficacy testing.

c) Testing Frequency

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

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

d) Packaging Material

The testing should be carried out in the final packaging proposed for marketing. Additional testing of unprotected FPP 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 ^{o}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. 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. A brief justification for the container size chosen, e.g. larger air volume, or largest surface contact, etc. should also be included.

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. are equal to, or better than, existing container closure systems, additional stability testing would usually not be required for solid dosage forms in the more protective packaging.

In instances where solid oral dosage forms 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 should be included in the MRF1 PART 3G / CTD Section 3.2.P.8.

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 should be submitted for bulk products that are stored for a period of time prior to packaging into the final immediate containers, i.e. for 25 % or more of the approved shelf-life.

e) 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 (e.g. dissolution rate for oral solid dosage forms).

The aim of the stability study is to establish, based on testing a minimum of three batches of the FPP for NCEs and two batches for well-known chemical entities, a shelf-life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar conditions. The degree of variability of individual batches affects the likelihood of a future production batch remaining 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. This can be done by 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.

Should the data show that minimum degradation and variability of the API occurred during stability testing, it may be inferred that the requested retest period will be granted. Under these circumstances, it would normally not be necessary to go through the formal statistical analysis. A full justification for the omission will suffice.

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

Any evaluation should not only cover the assay of the API, but also the levels of degradation products and other 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 FPPs 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 should be tested for at least the recommended storage period at 25 ^{o}C, even if the recommended storage temperature is 2 to 8 ^{o}C.

f) Statements/Labelling

The storage temperature should be based on the stability evaluation of the FPP. The use of terms such as “ambient conditions” or “room temperature” is unacceptable. The use of a temperature range, for example 15 to 25 ^{o}C, is generally not acceptable unless justified. Where applicable, specific requirements should be stated particularly for FPPs that cannot tolerate refrigeration or freezing. The recommendation, “Store at or below 25 °C. Do not refrigerate” or variations thereof as appropriate, could be considered.

There should be a direct link between the label statement and the demonstrated stability characteristics of the FPP.

g) Specific text for in use storage of reconstituted and diluted parenteral products [9]

i) Unpreserved sterile products

Chemical and physical in-use stability has been demonstrated for x hours/days at y ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

ii) Specific text for preparations for Infusion or Injection

Chemical and physical in-use stability has been demonstrated for x hours/days at y ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ºC, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

iii) Preserved sterile products

Aqueous preserved sterile products (including antimicrobial preservatives of intrinsically self-preserving)
Non-aqueous e.g. oily preparations

Chemical and physical in-use stability has been demonstrated for x hours/days at y ºC.

From a microbial point of view, once opened, the product may be stored for a maximum of z days at t ºC. Other in-use storage times and conditions are the responsibility of the user.

The Applicant should justify the values of z and t on a case by case basis; z should not normally be greater than 28 days.

1.2.2 Products containing New Chemical Entities

a) 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 system 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 meet the same quality specification to be applied to release of material. Where possible, batches of the FPP should be manufactured using identifiably different batches of API.

Where an application includes different manufacturers of APIs 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 API.

Data on laboratory scale batches are 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.

b) 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 the 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 allowed, if justified. Heat sensitive FPPs should be stored at 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 temperatures, e.g. suspensions or emulsions, which may sediment or cream; oils and semi-solid preparations, which may show an increase in 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 ^{o}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 ^{o}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 humidity applies particularly to solid dosage forms. Specific storage under conditions of high relative humidity is not necessary for products, such as solutions and suspensions, contained in packs designed to provide a permanent barrier to water loss, however 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) 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 which is close to saturation, stability data at low temperatures (2 to 8 ^{o}C) should be conducted for at least 14 days.

