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Committee for Veterinary Medicinal Products (CVMP)

Guideline on Stability Testing: Stability testing of existing active substances and related finished products

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This guideline replaces an earlier version of this guideline, EMEA/CVMP/846/99. The document reference number is changed to ensure correct document management.

Revision History

The guideline EMEA/CVMP/846/99 was revised to be brought in line with the requirements of the Note for Guidance on Stability Testing of New Veterinary Drug Substances and Medicinal Products (EMEA/CVMP/VICH/899/99-Rev.1).

As a consequence, the relative humidity at storage under intermediate conditions, i.e. presently 30 °C ± 2 °C/60% RH ± 5% RH, will be changed to 30 °C ± 2 °C/65% RH ± 5% RH. Within the EU, data from studies generated using the new conditions are accepted immediately. Furthermore, data from studies where the relative humidity has been changed from 60% RH to 65% RH during the study

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to meet the new requirements will also be accepted under the condition that the respective storage conditions and the date of the change are clearly documented and stated in the application file.

It is recommended that all marketing authorisation applications contain data from complete studies at the intermediate storage condition 30 °C ± 2 °C/65% RH ± 5% RH, if applicable, by 1 September 2011.

*Revision 2 consists of administrative changes made in order to align the guideline with Regulation (EU) 2019/6 and to align with the current EMA template for Guidance. The references to the legislation applicable and other scientific guidelines have also been updated as appropriate. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary.

**Correction 1 makes minor corrections in sections 2.1.2 (bullet point missing) and 2.2.7.4, 2.2.7.5 and 2.2.7.6 (missing the title of the actual sub-heading).

Keywords	Stability, Testing

Guideline on Stability Testing: Stability testing of existing active substances and related finished products

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1. Introduction

1.1. Objectives of the Guideline

The following guideline is an extension of the Guideline on Stability testing of New Veterinary Drug Substances and Medicinal Products (EMEA/CVMP/VICH/899/99-Rev.1) and sets out the stability testing requirements for existing active substances and related finished products. For the purposes of this guideline, an existing active substance is one that has been authorised previously through a veterinary medicinal product within the European Union[1].

This guideline is applicable to non-biological active substances and related finished products, herbal drugs, herbal drug preparations and related herbal medicinal products and not to radiopharmaceuticals, biologicals and products derived by biotechnology.

The guideline seeks to exemplify the core stability data package required for such active substances and finished products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

1.2. Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for existing active substances and related finished products.

For herbal drugs, herbal drug preparations and herbal medicinal products, reference is made to the stability section of the Guideline on quality of herbal medicinal products/traditional herbal medicinal products (EMA/HMPC/CHMP/CVMP/201116/2005).

1.3. General Principles

The purpose of stability testing is to provide evidence on how the quality of an active substance or finished product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the active substance or a shelf life for the finished product and recommended storage conditions.

The choice of test conditions defined in this guideline refers to the Guideline on Stability testing of New Veterinary Drug Substances and Medicinal Products (EMEA/CVMP/VICH/899/99-Rev.1).

2. Guidance

2.1. Active Substance

2.1.1. General

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation. Two options are available:

[1] The principles of this guideline may also apply if an active substance, which is new in veterinary medicine, has been authorised previously through a human medicinal product within the European Union.

a) The applicant should specify that the active substance complies with the specification immediately prior to manufacture of the finished product. In this case no stability studies are required on condition that the suitability of the specification has been demonstrated for the particular named source (refer to the Note for Guidance on Summary of Requirements for Active Substances in the Quality Part of the Dossier (EMEA/CVMP/1069/02));

b) The applicant should fix a re-test period based on the results of long term testing, taking the results of testing under accelerated or, where applicable, intermediate storage conditions, into consideration (see 2.1.7 Storage Conditions).

In the case of herbal medicinal products, active substances include herbal drugs and herbal drug preparations. Herbal drugs which are used as starting material in the manufacturing process for an herbal drug preparation shall comply with specification before use (e.g. before extraction).

