



DRAFT
**STABILITY TESTING OF ACTIVE PHARMACEUTICAL
INGREDIENTS AND FINISHED PHARMACEUTICAL
PRODUCTS**

This new revision is based on comments received and reviewed during an informal consultation to discuss stability studies in a global environment which was held in the WHO Eastern Mediterranean Regional Office (EMRO) in Cairo on 19-21 August 2008. The WHO Expert Committee on Specifications for Pharmaceutical Preparations had agreed in October 2006 in general to prepare this working document as a draft that could serve as a replacement for the *WHO guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms*, which were published in 1996, and to include a list of long-term stability conditions as required by WHO Member States.

More information can be found on stability-related issues at the following web site: http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/index.html

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**SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT
QAS/06.179/Rev.3 WITH A VIEW TO ITS REPLACEMENT OF THE GLOBAL WHO
GUIDELINES FOR STABILITY TESTING OF PHARMACEUTICAL PRODUCTS
CONTAINING WELL ESTABLISHED DRUG SUBSTANCES IN CONVENTIONAL
DOSAGE FORMS**

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

Revised draft for comment

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1. INTRODUCTION

1.1 Objectives of these guidelines

These guidelines seek to exemplify the core stability data package required for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPP) for registration, replacing the previous WHO guidelines in this area (1,2). However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in International Conference on Harmonisation (ICH) guidelines (3).

It is recommended that these guidelines should also be applied to products that are marketed, with allowance for an appropriate transition period, e.g. upon re-registration or upon re-evaluation.

1.2 Scope of these guidelines

These guidelines apply to new and existing active pharmaceutical ingredients (APIs) and address information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use. These guidelines are not applicable to stability testing for biologicals (for details on vaccines please see *WHO guidelines for stability evaluation of vaccines* (4)).

1.3 General principles

The purpose of stability testing is to provide evidence on how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes study of product-related factors that influence the quality, for example, interaction of API with excipients, container closure systems and packaging materials. In fixed-dose combination FPPs (FDCs) the interaction between two or more APIs also has to be considered.

As a result of stability testing a re-test period for the API (in exceptional cases, e.g. for unstable APIs a shelf-life is given) or a shelf-life for the FPP can be established and storage conditions can be recommended.

There have been various analyses to identify adequate testing conditions for WHO Member States based on climatic data and published in the literature (5,6,7,8) on the basis of which each Member State can base its decision for long-term (real-time) stability testing conditions. Those Member States that have notified WHO of their long-term stability testing conditions required when requesting a marketing authorization are listed in Annex 1.

2. GUIDELINES

2.1 Active pharmaceutical ingredient (API)

2.1.1 General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be tested on an API during stability testing are listed in the Examples of testing parameters (Annex 2).

The re-test period or shelf-life assigned by the API manufacturer for an API should be derived from stability testing data.

2.1.2 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. The nature of the stress testing will depend on the individual API and the type of FPP involved.

For an API the following approaches may be used:

- when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
- when no data are available, stress testing should be performed.

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) and, where appropriate, oxidation and photolysis on the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension (9).

Photostability testing should be an integral part of stress testing. More details can be found in other guidelines (3).

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3 Selection of batches

Data from stability studies should normally be provided on at least three primary batches of the API. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. The overall quality of the batches of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

For existing active substances that are known to be stable, data from at least two primary batches should be provided.

2.1.4 Container closure system

The stability studies should be conducted on the API packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

2.1.5 Specification

Stability studies should include testing of those attributes of the API that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes (3). A guide for potential attributes to be tested in the stability studies are listed in ... (Annex 2). Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies (8).

2.1.6 Testing frequency

For long-term studies frequency of testing should be sufficient to establish the stability profile of the API. For APIs with a proposed re-test period or shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter through the proposed re-test period or shelf-life.

At the accelerated storage condition a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9, 12 months), from a 12-month study is recommended.

2.1.7 Storage conditions

In general an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage conditions tolerances are defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in this guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The long-term testing should normally cover a minimum of 12 months' duration the number of batches specified in section 2.1.3 at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period or shelf-life. For existing substances that are known to be stable, data covering a minimum of six months may be submitted. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities upon request. Data from the accelerated storage condition and, if

appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for APIs are detailed in the sections 2.1.7.1 to 2.1.7.3. The general case applies if the API is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

If long-term studies are conducted at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ and “significant change” occurs at any time during six months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case, testing at the intermediate storage condition should include all long-term tests, unless otherwise justified, and the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

“Significant change” for an API is defined as failure to meet its specification.

2.1.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	$25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$	12 months or 6 months as described in point 2.1.7
Intermediate**	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$	6 months
Accelerated	$40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$	6 months

* Whether long-term stability studies are performed at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ is determined by the climatic condition in which the API is intended to be stored (see Annex 1). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. $25^{\circ}\text{C}/60\% \text{RH}$ or $30^{\circ}\text{C}/65\% \text{RH}$.

** If $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ is the long-term condition if there is no intermediate condition.

2.1.7.2 *Active pharmaceutical ingredients intended for storage in a refrigerator*

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated *	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH	6 months

* Whether accelerated stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored. Testing at a more severe long-term condition can be an alternative to storage testing at 25°C/60%RH or 30°C/65%RH”.

Data from refrigerated storage should be assessed according to the evaluation section of this guidelines, except where explicitly noted below.

If significant change occurs between three and six months’ testing at the accelerated storage condition the proposed re-test period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months’ testing at the accelerated storage condition a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API through six months when a significant change has occurred within the first three months.

2.1.7.3 *Active pharmaceutical ingredients intended for storage in a freezer*

Study	Storage condition	Minimum time period covered by data at submission
Long-term	- 20°C ± 5°C	12 months

In the rare case of any API of non-biological origin intended for storage in a freezer, the re-test period or shelf-life should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5°C ± 3°C or 25°C ± 2°C or 30°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

2.1.7.4 *Active pharmaceutical ingredients intended for storage below -20°C*

APIs intended for storage below - 20°C should be treated on a case-by-case basis.

2.1.8 Stability commitment

When available long-term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the re-test period or shelf-life.

Where the submission includes long-term stability data on the number of production batches specified in section 2.1.3 covering the proposed re-test period, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

1. If the submission includes data from stability studies on at the number of production batches specified in section 2.1.3 a commitment should be made to continue these studies through the proposed re-test period.
2. If the submission includes data from stability studies on fewer than the number of production batches specified in section 2.1.3 a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed re-test period.
3. If the submission does not include stability data on production batches a commitment should be made to place on the first two or three production batches (see section 2.1.3) on long-term stability studies through the proposed re-test period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

2.1.9 Evaluation

The purpose of the stability study is to establish, based on testing a minimum of the number of batches specified in section 2.1.3, unless otherwise justified and authorized, of the API and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests), a re-test period applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested re-test period will be granted. Under these circumstances it is normally unnecessary to go through the statistical analysis; providing a justification for the omission should be sufficient.

An approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. 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 first applying appropriate statistical tests (e.g. 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 re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed 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.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the re-test period can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

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

2.1.10 Statements/Labelling

A storage statement should be established for the labelling based on the stability evaluation of the API. Where applicable specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as “ambient conditions” or “room temperature” must be avoided.

The following statements should be used if supported by the stability studies:

Testing condition where the stability of the active pharmaceutical ingredient has been shown	Recommended labelling statement*
25°C/60% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 25°C”
25°C/60% RH (long-term) 30°C/65% RH (intermediate, failure of accelerated)	“Do not store above 25°C”**
30°C/65% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 30°C”**
30°C/75% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 30°C”
5°C ± 3°C	”Store in a refrigerator (2°C to 8°C)”
- 20°C ± 5°C	"Store in freezer"

* During storage, shipment and distribution of the API, the current Good Trade and Distribution Practices (GTDP) for pharmaceutical starting materials are to be observed (11). Details on storage and labelling requirements can be found in WHO good storage practices (12).

** In addition "Protect from moisture" should be added as applicable.

A re-test period should be derived from the stability information, and a re-test date should be displayed on the container label if appropriate.

2.1.11 Ongoing stability studies

The stability of the API should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the labelled storage conditions within the re-test period in all future batches.

The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the re-test period and shelf-life and should include, but not be limited to, the following parameters:

- Number of batch(es) and different batch sizes, if applicable;
- Relevant physical, chemical, microbiological and biological test methods;
- Acceptance criteria;
- Reference to test methods;
- Description of the container closure system(s);
- Testing frequency;
- Description of the conditions of storage (standardized conditions for long-term testing as described in this guidelines, and consistent with the API labelling, should be used);
- Other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability (13). In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the synthetic route, process or container closure system which may impact upon the stability of the API (14).

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, or out-of-specification result, or significant atypical trend should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

2.2 Finished pharmaceutical product

2.2.1 General

The design of the stability studies for the finished pharmaceutical product (FPP) should be based on knowledge of the behaviour and properties of the API, and from stability studies on the API and on experience gained from preformulation studies and investigational FPPs.

2.2.2 Selection of batches

Data from stability studies should be provided on at least three primary batches of the FPP. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. In the case of conventional dosage forms with APIs that are known to be stable, data from at least two primary batches should be provided.

Two of the three batches should be at least pilot-scale batches and the third one can be smaller, if justified. Where possible batches of the FPP should be manufactured by using different batches of the API(s).

Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied.

2.2.3 Container closure system

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.4 Specification

Stability studies should include testing of those attributes of the FPP that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant, antimicrobial preservative) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies is listed in Annex 2. Analytical procedures should be fully validated and stability- indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the FPP should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

2.2.5 Testing frequency

For long-term studies frequency of testing should be sufficient to establish the stability profile of the FPP. For products with a proposed shelf-life of at least 12 months the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter through the proposed shelf-life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (3).

2.2.6 Storage conditions

In general a FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (3)

Storage conditions tolerances are usually defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The long-term testing should cover a minimum of six or 12 months' duration at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf-life. For an FPP containing an API that is known to be stable, data covering a minimum of six months should be submitted. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section (2.1.7.1). Alternative storage conditions can be used if justified, e.g. for FPPs, heat- or temperature-sensitive preparations.

2.2.6.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH	12 months or 6 months as referred to in 2.2.6
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* Whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage condition at 25°C/60%RH or 30°C/65%RH”.

** 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.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and “significant change” occurs at any time during six months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

In general “significant change” for an FPP is defined as:

1. A 5% change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note: Other values may be applied if justified to certain products such as multivitamins*).
2. Any degradation product exceeding its acceptance criterion.
3. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendibility, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

and, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH,
- or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.6.2 FPPs packaged in impermeable containers

Parameters required to classify the packaging materials as permeable or impermeable depend on the packaging material characteristics such as thickness and permeability coefficient. The suitability of the packaging material used for a particular product is determined by its product characteristics. Generally considered moisture-impermeable containers include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus

stability studies for products stored in impermeable containers can be conducted under any controlled or ambient relative humidity condition.

2.2.6.3 FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately it should be demonstrated that aqueous-based FPPs stored in semi-permeable containers could withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months
"Intermediate"	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

* Whether long-term stability studies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH is determined by the climatic condition in which the FPP is intended to be marketed. Testing at 30°C/35% RH can be an alternative to storage condition at 25°C/40%RH.

Products meeting either of the long-term storage conditions and the accelerated conditions, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product would not have significant water loss throughout the proposed shelf-life if stored at 25°C/40% RH or 30°C/35% RH.

For long-term studies conducted at 25°C ± 2°C/40% RH ± 5% RH, that fail the accelerated testing in water loss and any other parameters, additional testing at the "intermediate" storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40°C/NMT 25% RH. However, for small containers (1 ml or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the low relative humidity as recommended in the table above (for either long-term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the low relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container

closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed FPP.

Example of an approach for determining water loss

For a product in a given container closure system, container size and fill, an appropriate approach for deriving the water loss rate at the low relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, e.g. 40°C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-humidity testing conditions	Alternative testing condition	Ratio of water loss rates	Calculation
25°C/40% RH	25°C/60% RH	1.5	(100-40)/(100-60)
30°C/35% RH	30°C/65% RH	1.9	(100-35)/(100-65)
30°C/35% RH	30°C/75% RH	2.6	(100-35)/(100-75)
40°C/NMT 25% RH	40°C/75% RH	3.0	(100-25)/(100-75)

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

2.2.6.4 FPPs intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH	6 months

* Whether accelerated stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH or 30°C ± 2°C/75% RH ± 5% RH is determined by the climatic condition in which the FPP is intended to be marketed (see Annex 1). Testing at a more severe accelerated condition can be an alternative to storage condition at 25°C/60%RH or 30°C/65%RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf-life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through six months when a significant change has occurred within the first three months.

2.2.6.5 FPPs intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	- 20°C ± 5°C	12 months

For FPPs intended for storage in a freezer, the shelf-life should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5°C ± 3°C or 25°C ± 2°C or 30°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

2.2.6.6 FPPs intended for storage below - 20°C

FPPs intended for storage below - 20°C should be treated on a case-by-case basis.

2.2.7 Stability commitment

When available long-term stability data on primary batches do not cover the proposed shelf-life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the shelf-life.

Where the submission includes long-term stability data from the production batches as specified in section 2.2.2 covering the proposed shelf-life, a post-approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least the number of production batches as specified in section 2.2.2, a commitment should be made to continue the long-term studies through the proposed shelf-life and the accelerated studies for six months.
2. If the submission includes data from stability studies on fewer than the number of production batches as specified in section 2.2.2, a commitment should be made to continue the long-term studies through the proposed shelf-life and the accelerated studies for six months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf-life and on accelerated studies for six months.