Storage Test Conditions for Products containing New Chemical Entities

	Storage conditions	**Minimum time period at submission
Long-term testing	25 ± 2 ^{o}C/ 60 % ± 5 % RH *	12 months
Intermediate	30 ± 2 ^{o}C/ 65 % ± 5 % RH	6 months if significant change at accelerated
Accelerated	40 ± 2 ^{o}C / 75 % ± 5 % RH	6 months

* Long-term storage at 30 ± 2 °C /65 % ± 5 % RH or 30 ± 2 ^{o}C/75 % ± 5 % RH is also acceptable.

** However, all the stability data that should reasonably be available at the time of submission should be submitted. At the time of responding to a Pharmaceutical and Analytical Committee recommendation, any available further/follow-up stability data may/should be submitted provided that the stability data previously submitted is also included, i.e. a complete data set of PART 3G/Module 3.2.P.8 with the additional data excluding unchanged analytical methods and analytical method validation. *Refer to 4.5 below*.

Please note, if 30 °C ± 2 °C/65 % RH ± 5 % RH (or 30 °C ± 2 °C/75 % RH ± 5 % RH) is the long-term condition, there is no intermediate condition.

1.2.2 Products containing New Chemical Entities - Storage Test Conditions - continued

Where "significant change" occurs due to accelerated testing, long-term data for a period longer than 12 months may be required to justify a provisional shelf-life of 24 months. "Significant change" at accelerated testing conditions 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.

Where 25 ± 2 ^{o}C / 60 % ± 5 % RH is the long-term testing condition, and "significant change" occurs due to / at accelerated testing, additional testing at an intermediate condition e.g. 30 ± 2 ^{o}C / 65 % ± 5 % RH should be conducted.

Should significant change occur at 40 ± 2 ^{o}C / 75 % ± 5 % RH then the initial application for registration should include a minimum of six months' data from an ongoing 1 year study at 30 ± 2 ^{o}C / 65 % ± 5 % RH. The same significant change criteria shall apply

The long-term testing will be continued for a sufficient time beyond 12 months to cover the shelf-life at appropriate test periods. Long-term stability studies may also be performed at 30 ± 2 ^{o}C / 65 % ± 5 % RH, in which case no additional data under intermediate conditions are required (Zone III and IV).

1.2.3 Products containing well-known chemical entities (generics)

a) 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, of the same manufacturing process with API from the API manufacturer(s) being applied for (PART 3A / Section 3.2.S), in the containers and closure system proposed for marketing (PART 3D / section 3.2.P.7).

Pharmaceutical equivalence should be demonstrated for API from different manufacturers. 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).

Data on laboratory scale is not acceptable as primary stability information. Data on associated formulations or packaging may be submitted as supporting information provided that the difference in formulation is clearly stated.

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.

The long-term testing should cover at least nine 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 meet the same quality specification that are to be applied to release of material.

b) Storage Test Conditions

	Storage conditions	**Minimum time period at submission
Long-term testing	25 ± 2 ^{o}C / 60 % ± 5 % RH *	9 months
Intermediate	30 ± 2 ^{o}C/ 65 % ± 5 % RH	6 months if significant change at accelerated
Accelerated	40 ± 2 ^{o}C / 75 % ± 5 % RH	3 months

1.2.3 Products containing well-known chemical entities (generics) – Sotrage Test Conditions - continued

* Long-term storage at 30 ± 2 °C/65 % ± 5 % RH or 30 ± 2 °C/75 % ± 5 % RH is also acceptable.

** However, all the stability data that should reasonably be available at the time of submission should be submitted. At the time of responding to a Pharmaceutical and Analytical Committee recommendation, any available further/follow-up stability data may/should be submitted provided that the stability data previously submitted is also included, i.e. a complete data set of PART 3G / Module 3.2.P.8 with the additional data excluding unchanged analytical methods and analytical method validation. *Refer to 4.5 below*.

Please note, if 30 °C ± 2 °C/65 % RH ± 5% RH (or 30 °C ± 2 °C/75 % RH ± 5 % RH) is the long-term condition, there is no intermediate condition.

Where "significant change" occurs due to accelerated testing, long-term data for a period longer than nine months may be required to justify a provisional shelf-life of 24 months. "Significant change" at accelerated testing conditions 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.

