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GUIDE FOR THE DEVELOPMENT OF STABILITY STUDIES OF VETERINARY MEDICINES.

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GUIDE FOR THE DEVELOPMENT OF STABILITY STUDIES OF VETERINARY MEDICINES

1. INTRODUCTION

The scope in stability studies is to supply evidence about quality alterations in a substance or pharmaceutical product along time, influenced by environmental factors such as temperatura, humidity, or light exposure and to establish the validity period of product in the chosen packing material and its storage conditions, as well as to define re-test periods for these substances or products.

This document about requirements in "stability studies for veterinary medicines registration for all CAMEVET countries" is an agreement of minimal requirements with enough flexibility to use different focus for diverse products as long as they are supported by well-known scientific references .

For its implementation in the level of demand were taken into consideration:

1.1. Reports from different countries.
1.2. Stability testing of new veterinary drug sustances and medical products recommended for implementation at step 7 of the VICH Steering Comitee
1.3. The current report for Public Health Mercosur.
1.4. EMEA/CVMP/846/99 (Issued by the Veterinary Products Committee of the EU)
1.5. It was also taken into consideration the particular problems derived from veterinary pharmaceutical industry in Latin America and the Caribbean Region.

2. OBJETIVE AND SCOPE:

Set standards to perform stability studies of veterinary medicines in order to determine its shelf life.
Biological products are not included.

These studies could be required at registration time and in the following situations:

2.1. Shelf life changes, expiry or validity.
2.2. In the renewal when the original study didn't fit in the present regulations.
2.3. Change or addition of new primary packaging materials, as long as regulatory authority considered it suitable.
2.4. Qualitative or quantitative modification of excipients, as long as regulatory authority considered it suitable, .
2.5. Modification of the manufacture process, as long as regultory authority considered it suitable.
2.5. New manufacturing site, when considered necessary by the health authority.
2.6. Changes in active drug specifications, when considered suitable.

3. TERMS AND DEFINITIONS

3.1 Accelerated stability studies: These studies are designed to increase the rate of chemical degradation or physical modification of veterinary pharmaceutical products, using forced conditions of storage, in order to predict the tentative shelf life at commercial storage conditions. Results of accelerated stability studies are not always predictive of physical changes. The validity period so defined by prediction upon these accelerated tests, must be confirmed afterwards by the long-term stability tests.

3.2 Long-term stability studies: These are studies done under certain storage conditions for veterinary pharmaceuticals products according to the climatic zone of the market that is targeted, in a period not less than the period proposed (or approved) for shelf life. In this kind of study, physical, chemical, biological and microbiological characteristics of veterinary pharmaceutical products are evaluated, in order to determine the definitive shelf life.

3.3. Climatic zones: They are the four zones in which the world is divided based on the prevalent annual climatic conditions

Stability study program must consider the climatic zones in which the veterinarian pharmaceutical product will be used.

Climatic zone	**Definition**
I	Warm
II	Subtropical with possible high humidity
III	Hot and dry
IV	Hot and wet

World Health Organization, published in the guidelines "stability studies of pharmaceutical products containing known drugs in conventional dosage forms" Technical Report No. 863. Annex 5, 1996

4. SYMBOLS AND MEASUREMENT UNITS

a. % RH: Relative Humidity
b. °C: Celsius degrees

5. PROCEDURES:

5.1 Stability Studies

In general terms it is considered that the main objectives of stability studies are:

DEFINITION	STUDY TYPE	USE
Select properly (from the perspective of stability) formulations, and packaging and container closure systems of veterinary pharmaceutical products. Establish the proper conditions to store the product. Evaluate effect of temperature excursions out of recommended conditions	Accelerated	Product Development
Determine shelf life and storage conditions	Accelerated and long term or Long term only	Registration dossier. Once finished, long-term stability tests

		must be presented to regulatory authority for evaluation.
Support the shelf life stated or authorized	Long term and/or on going *	Registration renewal (when required)
Verify that the changes that have been introduced in the formulation or manufacturing process or manufacturing site affected or not product stability, when considered necessary by the competent authority.	Accelerated and long term or Long term only	Modification of the approval conditions that could affect stability

*On-going stability, in-use stability and stability of reconstituted product are not within the scope of this guideline. Specific documents will be prepared for those tests.

