The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines and Information Technology

EMEA/CVMP/846/99 – FINAL

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE ON STABILITY TESTING OF EXISTING ACTIVE SUBSTANCES AND RELATED FINISHED PRODUCTS

ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	December 1999
START OF CONSULTATION	December 1999
END OF CONSULTATION	30 June 2000
APPROVAL BY QUALITY WORKING PARTY	October 2000
FINAL ADOPTION BY CVMP	November 2000
DATE OF COMING INTO EFFECT	1 July 2002

Public

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STABILITY TESTING OF EXISTING ACTIVE SUBSTANCES AND RELATED FINISHED PRODUCTS

Preamble

The following guideline is an extension of the CVMP/VICH Guideline on Stability Testing of New Veterinary Active Substances and Medicinal Products (VICH GL 3) 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 Community[1].

This guideline is applicable to chemical active substances and related finished 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. It is not always necessary to follow this when there are scientifically justifiable reasons for using alternative approaches.

The guideline provides a general indication on the requirements for stability testing, but leaves sufficient flexibility to encompass the variety of different practical situations required for specific scientific situations and characteristics of the material being evaluated.

Objective

The purpose of stability testing is to provide evidence on how the quality of a substance or product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

Scope

The guideline addresses the stability information on active substances and related finished products to be included in applications for Marketing Authorisations**.** All new stability studies should be conducted in accordance with this guideline. For variations such as reformulation or pack type submitted after the implementation date, the supporting stability studies should be in accordance with this guideline.

The choice of test conditions defined in this guideline refers to the CVMP/VICH Guideline on Stability Testing of New Veterinary Active Substances and Medicinal Products.

[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.

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ACTIVE SUBSTANCE

General

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

Stress Testing

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

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) no data are required on the degradation products if they are named under the headings "purity test" and / or "transparency statement"; in this case no stress testing is required;

b) when available, it is acceptable to provide the relevant data published in the literature to support the proposed degradation pathways;

c) when no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed.

Formal Studies

Primary stability studies are intended to show that the active substance will remain within specification during the re-test period if stored under recommended storage conditions in the proposed bulk storage container.

The re-test period is based on the results of long term stability studies performed by the active ingredient manufacturer or the applicant.

For active substances not described in an official pharmacopoeial monograph (European Pharmacopoeia or the Pharmacopoeia of a European Union Member State) stability studies are required.

For active substances described in a official pharmacopoeial monograph (European Pharmacopoeia or the Pharmacopoeia of a European Union Member State) 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:

a) the applicant should specify that the active substance complies with the pharmacopoeial monograph immediately prior to manufacture of the finished product. In this case no stability studies are required on condition that the suitability of the pharmacopoeial monograph has been demonstrated for the particular named source;

b) the applicant should fix a re-test period based on the results of long term testing stability studies.

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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 synthetic route and procedure described in part II C 1.2 of the application. The long term testing and accelerated testing should cover a minimum of 6 months duration at the time of submission. A further production batch of active substance manufactured post-approval should be placed on long term stability studies using the same stability protocol as in the approved drug application. The results of the stability studies, when available, should be submitted to the Competent Authorities.

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 synthetic route and procedure described in part IIC 1.2 of the application. The long term testing should cover a minimum of 12 months duration and accelerated testing should cover a minimum of 6 months duration at the time of submission.

In this option the first three production scale batches of active substance manufactured post-approval should be placed on long term stability studies using the same stability protocol as in the approved medicinal product application. The results of the stability studies, when available, should be submitted to the Competent Authorities.

Test Procedures and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Stability information should cover as necessary the physical, chemical and microbiological test characteristics. Validated stability indicating test methods must be applied.

Specification

Limits of acceptability should be justified. The specification should include individual and total upper limits for impurities including degradation products, the justification for which should be based on safety and/or efficacy considerations.

Storage Conditions

The duration of studies and storage conditions required are normally:

	Conditions	**Minimum time Period at Submission**
Long term testing	25°C ± 2°C / 60% RH ± 5%	6 months (option a) 12 months (option b)
Accelerated testing	40°C ± 2°C / 75% RH ± 5%	6 months

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Other storage conditions are allowable if justified. In particular, temperature sensitive active substances should be stored under an alternative, lower temperature condition which will then become the designated long term testing storage temperature. The six months accelerated testing should then be carried out at a temperature at least 15°C above this designated long term storage temperature (together with the appropriate relative humidity conditions for that temperature).