Where 25 ± 2 °C / 60 % ± 5 % RH is the long-term testing condition, and "significant change" occurs due to / at accelerated testing, additional testing at an intermediate condition e.g. 30 ± 2 °C / 65 % ± 5 % RH should be conducted.

Should significant change occur at 40 ± 2 °C / 75 % ± 5 % RH then the initial application for registration should include a minimum of six months' data from an ongoing 1year study at 30 ± 2 °C / 65 % ± 5 % RH. The same significant change criteria shall apply.

The long-term testing will be continued for a sufficient time beyond nine months to cover the shelf-life at appropriate test periods. Long-term stability studies may also be performed at 30 ± 2 °C / 65 % ± 5 % RH, in which case no additional data under intermediate conditions are required (Zone III and IV).

Heat-sensitive FPPs should be stored under an alternative lower temperature, which will eventually become the designated long-term storage temperature. Where a lower temperature 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).

2 PRESENTATION OF STABILITY DATA

2.1 The criteria for acceptance of each parameter (minimum and maximum values), relating to stability, should be stated.

2.2 Overages in the formulation of batches, included in the stability investigation, should be clearly stated.

2.3 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) should be provided in a tabulated form. For products predicted to degrade rapidly, more frequent sampling is necessary.

2.4 The container closure system used should be clearly indicated, e.g. the type, nature, grade and colour of the material of the container and closure should be stated. The composition of strip packaging, blister packaging and liners, and size of the container(s) or pack-size, should also be clearly stated.

2 Presentation of Stability Data - continued

2.5 Storage conditions should be clearly defined in respect of the temperature, light, humidity, opening and closing of container, whether stored upright or inverted, whether a desiccant is included in the container and the inclusion of foam/cotton wool.

2.6 The name and strength of the product, dosage form, batch size, batch number, name of final product manufacturer, manufacturer of API, dates of final product manufacture and initial testing, should be stated.

2.7 The actual result obtained for an assay at the beginning of the stability trial should be recorded and compared with subsequent values.

2.8 Assay results should be expressed as a percentage of the label claim. Assay results for subsequent checkpoints should be given in the same way, as a percentage.

2.9 Quantitative results should be reflected wherever relevant, in which case, the expression “complies” will not suffice.

2.10 All results obtained should be discussed and conclusions drawn from the stability studies should be stated. A shelf-life should be extrapolated or derived from the results. Explanations should be given where necessary, e.g. for anomalous or unusual results, change in assay method. Results should be processed utilising current statistical methods and any assumption made should be statistically tested at the 90 to 95 % confidence level.

2.11 A stability-indicating method refers to a specific analytical method and does not absolve the applicant from submitting reasons why the assay methods used are assumed to be stability-indicating.

2.12 An assurance that long-term testing will continue to cover the shelf-life period should be given in PART 3G / Section 3.2.P.8 (a 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.

2.13 The stability data should be presented in tabulated format, e.g.:

Product Name: Batch No.: Batch Size: Date of Manufacture:		Packaging (material and pack sizes): Storage conditions: Name of manufacturer: Manufacturer of API:					
Date of commencement of stability study:		Time intervals (months)					
Title of Specification	Limits	0	3	6	9	12	24

3 PREDICTION OF SHELF-LIFE

3.1 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 should be available at the time for consideration of a provisional shelf-life of 24 months. For products containing new chemical entities, the data accumulated over a sufficient period of time, beyond the initial 12 months to cover appropriate test periods, should be available.

3.2 Generally a provisional shelf-life shall only be assigned provided that the stability investigation of the product, as above, has been satisfactorily completed.

3.2.1 APIs and FPPs intended for room temperature storage

3.2.1.1 Long-term and accelerated show little or no change and little or no variability

Extrapolation of the retest period or shelf life up to twice, but not more than 12 months beyond the period covered by long-term data, can be proposed.

