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Draft regional guidelines on stability testing of active substances and pharmaceutical products

These guidelines were developed during the WHO Consultation on Regional Guidelines on Stability Studies of Medicines and Biologicals, held in Jeddah in February 2006. The final draft is recommended for adoption by the Regional Committee for the Eastern Mediterranean

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Introductory note

Quality and safety of medicines are one of the main components of WHO Medicine Strategy. Development of norms and standards is one of the core functions of WHO. According to Article 2 of the WHO Constitution, WHO is required to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products."

WHO has been active in that field through the WHO Expert Committees which publish guidelines, standards and recommendations that provide national authorities with the tools to develop the national medicine quality assurance system. International harmonization is one of the recent challenges of globalization.

Currently, WHO attends meetings of the Steering Committee and the Global Cooperation Group of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) with observer status; these roles are important and should be maintained. However, appropriate strategies for consultation and communication with Member States need to be developed to ensure that WHO is not seen as de facto automatically endorsing ICH products, but as providing advice on the potential impact of those products on non-ICH Member States.

The WHO Regional Office for the Eastern Mediterranean, in its efforts to contribute to regional harmonization, organized a Consultation on Regional Guidelines on Stability Studies of Medicines on 25–28 February 2006 in Jeddah, Saudi Arabia. The consultation was attended by experts from Bahrain, Egypt, Jordan, Islamic Republic of Iran, Kuwait, Lebanon, Morocco, Oman, Pakistan, Saudi Arabia, Sudan and United Arab Emirates, as well as international experts from Italy and Sweden. The consultation reviewed and discussed relevant national, regional and international guidelines. The consultation also discussed climatic conditions in the Region, with particular emphasis on determining the mean kinetic temperature and the appropriate climate zone for each country of the Region.

The Draft Regional Guidelines on Stability Testing of Active Substances and Pharmaceutical Products are the product of the consultation. These guidelines are based in part on existing guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, European Agency for the Evaluation of Medicinal Products, and Gulf Cooperation Council. The Regional Office acknowledges the work of these bodies, as well as the contributions of the experts involved in developing the draft regional guidelines.

The Regional Committee is invited to advise on the adoption of the attached draft guidelines on Stability Testing of Active Substances and Pharmaceutical Products in countries of the Eastern Mediterranean Region.

1. Introduction

1.1 Objective of the guidelines

These guidelines are intended to define the stability data package for active substances and pharmaceutical products that is sufficient for a registration application within countries of the World Health Organization's Eastern Mediterranean Region [1]. Countries of the Region have agreed to accept stability information that is consistent with these guidelines [2].

The guidelines seek to exemplify the core stability data package required for registration. Alternative approaches can also be used when they are scientifically justified. Further guidance can be found in guidelines published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [3].

1.2 Scope

The guidelines address the information to be submitted in applications for registration of New Chemical Entities as well as existing active substances and their related pharmaceutical products for human use.

1.3 General principles

The purpose of stability testing is to provide evidence on how the quality of an active substance or pharmaceutical product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. In addition, product-related factors influence the stability, e.g. the chemical and physical properties of the active substance and the pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of the container-closure system, and the properties of the packaging materials. As well, the stability of excipients that may contain or form reactive degradation products have to be considered. The interaction of all these features affect the eventual stability of the product.

As a result of stability testing, a re-test period for the active substance or a shelf life for the pharmaceutical product can be established, and storage conditions can be recommended.

In order to identify adequate testing conditions, the climate in countries of the Eastern Mediterranean Region has been analysed using the climatic data extracted from the ERA-40 reanalysis conducted by the European Centre for Medium-Range Weather Forecasts [4]. The mean kinetic temperature, which includes the reaction rate constants in the evaluation of heat effects on pharmaceutical products, and the mean partial water vapour pressure in any part of the region were calculated, and accordingly climatic zones were assigned for each country of the Region (see Annex 1).