3. If the submission does not include stability data on production batches, a commitment should be made to place the on the first two or three production batches (see section 2.2.2) on long-term stability studies through the proposed shelf-life and on accelerated studies for six months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

2.2.8 Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of batches of the FPP as specified in section 2.2.2, a shelf-life and label storage instructions applicable to all future batches of the FPP manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf-life.

Where the data show 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 statistical analysis. However, a tentative shelf-life of 24 months may be established provided the following conditions are satisfied:

- the API is known to be stable (not easily degradable);
- stability studies as outlined above in section 2.1.11 have been performed and no significant changes have been observed;
- supporting data indicate that similar formulations have been assigned a shelf-life of 24 months or more; and
- the manufacturer will continue to conduct real-time studies until the proposed shelf-life has been covered, and the results obtained will be submitted to the national drug regulatory authority.

An approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. 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 first applying appropriate statistical tests (e.g. 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 should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed 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.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the shelf-life can be undertaken, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

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

2.2.9 Statements/Labelling

A storage statement should be established for the labelling based on the stability evaluation of the FPP. Where applicable, specific instruction should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” must be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

The following statements should be used if supported by the stability studies:

Testing condition where the stability of the active pharmaceutical ingredient has been shown	Recommended labelling statement*
25°C/60% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 25°C”
25°C/60% RH (long-term) 30°C/65% RH (intermediate, failure of accelerated)	“Do not store above 25°C” **
30°C/65% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 30°C”
30°C/75% RH (long-term) 40°C/75% RH (accelerated)	“Do not store above 30°C”
5°C ± 3°C	”Store in a refrigerator (2°C to 8°C)”
- 20°C ± 5°C	"Store in freezer"

* During storage, shipment and distribution of the FPP, the current *Good Distribution Practices (GDP) for pharmaceutical products* are to be observed (11). Details on storage and labelling requirements can be found in the *Good Storage Practices (12)*.

** In addition "Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior

packaging. The following additional labelling statements could be used in cases where the result of the stability testing demonstrate limiting factors:

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate refrigerating	“Do not refrigerate or freeze”*
FPPs that cannot tolerate freezing	“Do not freeze”*
Light-sensitive FPPs	“Protect from light”
FPPs that cannot tolerate excessive heat, e.g. suppositories	“Store and transport not above 30°C”
Hygroscopic FPPs	“Store in dry condition”

* Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semi-solids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

2.2.10 In-use stability

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution/reconstitution before use. At intervals comparable to those, which occur in practice, appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The appropriate physical, chemical and microbial properties of the FPP susceptible to change during storage should be determined over the period of the proposed in-use shelf-life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf-life on the final remaining amount of the FPP in the container. Specific parameters, e.g. for liquids and semi-solids, preservatives, content/effectiveness, need to be studied.

A minimum of two batches, at least pilot scale batches, should be subjected to the test. At least one of the batches should be chosen towards the end of its shelf-life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on the reconstituted or diluted FPP through the proposed in-use period on primary batches as part of the stability studies at initial and final time points and, if full shelf-life, long-term data are not available before submission, at 12 months or the last time point for which data will be available.

In general this testing need not be repeated on commitment batches (see 2.2.10).

2.2.11 Variations

Once the FPP has been registered, additional stability studies are required whenever variations that may affect the stability of the API or FPP are made, such as major variations (15).

The following can serve as examples:

1. Change in the manufacturing process.
2. Change in the composition of the FPP.
3. Change of the immediate packaging.
4. Change in the manufacturing process of an active pharmaceutical ingredient.

In all cases of variations, the applicant has to investigate whether the intended change will have an impact or not on the quality characteristics of APIs and/or FPPs and consequently on their stability.

The scope and design of the stability studies for variations and changes are based on the knowledge and experience acquired on APIs and FPPs.

The results of these stability studies should be communicated to the regulatory authorities concerned (16).

2.2.12 Ongoing stability studies

After a marketing authorization has been granted, the stability of the FPP should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in its marketed container closure system. The purpose of the ongoing stability programme is to monitor the product over its shelf-life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

This mainly applies to the FPP in the container closure system in which it is supplied, but consideration should also be given to inclusion in the programme of bulk products. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied. In addition, consideration should be given to intermediates that are stored and used over prolonged periods.

The ongoing stability programme should be described in a written protocol, and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

- Number of batch(es) per strength and different batch sizes, if applicable.
- Relevant physical, chemical, microbiological and biological test methods.
- Acceptance criteria.
- Reference to test methods.
- Description of the container closure system(s).
- Testing frequency.

- Description of the conditions of storage (standardized conditions for long-term testing as described in this guidelines, and consistent with the product labelling, should be used).
- Other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing, or when updating to revised recommendations).

The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (17).

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion. (Ref. *Guidance on variations to a prequalified product dossier*, Annex 6, *WHO Technical Report Series*, No. 943, 2007).

Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, or out-of-specification result, or significant atypical trend should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

3. GLOSSARY

The following definitions are provided to facilitate interpretation of the guidelines. The definitions are consistent with those published in other WHO quality assurance guidelines (Ref. *WHO Quality Assurance nomenclature database*).

Accelerated testing

Studies designed to increase the rate of chemical degradation and physical change of an active pharmaceutical ingredient or finished pharmaceutical product (FPP) by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from real-time stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or

other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Batch

A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g. strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or 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). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic zone

The zones into which the world is divided based on the prevailing annual climatic conditions (see Annex 1).

Commitment batches

Production batches of an active pharmaceutical ingredient or finished pharmaceutical product (FPP) for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Container closure system

The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the finished pharmaceutical product (FPP). A packaging system is equivalent to a container closure system.

Dosage form

The form of the finished pharmaceutical product (FPP), e.g. tablet, capsule, elixir or suppository.

Excipient

A substance or compound, other than the active pharmaceutical ingredient (API) and packaging materials, that is intended or designated to be used in the manufacture of a finished pharmaceutical product (FPP).

Expiry date

The date given on the individual container (usually on the label) of a product up to and including which the active pharmaceutical ingredient (API) and finished pharmaceutical product (FPP) is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

Finished pharmaceutical product

A product that has undergone all stages of production, including packaging in its final container and labeling. A finished pharmaceutical product (FPP) may contain one or more active pharmaceutical ingredients (API).

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions.

Long-term stability studies

Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an active pharmaceutical ingredient or finished pharmaceutical product (FPP), during and beyond the expected shelf-life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the re-test period, respectively shelf-life, to confirm the projected re-test period and shelf-life, and to recommend storage conditions.

Mass balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same finished pharmaceutical product (FPP) should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Ongoing stability study

The study carried out by the manufacturer on production batches according to predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the active pharmaceutical ingredient (API), or confirm or extend the shelf-life of the finished pharmaceutical product (FPP).

Pilot scale batch

A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a

minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger; for paediatric formulations the size of the pilot scale batch may be smaller.

Primary batch

A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life, as the case may be. A primary batch of an API should be at least a pilot scale batch. For an FPP, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch

A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) manufactured at production scale by using production equipment in a production facility as specified in the application.