3.2.1.2 Long-term or accelerated data show change over time and/or variability

Extrapolation of the retest period or shelf life up to one and a half times, but not more than 6 months beyond the period covered by long-term data, can be proposed.

For data amenable to statistical analysis and supported by statistical analysis and relevant supporting data, extrapolation of the retest period or shelf life up to twice but not more than 12 months beyond the period covered by long-term data, can be proposed.

3.2.2 APIs and FPPs intended for storage in a refrigerator

3.2.2.1 Long-term and accelerated data show no or little change and no or little variability

Extrapolation of the retest period or shelf life up to one and a half times, but not more than 6 months beyond the period covered by long-term data, can be proposed.

3.2.2.2 Accelerated data show significant change between 3 and 6 month's testing at accelerated

If significant change occurs between 3 and 6 months testing at the accelerated condition, the proposed retest period should be based on the long term data, extrapolation is not considered appropriate.

3.2.3 APIs and FPPS intended for storage in a freezer

The retest period or shelf life should be based on long term data.

3.3 Applicants are reminded that a provisional retest period or shelf-life allocated on the basis of extrapolation is granted on condition that the applicant has undertaken to continue and complete the required studies and to submit the results as they become available. Care should be taken to include in the protocol for commitment batches, a time point that corresponds to the end of the extrapolate retest period or shelf life.

4 FOLLOW-UP STABILITY DATA

4.1 For well-known chemical entities the provisional shelf-life should be confirmed by stability data, derived from at least two production batches, stored at the maximum recommended storage conditions for the full duration of the shelf-life.

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.

4.2 For products containing new chemical entities (NCEs), the provisional shelf-life should be confirmed 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.

4.3 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 programme.

4.4 Stability trials, involving the product stored at the maximum recommended temperature, should be continued for the full period to confirm the provisional shelf-life.

4.5 The application should include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches). Reference alone to data submitted previously, is not acceptable.

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. It should also be verified that the batch will meet the final product specification for the full period of the allocated shelf-life.

The date of production of a batch is defined as the date that the first step is performed involving combining the API(s) with other IPIs. For medicinal products consisting of a single API filled into a container, the initial date of the filling operation is taken as the date of production.

Not applicable to biological, vaccines, sera, toxins, allergens products derived from human blood and plasma as well as medicinal products prepared biotechnologically.

6 STORAGE IN BULK

The applicant should 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 (Refer to the Amendments guideline)

The shelf-life may not be extended until the data have been evaluated and approved. The application should include all the stability data in support of the shelf-life extension (including previously submitted data for the relevant batches). Reference alone to data, submitted previously, is not acceptable.

8 AMENDMENTS

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

APPENDIX I

GLOSSARY

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

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of an API or product by using exaggerated storage conditions as part of the formal, definitive, storage programme. 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 that may occur.

Active Pharmaceutical Ingredient (API)/ Active substance / Drug Substance/Medicinal Substance

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product (generally with pharmaceutical ingredients) as a pharmacologically active compound.

Bracketing

The design of a stability schedule so that at any time point, only the samples at the extremes, for example of container size and/or dosage strengths, are tested. The design assumes that those at the extremes represent the stability of the intermediate samples. Where a range of dosage strengths are to be tested, bracketing designs are particularly applicable if the strengths are very closely related in composition. Examples include a tablet range made with different compression masses of a similar basic granulation, or a capsule range made by filling different plug fill masses 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 composition of the material from which the containers are made, and the type of closure, are the same throughout the range.

Climatic Zones

This refers to the concept of dividing the world into four zones based on the prevalent annual climatic conditions. South Africa is classified in CZII (Subtropical & Mediterranean climate) to take into account the climate in South Africa that would most affect the storage of pharmaceuticals/medicines. The South African Weather Service Climatic classification of South Africa ranges from “Desert (arid)” in the west to “All-year rain with hot summers” in the eastern coastal region. Zone IV conditions are regarded as a global zone of highest stringency.