2. Guidelines

2.1 Active substances

2.1.1 General

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation. For active substances not described in an official pharmacopoeial monograph, stability studies are required. For active substances described in an official pharmacopoeial monograph, which covers the degradation products and for which suitable limits have been set but a re-test period is not defined, two options are acceptable:

- The manufacturer of the pharmaceutical product confirms that the active substance complies with the pharmacopoeial monograph immediately prior to the manufacture

of the pharmaceutical product. In this case no stability studies on the active substance are required. The suitability of the pharmacopoeial monograph for the active substance used from a named source of supply has to be demonstrated.

- The manufacturer establishes a re-test period based on the results of long-term testing stability studies conducted on the active substance.

2.1.2 Stress testing

Stress testing of the active substance 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 active substance and the type of pharmaceutical product involved.

For an active substance the following approaches may be used.

a) When an active substance is described in an official pharmacopoeial monograph, and fully meets its requirements, no data are required on the degradation products if they are named under the headings “purity tests” and/or “section on impurities”.
b) For active substances not described in an official pharmacopoeial monograph, there are two options:
   - When available, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways;
   - When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed.

Stress testing is likely to be carried out on a single batch of the active substance. 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% relative humidity (RH) or greater) where appropriate, oxidation and photolysis on the active substance. The testing should also evaluate the susceptibility of the active substance to hydrolysis across a wide range of pH values when in solution or suspension.

Photostability testing should be an integral part of stress testing.

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

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

2.1.3 Selection of batches

For new active substances, data from formal stability studies should be provided on at least three primary batches of the active substance. 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 active substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale. Other supporting data can be provided.

For known active substances, in case the applicant is not the manufacturer of the active substance, stability data from the manufacturer should be submitted, e.g. Drug Master File, or a European Certificate of Suitability.

2.1.4 Container closure system

The stability studies should be conducted on the active substance 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 active substance that are susceptible to change during storage and are likely to influence quality, safety or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. 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.

2.1.6 Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the active substance. For active substances with a proposed re-test period 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.

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 6-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.

2.1.7 Storage conditions

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	12 months
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 is determined by the climatic condition in which the active substance is intended to be stored. Testing at higher humidities like 30°C ± 2°C/75% RH ± 5% RH is also acceptable.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

In general, an active substance 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, shipment and subsequent use with due regard to the climatic zone(s) in which the active substance is intended to be stored (see Annex 1).

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period. 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 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 active substances are detailed in the sections below. The general case applies if the active

substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

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. Testing at the intermediate storage condition should include all tests, unless otherwise justified. 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 active substance is defined as failure to meet its specification.

Active substances 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	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 is determined by the climatic zone in which the active substance is intended to be stored (see Annex 1). Testing at higher humidities like 30 °C ± 2 °C/75% RH ± 5% RH is also acceptable.

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, 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 real-time 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 active substance for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an active substance through six months when a significant change has occurred within the first three months.

Active substances 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 active substances intended for storage in a freezer, the re-test period should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for active substances 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.

Active substances intended for storage below –20°C

Active substances 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.

Where the submission includes long-term stability data on three production batches 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 least three production batches, 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 three production batches, 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 the first three production batches 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 two or three batches of the active substance 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 active substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the formal 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 extent 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 active substance. Where applicable, specific instructions should be provided, particularly for active substances that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” must be avoided.

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.

The temperature and humidity conditions during transport from the place of synthesis of the active substance to the manufacturer of the pharmaceutical product need to be taken into account, if applicable.

2.2. Pharmaceutical products

2.2.1 General

The design of the formal stability studies for the pharmaceutical product should be based on knowledge of the behaviour and properties of the active substance, and from stability studies on the active substance and on experience gained from pre-formulation studies and investigational pharmaceutical products. Attributes to be tested in the formal stability studies are listed in Annex 2.

2.2.2 Selection of batches

Data from stability studies should be provided on at least three primary batches of the pharmaceutical product. 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. 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 pharmaceutical product should be manufactured by using different batches of the active substance.