Where significant change occurs during six months storage under accelerated testing conditions at 40°C ± 2°C / 75% RH ± 5%, or if these conditions are inappropriate for physical reasons, additional testing at an intermediate condition (such as 30°C ± 2°C / 60% RH ± 5%) should be conducted for active substances to be used in the manufacture of finished products tested long term at 25°C / 60% RH. When an intermediate condition is applied, the Registration Application should include a minimum of 6 months data at time of submission on the basis of ongoing studies 12 months duration.

Significant change at 40°C / 75% RH or 30°C / 60% RH is defined as failure to meet the specification.

The duration of studies and storage conditions required for temperature sensitive active substances are:

	Conditions	**Minimum time Period at Submission**
Long term testing	5°C ± 3°C	6 months (option a) 12 months (option b)
Accelerated testing	25°C ± 2°C / 60% RH ± 5%	6 months

The designated long term testing conditions will be reflected in the labelling and re-test date.

The long term testing may be continued for a sufficient period of time beyond 6 months to cover all appropriate re-test periods, and further accumulated data can be submitted to the Competent Authorities.

Testing Frequency

Testing under defined conditions will normally be every three months over the first year; every six months over the second year and then annually.

Packaging / Containers

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

Statements / Labelling

The storage conditions (temperature, light, humidity) indicated should be based on the stability evaluation of the active substance.

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

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FINISHED PRODUCT

General

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

Selection of Batches

At the time of submission stability information from accelerated and long term testing should be provided on batches of the same formulation and dosage form in the containers and closure proposed for marketing (see: Packaging/Container).

Two options are possible

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 (e.g. prolonged release forms) or when the active substances are known to be unstable, stability data on three batches are to be provided. Two of the three batches should be at least pilot scale, the third batch may be smaller.

The manufacturing process to be used should meaningfully simulate that which would be applied to large scale batches for marketing. The process should provide product of the same quality intended for marketing, and meeting the same quality specifications as to be applied for release material. Where possible, batches of the finished product should be manufactured using identifiably different batches of active substance.

The first three production scale batches manufactured post approval, if not submitted in the original Registration application should be placed on accelerated and long term testing stability studies using the same stability protocols as in the approved finished product application. The results of the stability studies when available, should be submitted to the Competent Authorities.

Test Procedure and Test Criteria

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy. Analytical test procedures should be fully validated and the assays should be stability-indicating.

The range of testing should cover not only chemical and biological stability but also loss of preservative, physical properties and where required, microbiological attributes. Preservative efficacy testing and assays on stored samples should be carried out to determine the content and efficacy of antimicrobial preservatives.

Specifications

Limits of acceptance should relate to the release limits (where applicable), to be derived from consideration of all available stability information. The shelf life specification could allow acceptable and justifiable deviations from the release specification based on the stability evaluation and the changes observed on storage. It will need to include specific upper limits for degradation products, the justification for which should be based on safety and/or efficacy considerations. The justification

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for the limits proposed for certain other tests such as particle size and/or dissolution rate will require reference to the results observed for batch(es) used in bioequivalence or bioavailability studies. Any differences between the release and shelf life specifications for antimicrobial preservatives should be supported by preservative efficacy testing at the lower shelf-life limits or below.

Storage Test Conditions

The duration of studies and storage conditions required are normally:

	Conditions	**Minimum time Period at Submission**
Long term testing	25°C ± 2°C / 60% RH ± 5%	6 months
Accelerated testing	40°C ± 2°C / 75% RH ± 5%	6 months

Other storage conditions are allowable if justified. Heat sensitive finished products should be stored under an alternative lower temperature condition, which will eventually become the designated long term storage temperature. Special consideration may need to be given to products which change physically or even chemically at lower storage conditions e.g., suspensions or emulsions which may sediment or cream, oils and semi-solid preparations which may show an increased viscosity. Where a lower temperature is used, the six months accelerated testing should be carried out at a temperature at least 15°C above its designated long term storage temperature (together with appropriate relative humidity conditions for that temperature). For example for a product to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25°C ± 2°C / 60 % RH ± 5% (See below). The designated long term testing conditions will be reflected in the labelling and expiration date.

Storage under conditions of high relative humidity applies particularly to solid dosage forms. For products such as solutions, suspensions, etc., contained in packs designated to provide a permanent barrier to water loss, specific storage under conditions of high relative humidity is not necessary but the same range of temperatures should be applied. Low relative humidity (10 - 20% RH) can adversely affect products packed in semi-permeable containers (e.g., solutions in plastic bags, nose drops in small plastic containers) and consideration should be given to appropriate testing under such conditions.