5.2 Accelerated stability studies

5.2.1. Test conditions will be determined by pharmaceutical form of product.

5.2.2. Accelerated stability studies on veterinary pharmaceutical products submitted in semipermeables container-closure systems, must consider temperature and humidity as catalytic factors of degradation.
Consequently, when the veterinary pharmaceutical product was packaged in impermeable containers, stability studies could be conducted under any condition of relative humidity.

5.2.3. The conditions of accelerated stability study are:

1. Medicinal products intended for storage at room temperature

Climatic zone	Definition	
I	Warm	40º ± 2 °C / 75 % ± 5% HR 6 months
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

2. Medicinal products intended for storage under refrigeration

Climatic zone	Definition	
I	Warm	25º ± 2 °C / 60 % ± 5% HR 6 months
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

5.2.4 When there are significant changes in the accelerated stability study, additional tests can be performed under intermediate conditions. These changes must be sustained. As examples of significant changes it could be mentioned: an active drug content decrease of more than 5 % related to the inicial value, or not compliance with

acceptance criteria for potency in biological or immunological methods; a rise in degradation products level exceeding specifications, not compliance with dissolution test specifications, decrease or rise in pH value or other parametres out of specifications limits; failure of physical parameters such as apperance, color.

5.3. Long-term stability study

5.3.1 The conditions of the study must be: storage with temperature and relative humidity controlled according to climatic zone of the target market of the product.

1. Medicinal products intended for storage at room temperature

Climatic zone	Definition	Storage conditions
I	Warm	21º C±2ºC - 45%± 5% HR
II	Subtropical with possible high humidity	25º C±2ºC - 60% ± 5%HR
III	Hot and dry	30º C±2ºC - 35% ± 5%HR
IV	Hot and wet	30ºC±2ºC - 65% ± 5%HR

2. Medicinal products intended for storage under refrigeration

Climatic zone	Definition	Storage conditions
I	Warm	5º ± 3 °C
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

3. Medicinal products intended for storage in a freezer

Climatic zone	Definition	Storage conditions
I	Warm	-20º ± 5 °C
II	Subtropical with possible high humidity	
III	Hot and dry	
IV	Hot and wet	

World Health Organization, published in the guidelines "stability studies of active pharmaceutical ingredients and finished products" Technical Report No. 953. Annex 2, 2009

Different conditions to the established can be used when tecnhically justified. These changes must be reflected in the product label.

The sponsor have to submit to the regulatory authorities the long term stability study supporting the approved validity period when it was finished,

5.4 Labeling (Storage Conditions Indications)

After concluded the stability studies, one of the following recommendations must be included in the packaging (label or secondary packaging)

Conditions under which stability study was carried out	Labeling Recommendations	Additional statements, if relevant
25°C/60% RH (long-term) 40°C/75% RH (Accelerated)	Do not store above 25ºC	Do not expose to refrigerating temperatures. Do not freeze
25°C/60% RH (long term) 30°C/65% (intermediate conditions)		
30°C/65% RH (long-term) 40°C/75% RH (Accelerated)	Do not store above 30ºC	Do not expose to refrigerating temperatures. Do not freeze
5°C ± 3 °C	Store refrigerated (between 2 ° C and 8 ° C)	Do not freeze
-20°C ± 5°C (*)	Store frozen (between -25ºC and -15ºC)	-

Reference: WHO Technical Report Series, Nº953, 2009 – Annex 2 – Stability testing of active pharmaceutical ingredients and finished pharmaceutical products.
Appendix 3 Recommended labelling statements
(*) Ultra-frozen products, intended to be stored at temperatures lower than -25ºC, are out of the scope of this guideline

Any other different temperature range could be accepted, at the registry owner request, according to the regulatory authority approval, as long as it was defined within the range indicated in the chart above.

Labeling statements out of the above mentioned ranges, must be duly justified by an specific stability test, which approval will depend on evaluation of the regulatory authority

It should always be included, as appropriate, any additional information such as:
Protect from light, keep in a dry place, protect from freezing, discard the remaining product after opening (for multidose containers if no in-use stability test was available), discard the remaining product after dilution/reconstitution (if no reconstituted stability test was available).

5.5 Study design

5.5.1. Storage conditions, study duration, sampling times and batch conditions chart.

	Accelerated stability studies*	**Stability study of long-term**
Study Duration	Not less than 6 months	Not less than the shelf life proposed
Sampling times	At least 0, 3 and 6 months	At least every 6 months during the first 2 years (0, 6, 12, 18, 24 months).And for every additional year, at least every 12 months (36, 48, 60 months).