Stability studies should be performed on each individual strength and container size of the pharmaceutical product unless bracketing or matrixing is applied.

Other supporting data can be provided.

2.2.3 Container closure system

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the pharmaceutical product 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 pharmaceutical product that are susceptible to change during storage and are likely to influence quality, safety 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). 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 pharmaceutical product 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 pharmaceutical product. 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 6-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.

2.2.6 Storage conditions

In general, a pharmaceutical product should be evaluated under storage conditions (with appropriate 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 zone(s) in which the product is intended to be marketed (see Annex 1).

In addition as part of the development phase, stability studies conducted on one batch of the pharmaceutical product for up to three months at 50 °C/ambient humidity may be useful to identify the formulation and packaging material adequate for extremely hot and dry conditions.

Photostability testing should be conducted on at least one primary batch of the pharmaceutical product if appropriate.

Stability testing of the pharmaceutical product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long-term data will not be 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.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. 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 pharmaceutical products are detailed in the sections below. The general case applies if the pharmaceutical product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

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	12 months
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 is determined by the climatic zone in which the pharmaceutical product is intended to be marketed (see Annex 1). Testing at higher humidities like 30 °C ± 2 °C/75% RH ± 5% RH is also acceptable.

** If 30 °C ± 2 °C/65% 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. 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 a pharmaceutical product is defined as:

4. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
5. Any degradation product exceeding its acceptance criterion;
6. 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:

7. Failure to meet the acceptance criterion for pH; or
8. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Pharmaceutical products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for pharmaceutical products 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 humidity condition.

Pharmaceutical products 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 pharmaceutical products 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/35% 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 zone in which the pharmaceutical product is intended to be marketed (see Annex 1).

** If 30 °C ± 2 °C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25 °C ± 2 °C/40% RH ± 5% RH, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30 °C if significant change other than water loss occurs during the six months' testing at the accelerated storage condition. 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.

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 pharmaceutical product.

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.

Pharmaceutical products 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	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 is determined by the climatic zone in which the pharmaceutical product is intended to be marketed (see Annex 1). Testing at higher humidities like 30 °C ± 2 °C/75% RH ± 5% RH is also acceptable.

If the pharmaceutical product 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 the 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 real-time 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 pharmaceutical product 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.

Pharmaceutical products 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 pharmaceutical products 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 pharmaceutical products 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.

Pharmaceutical products intended for storage below –20 °C

Pharmaceutical products 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 three production batches 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 three production batches, 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 three production batches, 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 first three production batches 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 two or three batches of the pharmaceutical product, a shelf life and label storage instructions applicable to all future batches of the pharmaceutical product manufactured and packaged 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 formal statistical analysis.

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 extent 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 pharmaceutical product. Where applicable, specific instruction should be provided, particularly for pharmaceutical products 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 pharmaceutical product. An expiration date should be displayed on the container label. The following statements should be used if applicable:

Testing condition where the stability of the pharmaceutical product has been shown	**Recommended labelling statement**
For countries in Climatic Zones I and II: 25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	“Store below 30 °C” *
For countries in Climatic Zones III and IVA: 30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	“Store below 30 °C”
For countries in Climatic Zones I and II: 25 °C/60% RH (long-term) 30 °C/65% RH (intermediate)	“Store below 30 °C”
For countries in Climatic Zone III and IVA: 30 °C/65% RH (long-term)	“Store and transport below 30 °C”
For countries in Climatic Zones I and II: 25 °C/60% RH (long-term)	“Store below 25 °C”
5 °C ± 3 °C	”Store and transport in a refrigerator (2 °C to 8 °C)” **
–20°C ± 5°C	”Store in a freezer and transport frozen (-5 °C to -20 °C)” ***

* In the European Union, in this case the pharmaceutical product does not require any special storage condition on the label.

** In case stability data generated at 25 °C/60% RH, 30 °C/65% or 30 °C/75% RH (accelerated) support transport outside the refrigerator, a labelling statement “Store in a refrigerator” is acceptable.