Where significant change occurs due to accelerated testing conditions, additional testing at an intermediate condition (such as 30°C ± 2°C / 60 % RH ± 5%) should be conducted.

Significant change at the accelerated condition is defined as:

1. A 5% potency loss from the initial assay value of a batch;
2. Any specified degradant exceeding its specification limit;
3. The product exceeding its pH limits;
4. Dissolution exceeding the specification limit for 12 capsules or tablets;
5. Failure to meet specifications for appearance and physical properties e.g., colour, phase separation, resuspendability, delivery per actuation, caking, hardness...

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Should significant change occur at 40° / 75 % RH then the initial registration application should include a minimum of 6 months data from an ongoing one year study at 30°C / 60% RH; the same significant change criteria shall then apply.

The duration of studies and storage conditions required for temperature sensitive finished products are normally:

	Conditions	**Minimum time Period at Submission**
Long term testing	5°C ± 3°C	6 months
Accelerated testing	25°C ± 2°C / 60% RH ± 5%	6 months

The designated long term testing conditions will be reflected in the labelling and shelf life.

The long term testing will be continued for a sufficient period of time beyond 6 months to cover the proposed shelf life at appropriate test periods. The additional accumulated data, when available, should be submitted to the Competent Authorities.

Testing Frequency

Testing under defined conditions will normally be every three months over the first year, every six months over the second year, then annually.

The use for matrixing or bracketing designs can be applied, if justified.

Packaging/Containers

The testing should be carried out in the final packaging proposed for marketing. In some cases, smaller packaging simulating the actual packaging proposed for marketing may be acceptable. In these instances, a justification for smaller packaging simulating the actual market packaging should be provided. Additional testing of unprotected finished product can form a useful part of the stress testing and pack evaluation, as can studies carried out in other related packaging materials in supporting the definitive pack(s).

Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information which should cover as necessary physical, chemical, biological, microbiological quality characteristics, including particular properties of the dosage form (for example dissolution rate for oral solid dosage forms).

The design of the stability study is to establish, based on testing a minimum of two batches (for conventional dosage forms) or three batches (for critical dosage forms) of the drug product, a shelf life and label storage instructions applicable to all future batches of the dosage form manufactured and packed under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification until the expiration date.

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An acceptable approach for quantitative characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided confidence limit for the mean degradation curve intersects the acceptable lower specification limit. If analysis shows that the batch to batch variability is small, it is advantageous to combine the data into one overall estimate and this can be done by first applying appropriate statistical tests (for example, p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf-life may depend on the minimum time a batch may be expected to remain within acceptable and justified limits.

The nature of the degradation relationship will determine the need for transformation of the data for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Where the data shows so little degradation and so little variability that it is apparent from looking at the data that the requested shelf-life will be granted, it is normally unnecessary to go through the formal statistical analysis but only to provide a justification for the omission.

Limited extrapolation of the real time data beyond the observed range to extend expiration dating at approval time, particularly where the accelerated date supports this, may be undertaken. However, this assumes that the same degradation relationship will continue to apply beyond the observed data and hence the use of extrapolation must be justified in each application in terms of what is known about the mechanisms of degradation, the goodness of fit of any mathematical model, batch size, existence of supportive data, etc.

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

The stability of the medicinal product after reconstituting or diluting according to labelling, should be addressed to provide appropriate and supportive information for any claimed in use shelf-life.

Statements/Labelling

The storage conditions (temperature, light, humidity) indicated should refer to the CVMP Guideline "Declaration of Storage Conditions for Veterinary Pharmaceutical Products in the Product Particulars", the CVMP Guideline "Maximum Shelf Life for Sterile Veterinary Products after First Opening or Following Reconstitution" and the CVMP Guideline "In-Use Stability Testing of Veterinary Medicinal Products".

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

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ANNEX I

An active substance is considered as stable if it is within the initial specifications when stored at 25°C / 60 % RH (2 years) and 40°C / 75 % RH (6 months).

ANNEX II

Extrapolation of data

If real time data are supported by results from accelerated studies the shelf-life may be extended beyond the end of real time studies. Normally extrapolation to twice the length of the real time studies can be accepted. However, the maximum shelf-life justified by extrapolation should not exceed 3 years.