Dosage Form/Preparation

A pharmaceutical product type, for example tablet, capsule, solution, cream, etc. that contains an API generally but not necessarily, in association with inactive pharmaceutical ingredients.

Excipient/Inactive pharmaceutical ingredient (IPI)

Anything other than the API in the dosage form.

Expiry / Expiration Date

The date placed on the container/label 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 should not be used.

Finished Pharmaceutical Product (FPP)

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

Formal (Systematic) Studies

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

Long-Term (Real-Time) Testing

This refers to the stability evaluation of the physical, chemical, biological, and microbiological characteristics of a product and its API, which covers the expected duration of the shelf-life, and retest period, that are claimed in the application for registration, and which will appear on the label.

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 a 100 per cent of the initial value, with due consideration to the level of analytical precision. This concept is a useful scientific guide for evaluating data, but 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 such that only a fraction of the total number of samples is tested at any specific sampling point. At a subsequent sampling point, different sets of samples of the total number, would again 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 permits reduced testing when more than one variable is being evaluated. Thus the design of the matrix will be dictated by the factors that need to be covered and evaluated. The potential complexity precludes inclusion of specific details and examples here. It will, however, be prudent to discuss the design in advance with Council, where possible. It is essential that, in each case, all batches are tested initially, and at the end, of the long-term testing programme.

Mean Kinetic Temperature

When establishing the mean value of the temperature, the formula of Haynes (1971)* 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.

*Haynes, J.D. Pharm. Sci. J, 60, 927-929, 1971.

New Chemical Entity/New Molecular Entity/New API

A substance, which has not previously been registered as a new API, with the Council.

Pilot Plant Scale

The manufacture of either API, 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 batch, or a 100 000 tablets or capsules, whichever is greater.

Primary Stability Data

These are data on the API stored in the proposed packaging under storage conditions that support the proposed retest date. It also refers to data on the product stored in the proposed container-closure system for marketing under storage conditions that support the proposed shelf-life.

Retest Date

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

Retest Period

The period of time during which the API can be considered to remain within the specifications and, therefore, acceptable for use in the manufacture of a given FPP, provided that it has been stored under the defined conditions. After this period, the batch should be re-tested for compliance to its specifications 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 container and closure system.

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

- the least stable API to degrade to the specified, motivated and approved or proposed, fraction of the labelled quantity,
- some element of pharmaceutical elegance to drop to an unacceptable level, or
- an arbitrary minimum of two years, unless otherwise determined by Council.

The shelf-life could also reflect the length of time required for:

- a measurable increase in toxicity, as shown by either animal experiments or clinical adverse reaction reports, or
- 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 whether a product is suitable for release at the time of its manufacture.

Shelf-Life Specification

The combination of physical, chemical, biological and microbiological test requirements that an API should meet up to at its retest date or a product should meet throughout its shelf-life.

Stability-Indicating Assay Methodology

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

Stability

The capacity of an API 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 should be capable of controlling temperature to a range of ± 2 ^{o}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. greater than 2 ^{o}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 API, as well as other ingredients, requiring quantification.

Stress Testing (Active Pharmaceutical Ingredient API)

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 those used for accelerated tests. Stress testing is conducted to provide data on breakdown products and decomposition mechanisms for the API.

The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of the API. 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 extensiveness of the studies will depend on the individual API and type of FPP.

This testing is likely to be carried out on a single batch of material and will include the effect of temperature, in 10 °C increments above the accelerated temperature test condition (e.g. 50 ^{o}C, 60 ^{o}C, etc.), humidity where appropriate (e.g. 75 % or greater), oxidation and photolysis on the API, 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 recognised 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 conditions. Information on such degradation products may be useful in developing and validating suitable analytical methods. However, it may not always be necessary to test for such compounds, particularly if it has been demonstrated that in practice, these are not formed.

Stress Testing (FPP)

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, creams and emulsions) may require additional stress studies.

Supporting Stability Data

These include data other than primary stability data, such as stability data on early batches of API using a different route of synthesis, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, product presented in containers and/or closure systems 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.