*** In case stability data generated at 5 °C ± 3 °C (accelerated) support transport outside the freezer, a labelling statement “Store in a freezer” is acceptable.

In principle, pharmaceutical products should be packed in containers that ensure stability and protect the pharmaceutical product 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
Pharmaceutical products that cannot tolerate refrigerating	“Do not refrigerate or freeze”*
Pharmaceutical products that cannot tolerate freezing	“Do not freeze”*
Light sensitive pharmaceutical products	“Protect from light”
Pharmaceutical products that cannot tolerate excessive heat, e.g. suppositories	“Store and transport always below 30 °C”

* Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. emulsions. 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.

General precautionary statements, such as “store in a dry place”, may be included, but should not be used to conceal stability problems.

If applicable, recommendations should also be made as to the utilization period and storage conditions after opening and dilution or reconstitution of a solution, e.g. an antibiotic injection supplied as a powder for reconstitution.

In-use stability

The purpose of in-use stability testing is to establish–where applicable–the period of time during which a multi-dose product can be used while retaining acceptable quality once the container is opened and the first dose is removed.

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.

As far as possible the test should be designed to simulate the use of the product in practice taking into consideration the filling volume of the container and any dilution or 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. Sampling should take place under normal environmental conditions of use.

The appropriate physical, chemical and microbial properties of the product 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 product in the container. Specific parameters, e.g. preservatives, need to be studied.

Where relevant, studies on diluted or reconstituted material must be performed.

To accommodate certain specific pharmacy dosing regimes, up to three months open storage may be required.

Variations

Once the pharmaceutical product has been registered, additional stability studies are required whenever major variations are made like the following:

1. Change in the manufacturing process;
2. Change in the composition of the pharmaceutical product;
3. Change of the immediate packaging.

In all cases of variations, the applicant has to investigate whether the intended change will have an impact on the quality characteristics of active substances or pharmaceutical products 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 active substances and pharmaceutical products.

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

Ongoing stability studies

After approval, the stability of the pharmaceutical product 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 pharmaceutical product in the container closure system in which it is sold, but consideration should also be given to the inclusion of bulk products in the programme. 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 on-going 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 intervals (time points);
- Description of the conditions of storage (standardized conditions for long-term testing as described in this guideline, and consistent with the product labelling, should be used);
- Other applicable parameters specific to the pharmaceutical product.

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 are produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

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.

Out-of-specification results or significant atypical trends should be investigated. Any confirmed out-of-specification result, or significant negative trend should be reported 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.

Accelerated testing

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

Active substance

The unformulated active substance that may subsequently be formulated with excipients to produce the dosage form.

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 zones

The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions (see Annex 1).

Commitment batches

Production batches of an active substance or pharmaceutical product for which the stability studies are initiated or completed post approval through a commitment made in the registration 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 pharmaceutical product. A packaging system is equivalent to a container closure system.

Dosage form

A pharmaceutical product type (e.g. tablet, capsule, solution, cream) that contains an active substance generally, but not necessarily, in association with excipients.

Excipient

Anything other than the active substance in the dosage form.

Expiration date / Expiry date

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

Formal stability studies

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 of an active substance or the shelf life of a pharmaceutical product.

Impermeable containers

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

Long-term testing

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labelling.

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 pharmaceutical product 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.

Mean kinetic temperature

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to an active substance or pharmaceutical product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of Haynes [5] can be used.

New Chemical Entity (NCE)

An active pharmaceutical substance not previously contained in any pharmaceutical product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of an approved active substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pharmaceutical product

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

Pilot scale batch

A batch of an active substance or pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. 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.

Primary batch

A batch of an active substance or pharmaceutical product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of an active substance should be at least a pilot scale batch. For a pharmaceutical product, 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 substance or pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

Re-test date

The date after which samples of the active substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given pharmaceutical product.