		Accelerated stability studies*	Stability study of long-term
Batch size and number	For registration, for changes in formula, manufacturing site or procedure	At least 3 batches. Size: Industrial or representative.	At least 3 batches (they could be the same used in accelerated stability) Size: Industrial or representative.
	Shelf life checking or extension	Accelerated tests are not valid	At least 3 batches Size: Industrial

* Minimal requirements for initial registration consist of complete accelerated stability test up to at least 6 months. With this study, a 2 years provisory validity period is granted. With long-term stability finished, its conclusion will define the definitive validity period of product.

5.5.2 Minimum parameters to be assessed must be all that have been stated in final product quality specifications in the registration dossier. It must be considered the following: chemical (Ex.quantification), microbiological (Ex. Sterility), physical (Ex. Particle size), among other stability indicators. Degradation products must be previously evaluated and quantified when they had therapeutic or toxicological relevance.

5.5.3 For products with more than one active substance quantification of the least stable of them should be done at all time points. The rest of active substances may be just quantified at initial and final testing times.

5.5.4 Sterility testing or other microbiological tests should be done, when necessary, at least at the beginning and at the end of the study.

5.5.5 Analytical methods used in the tests have to distinguish quantitatively the active substance from its degradation products. Preferentially chromatographic methods shall be used, but other methods could be accepted if technically justified. Methods not described in pharmacopeias must be validated. Methods from pharmacopeias must be verified.

5.5.6 Manufacturing process for stability tests batches, shall be representative of industrial proceedings and must supply the same quality product and fulfill the same commercial final product specifications

5.5.7 For products demanding reconstitution before using, an additional stability test in the reconstituted condition must be performed. It must support the validity period after reconstitution proposed. If product use is immediate and complete, there is no need of an extra stability study, indicating this condition on product labels. Additionally, chemical and/or microbiological stability shall be performed on solvent/diluent, if suitable, along the same shelf-life proposed for product.

5.6 Containers into which the study is conducted

Studies must be developed in the same packaging in which product will be marketed. For products whose final packaging was of big size, the study may be developed in a container of less capacity as long as this container featured the same material, geometric characteristics and closure system of the marketed one.

For products that are marketed in several sizes into containers of the same material, stability study will be conducted at least in the smaller container since this is the one with the worst conditions in terms of container surface/product content rate.

If there were two or more packages of different materials the tests should be performed on each packaging material, unless delivery of technical tests of the packaging material showing the worst risk of deterioration of the product, and therefore the study should be conducted on this worst case container.

5.7 Stability study report

It must contain:

5.7.1 Title.
5.7.2 Product name (or identification code, in development stages)
5.7.3 Identification of the facilities/institution where the study was conducted
5.7.4 Identifications of the facilities where the product was manufactured
5.7.5 Name and signature of the person in charge of the study
5.7.6 General conditions of the study. (Manufacturing date, batch type and size, primary packaging, type of study and duration, batch number, storage conditions).

Example:

Batch N°	Manufacturing date	Batch type and size	Primary packaging	Study		Study duration
AA50107	01/10/2007	Representative/ 30 L	PET	Acc	40° ± 2°C / 75% ± 5% HR	6 months
			PET	LT	25° ± 2°C / 60% ± 5% HR	36 months
AB00207	15/10/2007	Industrial/ 300 L	PET	Acc	40° ± 2°C / 75% ± 5% HR	6 months
				LT	25° ± 2°C / 60% ± 5% HR	36 months
AB00307	20/11/2007	Industrial/ 300 L	PET	Acc	40° ± 2°C / 75% ± 5% HR	6 months
				LT	25° ± 2°C / 60% ± 5% HR	36 meses

References: Acc, accelerated study; LT, Long Term Study

5.7.7 Complete qualitative and quantitative product composition.
5.7.8 Justification of the chosen tracer compound, if suitable.
5.7.9 Type of material and primary container specifications, including closure system.
5.7.10 Data chart indicating active drug concentration versus time.
5.7.11 Specifications, analytical methods and analytical standard reference used. Documents supporting analytical standards origin may be requested.
5.7.12 According to the references supporting the proposed methodology, validation may be required .
5.7.13 Math calculations, statistical analysis and graphics used to determine shelf life.
5.7.14 Study conclusions: they must include clearly the storage conditions and shelf life proposed, signed by professional person responsible for the tests.