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.

Stress tests are usually considered unnecessary for herbal drugs and herbal drug preparations.

For an active substance the following approaches may be used:

a) When an active substance is described in an official pharmacopoeial monograph (European Pharmacopoeia or the Pharmacopoeia of a European Union Member State) and fully meets its requirements no data are required on the degradation products if they are named under the headings "purity test" and / or "section on impurities".

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

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% 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. The standard conditions for photostability testing are described in the Guideline on Photostability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/901/00).

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

2.1.3. Selection of batches

Two options are acceptable:

a) Stability information from accelerated and long term testing is to be provided on at least two production scale batches manufactured by the same manufacturing (synthetic) route and procedure described in part 2C (CTD: 3.2.S.2) of the application. The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission

   or

b) Stability information from accelerated and long term testing is to be provided on at least three pilot scale batches manufactured by the same manufacturing (synthetic) route and procedure described in part 2C (CTD: 3.2.S.2) of the application. The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission.

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 and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied.

Acceptance criteria are numerical limits, ranges and other criteria for the specific tests described and should include individual and total upper limits for impurities and degradation products. The justification of individual and total upper limits for degradation products should be based on safety and/or efficacy considerations. For active substances described in an official pharmacopoeial monograph (European Pharmacopoeia or the Pharmacopoeia of a European Union Member State) the testing should be performed in accordance with the monograph or by using a test that has been cross-validated against the compendial test and the justification should be given that all potential impurities (process impurities and degradation products) from the actual manufacturing (synthetic) route are adequately controlled.

Specifications for herbal drugs and herbal drug preparations should refer to the Guideline on Specifications: Test Procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products / Traditional Herbal Medicinal Products (EMA/HMPC/CHMP/CVMP/162241/2005).

2.1.6. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the active substance. The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period.

At the accelerated storage condition, a minimum of three 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.

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.

For herbal drugs and herbal drug preparations on which the applicant in the possession of historical batch data, the testing frequency may be reduced if justified by the applicant.

2.1.7. Storage conditions

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.

The long term testing for both options a and b should cover a minimum of 6 months' duration 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 a subsequent section does not specifically cover the active substance. Alternative storage conditions can be used if justified.

2.1.7.1. 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	6 months (option a and b)
Intermediate**	30°C ± 2°C/65%RH ± 5%RH	6 months
Accelerated**	40°C ± 2°C/75%RH ± 5%RH	6 months

* It is up to the applicant to decide 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. In the latter case, no additional data under intermediate conditions will have to be generated.

** For herbal substances and herbal preparations, testing at the accelerated storage condition or at the intermediate storage condition may be omitted if justified by the applicant and if the storage conditions below 25°C are clearly labelled on the product.

When "significant change" occurs at any time during 6 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 6 months' data from a 12-months study at the intermediate storage condition.

"Significant change" for an active substance is defined as failure to meet its specification.

2.1.7.2. 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	6 months (option a and b)
Accelerated	25°C ± 2°C/60%RH ± 5%RH	6 months

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 3 and 6 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 3 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 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test an active substance through 6 months when a significant change has occurred within the first 3 months.

2.1.7.3. 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	6 months (option a and b)

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) for an appropriate time period should be conducted. Such a study will address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

2.1.7.4. 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 extend the re-test period can be undertaken at approval time (see annex II), 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

The storage conditions (temperature, light, humidity) indicated should refer to the Guideline on Declaration of storage conditions for in the product information of pharmaceutical veterinary medicinal products and active substances (EMEA/CVMP/422/99-Rev.3).

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

2.2. Finished Product

2.2.1. General

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the active substance and the dosage form.

2.2.2. Photostability Testing

Photostability testing should be conducted on at least one primary batch of the finished product if appropriate. The standard conditions for photostability testing are described in the Guideline on Photostability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/901/00).