Re-test period

The period of time during which the active substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given pharmaceutical product, provided that the active substance has been stored under the defined conditions. After this period, a batch of active substance destined for use in the manufacture of a pharmaceutical product should be re-tested for compliance with the specification and then used immediately. A batch of active substance 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 biotechnological/biological 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 (also referred to as expiration dating period)

The time period during which a pharmaceutical product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification

See ICH Q6A and Q6B.

Specification – Release

The combination of physical, chemical, biological and microbiological tests and acceptance criteria that determine the suitability of a pharmaceutical product at the time of its release.

Specification - Shelf life

The combination of physical, chemical, biological and microbiological tests and acceptance criteria that determine the suitability of an active substance throughout its re-test period, or that a pharmaceutical product should meet throughout its shelf life.

Storage condition tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be 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 effect assessed.

Stress testing (active substance)

Studies undertaken to elucidate the intrinsic stability of the active substance. 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 (pharmaceutical product)

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

Supporting data

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include: 1) stability data on early synthetic route batches of active substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; 2) information regarding test results on containers; and 3) other scientific rationales.

Annex 1

Assignment of climatic zones and recommended storage conditions

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 Schumacher in 1972 [6] and Grimm in 1986 [7] and in 1998 [8] when they defined four different long-term test 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 became an established standard in developing pharmaceutical products.

At the 40th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva, October 2005 [9], it was recommended to split the current climatic zone IV (hot and humid) into CZ IVA – for which 30 °C/65% RH will remain the standard long-term testing condition – and CZ IVB, for which, if justified, 30 °C/75% RH will become the long-term testing condition. The following criteria [10] and long-term testing conditions are therefore proposed.

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

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

The detailed analysis of meteorological measurements as described above, and the evaluation of the climatic conditions in each country of the Region resulted in the following classification and recommended testing condition for long-term stability studies.

Country	CZ II	CZ III	CZ IVA	Recommended long-term testing condition*
Afghanistan	+	+		30 °C/65% RH
Bahrain			+	30 °C/65% RH
Djibouti			+	30 °C/65% RH
Egypt	+	+		30 °C/65% RH**
Iran, Islamic Republic of	+	+	+	30 °C/65% RH**
Iraq		+		30 °C/35% RH
Jordan	+	(+)		30 °C/65% RH**
Kuwait			+	30 °C/65% RH
Lebanon	+	(+)		25 °C/60% RH
Libyan Arab Jamahiriya	+	(+)		25 °C/60% RH
Morocco	+			25 °C/60% RH
Oman		(+)	+	30 °C/65% RH
Pakistan	+	+	+	30 °C/65% RH
Palestine	+			25 °C/60% RH
Qatar			+	30 °C/65% RH
Saudi Arabia		+	+	30 °C/65% RH**
Somalia			+	30 °C/65% RH
Sudan		+	+	30 °C/65% RH**
Syrian Arab Republic	+	(+)		25 °C/60% RH
Tunisia	+	(+)		25 °C/60% RH
United Arab Emirates		+	+	30 °C/65% RH
Yemen	+		+	30 °C/65% RH

+ Climatic zone assigned

(+) Deserted part of the country

* The hottest and most humid climatic zone has been selected to establish the adequate stability testing condition for a particular country.

** Aqueous-based solutions in semi-permeable packaging, and dosage forms sensitive to low humidity, e.g. hard-gelatin capsules, may require testing at low humidity according to the procedure described in this guideline.

Test results conducted at higher temperatures and humidities, e.g. at 30 °C/75% RH, should be acceptable for all countries.

Annex 2

Testing parameters

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.

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.

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 parenteral 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 and at appropriate intervals during the stability period. 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.

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

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol 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. Emulsions

Phase separation, pH, viscosity, level of microbial contamination, and mean size and distribution of dispersed globules.

4. Oral Solutions and Suspensions

Formation of precipitate, clarity for solutions, pH, viscosity, extractables, level of microbial contamination. Also, polymorphic conversion may be examined, if applicable.