Provisional 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 II

APPROPRIATE 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 submit data to show that it either does not occur, or that it is clearly recognised and defined. Where significant interaction with the packaging is likely, the effects on the product and on the packaging (e.g. due to leaching of extractables, or due to absorption of constituents), should be evaluated and the results reported. The following tests should 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. This includes published validated methods of analysis as well as compendial analytical methods, together with partial validation data, which only demonstrate suitability of in-house equipment and personnel. If a change in procedure is necessary during the stability trial, data should be generated (and processed), which prove that no statistically significant difference exists between the old and new method of analysis.

The stability-indicating methodology should be validated by the applicant and analytical procedures described in sufficient detail to permit independent 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 API has been used.

Physical properties

In addition to assaying the API and degradation products, it is necessary to ensure that the physical properties of the product are unimpaired after storage. Consideration should be given to the stereo-chemical integrity of the product. Additional tests will vary with the formulation and may include the following:

a) *Tablets and lozenges*

Dissolution rate (single point for immediate release, multipoint for modified release), disintegration time (not required if dissolution rate is done), 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 API is in solution after dispersion) for dispersible tablets. Intactness of coating in the case of coated tablets, unless justified.

b) *Capsules*

Moisture content, colour and appearance (capsule shell and contents), brittleness, disintegration time (when dissolution rate is not applicable) and dissolution rate (single point for immediate release, multipoint for modified release).

When 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.

c) *Emulsions and suspensions*

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

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”.

d) *Solutions*

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

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

e) *Powders and granules (including those for reconstitution)*

Moisture content, resuspendability/reconstitution time and appearance of reconstituted product, and microbial limits. The reconstituted product should be tested in accordance with requirements for a solution or suspension.

f) *Metered Dose Inhalation aerosols*

Uniformity of delivered dose, number of metered doses, particle size (suspensions), spray pattern, microbial limits and deposition of emitted dose.

Because the container contents are under pressure, filled containers should 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 quantity of API.

g) *Ointments and creams*

Homogeneity, pH, rheological properties, particle size and mass loss (plastic containers). Preserving ability if a preservative is present. Preserving ability of 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) and syringeability of non-aqueous products.

If uniformity of mass and moisture content for a container of freeze dried product that is reconstituted with solvent prior to administration as an injection, are already controlled, a requirement for loss in mass should not be necessary.

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

h) Parenterals continued

Tests should be performed to ensure the compatibility between the container-closure system 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 (LVPs), the smallest container-closure size should be studied, provided that all container-closure systems are identical in composition and have the same 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 include 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 system and the product. These data should be submitted.

i) *Suppositories*

Melting range point, breaking strength and disintegration. The effect of ageing may also be observed from hardening of the suppository base; therefore, control and stability testing should include disintegration time at 37 ºC. Accelerated studies should be conducted at 2 to 3 ºC below the melting point of the suppositories.

j) *Admixtures*

For any product intended for use as an additive to another product, the possibility of incompatibilities exists. In such cases, the product that is labelled to be administered by addition to another product (e.g. parenterals, aerosols) should be studied for stability and compatibility in admixture.

A suggested protocol should provide for tests to be conducted at zero-, 6-, 8- and/or 24- hour intervals thereafter. These should include:

- Assay of API and any other ingredient for which a limit is set in the final product specification;
- pH (especially for unbuffered LVPs), colour and clarity (particulate matter);
- interaction with the container;
- identification of precipitant/sediment (although the presence of any precipitant indicates that the product is already non-conforming)
- bacterial endotoxins and sterility (reconstituted solution for injection).

k) *Intra-uterine Devices (IUD)*

Tensile strength of the withdrawal string and integrity of the package (i.e. seal strength of the pouch) and sterility of the device. If the device contains a reservoir from which API diffuses through a controlled release membrane, it should be tested for total active content, degradation products and *in vitro* release rate of the API, in addition to the above tests.