Release specification

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) at the time of its release.

Re-test date (modified WHO)

The date after which a active pharmaceutical ingredient (API) should be re-examined to ensure that the material is still in compliance with the specification and thus that it is still suitable for use in the manufacture of a finished pharmaceutical product (FPP).

Re-test period

The period of time during which the active pharmaceutical ingredient (API) is expected to remain within its specification and, therefore, can be used in the manufacture of a given finished pharmaceutical product (FPP), provided that the API has been stored under the defined conditions. After this period a batch of API destined for use in the manufacture of a FPP should be re-tested for compliance with the specification and then used immediately. A batch of API can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf-life than a re-test period. The same may be true for certain antibiotics.

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf-life

The period of time during which an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP), if stored correctly, is expected to comply with the specification as

determined by stability studies on a number of batches of the API or FPP. The shelf-life is used to establish the expiry date of each batch.

Shelf-life specification

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a finished pharmaceutical product (FPP) should meet throughout its shelf-life, also certain unstable API might have a shelf-life specification (see 2.1.6.).

“Significant change”

→ see section 2.2.6.1.

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) should conform to be considered acceptable for its intended use.

Stability indicating methods

Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP), and that are specific so that the content of the API, degradation products, and other components of interest can be accurately measured without interference.

Stability studies (stability testing)

Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period (or shelf-life) of an active pharmaceutical ingredient (API) or the shelf-life of a finished pharmaceutical product (FPP).

Stress testing (active pharmaceutical ingredient)

Studies undertaken to elucidate the intrinsic stability of the active pharmaceutical ingredient (API). Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (finished pharmaceutical product)

Studies undertaken to assess the effect of severe conditions on the finished pharmaceutical product (FPP). Such studies include photostability testing and specific testing on certain products, (e.g. metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting stability data (WHO)

Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf-life and storage conditions.

Tentative shelf-life

A provisional expiry date which is based on acceptable accelerated and available long-term data for the finished pharmaceutical product (FPP) to be marketed in the proposed container closure system .

Utilization period

A period of time during which a reconstituted preparation of the finished dosage form in an unopened multi-dose container can be used.

REFERENCES

1. Guidelines for stability testing of pharmaceutical products pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series, No. 863).

This guideline was revised at the thirty-seventh and fortieth meetings of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. In: *WHO Technical Report Series, No. 908, p. 13 (2003)* and *WHO Technical Report Series, No. 937, p. 12 (2006)*, respectively.

2. *Regional Guidelines for the WHO Eastern Mediterranean Region. Stability testing of active substances and pharmaceutical products.* Draft April 2006.

3. The following ICH Guidelines may be consulted in the context of stability testing:

ICH Q1A (R2): Stability Testing of New Drug Substances and Products
<http://www.ich.org/LOB/media/MEDIA419.pdf>

ICH Q1B: Photostability Testing of New Drug Substances and Products
<http://www.ich.org/LOB/media/MEDIA412.pdf>

ICH Q1C: Stability Testing of New Dosage Forms
<http://www.ich.org/LOB/media/MEDIA413.pdf>

ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products <http://www.ich.org/LOB/media/MEDIA414.pdf>

ICH Q1E: Evaluation for Stability Data <http://www.ich.org/LOB/media/MEDIA415.pdf>

ICH Q2R1): Validation of Analytical Procedures: Text and Methodology
<http://www.ich.org/LOB/media/MEDIA417.pdf>

ICH Q3A: Impurities in New Drug Substances
<http://www.ich.org/LOB/media/MEDIA422.pdf>

ICH Q3B: Impurities in New Drug Products
<http://www.ich.org/LOB/media/MEDIA421.pdf>

ICH Q5C: Stability Testing of Biotechnological/Biological Products
<http://www.ich.org/LOB/media/MEDIA427.pdf>

ICH Q6A: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*

<http://www.ich.org/LOB/media/MEDIA430.pdf>

ICH Q6B: *Specifications: Test Procedures and Acceptance Criteria for*

Biotechnological/Biological Products <http://www.ich.org/LOB/media/MEDIA432.pdf>

Further information can be found on the ICH homepage:

<http://www.ich.org/cache/compo/276-254-1.html>.

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Additional reading

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Revised draft for comment

ANNEX 1
LONG-TERM STABILITY TESTING CONDITIONS AS IDENTIFIED BY
WHO MEMBER STATES

In order to be able to reduce the amount of stability testing, the number of different long-term testing conditions must be reduced to a sufficient extent. This was proposed by Paul Schumacher in 1972 (4) and by Wolfgang Grimm in 1986 (5), and in 1998 (6) when they defined four different long-term testing conditions, which match with the climatic conditions of the target markets categorized in just four different climatic zones (CZ). This concept is described in regulatory guidelines and pharmacopoeias and has become an established standard in developing finished pharmaceutical products (FPPs).

At the Fortieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, held in Geneva in October 2005 (1), it was recommended to split the current Climatic Zone IV (hot and humid) into Climatic Zone IVA – for which 30°C/65% RH will remain the standard long-term testing condition – and Climatic Zone IVB for which, if justified, 30°C/75% RH will become the long-term testing condition. The following criteria (7) and long-term testing conditions are, therefore, proposed:

CZ	Definition	Criteria	Long-term testing conditions
		Mean annual temperature measured in the open air/ Mean annual partial water vapour pressure	
I	Temperate climate	$\leq 15^{\circ}\text{C} / \leq 11 \text{ hPa}$	21°C / 45% RH
II	Subtropical and Mediterranean Climate	$> 15 \text{ to } 22^{\circ}\text{C} / > 11 \text{ to } 18 \text{ hPa}$	25°C / 60% RH
III	Hot and dry climate	$> 22^{\circ}\text{C} / \leq 15 \text{ hPa}$	30°C / 35% RH
IVA	Hot and humid climate	$> 22^{\circ}\text{C} / > 15 \text{ to } 27 \text{ hPa}$	30°C / 65% RH
IVB	Hot and very humid climate	$> 22^{\circ}\text{C} / > 27 \text{ hPa}$	30°C / 75% RH

Additional testing conditions, i.e. accelerated and – if applicable – intermediate conditions have to be used as described in this guidelines.

Since there are only a few countries in Zone I, there is general agreement to base stability on the conditions in Climatic Zone II when it is intended to market FPPs in temperate climates. For countries where certain regions are situated in Zones III and IV, and also with a view to global market, it is recommended that stability testing programmes should be based on the conditions corresponding to Climatic Zone IVA.

The evaluation of the climatic conditions by each WHO Member State resulted in the following recommended testing condition for long-term stability studies (in some of the countries listed, more extreme conditions are also accepted). The list is grouped by WHO Regional Offices.