Additionally for suspensions, redispersibility, rheological properties and mean size and distribution of particles should be considered.

5. Powders for oral solution or suspension

Water content, and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described in "Oral Solutions and Suspensions" above, after preparation according to the recommended labelling, through the maximum intended use period.

6. 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) and extractables/leachables from plastic and elastomeric components. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, the appearance of the valve components and container's contents should be evaluated microscopically for large particles and changes in morphology of the drug surface particles, extent of agglomerates, crystal growth, as well as foreign particulate matter. These particles lead to clogged valves or non-reproducible delivery of a dose. Corrosion of the inside of the container or deterioration of the gaskets may adversely affect the performance of the drug product.

7. 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/bleachable from plastic and elastomeric components of the container, closure and pump.

8. 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, resuspendability (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).

9. Suppositories

Softening range, dissolution (at 37 °C).

10. 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, redispersibility and rheological properties.

The stability studies for Emulsion for Injection should include in addition phase separation, viscosity, and mean size and distribution of dispersed phase globules.

11. Large Volume Parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin, and volume.

12. Transdermal Patches

In-vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

References

1. WHO. 1996. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. WHO Technical Report Series 863, Annex 5. These guidelines were revised at the 37th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva, 22–26 October 2001.

2. The development of a regional stability guideline initiated in 1993, when the World Health Organization (WHO) Regional Office for the Eastern Mediterranean (EMRO) organised a workshop in Amman, Jordan. A follow-up meeting in Damascus, Syrian Arab Republic, was held in 1994. In 1995, the Arab Union of the Manufacturers of Pharmaceutical and Medical Appliances (AUPAM) published the "*Arab Guidelines on Stability Testing of Pharmaceutical Products*", which were updated in 2002. In November 2003, the Executive Board of the Health Minister's Council for GCC States released "*The GCC Guidelines on Stability Testing of Pharmaceutical Products*".

3. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 as a joint regulatory/industry project to improve, through harmonization, the efficiency of the process for developing and registering new pharmaceutical products in Europe, Japan and the United States, in order to make these products available to patients with a minimum of delay. The World Health Organization (WHO) participated as observer at ICH Steering Committee meetings, and contributed to the development of ICH guidelines at ICH Expert Working Group (EWG) meetings.

   Further information can be found at the ICH homepage http://www.ich.org/cache/compo/276-254-1.html

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

   *ICH Q1A: "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 Q2A: "Text on Validation of Analytical Procedures"*http://www.ich.org/LOB/media/MEDIA417.pdf

   *ICH Q2B: "Validation of Analytical Procedures: Methodology"*http://www.ich.org/LOB/media/MEDIA418.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

4. The ERA-40 Reanalysis conducted by the European Centre for Medium-Range Weather Forecasts (ECMWF) is a process in which global weather observations are assembled to form a regular mesh covering the earth with a resolution of about 125 km. Measurements take place every 6th hour. Reanalysed temperatures and dewpoints from 1979 to 2002 were averaged into monthly means at 00:00 UTC, 06:00 UTC, 12:00 UTC and 18:00 UTC (Coordinated Universal Time). Vapour pressures – applying an updated version of Wexler's equation – and relative humidities were then determined using basic thermodynamic relationships. For further details see Uppala SM et al. The ERA-40 Reanalysis. *Quarterly journal of the Royal Meteorological Society*, 131:2961–3012.

5. Haynes JD. Worldwide virtual temperatures for product stability testing. *Journal of pharmaceutical sciences*, 1971, 60:927–9.

6. Schumacher P. Über eine für die Haltbarkeit von Arzneimitteln maßgebliche Klimaeinteilung [The impact of climate classification on the stability of medicines]. *Die Pharmazeutische Industrie*, 1972, 34:481–83.

7. Grimm W. Storage conditions for stability testing (Part 2). *Drugs made in Germany*, 1986, 29:39–47.

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