5.7.15 Instrumental records of the different tests performed are not part of the report but may be required by regulatory authorities. They must be performed in equipment that record the analysis date. Instrumental records, environmental conditions records, and batch records of the stability test prducts must exist as supporting documents of the study.

6. ANNEX

6.1 Annex 1. Guideline for evaluation parameters in stability tests

7. REFERENCES

7.1. MERCOSUR/GMC/Res.Nº 53/96 (issued by the Mercosur group of Public Health. Is the current document in the Mercosur to Human Health)
7.2. EMEA/CVMP/846/99 (issued by the Committee for veterinary medicinal products in the EU)
7.3. Stability Testing of New Veterinary Drug Substances and Medical Products
7.4. Recommends for Implementation at step 7 of the VICH Steering Committee
7.5. Stability reports submitted by different countries in the CAMEVET
7.6. Stability document of Brazil
7.7. World Health Organization, published in the guidelines "stability studies of active pharmaceutical ingredients and finished products" Technical Report No. 953.

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EST001 – Stability on veterinary medicines
ANNEX 1

GUIDELINE FOR EVALUATION PARAMETERS ON STABILITY TESTS

This guideline intends to mention a list of possible parameters to be considered in stability studies according to the pharmaceutical form of the veterinary medicine.
This list was prepared as a suggestion or guideline for stability protocol but it must not be taken as mandatory or excluding.
The product developers must choose, considering their knowledge of product and professional experience, the most accurate parameters to prove stability in the intended formulation for registration purposes.

Microbiological parameters, for any pharmaceutical form, when considered suitable, could be tested at initial and final time.

When photostability testing was considered necessary, a specific study should be designed. This test may be avoided when containers prove to be protective from deleterean effects of light on product.

- **Tablets, Coated tablets and dragees:**
  - concentration of active drug per unit,
  - organoleptic features,
  - friability,
  - disintegration,
  - dissolution
  - humidity (when appropriate).

- **Capsules:**
  - concentration of active drug per unit,
  - organoleptic features of capsule and of content,
  - dissolution
  - humidity (when appropriate).

- **Emulsions:**
  - concentration of active drug,
  - organoleptic features.
  - When appropriate:
    - viscosity,
    - microbial limits,
    - preservatives efficacy test (for multidose containers) and/or preservatives assay,
    - sterility

- **Solutions and suspensions:**
  - concentration of active drug,
  - organoleptic features,
  - pH (for acqueous base products).
  - When appropriate:

        - resuspensibility (in suspensions),
        - microbial limits (for acqueous or oil based products),
        - preservatives efficacy test (for multidose containers) and/or preservatives assay,
        - sterility.

- **Powders for oral solution/suspension:**
    - concentration of active drug,
    - organoleptic features,
    - humidity.
    - When appropriate:
        - microbial limits.
    - When reconstituted according to label instructions, parameters to be tested along recommended validity period are:
        - Concentration of active drug,
        - organoleptic features
        - pH (for acqueous solutions or suspensions);
        - When appropriate:
            - preservatives efficacy test (for multidose containers) and/or preservatives assay.

- **Solutions for injection, powders for solutions/suspensions for injection and lyophilized powders:**
    - concentration of active drug,
    - organoleptic features,
    - pH (for acqueous solutions/suspensions),
    - sterility.
    - When appropriate:
        - humidity (for powders),
        - preservatives efficacy test (for multidose containers) and/or preservatives assay
    - If product is to be reconstituted, prepare it following label instructions and parameters to be tested are:
        - concentration of active drug,
        - organoleptic features
        - pH (for acqueous solutions or suspensions).

- **Aerosols y nebulizers:**
    - concentration of active drug
    - organoleptic features.
    - Ratio propelent/concentrate. Net content.
    - When appropriate:
        - dosis homogeneity,
        - particle size (for suspensions).
        - microbial limits.

- **Creams, gels, pastes and ointments:**
    - concentration of active drug,
    - organoleptic features,
    - homogeneity,
    - viscosity.

- When appropriate:
  - pH (for acqueous base products),
  - microbial limits,
  - preservatives efficacy test (for multidose containers) and/or preservatives assay,
  - sterility.

- **Suppositories and ovules:**
  - Concentration of active drug per unit,
  - melting temperature,
  - organoleptic features.
  - When appropriate:
    - dissolution test
    - liquefaction/fussion time.