2.2.3. Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Two options are acceptable:

a) For conventional dosage forms (e.g. immediate release solid dosage forms, solutions) and when the active substances are known to be stable, stability data on at least two pilot scale batches are acceptable.

b) For critical dosage forms or when the active substances are known to be unstable, stability data on three primary batches are to be provided. Two of the three batches should be of at least pilot scale, the third batch may be smaller.

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. Where possible, batches of the finished 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 finished product unless bracketing or matrixing is applied.

Other supporting data can be provided.

2.2.4. 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 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. In some cases, a smaller container closure system simulating the actual container closure system for marketing may be acceptable. In these instances, a justification for using a smaller container closure system should be provided.

2.2.5. Specification

Stability studies should include testing of those attributes of the finished product 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). 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 finished 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.

2.2.6. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the finished product. The frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three 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. For herbal medicinal products on which the applicant in the possession of historical batch data, the testing frequency may be reduced if justified by the applicant.

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.

2.2.7. Storage Conditions

In general, a finished 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.

Stability testing of the finished 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 six 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 6 months' duration 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 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 finished products are detailed in the sections below. The general case applies if a subsequent section does not specifically cover the finished product. Alternative storage conditions can be used, if justified.

2.2.7.1. 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	6 months (option a and b)
Intermediate	30°C ± 2°C/65%RH ± 5%RH	6 months
Accelerated	40°C ± 2°C/75%RH ± 5%RH	6 months

* It is up to the applicant to decide 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. In the latter case, no additional data under intermediate conditions will have to be generated.

When a "significant change" occurs at any time during 6 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 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a finished product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
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.

2.2.7.2. Finished products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for finished 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.

2.2.7.3. Finished 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 finished 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	6 months (option a and b)
Intermediate	30°C ± 2°C/65%RH ± 5%RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25%RH	6 months

When a significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, 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 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 finished product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 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 3 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 3 months' storage at 40°C/NMT 25%RH may be appropriate, if justified.

An alternative approach to studying at the reference 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 reference 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 finished 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 reference 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.

Reference relative humidity	General testing conditions at the same temperature	Ratio of water loss rates at a given temperature
25°C/25%RH	25°C/60%RH	1.9 = (100-25) : (100-60)
25°C/40%RH	25°C/60%RH	1.5 = (100-40) : (100-60)
40°C/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.

2.2.7.4. Finished products intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	6 months (option a and b)
Accelerated	25°C ± 2°C/60%RH ± 5%RH	6 months

If the finished 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 this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 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 3 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 finished product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

2.2.7.5. Finished products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	-20°C ± 5°C	6 months (option a and b)

For finished 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 finished 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) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

2.2.7.6. Finished products intended for storage below -20 °C

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

2.2.8. 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 on 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.
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 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 6 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 6 months.

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

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

2.2.9. 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 finished product, a shelf life and label storage instructions applicable to all future batches of the finished 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; providing a justification for the omission should be sufficient.

An approach for analysing 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 at approval time (see annex II), if justified. This justification should be based on what is known about the mechanisms 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.

2.2.10. Statements/Labelling

The storage conditions (temperature, light, humidity) indicated should refer to the Guideline on Declaration of storage conditions in the product information of pharmaceutical veterinary medicinal products and active substances (EMEA/CVMP/422/99-Rev.3).

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

Annex I

An active substance is considered as stable if it is within the defined/regulatory specifications when stored for at least 2 years at 25 °C/60% RH or at the alternative storage condition 30 °C/65% RH and for at least 6 months at 40 °C/75% RH.

Annex II

Extrapolation of data

If real time data are supported by results from studies conducted under accelerated or intermediate storage conditions, the re-test period/shelf life may be extended beyond the end of real time studies. The extrapolated retest period or shelf-life may be up to twice, but should not be more than 12 months beyond, the period covered by real time data, depending on the change over time, variability of data observed, proposed storage conditions and extent of statistical analyses performed. The decision tree depicts the various situations envisaged.

Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Active Substances or Finished Products (excluding Frozen Products)