Table to Annex 1. Stability conditions for WHO Member States by Regions

	STABILITY CONDITIONS
Name	Confirmed long-term testing condition
<u>Regional Office for Africa (AFRO)</u>	
<u>Algeria</u>	
<u>Angola</u>	
<u>Benin</u>	
<u>Botswana</u>	
<u>Burkina Faso</u>	
<u>Burundi</u>	
<u>Cameroon</u>	
<u>Cape Verde</u>	
<u>Central African Republic</u>	
<u>Chad</u>	
<u>Comoros</u>	
<u>Congo</u>	
<u>Côte d'Ivoire</u>	
<u>Democratic Republic of the Congo</u>	
<u>Equatorial Guinea</u>	
<u>Eritrea</u>	
<u>Ethiopia</u>	
<u>Gabon</u>	
<u>Gambia</u>	
<u>Ghana</u>	
<u>Guinea</u>	
<u>Guinea-Bissau</u>	
<u>Kenya</u>	
<u>Lesotho</u>	
<u>Liberia</u>	
<u>Madagascar</u>	
<u>Malawi</u>	
<u>Mali</u>	
<u>Mauritania</u>	
<u>Mauritius</u>	
<u>Mozambique</u>	
<u>Namibia</u>	
<u>Niger</u>	
<u>Nigeria</u>	
<u>Rwanda</u>	
<u>Sao Tome and Principe</u>	
<u>Senegal</u>	
<u>Seychelles</u>	
<u>Sierra Leone</u>	

<u>South Africa</u>	
<u>Swaziland</u>	
<u>Togo</u>	
<u>Uganda</u>	
<u>United Republic of Tanzania</u>	
<u>Zambia</u>	25°C/60% or 30°C/65% RH
<u>Zimbabwe</u>	
<u>Regional Office for the Americas (AMRO)</u>	
<u>Antigua and Barbuda</u>	
<u>Argentina</u>	
<u>Bahamas</u>	
<u>Barbados</u>	
<u>Belize</u>	
<u>Bolivia</u>	
<u>Brazil</u>	30°C/75% RH
<u>Canada</u>	25°C/60% or 30°C/65% RH
<u>Chile</u>	
<u>Colombia</u>	
<u>Costa Rica</u>	
<u>Cuba</u>	
<u>Dominica</u>	
<u>Dominican Republic</u>	
<u>Ecuador</u>	
<u>El Salvador</u>	
<u>Grenada</u>	
<u>Guatemala</u>	
<u>Guyana</u>	
<u>Haiti</u>	
<u>Honduras</u>	
<u>Jamaica</u>	
<u>Mexico</u>	
<u>Nicaragua</u>	
<u>Panama</u>	
<u>Paraguay</u>	
<u>Peru</u>	30°C/75% RH
<u>Saint Kitts and Nevis</u>	
<u>Saint Lucia</u>	
<u>Saint Vincent and the Grenadines</u>	
<u>Suriname</u>	
<u>Trinidad and Tobago</u>	
<u>United States of America</u>	25°C/60% or 30°C/65% RH
<u>Uruguay</u>	
<u>Venezuela (Bolivarian Republic of)</u>	
<u>Regional Office for the Eastern Mediterranean (EMRO)</u>	
<u>Afghanistan</u>	30°C/65% RH
<u>Bahrain</u>	30°C/65% RH
<u>Djibouti</u>	30°C/65% RH

<u>Egypt</u>	30°C/65% RH
<u>Iran (Islamic Republic of)</u>	30°C/65% RH
<u>Iraq</u>	30°C/35% RH
<u>Jordan</u>	30°C/65% RH
<u>Kuwait</u>	30°C/65% RH
<u>Lebanon</u>	25°C/60% RH
<u>Libyan Arab Jamahiriya</u>	25°C/60% RH
<u>Morocco</u>	25°C/60% RH
<u>Oman</u>	30°C/65% RH
<u>Pakistan</u>	30°C/65% RH
<u>Qatar</u>	30°C/65% RH
<u>Saudi Arabia</u>	30°C/65% RH
<u>Somalia</u>	30°C/65% RH
<u>Sudan</u>	30°C/65% RH
<u>Syrian Arab Republic</u>	25°C/60% RH
<u>Tunisia</u>	25°C/60% RH
<u>United Arab Emirates</u>	30°C/65% RH
<u>Yemen</u>	30°C/65% RH
<u>Regional Office for Europe (EURO)</u>	
<u>Albania</u>	
<u>Andorra</u>	
<u>Armenia</u>	
<u>Austria</u>	25°C/60% or 30°C/65% RH
<u>Azerbaijan</u>	
<u>Belarus</u>	
<u>Belgium</u>	25°C/60% or 30°C/65% RH
<u>Bosnia and Herzegovina</u>	
<u>Bulgaria</u>	25°C/60% or 30°C/65% RH
<u>Croatia</u>	
<u>Cyprus</u>	25°C/60% or 30°C/65% RH
<u>Czech Republic</u>	25°C/60% or 30°C/65% RH
<u>Denmark</u>	25°C/60% or 30°C/65% RH
<u>Estonia</u>	25°C/60% or 30°C/65% RH
<u>Finland</u>	25°C/60% or 30°C/65% RH
<u>France</u>	25°C/60% or 30°C/65% RH
<u>Georgia</u>	
<u>Germany</u>	25°C/60% or 30°C/65% RH
<u>Greece</u>	25°C/60% or 30°C/65% RH
<u>Hungary</u>	25°C/60% or 30°C/65% RH
<u>Iceland</u>	
<u>Ireland</u>	25°C/60% or 30°C/65% RH
<u>Israel</u>	
<u>Italy</u>	25°C/60% or 30°C/65% RH
<u>Kazakhstan</u>	
<u>Kyrgyzstan</u>	
<u>Latvia</u>	25°C/60% or 30°C/65% RH
<u>Lithuania</u>	25°C/60% or 30°C/65% RH
<u>Luxembourg</u>	25°C/60% or 30°C/65% RH

<u>Malta</u>	25°C/60% or 30°C/65% RH
<u>Monaco</u>	
<u>Montenegro</u>	
<u>Netherlands</u>	25°C/60% or 30°C/65% RH
<u>Norway</u>	
<u>Poland</u>	25°C/60% or 30°C/65% RH
<u>Portugal</u>	25°C/60% or 30°C/65% RH
<u>Republic of Moldova</u>	
<u>Romania</u>	25°C/60% or 30°C/65% RH
<u>Russian Federation</u>	
<u>San Marino</u>	
<u>Serbia</u>	
<u>Slovakia</u>	25°C/60% or 30°C/65% RH
<u>Slovenia</u>	25°C/60% or 30°C/65% RH
<u>Spain</u>	25°C/60% or 30°C/65% RH
<u>Sweden</u>	25°C/60% or 30°C/65% RH
<u>Switzerland</u>	25°C/60% or 30°C/65% RH
<u>Tajikistan</u>	
<u>The former Yugoslav Republic of Macedonia</u>	
<u>Turkey</u>	
<u>Turkmenistan</u>	
<u>Ukraine</u>	
<u>United Kingdom</u>	25°C/60% or 30°C/65% RH
<u>Uzbekistan</u>	
<u>Regional Office for South-East Asia (SEARO)</u>	
<u>Bangladesh</u>	
<u>Bhutan</u>	
<u>Democratic People's Republic of Korea</u>	
<u>India</u>	30°C/70% RH
<u>Indonesia</u>	30°C/75% RH
<u>Maldives</u>	
<u>Myanmar</u>	30°C/75% RH
<u>Nepal</u>	
<u>Sri Lanka</u>	
<u>Thailand</u>	30°C/75% RH
<u>Timor-Leste</u>	
<u>Regional Office for the Western Pacific (WPRO)</u>	
<u>Australia</u>	
<u>Brunei Darussalam</u>	30°C/75% RH
<u>Cambodia</u>	30°C/75% RH
<u>China</u>	
<u>Cook Islands</u>	
<u>Fiji</u>	
<u>Japan</u>	25°C/60% or 30°C/65% RH
<u>Kiribati</u>	