Vaginal devices such as doughnut-shaped silastic or other polymeric matrices which contain an API uniformly dispersed throughout the matrix, should be checked for *in vitro* release rate of the API and extraneous extractable substances, to establish stability and compatibility of the API with the matrix.

l) *Transdermal patches*

Release rate, seal integrity, mass variation and 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. the 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 include a minimum storage period of nine months at real-time storage conditions or 6 months accelerated conditions for those products for which the effect of ageing on preservative effectiveness needs to be demonstrated, e.g. suspensions, creams.

Those products requiring control of microbial quality, and which 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 3F / Section 3.2.P.5) for bio burden.

These tests include, e.g. Microbial limit Tests of the USP or BP, which includes a limit for total microbial count and for absence of *Staphylococcus aureus*, *Escherichia 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 ophthalmic preparations, 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 the MRF1 PART 1C / Section 1.3.

Desiccants

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

REFERENCES

1) Guidance for Industry Q1A Stability testing of new drug substances and drug products. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2001.
2) CPMP Note for Guidance on Stability Testing: Stability testing of existing active substances and related finished products. CPMP/QWP/122/02, corr*
3) CPMP Note for Guidance on evaluation of stability data. CPMP/ICH/420/02 (Date of coming into operation August 2003)
4) CPMP Note for Guidance on Stability Data Package for registration applications in Climatic Zones III and IV. CPMP/ICH/421/02 (Date of coming into operation August 2003)
5) Guidance for Industry Q1D Bracketing and Matrixing Designs for Stability Testing of new drug substances and products. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), January 2003.
6) CPMP Note for guidance on the photostability testing of new active substances and medicinal products CPMP/ICH/279/95 ICH Topic Q1B
7) CPMP Note for Guidance on stability testing: Stability testing of new drug substances and products (revision 2) Date for coming into operation August 2003
8) WHO Technical Report Series, No. 953, 2009, Annex 2
9) CPMP/QWP/159/96corr

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Date for implementation	October 2004
Change to stability requirements at time of submission 1.2.3 a) b) Editing of Appendix II text of Physical properties a) , c) , d) and h)	October 2004
Editing of 1.2.3 b) to indicate requirement at time of registration Editing of 3.1 in line with 1.2.3 b) & editing of 1.1.1g), 1.1.2, 1.2.1 f), 3, 4, Appendix 1 p20 Standardisation of the use of the word "provisional" as opposed to "tentative"	January 2005
Version 3: Editing of 1.1.2	June 2006
Date for implementation	12 July 2006
Version 4: Amendment of Introductory section and of long-term testing conditions and minimum time period at submission for dosage forms - 1.2.2 b), 1.2.3 a) & b)	April 2009
Date for implementation - withdrawn	
Version 5: Amendment of Introductory section and of long-term testing conditions and minimum time period at submission for dosage forms – 1.2.2 a) & b), 1.2.3 a) & b); clarification of 2.6; definition of Climatic Zones page 16.	I July 2010
Version 6: Correction 1.2.2 b) & 1.2.3 b); source replaced with manufacturer 1.1.2, 1.2.2a), 1.2.3a), 2.8, 2.13; 5 Addition for clarification; 7 & 8 Amendments guideline name change; 7 amendment of shelf-life extension in line with Amendments guideline	March 2011
Date for implementation	March 2011
Version 7: Data at time of submission 1.2.2 b) and 1.2.3. b) and format of follow-up data section 4.5 Clarification of section 1.1.2 Replacement of ‘drug substance’ and ‘drug product’ with ‘API’ and FPP respectively. Inclusion of “at or below” in 1.2.1 f) Inclusion of examples of extrapolation that may be proposed in 3 Inclusion of references to relevant CTD Sections	June 2012
Date for implementation	9 July 2012
Version 7.1: Inclusion of section on in-use storage of reconstituted and diluted parenteral products under 1.2.1 g). Inclusion of additional reference 9)	July 2012
Date for implementation	August 2012