<u>Lao People's Democratic Republic</u>	30°C/75% RH
<u>Malaysia</u>	30°C/75% RH
<u>Marshall Islands</u>	
<u>Micronesia (Federated States of)</u>	
<u>Mongolia</u>	
<u>Nauru</u>	
<u>New Zealand</u>	
<u>Niue</u>	
<u>Palau</u>	
<u>Papua New Guinea</u>	
<u>Philippines</u>	30°C/75% RH
<u>Republic of Korea</u>	
<u>Samoa</u>	
<u>Singapore</u>	30°C/75% RH
<u>Solomon Islands</u>	
<u>Tonga</u>	
<u>Tuvalu</u>	
<u>Vanuatu</u>	
<u>Viet Nam</u>	30°C/75% RH

Revised draft for comment

ANNEX 2 EXAMPLES OF TESTING PARAMETERS

Section I for active pharmaceutical ingredients

In general, appearance, assay, and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Other API parameters that may be susceptible to change should also be studied where applicable (18).

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide for the types of tests to be included in a stability study. In general appearance, assay and degradation products should be evaluated for all dosage forms, as well as preservative and antioxidant content if applicable (18).

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf-life (19).

It is not expected that every listed test be performed at each time point. This applies in particular to sterility testing, which may be conducted for most sterile products at the beginning and at the end of the stability test period. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested no less than at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorization for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every listed test be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol where product contact with the closure system may be expected to affect the stability of the products contained, or where there has been a change in the container/closure system.

1. Tablets
Dissolution (or disintegration, if justified), water content and hardness/friability.
2. Capsules
Hard gelatin capsules: brittleness, dissolution (or disintegration, if justified), water content and level of microbial contamination.
Soft gelatin capsules: dissolution (or disintegration, if justified), level of microbial contamination, pH, leakage, and pellicle formation.

3. Oral solutions, suspensions and emulsions
Formation of precipitate, clarity for solutions, pH, viscosity, extractables, level of microbial contamination.

Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.

Additionally for emulsions, phase separation, mean size and distribution of dispersed globules.
4. Powders and granules for oral solution or suspension
Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described in “Oral solutions suspensions and emulsions” above, after preparation according to the recommended labelling, through the maximum intended use period.
5. Metered-dose inhalers and nasal aerosols
Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/ leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractable/leachable from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopical evaluation of appearance of the valve components and container’s contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets .
6. Nasal sprays: solutions and suspensions
Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractable/leachable from plastic and elastomeric components of the container, closure and pump.
7. Topical, ophthalmic and otic preparations
Included in this broad category are ointments, creams, lotions, paste, gel, solutions, eye drops, and cutaneous sprays.

Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).

Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable.

Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

8. Suppositories
Softening range, disintegration and dissolution (at 37°C).
9. Small volume parenterals (SVPs)
Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.
Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended in labelling, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter.

The stability studies for Suspension for injection should include, in addition, particle size distribution, dispersibility and rheological properties.

The stability studies for Emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.
10. Large volume parenterals (LVPs)
Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.
11. Transdermal patches
In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

ANNEX 3

MODEL STABILITY PROTOCOL AND REPORT OF AN ACTIVE PHARMACEUTICAL INGREDIENT (API) (15) For submission of data for marketing authorization and to the prequalification dossier (16)

Prepared by:
Approved by:
Date:

Model Stability Protocol and Report of an Active Pharmaceutical Ingredient (API)

Recommended International Nonproprietary Name (INN)

1. BATCHES TESTED

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Batch type (primary, production, etc.)			
Primary packing materials			
Date of initial analysis			

Note: The batches to be sampled should be representative of the manufacturing synthesis process and should be manufactured from different batches of key intermediates, and preferably also from different API batches.

2. GENERAL INFORMATION

- Structure of API(s)
- International Nonproprietary Name (INNs)
- Chemical Abstracts Service (CAS) registry number
- Antecedents of stability testing

3. CONTAINER/CLOSURE SYSTEM

A description of the container/closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification.

4. LITERATURE AND SUPPORTING DATA¹

Before stability studies are initiated, information on the stability of the active pharmaceutical ingredient (API) should be sought, collected and analysed. Published decomposition process and degradability of the API and the FPPs should be referred to.²

Supporting stability data can be presented on laboratory- and pilot-scale batches and on synthesis routes other than those proposed for marketing.

5. STABILITY-INDICATING ANALYTICAL METHODS

Make reference to the release specification number containing the description of validated, stability-indicating methods.

The accuracy as well as the precision (standard deviations) of the methods should be recorded. The tests for impurities and degradation products should be validated to demonstrate that they are specific to the API being examined and are of adequate sensitivity

6. TESTING PLAN

Calculate the number of samples required for the testing plan.

Storage condition	Storage time (months)							
	0	3	6	9	12	18	24	36
Accelerated: 40±2°C/75±5% RH	X							
		X	X					
Intermediate: 30±2°C/65±5% RH (backup for accelerated, if relevant)								

¹ Literature data, if available, should be scrutinized, sometimes experimentally verified, and completed with information on polymorphism, particle size, hygroscopicity, etc., if applicable.

² Full references of the publications cited should be included in the report, with copies of the relevant parts if applicable.

Long-term: 30±2°C/75±5% RH or 30±2°C/65±5% RH or 25±2°C/60±5% RH	X							
		X	X	X	X	X	X	X

7. TEST RESULTS

Batch No.:

Container:

Chemical characteristics (e.g. assay, contents of impurities and degradants)

Chemical data

(long-term storage conditions, example for 30°C/65% RH, and accelerated 40°C/75% RH)

Initial values			
Storage condition	Assay (mg)	Impurity 1 (%)	Impurity 2 (%)
3 months 40±2°C/75±5%RH			
3 months 30±2°C/65±5% RH			
6 months 40±2°C/75±5%RH			
6 months 30±2°C/65±5% RH			
9 months 30±2°C / 65±5 % RH			
12 months 30±2°C/65±5% RH			
18 months 30±2°C/65±5% RH			
24 months 30±2°C/65±5% RH			
36 months 30±2°C/65±5% RH			

Batch No.:

Container:

Physical characteristics

(e.g. appearance, including possible change in colour, moisture content, as well as polymorphs, if applicable)

Physical data

(long-term storage conditions, example for 30°C/65% RH, and accelerated 40°C/75%RH)

Initial values			
Storage condition	Appearance	Critical polymorph	Critical particle size
3 months 40±2°C/75±5%RH			
3 months 30±2°C/65±5% RH			
6 months 40±2°C/75±5%RH			
6 months 30±2°C/65±5% RH			
9 months 30±2°C/65±5% RH			
12 months 30±2°C/65±5% RH			
18 months 30±2°C/65±5% RH			
24 months 30±2°C/65±5% RH			
36 months 30±2°C/65±5% RH			

Note: change headings and add tables, as necessary.

- Photostability testing should be conducted on at least one primary batch of the API.
- Microbiological attributes (total microbial count and absence of pathogens, every year) when the API is intended to be used in a parenteral dosage form.

Microbial attributes

(total microbial count and absence of pathogens, when used in parenteral formulations)

8. EVALUATION

8.1 A stability report should be prepared giving details of the study results and conclusions. The results should preferably be presented both as a table and as a graph.

8.2 A re-test period, shelf-life and storage conditions should be proposed on the basis of these results.

8.3 Storage conditions recommended on the basis of stability studies should be prominently indicated on the label.

8.4 Once the API supplier has been approved, additional stability studies are required whenever major modifications are made to the manufacturing synthesis process, packaging materials or methods.

9. CONCLUSIONS

The obtained stability data support a proposed retest period (or shelf-life) of ... months.

Storage conditions and retest period (or shelf-life) approved by the national drug regulatory authority on the basis of stability studies should be prominently indicated on the label.

Contact person in applicant's company

Name:

Position in company:

Postal address:

Telephone number:

Fax number:

E-mail address:

ANNEX 4
MODEL STABILITY PROTOCOL AND REPORT
OF CAPSULES/TABLETS

The following Protocol Stability Study is an example taken from the ASEAN Guideline on Stability Study of Drug Product. Update revision: 22 February 2005. 9th ACCSQ-PPWG meeting, Philippines, 21-24 February 2005, Sections 5.1 and 5.2 (17).

Revised draft for comment

5.1 Protocol of Stability Study (example)

5.1.1 PARACETAMOL TABLET 500 MG PACKED IN PVC BLISTER

1. Purpose

To evaluate stability of product due to the scaling up from the Research and Development to the Manufacturing Site.

2. Test Design

The product is packed in PVC blister and will be stored according to storage condition or mentioned in manufacturing instruction

2.1. Test Material

- Push-through foil
Alufoil of 20 micron thickness, heat-seal lacquered, PVC layered (8 g/m²), hard temper, bright side finish silver-tinted.
Forming foil
PVC foil of 250 micron thickness.

Batch No.	Packaging type	Storage Condition/Period
001	PVC Blister	Real Time (60 months); Accelerated (6 months)
002	PVC Blister	Real Time (60 months); Accelerated (6 months)
003	PVC Blister	Real Time (60 months); Accelerated (6 months)

2.2 Testing Plan

2.2.1 Storage condition and sampling intervals

Paracetamol tablet is filled and sealed in PVC blister, 10 blisters are packed in carton folding box and stored at the following storage condition:

Storage Condition	Sampling Intervals
Real Time storage 30°C/75% RH	0, 3, 6, 9, 12, 18, 24, 36, 48, 60 months
Accelerated 40°C/75% RH	0, 1, 3, 6 months

The detail schedule is attached.



2.2.2 Testing and Test Criteria

QA/QC Dept. is responsible for storing and testing the sample in accordance with the storage condition and the valid test method.

The samples are taken out of the storage prior to the planned testing date, and kept at 5°C until the time for analysis.

The analytical work should be concluded not later than 4 weeks after the samples have been out of storage.

The testing procedure is: No. XXXX and the parameters to be tested are as follows:

- a. Physical test
 - appearance
 - average weight
 - dissolution
 - disintegration time
 - hardness
 - friability
 - water content
- b. Content : Paracetamol
- c. Degradation Product : p-aminophenol

3. Number of Samples (of one batch / storage condition)

3.1. Accelerated Test

- Appearance	:	0*	tablets	number of testing : 4 times
- water content	:	10	tablets	Quantity needed
- disintegration	:	6	tablets	= 4 x 100 tablets
- dissolution	:	6	tablets	= 400 tablets
- content & impurity	:	10	tablets	= 40 blisters of 10 tablets
- hardness	:	10	tablets	= 4 boxes
- friability	:	50	tablets	
		→	= 92	tablets ~ rounded to 100 tablets

3.2. Real Time Stability Study

- Appearance	:	0*	tablets	number of testing : 9 times
- water content	:	10	tablets	quantity needed
- disintegration	:	6	tablets	= 9 x 100 tablets
- dissolution	:	6	tablets	= 900 tablets
- content & impurity	:	10	tablets	= 90 blisters of 10 tablets
- hardness	:	10	tablets	= 9 boxes
- friability	:	50	tablets	
		→	= 92	tablets ~ rounded to 100 tablets

Total = 13 boxes of 10 blisters

* = observation made on tablets allocated for other tests

4. Report Content :

1. Responsibility
2. Summary
3. Objective
4. Test Material
5. Composition
6. Packaging
7. Storage condition and testing materials (Schedule)
8. Analytical Procedures
9. Reference Standard
10. Results
 - 10.1. Physical Stability
 - 10.2. Chemical Stability
 - 10.2.1. Stability under real time storage condition
 - 10.2.2. Stability under accelerated storage condition
11. Discussion/Conclusion
12. Test result in tabular form

Approved by :

Checked by:

Prepared by :

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5.1.2. Schedule for Stability Study
Paracetamol Tablet 500 mg

Dated:
02.07.1997

Storage		Schedule		
		Batch No.	Batch No.	Batch No.
Period	Condition	001	002	003
Initial	Accelerated	July 02, 1997	July 09, 1997	July 16, 1997
	Real Time	July 04, 1997	July 12, 1997	July 18, 1997
1 Month	Accelerated	Aug 02, 1997	Aug 09, 1997	Aug 16, 1997
3 Months	Accelerated	Oct 02, 1997	Oct 09, 1997	Oct 16, 1997
	Real Time	Oct 04, 1997	Oct 12, 1997	Oct 18, 1997
6 Months	Accelerated	Jan 02, 1998	Jan 09, 1998	Jan 16, 1998
	Real Time	Jan 04, 1998	Jan 12, 1998	Jan 18, 1998
9 Months	Real Time	Apr 04, 1998	Apr 12, 1998	Apr 18, 1998
12 Months	Real Time	Jul 04, 1998	Jul 12, 1998	Jul 18, 1998
18 Months	Real Time	Jan 02, 1999	Jan 12, 1999	Jan 18, 1999
24 Months	Real Time	Jul 04, 1999	Jul 12, 1999	Jul 18, 1999
36 Months	Real Time	Jul 04, 2000	Jul 12, 2000	Jul 18, 2000
48 Months	Real Time	Jul 04, 2001	Jul 12, 2001	Jul 18, 2001
60 Months	Real Time	Jul 04, 2002	Jul 12, 2002	Jul 18, 2002
<p>Remarks :</p> <p>Accelerated : 40°C ± 2°C/75% RH ± 5% RH Real Time : 30°C ± 2°C/75% RH ± 5% RH</p>				

Approved by:

Checked by:

Prepared by :

5.2. Report Format (example)

DRUG PRODUCT: PARACETAMOL TABLET

STRENGTH: 500 mg Date: 23/07/02

Doc. No.: XXXX Page 20 of 1

Study Type: Pre- and post-market Stability

Objective: Stability profile of the drug product for storage under
real time and accelerated conditions

Period of Investigation: 60 Months

Packaging: PVC Blister

Originating Site : MMM Ltd
Jakarta - Indonesia

Stability Study Unit : R&D Dept.
John Doe

Quality Assurance : Tom Smith

1. RESPONSIBILITY

Persons in Charge	Site / Department	Responsibility
John Doe	R&D	Physical and chemical tests
John Doe	R&D	Microbiological tests

2. SUMMARY

This report presents the stability data on Paracetamol tablet 500 mg stored up to 60 months in the primary packaging used for marketing.

Any storage-related changes occurring in the finished product were monitored by means of stability-specified control tests. The test design was based on the stability profile of the drug substance paracetamol and on the specific requirements of the dosage form.

Shelf-life:

The product has a shelf-life of five years

Storage Directions:

The finished product is not labelled with any storage directions.

3. OBJECTIVE

The objective of the present study on Paracetamol tablet 500 mg is the assessment of the stability profile for storage under real time and accelerated conditions. The samples were in inverted position to ensure contact with the container closure system.

4. TEST MATERIAL

The batches under stability testing are listed in the following table with further details:

Dosage	Batch No.	Manufacturing		Scale	Batch Size (Pack)	Drug Substance Batch No.
		Date	Site			
500 mg/tab	001	July 02, 1997	Jakarta	Production	2800	004
500 mg/tab	002	July 09, 1997	Jakarta	Production	2800	005
500 mg/tab	003	July 16, 1997	Jakarta	Production	2800	006

5. COMPOSITION

1 tablet of Paracetamol contains :

Composition	Weight [mg]
Paracetamol	500.00
Lactose 1H ₂ O	79.00
Maize Starch	65.50
Pregelatinized Maize Starch	5.00
Talc	3.00
Colloidal Anhydrous Silica (Aerosil 200)	2.00
Magnesium Stearate	0.50
Total	655.00

6. PACKAGING

The stability tests on the batches listed above are performed in the following primary packaging:

The product is packed in PVC blister consisting of:

- Push trough foil : Alufoil of 20 micron thickness, heat-seal lacquered, PVC layered (8 g/m²), hard temper, bright side finish silver-tinted.
- Forming foil : PVC foil of 250 micron thickness.



7. STORAGE CONDITIONS AND TESTING INTERVALS

The various samples of the packaged drug product have been / will be tested according to the following schedule:

Storage Condition											
	0	1	3	6	9	12	18	24	36	48	60
30°C ± 2°C/75% RH ± 5% RH	X	-	X	X	X	X	X	X	X	X	X
40°C ± 2°C/75% RH ± 5% RH	X	X	X	X	-	-	-	-	-	-	-

8. ANALYTICAL PROCEDURES

The stability tests on Paracetamol were performed according to the control tests of USP.

In the course of the stability testing the main emphasis was put on the stability-relevant test items as listed below:

Test Item	Control Test No.	Specification
Hardness	USP	≥ 70 N
Friability	USP	≤ 2%
Degradation Product • p-aminophenol	USP	≤ 0.005%
Microbial Contamination	USP	Total count ≤ 10 ³ CFU E.coli : absent
Content (LC)	USP	95.0 – 105.0 %

Note: As mentioned in 2.1.2, 3.1 and 3.2, Disintegration Time and Dissolution should be added.

9. REFERENCE STANDARD

Standard Paracetamol USP, 99.5%, was used.

10. RESULTS

The test results of the study are presented in the tables attached.

10.1. Physical Stability

The physical stability of Paracetamol tablet 500 mg proved to be unchanged after storage up to 60 months at 30°C/75% RH and after 6 months under accelerated conditions at 40°C/75% RH.

The result obtained for the test item's "appearance" was not changed significantly.

10.2. Chemical Stability

10.2.1. Stability under Real time Conditions

Storage for up to 60 months at 30°C/75% RH had no significant effect on the chemical stability of the drug product. With regard to test item "Organic Impurity" only slight changes were observed. The p-aminophenol concentration was below 0.005%.

The content of paracetamol did not change significantly after storage under real time conditions compared to initial assay of the batches.

10.2.2. Stability under Accelerated Conditions

Storage under accelerated conditions for 6 months did not effect the chemical stability.

The content of paracetamol was not significantly changed compared to the initial value of the batches.

11. DISCUSSION / CONCLUSIONS

Storage under real time testing conditions causes insignificant change of assay results of paracetamol. Significant changes in physical and chemical stabilities were not observed. Since the long-term data and accelerated data show little or no change over time and little variability, a statistical analysis is considered unnecessary.

Shelf-life:

Based on the result data the shelf-life has been established for five years.

Storage Directions:

The product can be labelled with "Store below 30°C"

Summary of Stability Study Result

Table 1

Drug Product : Paracetamol
 Dosage : 500 mg/tablet
 Packaging : PVC Blister
 Batch No. : 001

Storage		Appearance	Hardness [N]	Friability [%]	Content : Paracetamol 500 mg	Degradation Product	Microbial Contamination
Time [Months]	Conditions					p-aminophenol [%]	
Specifications		White, round-flat tablet	≥ 70 N	≤ 2 %	95.0 – 105.0%	≤ 0.005%	Total count ≤ 10 ⁵ CFU E.coli: absent
Initial	-	Complies	80	1	98.8	0.001	Complies
3	30°C ± 2°C/ 75% RH ± 5%RH	Complies	80	1	101.4	0.002	Complies
6		Complies	85	0.5	98.3	0.004	Complies
9		Complies	90	0.5	99.6	0.001	Complies
12		Complies	85	1	98.9	0.003	Complies
18		Complies	97	1	99.0	0.003	Complies
24		Complies	94	0.5	98.9	0.004	Complies
36		Complies	87	1	99.1	0.002	Complies
48	Complies	98	1	99.5	0.001	Complies	
60	Complies	93	0.5	99.3	0.001	Complies	
3	+40°C ± 2°/75% RH ± 5%RH	Complies	96	0.5	100.5	0.004	Complies
6		Complies	80	0.5	99.6	0.004	Complies

Note: - More data on disintegration time or dissolution are required for each batch.
 - For batch number 002 and 003, study results are provided in the same format as batch number 001.

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